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Management of Acute Otitis Media: Update

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report was requested by the American Academy of Pediatrics (AAP). The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to **epc@ahrq.gov.**

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Structured Abstract

Context: Acute Otitis Media (AOM), a viral or bacterial infection of the ear, is the most common childhood infection for which antibiotics are prescribed in the United States. In 2001, the Southern California Evidence-based Practice Center conducted a systematic review of the evidence comparing treatments of AOM.

Objectives: This review updates the 2001 review findings on diagnosis and treatment of uncomplicated AOM, assesses the evidence for treatment of recurrent AOM, and assesses the impact of the heptavalent pneumococcal conjugate (PCV7) vaccine on the microbiology of AOM.

Data Sources and Study Selection: Searches of PubMed and the Cochrane databases were conducted from January 1998—July 2010 using the same search strategies used for the 2001 report, with the addition of terms not considered in the 2001 review. The Web of Science was also searched for citations of the 2001 report and its peer-reviewed publications.

Data Extraction: After review by two investigators against pre-determined inclusion/exclusion criteria, we included existing systematic reviews and randomized controlled clinical trials for assessment of treatment efficacy and safety. Pooled analysis was performed for comparisons with three or more trials.

Results and Conclusions: Few studies were found that examined the accuracy and precision of the diagnosis of AOM. Since PCV7's introduction, AOM microbiology has shifted significantly, with Streptococcus pneumoniae becoming less prevalent and Haemophilus influenzae (HF) increasing in importance. For uncomplicated AOM, pooled analysis indicates that nine children (95% CI: 6, 20) would need to be treated with ampicillin or amoxicillin rather than placebo to note a difference in the rate of clinical success. However, in four studies of *delayed* treatment approaches for uncomplicated AOM, two had higher rates of clinical success with immediate antibiotic therapy while two did not, and in three studies, a marked decrease in antibiotic utilization was noted. We are unable to draw definitive conclusions regarding the comparative effectiveness of different antibiotics for AOM in children with recurrent otitis media (ROM). For ROM, long-term antibiotic administration will decrease AOM episodes from 3 to 1.5 for every 12 months of treatment per otitis prone child during active treatment (95% CI: 1.2, 2.1); however, potential consequences of long-term treatment need to be considered. Data were insufficient to draw conclusions about comparative effectiveness of different treatment strategies in subgroups of children with uncomplicated AOM. Adverse events were generally more frequent for amoxicillin-clavulanate than for cefdinir, ceftriaxone, or azithromycin. Higher quality studies and improved reporting of study characteristics related to quality are needed to provide definitive conclusions for AOM and ROM treatment options.

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Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/otitis/otitisup.pdf.

Executive Summary

Introduction

Acute Otitis Media (AOM)[1] is a viral and/or bacterial infection of the middle ear and represents the most common childhood infection for which antibiotics are prescribed in the United States. Timely and accurate diagnosis and management of AOM can have significant individual and public health consequences.

The 2001 AHRQ evidence report on the management of AOM analyzed the evidence on the initial management of uncomplicated AOM in children, focusing on the natural history of the disease and the use of antibiotics in management. Although the 2001 report provided valuable analysis of the literature on the management of uncomplicated AOM in children, it did not address issues related to diagnostic accuracy and precision, management of AOM in specific subgroups of children, or the impact of immunization with Heptavalent Pneumococcal Conjugate Vaccine (PCV7) on the microbiology of AOM, recommended for widespread use in 2000. Additionally, new trials of treatment continue to be published. The purpose of this current AHRQ evidence report is to examine and analyze the evidence on three broad areas of inquiry: 1) accuracy and consistency of the clinical diagnosis of AOM, 2) the impact of PCV7 on AOM microbial epidemiology, and 3) the comparative effectiveness of different treatment options for uncomplicated AOM in average risk children and in children with recurrent (defined as three or more episodes in six months or four or more episodes within 12 months) or persistent AOM.

Methods

Key Questions

The American Academy of Pediatrics, the nominating organization, proposed six key questions aimed at assessing the comparative efficacy of interventions to treat uncomplicated and recurrent AOM in terms of treatment success, the safety of such treatments, and the effect on children in specific subgroups. In conjunction with a technical expert panel we refined these questions:

I. Diagnosis of AOM: What are the operating characteristics (sensitivity, specificity, and likelihood ratios) of clinical symptoms and otoscopic findings (such as bulging tympanic membrane), both individual and composite, to diagnose uncomplicated AOM and to distinguish it from otitis media with effusion (OME)?[2]

II. What has been the impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM microbial epidemiology (including acute mastoiditis and suppurative complications), with respect to both the organisms associated with AOM and the patterns of antimicrobial resistance?

III. What is the comparative effectiveness of different treatment options for treating uncomplicated AOM in average risk children?

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[1] A diagnosis of AOM requires 1) a history of acute onset of signs and symptoms, 2) the presence of middle ear effusion (MEE), and 3) signs and symptoms of middle-ear inflammation. (Marcy, Takata, Shekelle, et al., 2001).

[2] Otitis media with effusion (OME) is defined as fluid in the middle ear without signs or symptoms of acute infection. Distinguishing AOM from OME often poses a diagnostic challenge.

IV. What is the comparative effectiveness of different management options for recurrent otitis media (uncomplicated) and persistent otitis media or relapse of AOM?

V. Do treatment outcomes in Key Question3 (KQ3) and KQ4 differ by characteristics of the condition (AOM), patient, environment, and/or health care delivery system, including but not limited to the following: A. Laterality, i.e., unilateral vs. bilateral; B. Otorrhea or perforation; C. AOM severity, i.e., as defined as defined by the AAFP/AAP AOM Guideline (2004); D. Comorbidities, e.g., asthma; E. Age groups, e.g., <4 weeks, 4weeks to <6 months, 6mos-<2 years, 2-5 years; F. Race; G. Ethnicity; H. Day care attendance?

VI. What adverse effects have been observed for the treatments whose outcomes are addressed in KQ III and KQ IV?

Literature Searches

Searches of PubMed and the Cochrane Databases of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Education Resources Information Center were conducted from January 1998 through July 2010 using the same search strategies used for the 2001 report, with the addition of terms for conditions not considered in the 2001 review (recurrent otitis media), new drugs, and the heptavalent vaccine. The Web of Science was also used to search for citations of the 2001 report and its peer-reviewed publications. Among the 8, 945 titles identified were a number of recent, good-quality systematic reviews, which were included and which were examined for references. Titles were screened independently by two pediatricians with experience in conducting systematic reviews. For the question pertaining to diagnosis, we searched primarily for studies that included an assessment of sensitivity and specificity relative to a defined gold standard; we identified one good-quality 2003 meta-analysis and replicated its search strategy to obtain subsequent studies not included in their analysis. For the question pertaining to the effect of the vaccine on epidemiology and microbiology, we searched for studies that compared microbiology in the same populations before and after introduction of the vaccine or studies that compared microbiology across vaccinated and unvaccinated populations. For the efficacy and safety questions, we searched primarily for controlled trials or large observational studies aimed at identifying adverse effects.

Literature Review, Data Abstraction, and Analysis

In total, the reviewers examined 8,945 titles for the draft version of this report; 739 titles were identified for further review. Of those, 72 articles that met the predetermined inclusion criteria were reviewed in detail for efficacy and safety results. Investigators abstracted data into standard evidence tables with abstraction checked by a second investigator. Studies were quality-rated by two investigators using established criteria. For randomized controlled trials (RCT), the Jadad criteria were used. QUADAS criteria were used to evaluate the studies that pertained to diagnosis. Data abstracted included parameters necessary to define study groups, inclusion/exclusion criteria, influencing factors, and outcome measures. Data for the analysis were abstracted by a biostatistician and checked by a physician reviewer. We used a sequential resolution strategy to match and resolve the screening and review results of the two reviewers.

For the assessment of treatment efficacy, pooled analysis was performed for comparisons for which three or more trials could be identified. The articles eligible for analysis for the key questions pertaining to treatment efficacy were grouped according to the specific treatment options they compared. Each comparison consisted of articles that were considered homogeneous from the standpoint of clinical practice. Since the question of treatment efficacy was addressed in the first evidence report published in 2001, we combined the articles identified in that report with articles newly identified for this evidence report that addressed the same populations and reported the same types of outcomes. We pooled data for comparisons that included three or more articles from the old and new searches and performed meta-analyses or quantitative syntheses. We used the Der Simonian and Laird random effects model to pool rate differences across studies. Among the three effect measures—rate difference, relative risk, and odds ratio—the Technical Expert Panel and the project staff chose as most suitable the rate difference and its 95 percent confidence interval. We also reported the findings on the success rate instead of the failure rate throughout the report as recommended by the Technical Expert Panel. A test of heterogeneity was performed using the I^2 statistic. GRADE criteria were applied to assess the quality of the evidence for each comparison. In addition to the pooled estimate, we report the Q statistic and p-value for the Chi-squared test of heterogeneity.

For the assessment of the adequacy of evidence in arriving at a conclusion on the effectiveness of a particular treatment using a particular outcome, we use the concept of the "minimal clinically important difference (MCID)" against which the location of the 95% confidence interval of the pooled outcome was compared. Confidence intervals falling within the zone of MCID were considered to establish evidence of no difference, and confidence intervals outside the zone of MCID were considered to establish difference. If the confidence intervals crossed into the zone of MCID, an effect (positive or negative) of the treatment option on the outcome could not be established. While the MCID for treatment of AOM has not been empirically determined, we used an MCID of 5%, as this value represents approximately the lower limit of what Cohen would classify as a "small" effect size for treatment of AOM. Users of this evidence report who consider larger or smaller differences to be the minimum clinically important effect may reach different conclusions than we do here.

Results

Key Question I. Diagnosis of AOM: What Are the Operating Characteristics (Sensitivity, Specificity, and Likelihood Ratios) of Clinical Symptoms and Otoscopic Findings (Such As Bulging Tympanic Membrane) to Diagnose Uncomplicated AOM and to Distinguish It from OME?

Three clinical criteria are necessary to diagnose AOM: 1. acute symptoms of infection, 2. evidence of acute tympanic membrane (TM) inflammation, and 3. presence of middle ear effusion (MEE). To address this key question, we searched for studies that examined clinicians' accuracy and precision in identifying each of these clinical criteria, or their accuracy and precision in identifying all three together. A 2003 systematic review and three additional original studies met the inclusion criteria for the present review. The systematic review found that among

symptoms, only otalgia (ear pain) (sensitivities of 54%, 60%, 100% in three different studies; specificities 82%, 92%; positive likelihood ratio [LR] 3.0 [2.1-4.3], 7.3 [4.4-12.1]) and ear rubbing (sensitivity 42%; specificity 87%; positive LR 3.3 [2.1-5.1] seemed to predict a clinical diagnosis of AOM. An article published subsequent to the 2003 review found that among 469 children ages 6-36 months with parent-suspected AOM in primary care offices, AOM diagnosis was not associated with the occurrence, duration, or severity of parent-reported symptoms (e.g., ear pain: sensitivity 92%, specificity 8%, positive LR 1.0 [1.0-1.1]; ear rubbing: sensitivity 70%, specificity 22%, positive LR 0.9 [0.8-1.0]; fever: sensitivity 43%, specificity 65%, positive LR 1.2 [1.0-1.6]).[1]

One of the studies examined in this 2003 review assessed the accuracy of individual physical exam findings (cloudy, bulging, immobile, or red TM); they found these signs to be positively associated with AOM determined by the presence of MEE on tympanocentesis and clinical symptoms.

A study published subsequent to the 2003 review examined the accuracy of otoscopic and tympanometric findings compared with tympanocentesis as the criterion standard to determine the presence of MEE. The investigators performing otoscopy were not blinded to the tympanogram (a tool that evaluates middle ear function) results; further, the criterion standard of tympanocentesis was performed only when otoscopic or tympanometric findings suggested MEE. Ninety-seven percent of children with MEE on tympanocentesis had "Type B" tympanogram findings (abnormal), and all children with MEE on tympanocentesis had an otoscopic exam consistent with AOM. However, positive LR estimates are not as useful, since all participants had an AOM diagnosis at enrollment.

The second study published subsequent to the review included 137 eardrums that were either assumed to be or were diagnosed as AOM by general practitioners (GP). Of these, 78% were confirmed by ear-nose-and-throat (ENT) exam and the remaining were not, because the otolaryngologist diagnosed OME, viral otitis, or a normal TM. The ENT exam confirmed the GP diagnoses more often when redness and bulging were noted by the GP (83%) than when redness only was noted (75%).

The prior review and three additional studies that we identifieded for this key question did not directly or completely answer it; however, the studies do suggest that clinical findings of MEE (decreased mobility or abnormal position) and middle ear inflammation (distinctly red color of the TM) are positively associated with AOM, defined by positive tympanocentesis and acute onset of symptoms. Further, studies comparing diagnostic accuracy between generalist or primary care physicians and otolaryngologist suggest that clinicians' accuracy in identifying all three clinical criteria in one patient is moderate, at best. The overall quality of evidence for this Key Question is considered low, meaning that 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.

Key Question II. What Has Been the Impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM Microbial Epidemiology: What Organisms (bacterial and viral) are Associated with AOM Since the Introduction of PCV7; and What Are the Patterns of Antimicrobial Resistance in AOM Since the Introduction of PCV7?

Two types of studies could address this question: observational studies that compared the types of organisms associated with AOM among children prior to and following introduction of the PCV7 vaccine in 2000 and RCTs of vaccine efficacy that compared the causative agents between a group of unvaccinated children and those who were vaccinated. Both study types are complementary. RCTs provide a better assessment of cause-and-effect for the relationship between the vaccine and changes in organisms, but often enroll highly restricted patient populations. Observational studies complement RCTs by providing data on more representative populations.

We identified six original studies (four observational studies and two RCTs) that provided some information on this question. Since the introduction of PCV7, the observational studies generally report that Haemophilus influenzae (HF) has become more prevalent as a causative agent of AOM and Streptococcus pneumoniae (SP) has become less prevalent, although SP remains an important agent as well. The introduction of the vaccine has also resulted in a greater proportion of non-vaccine serotypes and a smaller proportion of the vaccine serotypes. The RCTs provided findings consistent with those results.

We were also asked to assess the evidence for subpopulations of children according to prior antibiotic use. However we found no studies that analyzed the effects of the vaccine on causative agents according to whether the children had or had not received antibiotics in the past.

The overall quality of evidence for this Key Question is considered high for the conclusion that use of the PCV7 vaccine has resulted in shifts in the prevalence of causative agents, meaning further research is very unlikely to change our confidence in the estimate of effect. The quality of evidence is very low for the special populations (such as patients with recurrent or persistent AOM) since we found fewer studies examining the vaccine's effect on these special populations.

Key Question III. What Is the Comparative Effectiveness of Different Treatment Options for Treating Uncomplicated AOM in Average Risk Children?

For the comparison of treatment success for children with uncomplicated AOM, we identified 63 comparisons of treatment options for uncomplicated AOM that encompassed different antibiotics and regimens. Our analyses yielded inconclusive results for many of these comparisons. For 12 comparisons, we reached stronger conclusions. Table S-1 shows key comparisons from the first AOM report, the present report, and where possible, combined results.

Table S-1. Comparative Effectiveness of Different Treatment Options for Treating Uncomplicated Acute Otitis Media (AOM) in Average Risk Children in the 2001 Report and the Present Report

Comparison	2001 Report		2010 Update			Conclusion[a]
	Number of trials	Success rate difference (95% CI)	Number of new trials	Total number of trials	Success rate difference	
Drug vs. placebo, wait-and-see, and/or prescription-to-hold						
Ampicillin or amoxicillin vs. placebo	5	12% (3%, 22%)	2	7	12%(5%, 18%)	Ampicillin or amoxicillin was more successful than placebo
Amoxicillin tid (7d) vs. prescription-to-hold)[2]	0	N/A	1	1	16% (6, 26)	Amoxicillin was more successful than prescription-to-hold (defined as success at day 3)
Antibiotic vs. prescription-to-hold)[2]	0	N/A	1	1	3% (-8, 14)	Inconclusive (defined as otalgia at day 4-6)
Amoxicillin 90mg/kg/d bid (10d) vs. wait-and-see[3]	0	N/A	1	1	15% (6, 24)	Amoxicillin was more successful (defined as success at day 12)
PcV vs. wait-and-see[3]	0	N/A	1	1	-3% (-14, 8)	Inconclusive (defined as success at day 14)
Drug vs. drug						
Ampicillin or amoxicillin vs. Ceftriaxone	**3**	3% (-2%, 9%)	1	4	0.1% (-7%, 7%)	Inconclusive
Amoxicillin 50mg/kg/d (bid, 10d) vs. erythromycin 40mg/kg/d (bid, 10d)[4]	0	N/A	1	1	0.6% (-3, 4)	Treatments were equivalent (when success defined as freedom from recurrence day 31-40)
Amoxicillin-clavulanate vs. amoxicillin sulbactam (80mg/kg/d; bid 10d	0	N/A	1	1	0% (-3.3, 3.3)	Treatments were equivalent (success d.12-14)
Amoxicillin-clavulanate (>6 yrs old: 250 mg tid x 7d; < 6 yrs old: 125 mg tid x7d) vs.	0	N/A	1	1	13% (5, 21)	Amoxicillin-clavulanate was more effective than cefaclor (success at day 28-34, as

Comparison	2001 Report		2010 Update			Conclusion[a]
	Number of trials	Success rate difference (95% CI)	Number of new trials	Total number of trials	Success rate difference	
cefaclor (125 or 250 mg tid x 7 d)[5]						defined by clinical symptoms but not by culture)
Cefaclor vs. trimethoprim-sulfamethoxazole	3	-6% (-13, 2) (success at less than 14 d)	0	3	N/A	Inconclusive (defined as success at less than day 14); no new data but using MCID
Cefaclor vs. Ampicillin or amoxicillin	4	-5% (-15, 6) (success at d. 3-7)	0	4	N/A	Inconclusive (defined as success at day 3-7); no new data; no new data but using MCID
Cefixime vs. Ampicillin or amoxicillin	4	0.1% (-3.9, 4.2) (success at d. 10-15)	0	4	N/A	Treatments were equivalent; no new data
Penicillin vs. ampicillin or amoxicillin	3	-5% (-11, 2) (success at d. 7-14)	0	3	N/A	Inconclusive (defined as success at day 7-14); no new data but using MCID
High vs. Low Dose Treatment						
Amoxicillin-clavulanate >60mg/kg/d vs. amoxicillin-clavulanate 40mg/kg/d	1	1.5% (-3, 13)	0	1	N/A	Inconclusive (defined as persistent clinical cure with no recurrence at follow-up); no new data
High-dose amoxicillin bid vs. lower-dose amoxicillin tid	1	-4% (-14, 7)	0	1	N/A	Inconclusive (defined as success at day 15); no new data
Amoxicillin-clavulanate 45/64 mg/kg/day / bid for 7-10 days vs. Amoxicillin-clavulanate 40/10 mg/kg/day / tid for 7-10 days[6]	0	N/A	1	1	0.1% (-4.8, 4.6)	Treatments were equivalent (success d. 7-12)
Short vs. Long Treatment Duration[b]						

Comparison	2001 Report		2010 Update			Conclusion[a]
	Number of trials	Success rate difference (95% CI)	Number of new trials	Total number of trials	Success rate difference	
Ampicillin or amoxicillin (7-10d) vs. Ceftriaxone (1 dose)	3	3% (-2%, 9%) (success rate at 5-10d)	1	4	0% (-7%, 7%)	Inconclusive
Amoxicillin-Clavulanate (7-10 d) vs. Ceftriaxone (1 dose)	2	N/A	3	5	3% (-2%, 7%)	Inconclusive
Cefaclor (7-10d) vs. Azithromycin (<5d)	1	N/A	2	3	-1% (-4%, 3%)	Treatments were equivalent
Amoxicillin (7d) vs. Azithromycin (1 dose)	0	N/A	1	1	1% (-1%, 4%)	Treatments were equivalent (defined as no new pain between day 6 and 11)
Amoxicillin-clavulanate (7-10d) vs. Azithromycin (≤5d)	5	2% (1, 5%) (success at 10-14d)	4	9	-0.3% (-6%, 6%)	Inconclusive
Amoxicillin-clavulanate 45/6.4 mg/kg/d (bid, 10d) vs. azithromycin 10 mg/kg/d (qd for 1 day), 5 mg/kg/d (qd for 4d)[7]	0	N/A	1	1	26% (6,36)	Longer-term amoxicillin-clavulanate is more successful than shorter-term azithromycin (at d. 12-14, when pathogen is H. influenzae)
Cefaclor 50mg/kg/d; bid 5 d) vs. cefaclor 40mg/kg/d; bid 10d)	0	N/A	1	1	0.7% (-3.5-4.9)	Treatments were equivalent

Table Notes: bid twice a day; CI confidence intervals; d day(s); kg kilograms (body weight); mg milligrams; NNT number needed to treat; PcV phenoxymethylpenicillin; qd once a day;

[a] Confidence intervals falling within the zone of indifference were considered to establish evidence of *no difference*, and confidence intervals outside the zone of indifference were considered to *establish difference*. If the confidence intervals crossed into the zone of indifference, an effect (positive or negative) of the treatment option on the outcome could not be established (*inconclusive*). For the 2010 systematic review, we used a ***zone of clinical indifference of +/- 5%*** for the difference in success rate between two treatment options.

[b]Short vs. long term duration refers to the length of treatment from the patient perspective, rather than from the perspective of drug action.

Meta-analyses of the comparison of ampicillin or amoxicillin vs. placebo indicates that nine children (95% CI: 6, 20) with uncomplicated AOM would need to be treated with immediate antibiotic therapy rather than placebo to note a difference in the rate of clinical success by day 14. For the comparison of ampicillin or amoxicillin vs. placebo, the quality of evidence is moderate due to heterogeneity in the results of studies, with the higher quality studies reporting smaller benefits, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate. In four studies of delayed treatment approaches for uncomplicated AOM, (1) two had higher rates of clinical success with immediate antibiotic therapy, i.e. Little (2001) and McCormick (2005) individually demonstrated higher clinical success rates for amoxicillin than for prescription-to-hold at day 3 (NNT=6; 95% CI: 4, 17) and wait-and-see at day 12 (NNT=7; 95% CI: 4, 17) options, respectively, (2) two did not demonstrate a difference in clinical success between immediate vs. delayed antibiotics, and (3) three studies showed a marked decrease in antibiotic utilization in the delayed antibiotic group.

Four trials, one newly identified for this report and three identified for the original AOM report addressed the comparison of ampicillin or amoxicillin vs. ceftriaxone. No difference (RD=0%, 95% CI: -7, 7) was found between these treatments for clinical success by day 14 though this finding was inconclusive utilizing an MCID of 5% (one trial found a slight advantage for ceftriaxone, whereas the others found ceftriaxone to be slightly less effective). The quality of evidence for this conclusion is moderate, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Five trials, two newly identified and three identified for the original AOM report, compared amoxicillin-clavulanate (7-10 days) with single-dose ceftriaxone. No difference (RD=3%, 95% CI: -2, 7) was found between these treatments for clinical success by day 16 though this finding was inconclusive utilizing an MCID of 5%. The quality of evidence for this conclusion is moderate, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Meta-analysis of three studies demonstrated equivalence of day-14 clinical success rates (RD=-0.7%, 95% CI: -4, 3) between cefaclor (7-10 days) and azithromycin (≤ 5 days) in treatment of uncomplicated AOM. In addition, single studies of comparisons (that could not be pooled) produced strong results. The quality of evidence for this conclusion is considered high, meaning further research is very unlikely to change our confidence in the estimate of effect.

In pooled analysis, no difference (RD=-0.3%, 95% CI: -7, 6) was noted in clinical success at day 14 comparing amoxicillin-clavulanate to azithromycin though this finding was inconclusive utilizing an MCID of 5%. In a single study, amoxicillin-clavulanate (for 10 days) was shown to have higher clinical success rates than azithromycin (single dose, one day) by day 14 when the pathogen was HF (NNT=4, 95% CI: 2, 17) and higher success rates than cefaclor by day 34 when success was defined by clinical symptoms (NNT=4, 95% CI: 2, 17). The quality of evidence for this conclusion is moderate due to heterogeneity in the results of studies, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Equivalent clinical success rates were demonstrated in individual studies of amoxicillin vs. azithromycin, amoxicillin vs. erythromycin, amoxicillin-clavulanate vs. amoxicillin-sulbactam, cefixime vs. ampicillin or amoxicillin,cefaclor 50 mg/kg/day vs. 40 mg/kg/day, and amoxicillin-clavulanate 45/64/mg/kg/day divided into two daily doses vs. 40/10/mg/kg/day divided into three

daily doses. In addition, individual studies of amoxicillin-clavulanate >60mg/kg/d vs. amoxicillin-clavulanate 40mg/kg/d and high-dose amoxicillin bid vs. lower-dose amoxicillin tid that in the 2001 Report were assessed as demonstrating equivalent clinical success rates are now assessed as inconclusive utilizing an MCID of 5%. Each of these single study results requires replication before strong conclusions can be reached.

Key Question IV. What Is the Comparative Effectiveness of Different Management Options for Recurrent Otitis Media (Uncomplicated) and Persistent Otitis Media or Relapse of AOM?

In approaching this question, studies were divided into those that examined treatment and those that examined prevention.

The available evidence did not allow us to reach strong conclusions regarding the following comparisons identified by this study for treatment of AOM in children with ROM, persistent AOM, or AOM treatment failure: amoxicillin-clavulanate vs. gatifloxacin, amoxicillin-clavulanate vs. levofloxacin, and amoxicillin-clavulanate vs. azithromycin. The overall quality of evidence for these comparisons is considered low, meaning that 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. One systematic review and additional new studies were identified examining otic antibiotics for treatment of AOM in children with tympanostomy tubes; however, it was not clear from the reports if the tympanostomy tubes were placed for ROM, persistent AOM, or some other chronic middle-ear condition, so these results cannot be generalized.

Several prior systematic reviews addressed the *prevention* of AOM in children with ROM. One review concluded that long-term antibiotics, defined as six weeks or longer, decreased episodes of AOM from 3 to 1.5 (95% CI: 1.2, 2.1) for every 12 months of treatment per otitis-prone child during active treatment. However data are missing regarding the safety of long-term antibiotic administration and the potential consequences on bacterial resistance. The role of tympanostomy tube placement was examined in a pooled analysis of two studies. This analysis found that tympanostomy tubes played a significant role in maintaining a disease-free state in the first six months after tube insertion in children with ROM. This conclusion is qualified by the small number of studies included in the analysis.

The available evidence did not allow for any definitive conclusions about the comparative role of amoxicillin vs. azithromycin, amoxicillin vs. sulfisoxazole, amoxicillin vs. placebo, sulfisoxazole vs. placebo, ceftibuten five-day vs. 10-day, probiotics vs. placebo, sulfafurazole vs. adenoidectomy, adenoidectomy vs. placebo, adenoidectomy vs. adenotonsillectomy, adenotonsillectomy vs. placebo, and adenoidectomy plus tympanostomy vs. tympanostomy in preventing AOM in children with ROM. The overall quality of evidence for each of these comparisons is considered low, meaning that 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.

Key Question V. Do Treatment Outcomes in Key Question3 (KQ3) and KQ4 Differ by Characteristics of the Condition (AOM), Patient, Environment, and/or Health Care Delivery System?

Of the 48 randomized clinical trials newly identified in our review that addressed the effectiveness of treatment options in uncomplicated AOM, 15 trials reported analyses for subgroups stratified by age, presence of MEE, laterality, parent/caretaker, hearing deficit presence/severity, otorrhea, examiner, and pneumococcal vaccine. Of the 10 trials identified in our review that addressed the effectiveness of treatment options in ROM, three reported analysis by age subgroups, and one reported stratified analysis by laterality and severity of otitis media.

For uncomplicated AOM, the available evidence indicated that antibiotic effect may be modified by age, laterality, and otorrhea. Definitive conclusions could not be made regarding subgroup analyses by other characteristics of AOM such as severity, characteristics of the patient such as presence of hearing deficit, characteristics of the environment such as the primary daytime caretaker, or characteristics of the healthcare delivery system such as the examiner.

In general, the results of individual trials and of meta-analyses show that children over the age of 2 have better outcomes from AOM, regardless of whether they are treated with antibiotics or not, compared to children 2 years of age or younger. No differences were seen in our meta-analyses in the rate difference for treatment success between children younger or older than 2 years when comparing ampicillin/amoxicillin to placebo or when comparing amoxicillin clavulanate to azithromycin. Similar conclusions were found in an individual patient meta-analysis.

In general, the results of individual trials and meta-analyses show that children with bilateral disease responded as well to treatment as those with unilateral disease. If left untreated, children with unilateral disease did better than those with bilateral disease. Further, the effect of antibiotic (compared with placebo) was greater in children with otorrhea than in those without otorrhea.

Key Question VI. What Adverse Effects Have Been Observed for the Treatments Whose Outcomes Are Addressed in KQ3 and KQ4?

We examined the incidence of adverse events in the RCTs identified for this report that compared the effectiveness of one or more treatment options. We also searched the FDA MedWatch Database for adverse events associated with use of medications for the treatment of AOM; however, none could be identified.

In general we could not make definitive conclusions regarding differences in adverse event rates among antibiotics when taking into account a MCID of 5%. However, Table S-2 shows the significant differences in adverse event rates that we noted (Table S-2 also shows the comparisons for the original report, those unique to the present report, and those that could be combined across both reports). Adverse events were generally more frequent for amoxicillin-clavulanate than for cefdinir, ceftriaxone, or azithromycin.

Table S-2 Comparison of Rates of Adverse Events Between Drugs (Significant Differences Only)

Comparison	2001 Report		2010 Update			Conclusion
	Number of trials	AE rate Difference (95% CI)	Number of new trials	Total number of trials	AE rate difference (95% CI)	
Uncomplicated AOM						
Overall Adverse Events						
Amoxicillin-clavulanate (7-10d) vs. Azithromycin (5d)	3	19%(9%, 29%)	0	3	N/A	Amoxicillin-clavulanate associated with greater overall AE rate
Amoxicillin-clavulanate vs. cefdinir (qd)	0	N/A	1	1	28% (17%, 39%)	Amoxicillin-clavulanate associated with greater overall AE rate
Amoxicillin-clavulanate vs. cefdinir (bid)	0	N/A	1	1	19% (8%, 31%)	Amoxicillin-clavulanate associated with greater overall AE rate
Amoxicillin clavulanate vs. ceftriaxone	0	N/A	1	1	16% (9%, 24%)	Amoxicillin-clavulanate associated with greater overall AE rate
Gastrointestinal Adverse Events						
Amoxicillin-clavulanate (7-10d) vs. Azithromycin (5d)	3	18% (8%, 28%)	0	0	N/A	Amoxicillin-clavulanate associated with greater rate of GI AE
Diarrhea						
Ampicillin or amoxicillin vs. cefixime	5	-8% (-13, -4)	0	0	N/A	Cefixime associated with greater rate of diarrhea
Amoxicillin clavulanate vs. cefdinir	0		1	1	25% (15%, 35%) in Cef QD and 22% (11%, 32%)in Cef BID	Amoxicillin clavulanate associated with greater rate of diarrhea
Amoxicillin clavulanate vs. ceftriaxone	0		1	1	13% (6%, 20%)	Amoxicillin clavulanate associated with greater rate of diarrhea
Recurrent Otitis Media						
Diarrhea						
Amoxicillin-clavulanate vs.	0	N/A				Greater for amoxicillin-

Comparison	2001 Report		2010 Update			Conclusion
	Number of trials	AE rate Difference (95% CI)	Number of new trials	Total number of trials	AE rate difference (95% CI)	
ciprofloxacin-dexamethasone ear drops						clavulanate in 1 study, but equivalent in 41; no conclusion possible in 23 comparisons

Table notes: AE adverse event; bid twice a day; CI confidence interval; d day; NNT number needed to treat; qd once a day

Of the 44 RCTs newly identified for this report that compared the effectiveness of treatment options in uncomplicated AOM, there are 61 treatment comparisons. Of the 61 treatment comparisons, 42 included comparisons of the percent of cases that had experienced an adverse event between two treatment options. For treatment of uncomplicated AOM, five adverse event rate comparisons showed a significant difference between two treatment options. Amoxicillin-clavulanate was associated with diarrhea more often than was cefdinir (NNT=four) and more often than was ceftriaxone (NNT= seven). The adverse event rates ranged from 27% to 35% for amoxicillin-clavulanate and from 10% to 14% for the other treatment options. For mention of any adverse event, amoxicillin-clavulanate had a higher rate than cefdinir given once or twice daily and a higher rate than ceftriaxone. However, in one study, the dose of amoxicillin was 40mg/kg/day, whereas in the other study, it was 80mg/kg/day (the clavulanate dosage was 10mg/kg/day in both studies). Equivalence was demonstrated in 29 comparisons, leaving 99 comparisons inconclusive.

These findings complement the findings from the first review, which showed that for uncomplicated AOM, children treated with amoxicillin-clavulanate for seven to ten days had a 19% (95% CI: 9, 29; NNT=5) higher rate of overall adverse effects and a 18% (95% CI: 8, 28; NNT=6) higher rate of gastrointestinal adverse effects than children treated with five days of azithromycin. (Although it was not specified in the studies, the original formulation was 31.25 mg clavulanate per 125 mg of amoxicillin). Eight children would need to be treated with azithromycin rather than amoxicillin-clavulanate to avoid a gastrointestinal adverse event. The original review also found that children treated with cefixime had an 8% (95% CI: 4, 13; NNT=12) greater rate of diarrhea than children treated with ampicillin or amoxicillin, so 12 children would need to be treated with ampicillin or amoxicillin rather than cefixime to avoid one case of diarrhea.

We also examined adverse event rates in children with presumed or explicitly defined ROM who were being given antibiotics for the treatment or prevention of AOM. Among the fourteen studies focused on children with ROM, persistent AOM, or AOM treatment failure, there were 21 treatment comparisons: eight involving the treatment of AOM in children with presumed or explicitly defined recurrent and/or persistent AOM, and/or AOM with treatment failure and the remainder in children being given the drugs prophylactically for prevention of AOM. For *treatment* of AOM in children with ROM and/or persistent otitis media, and/or AOM with treatment failure, we found one study that identified a significant difference in adverse event rates. In that study, amoxicillin-clavulanate (amoxicillin 90mg/kg/day; clavulanate 6.4mg/kg/day) was associated with diarrhea more often than was ciprofloxacin-dexamethasone ear drops (NNT=5). However, in 41 other comparisons, the adverse event rates were equivalent.

In 23 comparisons, a definitive conclusion was not possible. For studies that examined *prevention* of AOM in children with ROM, we did not find any significant differences in any of the adverse event rate comparisons.

Conclusions

This section begins with a brief review of the limitations identified for this review. We then present our conclusions and recommendations for future research.

Limitations

The conclusions that can be drawn from this review of the evidence are limited by a number of factors, some associated with specific questions and some that cross the entire body of literature.

• Assessing the precision of methods used to diagnose AOM is severely limited by the continued absence of a true gold standard and the reliance on the clinical definition. Although tympanocentesis is employed as the gold standard in some studies, its reliability and validity are limited by the need for specially trained operators, and studies that use tympanocentesis rarely perform the procedure on asymptomatic ears.

• Assessing the possible impact of the PCV7 vaccine on AOM microbial epidemiology and the development of antibiotic resistance is limited by several factors. First, tympanocentesis is not routinely done in children with uncomplicated AOM. Thus, most of the studies that compared the microbiology of AOM before and after the introduction and use of PCV7 examined middle-ear fluid samples for children with complicated, recurrent, or persistent OM. Another limitation is that we do not have adequate data to understand the possible impact of PCV7 on non-bacterial agents (i.e., viruses). Although the importance of non-bacterial agents has been studied for AOM, we were unable to find studies examining the impact of PCV7 on the importance of non-bacterial causes of AOM.

• The assessment of treatment efficacy was limited by the finding that the definitions of clinical success were usually not equivalent among studies comparing the same treatments. For example, studies used different clinical criteria to define success, and success was often measured at different time points. Another limitation to our assessment of treatment efficacy is that because we pooled studies across different time periods, we could not take temporal changes in microbiology into account, that is older studies might have had a microbiology more (or less) responsive to antibiotics than newer studies.

• The inclusion criteria for participantss also varied widely among studies. Some studies used only one of the three criteria included in the definition of AOM for diagnosis, while others considered two or all three. It is possible that some studies with less stringent inclusion criteria may have included participants who did not have AOM, but rather had OME or no middle ear infective process at all. In addition, if the operating characteristics of criteria used to diagnose AOM differ by age, then it is possible that treatment outcomes by age may be confounded by a differential rate of inclusion of children who actually do not have AOM into a particular age group.

• Few studies assessed the effect of patient characteristics on treatment outcomes, beyond the effect of age, laterality, or otorrhea.

• Studies that compared adverse effects between treatments almost never explicitly included the collection of adverse event information in their designs and were rarely, if ever, powered to assess differences in rates of adverse effects between treatments. In addition, differences in the ways adverse events were reported and categorized from one study to another made it difficult to try to pool these results.

Discussion

AOM is a clinical diagnosis with three components: acute signs of infection and evidence of middle ear inflammation and effusion.12 Evidence suggests that certain otoscopic findings (i.e., a red and immobile or bulging TM) predict AOM, but the accuracy or precision of a clinical diagnosis has not been determined. Given the absence of a gold standard for diagnosing AOM, it is difficult to draw firm conclusions from existing studies or to design new studies to assess the precision of diagnostic methods or criteria for diagnosing AOM. Perhaps the most important way to improve diagnosis is to increase clinicians' ability to recognize and rely on key otoscopic findings. Since the introduction of the PCV7 vaccine, AOM microbiology has shifted considerably. Our review indicates that overall, the SP serotype is becoming less prevalent, yet still important, while HF is increasing in its importance as an infectious agent of AOM. No studies that fit the inclusion criteria for the report examined the impact of the introduction of PCV7 on antimicrobial resistance.

For the treatment of uncomplicated AOM, immediate ampicillin/amoxicillin treatment has a modest benefit compared to placebo or delayed antibiotics, but also may be associated with more diarrhea and rash. Of 100 average-risk children with AOM, we could expect approximately 80 to get better within about 10 days without antibiotics. If all were treated with immediate ampicillin/amoxicillin, we would expect an additional 12 to improve, but 3 to 10 children would develop rash and 5 to 10 would develop diarrhea. Clinicians need to weigh these risks (including possible long-term effects on antibiotic resistance) and benefits before prescribing immediate antibiotics for uncomplicated AOM.

In head-to-head comparisons, most antibiotic regimens demonstrated comparable clinical success rates. Because of the relatively small number of studies on treatment of AOM in children with ROM, we are unable to draw any definitive conclusions regarding the comparative effectiveness of different antibiotic treatments. The evidence suggests that long term antibiotics decrease episodes of AOM from three to 1.5 for every 12 months of treatment per otitis-prone child during active treatment. However, the drawbacks of long-term antibiotics, which include adverse effects such as diarrhea, allergic reactions, and emergence of bacterial resistance, must be weighed against that of recurrence. Further, we can also conclude that tympanostomy tubes can help decrease the likelihood of a repeat infection in a child with a history of ROM within the first six months after tube insertion. This conclusion may be tempered by the issue of AOM diagnostic accuracy in the presence of tympanostomy tubes possibly confounding these results, i.e. the pressure equalization and drainage afforded by the tubes and their physical presence decreasing the intensity or visibility of signs and symptoms used to diagnose AOM, leading to false negatives. Again, whether or not the benefit of avoiding a repeat episode of AOM over six months outweighs the costs of a tympanostomy tube placement will depend on the clinician's

assessment of the child with AOM, and discussions of advantages and disadvantages with the family.

While the 2001 evidence review identified only sufficient evidence to allow the assessment of the effects of age on treatment effectiveness, the current review identified information to assess the effect of laterality and otorrhea as well. The current review suggests that overall, children over the age of two years had better outcomes with various antibiotic options than children under age two and that laterality and otorrhea do have effects as well. These findings suggest that clinicians may need to more closely monitor response to treatment and outcomes when treating very young children with AOM, in particular those with bilateral AOM and those with otorrhea.

Although the evidence was generally insufficient to allow definitive conclusions regarding differences in adverse event rates, the available evidence across all studies did indicate an increased rate of gastrointestinal effects and diarrhea specifically with amoxicillin-clavulanate (compared with oral cefdinir, oral ceftriaxone, or ciprofloxacin-dexamethasone ear drops) and with cefixime (compared with ampicillin or amoxicillin). In addition amoxicillin-clavulanate appeared to have a higher overall adverse effect rate than cefdinir, ceftriaxone, or azithromycin.

Future Research Suggestions

Based on the findings of this review, we provide the following suggestions for future research directions.

Diagnosis of AOM

Additional studies are needed to more fully understand the precision of the current diagnostic criteria for AOM: acute onset of signs and symptoms, MEE, and middle ear inflammation. For example, although it has been determined that all three are necessary for a diagnosis of AOM, evidence is insufficient to guide clinicians on the most effective and efficient ways to assess each of these elements in the clinical setting. Also needed are more studies that use a reference standard that can take into account all three criteria of an AOM diagnosis. Thus, a reference standard that takes into account only MEE does not provide sufficient evidence on overall diagnostic accuracy for AOM.

Influence of the PCV7 Vaccine on Microbiology/Epidemiology

Studies are needed to address the implications of the observed evolution in microbiology subsequent to introduction of the PCV7 vaccine. For example, will this shift in microbiology translate to a shift in the type and incidence of suppurative and other complications? Further research is needed to explore the impact of PCV7 on the clinical progression and outcomes of uncomplicated AOM, and of AOM in otitis-prone children with recurrent AOM.

More inquiry is needed into microbiologic shifts in AOM, especially as it relates to resistance patterns of the non-PCV7 serotypes of SP that seem to be increasing since the introduction of PCV7. Such research will require continued surveillance of both shifts in the causative organisms of AOM and in the antibiotic resistance/susceptibility of these organisms.

A recent study of a single pediatric practice, not meeting our inclusion criteria, found evidence suggesting that an increase in the proportion of AOM with non-vaccine SP serotypes may be leading to another shift in AOM microbiology.[8] These new data support the need for ongoing surveillance of AOM isolates.

Continued surveillance will also help us understand the impact of new pneumococcal vaccines that include more serotypes than PCV7 currently does, such as the newly-licensed PCV13. It will be important to have information to help conduct cost-benefit analysis of vaccines that cover more than the current seven serotypes. A growing body of research is assessing the efficacy of the vaccine in preventing AOM. Although a review of this literature was beyond the scope of this report, such a review may be warranted in the near future.

Treatment Efficacy and Adverse Effects

Research issues identified in the original AOM review are still applicable to the review update as it relates to treatment of uncomplicated AOM as well as to treatment of ROM, which was not previously addressed. Though we report several definitive conclusions, the usefulness of these conclusions to the practitioner is limited because of concerns regarding the internal validity of some of the source studies and the generalizability of the findings because of differences in the definitions of AOM and ROM—as well as treatment outcomes—across studies; the variability of study quality; and the relative paucity of evidence related to influencing factors such as characteristics of AOM including severity, the patient, the environment, and the healthcare delivery system. Standard definitions of AOM and ROM that lead to standard diagnostic criteria and that are acceptable to both researchers and practitioners have not been developed since the initial review and are still needed. The continued diversity of definitions for AOM as well as for ROM and, therefore, the diversity of diagnostic criteria that control entry of participants into these treatment trials make it difficult to synthesize and generalize findings, as it is unclear if the same condition is being assessed across studies. Greater knowledge regarding the effect of children's age on the operating characteristics of diagnostic criteria will also help to assess results of studies comparing treatment options, e.g., by clarifying whether children of different ages who have been diagnosed with and are being treated for AOM truly have the condition. In addition, improved knowledge of the effect of tympanostomy tube presence on these diagnostic operating characteristics will help to better assess the true impact of tympanostomy tubes on prevention of AOM in children with ROM.

Standard definitions related to the quality of AOM management in terms of specific structures, processes, and outcomes are still needed. Differences in terminology and in particular outcome choice and definitions between studies make it difficult to synthesize the results across studies and to generalize findings. This issue should be addressed in future studies.

Evidence Report

Chapter 1. Introduction

Acute Otitis Media (AOM) is a viral or bacterial infection of the middle ear and represents the most common childhood infection for which antibiotics are prescribed in the United States (US).[9-11] A 2009 analysis estimated the annual medical expenditures for treating OM in US children (including AOM and OM with effusion) to be approximately $2 billion.[12] Timely and accurate diagnosis and management of AOM can have significant individual and public health consequences. The 2001 AHRQ evidence report on the management of AOM analyzed the evidence on the initial management of uncomplicated AOM in children, focusing on the natural history of the disease and the use of antibiotics in management. The report concluded that among children not treated with antimicrobials, the clinical failure rate was highly variable.[13] Antibiotic treatment with either ampicillin or amoxicillin did reduce clinical failure rates, and among the antibiotic regimens assessed, there were no differences in clinical failure rates; however some antibiotic regimens were associated with more adverse events than others.

Although the 2001 report provided valuable analysis of the literature on the management of uncomplicated AOM in children, it did not address issues related to diagnostic accuracy and precision, management of AOM in specific subgroups of children, or the impact of immunization with Heptavalent Pneumococcal Conjugate Vaccine (PCV7), recommended for widespread use in 2000, on the microbiology of AOM. Additionally, new trials of treatment continue to be published. The purpose of this current AHRQ evidence report is to examine and analyze the evidence on three broad areas of inquiry: 1) the diagnosis of AOM, 2) the impact of PCV7 on AOM microbial epidemiology, and 3) the comparative effectiveness and safety of different treatment options for uncomplicated AOM in average risk children, and in children with recurrent or persistent AOM.

Diagnostic Accuracy

Otitis media with effusion (OME) is defined as fluid in the middle ear without signs or symptoms of acute infection. Distinguishing AOM from OME often poses a diagnostic challenge.[14, 15] Key elements of the diagnosis of AOM include the acute onset of symptoms, presence of middle ear effusion (MEE), and signs of middle ear inflammation.[16-18] Errors often occur when the clinician makes a diagnosis of AOM in the absence of MEE.[14] At least at the time of the first systematic review on management of AOM, diagnostic certainty appeared to be linked to patients' age: Older children (>30 months) were more likely to have a certain diagnosis of AOM than children ≤ 12 months of age.[19] Given the uncertainty associated with diagnosis, particularly in young children, it is important to continually assess the validity of the clinical signs and symptoms used to diagnose AOM.

Management

Traditional management approaches have centered on the use of antimicrobials; a 2009 study found that prescription of broad-spectrum antibiotics for AOM increased from 34% of doctor visits in 1998 to 45% of visits in 2004.[20] However, debate is increasing over their benefits. Concerns regarding increased antimicrobial resistance and uncertainty about the benefits of antibiotic treatments (e.g., AOM may be either bacterial or viral) have resulted in a number of clinical guidelines proposing more judicious use of antimicrobials.[16, 21] The 2004 guidelines released by the American Academy of Pediatrics (AAP) and American Academy of Family Practice (AAFP) recommend antibiotics for all children under 6 months and an observation

approach for otherwise healthy children ages 6 months to less than 2 years who have BOTH an uncertain diagnosis and non-severe disease. Observation is also an option for otherwise healthy children 2 years of age or older with either non-severe disease or uncertain diagnosis.[16] However, the benefits of a watchful waiting approach in young patients with a certain diagnosis of AOM are unclear.

Amoxicillin is often recommended as the first-line antibiotic for children.[16, 21] Although empiric therapy recommendations vary depending on the local antimicrobial resistance patterns, evidence of recent microbiologic shifts and changing resistance patterns associated with PCV7 warrant determining the effectiveness and safety of the current recommendations and evaluating additional antimicrobial agents and other management strategies.

Recurrent otitis media (ROM), defined as three or more episodes in six months or four or more episodes within 12 months, occurs in 20% of children under six months of age.[9] Antibiotic resistant *Streptococcus pneumoniae* (SP) is commonly associated with ROM and presents a significant therapeutic challenge.[22, 23] The choice of antimicrobial is not always clear, and the role of prophylactic antibiotics remains uncertain.

Pneumococcal Conjugate Vaccine

SP is a common bacterial isolate from the middle ear fluid of children with otitis media.[24] In February 2000, a heptavalent pneumococcal polysaccharide protein conjugate vaccine (PCV7) was recommended for use in children aged 2-23 months and for children aged 24-59 months at increased risk for pneumococcal disease.[25] These recommendations were expanded in 2007 to include all healthy, previously unvaccinated children 24-59 months of age. A question that needs to be addressed is whether PCV7 vaccination is associated with a microbiologic shift among pathogens commonly responsible for otitis media.

Chapter 2. Methods

Original Proposed Key Questions

The American Academy of Pediatrics requested that AHRQ commission an update of the 2001 evidence review, Management of Acute Otitis Media. AHRQ provided an initial list of questions.

1. **What is the validity of clinical symptoms and otoscopic findings such as a bulging tympanic membrane to diagnose AOM? Do these clinical findings aid physicians in distinguishing AOM from OME?**
2. **What organisms (bacterial and viral) are associated with otitis media since the introduction of PCV7?**
3. **What are the patterns of antimicrobial resistance since the introduction of PCV7?**
    a. New infections
    b. Recurrent infections
4. **What is the comparative effectiveness of different treatment options (defined below) for treating AOM in average risk children ages <2 years, ages 2 years to <5years and ages ≥ 5 years?**
    a. Treatment options include but not limited to:
        i. Amoxicillin (including high dose vs. low dose)
        ii. Amoxicillin-clavulanate (including high-dose vs. low-dose)
        iii. Cephalosporins (e.g. ceftriaxone, cefdinir, cefixime)
        iv. "Wait and see approach"
        v. Placebo
        vi. Duration of treatment
    b. Outcomes to consider but not limited to:
        i. Parent satisfaction
        ii. Duration of symptoms/illness
        iii. Treatment failure, mastoiditis, bacteremia, clinical cure, bacteriologic cure
        iv. Disease recurrence
5. **What is the comparative effectiveness of different management options for recurrent otitis media?**
    a. Management options include but not limited to:
        i. Amoxicillin-clavulanate
        ii. Cephalosporins (e.g. ceftriaxone, cefuroxime)
        iii. Quinolones
        iv. Antibiotic prophylaxis
    b. Outcomes to consider but not limited to:
        i. Parent satisfaction
        ii. Duration of symptoms/illness
        iii. Treatment failure, mastoiditis, bacteremia/ Cure rates
6. **What is the evidence that the comparative effectiveness of different treatment options in KQ 3 differs in subpopulations of patients?**
    a. Subpopulations to include (but not limited to):

i. Bilateral disease
ii. Comorbidities (e.g. asthma –will need to define further)
iii. Age groups (e.g. <1 month, 1-<2 months, 2-<6 mos, 6mos-<2 years, 2-5 years)
iv. Race/Ethnicity
v. Day care attendance

7. What are the comparative harms of different treatment options?

a. Outcomes to consider (but not limited to):
   i. Antibiotic resistance
   ii. Diarrhea/vomiting

The final key questions, which were slightly revised in coordination with the technical expert panel, appear in Chapter 3 (Results).

Technical Expert Panel

Each AHRQ evidence report is guided by a Technical Expert Panel (TEP). We invited a distinguished group of scientists and clinicians, including individuals with expertise in otolaryngology, audiology, infectious disease, epidemiology, and health services, to participate in the TEP for this report. Efforts were made to include the project leader and TEP members from the 2001 AHRQ AOM report. The list of TEP members is included in Appendix F. Two conference calls were held with the TEP.

The first call, held on September 25, 2008, reviewed the draft key questions (above) and proposed definitions for AOM and ROM (see below). TEP members proposed small revisions to the wording of the key questions, definitions, and outcomes and influencing factors to consider. A summary of this meeting is provided in Appendix F. The revised key questions appear in Chapter 3. The definitions that were accepted appear below and in Appendix A.

Between the first and second TEP calls, we polled the TEP about several points. In November, we polled the panel via email to clarify whether to accept studies that used nasopharyngeal cultures for diagnosis and characterization. The consensus was that we should not; the summary of responses appears in Appendix F. In February, we provided the TEP with a list of the trials included to that point to ascertain whether we had excluded any important studies.

The second call was held on March 10, 2009. During this call, we once again asked the TEP's help in identifying any studies we had neglected to include. We also reviewed the scope of work to assess its completeness and discussed the TEP's expectations for reporting of findings in the final report. A summary of this call appears in Appendix F. The scope appears in Appendix A.

Definitions of Acute Otitis Media and Recurrent Otitis Media

Definition of AOM: A diagnosis of AOM requires 1) a history of acute onset of signs and symptoms, 2) the presence of MEE, and 3) signs and symptoms of middle-ear inflammation.[13]

Elements of the definition of AOM are all of the following:

1. Recent, usually abrupt, onset of signs and symptoms of middle-ear inflammation and MEE
2. The presence of MEE that is indicated by any of the following:

a. Bulging of the tympanic membrane
b. Limited or absent mobility of the tympanic membrane
c. Air-fluid level behind the tympanic membrane
d. Otorrhea

3. Signs or symptoms of middle-ear inflammation as indicated by either
   a. Distinct erythema of the tympanic membrane or
   b. Distinct otalgia (discomfort clearly referable to the ear[s] that results in interference with or precludes normal activity or sleep)

Definition of Recurrent AOM (ROM): A diagnosis of ROM requires three or more episodes of AOM within six months or four episodes within 12 months, including at least one episode during the preceding six months.[26-28]

Definition of Persistent Otitis Media: Persistent otitis media is manifested by persistence during antimicrobial therapy of symptoms and signs of middle ear infection (treatment failure) and/or relapse of AOM within one month of completion of antibiotic therapy. When two episodes of otitis media occur within one month, it may be difficult to distinguish recurrence of AOM (i.e. a new episode) from persistent otitis media (i.e., relapse).[23]

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The second call was held on March 10, 2009. During this call, we once again asked the TEP's help in identifying any studies we had neglected to include. We also reviewed the scope of work to assess its completeness and discussed the TEP's preferences for the format used to describe findings in the final report. A summary of this call appears in Appendix F. The scope appears in Appendix A.

Literature Search

Our search for studies began in July 2008 with an electronic search of PubMed® for reports on AOM diagnosis, treatment outcomes, and the effects of the PCV7 vaccine on the microbiology and epidemiology of AOM, using the search strategies designed for the first AOM systematic review supplemented with additional key words for newer treatment modalities, vaccine outcomes, and recurrent AOM. Separate sets of searches were conducted for Key Question I, Key Question II, and Key Questions III through VI (see Chapter 3); these searches are described further in Chapter 3 (Appendix A shows our specific search terms and strategies; Appendix H shows a conceptual framework that helped guide the searches and approach). Simultaneously, we also searched for and identified a number of systematic reviews that addressed several of the key questions.

We also searched the Cochrane Controlled Clinical Trials Register Database and the Cochrane Database of Reviews of Effectiveness (DARE). (The Cochrane Collaboration is an international organization that helps people make well-informed decisions about health care by preparing, maintaining, and promoting the accessibility of systematic reviews on the effects of heath care interventions.) Finally, we searched the Web of Science for relevant proceedings. Search updates were conducted in January and August 2009, and in August 2010.

In addition to the keyword searches, relevant articles were identified by using the Science Citation Index to search for articles that cited the 2001 AOM report and its resulting publications and by reference mining other relevant systematic reviews as well as the articles accepted for inclusion. We also identified several relevant international meeting proceedings and sought abstracts that responded to the key questions (the findings reported in most of these abstracts had been subsequently published in full-text articles). Finally, as described above, we polled the TEP for any studies we had overlooked.

Article Review

Study Inclusion

Although our literature search was unrestricted by study design, the studies included in the review are of one of the following types of designs.

Review articles identified by the search were classified as either systematic (including meta-analyses) or nonsystematic. Systematic reviews were identified by reading the methods section of the article to determine whether an acceptable method was employed to identify evidence (such as a description of the name of the computerized database searched and the full set of search terms used, as well as details about the method for accepting and rejecting identified articles). Only systematic reviews were included.

Randomized controlled trials (RCTs) are studies where the participants are definitely assigned prospectively to one of two (or more) alternative forms of intervention, using a process of random allocation (e.g., random number generation, coin flips).

Controlled clinical trials (CCTs) are studies where participants (or other units) are either

(a) definitely assigned prospectively to one of two (or more) alternative forms of health care using a quasi-random allocation method (e.g., alternation, date of birth, patient identifier)

OR

(b) possibly assigned prospectively to one of two (or more) alternative forms of health care using a process of random or quasi-random allocation.

Observational studies (such as cohort and cases series) are those where the investigators do not control who gets the interventions. The decision was made to exclude observational studies unless controlled trials were insufficient to answer the key questions pertaining to treatment.

To be included, studies had to report on diagnosis or treatment of AOM, primary or recurrent; or the effects of the Prevnar® vaccine on bacterial microbiology/epidemiology.

Screening

Two reviewers, both pediatricians trained in the critical analysis of scientific literature, independently reviewed lists of titles obtained from each search. Abstracts were obtained for all potentially relevant titles, and the clinicians independently reviewed the abstracts, resolving disagreements by consensus. Using a single-page "screening form" (included in Appendix B), they reviewed the abstracts retrieved from the various sources to assess whether they reported original data (or appeared to be systematic reviews) and responded to one of the key questions.

Full text articles were obtained for all accepted abstracts. Relevant study-level information was then abstracted from these articles onto review forms. This information included study design, sample size and identity, treatment protocol, types of outcomes reported and by whom, potential influencing factors, and study quality. The two reviewers independently reviewed each study and resolved disagreements by consensus. The lead investigator resolved any disagreements that remained after discussions between the reviewers.

Data Abstraction & Synthesis of Results

Review and Assessment of Study Quality

The criteria for the assessment of study quality were established prior to the review of articles. The criteria developed by Jadad, Moore, Carroll et al. (1996) were used to evaluate the quality of RCTs.[29] For a given study, we awarded one point if the study was described as randomized, one point if the study was described as double-blind, and one point if it described withdrawals and dropouts. We awarded an extra point if the method of randomization was appropriate and another if the method of double-blinding was appropriate; conversely, we subtracted one point each if the method of randomization or double-blinding was inappropriate. Thus, studies could receive a Jadad score ranging from 0 to 5 points.

The criteria used to evaluate the quality of cohort studies and case-control studies were based on the work by the McMaster University Group.[30-32] The quality of cohort studies was evaluated against eight components, which included the presence or absence of a clear definition of the study cohort, an early inception point, a clear pathway of patient entry, complete follow-up, description of dropouts, objective outcome criteria, 'blind' outcome assessment, and adjustment for extraneous factors. The quality of studies that examined diagnostic tests was evaluated using QUADAS criteria.[33] The quality of systematic reviews was evaluated using the Assessment of Multiple Systematic Reviews (AMSTAR) criteria. Quality reviews were carried out in the same manner as the screening of articles for inclusion/exclusion. Articles were not masked prior to review. Two physician reviewers independently evaluated the quality of the articles and filled out the quality review forms. Conferences were held to resolve discrepancies whenever needed.

Data Abstraction

For the articles eligible for inclusion in the Evidence Report, data abstraction was carried out by two physician reviewers. Data abstracted included parameters necessary to define study groups, inclusion/exclusion criteria, influencing factors, and outcome measures. Data for analysis were abstracted by a biostatistician and checked by a physician reviewer. We used a sequential resolution strategy to match and resolve the screening and review results of the two reviewers. The data abstraction form used is included in Appendix B.

Supplemental Analysis for Key Question III

Key Question III addresses the comparative effectiveness of different treatment options for treating uncomplicated AOM in average risk children for treatment options including but not

limited to antibiotics, "wait-and-see" approach, analgesics, and placebo and for outcomes including but not limited to treatment failure, invasive infections, bacteriologic cure, disease recurrence, quality of life or functional outcome, and parent satisfaction. Among the included articles we tabulated the number of articles by treatment options and by outcomes in order to assess whether there was an adequate number of articles for pooling analysis.

Our review of data to address this key question (as well as questions pertaining to prevention and treatment of ROM) had several limitations. First, definitions for clinical success were usually not equivalent between studies comparing the same treatments. For example, studies used different clinical criteria to define success, and success was often measured at different time points. Second, the inclusion criteria for participants also varied widely among studies. Some studies used only one of the three criteria for AOM diagnosis, while others considered two or all three. It is possible that some studies with less stringent inclusion criteria may have included participants who did not have AOM, but rather had OME or no middle ear infective process at all. Third, the timing of study completion could affect results. In analysis, the articles eligible for analysis for the key question were grouped according to the specific treatment options they compared. Each comparison consisted of articles that were considered homogeneous from the standpoint of clinical practice.

Since this key question was addressed in the first evidence report published in 2001, we combined the articles identified in that report with newly identified articles in this evidence report. Comparisons that included three or more articles from the old and new searches were subjected to meta-analyses or quantitative syntheses where their data were pooled.

We used the Der Simonian and Laird random effects model[34] to pool rate differences across studies. This method produces a summary measure that is a weighted mean. It weights each study's measure by the inverse of the sum of the within-study variance and the between-study variance. This approach allows both sampling variation and between-study heterogeneity to affect the pooled estimate. Among the three effect measures—rate difference, relative risk, and odds ratio—the TEP and the project staff chose as most suitable the rate difference and its 95 percent confidence interval. It should be noted that we have used the absolute rate difference rather than the relative rate difference to measure the effect size throughout the report. Further, we reported the findings on the success rate instead of the failure rate throughout the report as recommended by the TEP.

In addition to the pooled estimate, we report the Q statistic and p-value for the Chi-squared test of heterogeneity, which tests the null hypothesis that the individual study results are homogeneous.[35] A test of heterogeneity was performed using the I^2 statistic.[36] I^2 values close to 100% represent very high degrees of heterogeneity. The I^2 statistic uses the Q statistic to measure the degree of inconsistency (excess variability) across studies: $I^2=100\%x(Q-[k-1])/Q$, where k is the number of studies included in the analysis. Its advantage is that it can be used for studies with different outcomes and it provides an assessment of the degree of heterogeneity.

For assessment of publication bias, we examined funnel plots and derived the Egger's asymmetry test.

We used Stata 10.0 to perform the meta-analyses.[37]

Supplemental Analysis for Key Question IV

Key Question IV is the same question as Key Question III except that the study population comprises children with RECURRENT otitis media. The same analytical approach was taken. First we tabulated the number of articles by treatment options and by outcomes in order to assess whether the number of articles was adequate for pooled analysis.

The articles eligible for analysis for the key question were grouped by comparisons of treatment options. Each comparison consisted of articles that were considered homogeneous from the standpoint of clinical practice. Although this key question was NOT addressed in the 2001 evidence report, we used the articles identified in that report along with articles newly identified for this report. Comparisons that involved three or more articles were subjected to meta-analyses or quantitative syntheses where their data were pooled.

Supplemental Analysis for Key Question V

Key Question V poses the same question as Key Questions III and IV except that this question specifies analysis of the treatment effectiveness by characteristics of the condition (AOM), patient, environment, and/or health care delivery system, including but not limited to laterality, otorrhea or perforation, AOM severity, comorbidities (e.g. asthma), age group, race, ethnicity, and day care attendance. For this key question, we further divided the articles within each comparison into subgroups by influencing factors to the extent possible. The same analytical approach was taken. Comparisons that involved three or more articles were subjected to meta-analyses or quantitative syntheses where their data were pooled.

Supplemental Analysis for Key Question VI

Key Question VI addresses the comparative safety of the various treatment options used for a) treating uncomplicated AOM, b) preventing AOM in children with ROM, or c) treating AOM in children with ROM. Among the included articles, we identified the number of articles by treatment options in order to assess whether there were an adequate number of articles for pooling analysis.

Adverse events were recorded onto a spreadsheet that identified each trial arm, the description of the adverse event from the original article, the number of participants in each group, and the number of participants affected. We counted each event as if it had been experienced by a unique individual. However, because a single individual might have experienced more than one event, our assumption may have overestimated the actual number of people who experienced an adverse event.

If a trial report mentioned a particular type of adverse event in the discussion but did not report data on that adverse event (either that no participants experienced that adverse event or some number of participants experienced the adverse event), we excluded that trial from the analysis of that particular type of event. In other words, we did not assume an adverse event occurred unless the trial report specifically stated that some number of events was observed (at the same time, for such studies, we did not assume that NO participants experienced the event).

By taking this approach, we may have either overestimated or underestimated the number of participants who experienced a particular adverse event, respectively

After abstracting the data, we identified mutually exclusive groups of similar events, based on clinical expertise. For each adverse-event subgroup, we report the number of trials that provided data for any event in the subgroup. We also report the total number of individuals in the medication groups in the relevant trials who were observed to have experienced the event and the total number of patients in the medication groups in those trials. We then report the analogous counts for the control groups in the relevant trials. We analyzed and pooled the findings of the articles in the same way for this question as for Key Questions III and IV except that the outcome measure was the adverse event rate. Comparisons that included three or more articles were subjected to meta-analyses or quantitative syntheses where their data were pooled. We used the Der Simonian and Laird random effects model[34] to pool rate differences across studies.

Use of Observational Studies to Assess Comparative Effectiveness

Observational studies can help augment the evidence from trials about the comparative effectiveness of treatments. Such studies can provide evidence of benefits and harms in populations of patients with less restrictive clinical characteristics than those typically enrolled in trials, and large observational studies can provide the statistical power needed to detect rare adverse effects. We searched for large observational studies assessing benefits or harms of treatment of AOM in children, but found none that addressed the key questions pertaining to treatment efficacy or safety. However, a small number of observational studies were included for the purpose of responding to Key Question I, on diagnostic criteria, and Key Question II, on the impact of the PCV7 vaccine.

Rating the Overall Quality of Scientific Evidence

We assessed the overall quality of evidence for outcomes using a method developed by the GRADE Working Group, which considers four key elements to classify the quality of evidence: study design, study quality, consistency, and directness.

- Study design refers to the basic design of the study (i.e., RCT, observational studies).
- Study quality refers to the study methods and execution.
- Consistency refers to the similarity of effects estimates across studies.
- Directness refers to the extent to which the study details (participants, interventions, outcome measures) are generalizable to those of interest.

Based on these four criteria, GRADE classifies the quality of evidence as high, moderate, low, or very low, where

- High = Further research is very unlikely to change our confidence on the estimate of effect.
- Moderate = Further research is likely to have an important impact in our confidence in the estimate of effect and may change the estimate.
- Low = 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.

- Insufficient = Any estimate of effect is very uncertain (this term was modified from "Very Low" by the EPC).

The criteria for consideration when assigning grade of evidence are as follows.

Type of evidence:

- Randomized trial = high
- Observational study = low
- Any other evidence = insufficient

Decrease grade if:

- Serious (-1) or very serious (-2) limitation to study quality
- Important inconsistency (-1)
- Some (-1) or major (-2) uncertainty about directness
- Imprecise or sparse data (-1)
- High probability of reporting bias (-1)

Increase grade if:

- Strong evidence of association-significant relative risk of > 2 (or < 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1)
- Very strong evidence of association-significant relative risk of > 5 (or < 0.2) based on direct evidence with no major threats to validity (+2)
- Evidence of a dose-response gradient (+1)
- All plausible confounders would have reduced the effect (+1)

As part of our consideration in rating the quality of scientific evidence, we also assessed the quantitative strength of the evidence, taking into consideration the magnitude of treatment effects, the number of studies that have evaluated the given topic, and the overall sample size across all included studies.

When comparing an outcome between two groups, statistical significance is used to answer the question "is there a difference?" If there is a difference, the next question is "is this difference clinically important?" Not all differences that are statistically significant are clinically important. The concept of the "minimum clinically important difference" (MCID) sets a threshold for the smallest difference that would be clinically meaningful. Ideally, this would be determined empirically, through studies of construct validity of different thresholds for the clinical question of interest. Such work has been done in conditions like rheumatoid arthritis and back pain. When empirical data are not present, the MCID is often arrived at by using clinical judgment or rules of thumb. Cohen first proposed a commonly used classification scheme for considering the size of a treatment effect.[38] In Cohen's classification, effect sizes of 0.20 are considered "small" effects. We used this threshold to set the MCID for the treatment of AOM at 5%.

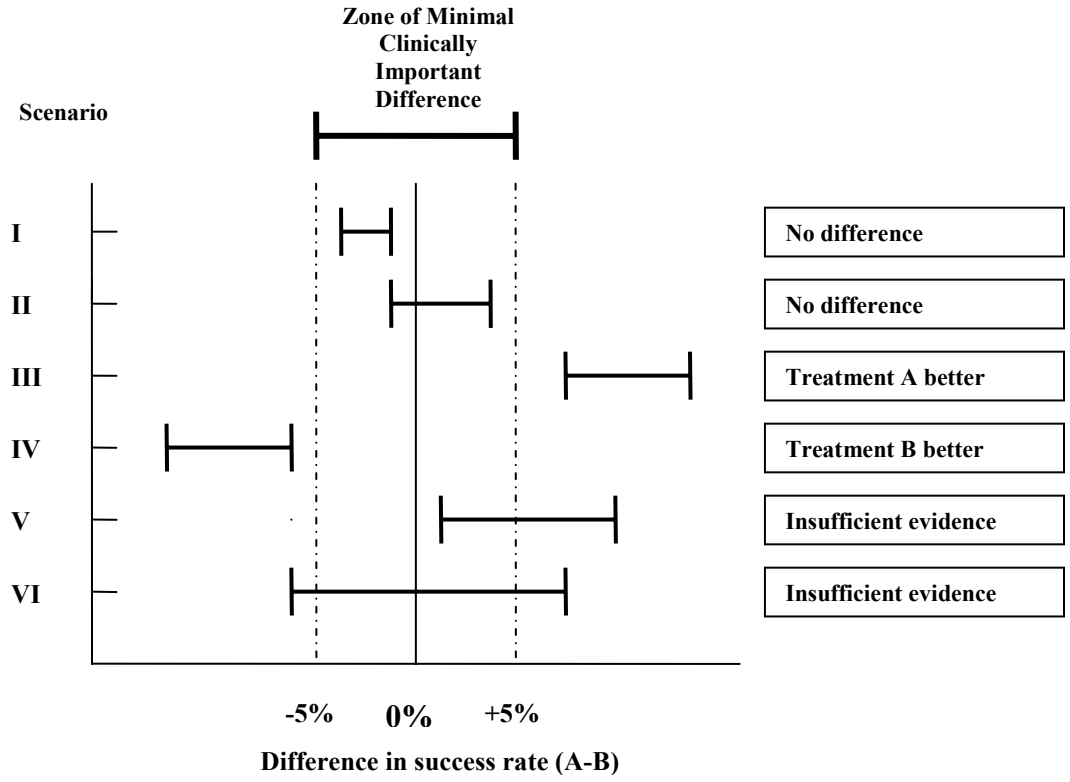
Hypothetical examples of the application of the MCID and the statistical significance are presented below. Scenario I is a situation where there exists a statistically significant difference between AOM outcomes in a trial comparing two treatments, but that difference is only 3%. Scenario II is where a trial finds no statistically significant difference in outcomes between treatments. In Scenarios I and II, since the 95% confidence intervals lie completely inside the zone of MCID, we conclude that there is sufficient evidence that Treatment A and Treatment B

are not clinically different even though in scenario I the difference between treatments is statistically significant. In Scenario III, where the 95% confidence interval lies outside the zone of MCID to the right, we conclude that there is sufficient evidence that Treatment A is clinically better than Treatment B. In Scenario IV, where the 95% confidence interval lies outside the zone of MCID to the left, we can conclude that there is sufficient evidence that Treatment B is clinically better than Treatment A. In Scenarios V and VI, the 95% confidence intervals cross into the zone of MCID, and we conclude that there is insufficient evidence to make any conclusion on the relative effectiveness of Treatments A and B.

It should be noted that the determination of the size of the zone of MCID must take into consideration the topic, the treatment options, the outcome measures, and the balance of proving equivalence or significance. The zone of MCID must be the limits within which any difference found between two treatment options is considered clinically irrelevant. A narrow zone of MCID will allow more differences to be significant but will make it more difficult (require a larger sample size) to prove equivalence. A wide zone of MCID will make it easier to prove equivalence (i.e., permit a smaller sample size) but more difficult to prove significance (i.e., require a larger sample size).

Readers who believe the MCID should be smaller or larger can adjust their interpretations of the evidence to fit their own assumptions.

Figure 1. Statistical Inference Using Confidence Interval (CI) and Minimal Clinically Important Difference (MCID)



Peer Review

A draft of this report was prepared in May 2009 and sent to the TEP members and national and international experts for review. Peer reviewer comments were considered by the EPC in preparation of the final report. Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers, and service as a peer reviewer or member of the TEP cannot be construed as endorsement of the report's findings.

Chapter 3. Results

This chapter presents the results of the literature searches, reviews of pertinent systematic reviews, the accepted key questions, and the findings and analyses for each key question.

In total, the reviewers examined 8, 946 titles for the draft version of this report (including 7,356 from the original searches with three updated searches producing 1, 300 titles (Appendix A).

The reviewers selected 739 titles for further review. Of those 739, four were excluded because they were duplicates; 500 were further rejected as they were determined not to be relevant to the project, they reported duplicate findings from a study already included; the age of the study population was ≥ 18 years; or the study population had immunodeficiencies or craniofacial deformities or were non-human subjects.

Screening of the remaining 235 retrieved articles resulted in exclusion of 11 due to publication being before 2002; no key question addressed; or for being included as part of a diagnostic review article; 67 were excluded for study design, not being a valid pre/post vaccine study, or reporting duplicate data. Eighty three observational studies were set aside for possible review of efficacy or adverse events at a later time; they were subsequently determined not to add further evidence. One RCT was rejected for not addressing the key question, and one article for lack of translation resources. The remaining 72 were reviewed in detail. The literature search and review flow appear in Appendix A. The list of excluded studies appears in Appendix D.

Key Question I. Diagnosis of AOM: What are the Operating Characteristics (Sensitivity, Specificity, and Likelihood Ratios) of Clinical Symptoms and Otoscopic Findings (Such As Bulging Tympanic Membrane) to Diagnose Uncomplicated AOM *and to Distinguish It from OME*?

Description of the Studies

In our initial search, we identified a 2003 systematic review that addressed the question and included six original research studies. We requested the search strategy from the principal investigator for the review and, using that strategy, re-ran the literature search on PubMed for articles published after 2002. This search identified three articles published subsequent to the Rothman review. Details of all accepted articles are presented in Tables 1 through 3 below.

Findings for Key Question I

A systematic review by Rothman and colleagues[15] examined the study question of diagnostic operating characteristics for AOM. The authors searched for articles from 1966 through May 2002 (English language only) that specifically examined the role of any sign or symptom directly

related to the diagnosis of AOM. Five studies met the criteria for inclusion in this review; study participants ranged in age from birth to 15 years (although the findings were not stratified by age). Partly based on the findings of a single study, the authors concluded that the diagnosis of AOM was often uncertain; agreement between pediatric residents and otolaryngologists was fair for overall diagnosis (kappa statistic 0.30) and slight to fair (Kappa statistics range from 0.16 to 0.40) for specific TM findings.

Furthermore, the authors concluded that among symptoms, only otalgia (ear pain) in three studies (reported sensitivity/specificity/positive likelihood ratio [95% confidence interval]/negative likelihood ratio [95% confidence interval]: 54%/82%/3.0 [2.1-4.3]/0.6 [0.5-0.7]; 60%/92%/7.3 [4.4-12.1]/0.4[0.4-0.5]; 100%/NA/NA/NA), and ear rubbing in one study 42%/87%/3.3 [2.1-5.1]/0.7[0.6-0.8]) seemed to predict a clinical diagnosis of AOM. Other symptoms, such as fever, did not show much effect, whether present or absent (two studies showed no effect, one study showed a slightly increased likelihood ratio [LR]). The major drawback to these types of studies examining the accuracy of symptoms in the clinical diagnosis of AOM is that the criterion standard is the clinical diagnosis itself, which can include these same acute symptoms.

One of the studies examined in this review assessed the accuracy of individual physical exam findings (cloudy, bulging, immobile, or red TM) using tympanocentesis as the criterion standard. Otoscopy was performed by an otolaryngologist and a pediatrician. They found these signs to be positively associated with AOM (determined by the presence of MEE on tympanocentesis and clinical symptoms). Specifically, a TM that was cloudy (adjusted positive LR 34 [28-42]; sensitivity and specificity not reported), bulging (adjusted positive LR 51 [37-73]), or distinctly immobile (adjusted positive LR 31 [26-37]) greatly increased the likelihood of AOM, and a moderately or strongly red TM also increased the likelihood of AOM but with a much lower adjusted positive LR (8.4 [6.7-11]).

Using the same inclusion criteria as this systematic review, we searched for articles published after May 2002 and found three additional relevant publications. Similar to the articles in the systematic review discussed above, these three additional articles met the 2003 review's quality criteria for evidence level 4 (on a 1-5 scale, with 1 being the highest and 5 being the lowest, e.g., with scores of 1-2 reserved for studies that used an independent blind comparison of signs/symptoms against a criterion standard among consecutive patients). We additionally used the QUADAS (Quality Assessment of Diagnostic Accuracy of Studies) criteria to assess the quality of these two studies; QUADAS is a widely-used quality scale for studies of diagnostic accuracy. The total QUADAS scores and the answers for each of the 14 QUADAS questions are detailed for each article in Table 1. Tables 2 and 3 present the findings on the accuracy of signs and symptoms.

Table 1. Evidence for Key Question I (Diagnosis)

Author, Year	Time/Place/Affiliation Inclusion/Exclusion Criteria Patient Characteristics	Examiner Group(s) and Sample Size	Comparison(s) Influencing factors Diagnostic Methods (Dx), cutpoints Gold Standards (GS), cutpoints	Findings	Quality[a]
Saeed, 2004[39]	**Time** Recruitment period: Sept 1995-May 1998 Place: pediatric clinics **Affiliation** University of Texas Medical Branch, Galveston **Inclusion** Clinical diagnosis of AOM by: - acute symptoms - acute TM inflammation - evidence of MEE by pneumatic otoscopy and/or tympanometry **Exclusion** - ear or nasopharynx defects - tympanostomy tubes - major medical condition - antibiotic treatment w/in 7 days of enrollment - treatment of AOM	**Examiner(s)** Pneumatic otoscopy-Pediatrician/investigator Tympanometry-research assistant Tympanostomy-same Pediatrician/investigator as otoscopy examiner **Group** children with a dx of AOM and findings from otoscopy, tympanometry, and tympanocentesis available **Sample size** N=81 participants, 130 ears	**Comparisons** 1. Pneumatic otoscopy Dx- : no AOM Dx+ : AOM Tympanostomy GS- : no MEE GS+ : MEE present 2. Tympanogram Dx- :Type A (normal) Dx+ Type B (abnormal) Tympanostomy GS- : no MEE GS+ :MEE present	**Comparisons** 1. Tympanogram Sensitivity: 97% Specificity: 7% PPV 88% NPV: 25% falsely low true negatives b/c GS test not performed on normal ears 2. Pneumatic otoscopy Sensitivity: 100% Specificity: 5% PPV 86% NPV: 100% falsely low true negatives b/c GS test not performed on normal ears	**Study Quality Assessment** Rothman scale: 4 QUADAS: 11 y, y, y, y, n, n, y, y, y, y, n, y, y, y

Author, Year	Time/Place/Affiliation Inclusion/Exclusion Criteria Patient Characteristics	Examiner Group(s) and Sample Size	Comparison(s) Influencing factors Diagnostic Methods (Dx), cutpoints Gold Standards (GS), cutpoints	Findings	Quality[a]
	w/in 30 days - allergy to study medication **Patient Characteristics** - mean age 19.2 months, age range 3-72 months - part of clinical trial (double blind RCT) to evaluate adjunctive drugs in AOM with AOM from pediatric clinics - all participants received IM ceftriaxone.				
Legros, 2007[40]	**Time** Recruitment period: December 04-March 05 and October 05-January 06 **Place** GP clinics **Affiliation** Angers Medical School, France **Inclusion**	**Examiner(s)** GP clinical exam: by GP ENT clinical diagnosis: by ENT **Group** first 6 children either suspected or diagnosed with AOM by a GP	**Comparisons** 1. GP clinical diagnosis/suspicion Dx- : no AOM Dx +: AOM ENT clinical diagnosis GS- : no AOM GS+ : has AOM	1. GP clinical diagnosis/ suspicion 137 AOM diagnoses/ suspicions by GPs of these, 122 based on visible/partially visible TMs (54 had redness and bulging of TM; 32 had redness only), 13 based on non-visible	**Study Quality Score** Rothman scale: 4 QUADAS: 13 y, y, y, u, y, y, y, y, y, y, y, u, y, y, y

Author, Year	Time/Place/Affiliation Inclusion/Exclusion Criteria Patient Characteristics	Examiner Group(s) and Sample Size	Comparison(s) Influencing factors Diagnostic Methods (Dx), cutpoints Gold Standards (GS), cutpoints	Findings	Quality[a]
	- children from 1-4 years old who had been suspected of having AOM or diagnosed with AOM by GP - Parents had to agree to see ENT within 48 hours at another location **Exclusion** - chronic ear pathology **Patient Characteristics** - mean age 27.1 months, range 12-48 months	**Sample Size** N=104 participants, 137 ears	2. GP clinical diagnosis/suspicion when eardrum only partially visible or not visible (subset of #1) Dx- : no AOM Dx+ : AOM ENT clinical diagnosis GS- : no AOM GS+ : has AOM	TM, 2 based on otorrhea Of the 137: ENTs diagnosed-107 as AOM, and 30 as not AOM. of these 30, --- 16 as OME, 4 as viral otitis, and 10 as normal 2. Study also gives descriptions of what happened with the cases based on non-visible TMs. 19 of the 24 cases of non-visible TMs did not have a contralateral ear w/ AOM. Of these, the main signs noted by GP for diagnosis were night cries, irritability, pain, ear pulling, and fever. GP diagnoses/suspicions based on 42 visible/partially	

Author, Year	Time/Place/Affiliation Inclusion/Exclusion Criteria Patient Characteristics	Examiner Group(s) and Sample Size	Comparison(s) Influencing factors Diagnostic Methods (Dx), cutpoints Gold Standards (GS), cutpoints	Findings	Quality[a]
				visible eardrums: 24 GP diagnoses/ suspicions of AOM 18/24 were confirmed by the ENT	
Laine, 2010[1]	**Time:** November 2006-December 2008 **Place:** Outpatient setting Affiliation: Turku University Hospital, Finland **Inclusion:** Parental suspicion of AOM in child based on symptoms **Patient Characteristics:** 6-35 months	**Examiner:** Study physician validated to assess TM findings **Group:** Children presenting to an outpatient setting with a parental suspicion of AOM by symptoms **Sample Size:** N= 469 children. 237 with AOM by study physician exam and 3 criteria, 232 without.	**Comparisons:** **1. Parental Suspicion** Dx-: no AOM Dx +: AOM **2. Ear-related symptoms** (pain, rubbing, fever, non-specific symptoms, respiratory symptoms)	1. Parental suspicion was correct for 51% of all children, 48% of children without a previous AOM diagnosis, and 52% of children with a previous AOM diagnosis. 2. The occurrence, duration, and severity of ear-related symptoms were not associated with AOM diagnosis	Rothman scale: 4 QUADAS: 12 n,y,y,y,y,y,y, y,y,y,n,y,y,y

Table Notes: B/c: because; Dx: diagnosis; GS: gold standard; MEE: middle ear effusion; NPV: negative predictive value; PPV: positive predictive value; TM: tympanic membrane

[a] QUADAS: 1 (y=yes); 2(n=no); 3(u=unclear). Answers to QUADAS questions presented in the following order:

1. Was the spectrum of patients representative of the patients who will receive the test in practice?
2. Were selection criteria clearly described?
3. Is the reference standard likely to correctly classify the target condition?
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard?
6. Did patients receive the same reference standard regardless of the index test result?
7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?

8. Was the execution of the index test described in sufficient detail to permit replication of the test?
9. Was the execution of the reference standard described in sufficient detail to permit its replication?
10. Were the index test results interpreted without knowledge of the results of the reference standard?
11. Were the reference standard results interpreted without knowledge of the results of the index test?
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
13. Were uninterruptible/intermediate test results reported?
14. Were withdrawals from the study explained?

Table 2. Accuracy of Symptoms

Source and Symptoms	Sensitivity, %	Specificity, %	Positive LR (95% CI)	Negative LR 95% CI)
Niemela et al, 1994[41]				
Ear pain	54	82	3.0 (2.1-4.3)	0.6 (0.5-0.7)
Ear rubbing	42	87	3.3 (2.1-5.1)	0.7 (0.6-0.8)
Fever	40	48	0.8 (0.6-1.0)	1.2 (1.0-1.5)
Cough	47	45	0.9 (0.7-1.1)	1.2 (0.9-1.4)
Rhinitis	75	43	1.3 (1.1-1.5)	0.6 (0.4-0.8)
Excessive crying	55	69	1.8 (1.4-2.3)	0.7 (0.5-0.8)
Poor appetite	36	66	1.1 (0.8-1.4)	1.0 (9.8-1.1)
Vomiting	11	89	1.0 (0.6-1.8)	1.0 (0.9-1.1)
Sore throat	13	74	0.5 (0.3-0.8)	1.2 (1.1-1.3)
Headache	9	76	0.4 (0.2-0.7)	1.2 (1.1-1.3)
Heikkenen & Ruuskannen, 1995[42]				
Ear pain	60	92	7.3 (4.4-12.1)	0.4 (0.4-0.5)
Fever	69	23	0.9 (0.8-1.0)	1.4 (0.9-2.0)
Cough	84	17	1.0 (0.9-1.1)	1.0 (0.6-1.6)
Rhinitis	96	8	1.0 (1.0-1.1)	0.5 (0.2-1.4)
Restless sleep	64	51	1.3 (1.1-1.6)	0.7 (0.5-0.9)
Ingvarsson, 1982[43]				
Ear pain	100	NA	NA	NA
Fever	79	70	2.6 (1.9-3.6)	0.3 (0.2-0.5)
URI	96	29	1.4 (1.2-1.6)	0.3 (0.2-0.5)_
Kontiokari et al, 1998[44]				
Parental suspicion of AOM	70	80	3.4 (2.8-4.2)	0.4 (0.3-0.5)
Laine et al, 2010[1]				
Ear pain	92	8	1.0 (1.0-1.1)	0.9 (0.5, 1.7)
Ear rubbing	70	22	0.9 (0.8-1.0)	1.4 (1.0, 1.8)
Fever	43	65	1.2 (1.0-1.6)	0.9 (0.8, 1.0)
Cough	79	26	1.1 (1.0, 1.2)	0.8 (0.6, 1.1)
Rhinitis	94	95	1.0 (0.9, 1.0)	1.2 (0.6, 2.6)
Excessive crying	87	88	1.0 (0.9, 1.1)	1.1 (0.7, 1.7)
Poor appetite	63	64	1.0 (0.9, 1.1)	1.0 (0.8, 1.3)
Vomiting	1	2	0.6 (0.1, 2.4)	1.0 (1.0, 1.0)

Table Notes: AOM: acute otitis media; CI: confidence interval; LR: likelihood ratio; URI: upper respiratory infection. Adapted from Rothman et al, 2003[15]

Table 3. Accuracy of Signs

ACCURACY OF SIGNS	Karma, et al 1989	
Signs	Unadjusted Positive LR	Adjusted Positive LR (95% CI)
Color		
Cloudy	11	34 (28-42)
Distinctly red	2.6	8.4 (6.7-11)
Slightly red	0.4	1.4 (1.1-1.8)
Normal	0.1	0.2 (0.19-0.21)
Position		
Bulging	20	51 (36-73)
Retracted	1.3	3.5 (2.9-4.2)
Normal	0.4	0.5 (0.49-0.51)
Mobility		
Distinctly impaired	8.4	31 (26-37)
Slightly impaired	1.1	4.0 (3.4-4.7)
Normal	.04	0.2 (0.19-0.21)

Adapted from Rothman et al, 2003[15]

Saeed examined the accuracy of otoscopic and tympanometric findings compared with tympanocentesis as the criterion standard to determine the presence of MEE.[39] The investigator performing the tympanocentesis was not blinded to the findings of tympanometry (performed by a research assistant) or otoscopic exam (performed by an "experienced" physician investigator), and only patients whose tympanometry or otoscopic exam suggested MEE received the criterion standard of tympanocentesis. Ninety-seven percent of children with MEE on tympanocentesis had "Type B" tympanogram findings (abnormal), and all children with MEE on tympanocentesis had an otoscopic exam consistent with AOM. However, LR and predictive value estimates are not as useful, since all participants had an AOM diagnosis at enrollment.

The second study (Legros, 2007) examined the diagnostic accuracy of French general practitioners (GP) compared with otolaryngologists' clinical diagnoses as the criterion standard.[45] The study used a consecutive sample of patients who had a suspected diagnosis of AOM by the GP and received the criterion standard (otolaryngology clinical exam). The study included 137 eardrums that were either assumed to be or were diagnosed as AOM by the GP. Of these 137, 78% (107) were confirmed by ear-nose-and throat (ENT) exam and the remaining were not, because the otolaryngologist diagnosed OME, viral otitis, or a normal TM. The ENT exam confirmed the GP diagnoses more often when redness and bulging were noted by the GP (83%) than when only redness was noted (75%). One major drawback to this study was that the criterion standard was not performed at the time of GP exam; in the majority of cases, the ENT exam occurred the following day when it was possible that GP-prescribed antibiotic treatment might have already altered the physical signs and clinical symptoms.

The third study published subsequent to the 2003 review found that among 469 children ages 6-36 months with parent-suspected AOM in primary care offices, AOM diagnosis was not associated with the occurrence, duration, or severity of parent-reported symptoms (e.g., ear pain: sensitivity 92%, specificity 8%, positive LR 1.0 [1.0-1.1]; ear rubbing: sensitivity 70%, specificity 22%, positive LR 0.9 [0.8-1.0]; fever: sensitivity 43%, specificity 65%, positive LR 1.2 [1.0-1.6]).[1]

In summary, there is limited evidence on clinicians' accuracy and precision in identifying each of the three clinical criteria necessary to diagnose AOM, or their accuracy and precision in identifying all three together. The prior review and studies examined above do not directly or completely answer our key question; however, they do suggest that clinical findings of MEE (decreased mobility or abnormal position) and middle ear inflammation (distinctly red color of the TM) are positively associated with AOM, defined by positive tympanocentesis and acute onset of symptoms. Further, studies comparing diagnostic accuracy between generalist or primary care physicians and otolaryngologists suggest that clinicians' accuracy in identifying all three clinical criteria in one patient is moderate, at best. The overall quality of evidence for this Key Question is considered low, meaning that further high-quality research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Key Question II.

What Has Been the Impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM Microbial Epidemiology (Including Acute Mastoiditis and Suppurative Complications)?

Description of the Studies

The combined searches for titles pertaining to this key question resulted in 1,044 titles. Of these 1,044 titles, 73 titles appeared potentially relevant and full-text articles were ordered. A second level of screening was conducted to identify only articles that assessed microbiology both pre- and post-implementation of the vaccine. Of the 73 articles screened, six were accepted for our report and 67 were rejected. Details of all accepted articles are described below and presented in Tables 4 and 5. The rejected articles and the reasons for rejection are listed in Appendix D.

Findings for Key Question II

In order to address this question, we searched for studies and RCTs that compared the organisms (bacterial and viral) that caused AOM in children who had received PCV7 to those in children who had not received PCV7. Two main types of studies would directly address this question: observational studies that take advantage of the time periods both before and after the licensure of PCV7 and RCTs of PCV7 efficacy.

This first group of studies consists of observational studies that either retrospectively or prospectively examine two separate cohorts of children, before and after 2000 (PCV7 was licensed in February 2000 and recommended for all children aged 2-23 months by the CDC Advisory Committee on Immunization Practices (ACIP) in June 2000).

We identified four such studies.[46-49] (Table 4). Casey and Pichichero (2004) reported data based on a prospective study of children diagnosed with AOM with treatment failure (AOMTF) and persistent AOM at a suburban pediatric private practice in Rochester, New York. Between 1995 and 2003, middle ear fluid (MEF) was obtained by tympanocentesis for 551 patients (minimum age 2 months) with persistent AOM (otalgia and AOM signs after 48 hours of antibiotic treatment) or AOMTF (clinical failure within 30 days of antibiotic completion). None of the 195 children in the 1995-1997 cohort had received PCV7, 4% of the 204 children in the 1998-2000 cohort received at least one dose of PCV7, and 85% of the 152 children in the 2001-2003 cohort received at least one dose. In each successive cohort, the proportion of all isolates that were S. pneumoniae (SP) decreased significantly, with 44% of isolates identified as SP in the 1998-2000 cohort and 31% of the 2001-2003 cohort ($p<0.017$). Conversely, the proportion of isolates that were found to be H. influenzae (HF) increased significantly from 43% in the 1998-2000 cohort to 57% in the 2001-2003 cohort ($p<0.012$). In addition to the decrease in SP isolates and increase in HF isolates from 1998-2000 to 2001-2003, the authors report an increase in the proportion of SP that was penicillin-susceptible (58% and 72% $p=0.017$) and variation in the proportion of HF that were B-lactamase-producing (33% and 55%, $p=0.44$) from 1998-2000 to 2001-2003.

Table 4. Overview of Studies that Reported on Microbiology

Study	Age	Setting	Study Design	Number Patients	Number of Specimens	Inclusive Years
Casey, 2004[47]	mean age 20-22 months	Pediatric practice, US	prospective observational cohort study	551 patients with AOM treatment failure or persistent AOM	551	1995-1997 1998-2000 2001-2003
Block, 2004[46]	7-24 months	Pediatric practice, US	prospective observational cohort study	379	419	1992-1998 2000-2003
Veenhoven, 2003[50]	12-84 months, median age 2 years	2 hospitals in the Netherlands	RCT of vaccine among unvaccinated toddlers/children with previous AOM)	383 patients with recurrent AOM; 181 with MEF samples	181	1998-2002
McEllistrem, 2005[48]	not reported	5 hospitals in the US	retrospective observational cohort study	not reported	505	1999-2002
Eskola, 2001[51]	infants enrolled <2 months; follow-up 6.5 to 25 months of age	8 clinics in Finland	RCT for vaccine efficacy	1662 (with 2,596 episodes of AOM)	2,444 episodes of AOM with cultures (685 with S. pneumoniae)	1995-1999
Brook, 2009[49]	1993-1998 cohort: 5 months- 12 years, median age 3 years, 1 month 2001-2006 cohort: 10 months – 12 years, median age 3 years, 8 months	Outpatient practice, US	retrospective observational cohort study	100 patients with AOM with a new spontaneous perforation	125	1993-1998 2001-2006

The second observational study described in Table 4 by Block (2004)[46] reports a similar decrease in SP isolates after PCV7 introduction. In this study, 419 MEF specimens from 379 patients from a pediatric practice in a rural Kentucky area in the U.S. were examined. The researchers compared 336 isolates with positive cultures from 1992-1998 with 83 isolates from 2000-2003 (all had three or more vaccine doses). The proportion of isolates due to SP decreased over these two time periods (48% in 1992-1998 and 31% in 2000-2003; p=0.007), while the proportion of isolates from HF increased (41% in 1992-1998 and 56% in 2000-2003; p=0.01). In addition, among the SP isolates, vaccine serotypes decreased, while vaccine-related and non-vaccine serotypes increased significantly (because of an error in shipping/storage, two serotypes could not be analyzed).

This change over time in the serogroup composition of SP isolates was also found in the third observational study (Table 4). This study examined only the MEF specimens that were positive for SP among 505 episodes of AOM in children in five hospitals across four states.[48] These SP-positive MEF specimens were obtained either from spontaneous otorrhea, myringotomy and/or tympanostomy tube placement, or tympanocentesis performed in children with AOMTF or in children with AOM in a clinical trial. Comparing specimens from 1999 to 2002, a significant decrease was reported in the proportion of SP isolates that were of a vaccine serogroup (76% in 1999 and 52% in 2002; $p<0.01$) while isolates from non-vaccine serogroups increased (12% in 1999; 32% in 2002, $p<0.01$). The authors of this study recognized a limitation to observational studies that retrospectively or prospectively rely on tympanocentesis performed in children with AOM for analysis of AOM bacteriology—in most cases, tympanocentesis is not performed in uncomplicated, non-recurrent, non-persistent cases of AOM. To address this limitation, the authors separately analyzed those AOM cases when tympanocentesis was not performed but MEF specimens were obtained by collection of spontaneous otorrhea. Results were similar to the entire sample; the proportion of greater SP isolates due to vaccine serotypes decreased and the proportion due to non-vaccine serotypes increased over time. Additionally, among the vaccine serotype isolates, the proportion that were penicillin non-susceptible increased (60% in 1999 to 100% in 2002, $p<0.01$).

The final observational study examined was smaller; it examined middle ear fluid from 50 children diagnosed with AOM with perforation (collected by aspiration with a syringe inserted through the TM perforation) between 1993 and 1998 with 50 children with the same diagnosis between 2001 and 2006. Ninety-two percent of children in the group from 2001-2006 had received PCV7. This study did not find changes in microbiology described above; however, the authors did find that methicillin-resistant S. aureus (MRSA) was significantly greater in children from the later time period. There was no MRSA isolated from middle ear fluid samples during 1993-1998, but there were five MRSA isolates in middle ear fluid samples collected from 2001-2006.[49] The three previous studies described above either did not report S. aureus isolates,[46, 48] or did not report on methicillin resistance of S. aureus isolates.

Two RCTs addressed our study question directly as well (Table 5). Eskola (2001)[51] report the results of a double-blind RCT of the efficacy of PCV7. In 1,662 children with 2,596 episodes of AOM, investigators collected MEF and found that 685 were positive for SP (33% in control group; 23% in the PCV7 group). Findings comparing the intervention (PCV7) and control groups are similar to the findings in the observational studies described above. Vaccine serotype isolates were less prevalent in the intervention group isolates than the control group isolates (40% vs. 60%), while non-vaccine serotype isolates were more prevalent in the intervention group isolates

than in the control group (46% vs. 23%). There were also fewer isolates from vaccine-related serotypes in the intervention vs. control group. The proportion of AOM episodes caused by HF (27% vs. 23%) was greater for the vaccine group and the proportion of AOM episodes caused by M. catarrhalis (MC) (32% vs. 30%) was similar across both groups.

Table 5. Studies That Reported on Microbiology, Specific Findings

Study	% of all specimens caused by SP (S. pneumoniae)	% of all – HF (H. influenzae)	% of all- MC (M. catarrhalis)	% of SP AOM caused by PCV7 serotypes	% of SP AOM caused by non-vaccine serotypes	% of SP vaccine-related serotypes	Other bacteria and subgroup analyses
Intervention/Post-vaccine vs. Control/Pre-vaccine							
Casey, 2004[47] **Differences in bold are significant at the p<0.05 level**	**31% vs. 48%** **1995-1997- 48%** **1998-2000- 44%** **2001-2003- 31%** Proportion by Susceptibility: <u>Susceptible:</u> 1995-1997- 54% 1998-2000- 58% 2001-2003- 72% <u>Intermediate-susceptibility:</u> 1995-1997- 12% 1998-2000- 18% 2001-2003- 14% <u>Resistant:</u> 1995-1997-	**57% vs. 38%** **1995-1997: 38%** **1998-2000: 43%** **2001-2003: 57%** Proportion by Susceptibility: B-lactamase positive: **1995-1997- 46%** **1998-2000- 33%** **2001-2003- 55%** B-lactamase negative: 1995-1997- 54% 1998-2000- 67% 2001-2003- 45%	1% vs. 4% 1995-1997: 4% 1998-2000: 5% 2001-2003: 1%	no serotype analysis	no serotype analysis	no serotype analysis	S. pyogenes: 1995-1997- 3% 1998-2000- 3% 2001-2003- 2% No growth (not included in total): [a]includes S. epidermidis. S. aureus and diphtheroids were considered non-pathogens 1995-1997- 47% 1998-2000- 44% 2001-2003- 42%

Study	% of all specimens caused by SP (S. pneumoniae)	% of all – HF (H. influenzae)	% of all- MC (M. catarrhalis)	% of SP AOM caused by PCV7 serotypes	% of SP AOM caused by non-vaccine serotypes	% of SP vaccine-related serotypes	Other bacteria and subgroup analyses
	34% 1998-2000- 24% 2001-2003- 14%						
Block, 2004[46]	31% vs. 48% p=0.007 Proportion by Susceptibility: <u>Susceptible:</u> 12% vs. 23% <u>Intermediate:</u> 13% vs. 16% <u>Resistant:</u> 6% vs. 9% PCV7 Serogroups: % of SP isolates that were nonsusceptible 27% vs. 46% Non-PCV7 Serogroups: % of SP isolates that were nonsusceptible 18% vs. 1% PCV7 Related	56% vs. 41% p=0.001 Proportion by Susceptibility: Non- B lactamase 20% vs. 18% B-lactamase 36% vs. 23%	11% vs. 9% (B-lactamase)	36% vs. 70% p=0.005	32% vs. 22% 1, 11, 15A, 29, and 33F	32% vs. 8% p=0.005 6A and 19A	S. Pyogenes 2% vs. 2% <u>Otitis prone</u> All SP- 85% vs. 43% PNSP- 81% vs. 53% Gram Negative- 78% vs. 45% <u>Antibiotics within 30 days</u> All SP- 62% vs. 58% PNSP-75% vs. 70% Gram Negative- 85% vs. 61% <u>Antibiotics within 3 days</u> All SP- 27% vs. 34% PNSP- 38% vs. 41% Gram Negative- 38% vs. 24%

Study	% of all specimens caused by SP (S. pneumoniae)	% of all – HF (H. influenzae)	% of all- MC (M. catarrhalis)	% of SP AOM caused by PCV7 serotypes	% of SP AOM caused by non-vaccine serotypes	% of SP vaccine-related serotypes	Other bacteria and subgroup analyses
	Serogroups: % of SP isolates that were nonsusceptible 27% vs. 5%						<u>Male</u> All SP- 67% vs. 59% PNSP- 75% vs. 60% Gram Negative- 58% vs. 51% <u>Day-care attendees</u> All SP-57% vs. 31% PNSP-63% vs. 40% Gram Negative- 69% vs. 29%
Veenhoven, 2003[50]	22% vs. 35% (re-calculated to exclude negative cultures)	35% vs. 43% PCV7: 21/60 Control: 23/54	13% vs. 11% PCV7: 8/60 Control: 6/54	31% vs. 42% PCV7: 4/13 Control: 8/19 vaccine serotypes: 4, 6B, 9V, 14, 18c, 19F, 23F	70% vs. 58% PCV7: 9/13 Control: 11/19 non-vaccine serotypes not specified		P. aeruginosa 10% vs. 17% PCV7: 9/60 Control: 6/54 S. aureus 34% vs. 17% (p=0.004) PCV7: 26/60 Control: 9/54 Group A Strep 10% vs. 7% PCV7: 6/60 Control: 4/54
McEllistrem, 2005[48]	All cases were SP	All cases were SP	All cases were SP	52% vs.. 76%[a]	32% vs.. 12%	13% vs. 10% 1999: 10	Subgroups: **<u>Antibiotic</u>**

Study	% of all specimens caused by SP (S. pneumoniae)	% of all – HF (H. influenzae)	% of all- MC (M. catarrhalis)	% of SP AOM caused by PCV7 serotypes	% of SP AOM caused by non-vaccine serotypes	% of SP vaccine-related serotypes	Other bacteria and subgroup analyses
	% that were PNSP: Overall nonsusceptible 1999: 62% 2000: 63% 2001: 50% 2002: 59%; p=0.21 <u>Intermediate</u> 1999: 23% 2000: 22% 2001: 19% 2002: 23%; p=0.74 <u>Resistant</u> 1999: 39% 2000: 41% 2001: 31% 2002: 35%; p=0.32 By number of PCV7 doses: 2-4 doses vs. ≤1 dose <u>Overall-</u> 56% vs. 60% p=.64 <u>Intermediate-</u> 22% vs. 22%; p=.88 <u>Resistant</u> 33% vs. 37%			1999: 76% 2000: 74% 2001:50% 2002: 52% p<0.01 By number of PCV7 doses: 2-4 doses vs. ≤1 dose 41% vs. 70% p<0.01	1999: 12 2000: 13 2001:30 2002: 32 p<0.01 By number of PCV7 doses: 2-4 doses vs. ≤1 dose 35% vs. 18% p<0.01	2000: 10 2001: 13 2002: 13 p<0.29 By number of PCV7 doses: 2-4 doses vs. ≤1 dose 19% vs. 10% p=0.05	**<u>within 30 days % of SP isolates that were nonsusceptible</u>** 1999: 65% 2000: 65% 2001: 65% 2003: 56% p=.23 2-4 doses 67% ≤1 dose- 63% p=.62

Study	% of all specimens caused by SP (S. pneumoniae)	% of all – HF (H. influenzae)	% of all- MC (M. catarrhalis)	% of SP AOM caused by PCV7 serotypes	% of SP AOM caused by non-vaccine serotypes	% of SP vaccine-related serotypes	Other bacteria and subgroup analyses
	p=.64 PCV7 Serogroups: % of SP isolates that were nonsusceptible 1999: 70% 2000: 71% 2001: 66% 2003: 88% p=.12 2-4 doses 89% ≤1 dose- 70% p=.08 Non-PCV7 Serogroups: % of SP isolates that were nonsusceptible 1999: 27% 2000: 12% 2001: 14% 2003: 23% p=.75 2-4 doses 24% ≤1 dose- 28% p=.86						

Study	% of all specimens caused by SP (S. pneumoniae)	% of all – HF (H. influenzae)	% of all- MC (M. catarrhalis)	% of SP AOM caused by PCV7 serotypes	% of SP AOM caused by non-vaccine serotypes	% of SP vaccine-related serotypes	Other bacteria and subgroup analyses
Eskola, 2009[51] **Comparisons in bold are significant at the p<0.05 level**	**23% vs. 33%** (p<0.001)	**27% vs.. 23%** (p=0.02) Denominator: all AOM episodes	32% vs.. 30% Denominator: all AOM episodes	**40% vs. 60%** (p<0.001) Denominator: all S.pne isolates vaccine serotypes: 4, 6B, 9V, 14, 18c, 19F, 23F (also separately analyzed)	**46% vs. 23%** p<0.001) Denominator: all S.pne isolates non-vaccine serotypes: 3, 11, 15, 16, 22, 33, 35, 38, and others combined: 7, 10, 12, 28, 34, pool G	**15% vs. 20%** Denominator: all S.pne isolates vaccine-related serotypes: 6A, 9N, 18B, 19A, 23A (also separately analyzed)	
Brook, 2009[49]	44% vs. 54% 1993-1998: 54% 2001-2006: 44% Proportion by Susceptibility: <u>Susceptible:</u> 1993-1998: 52% 2001-2006: 73% <u>Intermediate-Susceptibility</u> 1993-1998:	24% vs. 18% Proportion by Susceptibility: B-lactamase positive: 1993-1998: 67% 2001-2006: 50% B-lactamase negative: 1993-1998: 33% 2001-2006: 50%	12% vs. 10%	Not reported	Not reported	S. pyogenes 10% vs. 14%	Methicillin-sensitive S. aureus 1993-1998: 8% 2001-2006: 8% Methicillin-resistant S. aureus **1993-1998: 0%** **2001-2008: 10%** p<0.05

Study	% of all specimens caused by SP (S. pneumoniae)	% of all – HF (H. influenzae)	% of all- MC (M. catarrhalis)	% of SP AOM caused by PCV7 serotypes	% of SP AOM caused by non-vaccine serotypes	% of SP vaccine-related serotypes	Other bacteria and subgroup analyses
	33% 2001-2006: 23% <u>Resistant</u> 1993-1998: 15% 2001-2006: 4%						

Table Notes : PCV7 : Heptavalent pneumococcal vaccine ; PSSP: Penicillin sensitive SP; PNSP- Penicillin non-susceptible SP ; S. pne : staphylococcus pneumoniae

[a] (Vaccine serotype 19F did not decrease; molecular analyses and serologic data suggest that PCV7 may be less protective against 19F compared with other vaccine serotypes)

Another RCT for vaccine efficacy studied recurrent AOM in previously unvaccinated children with at least two episodes of AOM in the previous year.[50] The authors report fewer vaccine serotype SP isolates and more non-vaccine serotype SP isolates in the intervention (PCV7) group compared with the control group. There were no significant differences in the numbers of HF or MC isolates between the two groups; however, the sample size was very small, with 60 and 54 positive culture isolates in intervention and control groups, respectively. Further, a majority of MEF specimens were obtained from spontaneous otorrhea, calling into question the higher rate of S. aureus and P. aeruginosa cultures found in the intervention group.

Findings According to Antibiotic History

As part of our review, we were also asked to analyze changes in causative agents among the following subpopulations: children who have never had antibiotics for any reason; children who have had antibiotics for any reason, including ROM, persistent otitis media or relapse of AOM; children with unknown antibiotic history. We found that only a few studies separately analyzed data for these subpopulations.

The observational study by Casey, et al[47] specifically examined patients with AOMTF or persistent AOM; the study by McEllistrem and colleagues[48] performed a subgroup analysis of patients with AOM and spontaneous drainage to look for any differences in the microbiology patterns for children with uncomplicated AOM; and finally, the study by Block and colleagues[46] examined differences in SP resistance in otitis-prone children before and after the introduction of PCV7.

In summary, these six studies shed some light on the first part of our study question. Since the introduction of PCV7, these studies report that HF has become more prevalent as a causative agent of AOM, although SP remains an important agent as well. The introduction of the vaccine has also resulted in a greater proportion of non-vaccine serotypes and a smaller proportion of the vaccine serotypes. The overall quality of evidence for this Key Question is considered high for the conclusion that use of PCV7 vaccine has resulted in shifts in the prevalence of causative agents, meaning further research is very unlikely to change our confidence in the estimate of effect. The quality of evidence is insufficient for the special populations (such as patients with recurrent or persistent AOM) since we found virtually no evidence about the vaccine's effect on these special populations.

Key Question III.

What is the Comparative Effectiveness of Different Treatment Options for Treating Uncomplicated Acute Otitis Media in Average Risk Children?

Description of the Studies

Initial screening of the titles identified for Key Questions III-VI found 147 studies reporting on trials that appeared potentially relevant, and full-text articles were ordered. Of the 147 articles

that underwent further screening, 62 were accepted. A total of 85 articles were rejected; these articles and the reasons for rejection are listed in Appendix D. The studies that were accepted for analysis are described in the Evidence Table in Appendix C.

Findings for Key Question III

The present review updates the 2001 AOM systematic review report, which addressed the natural history of uncomplicated AOM, the efficacy of antibiotic vs. no antibiotic therapy, and the comparative efficacy of various antibiotic regimens, including amoxicillin or trimethoprim-sulfamethoxazole vs. other antibiotics, high-dose vs. standard-dose amoxicillin or amoxicillin-clavulanate, high-dose amoxicillin twice daily vs. standard-dose amoxicillin three times daily, and short-term vs. long-term antibiotic therapy. That review found no significant differences in clinical failure rates between the antibiotic regimens that were compared. The findings of that review that are relevant to specific treatment regimen comparisons are presented in the relevant sections below. Tables 6a-e summarize the studies that addressed the comparative effectiveness of different treatment options for uncomplicated AOM in average-risk children that were identified in the 2001 report, and further details can be found in the evidence and meta-analysis tables in that report.[3] Table 6f summarizes key findings of the comparisons in the 2001 report, those included only in the present report, and those in both reports.

Table 6a. Randomized Controlled Trials from Marcy (2001)[13] Addressing Comparative Effectiveness of Different Treatment Options for Treating Uncomplicated Acute Otitis Media in Average Risk Children

Author Year	RCT Quality[a]	AOM Definition[b]	Intervention[c]	Time	Place	Age
Appelman, 1991; Claessen, 1994	[1,1,1,1,1]	[0,0,1]	amox-clav vs. placebo	9/86-4/90	Netherlands	6 mo-<12 yr
Burke, 1991	[1,1,0,1,1]	[0,0,1]	amox vs. control	10/86-4/87; 10/87-4/88; 10/88-4/89	Great Britain	3-<10 yr
Halsted, 1967; 1968	[1,1,1,1,1]	[1,0,0]	amp vs. pcn G-sulfisoxazole vs. placebo	7/65-3/66	Cleveland, OH	2-66 mo
Howie, 1972	[1,0,0,0,0]	[1,0,0]	triple sulfa vs. ery vs. amp vs. ery-triple sulfa vs. placebo	12/68-7/70	Alabama	<=2.5 yr
Kaleida, 1991	[1,1,0,0,0]	[1,0,0]	amox vs. myringotomy vs. amox with myringotomy vs. placebo	5/81-8/85	Pittsburgh, PA	7 mo-12 yr
Laxdal, 1970	[1,0,0,1,0]	[0,0,0]	amp vs. pcn vs. symptomatic treatment	1/66-9/68	Canada	<15 yr
Mygind, 1981	[1,1,1,0,0]	[0,1,1]	pcn V vs. placebo	11/77-4/78	Denmark	1-10 yr
Thalin, 1985	[1,1,0,1,1]	[0,0,0]	pcn V vs. placebo	7/84- 6/85	Sweden	2-15 yr
van Buchem, 1981	[1,1,1,0,1]	[0,0,0]	myringotomy vs. amox vs. amox plus myringotomy vs. placebo	1/79-5/79; 10/80-3/81	Netherlands	2-12 yr
Barnett, 1997	[1,0,1,1,0]	[1,0,0]	ceftriaxone vs. tmp-smx	2/91-4/94	Boston	3 mo-3 yr

[a] Jadad study quality score components (1=present; 0=not present): randomization mentioned; double-blind mentioned; dropouts described; randomization appropriate; double-blinding appropriate.
[b] AOM definition components (1=required; 0=not required): MEE; rapid onset; acute inflammation
[c] amox=amoxicillin; clav=clavulanate; amp=ampicillin; pcn=penicillin; triple sulfa=triple sulfonamide; ery=erythromycin; tmp-smx=trimethoprim-sulfamethoxazole

Table 6b. Randomized Controlled Trials from Marcy (2001)[13] Addressing Other Antibiotic vs. Amoxicillin or Trimethoprim-Sulfamethoxazole

Author, Year	RCT Quality[a]	AOM Definition[b]	Intervention[c]	Time	Place	Age
Barnett, 1997	[1,0,1,1,0]	[1,0,0]	ceftriaxone vs. tmp-smx	2/91-4/94	Boston	3 mo-3 yr
Bass, 1967	[1,1,0,1,0]	[0,0,0]	oxytetracycline vs. procaine pcn & benzathine pcn G plus sulfisoxazole vs. pcn V plus sulfisoxazole vs. amp	1/66-5/66	?	2 mo-12 yr
Bass, 1973	[1,1,0,1,0]	[0,0,0]	pcn V vs. pcn V plus sulfa vs. ery vs. amp	11/68-8/71	Hawaii	2 mo-12 yr
Berman, 1983	[1,1,1,0,0]	[1,0,0]	amox vs. cefaclor	6/80-3/82	Denver, CO	<3 mo
Blumer, 1984	[1,1,1,0,0]	[1,0,0]	cefaclor vs. tmp-smx	?	Cleveland, OH	3 mo-7 yrs
Brodie, 1990	[1,0,1,0,0]	[0,0,0]	cefuroxime vs. amox	?	United Kingdom	3 mo-12 yr
Coles, 1993	[1,0,1,0,0]	[0,0,0]		7/91-1/92	United Kingdom	1-12yrs
Feigin. 1973	[1,0,1,1,0]	[0,0,0]	clindamycin vs. amp	3/70-12/71	St. Louis, MS	3mo-10yr
Feldman, 1990	[1,1,1,1,1]	[1,0,1]	tmp-smx vs. amox-clav	1987-1988	Canada	1-14 yrs
Foshee, 1992	[1,1,1,0,1]	[1,0,1]	loracarbef vs. amox	10/88-3/90	Finland; Iceland; Netherland	6m-12y
Giebink, 1984	[1,0,1,1,0]	[1,0,0]	cefaclor vs. amox	?	Minneapolis, MN	3mo-17yrs
Green, 1993	[1,1,1,0,1]	[0,0,1]	ceftriaxone vs. amox	9/90-6/91	California	5mo-5yrs
Halsted, 1967; 1968	[1,1,1,1,1]	[1,0,0]	amp vs. pcn G-sulfisoxazole vs. placebo	7/65-3/66	Cleveland, OH	2-66 mo
Howie, 1972	[1,0,0,0,0]	[1,0,0]	triple sulfa vs. ery vs. amp vs. ery-triple sulfa vs. placebo	12/68-7/70	Alabama	<=2.5 yr
Jacobson, 1979	[1,1,1,1,1]	[1,0,0]	Cefaclor vs. amox	5/77-8/78	Utah	1-12yrs
Johnson, 1991	[1,0,0,0,0]	[1,0,1]	cefuroxime vs. amox	10/86-6/89	Cleveland, OH	8wk-13yrs
Kara, 1998	[1,0,0,0,0		amox vs. cefuroxime	9/97 – 5/97	Turkey	6m-6yr
Laxdal, 1970	[1,0,0,1,0]	[0,0,0]	amp vs. pcn vs. symptomatic treatment	1/66-9/68	Canada	<15 yr
Leigh, 1989	[1,0,1,0,0]	[0,0,0]	cefixime vs. amox	?	United Kingdom	6mo-16 yrs
Lenoski, 1968	[1,0,1,1,0]	[0,0,0]	ery vs. ery plus triple sulfa vs. triple sulfa vs. amp	8/66-8/67	Los Angeles, CA	?
Marchant, 1984	[1,1,1,1,0]	[1,0,1]	cefaclor vs. tmp-smx	?	Cleveland, OH	2-24months
McLinn, 1979	[1,0,0,0,0]	[1,0,0]	cephradine vs. amox	?	Pennsylvania	4mo-14yrs

Author, Year	RCT Quality[a]	AOM Definition[b]	Intervention[c]	Time	Place	Age
McLinn, 1980	[1,0,0,1,0]	[1,0,0]	cefaclor vs. amox	?	Pennsylvania	1mo-11yrs
McLinn, 1987	[1,0,1,1,0]	[1,0,1]	cefuroxime vs. amox	4/85-9/85	United States	6mo-11yr
Nassar, 1974	[1,1,0,0,1]	[0,0,0]	cephalexin vs. amp	?	England	under 12yrs
Nilson, 1969	[1,1,1,1,0]	[1,0,0]	pcn V vs. pcn V plus sulfa vs. amp	12/66-2/68	Baltimore, MD	<3yr
Owen, 1993	[1,0,1,0,0]	[1,0,1]	cefixime vs. amox	10/87-3/88	Texas	2mo-6yrs
Ploussard, 1984	[1,0,0,1,0]	[1,0,0]	cefaclor vs. amox	?	?	5mo-5yr
Principi, 1991	[1,0,0,1,0]	[1,0,1]	cefixime vs. amox	?	Italy	<12yr
Pukander, 1993	[1,0,1,0,0]	[1,0,0]	clarithromycin vs. amox	12/90-3/92	Finland	1-12yrs
Rodriguez, 1985	[1,1,1,1,1]	[1,0,0]	ery vs. amox	2/80 – 5/82	Washington, DC	2mo-17yr
Scholz, 1998	[1,1,1,0,1]	[1,0,0]	ery vs. amox	5/95-1/96	Germany	6mo-11yr
Stechenberg, 1976	[1,0,1,0,0]	[0,0,0]	cephalexin vs. amp	7/73-7/75	St. Louis, MS	3mo-11.6yr
Varsano, 1988	[1,1,1,0,1]	[1,0,1]	ceftriaxone vs. amox	?	Israel	6mos-8yrs

[a] Jadad study quality score components (1=present; 0=not present): randomization mentioned; double-blind mentioned; dropouts described; randomization appropriate; double-blinding appropriate.
[b] AOM definition components (1=required; 0=not required):MEE; rapid onset; acute inflammation
[c] amox=amoxicillin; clav=clavulanate; amp=ampicillin; pcn=penicillin; triple sulfa=triple sulfonamide; ery=erythromycin; tmp-smx=trimethoprim-sulfamethoxazole

Table 6c. Randomized Controlled Trials from Marcy (2001)[13] Addressing High-Dose Amoxicillin vs. Standard-Dose Amoxicillin

Author Year	RCT Quality[a]	AOM Definition[b]	Intervention[c]	Time	Place	Age
Bottenfield, 1998	[1,0,0,0,0]	[0,0,0]	Amox-clav high dose vs. low dose	12/96-2/97	USA	3mo – 12yr

[a] Jadad study quality score components (1=present; 0=not present): randomization mentioned; double-blind mentioned; dropouts described; randomization appropriate; double-blinding appropriate.
[b] AOM definition components (1=required; 0=not required):MEE; rapid onset; acute inflammation
[c] amox=amoxicillin; clav=clavulanate; amp=ampicillin; pcn=penicillin; triple sulfa=triple sulfonamide; ery=erythromycin; tmp-smx=trimethoprim-sulfamethoxazole

Table 6d. Randomized Controlled Trials from Marcy (2001)[13] Addressing Twice a Day High-Dose Amoxicillin Therapy vs. Three Time a Day Amoxicillin

Author Year	**RCT Quality**[a]	**AOM Definition**[b]	**Intervention**[c]	Time	**Place**	**Age**
Principi, 1986	[1,0,1,0,0]	[1,0,1]	amox twice vs. three times daily	10/84-2/85	Italy	6mo-12yrs

[a] Jadad study quality score components (1=present; 0=not present): randomization mentioned; double-blind mentioned; dropouts described; randomization appropriate; double-blinding appropriate.
[b] AOM definition components (1=required; 0=not required):MEE; rapid onset; acute inflammation
[c] amox=amoxicillin; clav=clavulanate; amp=ampicillin; pcn=penicillin; triple sulfa=triple sulfonamide; ery=erythromycin; tmp-smx=trimethoprim-sulfamethoxazole

Table 6e: Randomized Controlled Trials from Marcy (2001)[13] Addressing Short- vs. Long-Term Antibiotic Therapy

Author Year	RCT Quality[a]	AOM Definition[b]	Intervention[c]	Time	Place	Age
Adam, 1995	[1,0,1,0,0]	[0,0,0]	cefpodoxime vs. cefaclor	?	Germany	3m-6yr
Arguedas, 1996	[1,0,1,1,0]	[1,0,0]	azithromycin vs. amox-clav	?	Costa Rica	6m-12y
Arguedas, 1997	[1,0,1,1,0]	[1,0,0]	azithromycin vs. clarithromycin	?	Costa Rica	6mo-12yrs
Aronovitz, 1996	[1,0,1,0,0]	[1,0,0]	azithromycin vs. amox-clav	?	USA	2-15yrs
Bain, 1985	[1,0,1,1,0]	[0,0,0]	amox 2 day vs. 7 day	winter 1983, 1984	?	3-10 yrs
Barnett, 1997	[1,0,1,1,0]	[1,0,0]	ceftriaxone vs. tmp-smx	2/91-4/94	Boston	3 mo-3 yr
Bauchner, 1996	[1,0,0,1,0]	[1,0,0]	ceftriaxone vs. amox-clav	10/93-5/94	USA	3mo-6yrs
Boulesteix, 1995	[1,0,1,0,0]	[0,0,0]	cefpodoxime vs. cefixime	9/91-3/92	France	6m-6yr
Chamberlain, 1994	[1,0,1,1,0]	[1,0,1]	ceftriaxone vs. cefaclor	?	Washington, DC	18mo-6yrs
Chaput de Saintongen, 1982	[1,1,1,0,1]	[0,0,0]	amox 3 day vs. 10 day	Winter 1979, 1980	England	2-10yrs
Cohen, 1997	[1,0,1,0,0]	[0,0,0]	cefpodoxime vs. amox-clav	10/93-3/94	France	4mos-4.5yrs
Cohen, 1998	[1,1,1,1,1]	[1,0,1]	amox-clav 5 day vs. 10 day	11/94-6/96	France	4m-2.5yr
Daniel, 1993	[1,0,1,0,0]	[1,0,1]	azithromycin vs. amox-clav	?	European	2-8yr
Gooch, 1996	[1,0,1,0,0]	[1,0,1]	cefuroxime vs. amox-clav	?	USA	3mos-12yrs
Green, 1993	[1,1,1,0,1]	[0,0,1]	ceftriaxone vs. amox	9/90-6/91	California	5mo-5yrs
Hendrickse, 1988	[1,1,1,1,1]	[1,0,1]	cefaclor 5 day vs. 10 day	?	USA	1mo-12yrs
Hoberman, 1997	[1,0,1,0,0]	[0,0,0]	amox-clav 5 day vs. 10 day	1/94-7/94	USA & Canada	2m-12yr
Ingvarsson, 1982	[1,0,0,0,0]	[0,0,0]	pcn V 5 day vs. 10 day	10/76-12/76; 2/77-4/77	Sweden	6m-7yr
Jones, 1986	[1,1,1,0,1]	[0,0,0]	cefaclor 3 day vs. 7 day	Winter 1983 and 1984	Great Britain	3-10yrs
Kafetzis, 1997	[1,0,1,0,0]	[0,0,1]	cefprozil 5 day vs. 10 day	?	Greece	2m-14.3yr
Kara, 1998	[1,0,0,0,0]	[0,0,0]	amox vs. cefuroxime vs. ceftriaxone	9/97 – 5/97	Turkey	6m-6yr
Khurana, 1996	[1,0,1,0,0]	[1,0,0]	erythromycin vs. amox-clav	?	USA	6mo-12yrs
Leigh, 1989	[1,0,1,0,0]	[0,0,0]	cefixime vs. amox	?	United Kingdom	6mo-16 yrs
McLinn, 1996	[1,1,1,0,1]	[1,0,0]	azithromycin vs. amox-clav	?	USA	1-15yr
Meistrup-Larsen, 1983	[1,1,0,0,1]	[0,1,1]	pcn 2 day vs. 7 day	11/80-5/81	Denmark	1-10yrs
Pestalozza,	[1,0,0,0,0]	[0,0,1]	azithromycin vs. amox-clav	?	Italy	11mo-9 yrs

Author Year	RCT Quality[a]	AOM Definition[b]	Intervention[c]	Time	Place	Age
1992						
Ploussard, 1984	[1,0,1,1,0]	[1,0,0]	cefaclor vs. amox	?	?	5mo-5yr
Principi, 1995	[1,0,1,0,0]	[1,0,1]	azithromycin vs. amox-clav	?	Italy	<12yr
Puczynski, 1987	[1,1,1,0,0]	[1,0,1]	amox vs. placebo	5/84-2/85	Chicago, IL	>2yrs
Rodriguez, 1996	[1,0,1,0,0]	[0,0,0]	azithromycin vs. cefaclor	?	Guatemala	6mo-13yrs
Rubenstein, 1965	[1,0,1,0,0]	[0,0,0]	benzathine pcn G plus procaine pcn vs. benzathine pcn G plus pseudoephedrine vs. benzathine pcn G plus triple sulfa vs. benzathine pcn G plus triple sulfa plus pseudoephedrine vs. tetracycline vs. tetracycline plus pseudoephedrine	11/63-4/64	Rochester, MN	<15yr
Schaad, 1993	[1,0,1,0,0]	[0,0,0]	azithromycin vs. amox-clav	?	Switzerland	0.5-10.2 yrs
Simon, 1997	[1,1,0,0,0]	[1,0,0]	ceftibuten 5 day vs. 10 day	?	Kentucky	6m-14yr
Stickler, 1967	[1,0,1,1,0]	[0,0,0]	pcn vs. pcn plus antihistamine vs. pcn plus triple sulfa vs. pcn plus triple sulfa	?	Rochester, MN	<15yr
Varsano, 1988	[1,1,1,0,1]	[1,0,1]	ceftriaxone vs. amox	?	Israel	6ms-8yrs
Varsano, 1997	[1,0,1,1,0]	[1,0,1]	ceftriaxone vs. amox-clav	?	Israel	4mo-6yr

[a] Jadad study quality score components (1=present; 0=not present): randomization mentioned; double-blind mentioned; dropouts described; randomization appropriate; double-blinding appropriate.

[b] AOM definition components (1=required; 0=not required): MEE; rapid onset; acute inflammation

[c] amox=amoxicillin; clav=clavulanate; amp=ampicillin; pcn=penicillin; triple sulfa=triple sulfonamide; ery=erythromycin; tmp-smx=trimethoprim-sulfamethoxazole

Table 6f. Comparative Effectiveness of Different Treatment Options for Treating Uncomplicated Acute Otitis Media in Average Risk Children in the 2001 Report and the Present Report

Comparison	2001 Report		2009 Update			Conclusion[a]
	Number of trials	Success rate difference (95% CI)	Number of new trials	Total number of trials	Success rate difference	
Drug vs. placebo, wait-and-see, and/or prescription-to-hold						
Ampicillin or amoxicillin vs. placebo	5	12% (-22%, -3%)	2	7	12%(5%, 18%)	Ampicillin or amoxicillin was more successful than placebo
Amoxicillin tid (7d) vs. prescription-to-hold) [2]	0	N/A	1	1	16% (6, 26)	Amoxicillin is more successful than prescription-to-hold (defined as success at day 3)
Antibiotic vs. prescription-to-hold)[2]	0	N/A	1	1	3% (-8, 14)	Inconclusive (defined as otalgia at day 4-6)
Amoxicillin 90mg/kg/d bid (10d) vs. wait-and-see [3]	0	N/A	1	1	15% (6, 24)	Amoxicillin was more successful (defined as success at day 12)
PcV vs. wait-and-see[3]	0	N/A	1	1	-3% (-14, 8)	Inconclusive (defined as success at day 14)
Drug vs. drug						
Ampicillin or amoxicillin vs. Ceftriaxone	3	3% (-8%, 2%)	1	4	0% (-7%, 7%)	Inconclusive
Amoxicillin 50mg/kg/d (bid, 10d) vs. erythromycin 40mg/kg/d (bid, 10d) [4]	0	N/A	1	1	0.6% (-3, 4)	Treatments were equivalent (when success defined as freedom from recurrence day 31-40)
Amoxicillin-clavulanate vs. amoxicillin sulbactam 80mg/kg/d; (bid 10d)	0	N/A	1	1	0% (-3.3, 3.3)	Treatments were equivalent (success d.12-14)
Amoxicillin-clavulanate (>6 yrs old: 250 mg tid x 7d; < 6 yrs old: 125	0	N/A	1	1	13% (5, 21)	Amoxicillin-clavulanate was more effective than cefaclor (success at

Comparison	2001 Report Number of trials	2001 Report Success rate difference (95% CI)	2009 Update Number of new trials	2009 Update Total number of trials	2009 Update Success rate difference	Conclusion[a]
mg tid x7d) vs. cefaclor (125 or 250 mg tid x 7 d) [5]						day 28-34, as defined by clinical symptoms but not by culture)
Cefaclor vs. trimethoprim-sulfamethoxazole	3	-6% (-13, 2) (success at less than 14 d)	0	3	N/A	Inconclusive (defined as success at less than day 14); no new data but using MCID
Cefaclor vs. Ampicillin or amoxicillin	4	-5% (-16, 6) (success at d. 3-7)	0	4	N/A	Inconclusive (defined as success at day 3-7); no new data but using MCID
Cefixime vs. Ampicillin or amoxicillin	4	0.1% (-3.9, 4.2) (success at d. 10-15)	0	4	N/A	Treatments were equivalent; no new data
Penicillin vs. ampicillin or amoxicillin	3	-5% (-11, 2) (success at d. 7-14)	0	3	N/A	Inconclusive (defined as success at day 7-14); no new data but using MCID
High vs. Low Dose Treatment						
Amoxicillin-clavulanate >60mg/kg/d vs. amoxicillin-clavulanate 40mg/kg/d	1	1.5% (-3, 13)	0	1	N/A	Inconclusive(defined as persistent clinical cure with no recurrence at follow-up)
High-dose amoxicillin bid vs. lower-dose amoxicillin tid	1	-4% (-14, 7)	0	1	N/A	Inconclusive (defined as success at day 15)t; no new data
Amoxicillin-clavulanate 45/64 mg/kg/day / bid for 7-10 days vs. Amoxicillin-clavulanate 40/10 mg/kg/day / tid for 7-10 days [6]	0	N/A	1	1	0.1% (-4.8, 4.6)	Treatments were equivalent (success d. 7-12)
Short vs. Long Treatment Duration[b]						
Ampicillin or	3	3% (-2%,	1	4	0% (-7%,	Inconclusive

Comparison	2001 Report		2009 Update			Conclusion[a]
	Number of trials	Success rate difference (95% CI)	Number of new trials	Total number of trials	Success rate difference	
Amoxicillin (7-10d) vs. Ceftriaxone (1 dose)		9%) (success rate at 5-10d)			7%)	
Amoxicillin-Clavulanate (7-10d) vs. Ceftriaxone (1 dose)	2	No meta-analysis	3	5	3% (-2%, 7%)	Inconclusive
Cefaclor (7-10d) vs. Azithromycin (<5d)	1	N/A	2	3	-1% (-4%, 3%)	Treatments were equivalent
Amoxicillin (7d) vs. Azithromycin (1 dose)	0	N/A	1	1	1% (-1%, 4%)	Treatments were equivalent (defined as no new pain between day 1 and 11)
Amoxicillin-clavulanate (7-10d) vs. Azithromycin (<5d)	5	2% (-1, 5%) (success at 10-14d)	4	9	-0.3% (-6%, 6%)	Inconclusive
Amoxicillin-clavulanate 45/6.4 mg/kg/d (bid, 10d) vs. azithromycin 10 mg/kg/d (qd for 1 day), 5 mg/kg/d (qd for 4d) [7]	0	N/A	1	1	26% (6,36)	Longer-term amoxicillin-clavulanate is more successful than shorter-term azithromycin (at d. 12-14, when pathogen is H. influenzae)
Amoxicillin-clavulanate 45/6.4 mg/kg/d (bid, 10d) vs. azithromycin 10 mg/kg/d (qd for 3 day) [52]	0	N/A	1	1	-20% (-34, -6)	Amoxicillin-clavulanate was worse than azithromycin (cure defined as negative culture)
Cefaclor 50mg/kg/d; bid 5 d) vs. cefaclor 40mg/kg/d; bid 10d)	0	N/A	1	1	0.7% (-3.5-4.9)	Treatments were equivalent

Table Notes: bid twice a day; CI confidence intervals; d day(s); kg kilograms (body weight); mg milligrams; NNT number needed to treat; PcV phenoxymethylpenicillin; qd once a day;

[a] Confidence intervals falling within the zone of indifference were considered to establish evidence of *no difference*, and confidence intervals outside the zone of indifference were considered to *establish difference*. If the confidence intervals crossed into the zone of indifference, an effect (positive or negative) of the treatment option on the outcome could not be established

(*inconclusive*). For the 2010 systematic review, we used a ***zone of clinical indifference of +/- 5%*** for the difference in success rate between two treatment options.
[b]Short vs. long term duration refers to the length of treatment from the patient perspective, rather than from the perspective of drug action.

We also identified seven new or updated systematic reviews of the comparative effectiveness of different options for treating uncomplicated AOM in average-risk children (Table 7 and Appendix I),[53-59] in addition to the four systematic reviews that we reported on in the 2001 report.[53, 60-64] Table 7 summarizes the key features of these reviews; the findings of these reviews are summarized in the relevant sections below or at the end of the descriptions of our pooled findings.

Table 7. Review Articles Examining Comparative Effectiveness of Treatment Strategies in Uncomplicated Acute Otitis Media[a]

Author (year) (quality)[b]	Review focus	Databases (included dates)	Study design	Target population	Outcomes	Number of trials and participants	Author's highlight conclusion
Marcy, 2001[13 c] (y,y,y,y,y,y, y,y,y,y,n)	natural history antibiotics (ab) vs. no ab ab regimen	CENTRAL (TCL, through Mar 1999), MEDLINE (1966-Mar 1999), HlthSTAR (1975-Mar 1999), IPA International Pharmaceutical Abstracts (1970-Mar 1999), CINAHL (1982-Mar 1999), BIOSIS (1970-Mar 1999), and EMBASE (1980-Mar 1999); hand search	RCT; Cohort, for natural history	AOM 4wk-18y	Clinical failure; adverse effects	80 trials total	Rx with amp/amox ↓ clinical failure by 12% vs. no a; ab regimen outcomes not different; cefixime & amoxicillin-clavulanate ↑ adverse effects
Rosenfeld, 1994[61] (y,y,n,y,n,y, y,y,y,n,n)	ab vs. no ab ab regimen	MEDLINE (Jan 1966-Jun 1992); Current Contents (3 months through Jun 29, 1992); hand search	RCT	AOM 4wk-18y	Clinical response; MEE presence	33 trials total	ab effect modest but significant; no significant difference between ab regimens studied

Author (year) (quality)[b]	Review focus	Databases (included dates)	Study design	Target population	Outcomes	Number of trials and participants	Author's highlight conclusion
Damoiseaux, 1998[62] (y,n,y,y,n,y, y,y,n,n,n)	ab vs. no ab	MEDLINE (1966-Jan 1997); EMBASE (1974-Jan 1997); hand search	RCT	AOM <2 years old	Clinical resolution within 7d	4 trials 416 children	No significant difference between ab and no ab in <2y olds
Kozyrskyj, 2000[53] (y,y,y,y,y,y, y,y,y,y,n)	ab <7d vs. ≥7d	MEDLINE (Jan 1966-Jul 1997); EMBASE (Jan 1966-Jul 1997); Science Citation Index (Mar 1998); Current Contents (Mar 1998); hand search	RCT	AOM 4wk-18y	Clinical resolution 31d & 1-3m; relapse; recurrence	32 trials total	ab 5d→effective Rx for AOM
Glasziou, 2004[54] (y,y,y,y,y,y, y,y,y,n,n)	ab vs. no ab	CENTRAL (1966-Jan 2000; TCL, issue 1, 2003); Current Contents (1966- Jan 2000); Index Medicus (1958-1965); MEDLINE (Jan 2000-Mar 2003); EMBASE (Jan 1990-Mar 2003); hand search	RCT	AOM Children, age not specified	Severity and duration of pain; mid- to long-term hearing problems; adverse effects; recurrent attacks	8 trials total	ab of small benefit for AOM Rx

Author (year) (quality)[b]	Review focus	Databases (included dates)	Study design	Target population	Outcomes	Number of trials and participants	Author's highlight conclusion
Foxlee, 2006[55] (y,y,y,y,y,y, y,y,y,n,n)	topical analgesia Subgroups: <2y vs. ≥2y ; concurrent ab	CENTRAL (TCL, issue 2, 2006); MEDLINE (1966-May 2006); EMBASE (1990-Dec 2005); LILACS (1982-Sep 2005); hand search	RCT or quasi-RCT	AOM without perforation in Adults and children	Pain severity and duration; parental satisfaction; days missed from school or work; adverse events	4 trials total	evidence insufficient to make conclusions on topical analgesia effectiveness
Rovers, 2006[56] (y,n/a,n,n,n,y,y,y,y,y,n)	ab vs. no ab Subgroups: <2y vs. ≥2y; laterality; otorrhea	CENTRAL; PubMed; EMBASE (dates not specified)	RCT	AOM 0-12 years	Pain &/or fever 3-7d	6 trials total	ab beneficial for <2 year old with bilat AOM & AOM with otorrhea
Spurling, 2007[57] (y,y,y,n,y,y, y,y,y,y,n)	Delayed (>48 hrs) ab vs. immediate ab	CENTRAL (TCL, issue 1, 2004; TCL, issue 4, 2006); MEDLINE (Jan 1966-Jan 2007); EMBASE (1990-Jan 2007); Current Contents (1998-Jan 2007)	RCT	Respiratory tract infections All ages (For identified AOM studies 6m-12y)	Clinical outcomes; ab use; patient satisfaction; health-seeking behaviors; alternative therapies (For identified AOM studies pain, malaise, and fever)	2 trials total for AOM in children	immediate ab→ improved pain and malaise on day 3; delayed ab→diarrhea reduced (thought not an a priori outcome of this review)

Author (year) (quality)[b]	Review focus	Databases (included dates)	Study design	Target population	Outcomes	Number of trials and participants	Author's highlight conclusion
Coleman, 2008[58] (y,y,y,y,y,y, y,y,y,y,n)	decongestant &/or antihista-mine	CENTRAL (TCL, issue 2, 2001; TCL, issue 3, 2003; TCL, issue 2, 2007); MEDLINE (Jan 1966-May 2007); EMBASE (Jan 1990-May 2007); hand search	RCT	AOM <18y	Clinical resolution at 2wk, 1wk, 4wk; symptom resolution; medication side effects; AOM complications	15 trials total	lack of benefit for decongestant &/or antihistamine; increased risk of side effects
Thanaviratananich, 2008[59] (y,y,y,y,y,y, y,y,y,y,y)	amox or amox-clav once or twice daily *vs.* three times daily	CENTRAL (TCL, issue 1, 2008); MEDLINE (Jan 1950-Mar 2008); EMBASE (1974-Mar 2008); Science Citation Index (2001-Mar 2008); NLM Gateway (HSR Project) (Mar 2008); hand search	RCT	AOM ≤12y	Clinical cure at end of antibiotic therapy, i.e. 7d and 14 d, with respect to otalgia, fever, bacteriologic cure; also, clinical cure during therapy and post-treatment, recurrent OM, acute mastoiditis, adverse reactions	6 trials total	evidence appears biased so no data pooling performed; no firm conclusions

[a]Abbreviations: ab=antibiotic; amox-clav=amoxicillin-clavulanate; CENTRAL=Cochrane Central Register of Controlled Trials; CINAHL=Cumulative Index to Nursing & Allied Health Literature; HlthSTAR=HealthSTAR; IPA=International Pharmaceutical Abstracts; MEE=middle ear effusion; Rx=treatment; TCL=The Cochrane Library

[b]AMSTAR quality criteria (Shea, Grimshaw, Wells, et al., 2007)

1. Was an 'a priori' design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e. grey literature) used as an inclusion criteria?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interested stated?

[c]Marcy (2001) is the 2001 AHRQ AOM systematic review that is being updated.

A total of 46 RCTs (published since the 2001 AOM report) that compared the effectiveness of treatment options in uncomplicated AOM were newly identified for this review update. They encompassed different antibiotics, different regimens, and different outcomes. The number of articles for each comparison for each reported outcome measure is provided in Table 8. These 46 trials were added to the trials identified in the 2001 AOM report (Tables showing the numbers of articles included from the 2001 AOM report as well as the articles included in these analyses are provided in Appendix G). We identified the treatment comparisons that involved three or more articles and conducted meta-analysis to pool the data for each. The following comparisons had three or more studies on the treatment success rate:

- Ampicillin or amoxicillin vs. placebo
- Ampicillin or amoxicillin vs. ceftriaxone (single dose)
- Amoxicillin-clavulanate (7-10 days) vs. ceftriaxone (single dose)

Amoxicillin-clavulanate (7-10 days) vs. Azithromycin (≤5 days)

- Azithromycin (<5 days) vs. cefaclor (7-10 days)
- Antibiotics vs. placebo

Findings for subgroups of patients are reported in the response to Key Question 5.

Table 8. Listing of Treatment Option Comparisons and Outcomes

Comp#	Comparison	Author, Year	Tx success/ failure[a]	Invasive infection[b]	Bacteriologic cure	Disease recurrence	Adverse effects	Quality of life	Parent Satisfaction	Cost	Other[c]
1	Amox vs. Amox+Fenspiride	Zielnik-Jurkiewicz, 2005[65]		1							
2	Amox vs. Azithromycin	Arguedas, 2005[66]		1		1	1				
3	Amox vs. Azithromycin	Morris, 2010[67]		1							1
4	Amox vs. Ceftriaxone	Zhang, 2003[68]		1							
5	Amox-clav vs. Amox-sulbactam	Casellas, 2005[69]		1	1	1	1				
6	Amox-clav vs. Azithromycin	Dagan, 2000[7]		1	1		1				
7	Amox-clav vs. Azithromycin	Dunne, 2003[70]		1			1				
8	Amox-clav vs. Azithromycin	Guven, 2006[52]		1	1	1	1				
9	Amox-clav vs. Azithromycin	Biner, 2007[71]		1		1	1				
10	Amox-clav vs. Cefaclor	Subba Rao, 1998[5]		1	1	1	1				
11	Amox-clav vs. Cefdinir 7mg	Block, 2000[72]		1			1				1
12	Amox-clav vs. Cefdinir 14mg	Block, 2000[72]		1			1				1
13	Amox-clav vs. Cefdinir 7mg	Adler, 2000[73]		1		1	1				
14	Amox-clav vs. Cefdinir 14mg	Adler, 2000[73]		1		1	1				
15	Amox-clav vs. Cefdinir	Cifaldi, 2004[74]							1	1	1
16	Amox-clav vs. Cefdinir	Block, 2004[75]		1			1		1	1	1

Comp#	Comparison	Author, Year	Tx success/ failure[a]	Invasive infection[b]	Bacteriologic cure	Disease recurrence	Adverse effects	Quality of life	Parent Satisfaction	Cost	Other[c]
17	Amox-clav vs. Cefprozil	Hedrick, 2001[76]	1				1				
18	Amox-clav vs. Ceftriaxone	Cohen, 1999[77]	1	1	1		1				1
19	Amox-clav vs. Ceftriaxone	Wang, 2004[78]	1				1				
20	Amox-clav vs. Ceftriaxone	Biner, 2007[71]	1			1	1				
21	Amox-clav 40 mg vs. Cefuroxime	Pessey, 1999[79]	1		1		1				
22	Amox-clav 80 mg vs. Cefuroxime	Pessey, 1999[79]	1		1		1				
23	Amox-clav vs. Ciprodex drops	Dohar, 2006[80]	1		1		1				
24	Azithromycin vs. Cefaclor	Dagan, 2000[81]	1		1						
25	Azithromycin vs. Cefaclor	Oguz, 2003[82]	1			1	1				
26	Azithromycin vs. Cefdinir	Block, 2005[83]	1				1		1		
27	Azithromycin vs. Ceftriaxone	Biner, 2007[71]	1			1	1				
28	Cefaclor vs. Cefprozil	Carvalho, 1998[84]	1				1				
29	Cefdinir vs. Cefprozil	Block, 2000[85]	1				1				
30	Cefaclor vs. Cefpodoxime	Tsai, 1998[86]	1			1	1				
31	Amox vs. Wait-and-see	McCormick, 2005[3]	1	1	1	1	1	1	1	1	
32	PcV vs. Wait-and-see	Neumark, 2007[87]	1	1						1	1
33	Amox vs. Placebo	Damoiseaux, 2000[88]	1				1				

Comp#	Comparison	Author, Year	Tx success/ failure[a]	Invasive infection[b]	Bacteriologic cure	Disease recurrence	Adverse effects	Quality of life	Parent Satisfaction	Cost	Other[c]
34	Amox vs. Placebo	Le Saux, 2005[89]	1	1			1				1
35	Lidocaine drop vs. Placebo	Bolt, 2008[90]	1				1				
36	Probiotic vs. Placebo	Hatakka, 2007[91]	1			1					
37	Homeopathic vs. Placebo	Jacobs, 2001[92]	1				1				
38	Amox vs. PrescriptionHold	Little, 2001[2]	1					1	1	1	
39	Amox vs. PrescriptionHold	Little, 2006[93]	1					1			
40	Antibiotic vs. PrescriptionHold	Spiro, 2006[94]	1				1		1	1	1
41	PrescriptionHold vs. Wait-and-see	Chao, 2008[95]	1						1		1
42	Amox high vs. low dose	Garrison, 2004[96]	1			1	1				1
43	Amox-clav high vs. low dose	Pessey, 1999[79]	1		1		1				
44	Amox-clav high vs. low dose	Bottenfield, 1998[97]	1			1	1				
45	Amox-clav bid vs. tid	Damrikarnlert, 2000[6]	1		1		1				1
46	Cefdinir high vs. low dose	Adler, 2000[73]	1			1	1				
47	Cefdinir high vs. low dose	Block, 2000[72]	1				1				1
48	Amox-clav 5-day vs. 10-day	Cohen, 1998[98]	1	1	1	1	1				1
49	Cefaclor 5-day vs. 10-day	Catania, 2004[99]	1			1	1				
50	Cefpodoxime 5-day vs. 10-day	Cohen, 2000[100]	1				1				

Comp#	Comparison	Author, Year	Tx success/ failure[a]	Invasive infection[b]	Bacteriologic cure	Disease recurrence	Adverse effects	Quality of life	Parent Satisfaction	Cost	Other[c]
51	Ceftriaxone vs. Ceftriaxone+Prednisolone	Chonmaitree, 2003[101]		1			1				1
52	Ceftriaxone vs. Ceftriaxone+Antihistamine	Chonmaitree, 2003[101]		1			1				1
53	Ceftriaxone vs. Ceftriaxone+Prednisolone+Antihistamine	Chonmaitree, 2003[101]		1			1				1
54	Ceftriaxone+Prednisolone vs. Cetriaxone+Antihistamine	Chonmaitree, 2003[101]		1			1				1
55	Ceftriaxone+Prednisolone vs. Ceftriaxone+Predinisolone+Antihistamine	Chonmaitree, 2003[101]		1			1				1
56	Ceftriaxone+Antihistamine vs. Ceftriaxone+Predinisolone+Antihistamine	Chonmaitree, 2003[101]		1			1				1
57	Otikon drops vs. Topical Anesthetic	Sarrell, 2001[102]		1				1	1		
58	Anesthetic vs. Anesthetic+Amox	Sarrell, 2003[103]		1				1			
59	Anesthetic vs. NHED	Sarrell, 2003[103]		1				1			
60	Anesthetic vs. NHED+Amox	Sarrell, 2003[103]		1				1			
61	Anesthetic+Amox vs. NHED	Sarrell, 2003[103]		1				1			

Comp#	Comparison	Author, Year	Tx success/ failure[a]	Invasive infection[b]	Bacteriologic cure	Disease recurrence	Adverse effects	Quality of life	Parent Satisfaction	Cost	Other[c]
62	Anesthetic+Amox vs. NHED+Amox	Sarrell, 2003[103]	1				1				
63	NHED vs. NHED+Amox	Sarrell, 2003[103]	1				1				
			61	**5**	**13**	**24**	**47**	**4**	**7**	**6**	**19**

[a] Included success/failure defined by improvement of signs and/or symptoms
[b] Included otologic complications
[c] Included healthcare utilization, compliance, tolerability, PE tube placement, need for change of treatment, duration of AOM

Ampicillin or Amoxicillin vs. Placebo

The 2001 report found a rate difference of -12% (95% CI: -22%, -3; NNT=8, 95% CI: 4, 33) (in terms of clinical failure rate) favoring ampicillin/amoxicillin treatment vs. placebo based on five trials.[104-108]

One new meta-analysis was identified relevant to this comparison. A meta-analysis by Glasziou (2004) reported a possible benefit for antibiotics for pain at 2 to 7 days with an odds ratio of 0.57 (95% CI: 0.45, 0.73) with a number needed to treat of 15 children, but not for pain at 24 hours, abnormal tympanogram at one or three months, perforation, contralateral otitis, or late recurrence.[109]

Two new RCTs[88, 89]were also identified that addressed the comparison of ampicillin or amoxicillin vs. placebo.

The ages of children in these studies ranged from 2 months to 14 years (no two studies included the same age range). The outcome assessed in the five older trials was success rate at days 2-18, whereas the outcome assessed in the two new trials was success rate at days 11-14. We considered the trials sufficiently clinically similar to justify pooling. Sample sizes ranged from 30 to 488. The studies reviewed for the initial report varied somewhat in their definitions of treatment success (including absence of persistent symptoms [fever, earache, crying, irritability], improvement, absence of otorrhea, cumulative clinical resolution); however, we felt these outcomes were sufficiently similar to pool. The Jadad quality scores of the five older studies were 5,2,1,4, and 2 out of 5; the two newer studies both had scores of 5.

The random effects pooled rate difference for clinical success by day 14 between ampicillin/amoxicillin and placebo was estimated at 12% (95% confidence interval [CI] 5%, 18%), and the NNT for a clinical success was nine (95% CI: 6, 20) (Figure 2 and Table 9). Using an *a priori* MCID of 5% (as will be used for all remaining comparisons in this report), ampicillin/amoxicillin has a significantly higher success rate than placebo.

Figure 2. Shrinkage Plot for Ampicillin/Amoxicillin vs Placebo for Treatment Success

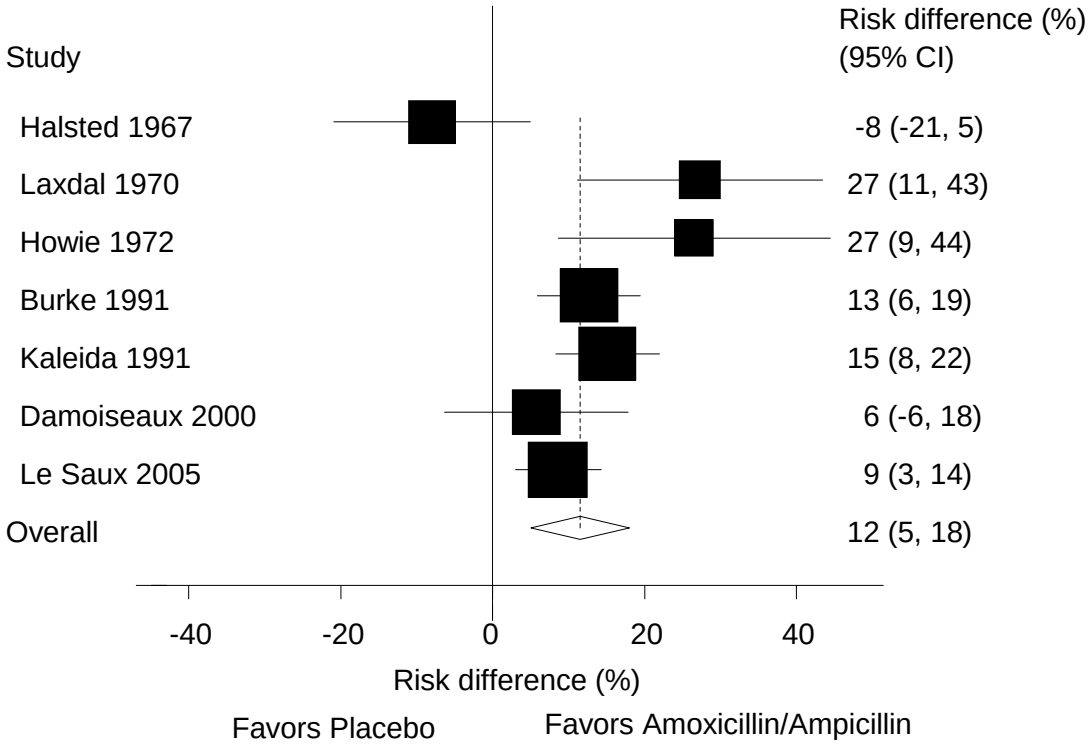


Table 9. Ampicillin/Amoxicillin vs. Placebo; Outcome Indicator: Treatment Success Rate

Author, Year	Age	Definition of outcome	Amoxicillin/ Ampicillin Sample Size	Placebo Sample Size	Amoxicillin Success Rate (%)	Placebo Success Rate (%)	Rate Difference In %	95% CI of Rate Difference In %
Halsted, 1967[104]	2-66 mos	Success at day 14-18	30	27	92.0	100.0	-8.0	-20.9, 4.9
Laxdal, 1970[105]	<15 yrs	Success at day 7	49	48	89.8	62.5	27.3	11.2, 43.4
Howie, 1972[106]	<=2.5 yrs	Success at day 2-7	36	116	47.2	20.7	26.5	8.6, 44.4
Burke, 1991[107]	3-<10 yrs	Success at day 7	114	118	98.2	85.6	12.7	5.9, 19.4
Kaleida, 1991[108]	7 mo-12 yrs	No effusion at day 14	401	408	53.1	38.0	15.1	8.3, 21.9
Damoiseaux, 2000[88]	6 mos-2yrs	Clinical success at day 11	112	120	35.7	30.0	5.7	-6.4, 17.8
Le Saux, 2005[89]	6 mos-5yrs	Clinical resolution at day 14	250	240	92.8	84.2	8.6	3.0, 14.3
Random effects estimates			987	1071	73.2	60.2	11.5	5.0, 18.0
Test of heterogeneity Chi-square test value							19.28	
Test of heterogeneity Chi-square test p-value							0.04	
Test of heterogeneity I-squared							68.9%	
Number Needed to Treat (NNT)							9 (6, 20)	
Test of publication bias, Egger's asymmetry test p-value							0.77	

The I^2 statistic for this analysis was 68.9%, indicating the presence of unexplained heterogeneity, which could be due to the differences in the populations studied and/or research methods employed. Therefore, caution is advised in interpreting overall summary measures. Egger's test did not yield evidence suggestive of publication bias (p=0.77).

As a sensitivity analysis, we excluded the study by Halsted (1967),[104] since it was clearly an outlier, in that the 95% confidence limits favored placebo far more strongly than any other individual study. The pooled analysis with the remaining six articles[88, 89, 105-108] yielded a rate difference of 13% (95% CI: 8%, 19%), with seven children (95% CI: 5, 12) needing treatment with ampicillin or amoxicillin to gain a case of clinical success (Figure 3 and Table 10). The I^2 statistic for the pooled analysis excluding the Halsted study was 61.9%. It is not clear why Halsted (1967) would introduce heterogeneity as it is from a similar time period as Laxdal (1970) and Howie (1972) and was of high quality, as were the studies by Burke (1991), Damoiseaux (2000), and LeSaux (2005).[88, 89, 104-107]

Figure 3. Shrinkage Plot for Ampicillin/Amoxicillin vs. Placebo for Treatment Success (Excluded Halsted 1967 Study)

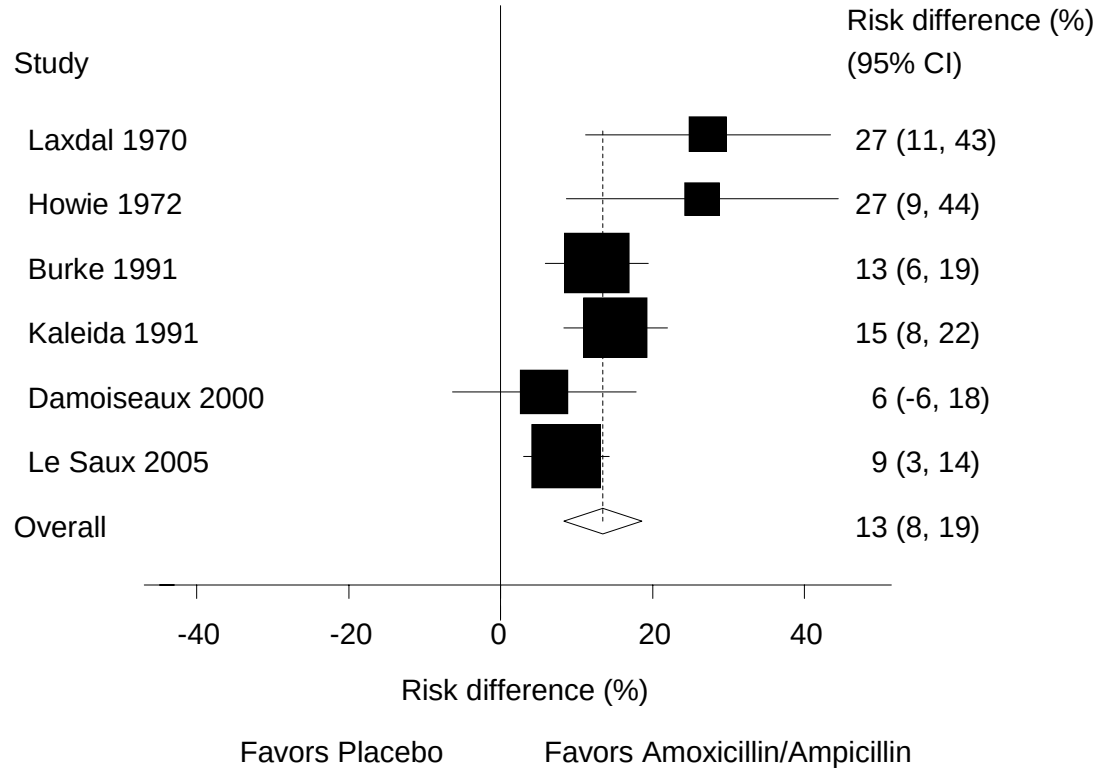


Table 10. Ampicillin/Amoxicillin vs. Placebo; Outcome Indicator: Treatment Success Rate (Excluded Halsted 1967 Study)

Author, Year	Age	Definition of outcome	Amoxicillin/ Ampicillin Sample Size	Placebo Sample Size	Amoxicillin Success Rate (%)	Placebo Success Rate (%)	Rate Difference In %	95% CI of Rate Difference In %
Laxdal, 1970[105]	<15 yrs	Success at day 7	49	48	89.8	62.5	27.3	11.2, 43.4
Howie, 1972[106]	<=2.5 yrs	Success at day 2-7	36	116	47.2	20.7	26.5	8.6, 44.4
Burke, 1991[107]	3-<10 yrs	Success at day 7	114	118	98.2	85.6	12.7	5.9, 19.4
Kaleida, 1991[108]	7 mo-12 yrs	No effusion at day 14	401	408	53.1	38.0	15.1	8.3, 21.9
Damoiseaux, 2000[88]	6 mos-2yrs	Clinical success at day 11	112	120	35.7	30.0	5.7	-6.4, 17.8
Le Saux, 2005[89]	6 mos-5yrs	Clinical resolution at day 14	250	240	92.8	84.2	8.6	3.0, 14.3
Random effects estimates			962	1050	70.1	53.5	13.4	8.3, 18.6
Test of heterogeneity Chi-square test value							9.51	
Test of heterogeneity Chi-square test p-value							0.09	
Test of heterogeneity I-squared							47.4%	
Number Needed to Treat (NNT)							7 (5, 12)	
Test of publication bias, Egger's asymmetry test p-value							0.18	

As an additional sensitivity analysis, we pooled the four studies with a quality score of at least 3 of 5[88, 89, 104, 107], which yielded a rate difference of 6% (95% CI: -1%, 13%) for a clinical success, which was about half that of the primary analysis and no longer met the conventional levels of statistical significance.[88, 89, 104, 107] (Figure 4 and Table 11) Further excluding the study by Halsted (1967) which continued to be an outlier among these four articles, yielded a rate difference of 10% (95% CI: 6%, 14%) or a NNT of 10 (95% CI: 7, 18) for a clinical success without apparent heterogeneity (I^2=0.0%) or publication bias.[88, 89, 107] This sensitivity analysis modestly changed the NNT: 10 children needed treatment with ampicillin or amoxicillin to gain a case of clinical success, rather than nine as with the original seven articles.[88, 89, 104-108] (Figure 5 and Table 12)

Figure 4. Shrinkage Plot for Ampicillin/Amoxicillin vs. Placebo for Treatment Success (Included Studies with Quality Score 3, 4, or 5)

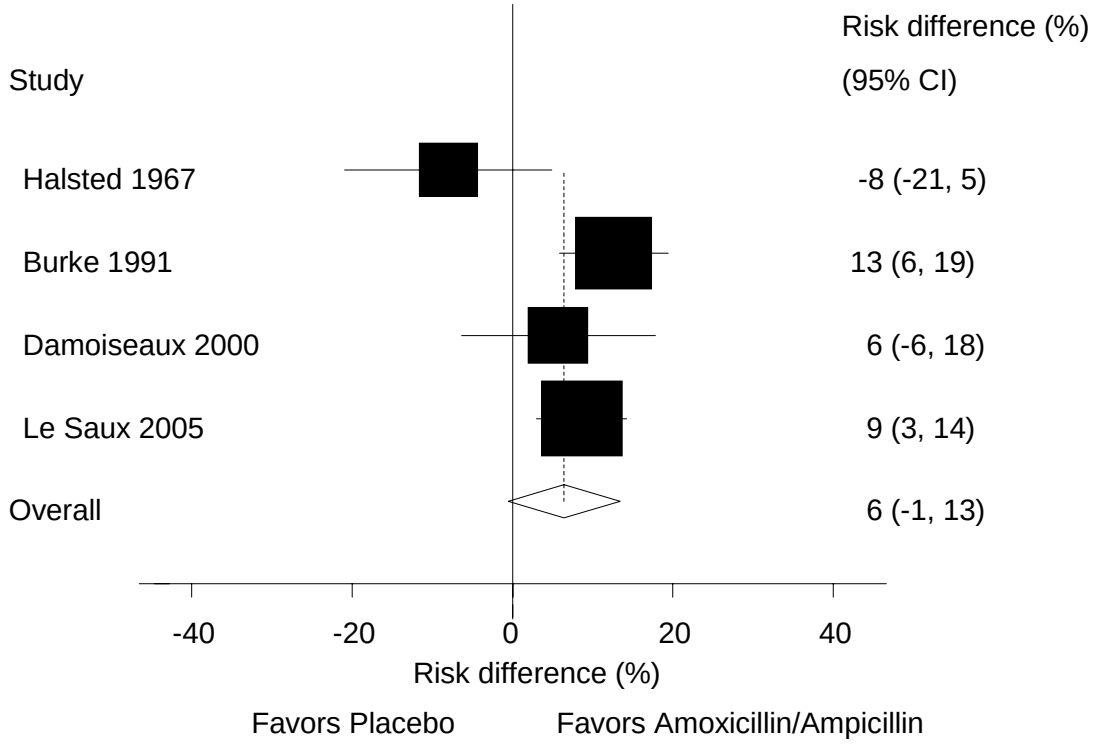


Table 11. Ampicillin/Amoxicillin vs. Placebo; Outcome Indicator: Treatment Success Rate (Included Studies with Quality Score 3, 4 or 5)

Author, Year	Age	Definition of outcome	Amoxicillin/ Ampicillin Sample Size	Placebo Sample Size	Amoxicillin Success Rate (%)	Placebo Success Rate (%)	Rate Difference In %	95% CI of Rate Difference In %
Halsted, 1967[104]	2-66 mos	Success at day 14-18	25	21	92.0	100.0	-8.0	-20.9, 4.9
Burke, 1991[107]	3-<10 yrs	Success at day 7	114	118	98.2	85.6	12.7	5.9, 19.4
Damoiseaux, 2000[88]	6 mos-2yrs	Clinical success at day 11	112	120	35.7	30.0	5.7	-6.4, 17.8
Le Saux, 2005[89]	6 mos-5yrs	Clinical resolution at day 14	250	240	92.8	84.2	8.6	3.0, 14.3
Random effects estimates			501	499	80.1.	75.2	6.4	-0.6, 13.4
Test of heterogeneity Chi-square test value							7.87	
Test of heterogeneity Chi-square test p-value							0.049	
Test of heterogeneity I-squared							61.9%	
Test of publication bias, Egger's asymmetry test p-value							0.26	

Figure 5. Shrinkage Plot for Ampicillin/Amoxicillin vs. Placebo for Treatment Success (Included Studies with Quality Score 3, 4, or 5 (Excluded Halsted 1967 Study)

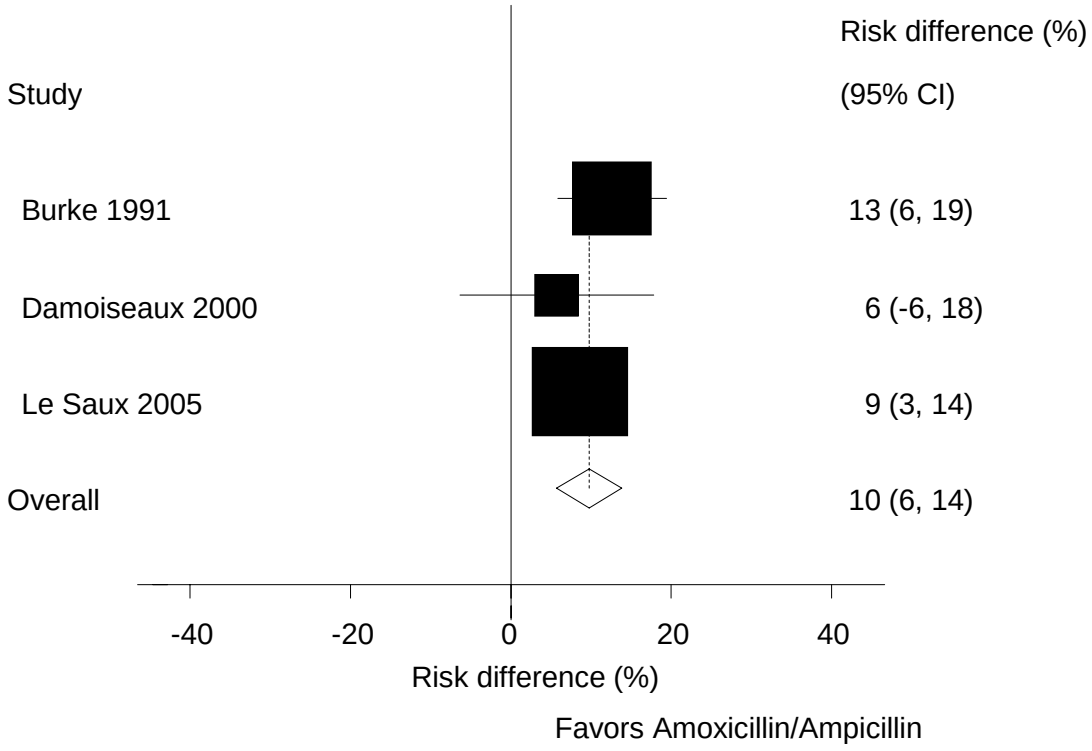


Table 12. Ampicillin/Amoxicillin vs. Placebo; Outcome Indicator: Treatment Success Rate (Included Studies with Quality Score 3, 4 or 5 (Excluded Halsted 1967 Study)

Author, Year	Age	Definition of outcome	Amoxicillin/ Ampicillin Sample Size	Placebo Sample Size	Amoxicillin Success Rate (%)	Placebo Success Rate (%)	Rate Difference In %	95% CI of Rate Difference In %
Burke, 1991[107]	3-<10 yrs	Success at day 7	114	118	98.2	85.6	12.7	5.9, 19.4
Damoiseaux, 2000[88]	6 mos-2yrs	Clinical success at day 11	112	120	35.7	30.0	5.7	-6.4, 17.8
Le Saux, 2005[89]	6 mos-5yrs	Clinical resolution at day 14	250	240	92.8	84.2	8.6	3.0, 14.3
Random effects estimates			476	478	76.3	66.7	9.8	5.7, 13.8
Test of heterogeneity Chi-square test value							4.69	
Test of heterogeneity Chi-square test p-value							0.48	
Test of heterogeneity I-squared							0.0%	
Number Needed to Treat (NNT							10 (7, 18)	
Test of publication bias, Egger's asymmetry test p-value							0.26	

The quality of evidence for this conclusion is moderate due to heterogeneity in the results of studies, with the higher quality studies reporting smaller benefits, meaning that further high quality research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Ampicillin or Amoxicillin vs. Ceftriaxone

One new RCT was identified that addressed this comparison.[68] The 2001 AOM report identified three trials.[110-112]

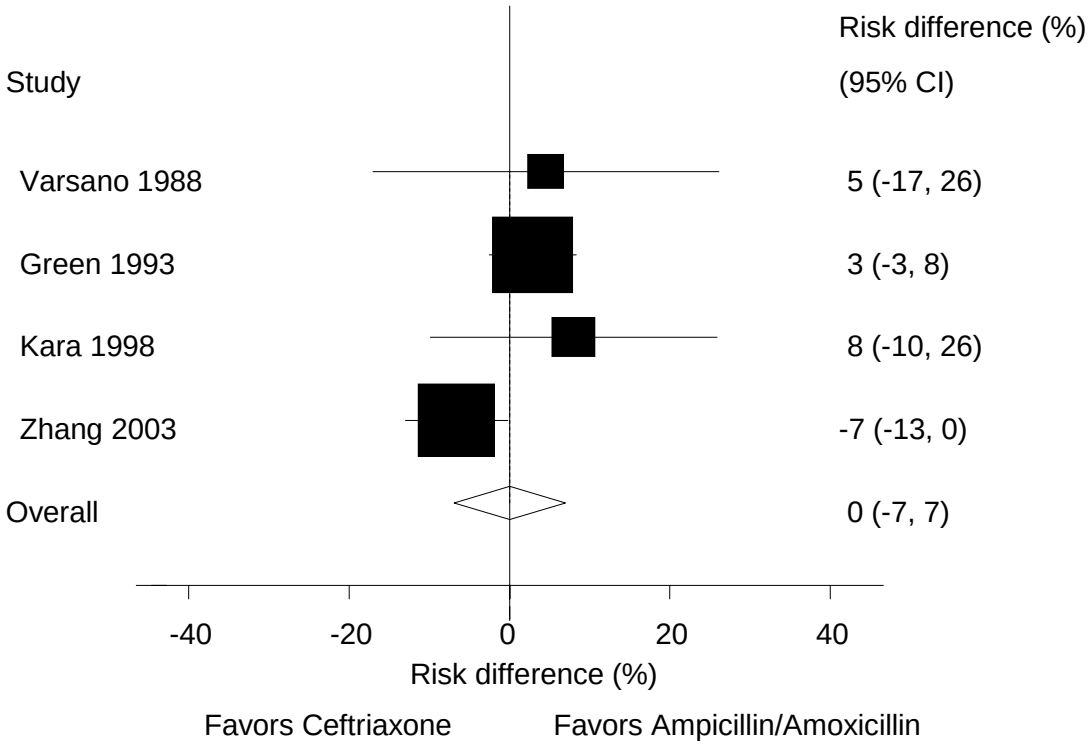
The ages of children in these trials ranged from 5 months to 12 years. Sample sizes ranged from 22 to 107. The outcome assessed in these four articles was treatment success rate at days 5-14. Definitions of treatment success in both the original and the new studies varied somewhat (e.g., clinical cure; rate of acute symptom resolution; clinical and tympanometric appearance of tympanic membrane); however, we felt these outcomes were sufficiently similar to justify pooling. The Jadad quality scores for the three older articles were 4, 4, and 1 out of 5; the newer study scored 2 out of 5.[68]

The random effects pooled rate difference for clinical success by day 14 between ampicillin/amoxicillin and ceftriaxone was estimated at 0% (95% CI:-7%, 7%) for a clinical success (Table 13, and Figure 6).Thus, it is not possible to establish an advantage of either antibiotic over the other or their equivalence based on the current evidence. In order to show equivalence, the 95% confidence interval must lie within the zone of MCID. It is also worth noting that Zhang and colleagues reported a negative rate difference favoring ceftriaxone, while the other three older articles reported no rate difference; however, Zhang (2003), unlike the other three articles, did not report stringent criteria for entry of patients into the study and, like Kara (1998), had low study quality.[68, 112]

Table 13. Ampicillin/Amoxicillin vs. Ceftriaxone; Outcome Indicator: Treatment Success Rate

Author, Year	Age	Definition of outcome	Amoxicillin/ Ampicillin Sample Size	Ceftriaxone Sample Size	Amoxicillin Success Rate (%)	Ceftriaxone Success Rate (%)	Rate Difference In %	95% CI of Rate Difference In %
Varsano, 1988[110]	6 mos-8 yrs	Success at day 7	22	22	86.4	81.8	4.5	-17.0, 26.1
Green, 1993[111]	5 mos-5 yrs	Success at day 10	107	105	97.2	94.3	2.9	-2.5, 8.3
Kara, 1998[112]	6 mos-6 yrs	Success at day 5	25	25	92.0	84.0	8.0	-9.9, 25.9
Zhang, 2003[68]	6 mos-12 yrs	Success at day 10-14	106	106	90.6	97.2	-6.6	-13.0, -0.2
Random effects estimates			260	258	93.1	93.4	0	-6.9, 7.0
Test of heterogeneity Chi-square test value							6.09	
Test of heterogeneity Chi-square test p-value							0.107	
Test of heterogeneity I-squared							50.7%	
Test of publication bias, Egger's asymmetry test p-value							0.70	

Figure 6. Shrinkage Plot for Ampicillin/Amoxicillin vs. Ceftriaxone for Treatment Success



The I^2 statistic for this analysis was 50.7%, indicating the presence of unexplained heterogeneity, which could be due to differences in population studied and/or research methods employed. Therefore, caution is advised in interpreting overall summary measures. Egger's test did not yield evidence suggestive of publication bias (p=0.70). The two higher quality studies[110, 111] showed no difference between amoxicillin and ceftriaxone, whereas one of the lower quality studies[112] showed no difference and the other[68] favored ceftriaxone.

The quality of evidence for this conclusion is moderate, meaning that further high quality research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Amoxicillin-Clavulanate (7-10 days) vs. Ceftriaxone (single dose)

Two new RCTs were identified that addressed this comparison.[71, 78] The 2001 AOM report identified three.[77, 113, 114]

The ages of the children ranged from 3 months to 10 years. Sample sizes ranged from 32 to 271. The outcome assessed in these five trials was treatment success rate at days 3-16. The definitions of treatment success varied slightly (improvement in clinical signs and symptoms; resolution; acute symptom resolution); however, we concluded that these studies were

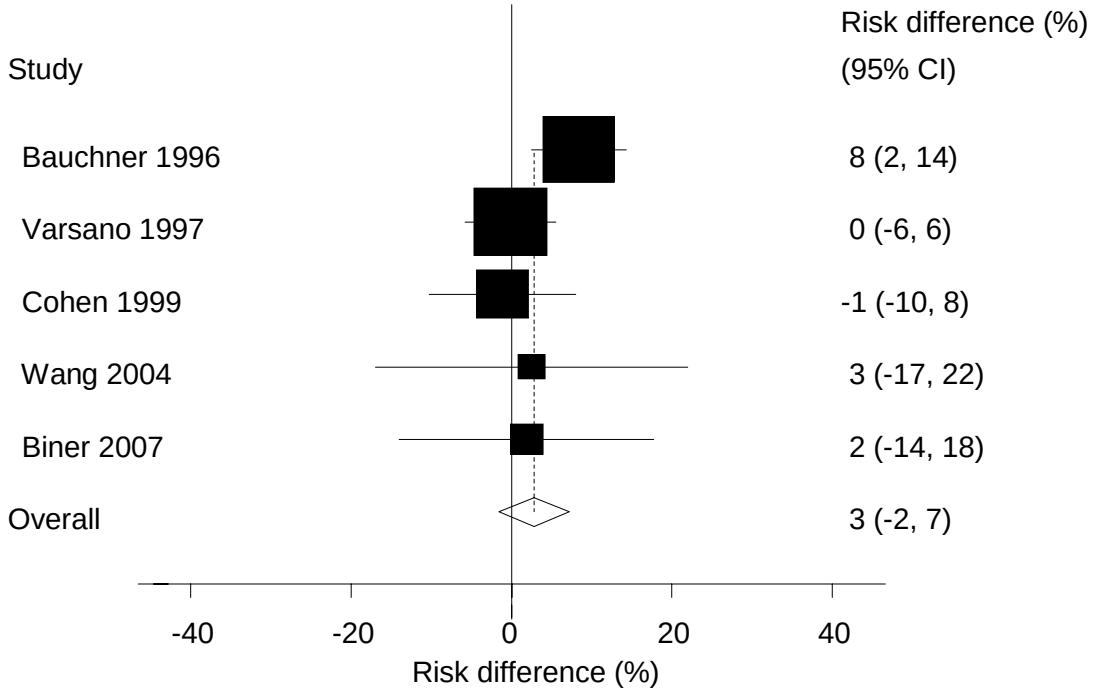
sufficiently clinically similar to justify pooling. The Jadad scores for the two newer trials were 1 and 2; the Jadad scores for the older trials were 2, 4, and 2 out of 5.

The random effects pooled rate difference for clinical success by day 16 between amoxicillin-clavulanate (7-10 days) and ceftriaxone (single dose) was estimated at 3% (95% CI: -2%, 7%) (Table 14 and Figure 7). Thus, the advantage of either antibiotic over the other cannot be established based on the current evidence.

Table 14. Amoxicillin-Clavulanate (7-10 Days) vs. Ceftriaxone (single Dose); Outcome Indicator: Treatment Success Rate

Author, Year	Age	Definition of outcome	Amox-clav Sample Size	Ceftriaxone Sample Size	Amox-clav Success Rate (%)	Ceftriaxone Success Rate (%)	Rate Difference In %	95% CI of Rate Difference In %
Bauchner, 1996[113]	3 mos-6 yrs	Success at day 14-16	271	267	89.7	81.3	8.4	2.5, 14.3
Varsano, 1997[110]	6 mos-8 yrs	Success at day 11	106	109	95.3	95.4	-0.1	-5.8, 5.5
Cohen, 1999[77]	4-30 mos	Success at day 12-14	228	235	48.2	49.4	-1.1	-10.2, 8.0
Wang, 2004[78]	3 mos-6 yrs	Success at day 10	32	41	78.1	75.6	2.5	-16.9, 22.0
Biner, 2007[71]	6 mos-10 yrs	Success at day 3	39	34	87.2	85.3	1.9	-14.0, 17.8
Random effects estimates			676	686	79.8	77.4	2.8	-1.6, 7.2
Test of heterogeneity Chi-square test value							5.19	
Test of heterogeneity Chi-square test p-value							0.27	
Test of heterogeneity I-squared							22.9%	
Test of publication bias, Egger's asymmetry test p-value							0.78	

Figure 7. Shrinkage Plot for Amoxicillin-clavulanate (7-10 days) vs. Ceftriaxone (single dose) for Treatment Success



The I^2 statistic for this analysis was 22.9%, indicating no evidence of heterogeneity. Egger's test did not yield evidence suggestive of publication bias (p=0.78).

The quality of evidence for this conclusion is moderate, meaning that further high quality research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Amoxicillin-Clavulanate (7-10 days) vs. Azithromycin (≤5 days)

Four new RCTs were identified that addressed this comparison.[7, 52, 70, 111] Five articles were identified in the 2001 report.[115-119]

The ages of the children in these trials ranged from 6 months to 12 years. Sample sizes ranged from 15 to 198 (total pooled sample was 875).The outcome assessed in these nine articles was treatment success rate at days 3-14. The definitions of treatment success varied (e.g., follow-up middle ear fluid culture negative or absent; complete resolution of signs or symptoms; bacteriologic cure; a score indicating absence of clinical and bacteriologic signs); however, we concluded that these studies were sufficiently clinically similar to justify pooling. The Jadad scores for the newer trials were 2, 5, 2, and 1 out of 5; the scores for the older trials were 1, 2, 2, 2, and 3 out of 5.

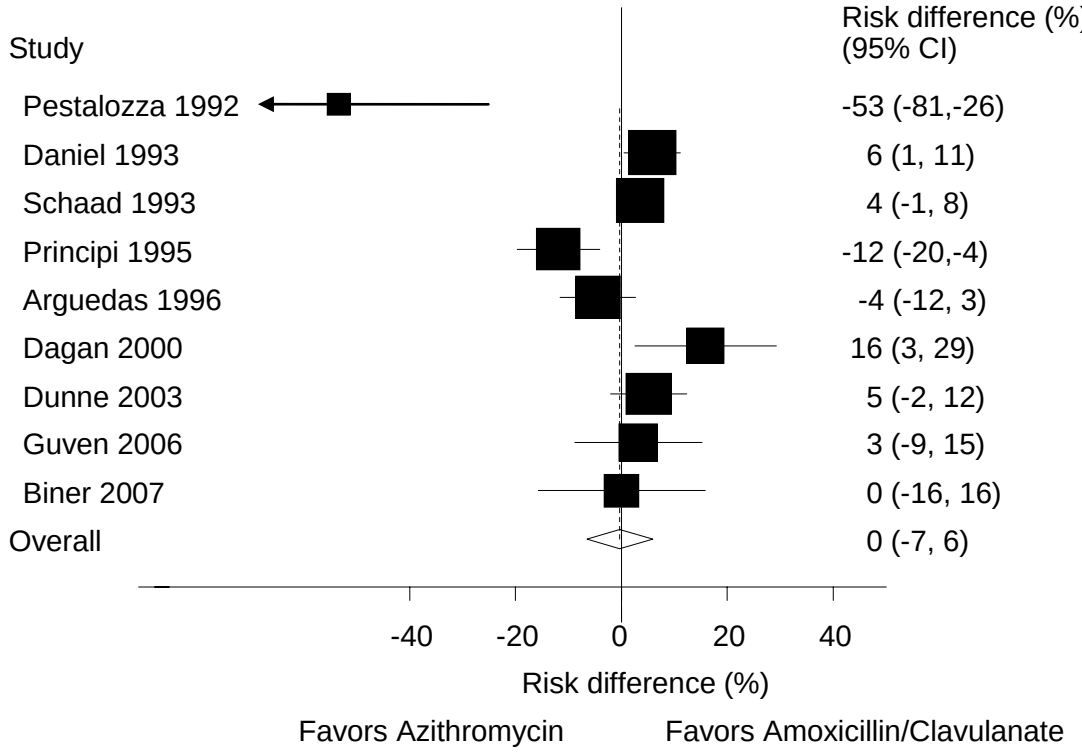
The random effects pooled rate difference for clinical success by day 14 between amoxicillin-clavulanate (7-10 days) and azithromycin (≤5 days) was estimated at -0.3% (95% CI: -7%, 6%) (Table 15, and Figure 8).Thus, the advantage of one antibiotic over the other or

their equivalence cannot be established based on the current evidence. It is worth noting that the magnitude of the 1992 Pestalozza study[115] result is an outlier compared to the results of the other eight studies. However, the only apparent difference is the small size of each treatment group, i.e., 15 each, compared with the other studies.

Table 15. Amoxicillin-Clavulanate (7-10 Days) vs. Azithromycin (≤5 Days); Outcome Indicator: Treatment Success Rate

Author, Year	Age	Definition of outcome	Amox-clav Sample Size	Azithromycin Sample Size	Amox-clav Success Rate (%)	Azithromycin Success Rate (%)	Rate Difference In %	95% CI of Rate Difference In %
Pestalozza, 1992[115]	11 mos-9 yrs	Success at day 12-14	15	15	40.0	93.3	-53.3	-81.2, -25.5
Daniel, 1993[116]	2-8 yrs	Success at day 10-12	54	103	100.0	94.2	5.8	0.5, 11.1
Schaad, 1993[117]	6 mos-10.2 yrs	Success at day 7-20	189	192	97.4	93.8	3.6	-0.5, 7.7
Principi, 1995[118]	6 mos-12 yrs	Success at day 10-14	198	215	73.2	85.1	-11.9	-19.7, -4.1
Arguedas, 1996[119]	6 mos-12 yrs	Success at day 10-11	45	47	95.6	100.0	-4.4	-11.6, 2.7
Dagan, 2000[7]	6 mos-9 yrs	Success at day 12-14	70	73	85.7	69.9	15.9	2.5, 29.2
Dunne, 2003[70]	6 mos-12 yrs	Success at day 10	181	185	87.8	82.7	5.1	-2.1, 12.4
Guven, 2006[52]	6 mos-12 yrs	Success at day 11-13	84	90	81.0	77.8	3.2	-8.8, 15.2
Biner, 2007[71]	6 mos-10 yrs	Success at day 3	39	31	87.2	87.1	0.1	-15.7, 15.9
Random effects estimates			875	951	86.1	86.4	-0.3	-6.5, 5.9
Test of heterogeneity Chi-square test value							39.8	
Test of heterogeneity Chi-square test p-value							<0.001	
Test of heterogeneity I-squared							79.9%	
Test of publication bias, Egger's asymmetry test p-value							0.28	

Figure 8. Shrinkage Plot for Amoxicillin-Clavulanate (7-10 days) vs. Azithromycin (≤5 days) for Treatment Success



The I^2 statistic for this analysis was 79.9%, indicating the presence of unexplained heterogeneity, which could be due to the differences in the population studied and/or research methods employed. Therefore, caution is advised in interpreting overall summary measures. Egger's test did not yield evidence suggestive of publication bias (p=0.28).

As a sensitivity analysis, we excluded the Pestalozza study (1992),[115] as it appeared to be an outlier. The pooled analysis with the remaining eight articles[52, 70, 71, 81, 116-119] yielded a rate difference of 2% (95% CI: -3%, 7%), so the advantage of one antibiotic over the other or their equivalence still cannot be established, confirming the primary analysis (Figure 9 and Table 16). Possible heterogeneity and publication bias were still present among the remaining eight articles (I^2=70.6%, Egger's test=0.85). Also, the two higher quality studies, Arguedas (1996) and Dunne (2003), both individually had insignificant results that could establish neither the advantage of one antibiotic over the other nor their equivalence.[70, 119] Amoxicillin-clavulanate was shown to have higher clinical success rates than azithromycin by day 14 when the pathogen was HF (RD =26%, 95% CI: 6, 46; NNT=4, 95% CI: 2, 17) in one study (Dagan, 2000).[7]

Figure 9. Shrinkage Plot for Amoxicillin-Clavulanate (7-10 days) vs, Azithromycin (≤ 5 days) for Treatment Success (Excluded Pestalozza 1992 Study)

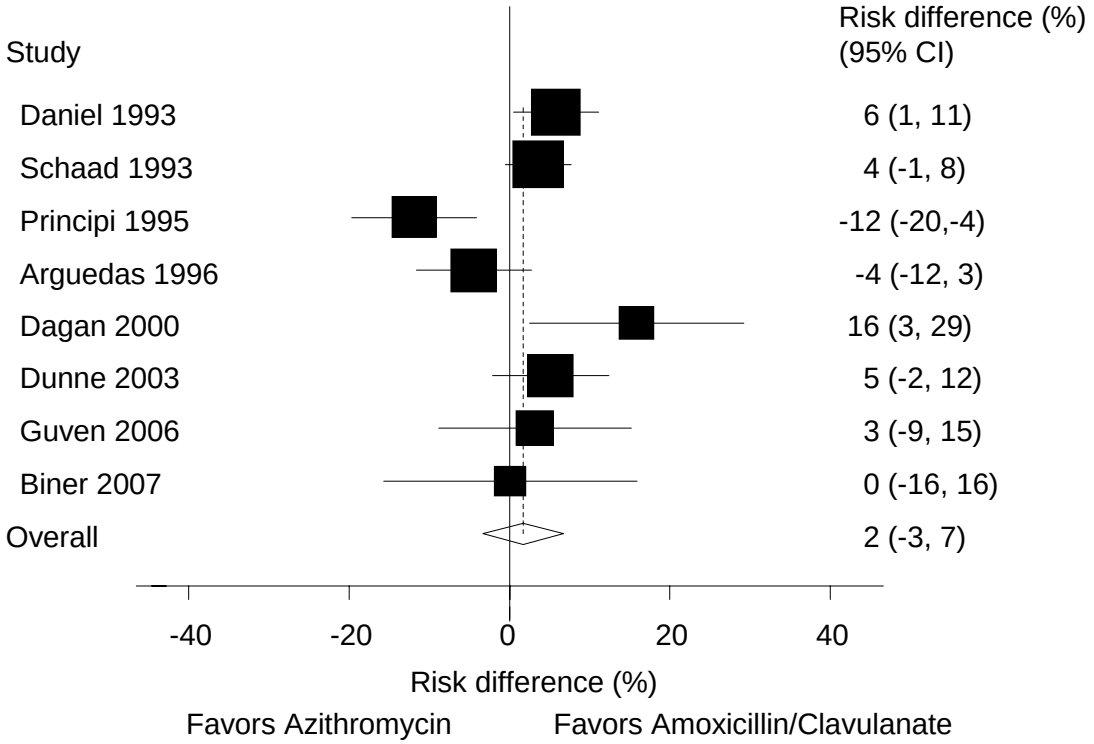


Table 16. Amoxicillin-Clavulanate (7-10 Days) vs. Azithromycin (≤5 Days); Outcome Indicator: Treatment Success Rate (Excluding Pestalozza 1992 Study)

Author, Year	Age	Definition of outcome	Amox-clav Sample Size	Azithromycin Sample Size	Amox-clav Success Rate (%)	Azithromycin Success Rate (%)	Rate Difference In %	95% CI of Rate Difference In %
Daniel, 1993[116]	2-8 yrs	Success at day 10-12	54	103	100.0	94.2	5.8	0.5, 11.1
Schaad, 1993[117]	6 mos-10.2 yrs	Success at day 7-20	189	192	97.4	93.8	3.6	-0.5, 7.7
Principi, 1995[118]	6 mos-12 yrs	Success at day 10-14	198	215	73.2	85.1	-11.9	-19.7, -4.1
Arguedas, 1996[119]	6 mos-12 yrs	Success at day 10-11	45	47	95.6	100.0	-4.4	-11.6, 2.7
Dagan, 2000[7]	6 mos-9 yrs	Success at day 12-14	70	73	85.7	69.9	15.9	2.5, 29.2
Dunne, 2003[70]	6 mos-12 yrs	Success at day 10	181	185	87.8	82.7	5.1	-2.1, 12.4
Guven, 2006[52]	6 mos-12 yrs	Success at day 11-13	84	90	81.0	77.8	3.2	-8.8, 15.2
Biner, 2007[71]	6 mos-10 yrs	Success at day 3	39	31	87.2	87.1	0.1	-15.7, 15.9
Random effects estimates			860	936	86.9	86.3	1.7	-3.3, 6.7
Test of heterogeneity Chi-square test value							23.8	
Test of heterogeneity Chi-square test p-value							<0.001	
Test of heterogeneity I-squared							70.6%	
Test of publication bias, Egger's asymmetry test p-value							0.85	

The quality of evidence for this conclusion is moderate due to heterogeneity in the results of studies, meaning that further high quality research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Cefaclor vs. Azithromycin

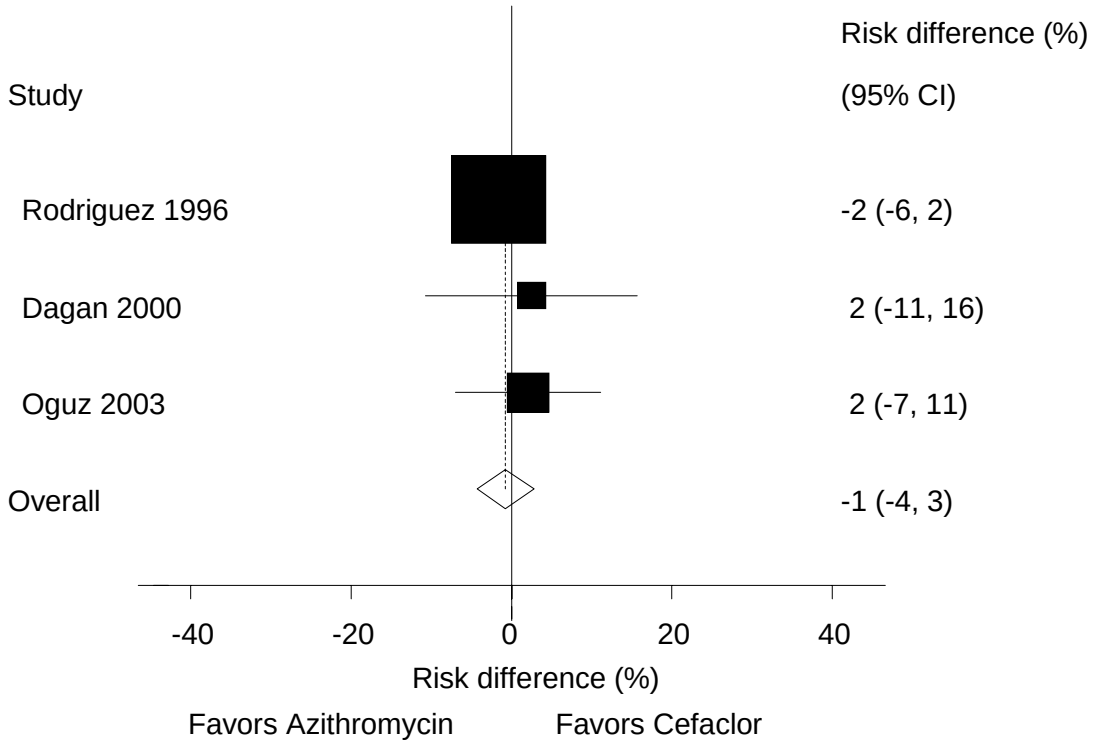
Two new RCTs were identified that addressed this comparison.[81, 82] The 2001 report identified only one article.[120]

The ages of the children included in these trials ranged from 6 months to 13 years. Sample size ranged from 33 to 120. The outcome assessed in these three articles was treatment success rate at days 10-14; the definition of treatment success varied among the studies (bacteriologic cure; a composite score; complete resolution of all clinical and otoscopic findings; disappearance or improvement in signs and symptoms). However, we concluded that the definitions were sufficiently clinically similar to justify pooling. The Jadad quality score for the article in the 2001 report was 2 out of 5 and those of the two newer articles were 2 and 3. The random effects pooled rate difference for clinical success by day 14 between cefaclor and azithromycin was estimated at -0.7% (95% CI: -4%, 3%) (Table 17, and Figure 10).Thus, the two drugs are equivalent in efficacy. Amoxicillin-clavulanate was shown to have higher clinical success rates than cefaclor by day 34 (RD =26%, 95% CI: 6, 46; NNT=4, 95% CI: 2, 17) in one study (Subba Rao, 1998).[5]

Table 17. Cefaclor vs. Azithromycin; Outcome Indicator: Treatment Success Rate

Author, Year	Age	Definition of outcome	Cefaclor Sample Size	Azithromycin Sample Size	Cefaclor Success Rate (%)	Azithromycin Success Rate (%)	Rate Difference In %	95% CI of Rate Difference In %
Rodriguez, 1996[120]	6 mos-13 yrs	Success at day 10-14	120	114	96.7	98.2	-1.6	-5.6, 2.4
Dagan, 2000[81]	6 mos-9 yrs	Success at day 10	59	62	84.7	82.3	2.5	-10.7, 15.7
Oguz, 2003[82]	6 mos-10 yrs	Success at day 10	33	39	97.0	94.9	2.1	-7.0, 11.2
Random effects estimates			212	215	94.0	93.0	-0.7	-4.3, 2.8
Test of heterogeneity Chi-square test value							1.03	
Test of heterogeneity Chi-square test p-value							0.60	
Test of heterogeneity I-squared							0.0%	
Test of publication bias, Egger's asymmetry test p-value							0.18	

Figure 10. Shrinkage Plot for Cefaclor vs. Azithromycin for Treatment Success



The I^2 statistic for this analysis was 0.0%, indicating the absence of unexplained heterogeneity. Egger's test did not yield evidence suggestive of publication bias (p=0.18).

The quality of evidence for this conclusion is considered high, meaning further high quality research is very unlikely to change our confidence in the estimate of effect.

Antibiotics vs. Wait-and-See/Prescription to Hold

One relevant meta-analysis was identified that compared the use of any antibiotics to that of the wait-and-see approach or the similar approach of prescribing antibiotics if needed. A meta-analysis by Spurling (2007) identified three studies that compared delayed vs. immediate antibiotic therapy.[2, 93, 94] Two new RCTs were identified that addressed these comparisons as well.[3, 87]

Two studies looked at the wait-and-see approach[3, 87], and two looked at the prescription-to-hold approach.[2, 93, 94] In all four studies, the majority of patients in the immediate antibiotic group complied with use of the prescribed antibiotic (range of 83% to 99%), and many of those in the wait-and-see and prescription-to-hold groups ultimately used prescribed antibiotics, as well (range of 1% to 38%).[3, 87]

Of the four studies in this comparison, one study compared amoxicillin to the wait-and-see approach[3] and another compared amoxicillin to the prescription-to-hold approach.[2] The McCormick (2005) article reported a 15% rate difference (95% CI: 6%, 23%; NNT=7, 95% CI: 4, 17), favoring amoxicillin compared to wait-and-see for success rate at day 12 as perceived by the parent. The Little (2001) article reported a 16% rate difference (95% CI: 6%, 26%; NNT=6, 95% CI: 4, 17), also favoring amoxicillin compared to prescription-to-hold for success at day 3 as perceived by the parent. We conclude that in both studies, immediate amoxicillin therapy has a higher success rate than the "no immediate treatment" approaches, even though 34% in the McCormick (2005) and 24% in the Little (2001) wait-and-see and prescription-to-hold groups, respectively were on antibiotics later in the course of the disease. (Table 18)

The Little (2006)[93] article reported the long-term outcomes (3-month and 1-year) on the same groups of patients whose short-term outcomes were reported in their 2001 article.[2] The Spiro (2006) article reported the difference between the antibiotic and prescription-to-hold approaches (91% of the prescription-to-hold group and 93% of the standard prescription group received prescriptions for amoxicillin; the remainder received prescriptions for other antibiotics) on health services utilization (filling prescriptions on day 4-6) as the primary outcome measure and presence of otalgia and fever at day 4-6 and 11-14 as the secondary outcomes.[94]The Neumark 2007 article compared phenoxymethylpenicillin with the wait-and-see approach. The findings from these three studies are reported in Table 22.[87]

It can be observed from the 95% confidence intervals of these outcome measures that no conclusion can be established with respect to the effectiveness of either treatment option in the pairs in terms of success rates. Although, the Spiro 2006 article established that those given prescriptions for immediate antibiotics filled the prescription more often than those who were given prescriptions "to hold," no differences were seen in absence of otalgia or fever between groups at either follow-up point.[94]

The quality of evidence for these conclusions is moderate, meaning that further high quality research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Table 18. Antibiotics vs. Wait-and-See/Prescription Hold Wait-and-See (WAS)

Author, Year	Outcome	Tx 1	Tx 2	Tx 1 Sample Size	Tx 2 Sample Size	Tx12 % on antibiotic	Tx22 % on antibiotic	Tx 1 Outcome Rate (%)	Tx 2 Outcome Rate (%)	% RD (95% CI)	NNT (95% CI)
McCormick, 2005[3]	Success day 12	amx	WAS	107	107	83	34	95	80	15 (6, 24)	7 (4, 17)
"	Cure Before day 30	"	"	109	100	"	"	77	66	11 (-1, 23)	n/a
"	AOM extra office visit	"	"	111	108	"	"	13	20	-7 (-17, 3)	n/a
"	AOM ED visit	"	"	111	108	"	"	1	4	-3 (-7, 1)	n/a
"	AOM extra phone call	"	"	111	108	"	"	23	24	-1 (-12, 10)	n/a
"	Parent missed school/work	"	"	111	108	"	"	14	9	5 (-3.5, 14)	n/a
Neumark, 2007[87]	Success day 14	PcV	WAS	87	82	83	1	82	85	-4 (-15, 7)	n/a
"	Pain Day 3-7	"	"	76	87	"	"	2	5	-3 (-9, 3)	n/a
"	Analgesic use Day 3-7	"	"	76	87	"	"	3	10	-7 (-15, 1)	n/a
"	Fever>38oC Day 3-7	"	"	76	87	"	"	3	6	-3 (-9, 3)	n/a
"	Success 3 months	"	"	86	75	"	"	85	84	1 (-10, 12)	n/a
"	Perforation 3 months	"	"	86	75	"	"	0	0	0	n/a
"	Serous OM 3 months	"	"	86	75	"	"	12	11	1 (-9,11)	n/a
"	Work Loss	"	"	76	87	"	"	56	53	3 (-12, 18)	n/a

Prescription Hold (PH)Author, Year	Outcome	Tx 1	Tx 2	Tx 1 Sample Size	Tx 2 Sample Size	Tx12 % on antibiotic	Tx22 % on antibiotic	Tx 1 Outcome Rate (%)	Tx 2 Outcome Rate (%)	% RD (95% CI)	NNT (95% CI)
Little, 2001, 2006[2, 93]	Success day 3	Amx	PH	135	150	99	24	86	70	RD 16 (6, 26)	6 (4, 17)
"	Parent belief ab effective	"	"	131	140	"	"	76	46	RD 31 (19, 42)	3 (2, 5)
"	Parent satisfied with treatment	"	"	131	150	"	"	94	77	RD 17 (9, 31)	6 (4, 11)
"	Parent likely to consult MD in future	"	"	132	147	"	"	83	63	RD 20 (9, 31)	5 (3, 11)
"	Earache 3 months	"	"	Not reported	Not reported	"	"	Not reported	Not reported	OR 0.89 (0.5, 1.7)	n/a
"	Earache 1 year	"	"	Not reported	Not reported	"	"	Not reported	Not reported	OR 1.03 (0.6, 1.8)	n/a
Spiro, 2006[94]	Did not fill prescription Day 4-6	Ab	PH	133	132	87	38	13	62	RD -49 (-59, -37)	2 (2, 3)
"	No analgesic Day 4-6	"	"	"	"	"	"	90	93	RD -3 (-10, 4)	n/a
"	No MD visit Day 4-6	"	"	"	"	"	"	92	90	RD 2 (-5, 9)	n/a
"	Otalgia Day 4-6	"	"	"	"	"	"	67	64	RD 3 (-8, 14)	n/a
"	Fever Day 4-6	"	"	"	"	"	"	35	32	RD 3 (-8, 14)	n/a
"	No Analgesic Day 11-14	"	"	123	124	"	"	11	5	RD 6 (-18, 6)	n/a
"	No MD visit Day 11-14	"	"	"	"	"	"	89	85	RD 4 (-4, 12)	n/a
"	Otalgia Day 11-14	"	"	"	"	"	"	61	67	RD -6 (-18, 6)	n/a
"	Fever Day 11-14	"	"	"	"	"	"	31	32	RD -1 (-13, 11)	n/a

Abbreviations: amx=amoxicillin; PcV=phenoxymethylpenicillin; NNT=number-to-treat; OR=odds ratio; RD=rate difference; Tx=treatment

[2] Estimates of patients in a treatment group on antibiotic are either directly from the study articles or based on information from the study articles for the treatment groups as a whole and not for the subgroup analyses within each study.

Other Meta-Analyses

Short duration vs. long duration antibiotic therapy. Kozyrskyj (2000) reported that five days of antibiotics were as effective as 10 days of treatment for uncomplicated AOM based on signs and symptoms, relapse, or re-infection, with a risk difference of 6% (95% CI: 2%, 10%) at 8 to 19 days, favoring 10 days treatment with a NNT of 17 children (95% CI: 10, 50) and a risk difference of 3% (95% CI: -0.3%, 6%) at 30 days.[53]

Amoxicillin or amoxicillin-clavulanate once or twice daily vs. three times daily. Thanaviratananich (2008) reported that the available evidence was biased, so no definitive conclusions could be drawn.[59]

Topical analgesia. A review by Foxlee (2006) concluded that the existing evidence was insufficient to make definitive conclusions on the effectiveness of topical analgesia.[55]

Decongestant and/or antihistamine treatment. Coleman (2008) reported that despite a slight benefit of combined decongestant-antihistamine at two weeks of persistent AOM with a fixed relative risk of 0.76 (95% CI: 0.60, 0.96; NNT=10, 95% CI: 8, 13), decongestants and /or antihistamines were not beneficial in general and specifically not for early cure rates, symptom resolution, prevention of surgery, or other complications, and resulted in an increased risk of other side effects (odds ratio 5 [95% CI: 2,14]).[58]

Summary

We identified 63 comparisons of treatment options for uncomplicated AOM that encompassed different antibiotics and regimens. Our analyses yielded inconclusive results for many of these comparisons. For 12 comparisons, we reached stronger conclusions (Table 19). Meta-analyses of ampicillin or amoxicillin vs. placebo (Table 9) demonstrated higher clinical success rates for ampicillin or amoxicillin, with nine children needing to be treated for a clinical success. Little (2001) and McCormick (2005) individually demonstrated higher clinical success rates as perceived by the parent for amoxicillin than for prescription-to-hold at day 3 and wait-and-see at day 12 options, respectively; however, these results are tempered by Spiro's comparison of immediate antibiotic therapy to the prescription-to-hold option (2006) and Neumark's comparison of immediate antibiotic therapy to the wait-and-see option (2007), which had inconclusive results. Meta-analysis of three studies demonstrated equivalence of clinical success rates between cefaclor and azithromycin in treatment of uncomplicated AOM (Table 17). In addition, single studies of comparisons (that could not be pooled) produced strong results. Amoxicillin-clavulanate was shown to have higher clinical success rates than azithromycin by day 14 when the pathogen was HF in one study (Dagan, 2000) and higher success rates than cefaclor by day 34 in another study (Subba Rao, 1998).[5, 7] Equivalent clinical success rates were also demonstrated in individual studies of amoxicillin vs. azithromycin for one of many outcomes assessed (Morris, 2010)[67], amoxicillin vs. erythromycin (Scholz, 1998)[4], amoxicillin-clavulanate vs. amoxicillin-sulbactam (Casellas, 2005), cefixime vs. ampicillin or amoxicillin (Table 36 in Marcy, 2001),cefaclor 50 mg/kg/day vs. 40 mg/kg/day (Catania, 2004), and amoxicillin-clavulanate 45/64/mg/kg/day divided into two daily doses vs. 40/10/mg/kg/day divided into three daily doses.[88] In addition, individual studies of amoxicillin-clavulanate

>60mg/kg/d vs. amoxicillin-clavulanate 40mg/kg/d and high-dose amoxicillin bid vs. lower-dose amoxicillin tid that in the 2001 report were assessed as demonstrating equivalent clinical success rates are now assessed as inconclusive utilizing an MCID of 5%.Each of these single study results requires replication before strong conclusions can be reached.

Table 19. Treatment Comparisons with Conclusive Evidence in Any Clinical Success Outcome in Uncomplicated Otitis Media

Article	Treatment 1		Rate for Treatment 1	Rate for Treatment 2	Rate Difference (95% CI)	Conclusion
7 studies Table 9	Ampicillin/ Amoxicillin	Placebo	69.0% (681/987)	53.1% (569/1071)	12% (5, 18)	**Amp/Amox better (success day 2-14)**
3 studies Table 17	Cefaclor	Azithromycin	93.4% (198/212)	93.0% (200/215)	-0.7% (-4.3, 2.8)	**Equivalence (success day 10-14)**
4 Studies Table 36 in Marcy (2001)	Cefixime	Ampicillin/Amoxicillin	90.0% (245/274)	91.1% (240/265)	0.1% (-3.9, 4.2)	**Equivalence** (success at day 10-15)
Casellas 2005[69]	Amoxicillin-clavulanate 80 mg/kg/day = bid for 10 days	Amoxicillin Sulbactam 80 mg/kg/day = bid for 10 days	98.3% (115/117)	98.3% (115/117)	0% (-3.3, 3.3)	**Equivalent** (success day 12-14)
Catania, 2004[99]	Cefaclor 50 mg/kg/day = bid for 5 days	Cefaclor 40 mg/kg/day = bid for 10 days	95.5% (195/204)	94.8% (195/206)	0.7% (-3.5, 4.9)	**Equivalent** (cured end of therapy)
Dagan, 2000[7]	Amoxicillin-clavulanate 45/6.4 mg/kg/day / bid for 10 days	Azithromycin 10 mg/kg/day = qd for 1 day, --- 5 mg/kg/day = qd for 4 days	90.9% (30/33)	64.7% (22/34)	26% (6, 36)	**Amox-clav better** (success day 12-14 when pathogen is H. Influ).

Article	Treatment 1		Rate for Treatment 1	Rate for Treatment 2	Rate Difference (95% CI)	Conclusion
Damrikarnlert, 2000[6]	Amoxicillin-clavulanate 45/64 mg/kg/day / bid for 7-10 days	Amoxicillin-clavulanate 40/10 mg/kg/day / tid for 7-10 days	94.0% (187/199)	94.1% (175/186)	0.1% (-4.8, 4.6)	**Equivalent (**success day 7-12)
Little, 2001[2]	Amoxicillin tid for 7 days	Prescription to Hold	85.9% (116/135)	70.0% (105/150)	16% (6, 26)	**Amox better** (success day 3)
McCormick, 2005[3]	Amoxicillin 90 mg/kg/day / bid for 10 days	Wait and see	95.3% (102/107)	80.4% (86/107)	15% (6, 24)	**Amox better** (success day 0-12)
Morris, 2010[67]	Amoxicillin 50 mg/kg/day / bid for 7 days	Azithromycin 30mg/kg as a single dose	99% (155/156)	98% (144/147)	1% (-1, 4)	**Equivalence** (no new pain between day 6-11)
Scholz, 1998[4]	Amoxicillin 50 mg/kg/day / bid for 10 days	Erythromycin 40 mg/kg/day / bid for 10 days	97.8% (136/139)	97.2% (137/141)	0.6% (-3, 4)	**Equivalence** (free of recurrence day 31-40)
Subba Rao, 1998[5]	Amoxicillin-clavulanate 250 mg for > 6 y = tid for 7 days, --- 125 mg for < 6 y = tid for 7 days	Cefaclor 125 or 250 mg = tid for 7 days	97.1% (102/105)	83.9% (94/112)	13% (5.3, 21)	**Amox-clav better** (success day 28-34)

Key Question IV.

What Is the Comparative Effectiveness of Different Management Options for Recurrent Otitis Media (Uncomplicated) and Persistent Otitis Media or Relapse of Acute Otitis Media?

Description of the Studies

This question was not addressed in the 2001 AOM report. Thus, in order to address this study question, we employed several strategies. We began by identifying articles from our searches on uncomplicated AOM (Key Question III) that dealt with recurrent, persistent, or relapsing AOM. Of the 62 RCTs identified in our review update that addressed the effectiveness of treatment options, 14 compared treatment options in children with ROM, persistent AOM, or AOM treatment failure. Among these studies are 21 treatment comparisons. Eight studied the treatment of AOM in children with presumed or explicitly defined recurrent and/or persistent AOM, and/or AOM with treatment failure. Thirteen studied the prevention of AOM in children with ROM. The 21 comparisons are listed in Tables 20 and 21 together with a description of the characteristics of the study populations and interventions and the main findings. Findings by patient subgroups are reported in the findings for Key Question V.

Also identified were seven systematic reviews that addressed the question of prevention of recurrent AOM. We present the results of these reviews below.

In addition to the literature search described for Key Question III, we also conducted a search of the literature from 1966 to the present using the strategy described in Appendix A. This search identified some 1400 titles. A screen of a sample of these titles revealed very few actually relevant to the topic. We therefore did not pursue this search strategy, which would have added mostly older (pre-2001) articles.

Table 20. Summary of Findings from Eight Studies on Effectiveness of Treatment of Acute Otitis Media in Recurrent Otitis Media or Persistent Acute Otitis Media

Comp #	Comparison	Author, Year	Patient Population	Intervention	Findings	Conclusion
1	Amoxicillin-clavulanate (Amox-clav) vs. gatifloxacin	Saez-Llorens, 2005[121]	0.5-7 years ROM and/or AOM treatment failure[a] 20 sites non-US	Amox-clav (45mg/6.4mg/kg/d in 2 divided doses) Gatifloxacin (10mg/kg, qd)	Success rate on day 3-10: Amox-clav: 84% (102/121) Gatifloxacin: 90% (222/246) Mean difference (95% CI): -5.9% (-12.9%, 1.1%)	Not enough evidence to conclude
2	Amox-clav vs. gatifloxacin	Sher, 2005[122]	0.5-7 years ROM and/or AOM treatment failure[a] 26 sites in US 1 site in Costa Rica	Amox-clav (90mg/6.4mg/kg/d in 2 doses), 10d Gatifloxacin (10mg/kg, qd) 10d	Success rate on day 10: Amox-clav: 79% (92/117) Gatifloxacin: 85% (105/124) Mean difference (95% CI): -6.1% (-15.9%, 3.7%)	Not enough evidence to conclude
3	Amox-clav vs. levofloxacin	Noel, 2008[123]	0.5-<5 years ROM and/or persistent AOM[b] 66 centers in 6 countries, including US	Amox-clav (45mg/kg bid, 10d) Levofloxacin (10mg/kg bid, 10d)	Success rate on day 2-5: Amox-clav: 91% Levofloxacin: 94% Mean difference (95% CI): -3.2% (-6.2%, -0.2%)	Not enough evidence to conclude
4	Amox-clav vs. azithromycin	Arrieta, 2003[124]	0.5-6 years ROM and/or persistent AOM[b] 13 US and 5 Latin American centers	Amox-clav (95mg/kg, bid, 10d) Azithromycin (20mg/kg, qd, 3d)	Success rate on day 12-16: Amox-clav: 84% (122/145) Azithromycin: 86% (128/149) Mean difference (95% CI): -1.8% (-10.0%, 6.4%)	Not enough evidence to conclude
5	Amox-clav vs. ciprofloxacin 0.3%-dexamethasone 0.1% (cipro-dex) otic drops	Dohar, 2006[80]	0.5-12 years with tympanostomy tubes 6 sites in US	Amox-clav (90mg/kg/d, bid, 10d) cipro-dex (4 drops, bid, 7d)	Success rate on day 18-21: Amox-clav: 58.5% (24/41) Cipro-dex: 84.6% (33/39) Mean difference (95% CI): -26% (-46%, -6%)	Cipro-dex higher success rate than amox-clav

Comp #	Comparison	Author, Year	Patient Population	Intervention	Findings	Conclusion
6	Cefaclor vs. cefuroxime	Turik, 1998[125]	3months-12 years AOM treatment failure 13 sites	Cefaclor (40mg/kg/d, bid, 10d) Cefuroxime (40mg/kg/d, bid, 10d)	Success rate on day 10: Cefaclor: 93.6% (73/78) Cefuroxime: 92.9% (65/70) Mean difference (95% CI): 0.7% (-7%, 9%) Success rate on day 20-26: Cefaclor: 85.9% (67/78) Cefuroxime: 87.1% (61/70) Mean difference (95% CI): -1.2% (-12%, 10%)	Not enough evidence to conclude
7	Cipro 0.3% otic drops vs. Cipro 0.3%-dex 0.1% otic drops	Roland, 2003[126]	0.5-12 years with tympanostomy tubes 18 sites in US	Cipro (3 drops, bid, 7d) Cipro-dex (3 drops, bid, 7d)	Success rate on day 8: Cipro: 91.2% (73/80) Cipro-dex: 94.2% (82/87) Mean difference (95% CI): -3% (-11%,4.9%) Success rate on day 14: Cipro: 93.8% (75/80) Cipro-dex: 98.9% (86/87) Mean difference (95% CI): -5% (-11%,0.5%)	Not enough evidence to conclude

Comp #	Comparison	Author, Year	Patient Population	Intervention	Findings	Conclusion
8	Cipro 0.3%-dex 0.1% otic drops vs. ofloxacin 0.3% otic drops	Roland, 2004[127]	0.5-12 years with tympanostomy tubes 39 sites in US	Cipro-dex (4 drops, bid, 7d) Ofloxacin (5 drops, bid, 10d)	Success rate on day 18-21: Cipro-dex: 90% (162/180) Ofloxacin: 78.2% (133/170) Mean difference (95% CI): 12% (4.2%, 19%) Success rate on day 3: Cipro-dex: 93.7% (194/207) Ofloxacin: 79.6% (172/216) Mean difference (95% CI): 14% (7.6%, 21%) Success rate on day 11: Cipro-dex: 96.1% (199/207) Ofloxacin: 89.8% (194/216) Mean difference (95% CI): 6% (1.4%, 11%) Success rate on day 18: Cipro-dex: 93.7% (194/207) Ofloxacin: 88.4% (191/216) Mean difference (95% CI): 5% (-0.2%, 11%) Otorrhea absence on day 3: Cipro-dex: 32.2% (62/207) Ofloxacin: 18.5% (40/216) Mean difference (95% CI): 14% (5.4%, 22%) Otorrhea absence on day 11: Cipro-dex: 84.6% (176/207) Ofloxacin: 63.4% (137/216) Mean difference (95% CI): 21% (13%, 30%) Otorrhea absence day 18: Cipro-dex: 85.0% (176/206) Ofloxacin: 70.8% (153/216) Mean difference (95% CI): 14% (6%, 22%)	Cipro-dex higher success rate than ofloxacin at day 3 & not enough evidence to conclude for days 11, 18, and 18-21; Cipro-dex higher otorrhea absence days 3, 11, and 18

[a] AOM Treatment Failure: infection within 14 days of last antibiotic dose or failure to improve after 48 hours
[b] Persistent AOM: signs or symptoms of AOM after 48 hours of treatment

Table 21. Summary of Findings from Seven Articles on Effectiveness of Prevention of Acute Otitis Media in Recurrent Otitis Media

Comp #	Comparison	Author, Year	Patient Population	Intervention	Findings	Conclusion
1	Amoxicillin vs. azithromycin	De Diego, 2001[128]	9-120 months 1 institution in Spain	Amoxicillin (20mg/kg/d, 3mos) Azithromycin (10mg/kg/wk, 3mos)	Effective rate (#AOM episodes dropped to <50% after prophylaxis) in 6-27 months: Amoxicillin: 89% (34/38) Azithromycin: 81% (25/31) Mean difference (95% CI): 8.9% (-7.8%, 25.6%)	Not enough evidence to conclude
2	Amoxicillin vs. sulfisoxazole	Teele, 2000[129]	0-1 year 2 sites in US	Amoxicillin (20mg/kg/d) Sulfisoxazole (50mg/kg/d)	Success rate (none or 1 AOM episode in 6 months Amoxicillin: 90% (36/40) Sulfisoxazole: 78% (28/36) Mean difference (95% CI): 12.2% (-4.2%, 28.6%) Success rate (none or 1 AOM episode in 1 year Amoxicillin: 68% (27/40) Sulfisoxazole: 64% (23/36) Mean difference (95% CI): 3.6% (-17.8%, 25.0%)	Not enough evidence to conclude
3	Amoxicillin vs. placebo	Teele, 2000[129]	0-1 year 2 sites in US	Amoxicillin (20mg/kg/d) Placebo	Success rate (none or 1 AOM episode in 6 months Amoxicillin: 90% (36/40) Placebo: 71% (29/41) Mean difference (95% CI): 19.3% (2%, 36.6%) Success rate (none or 1 AOM episode in 1 year Amoxicillin: 68% (27/40) Placebo: 66% (27/41) Mean difference (95% CI): 1.7% (-18.9%, 22.2%)	Not enough evidence to conclude

Comp #	Comparison	Author, Year	Patient Population	Intervention	Findings	Conclusion
4	Sulfisoxazole vs. placebo	Teele, 2000[129]	0-1 year 2 sites in US	Sulfisoxazole (50mg/kg/d) Placebo	Success rate (none or 1 AOM episode in 6 months Sulfisoxazole: 78% (28/36) Placebo: 71% (29/41) Mean difference (95% CI): 7.1% (-12.5%, 26.7%) Success rate (none or 1 AOM episode in 1 year Sulfisoxazole: 64% (23/36) Placebo: 66% (27/41) Mean difference (95% CI): -1.9% (-23.3%, 19.5%)	Not enough evidence to conclude
5	Sulfafurazole vs. placebo	Koivunen, 2004[130]	10mos-2yrs 1 hosp in Finland	Sulfafurazole (50mg/kg, qd, 6mos) Placebo	Success rate (<=1 in 2 months or <=2 in 6 months of AOM or <2 months of MEE) at 6 months Sulfafurazole: 63% (29/46) Placebo: 45% (21/47) Mean difference (95% CI): 18.3% (-2.0%, 38.6%) Success rate (<=1 in 2 months or <=2 in 6 months of AOM or <2 months of MEE) at 2 years Sulfafurazole: 34% (14/41) Placebo: 22% (10/45) Mean difference (95% CI): 11.9% (-7.1%, 30.9%)	Not enough evidence to conclude

Comp #	Comparison	Author, Year	Patient Population	Intervention	Findings	Conclusion
6	Sulfafurazole vs. adenoidectomy	Koivunen, 2004[130]	10mos-2yrs 1 hosp in Finland	Sulfafurazole (50mg/kg, qd, 6mos) Adenoidectomy	Success rate (<=1 in 2 months or <=2 in 6 months of AOM or <2 months of MEE) at 6 months Sulfafurazole: 63% (29/46) Adenoidectomy: 58% (34/59) Mean difference (95% CI): 5.4% (-13.5%, 24.3%) Success rate (<=1 in 2 months or <=2 in 6 months of AOM or <2 months of MEE) at 2 years Sulfafurazole: 34% (14/41) Adenoidectomy: 28% (16/58) Mean difference (95% CI): 6.5% (-11.9%, 24.9%)	Not enough evidence to conclude
7	Adenoidectomy vs. placebo	Koivunen, 2004[130]	10mos-2yrs 1 hosp in Finland	Adenoidectomy Placebo	Success rate (<=1 in 2 months or <=2 in 6 months of AOM or <2 months of MEE) at 6 months Adenoidectomy: 58% (34/59) Placebo: 45% (21/47) Mean difference (95% CI): 12.9% (-6.2%, 32.0%) Success rate (<=1 in 2 months or <=2 in 6 months of AOM or <2 months of MEE) at 2 years Adenoidectomy: 28% (16/58) Placebo: 22% (10/45) Mean difference (95% CI): 5.4% (-11.5%, 22.3%)	Not enough evidence to conclude

Comp #	Comparison	Author, Year	Patient Population	Intervention	Findings	Conclusion
8	Adenoidectomy vs. placebo	Paradise, 1999[26]	3-15yrs 1 hosp in US	Adenoidectomy Placebo	Success rate (% with no AOM episode) in 1 year in patients with no tonsil-related indications: Adenoidectomy: 31% (19/61) Placebo: 22% (17/79) Mean difference (95% CI): 9.6% (-5.0%, 24.2%) Success rate (% with<=1 AOM episode) in 1 year in patients with no tonsil-related indications: Adenoidectomy: 48% (29/61) Placebo: 51% (40/79) Mean difference (95% CI): -3.1% (-19.8%, 13.6%)	Not enough evidence to conclude
9	Adenoidectomy vs. adenotonsillectomy	Paradise, 1999[26]	3-15yrs 1 hosp in US	Adenoidectomy Adenotonsillectomy	Success rate (% with no AOM episode) in 1 year in patients with no tonsil-related indications: Adenoidectomy: 31% (19/61) Adenotonsillectomy: 37% (26/71) Mean difference (95% CI): -5.5% (-21.7%, 10.7%) Success rate (% with<=1 AOM episode) in 1 year in patients with no tonsil-related indications: Adenoidectomy: 48% (29/61) Adenotonsillectomy: 59% (42/71) Mean difference (95% CI): -11.7% (-28.7%, 5.4%)	Not enough evidence to conclude

Comp #	Comparison	Author, Year	Patient Population	Intervention	Findings	Conclusion
10	Adenotonsillectomy vs. placebo	Paradise, 1999[26]	3-15yrs 1 hosp in US	Adenotonsillectomy Placebo	Success rate (% with no AOM episode) in 1 year in patients with no tonsil-related indications: Adenotonsillectomy: 37% (26/71) Placebo: 22% (17/79) Mean difference (95% CI): 15.1% (0.6%, 29.6%) Success rate (% with<=1 AOM episode) in 1 year in patients with no tonsil-related indications: Adenotonsillectomy : 59% (42/71) Placebo: 51% (40/79) Mean difference (95% CI): 8.6% (-7.4%, 24.6%)	Not enough evidence to conclude
11	Ceftibuten 5d vs. Ceftibuten 10d	Roos, 2000[131]	0.5-8yrs 6 centers in Sweden	Ceftibuten 5d (9mg/kg/d) Ceftibuten 10d (9mg/kg/d)	Success rate (no recurrence after treatment) up to day 14 from start of treatment: Ceftibuten 5d: 79% (70/89) Ceftibuten 10d: 96% (85/89) Mean difference (95% CI): -17% (-27%, -7%) Success rate (no recurrence after treatment) up to day 40 from start of treatment: Ceftibuten 5d: 65% (58/89) Ceftibuten 10d: 70% (62/89) Mean difference (95% CI): -5.0% (-18.8%, 8.8%)	Ceftibuten 10d had a higher short-term success rate than Ceftibuten 5d but there is not enough evidence to conclude for success rate on day 40.

Comp #	Comparison	Author, Year	Patient Population	Intervention	Findings	Conclusion
12	Probiotics vs. placebo	Hatakka, 2007[91]	10mo-6yrs Helsinki, Finland	One probiotic capsule (Lactobacillus rhamnosus GG and LC705, Bifidobacterium breve 99 and propionibacterium freudenreichii JS) qd for 6mos Placebo, qd for 6mos	Success rate (% with no AOM) during 6-month intervention Probiotic: 28% (38/135) Placebo: 35% (47/134) Mean difference (95% CI): -7% (-18%, 4%) Success rate (%<3 AOM) during 6-month intervention Probiotic: 82% (111/135) Placebo: 83% (111/134) Mean difference (95% CI): -1% (-10%, 8%)	Not enough evidence to conclude
13	Adenoidectomy and tympanostomy vs. Tympanostomy only	Hammaren-Malmi, 2005[132]	1-2yrs Helsinki, Finland	Adenoidectomy + tympanostomy Tympanostomy only	Mean±SD (n) number of otitis media episodes during 1-year follow-up Adeno+Tympan: 1.9 ± 1.9 (74) Tympan only: 1.6 ± 1.6 (72) Difference of mean (95% CI): 0.30 (-0.28, 0.88)	Not enough evidence to conclude
14	Propolis and zinc vs. Elimination of environmental risk factors	Marchisio, 2010[133]	1-5yrs Italy	30% hydroglyceric extract of propolis; 1.2% zinc sulfate 0.3 ml/kg/d = QD for 3 months Plus Elimination of environmental risk factors	Outcome: ≥1 episode of AOM during 3-month study period Propolis+Zinc Controls Diff (95% CI) 51% (31/61) 71% (43/61) -20% (-37, -3) Outcome: mean number of episodes of AOM per child/month during 3-month study period Propolis/Zn Controls Diff(95% CI) p 0.23±0.26 0.34±0.29 0.11(0.01, 0.21) 0.3	Propolis and zinc had a lower proportion of children with AOM and mean number of AOM episodes than the control during the study period.

Findings on Treatment of Acute Otitis Media in Children With Recurrent Otitis Media

The systematic review by Abes (2003) is relevant only for children with tympanostomy tubes, presumably for ROM or persistent OME or some other chronic middle-ear condition not specified by the investigators.[134] Abes (2003) compared ofloxacin 0.3% otic solution to other otic antibiotic drops and oral antibiotics in treating acute or chronic suppurative otitis media in a systematic review that complied with nine of 11 quality criteria but was not focused solely on children.[134] They identified two studies of children 1-12 years old with tympanostomy tubes and AOM.[135, 136] Goldblatt (1998) reported a clinical success rate (Peto odds ratio) of 1.44 (95% CI: 0.86, 2.42) between ofloxacin otic solution received by 140 children and other medical treatments received by 146 children.[137] Dohar (1999) reported a clinical success rate (Peto odds ratio) of 2.76 (95% CI: 1.72, 4.42) between ofloxacin otic solution received by 143 children and other medical treatments received by 218 children.[136] Based on these two studies with different findings, we cannot draw any conclusion regarding the superiority of any of the treatments or their equivalence in these children with tympanostomy tubes who presumably had ROM or persistent otitis media with effusion or some other chronic middle-ear condition, not specified by Abes. Another review, by Wall (2009), complied with only two of 11 quality criteria, so the results are not reported here.[138](Table 22).

Table 22. Review Articles Examining Comparative Effectiveness of Treatment Strategies in Recurrent Acute Otitis Media or Persistent or Relapsing Acute Otitis Media[a]

Author (year) (quality)[b]	Review focus	Databases (included dates)	Study design	Target population	Outcomes	Number of trials and participants	Author's highlight conclusion
Bonati, 1992[139] (y,y,n,n,n, y,y,y,y,n,n)	ab prophylaxis in reducing ROM	MEDLINE (1966 through 1991); hand search	RCT	Patients with ROM[5]	AOM rate	8 studies 420 children	chemoprophylaxis effective in reducing AOM episodes during winter and spring
Williams. 1993[140] (y,y,y,y,n, y,y,n,y,n,n)	Use of antibiotics in preventing ROM and in treating OME	MEDLINE (1966 through April 1993); Current Contents (1990 through 1992); textbooks, monographs	RCT	Patients with ROM or OME	Number of episodes of AOM per patient-month while under treatment	9 studies 958 participants	antibiotics have beneficial but limited effect on ROM
Abes, 2003[134] (y,y,y,y,y,y, y,n,y,y,n)	ofloxacin otic solution	Medline through PubMed (1966 to 2000); CD version of the Cochrane Library; Centerwatch Clinical Trial Listing Service; Trial Banks; Research and Researcher Registry; Manual searches	RCT and non-randomized clinical trial	Adults and/or children with acute or chronic suppurative otitis media	Cure rate; resolution of otalgia; resolution of otorrhea; bacterial eradication; adverse events	2 studies (children with tympanostomy tubes and AOM)	No conclusion offered by authors on these two studies
Straetemans, 2004[141] (y,y,y,y,y, y,y,y,y,y,n)	PPV & PCV to prevent AOM	CENTRAL (TCL, Issue2, 2003); MEDLINE (Jan 1966-Jun 2003; EMBASE (Jan 1990-June 2003); hand search	RCT	0-12y	AOM total number; proportion of children with AOM; bacterial culture results	8 trials on PPV 4 trials on PCV	pneumococcal vaccine does not benefit children with ROM <1y old
Leach. 2008[142] (y,y,y,y,y, y,y,y,y,y,n)	long-term ab *vs.* placebo or no treatment to prevent AOM	CENTRAL (TCL, Issue 1, 2006); MEDLINE (Jan 1966-March week 3 2006); OLD MEDLINE (1950-1965); EMBASE (1990-Dec 2005); hand search	RCT	0-18y at increased risk for future AOM in otitis prone and high risk children[3]	AOM/CSOM during intervention; number of episodes of AOM/CSOM during intervention per child-year	13 studies 1358 children	long-term ab reduce AOM probability while on treatment; ab reduce number of AOM episodes per year from 3 to ~1.5

Author (year) (quality)[b]	Review focus	Databases (included dates)	Study design	Target population	Outcomes	Number of trials and participants	Author's highlight conclusion
McDonald. 2008[143] (y,y,y,n,y, y,y,y,y,n,n)	tympanostomy tube *vs.* non-surgical treatment to reduce ROM	CENTRAL (TCL, Issue 1, 2008); MEDLINE (1950-March 2008); EMBASE (1974-March 2008); CINAHL; mRCT; NRR; LILACS; KoreaMed; IndMed; PakMediNet; Zetoc; ISI Proceedings; Cambridge Scientific Abstracts; hand search (last search date Mar 2008)	RCT	0-16y with ROM[4]	AOM frequency following treatment; proportion of children with ROM following treatment	2 studies 148 children	ventilation tube plays significant role to maintain a disease-free state in the first six months after tube insertion.
Wall. 2009[138] (n,n,n,n,n,y, y,n,n/a,n/a,n)	ciprodex otic suspension *vs.* ciprofloxacin, ofloxacin, or amox-clav	MEDLINE; hand search	Not specified a priori RCTs identified	AOM in children with tympanostomy tubes & acute otitis externa (Identified studies included children 6m-12y)	Not specified a priori Identified studies included clinical outcome "per protocol" and bacteriologic cure	3 trials total	topical fluoroquinolones safe and efficacious in treatment of ear infections

[a]Abbreviations: ab=antibiotic; AOM=acute otitis media; CENTRAL=Cochrane Central Register of Controlled Trials; CINAHL=Cumulative Index to Nursing & Allied Health Literature; CSOM=chronic suppurative otitis media; HlthSTAR=HealthSTAR; IPA=International Pharmaceutical Abstracts; MEE=middle ear effusion; mRCT=*metaR*egister; NRR=National Research Register; Rx=treatment; PCV=pneumococcal conjugated vaccines; PPV=pneumococcal polysaccharide vaccines; TCL=The Cochrane Library

[b]AMSTAR quality criteria (Shea, Grimshaw, Wells, et al., 2007)[144]

1. Was an 'a priori' design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e. grey literature) used as an inclusion criteria?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interested stated?

[c] Otitis prone children with ≥3 AOM in 6 months or ≥4 AOM in 1 year; high-risk children with history of AOM with perforation; children in high-risk populations with CSOM prevalence ≥4%

[d] ROM defined as ≥3 AOM in six months or ≥4 AOM in 1 year

[e] Included patients with 3 or more documented episodes of RAOM/diagnosed on the basis of tympanic membrane exam, and who had received continued antimicrobial

The overall quality of evidence for these comparisons is considered low, meaning that further high quality research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Studies identified by the AOM review update on treatment of AOM in children with recurrent and/or persistent AOM. Five individual studies compared antibiotic treatments for AOM in children with ROM or persistent AOM. None of the studies demonstrated significant advantage for any particular treatment.[121-125]

Amoxicillin-clavulanate vs. gatifloxacin. Two RCTs addressed this comparison among 367 and 241 children with recurrent AOM and/or AOM with treatment failure (AOMTF), where AOMTF was defined as infection within 14 days of the last antibiotic dose or failure to improve after 48 hours. The children ranged in age from 6 months to 7 years.[121, 122] Saez-Llorens (2005) examined the success rate on day 3-10 while Sher (2005) examined the success rate on day 10. Saez-Llorens (2005) found a mean difference of –6% (95% CI: -13%, 1.%) and Sher (2005) found a mean difference of –6% (95% CI: -16%, 4%), both favoring gatifloxacin but without statistical significance. The advantage of either treatment over the other or their equivalence cannot be established based on the current evidence.

Amoxicillin-clavulanate vs. levofloxacin. One RCT addressed this comparison in children with recurrent and/or persistent AOM, where persistence was defined as signs or symptoms of AOM after 48 hours of treatment or after three days of treatment.[123] It compared the treatment success rates among children 6 months to 5 years of age in 6 different countries on day 2-5 of treatment (Jadad quality score 3 of 5). The success rate difference between amoxicillin-clavulanate and levofloxacin was -3% (95% CI: -6%, -0.2%). We cannot determine the advantage of either treatment or their equivalence based on the current evidence. In order to show equivalence, the 95% confidence interval must lie within the zone of MCID.

Amoxicillin-clavulanate vs. azithromycin. One RCT addressed this comparison in children with recurrent and/or persistent AOM.[124] The study, which included 294 children 6 months to 6 years of age (Jadad quality score 3 of 5), reported a treatment success rate difference of -2% (95% CI : -10%, 6%) between amoxicillin-clavulanate and azithromycin. We cannot draw any conclusion regarding the superiority of either treatment or their equivalence from the existing evidence.

Cefaclor vs. cefuroxime. One RCT addressed this comparison.[125] The study, which included 148 children 3 months to 12 years of age who had failed initial AOM treatment (Jadad quality score 2 of 5), reported a treatment success rate difference between cefaclor and cefuroxime at day 10 of 0.7% (95% CI : -7%, 9%) at day 10 and -1.2% (95% CI : -12%, 10%) at day 20-26. We cannot draw any conclusion regarding the superiority of either treatment or their equivalence from the existing evidence in these children, who had failed initial AOM treatment, presumably with persistent or relapsing AOM, although not specified by the authors.

The overall quality of evidence for these comparisons is considered low, meaning that 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.

Children with tympanostomy tubes. Three additional individual studies were identified that studied the effect of otic antibiotic drops in treatment of AOM in children who had tympanostomy tubes. As was the case for the studies included in the Abes (2003) review, these studies are unclear on the indication for tympanostomy tubes, whether for ROM or persistent

otitis media with effusion or some other chronic middle-ear condition, so it is difficult to assess the generalizability of the findings.[80, 126, 127]

Amoxicillin-clavulanate vs. ciprofloxacin-dexamethasone. One RCT addressed this comparison.[80] The study, which included 80 children 6 months to 12 years of age with tympanostomy tubes and AOM (Jadad quality score 2 of 5), reported a treatment success rate difference between amoxicillin-clavulanate and ciprofloxacin 0.3%-dexamethasone 0.1% otic drops at day 18-21 of -26% (95% CI: -46%, -6%). Ciprofloxacin-dexamethasone otic drops had a higher success rate than amoxicillin-clavulanate in these children with tympanostomy tubes for indications not specified by the investigators.

Ciprofloxacin vs. ciprofloxacin-dexamethasone. One RCT addressed this comparison.[126] The study, which included 167 children 6 months to 12 years of age with tympanostomy tubes and AOM (Jadad quality score 2 of 5), reported a treatment success rate difference between ciprofloxacin 0.3% otic drops and ciprofloxacin 0.3%-dexamethasone 0.1% otic drops at day 8 of -3% (95% CI: -11%, 5%) and at day 14 of -5% (95% CI: -11%, 0.5%). We cannot draw any conclusion regarding the superiority of either treatment or their equivalence from the existing evidence in these children with tympanostomy tubes for indications not specified by the investigators.

Ciprofloxacin-dexamethasone vs. ofloxacin. One RCT addressed this comparison.[127] The study, which included 423 children 6 months to 12 years of age with tympanostomy tubes and AOM (Jadad quality score 2 of 5), reported a treatment success rate difference between ciprofloxacin 0.3%-dexamethasone 0.1% otic drops and ofloxacin 0.3% otic drops of 14% (95% CI: 8%, 21%), at day 3, of 6% (95% CI: 1%, 11%) at day 11,of 5% (95% CI: -0.2%, 11%) at day 18, and difference in clinical cure rate at day 18-21 of 12% (95% CI: 4%, 19%). The study also reported a difference in otorrhea absence of 14% (95% CI: 5.4%, 22%) at day 3, 21% (95% CI: 13%, 30%) at day 11, and 14% (95% CI: 6%, 22%) at day 18. Ciprofloxacin-dexamethasone otic drops had a higher success rate than ofloxacin otic drops for clinical success at day 3, for clinical cure at days 18-21, and for otorrhea absence at days 3, 11, and 18 in these children with tympanostomy tubes for indications not specified by the investigators.

Findings on Prevention of Acute Otitis Media in Children with Recurrent Otitis Media

Previous systematic reviews. We identified five previous systematic reviews of prevention of AOM in children with ROM.[139-143] (See Appendix I for complete descriptions of these systematic reviews.) Three addressed antibiotic prophylaxis of children with ROM.[139, 140, 142] One addressed the role of tympanostomy tubes for children with ROM.[143] Table 22 summarizes the references found in these five systematic reviews and the controls, interventions, and outcomes utilized in each of the relevant studies from these systematic reviews. As comparison, Table 22 also includes the seven articles identified for this report on prevention of AOM in children with ROM. Of the articles identified for this report, only Teele (2000) was included in one of the previous systematic reviews (Leach, 2006), although the study by Koivunen (2004) was listed as pending assessment in that same review.[129, 130, 142] Note that these systematic reviews utilized the 95% confidence limits to judge significance of findings and did not use the concept of the zone of MCID.

Antibiotic prophylaxis. Because the 2006 review by Leach included all studies utilized by the earlier reviews by Bonati (1992) and Williams (1993), we will report only the main findings from Leach (2006).[139, 140, 142]

Leach (2006) conducted a literature search encompassing 1950–2006 and identified 16 studies[129, 145-159] that addressed the effectiveness of antibiotic prophylaxis to prevent AOM in children 0-18 years old at increased risk of future episodes of AOM as defined as otitis prone with three or more episodes of AOM in six months or four or more episodes of AOM in one year, high-risk children with a history of AOM with perforation, and children in high-risk populations with chronic suppurative otitis media prevalence ≥4%. The Leach (2006) systematic review scored affirmatively on 10 of 11 AMSTAR quality criteria but did not specifically address the conflicts of interest of each study included in the review.[142] The following are the primary outcomes of this review for all high-risk populations:

Pooling data from 13 studies, 12 on children with ROM of varying definition (of which seven met the current review's criteria and one was on children from a high-risk population), the risk ratio for any AOM during the intervention was 0.6 (95% CI: 0.5, 0.8; random-effects model, I^2=52%, p=0.02), i.e. an absolute risk reduction of 20%, equivalent to needing to treat five children (95% CI: 4, 6) with long-term antibiotics to prevent one child from getting an episode of AOM while on treatment.[129, 145, 146, 148, 150, 152-159] Pooling data from 12 studies, the incidence rate ratio for episodes of AOM during the intervention was 0.5 (95% CI: 0.4, 0.6; random effects-model, I^2=65%), but the studies were statistically hetereogeneous.[145, 147, 148, 150, 151, 153-157, 159] For both primary outcomes, none of the studies reported on AOM with perforation or chronic suppurative otitis media.

Perhaps more relevant to the current review, the Leach review (2006) did sub-group analysis of otitis prone vs. non-otitis-prone children for the primary outcomes. Pooling data from seven studies, the risk ratio for any AOM during the intervention for otitis prone children was 0.7 (95% CI: 0.6, 0.8; fixed-effect model, I^2=33%).[150, 151, 153-156, 159, 160]

Pooling data from eight studies, the incidence rate ratio for episodes of AOM during the intervention for otitis prone children was 0.5 (95% CI: 0.4, 0.7; random-effects model, I^2=73%), but the studies were statistically heterogeneous.[147, 150, 151, 153-156, 159] Leach (2006) concluded that antibiotics will prevent 1.5 episodes of AOM for every 12 months of treatment per otitis-prone child (95% CI: 1.2, 2.1) who would otherwise average three episodes of AOM annually. The results were not affected by sensitivity analyses.

Tympanostomy tubes. McDonald and colleagues (2008) conducted a literature search encompassing 1950–2008 and identified two studies that addressed the effectiveness of tympanostomy tube placement to prevent AOM in children 0-16 years old with ROM as defined as three or more AOM episodes in six months or four or more AOM episodes in one year.[161, 162] The McDonald (2008) systematic review scored affirmatively on eight of 11 AMSTAR quality criteria but did not address publication status, publication bias assessment, and conflicts of interest of each study included in the review.[143] Pooling data from two studies, the odds ratio for more than one episode of AOM for six months following tympanostomy tube placement was 0.2 (95% CI: 0.1, 0.4). [161, 162] McDonald (2008) concluded that ventilation tube placement played a significant role in maintaining a disease-free state in the first six months after tube insertion in children with ROM in these two studies.[143]

Studies identified by the AOM review update on prevention of AOM in children with ROM. Seven studies identified by our searches address the prevention of AOM in children with

ROM.[26, 91, 128-132] These studies include five not identified by or pertinent to previous systematic reviews, one excluded by a previous systematic review, and one included in a previous review for which we provide greater detail.[129]

Antibiotic or non-surgical treatment. Seven individual studies compared antibiotic or non-surgical treatments to prevent AOM in children with ROM. None of the studies demonstrated a long-term advantage for any particular antibiotic or non-surgical treatment.

Amoxicillin vs. azithromycin. One RCT addressed the comparison of amoxicillin and azithromycin (three months treatment duration) among 69 children ranging in age from 9 months to 10 years (Jadad quality score 2 of 5).[128] The treatment outcome of interest was 50% reduction in AOM episodes. The study reported a rate difference of 9% in this outcome between amoxicillin and azithromycin at six to 27 months (95% CI: -8%, 26%). No conclusion can be derived from the existing evidence regarding the superiority of one or the other agent or their equivalence. The overall quality of evidence for this comparison is considered low, meaning that further high quality research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

*Amoxicillin vs. sulfisoxazole***.** One RCT (Teele, 2000) addressed the comparison of amoxicillin and sulfisoxazole among 76 children ranging in age from birth to 1 year (Jadad quality score 3).[129] The study reported a success rate difference between amoxicillin and sulfisoxazole of 12% (95% CI: -4%, 29%) in six-month follow-up and a success rate difference of 4% (95% CI: -18%, 25%) in 12-month follow-up. No conclusion of antibiotic advantage or equivalence can be derived from the existing evidence. The overall quality of evidence for this comparison is considered low, meaning that further high quality research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Amoxicillin vs. placebo. The Teele (2000) study also compared amoxicillin vs. placebo among 81 children.[129] The study reported a success rate difference between amoxicillin and placebo of 19% (95% CI: 2%, 37%) in six-month follow-up and a success rate difference of 2% (95% CI: -19%, 22%) in 12-month follow-up. No conclusion can be derived from the existing evidence regarding the efficacy of amoxicillin with a MCID of ±5%. The overall quality of evidence for this comparison is considered low, meaning that further high quality research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Sulfisoxazole/sulfafurazole vs. placebo. Two RCTs addressed this comparison among 77 children, 0 to 12 months of age, and 93 children, 10 months to 2 years of age, respectively.[129, 130] The Teele 2000 article defined success as one or fewer AOM episodes at six-month or one-year follow-up, whereas Koivunen (2004) defined success as one or fewer AOM episodes in two months, two or fewer AOM episodes in six months, or less than two months of MEE at six-month or two-year follow-up (Jadad quality score 3 of 5).[129, 130] The Teele 2000 study reported a success rate difference between sulfisoxazole and placebo of 7% (95% CI: -13%, 27%) in six-month follow-up and a success rate difference of -2% (95% CI: -23%, 20%) in 12-month follow-up.[129, 130] reported a success rate difference between sulfafurazole and placebo of 18% (95% CI: -2%, 39%) at six-month follow-up and a success rate difference of 12% (95% CI of -7%, 31%) at two-year follow-up.[130] No conclusion can be derived from the existing evidence regarding the efficacy of sulfisoxazole/sulfafurazole for either outcome. The overall quality of evidence for this comparison is considered low, meaning that further high quality research is very likely to

have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Ceftibuten 5-day vs. ceftibuten 10-day. One trial compared five days with 10 days of ceftibuten.[131] The study included 178 children, ages 6 months to 8 years, and defined treatment success as no recurrence. Treatment success was measured at two different time points: at day 14 and at day 40. At day 14, the difference in treatment success between the five-day and 10-day treatment options was -17% (95% CI: -27%, -7%); the 95% CI for the day-14 success rate is outside the zone of MCID of ±5%, favoring the longer treatment option. At day 40, the difference in treatment success between the five-day and 10-day treatment options was -5% (95% CI: -19%, 9%), again favoring the longer treatment. The long-term effectiveness of the ceftibuten 10-day treatment option cannot be established at this point. The overall quality of evidence for this comparison is considered low, meaning that 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.

Probiotics vs. placebo. One RCT assessed the effects of treatment with probiotics compared with placebo in a group of 269 children ages 10 months to 6 years.[91] The Jadad quality score for this trial was 5. The treatment consisted of one capsule daily for six months; the capsule contained Lactobacillus rhamnosus GG and LC705, Bifidobacterium breve 99, and propionibacterium freudenreichii JS. Treatment success was defined by the number of AOM episodes during the 6-month intervention period (proportion of children experiencing no episodes of AOM, proportion experiencing fewer than three AOM episodes). The difference in treatment success between probiotics and placebo was -7% (95% CI: -18%, 4%) for no AOM episodes and -1% (95% CI: -10%, 8%) for fewer than three AOM episodes during the six-month follow-up period. No conclusion of treatment advantage or equivalence can be derived from the existing evidence for either outcome. The overall quality of evidence for this comparison is considered low, meaning that 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.

Propolis and zinc vs. elimination of environmental risk factors. Propolis is "a natural product collected by bees from the exudates of plants" (Marchisio, 2010).[133] One RCT assessed the effects of treatment with propolis and zinc plus elimination of environmental risk factors compared with elimination of environmental risk factors alone. The Jadad quality score for this trial was 2. The treatment consisted of 0.3 ml/kg/d of 30% hydroglyceric extract of propolis and 1.2% zinc sulfate once daily for three months. The proportion of children with AOM and febrile respiratory tract infections and of children treated with antibiotics for those conditions during the study period was measured as was the mean number of episodes of AOM and respiratory tract infections and antibiotic courses. Also, mean duration of bilateral OME and parental satisfaction were measured. The difference in the proportion of children with one or more episodes of AOM was 26.2% (95% CI: 9.6%, 42.8%) less in the treatment group as was the mean number of antibiotic courses for AOM, -0.34 (95% CI: -0.59, -0.09). The overall quality of evidence for this comparison is considered low, meaning that 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.

Surgical vs. surgical or non-surgical treatment. Six comparisons of surgical vs. surgical or non-surgical treatments to prevent AOM in children with ROM were identified. None of the comparisons demonstrated a significant advantage for any particular surgical or non-surgical treatment.

Sulfafurazole vs. adenoidectomy. Koivunen (2004) also reported a comparison between sulfafurazole and adenoidectomy.[130] The study defined treatment success as one or fewer episodes of AOM in two months or two or fewer episodes of AOM in six months or less than two months of MEE at six-month or two-year follow-ups. A total of 105 children were examined at six months. The reported difference in success rate between sulfafurazole and adenoidectomy was 5% (95% CI: -14%, 24%) at the six-month follow-up and a difference of 7% (95% CI: -12%, 25%) at the two-year follow-up, both favoring the drug. Thus, no conclusion of advantage or equivalence can be derived for either treatment from the existing evidence for either outcome. The overall quality of evidence for this comparison is considered low, meaning that further high quality research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Adenoidectomy vs. placebo. Two RCTs addressed this comparison.[26, 130] Paradise (1999) defined treatment success as no AOM episode in one year, or one or fewer AOM episodes in one year in patients with no tonsil-related indications.[26] This study compared 140 children ranging in age from 3 to 15 years and had a Jadad quality score of 2.[26] Koivunen (2004) defined treatment success as one or fewer episodes of AOM in two months, or two or fewer episodes of AOM in six months, or less than two months of MEE at the six-month or two-year follow-ups.[130] Paradise (1999) reported a difference in treatment success rates of 10% (95% CI: -5%, 24%) when success was defined as no AOM episodes during the year (favoring the procedure) and a difference of -3% (95% CI: -20%, 14%) when success was defined as one or fewer AOM episodes during the year.[26] Koivunen (2004) reported a difference of 13% (95% CI: -6%, 32%) at 6-month follow-up and a success rate difference of 5% (95% CI: -11%, 22%) at two-year follow-up, both favoring the procedure.[130] Thus, no conclusion of surgical advantage or equivalence can be derived from the existing evidence for any outcome. The overall quality of evidence for this comparison is considered low, meaning that further high quality research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Adenoidectomy vs. adenotonsillectomy. Paradise (1999) also compared adenoidectomy with adenotonsillectomy in a total of 132 children.[26] The study defined treatment success as no AOM episode in one year or as one or fewer AOM episodes in one year in patients with no tonsil-related indications. The reported difference in treatment success was -6% (95% CI: -22%, 11%) when success was defined as no AOM episodes during the year and -12% (95% CI: -29%, 5%) when success was defined as one or fewer AOM episodes during the year, both favoring adenotonsillectomy. Thus, no conclusion of advantage or equivalence for the surgical procedures can be derived from the existing evidence for either outcome. The overall quality of evidence for this comparison is considered low, meaning that further high quality research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Adenotonsillectomy vs. placebo. Paradise (1999) also compared adenotonsillectomy with placebo in a total of 150 children.[26] The study defined treatment success as no AOM episode in one year or as one or fewer AOM episodes in one year in patients with no tonsil-related indications. The difference in success rates was 15% (95% CI: 0.6%, 30%) when success was defined as no AOM episodes during the year and 9% (95% CI: -7%, 25%) when success was defined as one or fewer AOM episodes during the year, both favoring the procedure. Thus, no conclusion of advantage or equivalence can be derived for either intervention from the existing

evidence for either outcome with a MCID of ±5%. The overall quality of evidence for this comparison is considered low, meaning that further high quality research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Adenoidectomy plus tympanostomy vs. tympanostomy alone. One RCT compared the efficacy of adenoidectomy plus tympanostomy with that of tympanostomy alone for prevention of AOM in children with ROM.[132] The study, which enrolled a total of 198 children ranging in age from one to two years, defined treatment success as the mean number of otitis media episodes during one year of follow-up (Jadad quality score was 2 of 5). No conclusion of advantage or equivalence of the surgical procedure can be derived from the existing evidence for either outcome. The overall quality of evidence for this comparison is considered low, meaning that further high quality research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Summary

To answer the question, we assessed the efficacy of both treatment and prevention of AOM in children with ROM, persistent AOM, or AOM treatment failure.

Regarding the treatment of AOM in children with ROM, persistent AOM, or AOM treatment failure, the available evidence identified for this study provided the following conclusions:

- The evidence did not allow us to reach strong conclusions regarding the comparisons of amoxicillin-clavulanate vs. gatifloxacin, amoxicillin-clavulanate vs. levofloxacin, and amoxicillin-clavulanate vs. azithromycin.
- For children with tympanostomy tubes and AOM, ciprofloxacin 0.3%-dexamethasone 0.1% otic drops appeared to have higher success rate than amoxicillin-clavulanate at days 18-21 in one study.[80]
- In another study of children with tympanostomy tubes, ciprofloxacin-dexamethasone had a higher success rate than ofloxacin 0.3% otic drops at day three but not at days 11, 18, or 18-21 (end of treatment assessment), and produced a higher rate of otorrhea absence at days 3, 11, and 18.[127] However, in both studies it is not entirely clear why the children had tympanostomy tubes, whether for ROM, persistent otitis media with effusion, or some other chronic middle-ear condition; so, the generalizability of these findings is limited.

Regarding the prevention of AOM in children with ROM, the available evidence from prior systematic reviews provided the following conclusions:

- Long-term antibiotics, defined as weeks or longer, decreased episodes of AOM from 3 to 1.5 for every 12 months of treatment per otitis-prone child during active treatment.[142]
- Tympanostomy tube placement played a significant role in maintaining a disease-free state in the first six months after tube insertion in children with ROM.[143] This conclusion is qualified by the observation that only two studies contributed data to this pooled analysis. It may also be tempered by the issue of AOM diagnostic accuracy in the presence of tympanostomy tubes possibly confounding these results, i.e. the pressure equalization and drainage afforded by the tubes and their physical

presence decreasing the intensity or visibility of signs and symptoms used to diagnose AOM, leading to false negatives.

- A statement cannot be made regarding the role of pneumococcal vaccine in reducing AOM in children with ROM based on the available systematic review.[141] Although pooled analyses favored a modest benefit for the vaccine, methodologic problems with the original studies included in the analysis preclude a strong conclusion.

No definitive conclusions could be drawn regarding the 13 comparisons identified by this study for prevention of AOM in children with ROM that looked at amoxicillin vs. azithromycin, amoxicillin vs. sulfisoxazole, amoxicillin vs. placebo, sulfisoxazole vs. placebo, ceftibuten five-day vs. 10-day, probiotics vs. placebo, sulfafurazole vs. adenoidectomy, adenoidectomy vs. placebo, adenoidectomy vs. adenotonsillectomy, adenotonsillectomy vs. placebo, ceftibuten five-day vs. 10-day, probiotics vs. placebo and adenoidectomy plus tympanostomy vs. tympanostomy.

Key Question V.

Do Treatment Outcomes in Key Questions III and IV Differ by Characteristics of the Condition (AOM), Patient, Environment, and/or Health Care Delivery System?

Of the 48 RCTs newly identified in our review that addressed the effectiveness of treatment options in uncomplicated *acute otitis media* (Key Question 3), 15 trials reported analyses for subgroups stratified by age, presence of MEE, laterality, identity of daytime caretaker (use of daycare), hearing deficit and severity, otorrhea, examiner, and pneumococcal vaccine. Of the 10 trials identified in our review that addressed the effectiveness of treatment options in *recurrent otitis media* (Key Question 4), three reported analysis by age subgroups. One reported stratified analysis by laterality and severity of otitis media. A listing of the articles reporting subgroup analysis and the drug comparisons studied is provided in Table 23. In addition, we report relevant findings from previous systematic reviews as cited in the responses to Key Questions III and IV.

Table 23. Listing of Articles Reported Subgroup Analysis on Effectiveness of Treatment Options

(A) KQ3 – Uncomplicated Otitis Media

Factor	# Comp	Comparisons	Author, Year
Age	14	Amoxicillin vs. Azithromycin	Arguedas, 2005[66]
		Amoxicillin vs. Azithromycin	Morris, 2010[67]
		Amoxicillin vs. Erythromycin	Le Saux, 2005[89]
		Amoxicillin vs. Wait-and-see	McCormick, 2005[3]
		Amoxicillin (Amox)-clavulanate (clav) 5d vs. Amox-clav 10d	Cifaldi, 2004[74]
		Amox-clav vs. Cefdinir (qd10d)	Block, 2000[72]
		Amox-clav vs. Cefdinir (bid10d)	Block, 2000[72]
		Amox-clav vs. Cefdinir (bid5d)	Block, 2004[75]
		Amox-clav vs. Cefprozil	Hedrick, 2001[76]
		Amox-clav vs. Cefuroxime	Pessey, 1999[79]
		Azithromycin vs. Cefdinir	Block, 2005[83]

Factor	# Comp	Comparisons	Author, Year
		Cefpodoxime 5d vs. Cefpodoxime 10d	Cohen, 2000[100]
		Cefprozil vs. Cefdinir	Block, 2000[85]
Laterality	2	Amoxicillin vs. Erythromycin	Scholz, 1998[4]
		Amox-clav vs. Cefprozil	Hedrick, 2001[76]
Caretaker	2	Cefpodoxime 5d vs. Cefpodoxime 10d	Cohen, 2000[100]
		Amox-clav 5d vs. Amox-clav 10d	Cohen, 1998[98]
Hearing deficit and severity	1	Amox-clav vs. Cefprozil	Hedrick, 2001[76]
Otorrhea	1	Amoxicillin vs. Erythromycin	Scholz, 1998[4]
Examiner	1	Aqueous lidocaine drop vs. placebo	Bolt, 2008[90]
Pneumococcal vaccine	1	Amox-clav vs. Cefdinir	Block, 2004[75]

(B) KQ4 – Recurrent Otitis Media

Factor	# Comp	Comparisons	Author, Year
Age	3	Amox-clav vs. Levofloxacin	Noel, 2008[123]
		Amox-clav vs. Gatifloxacin	Sher, 2005[122]
		Amox-clav vs. Azithromycin	Arrieta, 2003[124]
Laterality	1	Amox-clav vs. Gatifloxacin	Sher, 2005[122]
Severity	1	Amox-clav vs. Gatifloxacin	Sher, 2005[122]

Age Factor in Uncomplicated Acute Otitis Media

We identified 14 trials for the review update that analyzed the effectiveness of treatment options by age group. The study by Cifaldi (2004) examined effectiveness from the parent's perspective only, whereas the other 13 articles reported other clinical outcomes. The latter 13 studies assessed 14 treatment comparisons by age group. Table 24 provides a summary of the findings on clinical success rate by age groups.

Table 24. Summary of Findings from 13 Articles (14 Comparisons) Assessing Clinical Success Rate of Interventions in Uncomplicated Acute Otitis Media Stratified by Age

<table>
<tr><th>Comp #</th><th>Comparison</th><th>Article</th><th>Patient Population</th><th>Intervention</th><th>Findings</th><th>Conclusion</th></tr>
<tr><td>1</td><td>Amoxicillin vs. Azithromycin</td><td>Arguedas, 2005[66]</td><td>6-30 months
Multi-centers in US, Finland, Chile, Costa Rica</td><td>Amoxicillin 90 mg/kg/day / bid for 10 days
vs.
Azithromycin 30 mg/kg/day = qd for 1 day</td><td>Outcome: Success rate (cure or improvement) at day 12-14: -0.2% (-10, 9)
<table>
<tr><td></td><td>Amox</td><td>Azithromycin</td><td>Diff (95% CI)</td></tr>
<tr><td>All pts</td><td>84.1% (127/151)</td><td>3.9% (130/155)</td><td>0.2% (-8, 8)</td></tr>
<tr><td><=2yrs</td><td>81.8% (99/121)</td><td>82.0% (109/133)</td><td>-0.2% (-10, 9)</td></tr>
<tr><td>>2yrs</td><td>93.3% (28/30)</td><td>95.4% (21/22)</td><td>-2.1% (-15, 11)</td></tr>
<tr><td>Diff (95% CI)</td><td>-12% (-26, 3.1)</td><td>-13% (-30, 3.2)</td><td></td></tr>
</table></td><td>Not enough evidence to conclude</td></tr>
<tr><td>2</td><td>Amoxicillin vs. Azithromycin</td><td>Morris, 2010[67]</td><td>6 months-6 years
Aboriginal
16 centers
Australia
Rural and remote communities</td><td>Amoxicillin 50 mg/kg/day / bid for 7 days
Vs.
Azithromycin 30 mg/kg as a single dose</td><td>Outcome: Clinical success between day 6 and day 11
<table>
<tr><td></td><td>Amox</td><td>Azithromycin</td><td>Diff (95% CI)</td></tr>
<tr><td>All pts</td><td>46% (72/155)</td><td>50% (83/165)</td><td>-4% (-15, 7)</td></tr>
<tr><td><=2yrs</td><td>46% (57/125)</td><td>51% (64/125)</td><td>-5% (-18, 7)</td></tr>
<tr><td>>2yrs</td><td>50% (15/30)</td><td>47% (19/40)</td><td>3% (-21, 26)</td></tr>
<tr><td>Diff (95% CI)</td><td>-4% (-24, 15)</td><td>4% (-14, 21)</td><td></td></tr>
</table></td><td>Not enough evidence to conclude</td></tr>
</table>

<table>
<tr><th>Comp #</th><th>Comparison</th><th>Article</th><th>Patient Population</th><th>Intervention</th><th>Findings</th><th>Conclusion</th></tr>
<tr><td>3</td><td>Amoxicillin vs. Erythromycin</td><td>Scholz, 1998[4]</td><td>6 months-11 years
19 centers in Germany
Pediatric practice</td><td>Amoxicillin 50 mg/kg/day / bid for 10 days
vs.
Erythromycin 40 mg/kg/day / bid for 10 days</td><td>Outcome: Clinical success on day 9-11
<table><tr><td></td><td>Amox</td><td>Erythromycin</td><td>Diff (95% CI)</td></tr><tr><td>By drugs</td><td>96% (133/139)</td><td>94% (132/141)</td><td>2% (-3, 7)</td></tr></table>
(combines both antibiotic groups)
<table><tr><td></td><td><=2yrs</td><td>>2years</td><td>Diff (95% CI)</td></tr><tr><td>By Age</td><td>90% (35/39)</td><td>95% (230/241)</td><td>-6% (-13, 2)</td></tr></table></td><td>Not enough evidence to conclude</td></tr>
<tr><td>4</td><td>Amoxicillin vs. Erythromycin</td><td>Le Saux, 2005[89]</td><td>6 months-5 years
Canada
Emergency room,
Pediatric practice</td><td>Amoxicillin 60 mg/kg/day / tid for 10 days
vs.
placebo</td><td>Outcome: Cumulative clinical resolution rates at 14 days
<table><tr><td></td><td>Amox</td><td>Placebo</td><td>Diff (95% CI)</td></tr><tr><td>All ages</td><td>93% (232/250)</td><td>84% (202/240)</td><td>-9% (-14, -3)</td></tr><tr><td>6-23 mo</td><td>85% (76/89)</td><td>79% (73/92)</td><td>-6% (-17,5.2)</td></tr><tr><td>2-5 yrs</td><td>97% (156/161)</td><td>87% (129/148)</td><td>-10% (-16, -3.8)</td></tr><tr><td>Diff (95% CI)</td><td>-12% (-19, -5.3)</td><td>-8% (-18, 1.6)</td><td></td></tr></table></td><td>Not enough evidence to conclude between treatment effectiveness within age group. Age <2 years had lower success rate than >=2 years</td></tr>
</table>

<table>
<tr><th>Comp #</th><th>Comparison</th><th>Article</th><th>Patient Population</th><th>Intervention</th><th>Findings</th><th>Conclusion</th></tr>
<tr><td>5</td><td>Amoxicillin vs. Wait-and-see</td><td>McCormick, 2005[3]</td><td>6 months-12years
U.S.
Hospital clinic/ outpatient, University/ academic</td><td>Amoxicillin 90 mg/kg/day / bid for 10 days
vs.
Wait and see</td><td>Outcome: Success rate at Day 0-12
<table>
<tr><td></td><td>Amox</td><td>Wait-and-see</td><td>Diff (95% CI)</td></tr>
<tr><td>Total</td><td>95% (102/107)</td><td>80% (86/107)</td><td>15% (6, 24)</td></tr>
<tr><td><2 yrs</td><td>94% (60/64)</td><td>78% (42/54)</td><td>16% (4, 28)</td></tr>
<tr><td>≥2 yrs</td><td>98% (42/43)</td><td>83% (44/53)</td><td>5% (-4, 13)</td></tr>
<tr><td>Diff (95% CI)</td><td>-4% (-12, 3.9)</td><td>-5% (-20, 10)</td><td></td></tr>
</table></td><td>Amox had higher success rate for all age; cannot conclude by age group.</td></tr>
</table>

<table>
<tr><th>Comp #</th><th>Comparison</th><th>Article</th><th>Patient Population</th><th>Intervention</th><th>Findings</th><th>Conclusion</th></tr>
<tr><td>6</td><td>Amox-clav vs. Azithromycin</td><td>Dunne, 2003[70]</td><td>6 months-12years
Multi-centers in U.S.</td><td>Amoxicillin-clavulanate 45 mg/kg/day / bid for 10 days
vs.
Azithromycin 10 mg/kg/day = qd for 3 days</td><td>Outcome: Clinical success (cure+improvement) at day 10
<table>
<tr><td></td><td>Amox-clav</td><td>Azithro</td><td>Diff (95% CI)</td></tr>
<tr><td>All ages</td><td>88% (159/181)</td><td>83% (153/183)</td><td>5%(-2, 12)</td></tr>
<tr><td>≤2 yrs</td><td>85% (44/52)</td><td>76% (45/59)</td><td>9% (-6, 24)</td></tr>
<tr><td>>2 yrs</td><td>73% (94/129)</td><td>86% (108/126)</td><td>-13%(-23, -3)</td></tr>
<tr><td>Diff (95% CI)</td><td>12% (-2, 26)</td><td>-10% (-22, 2)</td><td></td></tr>
</table>
Outcome: Clinical success (cure+improvement) at day 24-28
<table>
<tr><td></td><td>Amox-clav</td><td>Azithro</td><td>Diff (95% CI)</td></tr>
<tr><td>All ages</td><td>69% (124/180)</td><td>74% (134/182)</td><td>-5%(-14, 4.3)</td></tr>
<tr><td>≤2 yrs</td><td>58% (30/52</td><td>60% (35/58)</td><td>-2%(-20, 16)</td></tr>
<tr><td>>2 yrs</td><td>73% (94/128)</td><td>80% (99/124)</td><td>-7% (-18, 3.5)</td></tr>
<tr><td>Diff (95% CI)</td><td>-15% (-30, 0)</td><td>-20% (-34, -6)</td><td></td></tr>
</table></td><td>Clinical success at day 24-28 for Azithromycin higher among those >2yrs than ≤2yrs.

Others are inconclusive</td></tr>
</table>

<table>
<tr><th>Comp #</th><th>Comparison</th><th>Article</th><th>Patient Population</th><th>Intervention</th><th>Findings</th><th>Conclusion</th></tr>
<tr><td>7</td><td>Amox-clav vs. Cefdinir (QD 10days)</td><td>Block, 2000[72]</td><td>6 months-12years
Multi-centers in U.S.</td><td>Amoxicillin-clavulanate 40/10 mg/kg/day / tid for 10 days
vs.
Cefdinir 14 mg/kg/day = qd for 10 days</td><td>Outcome: Clinical success (cure or improvement) 2-4 days after treatment: Amox-clav vs. Cefdinir QD
<table>
<tr><td></td><td>A-C</td><td>CDR-QD</td><td>Diff (95% CI)</td></tr>
<tr><td>Total</td><td>86% (86/100)</td><td>83% (85/102)</td><td>0.7% (-7, 13)</td></tr>
<tr><td><2 yrs</td><td>79% (31/39)</td><td>80% (45/56)</td><td>-1% (-17, 15)</td></tr>
<tr><td>≥2 yrs</td><td>90% (55/61)</td><td>87% (40/46)</td><td>3% (-9, 15)</td></tr>
<tr><td>2-5 yrs</td><td>85% (35/41)</td><td>84% (31/37)</td><td>1.6% (-14, 18)</td></tr>
<tr><td>6-12 yrs</td><td>100% (20/20)</td><td>100% (9/9)</td><td>0.0%</td></tr>
<tr><td>Diff (95% CI)</td><td>-11% (-25, 2.8)</td><td>-7% (-22, 8)</td><td></td></tr>
</table></td><td>Not enough evidence to conclude</td></tr>
<tr><td>8</td><td>Amox-clav vs. Cefdinir (BID 10days)</td><td>Block, 2000[72]</td><td>6 months-12years
Multi-centers in U.S.</td><td>Amoxicillin-clavulanate 40/10 mg/kg/day / tid for 10 days
vs.
Cefdinir 7 mg/kg/day = bid for 10 days</td><td>Outcome: Clinical success (cure or improvement) 2-4 days after treatment: Amox-clav vs. Cefdinir BID
<table>
<tr><td></td><td>A-C</td><td>CDR-BID</td><td>Diff (95% CI)</td></tr>
<tr><td>Total</td><td>86% (86/100)</td><td>80% (81/101)</td><td>6% (-4, 16)</td></tr>
<tr><td><2 yrs</td><td>79% (31/39)</td><td>62% (30/48)</td><td>17% (-2, 36)</td></tr>
<tr><td>≥2 yrs</td><td>90% (55/61)</td><td>96% (51/53)</td><td>-6% (-15, 3.4)</td></tr>
<tr><td>2-5 yrs</td><td>85% (35/41)</td><td>95% (35/37)</td><td>-9% (-23, 4)</td></tr>
<tr><td>6-12 yrs</td><td>100% (20/20)</td><td>100% (16/16)</td><td>0.0%</td></tr>
<tr><td>Diff (95% CI)</td><td>-11% (-25, 2.8)</td><td>-34% (-50, -19)</td><td></td></tr>
</table></td><td>Not enough evidence to conclude relative effectiveness between treatments within each age group. Age <2 years had lower success rate with CDR-BID</td></tr>
</table>

<table>
<tr><th>Comp #</th><th>Comparison</th><th>Article</th><th>Patient Population</th><th>Intervention</th><th>Findings</th><th>Conclusion</th></tr>
<tr><td>9</td><td>Amox-clav vs. Cefdinir (BID 5-day)</td><td>Block, 2004[75]</td><td>6 months-6years
Multi-centers in U.S.</td><td>Amoxicillin-clavulanate 45/6.4 mg/kg/day / bid for 10 days
vs.
Cefdinir 14 mg/kg/day / bid for 5 days</td><td>Outcome: Success at end-of-treatment visit (study days 7-9 for Cefdinir; study days 12-14 for Amox-clav)
<table>
<tr><td></td><td>A-C</td><td>Cefdinir</td><td>Diff (95% CI)</td></tr>
<tr><td>Total</td><td>85% (164/192)</td><td>88% (170/194)</td><td>-2% (-9, 4.6)</td></tr>
<tr><td><2 yrs</td><td>78% (64/82)</td><td>88% (79/90)</td><td>-10% (-21, 2.4)</td></tr>
<tr><td>2-6 yrs</td><td>91% (100/110)</td><td>88% (91/104)</td><td>3% (-4.9, 12)</td></tr>
<tr><td>Diff (95% CI)</td><td>-13% (-23, -3)</td><td>0% (-9, 9)</td><td></td></tr>
</table></td><td>Not enough evidence to conclude</td></tr>
<tr><td>10</td><td>Amox-clav vs. Cefprozil</td><td>Hedrick, 2001[76]</td><td>6 months-7years
Multi-centers in U.S.</td><td>Amoxicillin-clavulanate 90/6.4 mg/kg/day / bid for 10 days
vs.
Cefprozil 30 mg/kg/day / bid for 10 days</td><td>Outcome: Clinical success (cure or improved) at day 4-7 after treatment
<table>
<tr><td></td><td>A-C</td><td>Cefprozil</td><td>Diff (95% CI)</td></tr>
<tr><td>Total</td><td>89% (116/130)</td><td>87% (110/127)</td><td>2% (-6, 10)</td></tr>
<tr><td><2 yrs</td><td>86% (55/64)</td><td>80% (47/59)</td><td>6% (-7, 19)</td></tr>
<tr><td>2-7 yrs</td><td>92% (61/66)</td><td>93% (63/68)</td><td>-1% (-10, 8)</td></tr>
<tr><td>Diff (95% CI)</td><td>-6% (-17, 4.7)</td><td>-13% (-25, -1.3)</td><td></td></tr>
</table></td><td>Not enough evidence to conclude</td></tr>
</table>

<table>
<tr><th>Comp #</th><th>Comparison</th><th>Article</th><th>Patient Population</th><th>Intervention</th><th>Findings</th><th>Conclusion</th></tr>
<tr><td>11</td><td>Amox-clav vs. Cefuroxime</td><td>Pessey, 1999[79]</td><td>6 months-3years
Multi-centers in France</td><td>Amoxicillin-clavulanate 40 mg/kg/day / tid for 10 days (A-C10d)
vs.
Amoxicillin-clavulanate 80 mg/kg/day / tid for 8 days (A-C8d)
vs.
Cefuroxime 30 mg/kg/day / bid for 5 days (CAE)</td><td>Outcome: Satisfactory clinical response post-treatment – A-C10d vs. CE
<table>
<tr><td></td><td>A-C10d</td><td>CAE</td><td>Diff (95% CI)</td></tr>
<tr><td>Total</td><td>88% (181/205)</td><td>86% (175/203)</td><td>2% (-4.5, 8.5)</td></tr>
<tr><td><1.5 yrs</td><td>89% (116/131)</td><td>83% (111/134)</td><td>6% (-2.4, 14)</td></tr>
<tr><td>1.5-3 yrs</td><td>88% (65/74)</td><td>93% (64/69)</td><td>-5% (-15, 4.7)</td></tr>
<tr><td>Diff (95% CI)</td><td>1% (-8, 10)</td><td>-10% (-20, 0)</td><td></td></tr>
</table>
Outcome: Satisfactory clinical response post-treatment – A-C8d vs. CE
<table>
<tr><td></td><td>A-C8d</td><td>CAE</td><td>Diff (95% CI)</td></tr>
<tr><td>Total</td><td>88% (145/165)</td><td>86% (175/203)</td><td>2% (-4.9, 9)</td></tr>
<tr><td><1.5 yrs</td><td>84% (83/99)</td><td>83% (111/134)</td><td>1% (-9, 11)</td></tr>
<tr><td>1.5-3 yrs</td><td>94% (62/66)</td><td>93% (64/69)</td><td>1% (-7, 9)</td></tr>
<tr><td>Diff (95% CI)</td><td>-10% (-20, 0)</td><td>-10% (-20, 0)</td><td></td></tr>
</table></td><td>Not enough evidence to conclude</td></tr>
</table>

<table>
<tr><th>Comp #</th><th>Comparison</th><th>Article</th><th>Patient Population</th><th>Intervention</th><th>Findings</th><th>Conclusion</th></tr>
<tr><td>12</td><td>Azithromycin vs. Cefdinir</td><td>Block, 2005[83]</td><td>6 months-6years
Multi-centers in U.S.</td><td>Azithromycin 10 mg/kg/day = qd for 1 day,
--- 5 mg/kg/day = qd for 4 days
vs.
Cefdinir 7 mg</td><td>Outcome: Clinical success (cure or improve) on day 7-9 at end-of-therapy
<table>
<tr><td></td><td>Azithro</td><td>Cefdinir</td><td>Diff (95% CI)</td></tr>
<tr><td>Total</td><td>85% (149/176)</td><td>87% (151/174)</td><td>-2% (-9, 5.3)</td></tr>
<tr><td>0-2 yrs</td><td>82% (54/66)</td><td>81% (48/59)</td><td>1% (-13, 15)</td></tr>
<tr><td>>2 yrs</td><td>86% (95/110)</td><td>90% (103/115)</td><td>-4% (-12, 4.5)</td></tr>
<tr><td>Diff (95% CI)</td><td>-4% (-15, 7)</td><td>-9% (-20, 1.6)</td><td></td></tr>
</table></td><td>Not enough evidence to conclude</td></tr>
<tr><td>13</td><td>Cefpodoxime 5d vs. Cefpodoxime 10d</td><td>Cohen, 2000[100]</td><td>4-30 months
Multi-centers in France</td><td>Cefpodoxime 8 mg/kg/day / bid for 10 days
vs.
Cefpodoxime 8 mg/kg/day / bid for 5 days</td><td>Outcome: Clinical success (cure or improve) on day 12-14 per protocol population
<table>
<tr><td></td><td>CPD 5d</td><td>CPD 10d</td><td>Diff (95% CI)</td></tr>
<tr><td>Total</td><td>84.1% (175/208)</td><td>92.4% (194/210)</td><td>-8% (-14, -2.1</td></tr>
</table>
Data by age group not reported.
Multivariable analysis showed that younger age (Odds ratio 1.074, p=0.0096), treatment duration (Odds ratio, not reported), day-care attendance (Odds ratio 0.390, p=0.0098), and history of otitis media with effusion (Odds ratio 0.346, p=0.0091) “were independently predictive of poor treatment” outcome.</td><td>Not enough evidence to conclude</td></tr>
</table>

<table>
<tr><th>Comp #</th><th>Comparison</th><th>Article</th><th>Patient Population</th><th>Intervention</th><th>Findings</th><th>Conclusion</th></tr>
<tr><td>14</td><td>Cefdinir
Vs.
Cefprozil</td><td>Block, 2000[85]</td><td>6months-12years
Multi-centers in U.S.</td><td>Cefprozil 30 mg/kg/day / bid for 10 days
vs.
Cefdinir 14 mg/kg/day / bid for 5 days</td><td>Outcome: clinical cure on day 9-11 (4-6 days post therapy for cefdinir and +/-1 day post therapy for Cefprozil)
<table>
<tr><td></td><td>Cefdinir</td><td>Cefprozil</td><td>Diff (95% CI)</td></tr>
<tr><td>Total</td><td>80.0% (152/190)</td><td>82.5% (151/183)</td><td>-2.5%(-10,5.4)</td></tr>
<tr><td><2yrs</td><td>71% (49/69)</td><td>71% (41/58)</td><td>0.3%(-16, 16)</td></tr>
<tr><td>≥2 yrs</td><td>84% (102/121)</td><td>88% (110/125)</td><td>-4% (-12, 4.9)</td></tr>
<tr><td>Diff (95% CI)</td><td>-13% (-25, 1.4)</td><td>-17% (-29, -5.5)</td><td></td></tr>
<tr><td>2-5yrs</td><td>85.1% (57/67)</td><td>87.1% (61/70)</td><td>-2% (-14, 10)</td></tr>
<tr><td>6-12yrs</td><td>83.3% (45/54)</td><td>89.1% (49/55)</td><td>-6% (-19, 7)</td></tr>
</table></td><td>Not enough evidence to conclude the effectiveness between treatments within age group. Age <2 years had lower success rate than age >=2 years when treated with Cefprozil.</td></tr>
</table>

Using the articles identified in the 2001 report and articles newly identified in this review that assessed the effectiveness of treatment options in uncomplicated AOM by age groups, we identified two treatment comparisons with more than two trials: Ampicillin/Amoxicillin vs. placebo and Amoxicillin-clavulanate (7-10 days) vs. Azithromycin (<5 days). The findings of the meta-analysis are presented in Tables 25, 26, 27, 28, and 29, respectively. The shrinkage plots are presented in Figures 11, 12, 13, and 14, respectively.

Table 25. Ampicillin/Amoxicillin vs. Placebo; Outcome Indicator: Treatment Success Rate for Age ≤2 Years

Author, Year	Age	Definition of outcome	Amoxicillin/ Ampicillin Sample Size	Placebo Sample Size	Amoxicillin Success Rate (%)	Placebo Success Rate (%)	Rate Difference In %	95% CI of Rate Difference In %
Howie, 1972[106]	≤2yrs	Success at day 2-7	36	116	47.2	20.7	26.5	8.6, 44.4
Kaleida, 1991[108]	≤2yrs	No effusion at day 2	226	209	47.8	32.1	15.7	6.7, 24.8
Damoiseaux, 2000[88]	≤2yrs	Clinical success at day 11	112	120	35.7	30.0	5.7	-6.4, 17.8
Le Saux, 2005[89]	≤2yrs	Clinical resolution at day 14	89	92	85.4	79.3	6.0	-5.0, 17.1
Random effects estimates			463	537	54.2	40.5	12.2	4.2, 20.2
Test of heterogeneity Chi-square test value							5.40	
Test of heterogeneity Chi-square test p-value							0.14	
Test of heterogeneity I-squared							44.5%	
Number Needed to Treat (NNT)							8 (5, 24)	
Test of publication bias, Egger's asymmetry test p-value							0.66	

Table 26. Ampicillin/Amoxicillin vs. Placebo; Outcome Indicator: Treatment Success Rate for Age >2 Years

Author, Year	Age	Definition of outcome	Amoxicillin/ Ampicillin Sample Size	Placebo Sample Size	Amoxicillin Success Rate (%)	Placebo Success Rate (%)	Rate Difference In %	95% CI of Rate Difference In %
Burke, 1991[107]	3-<10yrs	Success at day 7	114	118	98.2	85.6	12.7	5.9, 19.4
Kaleida, 1991[108]	>2-12yrs	No effusion at day 14	226	209	47.8	32.1	15.7	6.7, 24.8
Le Saux, 2005[89]	>2-5yrs	Clinical resolution at day 14	161	148	96.9	87.2	9.7	3.7, 15.7
Random effects estimates			501	475	81.3	68.3	11.9	7.9, 16.0
Test of heterogeneity Chi-square test value							1.54	
Test of heterogeneity Chi-square test p-value							0.46	
Test of heterogeneity I-squared							0%	
Number Needed to Treat (NNT)							8 (6, 13)	
Test of publication bias, Egger's asymmetry test p-value							0.19	

Table 27. Amoxicillin-Clavulanate (7-10 Days) vs. Azithromycin (<5 Days); Outcome Indicator: Treatment Success Rate for Age ≤2 Years

Author, Year	Age	Definition of outcome	Amox-clav Sample Size	Azithromycin Sample Size	Amox-clav Success Rate (%)	Azithromycin Success Rate (%)	Rate Difference In %	95% CI of Rate Difference In %
Schaad, 1993[117]	≤2yrs	Success at day 7-20	14	14	85.7	85.7	0.0	-25.9, 25.9
Principi, 1995[118]	≤2yrs	Success at day 10-14	49	61	61.2	75.4	-14.2	-31.6, 3.2
Dunne, 2003[70]	≤2yrs	Success at day 10	52	59	84.6	76.3	8.3	-6.3, 23.0
Random effects estimates			115	134	74.8	76.94	-1.6	-16.6, 13.4
Test of heterogeneity Chi-square test value							3.88	
Test of heterogeneity Chi-square test p-value							0.14	
Test of heterogeneity I-squared							48.4%	
Test of publication bias, Egger's asymmetry test p-value							0.81	

Table 28. Amoxicillin-Clavulanate (7-10 Days) vs. Azithromycin (<5 Days); Outcome Indicator: Treatment Success Rate for Age >2 Years

Author, Year	Age	Definition of outcome	Amox-clav Sample Size	Azithromycin Sample Size	Amox-clav Success Rate (%)	Azithromycin Success Rate (%)	Rate Difference In %	95% CI of Rate Difference In %
Daniel, 1993[116]	>2-8yrs	Success at day 10-12	54	103	100.0	94.2	5.8	0.5, 11.1
Schaad, 1993[117]	>2-10yrs	Success at day 7-20	175	178	98.3	94.4	3.9	0.0, 7.8
Principi, 1995[118]	>2-12yrs	Success at day 10-14	149	154	77.2	89.0	-11.8	-20.2, -3.4
Dunne, 2003[70]	>2-12yrs	Success at day 10	129	126	89.1	85.7	3.4	-4.7, 11.5
Random effects estimates			507	561	89.9	90.9	0.8	-6.6, 8.3
Test of heterogeneity Chi-square test value							18.2	
Test of heterogeneity Chi-square test p-value							<0.001	
Test of heterogeneity I-squared							83.5%	
Test of publication bias, Egger's asymmetry test p-value							0.38	

Table 29. Comparison of Treatment Success Rate Between Age ≤2 And Age >2 Years by Treatment Option Based on Pooled Data

Treatment	Studies	Success Rate in %		Rate Difference in % (95% CI)
Ampicillin/Amoxicillin	4 studies for age <=2 years (Howie, 1972[106]; Kaleida, 1991[108]; Damoiseaux, 2000[88]; Le Saux, 2005[89]) 3 studies for age >2 years (Burke, 1991[107]; Kaleida, 1991[108]; Le Saux, 2005[89])	Age <=2 Age > 2	52.% (241/463) 75% (376/501)	-23% (-29, -17)
Placebo	4 studies for age <=2 years (Howie, 1972[106]; Kaleida, 1991[108]; Damoiseaux, 2000[88]; Le Saux, 2005[89]) 3 studies for age >2 years (Burke, 1991[107]; Kaleida, 1991[108]; Le Saux, 2005[89])	Age <=2 Age > 2	37% (200/537) 63% (297/475)	-25% (-32, -19)
Amoxicillin-clavulanate (7-10 days)	3 studies for age <=2 years (Schaad, 1993[117]; Principi, 1995[118]; Dunne, 2003[70]) 4 studies for age >2 years (Daniel, 1993[116]; Schaad, 1993[117]; Principi, 1995[118]; Dunne, 2003[70])	Age <=2 Age > 2	75% (86/115) 90% (456/507)	-15% (-22, -8)
Azithromycin (<5 days)	3 studies for age <=2 years (Schaad, 1993[117]; Principi, 1995[118]; Dunne, 2003[70]) 4 studies for age >2 years (Schaad, 1993[117]; Principi, 1995[118]; Dunne, 2003[70])	Age <=2 Age > 2	77% (103/134) 91% (510/561)	-14% (-20, -8)

Figure 11. Shrinkage Plot for Ampicillin/Amoxicillin vs. Placebo for Treatment Success for AGE ≤2 Years

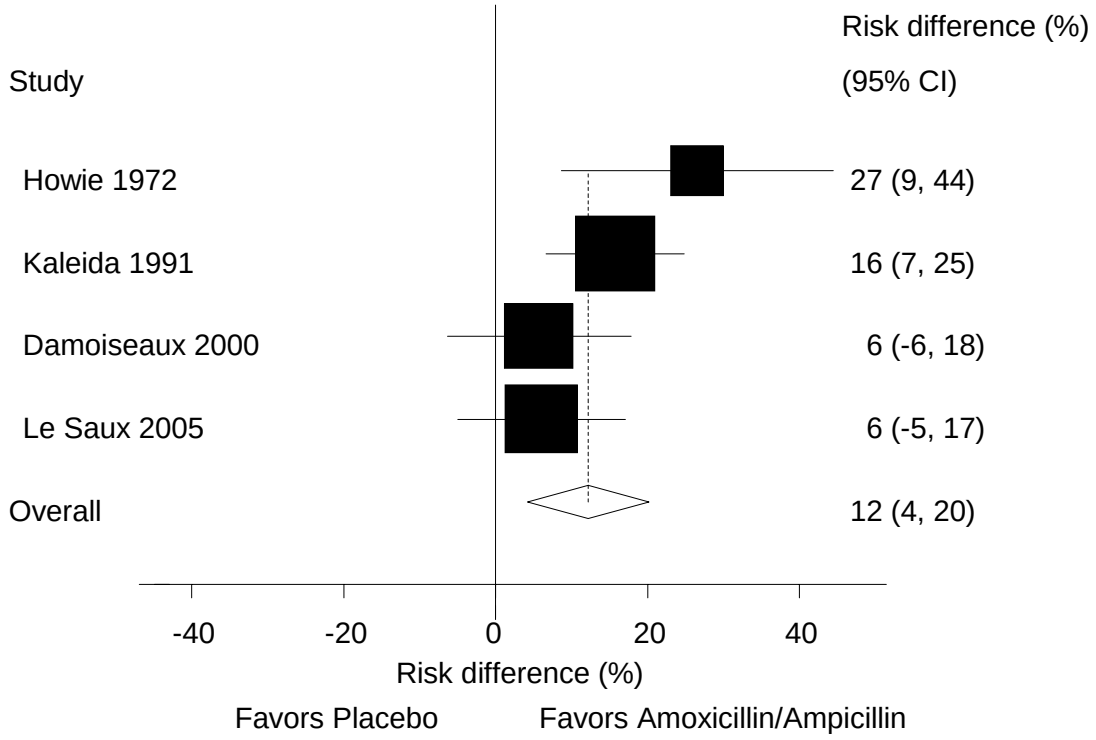


Figure 12. Shrinkage Plot for Ampicillin/Amoxicillin vs. Placebo for Treatment Success for AGE>2 Years

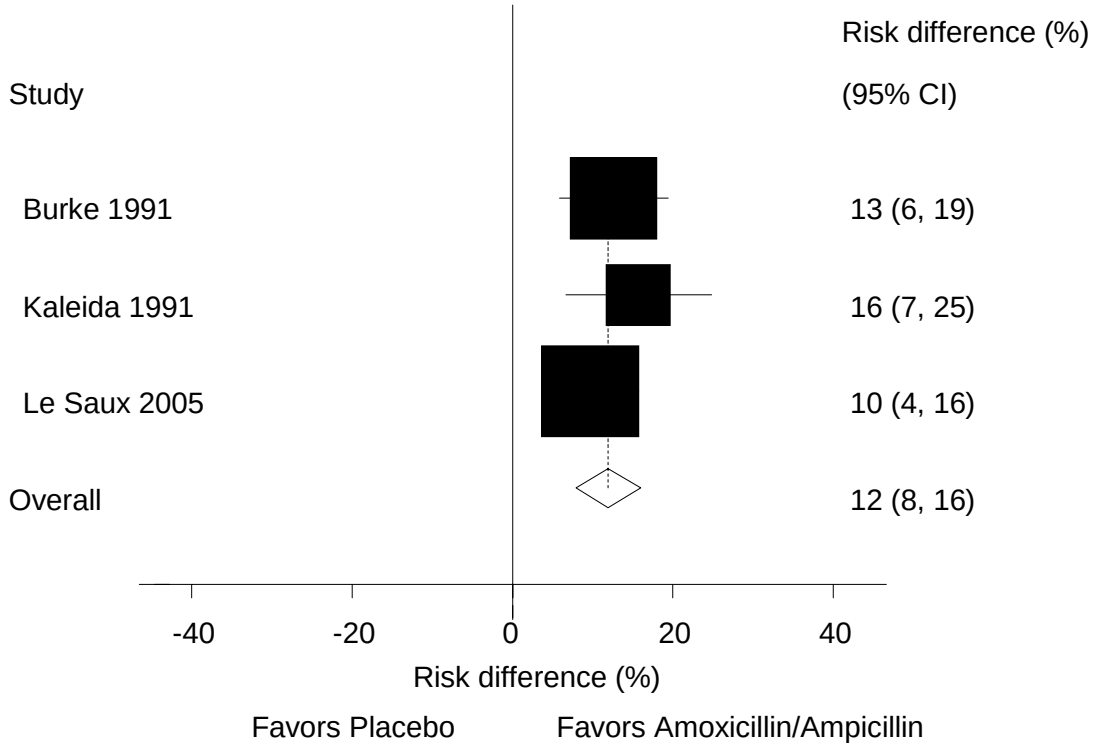


Figure 13. Shrinkage Plot for Amoxicillin-clavulanate (7-10 days) vs. Azithromycin (<5 days) for Treatment Success for AGE ≤2 Years

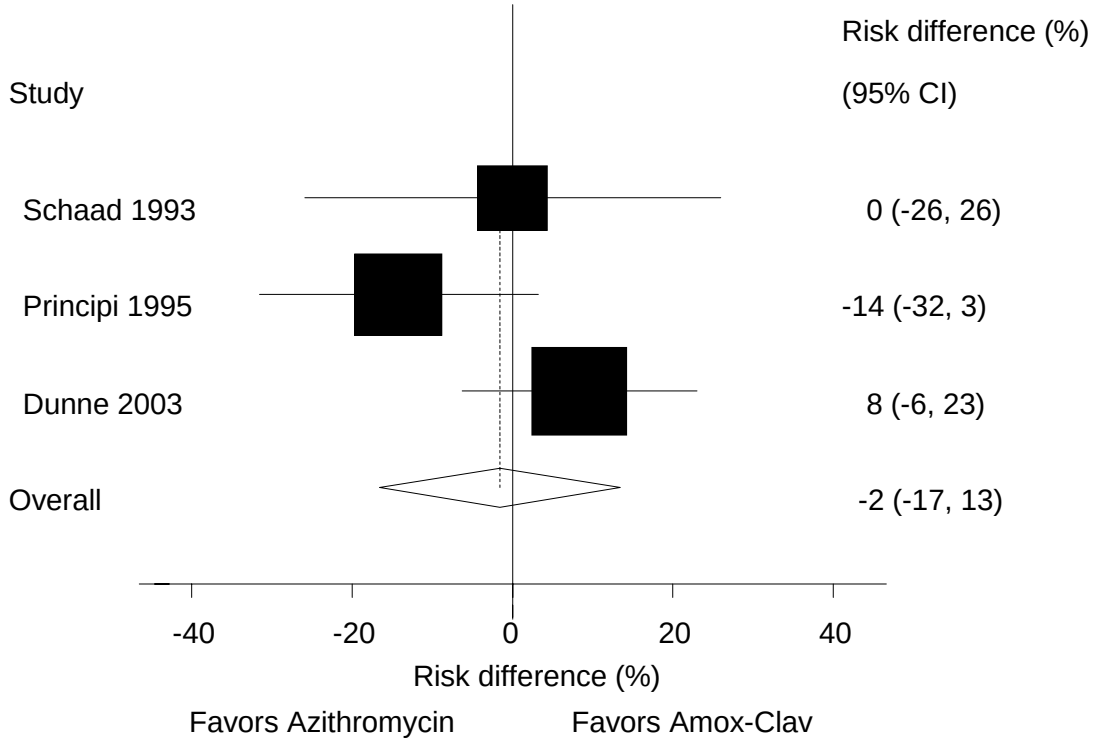
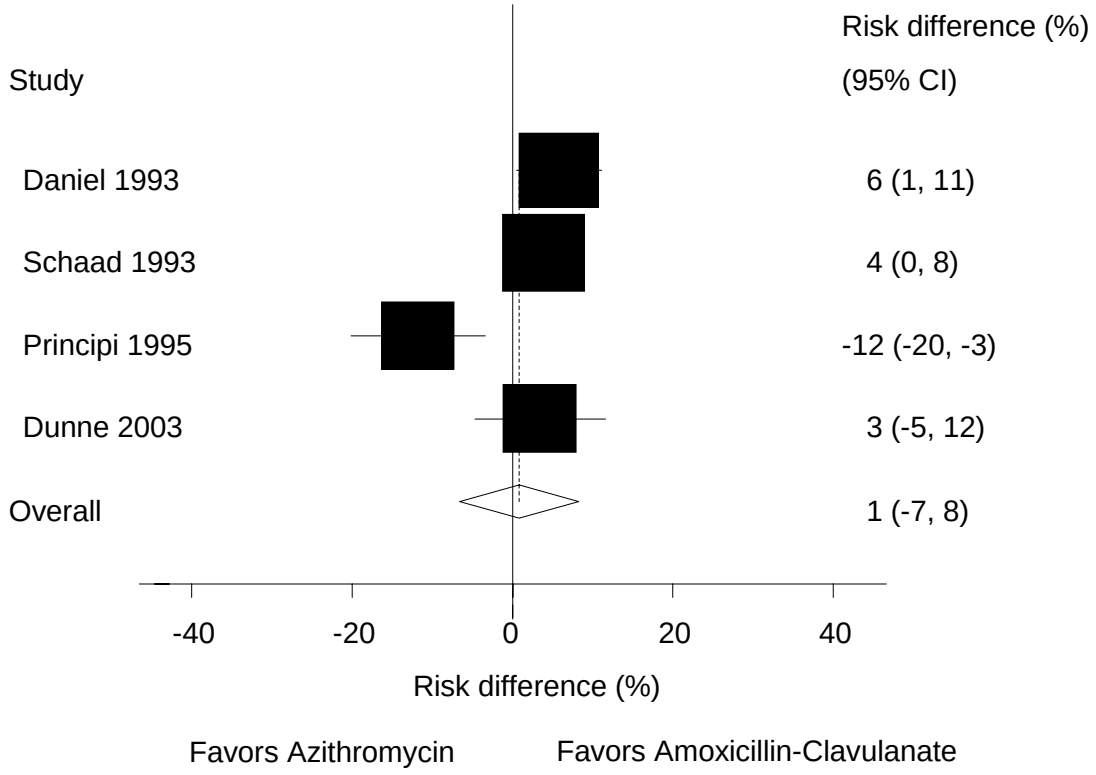


Figure 14. Shrinkage Plot for Amoxicillin-Clavulanate (7-10 days) vs. Azithromycin (<5 days) for Treatment Success for AGE >2 Years



Difference in treatment effect between age groups. In general, the results of individual trials and of meta-analyses show that children over the age of 2 have better outcomes from AOM, regardless of whether they are treated with antibiotics or not, compared to children 2 years of age or younger. No differences were seen in our meta-analyses in the rate difference for treatment success between children younger or older than 2 years when comparing ampicillin/amoxicillin to placebo or when comparing amoxicillin-clavulanate to azithromycin (Figures 11-14). Similar conclusions were found in an individual patient meta-analysis conducted by Rovers (2006).

Meta-analyses. Data from two trials, one comparing ampicillin or amoxicillin vs. placebo and the other comparing amoxicillin-clavulanate vs. azithromycin, demonstrated that children over 2 years old had better clinical success rates in both treatment arms for uncomplicated AOM than children 2 years old and under. First, comparing the clinical success between children 2 years old and under treated with ampicillin or amoxicillin in four trials[88, 89, 106, 108] with children over 2 years of age in three trials[89, 107, 108] treated with ampicillin or amoxicillin, a rate difference of -23% (95% CI: -29%, -17%; NNT=4 (95% CI: 3, 6)) favoring treatment of children over 2 years old was demonstrated (Table 29). A similar result was demonstrated utilizing the same trials to compare children 2 years of age and under with those over 2 years of age treated with placebo, resulting in a rate difference of -25% (95% CI: -32, -19%; NNT=4 (95% CI: 3, 5)

favoring children over 2 years old. Thus, children over 2 years of age had better clinical success rates in both ampicillin and placebo groups for treatment of uncomplicated AOM.

Comparing the clinical success between children 2 years old and under treated with amoxicillin-clavulanate in three trials[70, 117, 118] with those over 2 years old in four trials,[70, 116-118] a rate difference of -15% (95% CI: -22%, -8%); NNT=7 (95% CI: 5, 13), favoring treatment of children over 2 years old was demonstrated (Table 29). A similar result was demonstrated using the same trial to compare children 2 years old or less treated with azithromycin with those over 2 years old, resulting in a rate difference of -14% (95% CI: -20, -8; NNT=7, 95% CI: 5, 13), favoring treatment of children over 2 years old.

Thus, children over 2 years old also had better clinical success rates in both ampicillin/amoxicillin, amoxicillin-clavulanate and azithromycin groups for treatment of uncomplicated AOM. Children over 2 years were also more likely to get better on their own than children 2 and under.

Individual studies. Four additional individual RCTs demonstrated a higher clinical success rate for children older than two years of age than for children less than two years of age using an *a priori* established MCID of +/- 5%.

The 2005 study by LeSaux demonstrated success rate differences between 6-23-month-old children and 2-5-year-old children of –12% (95% CI: -19, -5.3; NNT=8, 95% CI: 5, 19) for amoxicillin treatment and of –8% (95% CI: -18, 1.6; NNT= 13, 95% CI: 5, 63) for placebo.[89]

A 2000 study by Block demonstrated a success rate difference for twice-daily cefdinir between children under 2 years old and those 2 years old and older of –34% (95% CI: -50, -19; NNT=3, 95% CI: 2, 5).[85]

Another 2000 study by Block also demonstrated a success rate difference for twice daily cefprozil between children under 2 years old and those 2 years old and older of –17% (95% CI: -29, -5.5; NNT=6, 95% CI: 3, 18).[85]

The 2000 study by Cohen that compared the effectiveness of 5- and 10-day cefpodoxime treatments did not report the clinical success rate by age but performed a multivariate analysis and reported that younger age (Odds ratio [OR] 1.074, p=0.0096), treatment duration (OR not reported), day-care attendance (OR 0.390, p=0.0098), and history of OME (OR 0.346, p=0.0091) "were independently predictive of poor treatment" outcome.[100]

Previous systematic reviews. Using individual patient data from six of ten eligible studies identified, a systematic review[56] provided information on the effect of antibiotic treatment of uncomplicated AOM between age groups. Though Rovers (2006) reported that the effect of antibiotics was not modified by age alone, their data indicate that children 2 years of age or older had less pain or fever at 3-7 days than those younger than 2 years old when not treated with antibiotics (RD=-17%, 95% CI: -24, -10; NNT=6, 95% CI: 4, 10) and also when treated with antibiotics (RD=-13%, 95% CI: -19,-7; NNT=8, 95% CI: 5, 14). As noted below, age and laterality together modify the effect of treatment.

Difference in treatment effect within age groups. A difference in treatment effect within age groups was demonstrated in one meta-analysis conducted for this review and in a previous meta-analysis that used individual patient data (Rovers, 2006). Another meta-analysis conducted for this review and a previous meta-analysis that looked only at children 2 years old or under (Damoiseaux, 1998) showed no difference between treatment groups.

Meta-analyses. Comparing ampicillin or amoxicillin vs. placebo by age group showed a rate difference of 12% (95% CI: 4%, 20%; NNT=8; 95% CI: 5, 25), favoring ampicillin/amoxicillin

in children 2 years old and under.[88, 89, 106, 108]and a rate difference of 12% (95% CI: 8%, 16%; NNT=8, 95% CI: 6, 13), favoring ampicillin/amoxicillin in children over 2 years old.[89, 107, 108]The meta-analyses showed no heterogeneity within each group of articles and no evidence of publication bias. (Table 25, Table 26, Figure 11 and Figure 12) It should be noted that the Howie (1972), Burke (1991), and Kaleida (1991) studies had 95% confidence intervals outside of the MCID favoring ampicillin/amoxicillin.[106-108]Thus, the only definitive conclusion possible from these data is that for children over 2 years old, ampicillin/amoxicillin appears to have an advantage over placebo (NNT=8, 95% CI: 6, 13).

Comparing amoxicillin-clavulanate vs. azithromycin by age group showed a rate difference of –2% (95% CI: -17%, 13%) in children 2 years old and under and a rate difference of 0.8% (95% CI: -7%, 8%) in children over 2 years old[70, 117, 118] in meta-analyses that showed possible heterogeneity within the group of articles reporting data for children over 2 years of age but no evidence of publication bias. (Table 27, Table 28, Figure 13, and Figure 14) It should be noted that the study by Principi (1995) had 95% confidence intervals clearly favoring azithromycin for children over 2 years, unlike the other studies.[118] Thus, no conclusion regarding the advantage of either treatment over the other or their equivalence for either age group can be made.

Previous systematic reviews. Two systematic reviews (Damoiseaux, 1998; Rovers, 2006) provide information on the role of age within treatment groups for uncomplicated AOM in average risk children. Damoiseaux (1998) studied children under two years old and found no effect of antibiotics on clinical improvement within seven days (OR 1.31, 95% CI: 0.83-2.08). Rovers found a positive effect of antibiotics on pain, fever, or both at 3-7 days for both age groups, and the rate difference for children 2 years old or under was –15% (95% CI: -23, -7; NNT=7, 95% CI: 4, 14), whereas that for children over 2 years old was –11% (95% CI: -16, -6; NNT=9, 95% CI: 6, 17).

Laterality Factor in Uncomplicated Acute Otitis Media

We identified two individual articles and one systematic review that analyzed the effectiveness of treatment options by laterality. Table 30 provides a summary of the findings.

Table 30. Summary of Findings from Two Articles and One Previous Systematic Review Reporting Effectiveness of Interventions in Uncomplicated Otitis Media Stratified by Laterality

<table>
<tr><th>Comp #</th><th>Comparison</th><th>Article</th><th>Patient Population</th><th>Intervention</th><th>Findings</th><th>Conclusion</th></tr>
<tr><td>1</td><td>Amoxicillin vs. Erythromycin</td><td>Scholz, 1998[4]</td><td>6 months-11 years
19 centers in Germany
Pediatric practice</td><td>Amoxicillin 50 mg/kg/day / bid for 10 days
vs.
Erythromycin 40 mg/kg/day / bid for 10 days</td><td>Outcome: Clinical success on day 9-11 by laterality (combines both antibiotic groups)<table><tr><td>Bilateral</td><td>Unilateral</td><td>Diff(95% CI)</td></tr><tr><td>87.3% (69/79)</td><td>97.5% (196/201)</td><td>-10%(-16, -4)</td></tr></table></td><td>Not enough evidence to conclude</td></tr>
<tr><td>2</td><td>Amox-clav vs. Cefprozil</td><td>Hedrick, 2001[76]</td><td>6 months-7years
Multi-centers in U.S.</td><td>Amoxicillin-clavulanate 90/6.4 mg/kg/day / bid for 10 days
vs.
Cefprozil 30 mg/kg/day / bid for 10 days</td><td>Outcome: Clinical success (cure or improved) at day 4-7 after treatment by Laterality<table><tr><td></td><td>A-C</td><td>Cefprozil</td><td>Diff (95% CI)</td></tr><tr><td>Total</td><td>89% (116/130)</td><td>87% (110/127)</td><td>2% (-6, 10)</td></tr><tr><td>Unilateral</td><td>93% (66/71)</td><td>89% (73/82)</td><td>4% (-5.2, 13)</td></tr><tr><td>Bilateral</td><td>85% (50/59)</td><td>82% (37/45)</td><td>3% (-11, 17)</td></tr><tr><td>Diff (95% CI)</td><td>8% (-3, 19)</td><td>7% (-5.4, 19)</td><td></td></tr></table></td><td>Not enough evidence to conclude</td></tr>
<tr><td>3</td><td>Antibiotic vs. placebo</td><td>Rovers, 2006[56]</td><td>0-12years
Systematic review of individual patient data from six studies</td><td>Antibiotics vs. No antibiotic</td><td>Outcome: Pain, fever, or both at 3-7 days by Laterality<table><tr><td></td><td>Unilateral</td><td>Bilateral</td><td>Diff (95% CI)</td></tr><tr><td>Antibiotic</td><td>24% (104/432)</td><td>27%(64/237)</td><td>-3%(-10, 4)</td></tr><tr><td>Placebo</td><td>30%(132/440)</td><td>47%(104/219)</td><td>-17%(-25, -10)</td></tr><tr><td>Diff (95% CI)</td><td>-6%(-12, 0)</td><td>-20%(-28, -11)</td><td></td></tr><tr><td><2 years old</td><td></td><td></td><td></td></tr><tr><td>Antibiotic</td><td>35%(45/129)</td><td>30%(42/139)</td><td>5%(-6, 16)</td></tr><tr><td>Placebo</td><td>40%(53/132)</td><td>55%(74/134)</td><td>-15%(-27, -3)</td></tr></table></td><td>In the no antibiotic group, a smaller proportion of children with unilateral disease had pain or fever at 3-7 days then children with bilateral disease; but, not enough evidence to conclude</td></tr>
</table>

Diff (95%CI)	-5%(-17, 7)	-25%(-36, -14)		when stratified by age.
≥ 2 years old				
Antibiotic	19%(59/304)	23%(20/87)	-4%(-14, 5)	
Placebo	26%(79/307)	35%(30/86)	-9%(-20, 2)	
Diff (95% CI)	-7%(-14, 0)	-12%(-25, 1)		

Difference in treatment effect between laterality groups. In general, the results of individual trials and meta-analyses show that children with bilateral disease responded as well to treatment as those with unilateral disease. If left untreated, children with unilateral disease did better than those with bilateral disease.

Individual studies. Scholz 1998 compared amoxicillin with erythromycin in 280 children ranging in age from 6 months to 11 years at days 9 to 11 after treatment initiation (Jadad quality score was 5 out 5).[127] This study demonstrated a success rate difference between unilateral and bilateral AOM for children on either amoxicillin or erythromycin of -10% (95% CI: -16, -4[NNT=10, 95% CI: 6, 25]).

Hedrick 2001 compared amoxicillin-clavulanate with cefprozil in 257 children ranging in age from 6 months to 7 years at days 4 to 7 after treatment initiation (Jadad quality score was 2 of 5).[128] This study demonstrated a lack of success rate differences between unilateral and bilateral AOM for amoxicillin-clavulanate of 8% (95% CI: -3%, 19%) and for cefprozil of 7% (95% CI: -5.4%, 19%).

Previous systematic reviews. A meta-analysis by Rovers (2006) of individual patient data from six studies reported data showing a greater proportion of children without pain or fever at 3-7 days in children with unilateral compared to bilateral disease when not treated with antibiotics (RD=-18, 95% CI: -25,-10; NNT=6, 95% CI: 4, 10).[53] The effect of laterality was not seen in the group treated with antibiotics (RD=-3%, 95% CI: -10, 4).

Treatment effect within laterality groups. The comparison of treatment effect in an individual study and a previous systematic review identified for the present review generally showed better clinical outcomes for children receiving antibiotics than for those receiving no treatment among children with bilateral AOM but not for those with unilateral disease; this difference was also seen in children less-than two years old.

Individual studies. The Hedrick 2001 study also demonstrated a lack of success rate differences between amoxicillin-clavulanate cefprozil treatment among patients with unilateral AOM (RD=4%, 95% CI: -5.2, 13) and those with bilateral AOM (RD= 3%, 95% CI: -11, 17).

Previous Systematic Reviews. Rovers' (2006) meta-analysis of individual patient data from six studies reported a benefit for antibiotics compared to placebo for resolving pain and/or fever at 3 to 7 days in children with bilateral disease (RD=-20%, 95% CI: -28%, -11%; NNT=5, 95% CI: 4, 9) but not for children with unilateral disease (RD=-6%, 95% CI: -12, 0). When stratified by age, this effect was seen in children under 2 years of age with bilateral AOM, as treatment with antibiotics resulted in a significant resolution of pain or fever at 3-7 days compared to placebo (RD=-25%, 95% CI: -36%, -14%; NNT=4, 95% CI: 3, 7) but not for children under 2 years old with unilateral disease (RD=-5%, 95% CI: -17, 7).

Childcare Setting Factor in Uncomplicated Otitis Media

We identified two studies by Cohen that analyzed the effectiveness of treatment options by child care setting (home vs. caretaker vs. sitter vs. external day care). Table 31 provides a summary of the findings.[98, 100] The 1998 study by Cohen compared the clinical success of 5-and 10-day regimens of amoxicillin-clavulanate by child care setting among 518 children 4 to 30 months of age (Jadad quality score was 5). The 2000 study by Cohen compared the clinical success of 5- and 10-day cefpodoxime regimens by child care setting among 649 children 4 to 30

months of age (Jadad quality score was 3). The following success rate differences were found between home and outside care sites (either sitter or day-care):

- Amoxicillin-clavulanate 5-day regimen, 14% (95% CI: 1.1%, 28%)
- Amoxicillin-clavulanate 10-day regimen, 3% (95% CI: -7%, 13%)
- Cefpodoxime 5-day regimen, 7% (95% CI: -3.4%, 17%)
- Cefpodoxime 10-day regimen, –0.3% (95% CI: -7.5%, 7%).

Table 31. Summary of Findings from 2 Articles Reporting Effectiveness of Interventions in Uncomplicated Otitis Media Stratified by Childcare Setting

<table>
<tr><th>Comp #</th><th>Comparison</th><th>Article</th><th>Patient Population</th><th>Intervention</th><th>Findings</th><th>Conclusion</th></tr>
<tr><td>1</td><td>Amox-clav 5d vs. Amox-clav 10d</td><td>Cohen, 1998[98]</td><td>4-30 months
Multi-centers in France</td><td>Amoxicillin-clavulanate 80/10 mg/kg/day / tid for 10 days
vs.
Amoxicillin-clavulanate 80/10 for 5 days</td><td>Outcome: Clinical success (cure or improve) per protocol population by setting of child care
<table>
<tr><th></th><th>Amox-clav 5d</th><th>Amox-clav 10d</th><th>Diff (95% CI)</th></tr>
<tr><td>Home</td><td>85.1% (57/67)</td><td>89.6% (69/77)</td><td>-4.5%(-15, 6)</td></tr>
<tr><td>Caretaker</td><td>70.8% (68/96)</td><td>86.8.% (79/91)</td><td>-16% (-28, -4.2)</td></tr>
<tr><td>Sitter</td><td>73.6%(39/53)</td><td>88.6% (39/44)</td><td>-15%(-31, 0.9)</td></tr>
<tr><td>Day-care</td><td>67.3% (29/43)</td><td>85.1% (40/47)</td><td>-18%(-35, 0.3)</td></tr>
<tr><td>Diff (H-C) (95% CI)</td><td>14% (1.1, 28)</td><td>3% (-7, 13)</td><td></td></tr>
</table></td><td>Not enough evidence to conclude</td></tr>
<tr><td>2</td><td>Cefpodoxime 5d vs. Cefpodoxime 10d</td><td>Cohen, 2000[100]</td><td>4-30 months
Multi-centers in France</td><td>Cefpodoxime 8 mg/kg/day / bid for 10 days
vs.
Cefpodoxime 8 mg/kg/day / bid for 5 days</td><td>Outcome: clinical success (cure or improve) per protocol population by day-care modality
<table>
<tr><th></th><th>CPD 5d</th><th>CPD 10d</th><th>Diff (95% CI)</th></tr>
<tr><td>Home</td><td>88.1% (74/84)</td><td>92.2% (95/103)</td><td>-4.1% (-13, 4.4)</td></tr>
<tr><td>Caretaker</td><td>81.4% (101/124)</td><td>92.5% (99/107)</td><td>-11% (-20, -2.3)</td></tr>
<tr><td>Sitter</td><td>86.8% (66/76)</td><td>100%(47/47)</td><td>-13% (-23, -3.2)</td></tr>
<tr><td>Day-care</td><td>72.9% (35/48)</td><td>86.7% (52/60)</td><td>-14% (-29, 1.2)</td></tr>
<tr><td>Diff (H-C) (95% CI)</td><td>7% (-3.4, 17)</td><td>-0.3% (-7.5, 7)</td><td></td></tr>
</table></td><td>Not enough evidence to conclude</td></tr>
</table>

Thus, no conclusion can be drawn regarding differences in clinical success of a treatment option with the type of caretaker and setting based on these two studies.

Other Factors Studied in Uncomplicated Otitis Media

We identified only four other factors whose influence on treatment effectiveness was assessed---severity factor, presence of otorrhea at initial visit, examiner (parent vs. physician), and pneumococcal vaccine status---and only one article assessed the effect of each of these factors. Table 32 provides a summary of the findings. With one exception (presence or absence of otorrhea at initial visit), no differences were seen.

Table 32. Summary of Findings from Articles Each Reporting Effectiveness of Interventions in Uncomplicated Otitis Media Stratified by a Risk Factor

(A) Hearing deficit and severity

Comp #	Comparison	Article	Patient Population	Intervention	Findings	Conclusion
1	Amox-clav vs. Cefprozil	Hedrick, 2001[76]	6 months-7 years Multi-centers in U.S.	Amoxicillin-clavulanate 90/6.4 mg/kg/day / bid for 10 days vs. Cefprozil 30 mg/kg/day / bid for 10 days	Outcome: Clinical success (cure or improved) at day 4-7 after treatment by Severity A-C: Moderate 92% (83/90); Severe 82% (32/39); Diff (95% CI) 10% (-2, 22) Cefprozil: Moderate 85% (64/75); Severe 88% (45/51); Diff (95% CI) -3% (-15, 9) Diff (95% CI): Moderate 7% (-2.7, 17); Severe -6% (-21, 9)	Not enough evidence to conclude

(B) Otorrhea

Comp #	Comparison	Article	Patient Population	Intervention	Findings	Conclusion
1	Amoxicillin vs. Erythromycin	Scholz, 1998[4]	6 months-11 years 19 centers in Germany Pediatric practice	Amoxicillin 50 mg/kg/day / bid for 10 days vs. Erythromycin 40 mg/kg/day / bid for 10 days	Outcome: Clinical success on day 9-11 by otorrhea at entry Otorrhea at entry: 94.7% (36/38) No Otorrhea at entry: 94.6% (229/242) Diff (95% CI): 0.1%(-8, 8)	Not enough evidence to conclude

(C) Examiner

Comp #	Comparison	Article	Patient Population	Intervention	Findings	Conclusion
1	Aqueous lidocaine drop vs. placebo	Bolt, 2008[90]	3-17 years Tertiary children's hospital emergency department in Australia	2% aqueous lidocaine 3 drops hourly for 1 day vs. Placebo	Outcome: Reduction by 50% in pain score on day 30 Lidocaine / Placebo / Diff (95% CI) By parent: 90% (28/31) / 63% (20/32) / **27%(6, 48)** By doctor: 84% (26/31) / 66% (21/32) / 18% (-3.4,39) Diff (95% CI): 6% (-11, 23) / -3% (-26, 20) /	Significantly more reduction in pain by parent if treated with lidocaine. Not enough evidence to conclude for doctor's assessment

(D) Pneumococcal vaccine

Comp #	Comparison	Article	Patient Population	Intervention	Findings	Conclusion
1	Amox-clav vs. Cefdinir	Block, 2004[75]	6 months-6years Multi-centers in U.S.	Amoxicillin-clavulanate 45/6.4 mg/kg/day / bid for 10 days vs. Cefdinir 14 mg/kg/day / bid for 5 days	Outcome: Success at end-of-treatment visit (study days 7-9 for Cefdinir; study days 12-14 for Amox-clav) by PCV7 Amox-clav / Cefdinir / Diff (95% CI) Had PCV7: 82% (102/124) / 92% (115/125) / -10%(-18, -2) No PCV7: 91% (62/68) / 80% (55/69) / 11% (-0.8, 23) Diff (95% CI): -9% (-20, 1.5) / 12% (2.4, 22) /	Not enough evidence to conclude

Moderate vs. severe disease. The 2001 study by Hedrick compared the clinical success of amoxicillin-clavulanate with that of cefprozil stratified by illness severity among 255 children ranging in age from 6 months to 7 years (Jadad quality score 2).[76] This study demonstrated success rate differences between moderate and severe disease for amoxicillin-clavulanate of 10% (95% CI: -2%, 22%) and for cefprozil of -3% (95% CI: -15%, 9%).

Presence or absence of otorrhea. Scholz (1998) compared the clinical success of amoxicillin vs. erythromycin, stratified by the presence or absence of otorrhea at initial visit, among 280 children, ranging in age from 6 months to 11 years (Jadad quality score 5).[4] This study demonstrated a success rate difference between those with and without otorrhea at study entry and treated with either amoxicillin or erythromycin of 0.1% (95% CI: -8, 8). Data from a systematic review by Rovers (2006) using individual patient data from six studies suggested that in children not treated with antibiotics, those with otorrhea were more likely to have pain, fever, or both at 3-7 days than those without otorrhea, a rate difference of 18% (95% CI: 4%, 32%), but this was not the case for children on antibiotics, where no difference was demonstrated (RD=-4%, 95% CI: -18%, 10%). The Rovers (2006) systematic review also found that the benefit from antibiotics vs. no antibiotics for resolution of pain, fever, or both at 3-7 days was greater for children with otorrhea (RD=-36%, 95% CI: -53%, -19%; NNT=3, 95% CI: 2, 5) than for children without otorrhea (RD=-14%, 95% CI: -23%, -5%; NNT=8, 95% CI: 4, 20).

Physician vs. parent assessment. Bolt (2008) compared the reduction in pain score using aqueous lidocaine drop vs. placebo, stratified by assessor— parent vs. doctor—among 162 children ranging in age from 3 to 17 years (Jadad quality score 4).[90] This study demonstrated 50% pain score reduction differences between those examined by a parent vs. a doctor when using lidocaine of 6% (95% CI: -11%, 23%) and for placebo of -3% (95% CI: -26, 20). Although the type of examiner had no significant effect within treatment groups, lidocaine was significantly better than placebo in the children with a parent examiner (difference of 27% [95% CI: 6%, 48%]).

Vaccine treatment. Block (2004) compared the clinical success of amoxicillin-clavulanate with cefdinir (5 days) stratified by whether the patient had received PCV7 vaccine or not, among 386 children ranging in age from 6 months to 6 years (Jadad quality score 2).[75] The study demonstrated success rate differences between those who received PCV7 and those who did not receive PCV7 of –9% (95% CI: -20%, 1.5%) for amoxicillin-clavulanate and of 12% (95% CI: 2.4%, 22%) for cefdinir.

Effectiveness of Treatments in Recurrent Otitis Media, Stratified by Age, Laterality, and Severity

We identified three studies that analyzed the effectiveness of treatment options by age groups in recurrent otitis media.[122-124] The 2005 study by Sher also provided subgroup analysis by laterality and severity.[122] Table 33 provides a summary of the findings.

Table 33. Summary of Findings from Three Articles Reporting Effectiveness of Interventions in *Recurrent* Otitis Media Stratified by *Age, Laterality,* and *Severity.*

(A) Age

Comp #	Comparison	Article	Patient Population	Intervention	Findings	Conclusion
1	Amox-clav vs. Azithromycin	Arrieta, 2003[124]	0.5-6 years 13 US and 5 Latin American centers	Amox-clav (95mg/kg, bid, 10d) Azithromycin (20mg/kg, qd, 3d)	Outcome: Success rate on day 12-16 | | Amox-clav | Azithromycin | Diff (95% CI) | | <=2yrs | 79% (73/92) | 85% (82/96) | -6% (-17, 5) | | >2yrs | 92% (49/53) | 87% (46/53) | 5% (-7, 17) | | Diff (95% CI) | -13% (-26, -0.5) | -2% (-14, 10) | |	Not enough evidence to conclude
2	Amox-clav vs. Gatifloxacin	Sher, 2005[122]	0.5-7 years 26 sites in US 1 site in Costa Rica	Amox-clav (90mg/6.4mg/kg/d in 2 doses), 10d Gatifloxacin (10mg/kg, qd) 10d	Outcome: Success rate on day 10 (test of day visit) by age group | | Amox-clav | Gatifloxacin | Diff (95% CI) | | <2yrs | 78% (45/58) | 79% (49/62) | -1% (-16, 14) | | >=2yrs | 80% (47/59) | 90% (56/62) | -11% (-23,2.7) | | Diff (95% CI) | -2% (-17, 13) | -11% (-24, 1.7) | |	Not enough evidence to conclude

Comp #	Comparison	Article	Patient Population	Intervention	Findings	Conclusion
3	Amox-clav vs. Levofloxacin	Noel, 2008[123]	0.5-<5 years 66 centers in 6 countries, incl US	Amox-clav (45mg/kg bid, 10d) Levofloxacin (10mg/kg bid, 10d)	Outcome: Clinical success (cure and improved) at 10-17 days	Not enough evidence to conclude difference in effectiveness between treatments within each age group. Age <=2yrs had lower success rate for both treatments.

	Levofloxacin	Amox-clav	Diff (95% CI)
0.5-2yr	79% (318/404)	76% (315/417)	-3.2 (-8.9, 2.6)
>2-<5yr	90% (267/296)	87% (263/302)	-3.1 (-8.2, 2.0)
Diff (95% CI)	-11% (-16, -5.5)	-11% (-17, -5.1)	

(B) Laterality

Comp #	Comparison	Article	Patient Population	Intervention	Findings	Conclusion
1	Amox-clav vs. Gatifloxacin	Sher, 2005[122]	0.5-7 years 26 sites in US 1 site in Costa Rica	Amox-clav (90mg/6.4mg/kg/d in 2 doses), 10d Gatifloxacin (10mg/kg, qd) 10d	Outcome: Success rate on day 10 (test of day visit) by laterality	Not enough evidence to conclude

	Amox-clav	Gatifloxacin	Diff (95% CI)
Unilateral	82% (40/49)	84% (48/57)	-3% (-17, 12)
Bilateral	76% (52/68)	85% (57/67)	-9% (-22, 4.7)
Diff (95% CI)	6% (-9, 21)	-1% (-14, 12)	

(C) Severity

<table>
<tr><th>Comp #</th><th>Comparison</th><th>Article</th><th>Patient Population</th><th>Intervention</th><th>Findings</th><th>Conclusion</th></tr>
<tr><td>1</td><td>Amox-clav vs. Gatifloxacin</td><td>Sher, 2005[122]</td><td>0.5-7 years
26 sites in US
1 site in Costa Rica</td><td>Amox-clav (90mg/6.4mg/kg/d in 2 doses), 10d
Gatifloxacin (10mg/kg, qd) 10d</td><td>Outcome: Success rate on day 10 (test of day visit) by severity
<table>
<tr><td></td><td>Amox-clav</td><td>Gatifloxacin</td><td>Diff (95% CI)</td></tr>
<tr><td>Mild/Mod</td><td>85% (45/53)</td><td>84% (47/56)</td><td>1% (-13, 15)</td></tr>
<tr><td>Severe</td><td>73% (47/64)</td><td>85% (58/68)</td><td>-12 (-26, 2)</td></tr>
<tr><td>Diff (95% CI)</td><td>12% (-3, 27)</td><td>-1% (-14, 12)</td><td></td></tr>
</table></td><td>Not enough evidence to conclude</td></tr>
</table>

The three studies compared the effectiveness of amoxicillin-clavulanate vs. three different treatments: azithromycin,[124] gatifloxacin,[122] and levofloxacin[123] by age groups. It can be observed from the 95% confidence intervals that no definitive conclusions could be made for the first two comparisons. For levofloxacin, Noel (2008) demonstrated a success rate difference by day 17 between 0.5-2-year-old children and 2-5 year old children treated with levofloxacin of –11% (95% CI: -16, -5.5); the confidence limit outside of the MCID (NNT=9, 95% CI: 6, 18), implies a lower success rate for younger children.[123] A similar age association was seen for amoxicillin-clavulanate in this study, with a success rate difference between the two age groups of –11% (95% CI: -17, -5; NNT=9, 95% CI: 6, 20). It should be noted that the differences in clinical success rate between levofloxacin and amoxicillin-clavulanate within each age group was not significant.

Sher (2005) included stratified analysis by laterality and by severity. Based on the 95% confidence intervals for the success rates, no definitive conclusions can be made, and more data or studies are needed.[122]

Summary

For uncomplicated AOM, the available evidence indicates that treatment effect may be modified by age, laterality, and otorrhea. In a meta-analysis conducted for this report, children over 2 years old did better than children two years old and under in the ampicillin/amoxicillin group (NNT=4, 95% CI: 3, 6) and in the placebo group (NNT=4, 95% CI: 3, 5). A systematic review by Rovers (2006) reported data that also show that children 2 years and older had less pain or fever at 3-7 days than younger children, whether treated or not treated with antibiotics. Comparing children over 2 years to those two and under, another meta-analysis in this review showed the older age group with better clinical success than the younger age group whether treated with amoxicillin-clavulanate (NNT=7, 95% CI: 5, 13) or with azithromycin (NNT=7, 95% CI: 5, 13). In addition three individual studies showed greater success rates in children older than two years of age in treatment of uncomplicated AOM with amoxicillin, cefdinir, and cefprozil and also in the placebo group of one study.[85, 89, 163]

In addition, for children over 2 years old, ampicillin/amoxicillin appeared to have an advantage over placebo (NNT=8, 95% CI: 6, 13). For children 2 years old and under, the 95% confidence interval also favored ampicillin/amoxicillin but crossed the +/-5% MCID, so a definitive conclusion could not be made. Meta-analyses by age sub-group for a comparison of amoxicillin-clavulanate vs. azithromycin were without definitive conclusion.

The systematic review by Rovers (2006) also found that the effect of antibiotics (compared to placebo or no treatment) was greater in children with bilateral AOM (NNT=5, 95% CI: 4, 9) than in those with unilateral AOM, in which there was no difference. Also, the increase in effect of antibiotics (compared to placebo or no treatment) in bilateral AOM was of greater magnitude in children 2 years and younger (NNT=4, 95% CI: 3, 7) than in children over 2 years old, in whom there was again no difference. We also identified two individual studies (Scholz, 1998; Hedrick, 2001) that assessed laterality, with results that did not allow for definitive conclusions and were not included in the Rovers (2006) systematic review.

Rovers (2006) also found that antibiotic effect was greater in children with AOM who had otorrhea (NNT=3, 95% CI: 2, 5) compared to those without otorrhea (NNT=8, 95% CI: 4, 20), and we identified one individual study (Scholz, 1998) that did not show such an effect.

Definitive conclusions could not be made regarding subgroup analyses by childcare setting, severity, examiner, or pneumococcal vaccine status.

For ROM, the available evidence in one study by Noel (2008) demonstrated an association of treatment success with age, favoring children older than two years of age treated with either levofloxacin (NNT=9, 95% CI: 6, 18) or amoxicillin-clavulanate (NNT=9, 95% CI: 6, 20).[123] However, the available evidence did not allow definitive conclusions when assessing available treatment options by laterality and severity, when taking into consideration both the 95% confidence limit and a +/-5 % zone of MCID.

The overall quality of evidence for these comparisons is considered low, meaning that further high quality research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Key Question VI.

What Adverse Effects Have Been Observed for the Treatments Whose Outcomes Are Addressed in Key Questions 3 and 4?

Description of the Studies

We examined the incidence of adverse events in the RCTs identified for this report that compared the effectiveness of one or more treatment options. We also searched the FDA MedWatch Database for adverse events associated with use of medications for the treatment of AOM; however, none could be identified.

Adverse Effects Observed In Treatment of Uncomplicated Acute Otitis Media

Of the 44 RCTs newly identified for this report that compared the effectiveness of treatment options in uncomplicated AOM, there are 63 treatment comparisons. Of the 63 treatment comparisons, 42 included comparisons of the percent of cases that had experienced an adverse event between pairs of treatment options. The incidence rate for each treatment group and the rate difference between two treatment options can be found in the Evidence Tables. The findings for newly identified RCTs are summarized in Table 34. The combined findings for the 2001 report and the present report are summarized in Table 34a.

Table 34. Findings of Adverse Events by Treatment Option Comparisons for Uncomplicated Otitis Media

Comp#	Comparison	Author, Year	Adverse effects reported	Significant Differences	Equivalence	Inconclusive
1	Amox vs. Amox+Fenspiride	Zielnik-Jurkiewicz, 2005[65]	No			
3	Amox vs. Ceftriaxone	Zhang, 2003[68]	No			
4	Amox vs. Erythromycin	Scholz, 1998[4]	Yes			Tx related, possibly tx related
5	Amox-clav vs. Amox-sulbactam	Casellas, 2005[69]	Yes		Severe diarrhea (0.7% in both treatment arm)	Any mention, diarrhea day 12-14, diarrhea day3, minor
6	Amox-clav vs. Azithromycin	Dagan, 2000[7]	Yes			Any mention, diarrhea, tx related, vomiting
7	Amox-clav vs. Azithromycin	Dunne, 2003[70]	Yes		Vomiting (1% vs. 2%)	Any mention, diarrhea, rash
8	Amox-clav vs. Azithromycin	Guven, 2006[52]	Yes			Any mention, abd pain, diarrhea
9	Amox-clav vs. Azithromycin	Biner, 2007[71]	Yes			Diarrhea, vomiting
10	Amox-clav vs. Cefaclor	Subba Rao, 1998[5]	Yes		Fever (0% vs. 1.7%)	Diarrhea, headache, vomiting
11	Amox-clav vs. Cefdinir	Block, 2000[72]	Yes	Any mention higher in Amox-clav (42% vs. 14% in CefQD and 23% in CefBID) Diarrhea higher in Amox-clav (35% vs. 10% in CefQD and 13% in CefBID)		Rash
12	Amox-clav vs. Cefdinir	Adler, 2000[73]	Yes			Any mention, diarrhea, tx related
13	Amox-clav vs. Cefdinir	Cifaldi, 2004[74]	No			
14	Amox-clav vs. Cefdinir	Block, 2004[75]	Yes			Diaper rash, diarrhea, vomiting
15	Amox-clav vs.	Hedrick, 2001[76]	Yes			Any mention, diarrhea,

Comp#	Comparison	Author, Year	Adverse effects reported	Significant Differences	Equivalence	Inconclusive
	Cefprozil					rash, vomiting
16	Amox-clav vs. Ceftriaxone	Cohen, 1999[77]	Yes	Any mention higher in Amox-clav (31% vs. 14%) Diarrhea higher in Amox-clav (27% vs. 14%)		
17	Amox-clav vs. Ceftriaxone	Wang, 2004[78]	Yes			Any mention, diarrhea, GI, skin and appendages, rash
18	Amox-clav vs. Ceftriaxone	Biner, 2007[71]	Yes			Diarrhea, vomiting
19	Amox-clav vs. Cefuroxime	Pessey, 1999[79]	Yes			Any mention, diarrhea
20	Azithromycin vs. Cefaclor	Dagan, 2000[81]	No			
21	Azithromycin vs. Cefaclor	Oguz, 2003[82]	Yes			Diarrhea, vomiting
22	Azithromycin vs. Cefdinir	Block, 2005[83]	Yes			Abnormal stool, diarrhea
23	Azithromycin vs. Ceftriaxone	Biner, 2007[71]	Yes			Diarrhea, vomiting
24	Cefaclor vs. Cefprozil	Carvalho, 1998[84]	Yes			Any mention, vomiting
25	Cefdinir vs. Cefprozil	Block, 2000[85]	Yes		Rash (3.2% vs. 3.8%)	Diarrhea
26	Cefaclor vs. Cefpodoxime	Tsai, 1998[86]	Yes			Any mention, abd discomfort, diarrhea, intolerable abd discomfort, intolerable urticaria, pruritis, skin rash, sweating
27	Cefaclor vs. Cefuroxime	Turik, 1998[125]	Yes		Asthma, respiratory disorder, vomiting (0% vs. 1%)	Any mention, diarrhea, diarrhea during tx, increased cough, rhinitis
28	Amox vs. Wait-and-see	McCormick, 2005[3]	Yes		Serious events (0% in both arms)	

Comp#	Comparison	Author, Year	Adverse effects reported	Significant Differences	Equivalence	Inconclusive
29	PcV vs. Wait-and-see	Neumark, 2007[87]	No			
30	Amox vs. Placebo	Damoiseaux, 2000[88]	Yes			Diarrhea day 4, diarrhea day 10
31	Amox vs. Placebo	Le Saux, 2005[89]	Yes			Diarrhea, rash
32	Lidocaine drop vs. Placebo	Bolt, 2008[90]	Yes			Ear discharge, dizziness
33	Probiotic vs. Placebo	Hatakka, 2007[91]	No			
34	Homeopathic vs. Placebo	Jacobs, 2001[92]	Yes		Any mention (0% in both arms)	
35	Amox vs. Prescription to Hold	Little, 2001[2]	No			
36	Amox vs. Prescription to Hold	Little, 2006[93]	No			
37	Antibiotic vs. Prescription to Hold	Spiro, 2006[94]	Yes	Diarrhea at 4-6 day follow-up higher in Antibiotic group (21% vs. 7%)		Diarrhea at 11-14 day follow-up, otalgia, vomiting
38	Prescription to Hold vs. Wait-and-see	Chao, 2008[95]	No			
39	Amox high vs. low dose	Garrison, 2004[96]	Yes			GI distress, skin rash
40	Amox-clav high vs. low dose	Pessey, 1999[79]	Yes			Any mention, diarrhea
41	Amox-clav high vs. low dose	Bottenfield, 1998[97]	Yes		Diaper rash (4% vs. 5%) Severe rash (1% vs. 0%) Severe erythema multiform (0% vs. 0.4%)	Any mention, need tx, cough, fever, severe diarrhea, URI, vomiting

Comp#	Comparison	Author, Year	Adverse effects reported	Significant Differences	Equivalence	Inconclusive
42	Amox-clav bid vs. tid	Damrikarnlert, 2000[6]	Yes		Severe GI (0% vs. 0.4%) Severe moniliasis (0.4% vs. 0%) Abd pain, enteritis, fever, rash (0.5% vs. 0%) Constipation, ear disorder, enlarged abdomen, enterocolitis, erythematous rash, nervousness, somnolence, stomatitis (ulcerative): (0% vs. 0.5%) Dermatitis (0.5% vs. 1.9%) Nervousness (1% vs. 0%) Otitis media (0.5% vs. 1%) Uticaria (0% vs. 1.5%) Vomiting (2% vs. 0.5%)	Tx related, diarrhea
43	Cefdinir high vs. low dose	Adler, 2000[73]	Yes			Any mention, diarrhea, tx related
44	Amox vs. Azithromycin	Arguedas, 2005 [66]	Yes		Rash (2.6% vs. 2.5%)	Abd pain, diarrhea, vomiting, tx related
45	Cefdinir high vs. low dose	Block, 2000[72]	Yes			Any mention, diarrhea, and rash

Comp#	Comparison	Author, Year	Adverse effects reported	Significant Differences	Equivalence	Inconclusive
46	Amox-clav 5-day vs. 10-day	Cohen, 1998[98]	Yes			Any mention, drug-related, diarrhea, skin rash
47	Cefaclor 5-day vs. 10-day	Catania, 2004[99]	Yes		Abd pain (1.5% vs. 2.4%) Skin rash (2.5% vs. 2.9%) Diarrhea (2.0% vs. 2.4%) Vomiting (0.5% vs. 0.5%)	New AOM episode
48	Cefpodoxime 5-day vs. 10-day	Cohen, 2000[100]	Yes			Any mention
49	Ceftriaxone vs. Ceftriaxone+Prednisolone	Chonmaitree, 2003[101]	No			
50	Ceftriaxone vs. Ceftriaxone+Antihistamine	Chonmaitree, 2003[101]	No			
51	Ceftriaxone vs. Ceftriaxone+Prednisolone+Antihistamine	Chonmaitree, 2003[101]	No			
52	Ceftriaxone+Prednisolone vs. Ceftriaxone+Antihistamine	Chonmaitree, 2003[101]	No			
53	Ceftriaxone+Prednisolone vs. Ceftriaxone+Prednisolone+Antihistamine	Chonmaitree, 2003[101]	No			

Comp#	Comparison	Author, Year	Adverse effects reported	Significant Differences	Equivalence	Inconclusive
54	Ceftriaxone+Antihistamine vs. Ceftriaxone+Prednisolone+Antihistamine	Chonmaitree, 2003[101]	No			
55	Ciprofloxacin-dexamethasone drops vs. Cipro otic drops	Roland, 2003[126]	Yes		Burning (1% vs. 2%) Excessive crying (1% vs. 1%) Pain (1% vs. 2%) Pruritus (1% vs. 1%) Taste perversion (0% vs. 1%)	Precipitate
56	Ciprofloxacin-dexamethasone drops vs. Ofloxacin drops	Roland, 2004[127]	Yes		Cough, crying, diarrhea, ear debris, edema eardrum, headache, hyperemia eardrum: (0% vs. 0.3%) Discomfort ear (3.4% vs. 1%) Dizziness, erythema, tinnitus, tympanostomy tube blockage: (0.3% vs. 0%) Super-Infection ear, irritation ear, pruritus ear, irritability, pruritus ear: (0% vs. 0.7%)	

Comp#	Comparison	Author, Year	Adverse effects reported	Significant Differences	Equivalence	Inconclusive
					Monilia oral (0.3% vs. 0.3%) Pain ear (2.4% vs. 3%) Precipitate ear (2.4% vs. 3%) Serious tx related (0% in both arms) Taste perversion (0.3% vs. 1%)	
57	Otikon drops vs. Topical Anesthetic	Sarrell, 2001[102]	Yes		Any mention (0% in both arms)	
58	Anesthetic vs. Anesthetic+Amox	Sarrell, 2003[103]	Yes		Any mention (0% in both arms)	
59	Anesthetic vs. NHED	Sarrell, 2003[103]	Yes		Any mention (0% in both arms)	
60	Anesthetic vs. NHED+Amox	Sarrell, 2003[103]	Yes		Any mention (0% in both arms)	
61	Anesthetic+Amox vs. NHED	Sarrell, 2003[103]	Yes		Any mention (0% in both arms)	
62	Anesthetic+Amox vs. NHED+Amox	Sarrell, 2003[103]	Yes		Any mention (0% in both arms)	
63	NHED vs. NHED+Amox	Sarrell, 2003[103]	Yes		Any mention (0% in both arms)	

Table 34a. Comparison of Rates of Adverse Events Between Drugs (Significant Differences Only)

Comparison	2001 Report		2009 Update			Conclusion
	Number of trials	AE rate Difference (95% CI)	Number of new trials	Total number of trials	AE rate difference (95% CI)	
Uncomplicated AOM						
Overall AE						
Amoxicillin-clavulanate (7-10d) vs. Azithromycin (5d)	3	19%(9%, 29%)	0	3	N/A	Amoxicillin-clavulanate associated with greater overall AE rate
Amoxicillin-clavulanate vs. cefdinir (qd)	0	N/A	1	1	28% (17%, 39%)	Amoxicillin-clavulanate associated with greater overall AE rate
Amoxicillin-clavulanate vs. cefdinir (bid)	0	N/A	1	1	19% (8%, 31%)	Amoxicillin-clavulanate associated with greater overall AE rate
Amoxicillin clavulanate vs. ceftriaxone	0	N/A	1	1	16% (9%, 24%)	Amoxicillin-clavulanate associated with greater overall AE rate
Gastrointestinal AEs						
Amoxicillin-clavulanate (7-10d) vs. Azithromycin (5d)	3	18% (8%, 28%)	0	0	N/A	Amoxicillin-clavulanate associated with greater rate of GI AE
Diarrhea						
Ampicillin or amoxicillin vs. cefixime	5	-8% (-13, -4)	0	0	N/A	Cefixime associated with greater rate of diarrhea
Amoxicillin clavulanate vs. cefdinir	0		1	1	25% (15%, 35%) in Cef QD and 22% (11%, 32%) in Cef BID	Amoxicillin clavulanate associated with greater rate of diarrhea
Amoxicillin clavulanate vs. ceftriaxone	0		1	1	13% (6%, 20%)	Amoxicillin clavulanate associated with greater rate of diarrhea

Comparison	2001 Report		2009 Update			Conclusion
	Number of trials	AE rate Difference (95% CI)	Number of new trials	Total number of trials	AE rate difference (95% CI)	
Recurrent Otitis Media						
Diarrhea						
Amoxicillin-clavulanate vs. ciprofloxacin-dexamethasone ear drops	0	N/A				Greater for amoxicillin-clavulanate in 1 study, but equivalent in 41; no conclusion possible in 23 comparisons

Table notes: AE adverse event; bid twice a day; CI confidence interval; d day; NNT number needed to treat; qd once a day

Using the 95% confidence intervals for the rate differences and the zone of MCID of 5% as reference, we grouped the findings into "significant differences," "equivalence," or "inconclusive." The findings in many studies are inconclusive. However some findings show significant differences or equivalence.

Diarrhea was found to be significantly higher in children treated with amoxicillin-clavulanate when compared to cefdinir[85] and ceftriaxone.[77] The adverse event rates ranged from 27% to 35% with amoxicillin-clavulanate and from 10% to 14% in the other treatment options. Diarrhea was also significantly higher in children treated with antibiotics (primarily amoxicillin) than in children given a prescription to hold on days 4-6 (23% vs. 8%; 95% CI: 6, 24) in one study.[94]

When any mention of an adverse event was considered, the rate for amoxicillin-clavulanate was found to be significantly higher than for cefdinir given once a day (42% vs. 14%),[85] higher than cefdinir given twice a day (42% vs. 23%),[85] and higher than ceftriaxone (31% vs. 14%).[77]

Findings of equivalence were identified in the following comparisons:

- Severe diarrhea in amoxicillin-clavulanate vs. amoxicillin-sulbactam (0.7% for both)[69]
- Vomiting in amoxicillin-clavulanate vs. azithromycin (1% vs. 2%)[70]
- Fever in amoxicillin-clavulanate vs. cefaclor (0% vs. 2%)[5]
- Rash in cefdinir vs. cefprozil (3% vs. 4%)[85]
- Serious events in amoxicillin vs. wait-and-see (0% for both)[3]
- Any mention of an adverse event in children receiving a homeopathic remedy vs. placebo (5% in both arms)[92]
- Diaper rash (4% vs. 5%), severe rash (1% vs. 0%), severe erythema multiform (0% vs. 0.4%), severe gastroenteritis (0% vs. 0.4%), and severe moniliasis (0.4% vs. 0%) in amoxicillin-clavulanate high dose vs. low dose[97]
- Abdominal pain, enteritis, fever, rash (0.5% vs. 0%), constipation, ear disorder, enlarged abdomen, enterocolitis, erythematous rash, nervousness, somnolence, ulcerative stomatitis (0% vs. 0.5%), dermatitis (0.5% vs. 2%), nervousness (1% vs. 0%), otitis media (0.5% vs. 1%), urticaria (0% vs. 1.5%), vomiting (2% vs. 0.5%) in amoxicillin-clavulanate twice daily vs. three times daily comparison[6]
- Rash (2.6% vs. 2.5%) in amoxicillin vs. azithromycin comparison[66]
- Abdominal pain (1.5% vs. 2.4%), skin rash (2.5% v. 2.9%), diarrhea (2% vs. 2.4%), vomiting (0.5% vs. 0.5%) in cefaclor 5-day vs. 10-day comparison[99]
- Any mention of an adverse event (0% in all arms) in comparisons between otikon drops, topical anesthetic, anesthetic plus amoxicillin, naturopathic treatment ear drops (NHED), and NHED plus amoxicillin[102]

Adverse Effects in Studies of Treatment of Acute Otitis Media in Children with Recurrent Otitis Media or Persistent Acute Otitis Media

Of the 58 RCTs identified in our review update that addressed the effectiveness of treatment options, 14 studied children with ROM, persistent AOM, or AOM treatment failure. Among the 14 studies are 21 treatment comparisons. Eight comparisons studied the treatment of AOM in children with presumed or explicitly defined recurrent and/or persistent AOM, and/or AOM with

treatment failure. Table 35 provides the findings on the comparison of the adverse event rates between treatment options for the eight comparisons.

Table 35. Comparison of Adverse Event Rates Between Treatment Options from Eight Comparisons on Effectiveness of Treatment of Acute Otitis Media in Recurrent Otitis Media

Comp #	Comparison	Author, Year	Patient Population	Intervention	Findings of Adverse Events	Conclusion
1	Amox-clav vs. gatifloxacin	Saez-Llorens, 2005[121]	0.5-7 years ROM and/or AOM treatment failure[a] 20 sites non-US	Amox-clav (45mg/6.4mg/kg/d in 2 divided doses, 10d) Gatifloxacin (10mg/kg, qday, 10d)		Arthralgia, diaper rash, serious events equivalent Drug-related, vomiting, diarrhea, abd pain inconclusive

	Amox-clav	Gatifloxacin	Diff(95%CI)
Any	59% (81/136)	55% (153/277)	4% (-6, 14)
Arthralgia	2% (2/136)	2% (6/277)	0% (-2.9, 2.9)
Drug-related	15% (20/136)	18% (49/277)	-3% (-11, 4.7)
Vomiting	5% (7/136)	8% (23/277)	-3% -8, 2.2)
Diarrhea	7% (10/136)	3% (8/277)	4% (-0.2, 8)
Abd pain	2% (2/136)	4% (11/277)	-2% (-5.7, 1.7)
Diaper rash	2% (3/136)	1% (2/277)	1%(-1.4, 3 .4)
Serious*	2% (2/136)	0% (0/277)	2%(0.3, 3.7)

* one was generalized seizure

Comp #	Comparison	Author, Year	Patient Population	Intervention	Findings of Adverse Events	Conclusion
2	Amox-clav vs. gatifloxacin	Sher, 2005[122]	0.5-7 years ROM and/or AOM treatment failure[a] 26 sites in US 1 site in Costa Rica	Amox-clav (90mg/6.4mg/kg/d in 2 doses, 10d) Gatifloxacin (10mg/kg, qd, 10d)		Abd pain, severe diarrhea, anorexia, arthralgia unrelated to treatment, deaths or serious drug-related equivalent. Diaper rash, diarrhea, vomiting inconclusive

	Amox-clav	Gatifloxacin	Diff(95%CI)
Any	27% (46/173)	24% (42/176)	3%(-6, 12)
Abd pain or diarrhea (severe in intensity)	0.6% (1/173)	0% (0/176)	0.6(-0.4,1.7)
Anorexia	0% (0/173)	0.6% (1/176)	-0.6%(-1.8,0.6)
Arthralgia event unrelated to treatment	1.2% (2/173)	0.5% (1/176)	0.6%(-1.4,2.6)
Deaths or Serious drug related events	0% (0/173)	0% (1/173)	0% (0, 0)
Diaper rash	6.4% (11/173)	5.1% (9/176)	1.3%(-3.6,6)
Diarrhea	18% (31/173)	10% (17/176)	8% (1, 15)
Vomiting	6% (10/173)	7% (12/176)	-1%(-6, 4)

Comp #	Comparison	Author, Year	Patient Population	Intervention	Findings of Adverse Events				Conclusion
3	Amox-clav vs. levofloxacin	Noel, 2008[123]	0.5-<5 years ROM and/or persistent AOM[b] 66 centers in 6 countries, incl US	Amox-clav (45mg/kg bid, 10d) Levofloxacin (10mg/kg bid, 10d)		Levofloxacin	Amox-clav	Diff(95%CI)	Arthralgia, arthralgia disorder, arthritis disorder, arthropathy, fever, gait disorder, muscle weakness, otitis media not related to treatment failure, pathologic fracture, musculoskeletal disorder, musculoskeletal adverse events, rhinitis, synovitis: equivalent Dermatitis, diarrhea, URI, vomiting: inconclusive
					1 or more up to visit 4	54% (448/827)	58% (475/823)	-4%(-8,1.3)	
					Arthralgia	1.5% (12/827)	0.7%(6/823)	0.8%(-0.2,1.8)	
					Arthralgia disorder	1.2% (10/827)	0.6% (5/823)	0.6%(-0.3,1.5)	
					Arthritis disorder	0.2% (2/827)	0% (0/823)	0.2%(-0.1,0.5)	
					Arthropathy	0% (0/827)	0.2% (2/823)	-0.2%(-0.5,0.1)	
					Dermatitis	13% (108/827)	16% (129/823)	-3%(-6, 0.8)	
					Diarrhea	13% (108/827)	20% (161/823)	-7%(-10, -3)	
					Fever	7% (60/827)	8% (64/823)	-1%(-3, 2)	
					Gait abnormality disorder	0.1% (1/827)	0% (0/823)	0.1%(-0.1,0.3)	
					Muscle weakness	0% (0/827)	0.1% (1/823)	-0.1%(-0.3,0.1)	
					Otitis media not related to treatment failure	5% (45/827)	4% (34/823)	1% (-0.8, 3.4)	
					Pathologic fracture	0% (0/827)	0.5% (4/823)	-0.5%(-1, 0)	
					Musculoskeletal disorder (DSMC)	1.5% (12/827)	0.6% (5/823)	1%(-0.1, 1.9)	
					Musculoskeletal adverse events	2.8% (23/827)	2.3% (19/823)	0.5%(-1, 2)	
					Rhinitis	5% (43/827)	5% (39/823)	0.5%(-1.6,2.6)	
					Synovitis	0.1% (1/827)	0% (0/823)	0.1%(-0.1,0.3)	
					URI	6% (53/827)	9% (78/823)	3%(-5.7,-0.5)	
					Vomiting	10% (81/827)	7% (61/823)	2%(-0.3, 5.1)	

<table>
<tr><th>Comp #</th><th>Comparison</th><th>Author, Year</th><th>Patient Population</th><th>Intervention</th><th>Findings of Adverse Events</th><th>Conclusion</th></tr>
<tr><td>4</td><td>Amox-clav vs. azithromycin</td><td>Arrieta, 2003[124]</td><td>0.5-6 years ROM and/or persistent AOM[b] 13 US and 5 Latin American centers</td><td>Amox-clav (95mg/kg, bid, 10d) Azithromycin (20mg/kg, qd, 3d)</td><td>
<table>
<tr><td></td><td>Amox-clav</td><td>Azithromycin</td><td>Diff(95%CI)</td></tr>
<tr><td>Any</td><td>42.2% (62/147)</td><td>32.0% (49/153)</td><td>10%(-0.7, 21)</td></tr>
<tr><td>Abd pain</td><td>2.0% (3/147)</td><td>3.9% (6/153)</td><td>-2%(-5.7, 2)</td></tr>
<tr><td>Anorexia</td><td>2.7% (4/147)</td><td>3.3% (6/153</td><td>-0.6%(-4, 3)</td></tr>
<tr><td>Dermatitis</td><td>2.0% (3/147)</td><td>0.7% (1/153)</td><td>1.3%(-1.3, 4)</td></tr>
<tr><td>Diarrhea</td><td>29.9% (44/147)</td><td>19.6% (30/153)</td><td>10%(0.5, 20)</td></tr>
<tr><td>Rash</td><td>4.8% (7/147)</td><td>3.3% (5/153)</td><td>1.5%(-3, 6)</td></tr>
<tr><td>Vomiting</td><td>8.2% (12/147)</td><td>5.2% (8/153)</td><td>3%(-2.6, 9)</td></tr>
</table>
</td><td>Anorexia, dermatitis: equivalent

Abd pain, diarrhea, rash, vomiting: inconclusive</td></tr>
<tr><td>5</td><td>Amox-clav vs. ciprofloxacin 0.3%-dexamethasone 0.1% (cipro-dex) otic drops</td><td>Dohar, 2006[80]</td><td>0.5-12 years with tympanostomy tubes 6 site in US</td><td>Amox-clav (90mg/kg/d, bid, 10d) Cipro-dex (4 drops, bid, 7d)</td><td>
<table>
<tr><td></td><td>Amox-clav</td><td>Cipro-Dex</td><td>Diff(95%CI)</td></tr>
<tr><td>Any</td><td>29% (12/41)</td><td>13% (5/39)</td><td>16%(-1.4,34)</td></tr>
<tr><td>Dermatitis</td><td>7% (3/41)</td><td>0% (0/39)</td><td>7%(-1,16)</td></tr>
<tr><td>Device block or taste perversion</td><td>0% (0/41)</td><td>3% (1/39)</td><td>-3%(-8,2.3)</td></tr>
<tr><td>Diarrhea</td><td>20% (8/41)</td><td>0% (0/39)</td><td>20%(6.4,33)</td></tr>
<tr><td>Ear pain</td><td>0% (0/41)</td><td>5% (2/39)</td><td>-5%(-2,1.7)</td></tr>
<tr><td>Gastroenteritis</td><td>5% (2/41)</td><td>0% (0/39)</td><td>5%(-2,12)</td></tr>
<tr><td>Infection skin or nausea or oral moniliasis</td><td>2.4% (1/41)</td><td>0% (0/39)</td><td>2.4%(-2.4,7)</td></tr>
<tr><td>Vomiting</td><td>2.4% (1/41)</td><td>2.6% (1/39)</td><td>-0.2%(-7, 7)</td></tr>
</table>
</td><td>Diarrhea: higher in amox-clav

Any, dermatitis, device block or taste perversion, ear pain, gastroenteritis, infection skin or nausea or oral moniliasis, vomiting: inconclusive</td></tr>
</table>

<table>
<tr><th>Comp #</th><th>Comparison</th><th>Author, Year</th><th>Patient Population</th><th>Intervention</th><th>Findings of Adverse Events</th><th>Conclusion</th></tr>
<tr><td>6</td><td>Cefaclor vs. cefuroxime</td><td>Turik, 1998[125]</td><td>3 months-12 years

AOM treatment failure

13 sites</td><td>Cefaclor (40mg/kg/d, bid, 10d)
Cefuroxime (40mg/kg/d, bid, 10d)</td><td>
<table>
<tr><th></th><th>Cefaclor</th><th>Cefuroxime axetil</th><th>Diff(95%CI)</th></tr>
<tr><td>Any</td><td>31% (32/104)</td><td>31% (32/104)</td><td>-5%(-18, 8)</td></tr>
<tr><td>Asthma or Bronchospasm unrelated to study drug or respiratory disorder or vomiting</td><td>0% (0/104)</td><td>1% (1/101)</td><td>-1%(-2.9, 0.9)</td></tr>
<tr><td>Diarrhea</td><td>2% (2/104)</td><td>1% (11/101)</td><td>-9%(-16,-2.3)</td></tr>
<tr><td>Diarrhea during treatment</td><td>0% (0/104)</td><td>8% (8/101)</td><td>-8%(-13,-2.5)</td></tr>
<tr><td>Increased cough</td><td>7% (7/104)</td><td>0% (0/101)</td><td>7% (1.7,12)</td></tr>
<tr><td>Rhinitis</td><td>9% (9/104)</td><td>10% (10/101)</td><td>-1%(-9, 7)</td></tr>
</table>
</td><td>Asthma or bronchospasm unrelated to study drug or respiratory disorder or vomiting: equivalent

Any, diarrhea, diarrhea during treatment, increased cough, rhinitis: inconclusive</td></tr>
<tr><td>7</td><td>Ciprofloxacin 0.3% (cipro) otic drops vs. Cipro 0.3%-dex 0.1% otic drops</td><td>Roland, 2003[126]</td><td>0.5-12 years with tympanostomy tubes
18 sites in US</td><td>Cipro (3 drops, bid, 7d)
Cipro-dex (3 drops, bid, 7d)</td><td>
<table>
<tr><th></th><th>Cipro alone</th><th>Cipro-dex</th><th>Diff(95%CI)</th></tr>
<tr><td>Excessive crying</td><td>1% (1/98)</td><td>1% (1/103)</td><td>0% (-2.8, 2.8)</td></tr>
<tr><td>Burning</td><td>1% (1/98)</td><td>2% (2/103)</td><td>-1%(-4.2,2.4)</td></tr>
<tr><td>Pain</td><td>1% (1/98)</td><td>2% (2/103)</td><td>-1%(-4.2,2.4)</td></tr>
<tr><td>Precipitate</td><td>3% (3/98)</td><td>0% (0/103)</td><td>3%(-0.3,6.5)</td></tr>
<tr><td>Pruritus</td><td>1% (1/98)</td><td>1% (1/103)</td><td>0%(-2.8,2.8)</td></tr>
<tr><td>Taste perversion</td><td>0% (0/98)</td><td>1% (1/103)</td><td>-1%(-3, 1)</td></tr>
</table>
</td><td>Excessive crying, burning, pain, pruritis, taste perversion: equivalent

Precipitate: inconclusive</td></tr>
</table>

<table>
<tr><th>Comp #</th><th>Comparison</th><th>Author, Year</th><th>Patient Population</th><th>Intervention</th><th>Findings of Adverse Events</th><th>Conclusion</th></tr>
<tr><td>8</td><td>Cipro 0.3%-dex 0.1% otic drops vs. ofloxacin 0.3% otic drops</td><td>Roland, 2004[127]</td><td>0.5-12 years with tympanostomy tubes
39 sites in US</td><td>Cipro-dex (4 drops, bid, 7d)
Ofloxacin (5 drops, bid, 10d)</td><td>
<table>
<tr><th></th><th>Cipro-dex</th><th>Ofloxacin</th><th>Diff(95%CI)</th></tr>
<tr><td>Cough or crying or diarrhea or ear debris or edema eardrum or headache or hyperemia eardrum</td><td>0% (0/297)</td><td>0.3% (1/302)</td><td>-0.3%(-0.9,0.3):</td></tr>
<tr><td>Discomfort ear</td><td>3.4% (10/297)</td><td>1% (3/302)</td><td>2.4%(0.1,4.7)</td></tr>
<tr><td>Dizziness or erythema or tinnitus or tympanostomy tube blockage</td><td>0.3% (1/297)</td><td>0%(0/302)</td><td>0.3%(-0.3,0.9)</td></tr>
<tr><td>Infection super ear or irritation ear or pruritus ear</td><td>0% (0/297)</td><td>0.7% (2/302)</td><td>-0.7%(-1.6,0.2)</td></tr>
<tr><td>Irritability</td><td>0.7% (2/297)</td><td>0% (0/302)</td><td>0.7%(-0.2,1.6)</td></tr>
<tr><td>Monilia oral</td><td>0.3% (1/297)</td><td>0.3% (1/302)</td><td>0%(-0.9,0.9)</td></tr>
<tr><td>Pain ear</td><td>2.4% (7/297)</td><td>3.0% (9/302)</td><td>-0.6%(-3.2,2)</td></tr>
<tr><td>Precipitate ear</td><td>0.7% (2/297)</td><td>1.0% (3/302)</td><td>-0.3%(-1.8,1.2)</td></tr>
<tr><td>Serious Tx related</td><td>0% (0/297)</td><td>0% (0/302)</td><td>0% (0, 0)</td></tr>
<tr><td>Taste perversion</td><td>0.3% (1/297)</td><td>1% (3/302)</td><td>-0.7%(-2,0.6)</td></tr>
</table>
</td><td>Cough or crying or diarrhea or ear debris or edema eardrum or headache or hyperemia eardrum; discomfort ear; dizziness or erythema or tinnitus or tympanostomy tube blockage; super-infection ear or irritation ear or pruritus ear; irritability; monilia oral; pain ear; precipitate ear; serious treatment related; taste perversion: equivalent</td></tr>
</table>

[a] AOM Treatment Failure: infection within 14 days of last antibiotic dose or failure to improve after 48 hours
[b] Persistent AOM: signs or symptoms of AOM after 48 hours of treatment

In the comparison between amoxicillin-clavulanate and gatifloxacin, equivalence was found with respect to the rate of arthralgia, diaper rash, and serious events (ranged from 0% to 2%).[121] The rates for other adverse events were inconclusive: abdominal pain 2% vs. 4%, diarrhea 7% vs. 3%, vomiting 5% vs. 8% and drug-related events 15% vs. 18%.

In the comparison between high-dose amoxicillin-clavulanate and gatifloxacin, equivalence was found with respect to the rate of abdominal pain, severe diarrhea, anorexia, arthralgia unrelated to treatment, deaths, or serious drug-related events (ranging from 0% to 1.2%).[122] The rates for the following adverse events were inconclusive: diaper rash 6% vs. 5%, diarrhea 18% vs. 10%, and vomiting 6% vs. 7%.

In the comparison between amoxicillin-clavulanate and levofloxacin, equivalence was found in a majority of adverse events including arthralgia, arthralgia disorder, arthritis disorder, arthropathy, fever, gait disorder, muscle weakness, otitis media not related to treatment failure, pathologic fracture, musculoskeletal disorder, musculoskeletal adverse events, rhinitis, and synovitis.[123] Their rates ranged from 0% to 8%. The rates for the following adverse events were inconclusive: dermatitis 13% vs. 16%, diarrhea 13% vs. 20%, upper respiratory infection 6% vs. 9%, and vomiting 10% vs. 7%.

In the comparison between amoxicillin-clavulanate and azithromycin, equivalence was found in anorexia (2.7% vs. 3.3%) and dermatitis (2% vs. 1%).[124] The rates for the following adverse events are inconclusive: abdominal pain 2% vs. 4%, diarrhea 30% vs. 20%, rash 5% vs. 3%, and vomiting 8% vs. 5%.

In the comparison between amoxicillin-clavulanate and ciprofloxacin-dexamethasone ear drops, diarrhea was found to be significantly higher in amoxicillin-clavulanate-treated children, with a rate difference of 20% (95% CI: 6%, 33%) and NNT=5.[80]

In the comparison between cefaclor and cefuroxime, equivalence was found with respect to the rate of asthma or bronchospasm unrelated to study drug, respiratory disorder, and vomiting (0% vs. 1%). The rates for the following adverse events were inconclusive: any adverse event 31% vs. 36%, diarrhea 2% vs. 1%, diarrhea during treatment 0% vs. 8%, increased cough 7% vs. 0%, and rhinitis 10% vs. –1%.[125]

In the comparison between ciprofloxacin-dexamethasone and ciprofloxacin ear drops, equivalence was found with respect to the rate of excessive crying (both 1%), burning (1% vs. 2%), pain (1% vs. 2%), pruritis (3% vs. 0%), and taste perversion (0% vs. 1%). The rate for the ear precipitate was inconclusive (3% vs. 0%).[126]

In the comparison between ciprofloxacin-dexamethasone and ofloxacin ear drops, equivalence was found with respect to the rate of cough or crying or diarrhea or ear debris or eardrum edema or headache or eardrum hyperemia (0% vs. 0.3%), ear discomfort (3% vs. 1%), dizziness or erythema or tinnitus or tympanostomy tube blockage (0.3% vs. 0%), ear super-infection or ear irritation or ear pruritus (0% vs. 0.7%), irritability (0.7% vs. 0%), oral monilia (both 0.3%), ear pain (2% vs. 3%), ear precipitate (0.7% vs. 1%), serious treatment related events (both 0%), and taste perversion (0.3% vs. 1%).[127]

Adverse Events Associated with Prevention of Acute Otitis Media in Children with Recurrent Otitis Media

Of the 58 RCTs identified in our review update that addressed the effectiveness of treatment options, 14 studied children with ROM. Among the 14 studies are 21 treatment comparisons. Thirteen comparisons studied the prevention of AOM in children with ROM. Of the 13 comparisons, four did not report or did not study adverse events. Table 36 provides the findings on the comparison of the adverse event rates between treatment options for the remaining comparisons.

Table 36. Findings of Adverse Events from Eight Articles on Effectiveness of Prevention of Acute Otitis Media in Recurrent Otitis Media

Comp #	Comparison	Author, Year	Patient Population	Intervention	Findings of Adverse Events	Conclusion
1	Amox vs. azithromycin	De Diego, 2001[128]	9-120 months 1 institution in Spain	Amoxicillin (20mg/kg/d, 3mos) Azithromycin (10mg/kg/wk, 3mos)	<table><tr><th></th><th>Amoxicillin</th><th>Azithromycin</th><th>Diff(95% CI)</th></tr><tr><td>GI</td><td>2.5% (1/40)</td><td>0% (0/31)</td><td>2.5%(-3. 8)</td></tr></table>	GI: Inconclusive
2	Amox vs. sulfisoxazole	Teele, 2000[129]	0-1 year 2 sites in US	Amoxicillin (20mg/kg/d) Sulfisoxazole (50mg/kg/d)	No adverse events studied.	
3	Amox vs. placebo	Teele, 2000[129]	0-1 year 2 sites in US	Amoxicillin (20mg/kg/d) Placebo	No adverse events studied.	
4	Sulfisoxazole vs. placebo	Teele, 2000[129]	0-1 year 2 sites in US	Sulfisoxazole (50mg/kg/d) Placebo	No adverse events studied.	
5	Sulfafurazole vs. placebo	Koivunen, 2004[130]	10mos-2yrs 1 hosp in Finland	Sulfafurazole (50mg/kg, qd, 6mos) Placebo	<table><tr><th></th><th>Sulfafurazole</th><th>Placebo</th><th>Diff (95% CI)</th></tr><tr><td>Any</td><td>8% (5/60)</td><td>3% (2/60)</td><td>5% (-3.4, 13)</td></tr><tr><td>Diarrhea</td><td>3% (2/60)</td><td>2% (1/60)</td><td>2% (-4.8,7.2)</td></tr><tr><td>Skin rash</td><td>3% (2/60)</td><td>0% (0/60)</td><td>3% (-1.3,7.9)</td></tr><tr><td>Unknown</td><td>2% (1/60)</td><td>2% (1/60)</td><td>0% (-4.6, 4.6)</td></tr></table>	Unknown adverse events equivalent. Any mention, diarrhea, and skin rash inconclusive.
6	Sulfafurazole vs. adenoidectomy	Koivunen, 2004[130]	10mos-2yrs 1 hosp in Finland	Sulfafurazole (50mg/kg,qd, 6mos) Adenoidectomy	<table><tr><th>AE</th><th>Sulfafurazole</th><th>Adenoidectomy</th><th>Diff(95% CI)</th></tr><tr><td>Any</td><td>8.3% (5/60)</td><td>0% (0/60)</td><td>8%(1.2,15)</td></tr><tr><td>Diarrhea</td><td>3% (2/60)</td><td>0% (0/60)</td><td>3%(-1.3, 8)</td></tr><tr><td>Skin rash</td><td>3% (2/60)</td><td>0% (0/60)</td><td>3%(-1.3,</td></tr></table>	Unknown adverse events equivalent. Any mention, diarrhea, and skin rash inconclusive.

Comp #	Comparison	Author, Year	Patient Population	Intervention	Findings of Adverse Events	Conclusion

				8)
Unknown	2% (1/60)	0% (0/60)	2%(-1.6,5.0)	

7	Adenoidectomy vs. placebo	Koivunen, 2004[130]	10mos-2yrs 1 hosp in Finland	Adenoidectomy Placebo		Diarrhea, skin rash and unknown are equivalent. Any mention inconclusive

	Adenoidectomy	Placebo	Diff (95% CI)
Any	0% (0/60)	3% (2/60)	-3% (-8, 1.3)
Diarrhea	0% (0/60)	2% (1/60)	-2% (-5.0,1.6)
Skin rash	0% (0/60)	0% (0/60)	0% (0, 0)
Unknown	0% (0/60)	2% (1/60)	-2% (-5.0,1.6)

8	Adenoidectomy vs. placebo	Paradise, 1999[26]	3-15yrs 1 hosp in US	Adenoidectomy Placebo		Inconclusive

	Adenoidectomy	Placebo	Diff(95% CI)
Erythematous rashes during treatment	7.2% (6/83)	3.9% (7/181)	3%(-2.3, 9)

9	Adenoidectomy vs. adenotonsillectomy	Paradise, 1999[26]	3-15yrs 1 hosp in US	Adenoidectomy Adenotonsillectomy		Equivalence in incipient malignant hyperthermia, postoperative pneumonia, postoperative persistent velopharyngeal insufficiency,

AE	Adenoidectomy	Adenotonsillectomy	Diff(95% CI)
Erythematous rashes during treatment	7.2% (6/83)	2.2% (4/178)	5% (0,10)
Hemorrhage after hospital	0% (0/83)	2.2% (4/178)	-2% (-5.4,1)

Comp #	Comparison	Author, Year	Patient Population	Intervention	Findings of Adverse Events				Conclusion
					discharge				and serious sickness during antimicrobial treatment.
					Incipient malignant hyperthermia	1.2% (1/83)	0.6% (1/178)	0.6% (-1.7,1)	
					Periop & postop complications	4.8% (4/83)	14.6% (26/178)	-10% (-18,-1.5)	Inconclusive in erythematous rashes during treatment, hemorrhage after hospital discharge, perioperative and postoperative complications, postoperative transient (under 44 days) velopharyngeal insufficiency, retained in hospital one additional day.
					Postop pneumonia	1.2% (1/83)	0% (0/178)	1.2% (-0.4,2.8)	
					Postop velopharyngeal insufficiency – persistent (9mo)	0% (0/83)	0.6% (1/178)	-0.6% (-2.3,1.1)	
					Postop velopharyngeal insufficiency-transient (<=43 d)	2.4% (2/83)	5.1% (9/178)	-2.7% (-8,2.6)	
					Retained in hospital 1 > day and/or readmitted to hospital due to fever, poor fluid intake orally, vomiting, and/or dehydration	0% (0/83)	6% (11/178)	-6% (-11,-0.8)	
					Serious sickness	0% (0/83)	0.6% (1/178)	-0.6% (-2.3,1.1)	

Comp #	Comparison	Author, Year	Patient Population	Intervention	Findings of Adverse Events				Conclusion
					during antimicrobial treatment				
10	Adenotonsillectomy vs. placebo	Paradise, 1999[26]	3-15yrs 1 hosp in US	Adenotonsillectomy Placebo					Inconclusive
						Adenotonsillectomy	Placebo	Diff (95% CI)	
					Erythematous rashes during treatment	2.2% (4/178)	3.9% (7/181)	-1.7% (-5.3,1.9)	
11	Ceftibuten 5d vs. Ceftibuten 10d	Roos, 2000[131]	0.5-8yrs 6 centers in Sweden	Ceftibuten 5d (9mg/kg/d) Ceftibuten 10d (9mg/kg/d)					Inconclusive
						Ceftibuten 5d	Ceftibuten 10d	Diff (95% CI)	
					GI disturbance	6.7% (6/90)	16.7% (15/900)	-10% (-19,-0.6)	
12	Probiotics vs. placebo	Hatakka, 2007[91]	10mo-6yrs Helsinki, Finland	One probiotic capsule (Lactobacillus rhamnosus GG and LC705, Bifidobacterium breve 99 and propionibacterium freudenreichii JS) qd for 6mos Placebo, qd for 6mos	No adverse events studied.				Equivalent

<table>
<tr><th>Comp #</th><th>Comparison</th><th>Author, Year</th><th>Patient Population</th><th>Intervention</th><th>Findings of Adverse Events</th><th>Conclusion</th></tr>
<tr><td>13</td><td>Adenoidectomy and tympanostomy vs. Tympanostomy only</td><td>Hammaren-Malmi, 2005[132]</td><td>1-2yrs Helsinki, Finland</td><td>Adenoidectomy + tympanostomy
Tympanostomy only</td><td><table><tr><th></th><th>Adeno+Tympan</th><th>Tympan only</th><th>Diff (95% CI)</th></tr><tr><td>Neck abscess or type 1 diabetes</td><td>0% (0/109)</td><td>1% (1/108)</td><td>-1%(-3, 1)</td></tr></table></td><td></td></tr>
<tr><td>14</td><td>Propolis and zinc vs. Elimination of environmental risk factors</td><td>Marchisio, 2010[133]</td><td>1-5yrs Italy</td><td>30% hydroglyceric extract of propolis; 1.2% zinc sulfate 0.3 ml/kg/d = QD for 3 months
Plus Elimination of environmental risk factors</td><td><table><tr><th></th><th>Propolis+Zinc</th><th>Controls</th><th>Diff (95% CI)</th></tr><tr><td>Vomiting</td><td>1.6% (1/61)</td><td>1.6% (1/61)</td><td>0% (-5, 5)</td></tr><tr><td>Rash</td><td>1.6% (1/61)</td><td>0.0% (0/61)</td><td>1.6% (-2, 5)</td></tr></table></td><td>Equivalence in vomiting and rash.</td></tr>
</table>

In the comparison between amoxicillin and azithromycin, the difference in gastrointestinal adverse event rate was inconclusive (2.5% vs. 0%).[128]

In the comparisons between sulfafurazole and placebo and between sulfafurazole and adenoidectomy, equivalence was found in "unknown" adverse events (2% in sulfafurazole and placebo, 0% in adenoidectomy).[130] The rates for the following adverse events are inconclusive: diarrhea (ranged from 0% to 3%), skin rash (ranged from 0% to 3%), and any mention (ranged from 0% in adenoidectomy to 8% in sulfafurazole).

In the comparison between adenoidectomy and placebo, equivalence was found in diarrhea, skin rash, and unknown events (range from 0% to 2%).[130] Difference in any mention of adverse event rate was inconclusive.

In the comparison between adenoidectomy and adenotonsillectomy, equivalence in adverse event rates was found in incipient malignant hyperthermia (1.2% vs. 0.6%), postoperative pneumonia (1.2% vs. 0%), postoperative persistent (9 months) velopharyngeal insufficiency (0% vs. 0.6%), and serious sickness during antimicrobial treatment (0% vs. 0.6%).[26] The rate differences for the following adverse events are inconclusive: erythematous rashes during treatment (7% vs. 2%), hemorrhage after hospital discharge (0% vs. 2%), perioperative and postoperative complications (5% vs. 15%), postoperative transient (under 44 days) velopharyngeal insufficiency (2% vs. 5%), and retention in hospital one additional day due to fever, poor fluid intake orally, vomiting, and/or dehydration (0% vs. 6%).

In the comparisons between adenoidectomy and placebo and between adenotonsillectomy and placebo, the difference in erythematous rashes during treatment rates between treatment options was inconclusive, ranging from 2% in adenotonsillectomy to 7% in adenoidectomy.[26]

In the comparison between ceftibuten 5-day and ceftibuten 10-day, the difference in gastrointestinal disturbance rates between the two treatment options (7% vs. 17%) was inconclusive.

In the comparison between propolis and zinc vs. the control, the rates of vomiting and rash were found to be equivalent (1.6% vs. 1.6% and 1.6% vs. 0%).

The Leach (2006) systematic review found that one additional child experienced diarrhea or an allergic reaction for every 100 children treated, which was not statistically significant (relative risk 2.0, 95% CI: 0.3, 15; random-effects model, I^2=53%) based on eleven studies (Casselbrant, 1992; Gaskins, 1982; Gonzalez, 1986; Gray 1981; Liston 1983; Perrin 1974; Principi, 1989; Schuller, 1983; Sigh, 1993; Teele, 2000; Varsano, 1985), they reiterated a concern in their discussion that antibiotics are not without risk.

Leach (2006) also studied the issue of antibiotic resistant organisms in two studies and found a statistically insignificant relative risk of 1.4 (95% CI: 0.8, 2.3; fixed-effect model, I^2=0%) though there appeared to be an increased carriage of resistant pneumococcus or haemophilus (Casselbrant, 1992; Mandel 1996). This review concluded that the choice of whether or not to treat children with ROM with antibiotics to prevent AOM would have to balance the benefits and these risks.

Summary

Although in general we could not reach definitive conclusions regarding clinically important differences in adverse event rates between most pairs of antibiotics, we noted significant

differences in adverse event rates for a few antibiotic comparisons and equivalence in adverse event rates for several comparisons. For treatment of uncomplicated AOM, five adverse event rate comparisons showed a significant difference between two treatment options. Amoxicillin-clavulanate was associated with diarrhea more often than was cefdinir (with a NNT of four)[85] and ceftriaxone (with a NNT of seven).[77] The adverse event rates ranged from 27% to 35% with amoxicillin-clavulanate and from 10% to 14% for the other treatment options. For mention of any adverse event, amoxicillin-clavulanate had a higher rate than cefdinir once or twice daily[85] and ceftriaxone.[77] However, in the Block (2000) study,[85] amoxicillin dose was 40mg/kg/day; whereas in the Cohen (1999) study,58 amoxicillin dose was 80mg/kg/day. Equivalence was demonstrated in 29 comparisons, leaving 99 comparisons inconclusive.

These findings complement the findings from the original review[13] that showed that children treated with amoxicillin-clavulanate for seven to ten days had a 19% increased rate of overall adverse effects and an 18% increased rate of gastrointestinal adverse effects compared to children treated with five days of azithromycin for uncomplicated AOM. (Though not specified in the studies, the clavulanate/amoxicillin ratio was likely 31.25 mg per 125 mg of amoxicillin, i.e. the original formulation.) Six children would need to be treated with azithromycin rather than amoxicillin-clavulanate to avoid a gastrointestinal adverse event. The original review also found that children treated with cefixime had an 8% greater rate of diarrhea than children treated with ampicillin or amoxicillin for uncomplicated AOM, so 12 children would need to be treated with ampicillin or amoxicillin rather than cefixime to avoid a case of diarrhea.

For treatment of AOM in children with presumed or explicitly defined recurrent and/or persistent otitis media, and/or AOM with treatment failure, we found one significant difference in adverse event rate comparisons. Amoxicillin-clavulanate (90 mg/kg/day and 6.4 mg/kg/day) was associated with diarrhea more often than ciprofloxacin-dexamethasone ear drops with a NNT of five.[80] (In the Dohar (2006) study amoxicillin 90mg/kg/day was prescribed with clavulanate 6.4mg/kg/day.) However, in 41 comparisons, the adverse event rates were equivalent. In 23 comparisons, a definitive conclusion was not possible.

For prevention of AOM in children with ROM, we did not find any significant differences in any of the adverse event rate comparisons. In 11 comparisons, the adverse event rates were equivalent, and in 18 comparisons, a definitive conclusion was not possible.

Although for all three groups, the evidence was generally insufficient to allow definitive conclusions, the available evidence did indicate an increased rate of gastrointestinal effects and diarrhea specifically with amoxicillin-clavulanate and cefixime in comparison with cefdinir, ceftriaxone, or ciprofloxacin-dexamethasone ear drops and with ampicillin or amoxicillin, respectively. In addition, amoxicillin-clavulanate appeared to have a higher overall adverse effect rate than cefdinir, ceftriaxone, or azithromycin.

Chapter 4. Discussion

Limitations

Publication Bias

Our literature search procedures were extensive and included canvassing experts from academia, the clinical arena, and the FDA MedWatch database for studies. However, it is possible that other unpublished trial results exist for the treatments included in our report. Publication bias may occur, resulting in an overestimation of the efficacy of these treatments. In a few instances, we detected statistical evidence of possible publication bias (these instances are noted in the text).

Study Quality

An important limitation common to systematic reviews is the quality of the original studies. Recent attempts to assess which elements of study design and execution are related to bias have shown that in many cases, such efforts are not reproducible. Therefore, the current approach is to avoid using quality criteria to reject studies, which could affect meta-analysis results. However, for the assessment of quality of trials, we did use the Jadad scale, which is the only set of quality criteria for trials for which there is empirical evidence of an association with bias. Where feasible, we performed sensitivity analyses that used only the "high quality" studies (those scoring 3 or more on Jadad's scale). In some cases, this sensitivity analysis yielded a pooled result that was lower than the result of the primary analysis, a result seen in other clinical settings. Therefore, it is possible that some individual trials and some primary pooled analyses overestimate the true effectiveness of treatments. To assess the quality of diagnostic studies, we used QUADAS criteria. As there is a lack of empirical evidence regarding other study characteristics and their relationship to bias, we did not attempt to use other criteria.

Further limitations are provided below with respect to each of the key questions.

Conclusions

Key Question I. Diagnosis of AOM

Limited evidence exists on clinicians' accuracy and precision in identifying the three clinical criteria necessary for a diagnosis of AOM. There is some evidence to suggest that clinicians accurately identify MEE by reliance on otoscopic findings of decreased mobility or abnormal position. However, there is little evidence to help us fully understand how accurate and precise clinicians are at identifying all three criteria in one patient to make a diagnosis of AOM.

We reviewed studies that examined the association of individual physical exam findings with a diagnosis of AOM, which did not fully address this key question. Further studies are needed that examine clinician's identification of all three clinical criteria of AOM in a patient, compared to identification of all three criteria by an independent examiner to serve as the criterion standard. These types of studies should clearly identify the level of expertise of the

studied clinicians to help evaluate the level of generalizability of results to clinicians in practice. Perhaps the most important way to improve diagnosis is to increase clinicians' ability to recognize and rely on key otoscopic findings.

Key Question II. The impact of the Pneumococcal Heptavalent Immunization (PCV7) on AOM Microbial Epidemiology

Since the introduction of PCV7, there have been significant shifts in AOM microbiology. Our review indicates that overall, SP is becoming less prevalent, yet still important, while HF is increasing in its importance as an infectious agent of AOM. The pattern of penicillin-susceptibility among SP isolates is unclear; some studies have indicated that the proportion of penicillin–non susceptibility among vaccine serotype SP isolates has increased, while others have indicated that the proportion of SP that are non-susceptible has decreased. Future studies may need to consider susceptibility separately for vaccine and non-vaccine SP serotypes.

One of the major limitations of our review for this particular key question is that tympanocentesis, which is required for the isolation of a microbiologic agent, is not routinely performed in children with uncomplicated AOM. Most of the studies that compared the microbiology of AOM before and after the introduction and use of PCV7 examined middle-ear fluid samples for children with complicated, recurrent, or persistent OM. Another limitation is that we do not have adequate data to understand the possible impact of PCV7 on non-bacterial agents (i.e., viruses). Although the importance of non-bacterial agents has been studied for AOM, we were unable to find studies examining the impact of PCV7 on the importance of non-bacterial causes of AOM.

Key Question III. Treatment of Uncomplicated AOM

Immediate antibiotic therapy is more effective than placebo for treating uncomplicated AOM. However, between eight and nine children would need to be treated with immediate antibiotics in order to observe this difference in clinical success. Clinicians will have to determine if this number needed to treat justifies the immediate prescription of antibiotics in children with uncomplicated AOM and average risk. The evidence for immediate antibiotic therapy vs. a delayed prescription or a wait-and-see approach is mixed, with two studies showing an advantage for immediate antibiotics and two studies showing inconclusive results.

Amoxicillin-clavulanate is superior to azithromycin in terms of clinical success by day 14 when the pathogen is HF. This finding has clinical significance, given the microbiologic shift following the introduction of PCV7 that seems to indicate that HF is becoming more prevalent than SP as a cause of AOM.

Our review of data to address this key question (as well as questions pertaining to prevention and treatment of ROM) had several limitations. First, as described above in our list of the general limitations, definitions for clinical success were usually not equivalent between studies comparing the same treatments. For example, studies used different clinical criteria to define success, and success was often measured at different time points. Second, the inclusion criteria for participants also varied widely among studies. Some studies used only one of the three criteria for AOM diagnosis, while others considered two or all three. It is possible that some studies with less stringent inclusion criteria may have included participants who did not have

AOM, but rather had OME or no middle ear infective process at all. Third, the timing of study completion could affect results. As evidenced by the analysis of changes in epidemiology, the microbiology of AOM is changing, in part, based on the introduction of PCV7. It is unclear how differences in AOM microbiology over time might affect our findings from pooled analyses. Because we considered a minimum clinically important difference (MCID) of 5%, we sometimes considered results as clinically insignificant that were statistically significant. Since the minimum clinically significant difference for AOM is not empirically known, readers who assume an MCID different than 5% would reach modestly different conclusions. Any decision to suggest antibiotic treatment or choice of antibiotic involves a trade-off between the expectation of benefit compared with the risks.

Key Question IV. Prevention or Treatment of Acute Otitis Media in Children with Recurrent Otitis Media

We are unable to draw any definitive conclusions regarding the comparative effectiveness of different antibiotic treatments for treatment of AOM in children with ROM. Leach (2006) found on systematic review that long-term antibiotics, defined as treatment for six weeks or longer, prevented 1.5 episodes of AOM for every 12 months of treatment per otitis-prone child during active treatment (95% CI: 1.2, 2.1) who would otherwise average three episodes of AOM annually without treatment. Since this reduced risk of AOM was present only during therapy, the drawbacks of long-term antibiotics (including adverse effects such as diarrhea and allergic reactions, and emergence of bacterial resistance to antibiotics) must be weighed against the occurrence of another episode of AOM in the patient. In addition, all of the studies on which this finding is based were conducted prior to the widespread introduction of the heptavalent pneumococcal vaccine, which may influence bacterial etiology and resistance as noted in the findings for Key Question II in this review. It was decided that a review of the effectiveness of vaccines in preventing AOM was beyond the scope of this report. Thus, it may be difficult to generalize the Leach (2006) findings to the current population of children with ROM.

Further, we can also conclude that tympanostomy tubes can help decrease the likelihood of a repeat infection in a child with a history of ROM within the first six months after tube insertion. This conclusion may be tempered by the issue of AOM diagnostic accuracy in the presence of tympanostomy tubes possibly confounding these results, i.e. the pressure equalization and drainage afforded by the tubes and their physical presence decreasing the intensity or visibility of signs and symptoms used to diagnose AOM leading to false negatives. Again, whether or not the benefit of avoiding a repeat episode of AOM over six months outweighs the costs of a tympanostomy tube placement will depend on the clinician's assessment of the child with AOM, and discussions of advantages and disadvantages with the family.

The limitations in our ability to address this question mirror those for Key Question III. The lack of uniformity of definitions for ROM and clinical success and differences in measurement times made synthesis of the available evidence difficult. Similar to Key Question III, one treatment comparison that demonstrated statistically significant results did not demonstrate clinically significant results in terms of the zone of MCID. We again acknowledge that others may practice from a zone of MCID different from the +/-5% standard utilized in this study.

Key Question V

Whereas the 2001 evidence review identified only sufficient evidence to allow the assessment of age on treatment effectiveness, the current review identified information to assess the effect of laterality and otorrhea, as well. Few to no conclusions can be made on the effect of other influencing factors such as characteristics of the patient, AOM episode, environment, and the health care system on the comparative effectiveness of treatment.

Meta-analysis conducted for this review indicates that children over the age of 2 years had better outcomes with various treatment options including placebo or no treatment than children under age 2. Data from a systematic review by Rovers (2006) utilizing individual patient data showed a similar effect of age on antibiotic treatment of uncomplicated AOM. In addition, Rovers (2006) found that laterality, especially in children 2 years and younger, and otorrhea had impacts on antibiotic effectiveness. These findings suggest that clinicians may need to monitor response to treatment and outcomes more closely when treating very young children with AOM, particularly those with bilateral AOM and those with otorrhea. The primary limitation related to this question was that the available evidence was limited and primarily focused on the association of age with AOM treatment, though other influencing factors are commonly cited as being important, such as AOM characteristics, including severity and characteristics of the patient, environment, and the healthcare delivery system. In addition, if the operating characteristics of AOM diagnostic criteria differ by age, then it is possible that treatment outcomes stratified by age may be confounded by a differential rate of inclusion of children who do not actually have AOM.

Key Question VI

The available evidence indicated an increased rate of gastrointestinal adverse effects and diarrhea specifically with amoxicillin-clavulanate and cefixime in comparison with cefdinir, ceftriaxone, or ciprofloxacin-dexamethasone ear drops and with ampicillin or amoxicillin, respectively. In addition amoxicillin-clavulanate appeared to have a higher overall adverse effect rate than cefdinir, ceftriaxone, or azithromycin.

The limitations in our assessment for this question are similar to those cited above. The lack of uniformity of definitions for AOM and ROM and adverse effects and the differences in measurement times made synthesis of the available evidence difficult. As with key questions III and IV, treatment comparisons that demonstrated statistically significant results did not always demonstrate clinically significant results in terms of the zone of MCID. We again acknowledge that others may practice from a zone of MCID that is different from the +/-5% standard used in this study.

Future Research Suggestions

Based on the findings of this review, we provide the following suggestions for future research directions.

Key Question I: Diagnostic Criteria for AOM

Additional studies are needed to more fully understand the precision of the current diagnostic criteria for AOM: acute onset of signs and symptoms, MEE, and middle ear inflammation. For example, evidence is insufficient to guide clinicians on the most effective and efficient ways to assess each of these elements in the clinical setting. Also needed are more studies that use a reference standard that can take into account all three criteria of an AOM diagnosis. Thus, a reference standard that takes into account only MEE does not provide sufficient evidence on overall diagnostic accuracy for AOM.

Key Question II: Effects of the PCV7 Vaccine

The five studies included in this report that address Key Question II provide information about the changing microbiologic patterns of otitis media since the introduction of PCV7, specifically, that HF has become more prevalent as a causative agent of AOM, although SP remains an important pathogen. The introduction of the vaccine has also resulted in a greater proportion of non-vaccine serotypes and a smaller proportion of vaccine serotypes as causative agents in AOM. However, none of the studies addressed the implications of this observed evolution in microbiology subsequent to introduction of the vaccine. For example, will this shift in microbiology translate to a shift in the type and incidence of suppurative and other complications? Further research is needed to explore the impact of PCV7 on the clinical progression and outcomes of uncomplicated AOM, and of AOM in otitis-prone children with recurrent AOM.

More inquiry is needed into microbiologic shifts in AOM, especially as it relates to resistance patterns of the non-PCV7 serotypes of SP that seem to be increasing since the introduction of PCV7. Such research will require continued surveillance of both shifts in the causative organisms of AOM and in the antibiotic resistance/susceptibility of these organisms.

A recent study of a single pediatric practice, not meeting our inclusion criteria, found evidence suggesting that an increase in the proportion of AOM with non-vaccine SP serotypes may be leading to another shift in AOM microbiology.[8] These new data support the need for ongoing surveillance of AOM isolates.

Continued surveillance will also help us understand the impact of new pneumococcal vaccines, such as the newly-licensed PCV 13, that include more serotypes than PCV7 currently does. It will be important to have information to help conduct cost-benefit analysis of vaccines that cover more than the current seven serotypes.

A growing body of research is assessing the efficacy of the vaccine in preventing AOM. Although a review of this literature was beyond the scope of this report, such a review may be warranted in the near future.

Key Questions III-VI: Treatment Efficacy and Adverse Effects

Research issues identified in the original AOM review[13] are still applicable to the review update as it relates to treatment of uncomplicated AOM as well as to treatment of ROM, which was not previously addressed. Though we report several definitive conclusions, the usefulness of

these conclusions to the practitioner is suspect because of concerns regarding the internal validity of some of the source studies and the generalizability of the findings because of a lack of standard definitions for AOM and ROM as well as for treatment outcomes across studies; the variability of study quality; and the relative paucity of evidence related to influencing factors such as AOM severity, and other important factors. In addition, the impact of PCV7 as noted in this review's findings for KQ2, and of changing patterns of AOM bacterial etiology and resistance in general, must be considered in designing future studies.

Standard definitions of AOM and ROM that lead to standard diagnostic criteria and that are acceptable to both researchers and practitioners have not been developed since the initial review and are still needed. In the studies newly identified for this review update, only two of the 43 articles on treatment of uncomplicated AOM and one of the fifteen articles on treatment of children with ROM, persistent AOM, or AOM treatment failure included all three AOM diagnostic criteria recommended by the AAP AOM guidelines. This finding represents a slight improvement compared to the original review (Table 37).[13] The continued diversity of definitions for AOM as well as for ROM and, therefore, the diversity of diagnostic criteria that control entry of participants into these treatment trials make it difficult to synthesize and generalize findings, as it is unclear if the same condition is being assessed across studies. Greater knowledge regarding the operating characteristics of criteria used to diagnose children of different ages will also help to assess results of studies comparing treatment options (e.g., are we more likely to be treating real AOM in an infant or an older child diagnosed with AOM?) In addition, knowledge of the effect of tympanostomy tube presence on these diagnostic operating characteristics will help to better assess the true impact of tympanostomy tubes on prevention of AOM in children with ROM.

Table 37. Number of Randomized Controlled Trials in the Original Review by Marcy (2001)[13] and the Review Update by Number of AOM Diagnostic Criteria Used and by Number of Jadad Study Quality Criteria Met

Topic	AOM diagnostic criteria			Jadad study quality criteria		
	Number	Number of studies (Percent)		Number	Number of studies (Percent)	
		Original Review	Review Update		Original Review	Review Update
Treatment of uncomplicated AOM	0	38 (35%)	8 (19%)	0	1 (1%)	0 (0%)
	1	34 (43%)	4 (9%)	1	8 (11%)	5 (12%)
	2	18 (23%)	29 (67%)	2	26 (35%)	14 (32%)
	3	0 (0%)	2 (5%)	3	21 (28%)	15 (35%)
				4	12 (16%)	3 (7%)
				5	6 (8%)	6 (14%)
Treatment of recurrent otitis media, persistent acute otitis media, or AOM treatment failure	0	n/a	6 (40%)	0	n/a	0 (0%)
	1		0 (0%)	1		1 (7%)
	2		8 (53%)	2		6 (40%)
	3		1 (7%)	3		6 (40%)
				4		0 (0%)
				5		2 (13%)
Total	0	38 (35%)	14 (24%)	0	1 (1%)	0 (0%)
	1	34 (43%)	4 (7%)	1	8 (11%)	6 (10%)
	2	18 (23%)	37 (64%)	2	26 (35%)	20 (34%)
	3	0 (0%)	3 (5%)	3	21 (28%)	21 (36%)
				4	12 (16%)	3 (5%)
				5	6 (8%)	8 (14%)

Standard definitions related to the quality of AOM management in terms of specific structures, processes, and outcomes are still needed. For example, Table 8 documents the diversity of high-level outcomes chosen for measurement in the 63 treatment option comparisons for uncomplicated AOM. Though 62 comparisons measured clinical success, only three measured invasive infections 14, bacteriologic cure; 24, disease recurrence; 48, adverse effects; four, quality of life; seven, patient satisfaction; six, cost; and 16, other outcomes. Information in the evidence table demonstrates the varying definitions of clinical success among the 62 comparisons. Differences in terminology and in particular outcome choice and definitions between studies make it difficult to synthesize the results across studies and to generalize findings. This issue should be addressed in future studies.

Higher quality studies as well as improved reporting of study characteristics related to quality are still needed to come to definitive conclusions for AOM and ROM treatment options. Of the 58 RCTs newly identified for this review update, reported compliance with the 5 Jadad study quality criteria was not universal: one criterion in six studies; two criteria in 20 studies; three criteria in 21 studies; four criteria in three studies; five criteria in eight studies. Thus, study quality is not improved compared to the original review.[13](Table 37) Although we recognize that the issue may be the documentation of study characteristics rather than the actual study quality, sensitivity analysis by quality in this review significantly affected the results of the comparisons of ampicillin/amoxicillin in treatment of uncomplicated AOM, changing the results from significant to not significant when pooling studies. This finding suggests that the quality of the studies as currently documented may indeed reflect the true quality of these studies and may have an effect on the study results.

Since the previous review, further evidence confirms that age is an important factor influencing treatment outcome in uncomplicated AOM and ROM with particular treatment options, and new evidence suggests a role for laterality and otorrhea. In addition, the role of laterality on antibiotic effect was associated with age and highlights the need to have studies of sufficient power to allow study of interactions as is suggested by the studies of Leibovitz (2007) and McCormick (2007), which describe the clinical and microbiologic characteristics of patients with bilateral vs. unilateral AOM. Both studies found that bilateral disease is more often associated with bacteria in the MEE, in particular HF; younger age; and greater severity disease. However, additional high quality research is needed to establish definitive conclusions regarding the influence of other factors, including characteristics of the AOM episode (such as disease severity), the patient, the environment (such as the daytime caretaker and use of daycare), and the healthcare delivery systems (such as the examiner) on treatment success. Future research must be designed so the selection of study participants balances the need for generalizability of findings with the need to study the applicability of findings to patients with specific characteristics. Practitioners take these unique characteristics into account when treating individual patients. Thus, future research will lead to greater improvements if it also addresses individual patient characteristics.

Finally, we recommend that the concept of an *a priori* established zone of MCID be included in assessing the impact of treatment options in addition to statistical significance. As noted throughout the report results, many instances of statistically significant results with clinically insignificant impacts were identified during the review update. Clinical practice should be guided by evidence that exceeds a MCID for the practitioner. However, we acknowledge that the minimal clinically important difference must be established by the clinician based on the particular decision in question.

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List of Acronyms/Abbreviations

AOM: acute otitis media
AMX: amoxicillin
CI: confidence interval
ENT: ear, nose, and throat specialist
GP: general practitioner
HF: Haemophilus influenzae
LR: likelihood ratio
MEE: middle ear effusion
MEF: middle ear fluid
NNT: number-to-treat
OME: Otitis media with effusion
OR: Odds ratio
PcV: phenoxymethylpencillin
PPV: polysaccharide pneumococcal vaccine
RCT: randomized controlled trial
RD: Rate difference
ROM: Recurrent otitis media
SP: streptococcus pneumoniae
TF: tympanic fluid
TM: tympanic membrane
Tx: treatment

Appendix A. Scope, Definitions and Search Strategies

Table A.1 Scope of the Report and Definitions

Disease Entity	Uncomplicated AOM, including recurrent and persistent AOM[1]
Patient Population	Age 4 weeks to 18 years Exclude: patients with immunodeficiencies and craniofacial deficiencies including cleft palate
Settings	All types of providers and practice settings
Interventions[2]	"Wait and see" approach/placebo
	Antibiotic treatment (all classes, schedule, dosage, length, and mode)
	Delayed antibiotic
	Analgesics/other non-antibiotic medical therapies/surgery (including PE tubes)
Influencing factors	Age
	Race/ethnicity
	Laterality
	Otorrhea or perforation
	AOM severity
	Signs and physical symptoms (ear pulling, otorrhea, irritability, fever, tympanic membrane (TM) inflammation, retracted TM, middle ear effusion [MEE])
	Comorbidities (e.g., asthma)
	Day care attendance
	Environmental factors
	Practitioner
	Setting
	Parent/caretaker
	Examiner
	Recurrent OM/otitis prone
	Persistent/relapse OM (continued on next page)
	Diagnostic mode (otoscopy; tympanocentesis; pneumatic otoscopy/ tympanometry; acoustic reflectometry

[1] Definition of AOM: A diagnosis of AOM requires 1) a history of acute onset of signs and symptoms, 2) the presence of middle ear effusion (MEE), and 3) signs and symptoms of middle-ear inflammation.

Elements of the definition of AOM are all of the following:

1. Recent, usually abrupt, onset of signs and symptoms of middle-ear inflammation and MEE
2. The presence of MEE that is indicated by any of the following:
    a. Bulging of the tympanic membrane
    b. Limited or absent mobility of the tympanic membrane
    c. Air-fluid level behind the tympanic membrane
    d. Otorrhea
3. Signs or symptoms of middle-ear inflammation as indicated by either
    a. Distinct erythema of the tympanic membrane or
    b. Distinct otalgia (discomfort clearly referable to the ear[s] that results in interference with or precludes normal activity or sleep)

Definition of Recurrent AOM (RAOM): A diagnosis of RAOM requires three or more episodes of acute otitis media within 6 months or four episodes within 12 months, including at least 1 episode during the preceding 6 months.

Definition of Persistent Otitis Media: Persistent otitis media is manifested by persistence during antimicrobial therapy of symptoms and signs of middle ear infection (treatment failure) and/or relapse of acute otitis media within 1 month of completion of antibiotic therapy. When two episodes of otitis media occur within 1 month, it may be difficult to distinguish recurrence of acute otitis media (i.e. a new episode) from persistent otitis media (i.e. relapse).

[2] Antibiotics and other treatment modalities are considered individually for questions 3-6 on treatment outcomes;

Appendix A. Scope, Definitions and Search Strategies

Outcome measures	Treatment failure
	Duration of symptoms or illness
	Presence of MEE by otoscopic findings (Bulging, cloudy, erythematous TM; air fluid level behind TM; Loss of landmarks; otorrhea)
	Presence of MEE by Pneumatic otoscopy/tympanometry (Limited or absent mobility of TM)
	Presence of MEE by acoustic reflectometry (presence of MEF)
	Presence of MEE by tympanocentesis
	Signs and symptoms of middle ear inflammation (MEI) by symptoms (otalgia, fullness)
	Signs or symptoms of MEI by otoscopy (distinct TM erythema)
	Other symptoms (decreased hearing, fever)
	Invasive infections
	Bacteriological cure/failure
	Disease recurrence
	Adverse effects of treatment (e.g., diarrhea, vomiting, bacterial resistance) and method of assessment
	Quality of life or functional outcome
	Parental satisfaction
	Cost of outcomes, e.g., Days school/daycare missed
	Bacteriologic outcomes by nasopharyngeal cultures
	Otologic complications- i.e., cholestetoma
	PE tube placement
	Health care utilization
	Microbial epidemiology and antibiotic resistance[3]
Time Period	1998-2009[4]
Literature Sources	Medline
	Web of Science
	Cochrane Database of Systematic Reviews
	Proceedings of International Society of Otolaryngology
	References
Languages	No restriction
Study Design	Randomized controlled trials, blinded and unblinded
	Non-randomized controlled trials, blinded and unblinded
	Prospective and retrospective observational studies[5]
	Case-control studies[6]

[3] These outcomes are considered only for question 2 on PNC7 vaccine.

[4] Search for articles on recurrent and persistent AOM spanned 1966-2009

[5] Where RCTs unavailable to answer a particular question

RAND LIBRARY

ACUTE OTITIS MEDIA – SEARCH METHODOLOGIES
UPDATES FROM JULY 2008-AUGUST 2010

JULY 2008 – JANUARY 2009 UPDATES (Searches run 1/13-1/15/09)

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 7/1/2008-1/13/2009

SEARCH STRATEGY:
otitis media

NUMBER OF ITEMS RETRIEVED: 288

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
Cochrane – 7/1/2008-1/13/2009

SEARCH STRATEGY:
otitis media.mp.

NUMBER OF ITEMS RETRIEVED:
Systematic Reviews - 14
DARE – 45
CCTR - 11

DATABASE SEARCHED & TIME PERIOD COVERED:
Web of Science – 2008-2009

SEARCH STRATEGY:
Topic=otitis media
NOT
Topic=(dog OR cat OR mice OR rats OR chinchilla* OR pig)

NUMBER OF ITEMS RETRIEVED: 725

==========

JANUARY – AUGUST 2009 UPDATES (Search run 8/24/09)

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2009

SEARCH STRATEGY:
otitis media

NUMBER OF ITEMS RETRIEVED: 412

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
Cochrane - 2009

SEARCH STRATEGY:
otitis media.mp.

NUMBER OF ITEMS RETRIEVED:
Systematic Reviews -87
DARE – 51
CCTR – 4

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
Web of Science Databases - SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH.
– 2009

SEARCH STRATEGY:
Topic=(otitis media) NOT Topic=(dog OR cat OR mice OR rats OR chinchilla* OR pig OR mouse)

NUMBER OF ITEMS RETRIEVED: 441

==========

AUGUST 2009 – MAY 2010 UPDATES (Searches run 5/5/10)

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 8/2009– 5/5/2010

SEARCH STRATEGY:
otitis media
NOT
animal NOT (human OR humans)
NOT
dog OR cat OR mice OR mouse OR rat OR rats OR chinchilla* OR pig

NUMBER OF ITEMS RETRIEVED: 426

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
Web of Science Databases - SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH.– 2009– 5/5/2010

SEARCH STRATEGY:
Topic=(otitis media)
NOT
Topic=(dog OR cat OR mice OR MOUSE OR RAT OR rats OR chinchilla* OR pig)

NUMBER OF ITEMS RETRIEVED: 879

==========

MAY-AUGUST 2010 UPDATES (Searches run 8/3/10):

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 4/1/2010– 8/3/2010

SEARCH STRATEGY:
otitis media

NUMBER OF ITEMS RETRIEVED: 200

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
Cochrane – 4/1/2010– 8/3/2010

SEARCH STRATEGY:
otitis media.mp.

NUMBER OF ITEMS RETRIEVED:
Reviews - 33
DARE - 4

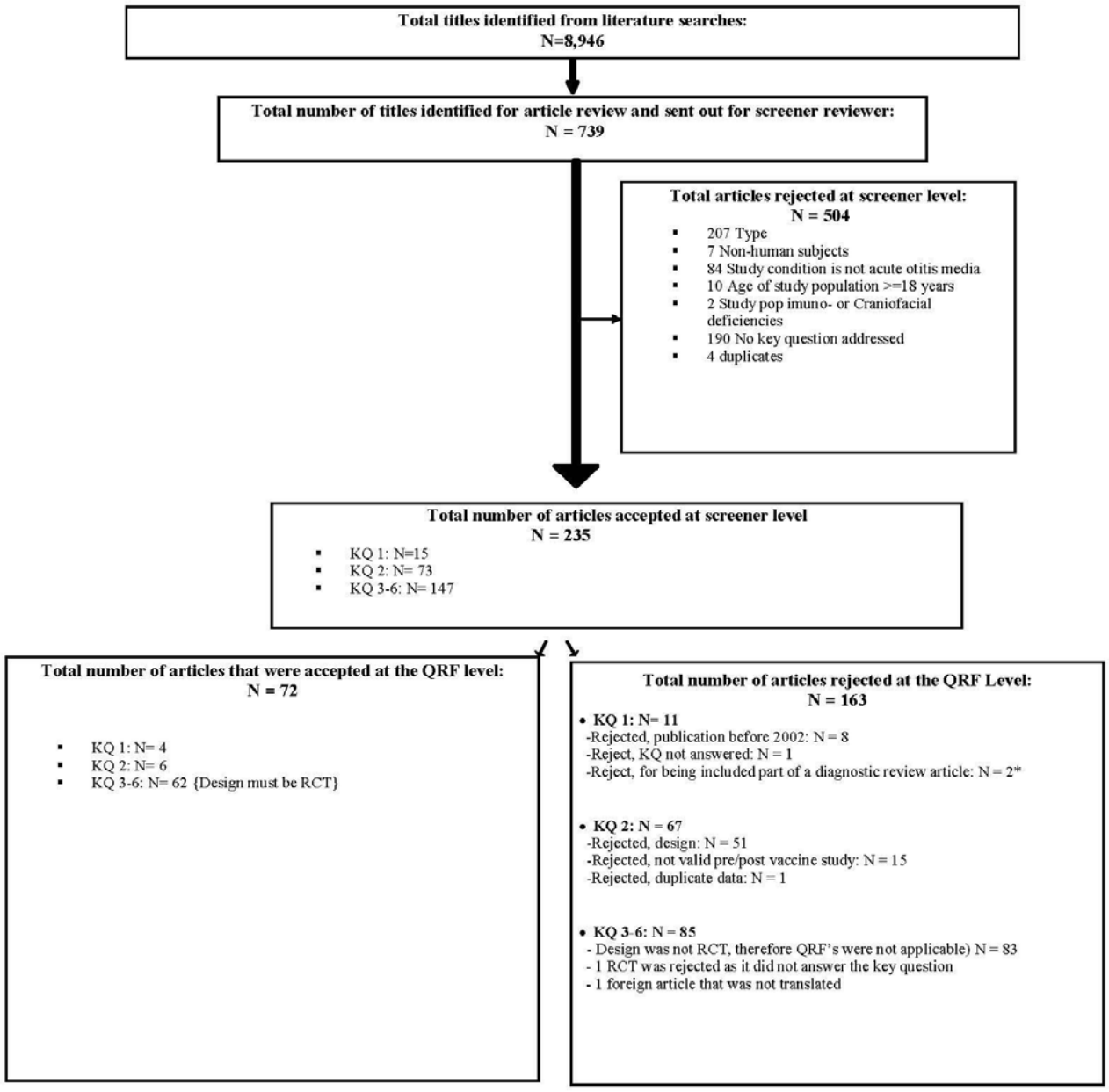
==========

DATABASE SEARCHED & TIME PERIOD COVERED:
Web of Science – 2010

SEARCH STRATEGY:
TS=(otitis media)
NOT
TS=(dog OR cat OR mice OR MOUSE OR RAT OR rats OR chinchilla* OR pig)

NUMBER OF ITEMS RETRIEVED: 374

Figure A.1. Literature Flow Diagram



*Diagnostic Review article that the two articles were in: Rothman R, Owens T, Simel DL. Does this child have acute otitis media? JAMA. 2003 Sep 24;290(12):1633-40.

Appendix B. Sample Data Abstraction Forms

Appendix B. Sample Data Abstraction Forms

Evidence-based Practice Center
Acute Otitis Media – Update

Form #1: Screening Form

Article ID: _____

Last Name of First Author:_____

Reviewer:___ _____

Year Published:___ _____

1. Type of article

Editorial, letter, opinion, commentary ..... 1 **(STOP)**
Clinical practice ..... 2 **(STOP)**
Overview ..... 3 **(STOP)**
Practice guidelines ..... 4 **(STOP)**
Consensus statements ..... 5 **(STOP)**
Unknown 6

2. Non-human subjects ..... ❒ **(STOP)**

3. Study condition is NOT acute otitis media ..... ❒ **(STOP)**

4. Age of study population >=18 years ..... ❒ **(STOP)**

5. Study population on patients with immunodeficiencies or Craniofacial deficiencies including cleft palate ..... ❒ **(STOP)**

6. Key questions addressed:

KQ1: Diagnosis of AOM ..... ❒
KQ2: Antimicrobial resistance and PNC7 ..... ❒
KQ3-7: Effectiveness of treatment options ..... ❒
Unknown ..... ❒
None of the above ..... ❒**(STOP)**

7. Country

United States ..... ❒
Canada ..... ❒
Europe - specify ____/____/____/____/____ ..... ❒
Asia - specify ____/____/____/____/____ ..... ❒
South or Central America or Mexico - specify ____/____/____/____/____ ..... ❒
Other - specify ____/____/____/____/____ ..... ❒
Not specified ..... ❒

8. Study design

Randomized controlled trial 1
Nonrandomized controlled trial 2
Comparative cohort study 3
Single cohort study (Before-After, Time series) 4
Case control study 5
Cross-sectional study 6
Case Series/Report 7
Review/meta-analysis 8
Other design 9
Unknown 10

DRAFT 03-09-2009

Acute Otitis Media KQ 2 Screener 2

Article ID:_____ Reviewer:_____

First Author: _____
(Last Name Only)

Study Number:
___of____Description:_____
(Enter '1of1' if only one) (if more than one study)

1. Study Design:

Randomized controlled trial 1
Non-randomized controlled trial 2
Prospective comparative cohorts 3
Retrospective comparative cohorts 4
Case control 5
Natural history/Observational/Longitudinal single cohort 6
Case study 7
Mixed 8
Unsure 9
None of the above ..... 10 (stop)

2. From where were the patients identified? (check one)

Single clinic or hospital 1
Multi-site - regional 2
Multi-site - national 3
Other 4

3. How were patients sampled?

Consective patients 1
Random sample of patients 2
Convenience sample 3
Unstated/unknown 4

4. What were the criteria for classifying patients as having AOM (or other relevant diagnoses)?

Acute onset of S&S ..... ☐
Presence of MEE ..... ☐
S&S of MEI ..... ☐
Not specified ..... ☐
Specified, but none of the above ..... ☐

5. How was middle ear fluid obtained?

Tympanocentesis ..... ☐
Myringotomy ..... ☐

6. Were the middle ear fluids subjected to the same tests in both the pre- and the post-vaccine period?

Yes 1
No 2
Don't know 3

7. Sample size (Enter number or 9999 for not reported)

a. Unit studied: (check all that apply);
Patient ..... ☐
Enrolled: _____ Followed up: _____

Eardrums ..... ☐
Enrolled: _____ Followed up: _____

8. Is there any adverse event data?

Yes 1
No 2

DRAFT 02-16-2009

Acute Otitis Media KQ 1 Long Form

Article ID:_____ Reviewer:_____

First Author: _____
(Last Name Only)

Study Number:
___of____Description:_____
(Enter '1of1' if only one) (if more than one study)

1. Does this article address one of the following?

Diagnosis of AOM..... ☐
Distinguishing AOM from OME..... ☐

2. Do you think that this article might include the same data as another study?

(CIRCLE ONE)
Yes 1
No/Don't know 2
If YES enter Trial name and/or IDs:
Trial name : _____
ID(s) : _____

3. What is the study test? (Write in)

_____

4. Who is the person performing the study test?

a. Training _____
b. Training level _____
c. Setting _____
d. Not reported/not applicable

5. What is the reference test? (Write in)

_____

6. Who is the person performing the reference test?

a. Training _____
b. Training level _____
c. Setting _____
d. Not reported/ Not applicable

7. Who is studied?

(CHECK ALL THAT APPLY)
A. Not reported ..... ☐
B. Unselected population..... ☐
C. Selected population ..... ☐

Referred to pediatrician..... ☐
Referred to ENT..... ☐
Referred to other specialist..... ☐
Other ..... ☐
Specify other: _____
_____
_____
_____

8. What were the sample size data? (Enter number or 9999 for not reported)

a. Unit studied: (check all that apply);
Patient..... ☐

Enrolled: _____ Followed up: _____

Eardrums ..... ☐

Enrolled: _____ Followed up: _____

Acute Otitis Media KQ 1 Long Form

9. Age

Enter numbers

	total	circle one
Mean age		mos/yrs
Min age		wks/mos/yrs
Max age		wks/mos/yrs

10. Does the article report sensitivity, specificity or data to construct 2 X 2 table? (CHECK ALL THAT APPLY)

- Sensitivity ☐
- Specificity ☐
- Correlation ☐
- Other: _____ ☐
- Not reported ☐

11. Inclusion Criteria

- URI ☐
- Suspected AOM ☐
- None reported ☐
- Other ☐

Specify other:_____
_____
_____
_____

12. Exclusion Criteria

- Prior PE tubes ☐
- Craniofacial deformity ☐
- Prior otic surgery ☐
- None reported ☐
- Other ☐

Specify other:_____
_____
_____

13. Diagnostic criteria studied:

a. Clinical symptoms:
- Fever ☐
- Irritability ☐
- Otalgia ☐
- Decreased hearing ☐
- Ear fullness ☐
- Other constitutional symptoms ☐

b. Otoscopic findings:
- Bulging TM ☐
- Cloudy TM ☐
- Loss of landmarks ☐
- Erythematous TM ☐
- Air fluid level behind TM ☐
- Otorrhea ☐

c. Pneumatic otoscopy/tympanometry findings-- consistent with limited/absent mobility of TM ☐

d. Acoustic reflectometry findings-- consistent with presence of MEF ☐

e. Other ☐

Specify other:_____
_____
_____

14. Influencing factors studied

Demographic
- Age of child ☐
- Ethnicity/race ☐

Signs/Symptoms & Severity of Signs & Symptoms
- Otalgia ☐
- Severity ☐
- Irritability ☐
- Hearing loss ☐
- Laterality ☐
- Otitis prone ☐
- Concurrent use of analgesics, etc. ☐
- Inability to express symptoms ☐
- Presence of tube ☐

Parent/caretaker
- Parent/caretaker availability ☐
- Parent/caretaker education ☐

Examiner
- Type of examiner ☐
- Skill to diagnose (validated) ☐
- Setting ☐

Monitoring during episode/therapy course
- When ☐

Other ☐

Specify other:_____
_____

Acute Otitis Media KQ 1 Long Form

QUADAS:

15. Was the spectrum of patients representative of the patients who will receive the test in practice?

(CIRCLE ONE)

Yes 1
No..... 2
Unclear 3

*How to score: Score 'yes' if based on information reported from study's authors, you believe the spectrum of patients included in the study is representative of those in whom the test will be used in practice. Judgment should be based on both method of recruitment and the characteristics of those recruited. Score 'no' if you think the population studied does not fit into what was specified as acceptable. Score 'no' if studies recruit a group of healthy controls and a group known to have the target disorder.

16. Were selection criteria clearly described?

(CIRCLE ONE)

Yes 1
No..... 2
Unclear 3

*How to score: Score 'yes' if you think all relevant information regarding how participants were selected for inclusion has been provided. Score 'no' if study selection criteria are not clearly reported.

17. Is the reference standard likely to correctly classify the target condition?

(CIRCLE ONE)

Yes 1
No..... 2
Unclear 3

*How to score: Score 'yes' if you believe the reference standard is likely to correctly classify the target condition or is the best method available. Score 'no' if you do not think the reference standard was likely to have correctly classified the target condition.

18. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?

(CIRCLE ONE)

Yes 1
No..... 2
Unclear 3

*How to score: For conditions that progress rapidly, should be scored 'yes' if delay between performance of index and ref test if very short. If condition is chronic, longer delay periods may be appropriate. You will have to determine what is 'short enough.' Score 'no' if you think performance of index test and reference standard was sufficiently long that disease status may have changed between the performance of the two tests.

19. Did the whole sample or a random selection of the sample, receive verification using a reference standard?

(CIRCLE ONE)

Yes 1
No..... 2
Unclear 3

*How to score: Score 'yes' if it is clear that all patients or a random selection of patient who received index test went on to receive verification of disease status using reference standard. Score 'no' if some patients did not receive verification of disease status and selection of patient to receive reference standard was not random.

20. Did patients receive the same reference standard regardless of the index test result?

(CIRCLE ONE)

Yes 1
No..... 2
Unclear 3

*How to score: Score 'yes' if it is clear that patients received verification of their true disease status using the same reference standard. Score 'no' if some patients received verification using a different reference standard.

21. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?

(CIRCLE ONE)

Yes 1
No..... 2
Unclear 3

Acute Otitis Media KQ 1 Long Form

*How to score: Score 'yes' if it is clear from the study that the index test did not form part of the reference standard. Score 'no' if it appears that the index test formed part of the reference standard.

22. Was the execution of the index test described in sufficient detail to permit replication of the test?

(CIRCLE ONE)

Yes 1
No 2
Unclear 3

*How to score: SEE following question

23. Was the execution of the reference standard described in sufficient detail to permit its replication?

(CIRCLE ONE)

Yes 1
No 2
Unclear 3

*How to score: Score 'yes' if study reports sufficient details or citations to permit replication of the index test and reference standard. Score as 'no' in other cases.

24. Were the index test results interpreted without knowledge of the results of the reference standard?

(CIRCLE ONE)

Yes 1
No 2
Unclear 3

*How to score: SEE following question

25. Were the reference standard results interpreted without knowledge of the results of the index test?

(CIRCLE ONE)

Yes 1
No 2
Unclear 3

*How to score: Score 'yes' if study clearly states that the test results (index or reference standard) were interpreted blind to the results of the other test. Score 'no' if it does not appear that test results were interpreted blind to results of the other test.

26. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?

(CIRCLE ONE)

Yes 1
No 2
Unclear 3

*How to score: Score 'yes' if clinical data would normally be available when the test is interpreted in practice and similar data were available when interpreting the index test in the study and when clinical data would not be available in practice and these data were not available when the index test results were interpreted. Score 'no' if this is not the case.

27. Were uninterruptible/intermediate test results reported?

(CIRCLE ONE)

Yes 1
No 2
Unclear 3

*How to score: Score 'yes' if it is clear that all test results, including uninterruptible/indeterminate/intermediate results are reported. Score 'no' if you think that such results occurred but have not been reported.

28. Were withdrawals from the study explained?

(CIRCLE ONE)

Yes 1
No 2
Unclear 3

*How to score: Score 'yes' if it is clear what happened to all patients who entered the study, for example if a flow diagram of study participants is reported. Score 'no' if it appears that some of the participants who entered the study did not completed the study (i.e. did not receive both the index test and reference standard and these patients were not accounted for).

Draft 12/19/2008

Acute Otitis Media - Quality Review Form

Article ID:_____ Reviewer: _____

First Author: _____ Year:_____

1. Study Design
- Randomized controlled trial 1
- Non-randomized controlled trial 2
- Prospective comparative cohorts 3
- Retrospective comparative cohorts 4
- Case control 5
- Natural history/Observational/Longitudinal single cohort 6
- Case study 7
- Mixed 8
- Unsure 9
- None of the above ..... 10 (stop)

2. Study time **OR** Enrollment time:
(CIRCLE ONE: USE ENROLLMENT TIME ONLY IF STUDY TIME N/A)
(enter 9999 for NS)

Study start month_____ year_____
Study end month_____ year_____

Enrollment start month_____ year_____
Enrollment end month_____ year_____

3. Setting: multicenter ..... ☐
Specify number: _____ (enter 9999 for NS)

4. Setting (Check all that apply)
- Hospital ..... ☐ (01)
  - Emergency room ..... ☐ (02)
  - Hospital clinic/outpatient ..... ☐ (03)
  - Hospital inpatient ..... ☐ (04)

Hospital type:
- Private ..... ☐ (05)
- County ..... ☐ (06)
- University/academic ..... ☐ (07)
- Children's ..... ☐ (08)
- Military ..... ☐ (09)

- Office setting/private practice ..... ☐ (10)

Practice type:
- General/family practice ..... ☐ (11)
- Pediatric practice ..... ☐ (12)
- ENT ..... ☐ (13)
- Infectious disease ..... ☐ (14)

- Public health center/clinic/CHC ..... ☐ (15)
- Home visits ..... ☐ (16)
- Not applicable (i.e. administrative data set) ..... ☐ (17)
  - Write in dataset name:_____
- Setting not specified ..... ☐ (18)

RCT Questions:

5 Was the study described as randomized?
- Yes 1
- No 2

6. Was randomization procedure appropriate? (Jadad)
- Yes 1
- No 2
- Method not described 8

Acute Otitis Media - Quality Review Form

7. **What were the inclusion criteria?**

(Check all that apply)
(must have/conditional)

	Must Have	Conditional
Acute onset S&S (parent/guardian report)	☐ (01)	☐ (101)
Presence of middle ear effusion (MEE)	☐ (02)	☐ (102)
a. otoscopic findings:		
bulging tympanic membrane [TM]	☐ (03)	☐ (103)
cloudy TM	☐ (04)	☐ (104)
loss of landmarks	☐ (05)	☐ (105)
erythematous TM	☐ (06)	☐ (106)
air fluid level behind TM	☐ (07)	☐ (107)
otorrhea	☐ (08)	☐ (108)
b. Pneumatic otoscopy/tympanometry (limited or absent mobility of TM)	☐ (09)	☐ (109)
c. Presence of MEF by acoustic reflectometry	☐ (10)	☐ (110)
S&S of middle ear inflammation (MEI)	☐ (11)	☐ (111)
a. symptoms		
otalgia (score___) (time____/NS)	☐ (12)	☐ (112)
b. otoscopy (distinct TM erythema)	☐ (13)	☐ (113)
Other symptoms- decreased hearing	☐ (14)	☐ (114)
Other symptoms- ear fullness	☐ (15)	☐ (115)
Other symptoms- fever (>___degrees C/F)	☐ (16)	☐ (116)
AOM (unspecified) _____days/weeks	☐ (17)	☐ (117)
AOM requiring antibiotic	☐ (18)	☐ (118)
AOM treated with antibiotic _____days	☐ (19)	☐ (119)
Non-severe AOM at onset	☐ (20)	☐ (120)
Recurrent AOM	☐ (21)	☐ (121)
New/first episode of AOM	☐ (22)	☐ (122)
At least ___days after Tx of previous AOM.	☐ (23)	☐ (123)
Onset of AOM symptoms within ____days/months before entry	☐ (24)	☐ (124)

(must have/conditional)

Tympanocentesis performed		
Fluid obtained	☐ (25)	☐ (125)
Not Specified	☐ (26)	☐ (126)
Bacterial culture positive	☐ (27)	☐ (127)
Attend school/day care > _____hus/wk	☐ (28)	☐ (128)
Physician enrolled ____ or more patients	☐ (29)	☐ (129)

Characteristics

Age of child		
Infants, age not specified	☐ (30)	☐ (130)
Children, age not specified	☐ (31)	☐ (131)
Lower age limit: ____wk ____mo _____yr		
Lower age limit not specified	☐ (32)	☐ (132)
Upper age limit: ____wk ____mo _____yr		
Upper age limit not specified	☐ (33)	☐ (133)
Weight of child		
Lower weight limit _____lbs _____kg		
Lower weight limit not specified	☐ (34)	☐ (134)
Upper weight limit _____lbs _____kg		
Upper weight limit not specified	☐ (35)	☐ (135)

Additional inclusion criteria

Enter code: _____, _____, _____, _____,

_____, _____, _____, _____

None reported ☐ (999)

Appendix B. Sample Data Abstraction Forms

8. **Definition of AOM used**

Acute onset of S&S ..... ☐ (01)
Presence of MEE ..... ☐ (02)
S&S of MEI ..... ☐ (03)
Not specified ..... ☐ (04)
Specified, but none of the above ..... ☐ (05)

9. **What were the exclusion criteria?**

(CHECK ALL THAT APPLY)

Viral exanthem ..... ☐ (01)
Allergic to antibiotic ..... ☐ (02)
penicillin/beta-lactams ..... ☐ (03)
macrolides ..... ☐ (04)
any antibiotic ..... ☐ (05)

Antibiotic

Antibiotic within ____ hr/ ____ dy/ ____ wk/ ____ mo. ☐ (06)
Any antibiotic during present illness ..... ☐ (07)
Any complications requiring antibiotics ..... ☐ (08)
Concomitant/Concurrent infection needing antibiotic treatment within _____ hours (9999 for NS) ..... ☐ (09)
Long acting antibiotic within ____ weeks ..... ☐ (10)
Other antibiotic Tx ..... ☐ (11)
Prior antibiotic for present AOM episode ..... ☐ (12)
Strong indication of antibiotics (bulging eardrum, perforation, pus, tubes) ..... ☐ (13)
Topical antibiotic drops prior to study ..... ☐ (14)
Topical antibiotic drops NOS ..... ☐ (15)
Without History of prior antibiotic use ..... ☐ (16)
Prior RX with azithromycin ..... ☐ (17)

TYPES OF OTITIS MEDIA

AOM
of ____ days/ ____ months duration ..... ☐ (18)
within ____ days ____ wks ____ mos (999 for NS) ..... ☐ (19)
no time specified ..... ☐ (20)
Recurrent AOM (> ____ episodes in ____ months) .... ☐ (21)
No AOM within ____ months ..... ☐ (22)
Otitis externa ..... ☐ (23)
Chronic suppurative OM ..... ☐ (24)
OME (serous OM, nonsuppurative OM, mucoid OM secretory OM, glue ear) ..... ☐ (25)

CHARACTERISTICS OF AOM

Tympanocentesis required ..... ☐ (26)
Lack of effusion on tympanocentesis ..... ☐ (27)
No symptoms of AOM ..... ☐ (28)
TM perforation/Otorrhea ..... ☐ (29)
____ hours ____ days ____ weeks ____ months
Complication of OM ..... ☐ (30)

SURGICAL HISTORY FOR AOM

History of otic/ME surgery (excluding tubes) ..... ☐ (31)
PE tubes/history of PE tubes ..... ☐ (32)

Diseases/conditions

Respiratory Illness ..... ☐ (33)
Cranio-facial ..... ☐ (34)
Endocrine disorders (diabetes) ..... ☐ (35)
GI disorders/Liver ..... ☐ (36)
Renal Disorders ..... ☐ (37)
Neurological disease/impairment ..... ☐ (38)
Immunosuppressed /compromised/deficient ..... ☐ (39)
Other Infectious diseases (meningitis) ..... ☐ (40)
Major Systemic disease/ condition, medical problem ... ☐ (41)
Pregnancy ..... ☐ (42)
Heme/Onc Disorders ..... ☐ (43)
Metabolic/Inborn Errors of metabolism ..... ☐ (44)

Drugs

1. ASA ..... ☐ (45)
2. Bowel function-altering meds within ____ hours .... ☐ (46)
3. Concurrent ergotamine, carbamazepine or digitalis .. ☐ (47)
4. Concurrent use of antihistamine ..... ☐ (48)
5. Cytochrome p450 medication ..... ☐ (49)
6. Investigational drug within _____ dy / wk / mo .... ☐ (50)
7. On other medication/treatment ..... ☐ (51)

Acute Otitis Media - Quality Review Form

Misc

Presumed denial of tympanocentesis ..... ☐ (52)
Disagreement about diagnosis among researchers ..... ☐ (53)
Hospitalization/need for admission ..... ☐ (54)
In other studies/trials ..... ☐ (55)
Unable/unlikely to return to follow-up ..... ☐ (56)
Lived more than ____ m from hospital ..... ☐ (57)
No bacteriologic sample before or after treatment ..... ☐ (58)
No telephone ..... ☐ (59)
Language barrier ..... ☐ (60)
Referral to another physician at initial visit ..... ☐ (61)

Additional exclusion criteria

Enter code: _____ , _____ , _____ , _____ ,

_____ , _____ , _____ , _____

None reported ..... ☐ (999)

10. Was the study described as double-blind? (Jadad)
    Yes 1
    No 2

11. Was blinding procedure appropriate? (Jadad)
    Yes 1
    No 2
    Double blinding method not described 8
    Not applicable 9

12. Treatment Allocation
    a. Was the method of randomization adequate?
    Yes 1
    No 2
    Don't know 8
    b. Was the treatment allocation concealed?
    Yes 1
    No 2
    Don't know 8

13. Was the outcome assessor blinded?
    Yes 1
    No 2
    Don't know 8

14. Was the care provider blinded?
    Yes 1
    No 2
    Don't know 8

15. Were patients blinded?
    Yes 1
    No 2
    Don't know 8

16. Were all randomized participants analyzed in the group to which they were originally assigned?
    Yes 1
    No 2
    Don't know 8

Acute Otitis Media - Quality Review Form

17. **Interventions**

Enter sample size and intervention/exposure data for each arm beginning with placebo or control, then in order of first mention.
Enter total number of arms _____ .

Arm/ Group	Interventions	Dose	Units ☐	÷ OR =	Frequency	Duration of treatment	Units	Route
___	Placebo ☐(01) Amoxicilli-clavulanate ☐(02) Amoxicillin ☐(03) Ampicillin ☐(04) Analgesics ☐(05) Antihistamine ☐(06) Azithromycin ☐(07) Benzathine penicillin G ☐(08) Cephalexin ☐(09) Cefaclor ☐(10) Cefprozil ☐(11) Cefuroxime ☐(12) Cefixime ☐(13) Cefpodoxime ☐(14) Ceftibuten ☐(15) Ceftriaxone ☐(16) Clarithromycin ☐(17) Clindamycin ☐(18) Erythromycin ☐(19) Erythromycin/ sulfa ☐(20) Sulfa alone ☐(21) Loracarbef (Lorabid) ☐(22) Myringotomy ☐(23) Perscription to Hold ☐(24) Wait and see ☐(25) Other treatment ☐(26) Specify other _____	_____ _____ _____ _____	mg/kg/day | units/kg mg/kg/day | units/kg mg/kg/day | units/kg	÷ | =	BID | TID | QID | QD BID | TID | QD BID | TID | QD	_____ _____ _____	_____ _____ _____	PO / IM PO / IM PO / IM
Enter arm number.	Check all that apply. Enter additional codes.	Enter # or range 998. NA 999. NR	Circle one	circle one	Circle one	Enter a number 997. Variable 998. NA 999. NR	Enter # 1.Day 2.Week 8.NA 9.NR	

Acute Otitis Media - Quality Review Form

17. **Interventions - continued**

Enter sample size and intervention/exposure data for each arm beginning with placebo or control, then in order of first mention.
Enter total number of arms _____ .

Arm/ Group	Interventions	Dose	Units ☐	÷ OR =	Frequency	Duration of treatment	Units	Route
___	Placebo .....☐(01) Amoxicilli-clavulanate .....☐(02) Amoxicillin .....☐(03) Ampicillin .....☐(04) Analgesics .....☐(05) Antihistamine .....☐(06) Azithromycin.....☐(07) Benzathine penicillin G.....☐(08) Cephalexin.....☐(09) Cefaclor .....☐(10) Cefprozil.....☐(11) Cefuroxime .....☐(12) Cefixime .....☐(13) Cefpodoxime .....☐(14) Ceftibuten.....☐(15) Ceftriaxone .....☐(16) Clarithromycin .....☐(17) Clindamycin.....☐(18) Erythromycin.....☐(19) Erythromycin/ sulfa.....☐(20) Sulfa alone .....☐(21) Loracarbef (Lorabid) .....☐(22) Myringotomy .....☐(23) Perscription to Hold .....☐(24) Wait and see .....☐(25) Other treatment.....☐(26) Specify other _____	_____ _____ _____	mg/kg/day | units/kg mg/kg/day | units/kg mg/kg/day | units/kg	÷ | = ÷ | = ÷ | =	BID | TID | QID | QD BID | TID | QD BID | TID | QD	_____ _____ _____	_____ _____ _____	PO / IM PO / IM PO / IM
Enter arm number.	Check all that apply. Enter additional codes.	Enter # or range 998. NA 999. NR	Circle one	circle one	Circle one	Enter a number 997. Variable 998. NA 999. NR	Enter # 1.Day 2.Week 8.NA 9.NR	

Acute Otitis Media - Quality Review Form

17. **Interventions - continued**

Enter sample size and intervention/exposure data for each arm beginning with placebo or control, then in order of first mention.

Enter total number of arms _____.

Arm/ Group	Interventions	Dose	Units ☐	÷ OR =	Frequency	Duration of treatment	Units	Route
___	Placebo ☐(01) Amoxicillin-clavulanate ☐(02) Amoxicillin ☐(03) Ampicillin ☐(04) Analgesics ☐(05) Antihistamine ☐(06) Azithromycin ☐(07) Benzathine penicillin G ☐(08) Cephalexin ☐(09) Cefaclor ☐(10) Cefprozil ☐(11) Cefuroxime ☐(12) Cefixime ☐(13) Cefpodoxime ☐(14) Ceftibuten ☐(15) Ceftriaxone ☐(16) Clarithromycin ☐(17) Clindamycin ☐(18) Erythromycin ☐(19) Erythromycin/ sulfa ☐(20) Sulfa alone ☐(21) Loracarbef (Lorabid) ☐(22) Myringotomy ☐(23) Prescription to Hold ☐(24) Wait and see ☐(25) Other treatment ☐(26) Specify other _____	_____	mg/kg/day | units/kg mg/kg/day | units/kg mg/kg/day | units/kg mg/kg/day | units/kg	÷ | = ÷ | = ÷ | = ÷ | =	BID | TID | QID | QD BID | TID | QD BID | TID | QD BID | TID | QD	_____ _____ _____ _____	_____ _____ _____ _____	PO / IM PO / IM PO / IM PO / IM
	Enter arm number.	Check all that apply. Enter additional codes.	Enter # or range 998. NA 999. NR	Circle one	circle one	Circle one	Enter a number 997. Variable 998. NA 999. NR	Enter # 1.Day 2.Week 8.NA 9.NR	

Acute Otitis Media - Quality Review Form

17. **Interventions - continued**

Enter sample size and intervention/exposure data for each arm beginning with placebo or control, then in order of first mention.
Enter total number of arms _____ .

Arm/ Group	Interventions	Dose	Units ☐	÷ OR =	Frequency	Duration of treatment	Units	Route
___	Placebo ☐(01) Amoxicilli-clavulanate ☐(02) Amoxicillin ☐(03) Ampicillin ☐(04) Analgesics ☐(05) Antihistamine ☐(06) Azithromycin ☐(07) Benzathine penicillin G ☐(08) Cephalexin ☐(09) Cefaclor ☐(10) Cefprozil ☐(11) Cefuroxime ☐(12) Cefixime ☐(13) Cefpodoxime ☐(14) Ceftibuten ☐(15) Ceftriaxone ☐(16) Clarithromycin ☐(17) Clindamycin ☐(18) Erythromycin ☐(19) Erythromycin/ sulfa ☐(20) Sulfa alone ☐(21) Loracarbef (Lorabid) ☐(22) Myringotomy ☐(23) Perscription to Hold ☐(24) Wait and see ☐(25) Other treatment ☐(26) Specify other _____	_____ _____ _____ _____	mg/kg/day | units/kg mg/kg/day | units/kg mg/kg/day | units/kg	÷ | =	BID | TID | QID | QD BID | TID | QD BID | TID | QD BID | TID | QD	_____ _____ _____ _____	_____ _____ _____ _____	PO / IM PO / IM PO / IM PO / IM
Enter arm number.	Check all that apply. Enter additional codes.	Enter # or range 998. NA 999. NR	Circle one	circle one	Circle one	Enter a number 997. Variable 998. NA 999. NR	Enter # 1.Day 2.Week 8.NA 9.NR	

18. Interventions given to EVERYONE in the study:

Interventions given to everyone	Dose	Units	Frequency	Duration of treatment	Units
Check all that apply:					
Acetaminophen ..... ☐(01)	____	____	____	____	____
Ibuprofen ..... ☐(02)	____	____	____	____	____
Steroids ..... ☐(03)	____	____	____	____	____
Sudafe d/t e congestants ... ☐(04)	____	____	____	____	____
Nose drops ..... ☐(05)					
Topical analgesics drops . ☐(06)					
Antihistamines ..... ☐(07)					
None ..... ☐(08)					
	Enter # or range 998. Not applicable 999. Not reported	Enter a number 1. g 2. mg 3. µg 4. I.U. 8. NA 9. NR	Enter a number 1. Daily 2. Weekly 3. Monthly 4. Yearly 8 NA 9. NR	Enter a number 997. Variable 998. NA 999. NR	Enter a number 1.Day 2.Week 3.Month 4.Year 8.NA 9. NR

19. **Outcomes**

a. Treatment failure, e.g., clinical cure, duration of symptoms or illness ..... ☐ (01)
1. Presence of MEE [also persistent effusion, OME] ☐ (02)
_____ days of effusion or Not specified ..... ☐ (03)
a. By otoscopic findings: ..... ☐ (04)
Bulging tympanic membrane [TM] ..... ☐ (05)
Cloudy TM ..... ☐ (06)
Loss of landmarks ..... ☐ (07)
Erythematous TM ..... ☐ (08)
Air fluid level behind TM ..... ☐ (09)
Otorrhea ..... ☐ (10)
b. By Pneumatic otoscopy/tympanometry (limited or absent mobility of TM) ..... ☐ (11)
c. By Presence of MEF by acoustic reflectometry ☐ (12)
d. By Tympanocentesis ..... ☐ (13)
2. Signs or symptoms of MEI ..... ☐ (14)
a. By symptoms (otalgia, ear fullness) ..... ☐ (15)
b. By otoscopy (distinct TM erythema) ..... ☐ (16)
3. Other symptoms: fever ..... ☐ (17)
4. Other symptoms: decreased hearing ..... ☐ (18)

b. Invasive infections, e.g., mastoiditis, bacteremia ..... ☐ (19)
c. Bacteriologic cure/failure, i.e., eradication of the etiologic bacteria from middle-ear fluid ..... ☐ (20)
d. Disease recurrence, i.e., relapse of AOM within 30 days, time to relapse ..... ☐ (21)
e. Adverse effects of treatment, i.e., diarrhea, vomiting, bacterial resistance ..... ☐ (22)
f. Quality of life or functional outcome ..... ☐ (23)
g. Parent satisfaction ..... ☐ (24)
h. Cost outcomes, e.g., days of school or daycare missed and days of parental work missed ..... ☐ (25)
i. Bacteriologic outcomes by nasopharyngeal cultures ..... ☐ (26)
j. Otologic complications - i.e., cholesteatoma ..... ☐ (27)
k. PE tube placement ..... ☐ (28)
l. Healthcare utilization ..... ☐ (29)

Other outcomes ..... ☐ (30)
Enter code: _____, _____, _____, _____, _____, _____

Not defined ..... ☐ (888)
None reported ..... ☐ (999)

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20. **What was the method of adverse events assessment?**

(Check all that apply)

Monitored ..... ☐ (01)
Elicited by investigator ..... ☐ (02)
Reported spontaneously by patient ..... ☐ (03)
Other (enter code: _____, _____, _____, _____) ..... ☐ (04)
Not reported ..... ☐ (05)

21. Other sources of potential bias:

a. Were co-interventions avoided or similar?
Yes 1
No 2
Don't know 8

b. Was the compliance acceptable in all groups?
Yes 1
No 2
Don't know 8

c. Was the timing of the outcome assessment similar in all groups?
Yes 1
No 2
Don't know 8

22. Sample size: (Enter N or 9999 for not reported)

N	placebo/ control	Intervention 1 _____	Intervention 2 _____	Intervention 3 _____
entering				
completing				
analyzed				
excluded				

23. Was there a description of withdrawals and dropouts? (Jadad)
Yes 1
No 2

24. Was the drop-out rate described and the reason given?
Yes 1
No 2
Don't know 8

25. Was the drop-out rate acceptable?
Yes 1
No 2
Don't know 8

26. **Characteristics**

Enter numbers by arm *or* total

	placebo/ control	intv 1	intv 2	intv 3	total	circle one
Male						N / %
Female						N / %
Mean age						mos/yrs
Min age						wks/mos/yrs
Max age						wks/mos/yrs

Acute Otitis Media - Quality Review Form

28. **Ethnicity/race**

	placebo/ control	intv 1	intv 2	intv 3	total	circle one
White						N / %
Black						N / %
Hispanic						N / %
Native American						N / %
Eskimo /Inuit						N / %
Other NOS						N / %
Other (specify) _____						N / %

Race not reported..... ☐

29. Were the groups similar at baseline regarding the most important prognostic indicators?

Yes 1
No.....2
Don't know 8

30. Were point estimates and measures of variability presented for the primary outcome measures?

Yes 1
No.....2
Don't know 8

31. **Subgroup analysis:**

Environmental..... ☐ (01)
Symptoms & Severity by history
Otalgia..... ☐ (02)
Hearing deficit and severity..... ☐ (03)
Signs/physical findings
Pulling of ear in an infant..... ☐ (04)
Otorrhea..... ☐ (05)
Irritability..... ☐ (06)
Fever _> _____ C/F ..... ☐ (07)
TM inflammation..... ☐ (08)
Retracted TM..... ☐ (09)
Middle ear effusion..... ☐ (10)
Laterality ..... ☐ (11)
..... ☐ (12)
Parent/caretaker ..... ☐ (13)
Examiner..... ☐ (14)
Race/ethnicity ..... ☐ (15)
Recurrent otitis media/ otitis prone..... ☐ (16)
Persistent/relapse otitis media..... ☐ (17)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Adler 2000[73]	Jadad quality score[1] (0-5):2 [1,0,1,0,0] Definition: Presence of MEE	Amoxicillin-clavulanate 13.3 mg/kg/day = tid for 10 days vs. Cefdinir 14 mg/kg/day = qd for 10 days vs. Cefdinir 7 mg/kg/day = bid for 10 days	Place: Multicenter: 38 centers Inclusion: 6 mo-12 yr, Presence of middle ear effusion (MEE), Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), Otoscopy (distinct TM erythema), AOM < 1 week Exclusion: Penicillin/beta-lactams, Antibiotic within 7 days, Concomitant/Concurrent infection needing antibiotic treatment, Topical antibiotic drops prior to study, Chronic suppurative OM, OME (serous OM, nonsuppurative OM, mucoid OM secretory OM, glue ear), TM perforation/Otorrhea, Complication of OM, PE tubes/history of PE tubes, Cranio-facial, GI disorders/Liver, Renal Disorders	Entering: N=752 N=251 Amoxicillin-clavulanate N=248 Cefdinir 14 mg QD N=253 Cefdinir 7 mg BID Completing: N=665 N=210 Amoxicillin-clavulanate N=226 Cefdinir 14 mg QD N=229 Cefdinir 7 mg BID Analyzed: N=595 N=197 Amoxicillin-clavulanate N=195 Cefdinir 14 mg QD N=203 Cefdinir 7 mg BID	Treatment failure; Presence of MEE [also persistent effusion, OME]; Signs or symptoms of MEI; Other symptoms: fever; Other symptoms: decreased hearing; Disease recurrence; Adverse effects of treatment	Outcome: Success rate (cure or improvement) at day 11-16 A-C 90% (177/197) Cef QD 91% (177/195) Diff (95%CI) -1% (-7, 4.8) A-C 90% (177/197) Cef BID 89% (180/203) Diff (95%CI) 1% (-5, 7) Cef QD 91% (177/195) Cef BID 89% (180/203) Diff (95%CI) 2% (-4, 8) Outcome: Adverse events A-C / Cef QD / Diff (95%CI) Any 26.3% (66/251) 16.5% (41/248) 10%(2.6, 17) Diarrhea 12.7% (32/251) 10.9% (27/248) 2% (-3.9, 7.5) Tx related 20.3% (51/251) 14.1% (35/248) 6% (-0.2, 13) A-C / Cef BID / Diff (95%CI) Any 26.3% (66/251) 23.3% (59/253) 3%(-4.5, 10) Diarrhea 12.7% (32/251) 15.8% (40/253) -3%(-9, 3) Tx related 20.3% (51/251) 17.8% (45/253) 2%(-4.4, 9) Cef QD / Cef BID / Diff (95%CI) Any 16.5% (41/248) 23.3% (59/253) -7% (-14, 0.2) Diarrhea 10.9% (27/248) 15.8% (40/253) 5% (-11, 1.1) Tx related 14.1% (35/248) 17.8% (45/153) -4% (-11, 3.6)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Arguedas 2005[66]	Jadad quality score[1] (0-5):3 [1,1,1,0,0] Definition: Presence of MEE, S&S of MEI	Amoxicillin 90 mg/kg/day / bid for 10 days vs. Azithromycin 30 mg/kg/day = qd for 1 day	Study Time: 9/2002-7/2003 Place: United States, Finland, Chile, Costa Rica Multicenter: 19 centers Inclusion: 6-30 mo, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Cloudy TM, Otorrhea, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), S&S of middle ear inflammation (MEI), Otalgia, Otoscopy (distinct TM erythema), Fever Exclusion: Penicillin/beta-lactams, Macrolides, Antibiotic within 30 days, Chronic suppurative OM, TM perforation/Otorrhea >24 hours, PE tubes/history of PE tubes, Major Systemic disease/ condition, medical problem, Resistant bacteria	Influencing factors: Middle ear effusion, Age, Baseline pathogen Entering: N=312 N=154 Amoxicillin N=158 Azithromycin Completing: N=306 N=151 Amoxicillin N=155 Azithromycin Analyzed: N=312 N=154 Amoxicillin N=158 Azithromycin	Treatment failure; Presence of MEE [also persistent effusion, OME]; Signs or symptoms of MEI; Disease recurrence; Adverse effects of treatment	Outcome: Success rate (cure or improvement) at day 12-14 Amoxicillin / Azithromycin / Diff (95%CI) All pts 84% (127/151) 84% (130/155) 0.2%(-8, 8) <=2yrs 82% (99/121) 82% (109/133) -0.2% (-10, 9) Outcome: Success rate (cure) at day 25-28 visit All pts 78% (117/151) 77% (117/152) -0.5% (-10, 9) <=2yrs 75% (91/121) 75% (98/130) -0.2%(-11,11) Outcome: Adverse events Abd pain: 1.9% (3/154) 3.8% (6/158) -2%(-5.6, 1.8) Diarrhea: 17.5% (27/154) 8.2% (13/158) 9%(2, 17) Rash: 2.6% (4/154) 2.5% (4/158) 0.1%(-3.4,3.6) Vomiting 8.4% (13/154) 8.2% (13/158) 0.2%(-6, 6) Tx related 28.6% (44/154) 19.6% (31/158) 9%(-0.5, 18)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Arrieta 2003[124]	Jadad quality score[1] (0-5):3 [1,1,1,0,0] Definition: Presence of MEE, S&S of MEI	Amoxicillin-clavulanate 45/45 vs. Azithromycin	Study Time: 3/2001-3/2002 Place: United States Multicenter: 18 centers Inclusion: 6 mo-6 yr, <25 kg, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Cloudy TM, Erythematous TM, Otorrhea, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), S&S of middle ear inflammation (MEI), Otalgia, Ear fullness, Recurrent AOM, Persistent AOM Exclusion: Penicillin/beta-lactams, Macrolides, Antibiotic within 30 days, TM perforation/Otorrhea, Complication of OM, PE tubes/history of PE tubes, GI disorders/Liver, Renal Disorders, Major Systemic disease/ condition, medical problem, Heme/Onc Disorders, Investigational drug within 1 month, Hospitalization/need for admission	Influencing factors: Age Completing: N=296 N=145 Amoxicillin-clavulanate N=151 Azithromycin Analyzed: N=296 N=145 Amoxicillin-clavulanate N=151 Azithromycin	Treatment failure; Bacteriologic cure/failure; Adverse effects of treatment; Other antibiotic: No new abx Rx/no change in abx Rx	Outcome: Success rate on day 12-16 Amox-clav / Azithromycin / Diff (95%CI) Total 84% (122/145) 86% (128/149) -2% (-10, 6) <=2yrs 79% (73/92) 85% (82/96) -6% (-17, 5) >2yrs 92% (49/53) 87% (46/53) 5% (-7, 17) Outcome: Adverse events Any 42.2% (62/147) 32.0% (49/153) 10%(-0.7, 21) Abd pain 2.0% (3/147) 3.9% (6/153) -2%(-5.7, 2) Anorexia 2.7% (4/147) 3.3% (6/153) -0.6%(-4, 3) Dermatitis 2.0% (3/147) 0.7% (1/153) 1.3%(-1.3, 4) Diarrhea 29.9% (44/147) 19.6% (30/153) 10%(0.5, 20) Rash 4.8% (7/147) 3.3% (5/153) 1.5%(-3, 6) Vomiting 8.2% (12/147) 5.2% (8/153) 3%(-2.6, 9)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Bezakova 2009[164]	Jadad quality score[1] (0-5):4 [1,1,0,1,1] Definition: Acute onset of S&S, S&S of MEI	Placebo vs. Amoxicillin 40 mg/kg/day / tid for 10 days	Study Time: 2/1996-5/1998 Place: Netherlands Multicenter: 53 centers Office setting/ private practice, General/ family practice Inclusion: 6-24 mo, Acute onset S&S (parent/guardian report), Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Erythematous TM, Otorrhea, S&S of middle ear inflammation (MEI), Otalgia, Fever, Irritability, Other constitutional symptoms NOS Exclusion: Penicillin/beta-lactams, Antibiotic within 4 weeks, Cranio-facial, Immunosuppressed /compromised/deficient	Entering: N=240 N=123 Placebo Completing: N=168 N=90 Placebo Analyzed: N=168 N=90 Placebo	Disease recurrence; Healthcare utilization	Outcome: Clinical outcome between 6 months and 3 years Amoxicillin / Placebo / Diff (95% CI) No recurrent AOM: 37% (28/75) / 57% (49/86) / -20% (-5, -35) No referral: 31% (24/78) / 30% (62/89) / 0% (-14, 14) No surgery: 79% (16/78) / 70% (27/90) / 9%(-23, 4)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Biner 2007[71]	Jadad quality score[1] (0-5):1 [1,0,0,0,0] Definition: Acute onset of S&S, Presence of MEE, S&S of MEI	Ceftriaxone 50 mg/kg/day = qd for 1 day vs. Azithromycin 10 mg/kg/day = qd for 1 day, Azithromycin 5 mg/kg/day = qd for 4 days vs. Amoxicillin-clavulanate 90 mg/kg/day / bid for 10 days	Study Time: 2/2001-4/2003 Place: Hospital, ENT Inclusion: 6 mo-10 yr, Acute onset S&S (parent/guardian report), Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Cloudy TM, Erythematous TM, S&S of middle ear inflammation (MEI), Otalgia, Fever >38 C Exclusion: Penicillin/beta-lactams, Macrolides, Antibiotic within 2 weeks, AOM within 1 months, Recurrent AOM (>3 episodes in 12 months), TM perforation/Otorrhea, PE tubes/history of PE tubes, Cranio-facial, Immunosuppressed /compromised/deficient, Major Systemic disease/ condition, medical problem, On other medication/treatment	Analyzed: N=104 N=34 Ceftriaxone N=31 Azithromycin N=39 Amoxicillin-clavulanate	Treatment failure; Presence of MEE [also persistent effusion, OME]; Signs or symptoms of MEI; Other symptoms: fever; Disease recurrence; Adverse effects of treatment	Outcome: Cumulative clinical resolution rate at day 3 after treatment initiation Amox-clav 87.2% (34/39) — Ceftriaxon 85.3% (29/34) — Diff (95%CI) 2%(-14, 18) Amox-clav 87.2% (34/39) — Azithro 87.1% (27/31) — Diff (95%CI) 0.1%(-16, 16) Outcome: Persistent middle ear fluid on day 30 Amox-clav — Ceftriaxon — Diff (95%CI) 14.7% (5/34) — 17.2% (5/29) — -2.5%(-21, 16) Amox-clav — Azithro — Diff (95%CI) 14.7% (5/34) — 22.2% (6/27) — -7.5%(-27, 12) Outcome: Adverse events Amox-clav — Ceftriaxon — Diff (95%CI) Diarrhea 7.7% (3/39) — 5.9% (2/34) — 2%(-10, 13) Vomiting 2.6% (1/39) — 2.9% (1/34) — -0.3%(-8, 7) Amox-clav — Azithro — Diff (95%CI) Diarrhea 7.7% (3/39) — 6.5% (2/31) — 1%(-11, 13) Vomiting 2.6% (1/39) — 3.2% (1/31) — -0.6%(-8, 7)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Block 2000[85]	Jadad quality score[1] (0-5):2 [1,0,1,0,0] Definition: Not specified	Cefprozil 30 mg/kg/day / bid for 10 days vs. Cefdinir 14 mg/kg/day / bid for 5 days	Study Time: 10/1996-2/1997 Place: United States Multicenter: 13 centers Inclusion: 6 mo-12 yr, Presence of middle ear effusion (MEE), Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), Otoscopy (distinct TM erythema), AOM Exclusion: Penicillin/beta-lactams, Antibiotic within 7 days, Topical antibiotic drops prior to study, Chronic suppurative OM, OME (serous OM, nonsuppurative OM, mucoid OM secretory OM, glue ear), TM perforation/Otorrhea, Complication of OM, PE tubes/history of PE tubes, Cranio-facial, GI disorders/Liver, Renal Disorders, Major Systemic disease/ condition, medical problem, On other medication/treatment	Influencing factors: Age Entering: N=435 N=216 Cefprozil 10 days N=219 Cefdinir 5 days Completing: N=373 N=183 Cefprozil 10 days N=190 Cefdinir 5 days Analyzed: N=373 N=183 Cefprozil 10 days N=190 Cefdinir 5 days	Treatment failure; Presence of MEE [also persistent effusion, OME]; Signs or symptoms of MEI; Adverse effects of treatment	Outcome: clinical cure on day 9-11 (4-6 days post therapy for cefdinir and +/-1 day post therapy for Cefprozil) Cefdinir / Cefprozil / Diff (95%CI) Total 80.0% (152/190) / 82.5% (151/183) / -2.5%(-10,5.4) <2yrs 71.0% (49/69) / 70.7% (41/58) / 0.3%(-16, 16) 2-5yrs 85.1% (57/67) / 87.1% (61/70) / -2% (-14, 10) 6-12yrs 83.3% (45/54) / 89.1% (49/55) / -6% (-19, 7) Outcome: clinical cure on test-of-cure visit on 17-21 day post therapy (days 17-21 for cefdinir and days22-26 for Cefprozil) Cefdinir / Cefprozil / Diff (95%CI) Total 65.3% (124/190) / 64.5% (118/183) / 0.8% (-9, 10) <2yrs 49.3% (34/69) / 48.3% (28/58) / 1% (-16, 18) 2-5yrs 73.1% (49/67) / 64.3% (45/70) / 9% (-7, 24) 6-12yrs 75.9% (41/54) / 81.8% (45/55) / -6%(-21, 9) Outcome: Adverse events Cefdinir / Cefprozil / Diff (95%CI) Diarrhea 7.9% (15/190) / 4.4% (8/183) / 3.5%(-1.4,8) Rash 3.2% (6/190) / 3.8% (7/183) / -0.6%(-4.3,3.1)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Block 2000[72]	Jadad quality score[1] (0-5):2 [1,0,1,0,0] Definition: Presence of MEE, S&S of MEI	Amoxicillin-clavulanate 40/10 mg/kg/day / tid for 10 days vs. Cefdinir 14 mg/kg/day = qd for 10 days vs. Cefdinir 7 mg/kg/day = bid for 10 days	Enrollment Time: 4/1992-8/1993 Place: United States Multicenter: 13 centers Inclusion: 6 mo-12 yr, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Loss of landmarks, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), S&S of middle ear inflammation (MEI), Otalgia, Otoscopy (distinct TM erythema), Decreased hearing, Onset of AOM symptoms within 7 days before entry, Irritability, Other constitutional symptoms NOS Exclusion: Antibiotic within 7 days, TM perforation/Otorrhea, PE tubes/history of PE tubes, Resistant bacteria	Influencing factors: Age Entering: N=384 N=128 Amoxicillin-clavulanate N=128 Cefdinir 14 mg QD N=128 Cefdinir 7 mg BID Completing: N=303 N=100 Amoxicillin-clavulanate N=102 Cefdinir 14 mg QD N=101 Cefdinir 7 mg BID Analyzed: N=303 N=100 Amoxicillin-clavulanate N=102 Cefdinir 14 mg QD N=101 Cefdinir 7 mg BID	Treatment failure; Presence of MEE [also persistent effusion, OME]; Signs or symptoms of MEI; Adverse effects of treatment; Other antibiotic: No new abx Rx/no change in abx Rx	Outcome: Clinical success (cure or improvement) 2-4 days after treatment: Amox-clav vs. Cefdinir QD A-C / CDR-QD / Diff (95%CI) Total 86% (86/100) / 83.3% (85/102) / 0.7%(-7, 13) <2yrs 79% (31/39) / 80% (45/56) / -0.9%(-17,15) 2-5yrs 85% (35/41) / 84% (31/37) / 1.6%(-14, 18) 6-12yrs 100% (20/20) / 100% (9/9) / 0.0% Outcome: Clinical success (cure or improvement) 2-4 days after treatment: Amox-clav vs. Cefdinir BID A-C / CDR-BID / Diff (95%CI) Total 86% (86/100) / 80% (81/101) / 5.9% (-4, 16) <2yrs 79% (31/39) / 62% (30/48) / 17% (-2, 36) 2-5yrs 85% (35/41) / 95% (35/37) / -9%(-23, 4) 6-12yrs 100% (20/20) / 100% (16/16) / 0.0% Outcome: Clinical success (cure or improvement) 2-4 days after treatment: Amox-clav vs. Cefdinir BID CDR-QD / CDR-BID / Diff (95%CI) Total 83% (85/102) / 80% (81/101) / 3% (-7, 14) <2yrs 80% (45/56) / 62% (30/48) / 18%(0.6,35) 2-5yrs 84% (31/37) / 95% (35/37) / -11%(-25, 3) 6-12yrs 100% (9/9) / 100% (16/16) / 0.0% Outcome: Adverse events A-C / CDR-QD / Diff (95%CI) Any 42% (54/128) / 14% (18/128) / 28%(17, 39) Diarrhea 35% (45/128) / 10% (13/128) / 25%(15, 35) Rash 8% (10/128) / 5% (6/128) / 3%(-2.8, 9) A-C / CDR-BID / Diff (95%CI) Any 42% (54/128) / 23% (29/128) / 20%(8, 31) Diarrhea 35% (45/128) / 13% (17/128) / 22%(11, 32) Rash 8% (10/128) / 6% (8/128) / 2%(-4.8, 7.8) CDR-QD / CDR-BID / Diff (95%CI) Any 14% (18/128) / 23% (29/128) / -9%(-18,0.9) Diarrhea 10% (13/128) / 13% (17/128) / -3%(-11,4.8) Rash 5% (6/128) / 6% (8/128) / -2%(-7, 4)

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Block 2004[75]	Jadad quality score[1] (0-5):2 [1,0,1,0,0] Definition: Presence of MEE, S&S of MEI	Amoxicillin-clavulanate 45/6.4 mg/kg/day / bid for 10 days vs. Cefdinir 14 mg/kg/day / bid for 5 days	Enrollment Time: 2/2003-4/2003 Place: United States Multicenter: 28 centers Inclusion: 6 mo-6 yr, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Cloudy TM, Air fluid level behind TM, Otorrhea, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), Presence of MEF by acoustic reflectometry, Otalgia, Decreased hearing Exclusion: Antibiotic within 2 weeks, Concomitant/Concurrent infection needing antibiotic treatment, Long acting antibiotic within 4 weeks, Otitis externa, Chronic suppurative OM, No symptoms of AOM, PE tubes/history of PE tubes	Influencing factors: Age, Pneumococcal Vaccine Entering: N=425 N=214 Augmentin [Amoxicillin-clavulanate] N=211 Cefdinir Completing: N=425 N=214 Augmentin [Amoxicillin-clavulanate] N=211 Cefdinir Analyzed: N=425 N=214 Augmentin [Amoxicillin-clavulanate] N=211 Cefdinir	Treatment failure; By otoscopic findings:; Bulging tympanic membrane [TM]; Loss of landmarks; Air fluid level behind TM; Presence of MEF by acoustic reflectometry; Signs or symptoms of MEI; By symptoms (otalgia, ear fullness); By otoscopy (distinct TM erythema); Other symptoms: fever; Other symptoms: decreased hearing; Adverse effects of treatment	Outcome: Success at end-of-treatment visit (study days 7-9 for Cefdinir; study days 12-14 for Amox-clav) by age group Amox-clav / Cefdinir / Diff (95%CI) Total 85% (164/192) / 88% (170/194) / -2% (-9, 4.6) <2yrs 78% (64/82) / 88% (79/90) / -10%(-21, 1.4) 2-6yrs 91% (100/110) / 88% (91/104) / 3% (-4.9, 12) Outcome: Success at end-of-treatment visit (study days 7-9 for Cefdinir; study days 12-14 for Amox-clav) by PCV7 Amox-clav / Cefdinir / Diff (95%CI) Total 85% (164/192) / 88% (170/194) / -2% (-9, 4.6) HadPCV7 82% (102/124) / 92% (115/125) / -10%(-18, -2) NoPCV7 91% (62/68) / 80% (55/69) / 11% (-0.8, 23) Outcome: Adverse events Amox-clav / Cefdinir / Diff (95%CI) Dia.rash 10% (21/214) / 8% (17/211) / 2%(-4, 7) Diarrhea 10% (21/214) / 7% (15/211) / 3%(-3, 8) Vomiting 5% (11/214) / 1% (2/211) / 4%(1, 7.5)

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Block 2005[83]	Jadad quality score[1] (0-5):3 [1,0,1,1,1] Definition: Presence of MEE, S&S of MEI	Azithromycin 10 mg/kg/day = qd for 1 day, --- 5 mg/kg/day = qd for 4 days vs. Cefdinir 7 mg/kg/day = bid for 5 days	Enrollment Time: 11/2003-1/2004 Place: United States Multicenter: 27 centers Inclusion: 6 mo-6 yr, Bulging tympanic membrane [TM], Loss of landmarks, Erythematous TM, Otorrhea, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), Presence of MEF by acoustic reflectometry, Otalgia, Decreased hearing, Ear fullness, AOM < 1 week Exclusion: Antibiotic within 2 weeks, Concomitant/Concurrent infection needing antibiotic treatment, Long acting antibiotic within 4 weeks, Otitis externa, Chronic suppurative OM, TM perforation/Otorrhea >24 hours, PE tubes/history of PE tubes	Influencing factors: Age Entering: N=357 N=181 Azithromycin N=176 Cefdinir Completing: N=350 N=176 Azithromycin N=174 Cefdinir Analyzed: N=350 N=176 Azithromycin N=174 Cefdinir	Treatment failure; By otoscopic findings:; Bulging tympanic membrane [TM]; Cloudy TM; Loss of landmarks; Erythematous TM; Air fluid level behind TM; Otorrhea; By Pneumatic otoscopy/tympanometry; Presence of MEF by acoustic reflectometry; By symptoms (otalgia, ear fullness); By otoscopy (distinct TM erythema); Other symptoms: fever; Other symptoms: decreased hearing; Adverse effects of treatment; Parent satisfaction; Cost outcomes; Healthcare utilization	Outcome: Clinical success (cure or improve) on day 7-9 at end-of-therapy Azith / Cefdinir / Diff (95%CI) Total 85% (149/176) 87% (151/174) -2% (-9, 5.3) 0-2yrs 82% (54/66) 81% (48/59) 1% (-13, 15) >2yrs 86% (95/110) 90% (103/115) -4% (-12, 4.5) Outcome: Adverse events Azith / Cefdinir / Diff (95%CI) Abn Stool 4% (7/176) 7% (12/174) -3%(-8,2) Diarrhea 3% (5/176) 6% (10/174) -3%(-6,0.6)

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Bolt 2008[90]	Jadad quality score[1] (0-5):4 [1,1,1,0,1] Definition: Presence of MEE, S&S of MEI	Placebo vs. 2% aqueous lidocaine 3 drops hourly for 1 day	Enrollment Time: 10/2003-7/2004 Place: Emergency room Inclusion: 3-17 yr, 34-35 lbs, Bulging tympanic membrane [TM], Cloudy TM, Erythematous TM, Otalgia within last 3 days Exclusion: Any antibiotic, TM perforation/Otorrhea, PE tubes/history of PE tubes, GI disorders/Liver, Renal Disorders, Neurological disease/impairment, Major Systemic disease/ condition, medical problem	Influencing factors: Examiner Entering: N=63 N=32 Placebo N=31 Lidocaine Completing: N=60 N=31 Placebo N=29 Lidocaine Analyzed: N=60 N=31 Placebo N=29 Lidocaine	By symptoms (otalgia, ear fullness); Adverse effects of treatment	Outcome: Reduction by 50% in pain score on day 30 Lidocaine / Placebo / Diff (95%CI) By parent 90% (28/31) / 63% (20/32) / 27%(6, 48) By doctor 84% (26/31) / 66% (21/32) / 18% (-3.4,39) Outcome: Reduction by 25% in pain score on day 30 Lidocaine / Placebo / Diff (95%CI) By parent 95% (28/31) / 78% (25/32) / 21%(1, 41) By doctor 90% (28/31) / 78% (25/32) / 12%(-6, 30) Outcome: Adverse events Lidocaine / Placebo / Diff (95%CI) Ear Discharge 6% (2/31) / 9% (3/32) / -3%(-16,10) Dizziness 10% (3/31) / 0% (0/32) / 10%(-0.8,20)

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Bottenfield 1998[97]	Jadad quality score[1] (0-5):3 [1,1,1,0,0] Definition: Presence of MEE, S&S of MEI	Amoxicillin-clavulanate 45/6.4 mg/kg/day / bid for 10 days vs. Amoxicillin-clavulanate 90/6.4 mg/kg/day / bid for 10 days	Enrollment Time: 12/1996-2/1997 Place: United States Multicenter: 19 centers Inclusion: 3 mo-12 yr, <40 kg, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Cloudy TM, Erythematous TM, Otorrhea, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), S&S of middle ear inflammation (MEI), Otalgia, Otoscopy (distinct TM erythema) Exclusion: Penicillin/beta-lactams, Concomitant/Concurrent infection needing antibiotic treatment, OME (serous OM, nonsuppurative OM, mucoid OM secretory OM, glue ear), TM perforation/Otorrhea 24 hours, PE tubes/history of PE tubes, Cranio-facial, GI disorders/Liver, Renal Disorders, Major Systemic disease/ condition, medical problem, Metabolic/Inborn Errors of metabolism, Bowel function-altering meds within 48 hours, On other medication/treatment	Entering: N=453 N=230 Amoxicillin-clavulanate 45 mg N=223 Amoxicillin-clavulanate 90 mg Completing: N=404 N=207 Amoxicillin-clavulanate 45 mg N=197 Amoxicillin-clavulanate 90 mg Analyzed: N=404 N=207 Amoxicillin-clavulanate 45 mg N=197 Amoxicillin-clavulanate 90 mg	Treatment failure; Disease recurrence; Adverse effects of treatment	Outcome: Clinical success at the end of therapy A-C 90: 84.1%(149/177); A-C 45: 78.8% (149/189); Diff (95% CI): 5% (-3, 13) Outcome: Global clinical success including recurrence on days 22-28 A-C 90: 68.9% (122/177); A-C 45: 67.9% (128/189); Diff (95%CI): 1% (-8, 10) Outcome: Adverse events Any: A-C 90 45% (101/223); A-C 45 43% (98/230); Diff (95%CI) 3%(-6,12) Need Tx: 24% (54/223); 26% (61/230); -2%(-10,5.7) Cough: 11% (24/223); 6% (14/230); 5%(-0.4,10) Fever: 5% (11/223); 4% (8/230); 1%(-2.3,5.1) Dia Rash: 4% (9/223); 5% (11/230); -1%(-4.6,3) Sev diarr: 10% (22/223); 8% (19/230); 2%(-3.7, 7) Sev Rash: 1% (3/223); 0% (0/230); 1%(-0.2,2.8) Sev erythema multiform: 0% (0/223); 0.4% (1/230); -0.4(-1.2,0.4) Sev GI: 0% (0/223); 0.4% (1/230); -0.4(-1.2,0.4) Sev moniliasis: 0.4% (1/223); 0% (0/230); 0.4(-0.4,1.2) URI: 3% (6/223); 8% (19/230); -6%(-10,-1.4) Vomiting: 6% (13/223); 7% (16/230); -1%(-5.7,3.3)

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Carvalho 1998[84]	Jadad quality score[1] (0-5):1 [1,0,0,0,0] Definition: Other	Cefprozil 30 mg/kg/day / bid for 10 days vs. Cefaclor 40 mg/kg/day / tid for 10 days	Inclusion: Otalgia, Fever, Irritability, Otoscopy characteristics Exclusion: Antibiotic within 7 days, Long acting antibiotic within 2 weeks, Cranio-facial, GI disorders/Liver, Renal Disorders	Entering: N=40 N=21 Cefprozil N=19 Cefaclor	Treatment failure; Presence of MEE [also persistent effusion, OME]; By otoscopic findings:; Bulging tympanic membrane [TM]; Signs or symptoms of MEI; By symptoms (otalgia, ear fullness); Other symptoms: fever; Adverse effects of treatment	Outcome: Clinical success at the end of therapy (3rd visit) Cefaclor / Cefprozil Cured: *(18/19) / 95.2% (20/21) Partial cure: 0 / 0 Failure: 0 / 4.8% (1/21) *Incomplete data: 1 / 0 Outcome: Adverse events Cefaclor / Cefprozil / Diff995CI) Any: 11% (2/19) / 0% (0/21) / 11% (-3, 24) Vomiting: 0% (0/19 / 10% (2/21) / -10% (-23, 4)

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Casellas 2005[69]	Jadad quality score[1] (0-5):2 [1,0,1,0,0] Definition: Presence of MEE, S&S of MEI	Amoxicillin-clavulanate 80 mg/kg/day = bid for 10 days vs. Amoxicillin Sulbactam 80 mg/kg/day = bid for 10 days	Study Time: 10/2001-10/2003 Place: Argentina Multicenter: 4 centers Inclusion: 6-48 mo, >6 kg, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Erythematous TM, S&S of middle ear inflammation (MEI), Otalgia, Otoscopy (distinct TM erythema), Fever, New/first episode of AOM Exclusion: Penicillin/beta-lactams, Antibiotic within 2 weeks, Recurrent AOM, TM perforation/Otorrhea, Complication of OM, PE tubes/history of PE tubes, GI disorders/Liver, Renal Disorders, Immunosuppressed /compromised/deficient	Entering: N=289 N=149 Amoxicillin-clavulanate N=140 Amoxicillin Sulbactam Completing: N=234 N=117 Amoxicillin-clavulanate N=117 Amoxicillin Sulbactam Analyzed: N=234 N=117 Amoxicillin-clavulanate N=117 Amoxicillin Sulbactam	Treatment failure; Signs or symptoms of MEI; Disease recurrence; Adverse effects of treatment; Bacteriologic outcomes by nasopharyngeal cultures	Outcome: Clinical success at days 12-14 A-C: 98% (115/117); A-S: 98% (115/117); Diff (95%CI): 0% (-3.3, 3.3) Outcome: Clinical success at days 28-42 A-C: 95% (98/103); A-S: 94% (97/103); Diff (95%CI): 1% (-5.2, 7) Outcome: Adverse events A-C / A-S / Diff (95%CI) Any: 27% (40/149) / 36% (50/140) / -9%(-20, 1.8) Diarrhea, day 12-14: 3% (4/149) / 6% (8/140 / -3%(-8, 2) Diarrhea, day 3: 5% (7/149) / 16% (23/140) / -12%(-19, -4.7) Minor: 26% (39/149) / 36% (50/140) / -10%(-20, 1.2) Severe diarrhea: 0.7% (1/149) / 0.7% (1/140) / 0% (-1.9, 1.9)

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Catania 2004[99]	Jadad quality score[1] (0-5):3 [1,0,1,1,0] Definition: Other	Cefaclor 50 mg/kg/day = bid for 5 days vs. Cefaclor 40 mg/kg/day = bid for 10 days	Study Time: 11/2001-3/2002 Place: Pediatric practice Multicenter: 22 centers Inclusion: 2-6 yr, Erythematous TM, Otalgia, Fever >38 C, Onset of AOM symptoms within 2 days before entry Exclusion: Allergic to other medication NOS, Antibiotic within 72 hours, GI disorders/Liver, Renal Disorders, Immunosuppressed /compromised/deficient, Heme/Onc Disorders	Entering: N=410 N=204 Cefaclor 50 mg/5 days N=206 Cefaclor 40 mg/10 days Completing: N=400 N=204 Cefaclor 50 mg/5 days N=196 Cefaclor 40 mg/10 days Analyzed: N=400 N=204 Cefaclor 50 mg/5 days N=196 Cefaclor 40 mg/10 days	Treatment failure; By otoscopic findings:; Bulging tympanic membrane [TM]; Otorrhea; Signs or symptoms of MEI; By symptoms (otalgia, ear fullness); Other symptoms: fever; Disease recurrence; Adverse effects of treatment	Outcome: Cured at end of therapy Cef 5D: 95.5% (195/204) Cef10D: 94.8% (195/206) Diff (95%CI): 1%(-3.5, 4.9) Outcome: Adverse events Any: Cef5D 6% (12/204) Cef10D 8% (17/206) Diff (95%CI) -2%(-7, 3.2) Abd pain: Cef5D 1.5% (3/204) Cef10D 2.4% (5/206) Diff (95%CI) -1%(-3.6, 1.8) Cut rash: Cef5D 2.5% (5/204) Cef10D 2.9% (6/206) Diff (95%CI) -0.4%(-2.5,2.7) Diarrhea: Cef5D 2.0% (4/204) Cef10D 2.4% (5/206) Diff (95%CI) -0.4%(-3.2,2.4) New OMA episode: Cef5D 9% (19/204) Cef10D 8% (17/206) Diff (95%CI) 1%(-4.5, 6.5) Vomiting: Cef5D 0.5% (1/204) Cef10D 0.5% (1/206) Diff (95%CI) 0% (-1.4, 1.4)

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Chao 2008[95]	Jadad quality score[1] (0-5):3 [1,0,1,1,0] Definition: Not specified	Wait and see vs. Prescription to Hold	Study Time: 12/2005-11/2006 Place: Emergency room Inclusion: 2-12 yr, AOM Exclusion: Any antibiotic during present illness, Concomitant/Concurrent infection needing antibiotic treatment, AOM within 30 days, Cranio-facial, Immunosuppressed /compromised/deficient, No telephone, Prolonged ear pain	Entering: N=232 N=117 Wait and see N=115 Prescription to Hold Completing: N=206 N=100 Wait and see N=106 Prescription to Hold Analyzed: N=206 N=100 Wait and see N=106 Prescription to Hold	Parent satisfaction; Duration of AOM; Other antibiotic: No new abx Rx/no change in abx Rx	No clinical success rate studied. Adverse events not reported

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Chonmaitree 2003[101]	Jadad quality score[1] (0-5):2 [1,1,0,0,0] Definition: Presence of MEE, S&S of MEI	Ceftriaxone 50 mg/kg/day = qd for 1 day vs. Ceftriaxone 50 mg/kg/day = qd for 1 day, Prednisolone 2 mg/kg/day / tid for 5 days vs. Ceftriaxone 50 mg/kg/day = qd for 1 day, Antihistamine 0.35 mg/kg/day / tid for 5 days vs. Ceftriaxone 50 mg/kg/day = qd for 1 day, Antihistamine 0.35 mg/kg/day / tid for 5 days, Prednisolone 2 mg/k	Enrollment Time: 7/1995-6/2000 Place: United States Hospital clinic/ outpatient Inclusion: 3 mo-6 yr, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Cloudy TM, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), S&S of middle ear inflammation (MEI), Otalgia, Otoscopy (distinct TM erythema), Fever, Recurrent AOM Exclusion: Penicillin/beta-lactams, Antibiotic within 7 days, PE tubes/history of PE tubes, Cranio-facial, Major Systemic disease/ condition, medical problem, On other medication/treatment, Exposure to varicella w/in 3 weeks	Completing: N=179 N=46 Placebo N=45 Prednisolone N=44 Antihistamine N=44 Prednisolone & antihistamine Analyzed: N=179 N=46 Placebo N=45 Prednisolone N=44 Antihistamine N=44 Prednisolone & antihistamine	Treatment failure; Presence of MEE [also persistent effusion, OME]; Signs or symptoms of MEI; Disease recurrence; PE tube placement; Healthcare utilization	Outcome: Clinical success on days 5-14 Corticosteroid 84.4% (38/45) Placebo 78.3% (36/46) Diff (95%CI) 6%(-10, 22) Antihistamine 75.0% (33/44) Placebo 78.3% (36/46) Diff (95%CI) -3%(-21, 14) Both drug 88.6% (39/44) Placebo 78.3% (36/46) Diff (95%CI) 10%(-5.1, 26) Corticosteroid 84.4% (38/45) Antihistamine 75.0% (33/44) Diff (95%CI) 9% (-7, 26) Corticosteroid 84.4% (38/45) Both drugs 88.6% (39/44) Diff (95%CI) -4%(-18, 10) Antihistamine 75.0% (33/44) Both drugs 88.6% (39/44) Diff (95%CI) -14%(-30,2.5) Adverse events not reported

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Cifaldi 2004[74]	Jadad quality score[1] (0-5):1 [1,0,0,0,0] Definition: Not specified	Amoxicillin-clavulanate 45/6.4 mg/kg/day / bid for 10 days vs. Cefdinir 14 mg/kg/day / bid for 5 days	Place: Multicenter Inclusion: 6 mo-6 yr, AOM Exclusion: NR	Influencing factors: Age	Parent satisfaction; Cost outcomes; Compliance; Tolerability	This study does not report clinical success. It reports parent-reported outcomes.
Cohen 1998[98]	Jadad quality score[1] (0-5):5 [1,1,1,1,1] Definition: Presence of MEE, S&S of MEI	Amoxicillin-clavulanate 80/10 mg/kg/day / tid for 10 days vs. Amoxicillin-clavulanate 80/10 for 5 days	Enrollment Time: 2/1995-5/1996 Place: France Multicenter Inclusion: 4-30 mo, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Erythematous TM, S&S of middle ear inflammation (MEI), Otalgia, Fever Exclusion: Penicillin/beta-lactams, Antibiotic within 7 days, TM perforation/Otorrhea, PE tubes/history of PE tubes, Major Systemic disease/ condition, medical problem	Influencing factors: Parent/caretaker Entering: N=385 N=191 Amoxicillin-clavulanate 10 day N=194 Amoxicillin-clavulanate 5 day Completing: N=331 N=168 Amoxicillin-clavulanate 10 day N=163 Amoxicillin-clavulanate 5 day Analyzed: N=378 N=186 Amoxicillin-clavulanate 10 day N=192 Amoxicillin-clavulanate 5 day	Treatment failure; Presence of MEE [also persistent effusion, OME]; Signs or symptoms of MEI; Other symptoms: fever; Disease recurrence; Adverse effects of treatment; Bacteriologic outcomes by nasopharyngeal cultures; Otologic complications, i.e., cholestetoma; Other antibiotic: No new abx Rx/no change in abx Rx	Outcome: Clinical success (cure or improve) per protocol population By outcome days Amox-clav 5d / Amox-clav 10d / Diff (95%CI) 12-14 d: 76.7% (125/163) / 88.1% (148/168) / -11%(-20,-3.2) 28-42 d: 40.4% (57/141) / 46% (64/139) / -5.6%(-17, 6) Outcome: Clinical success 9cure or improve) per protocol population by setting of child care Amox-clav 5d / Amox-clav 10d / Diff (95%CI) Home: 85.1% (57/67) / 89.6% (69/77) / -4.5%(-15, 6) Caretaker: 70.8% (68/96) / 86.8% (79/91) / -16% (-28,- 4) Sitter: 73.6% (39/53) / 88.6% (39/44) / -15%(-31, 0.9) Day-care: 67.3% (29/43) / 85.1% (40/47) / -18%(-35, 0.3) Outcome: Adverse events Amox-clav 5d / Amox-clav 10d / Diff (95%CI) Any: 45% (88/194) / 43% (80/188) / 2.8%(-7, 13) Drug-related: 31% (60/194) / 29% (55/188) / 2%(-8,, 11) Diarrhea: 23% (44/194) / 26% (49/188) / -3%(-12, 5.2) Skin rash: 4% (8/194) / 7% (13/188) / -3%(-7, 1.8)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Cohen 1999[77]	Jadad quality score[1] (0-5):3 [1,0,1,1,0] Definition: Presence of MEE, S&S of MEI	Amoxicillin-clavulanate 80/10 mg/kg/day / tid for 10 days vs. Ceftriaxone 50 mg/kg/day = qd for 1 day	Enrollment Time: 2/1995-5/1996 Place: France Multicenter Inclusion: 4-30 mo, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Erythematous TM, Otalgia, Otoscopy (distinct TM erythema), Fever Exclusion: Penicillin/beta-lactams, Antibiotic within 7 days, TM perforation/Otorrhea, PE tubes/history of PE tubes, Major Systemic disease/ condition, medical problem	Entering: N=513 N=258 Amoxicillin-clavulanate N=255 Ceftriaxone Completing: N=463 N=228 Amoxicillin-clavulanate N=235 Ceftriaxone Analyzed: N=513 N=258 Amoxicillin-clavulanate N=255 Ceftriaxone	Treatment failure; Signs or symptoms of MEI; Other symptoms: fever; Adverse effects of treatment; Bacteriologic outcomes by nasopharyngeal cultures; Otologic complications, i.e., cholestetoma; PE tube placement	Outcome: Success rate at days 12-14: Amox-clav / Ceftriaxon / Diff (95%CI) Per Protocol: 82.5% (188/228) / 79.2% (186/235) / 3% (-3.9, 10) Intent-to-treat: 77.1% (199/258) / 74.5% (190/255) / 3% (-4.8, 10) Outcome: Success rate at days 28-42: Amox-clav / Ceftriaxon / Diff (95%CI) Per Protocol: 55.1% (103/187) / 59.0% (108/183) / -4% (-14, 6.2) Intent-to-treat: 55.8% (111/199) / 58.9% (112/190) / -3% (-13, 6.7) Outcome: Otitis media with effusion at days 28-42: Amox-clav / Ceftriaxon / Diff (95%CI) Per Protocol: 20.3% (38/187) / 16.9% (31/183) / 3% (-4.5, 11) Intent-to-treat: 20.6% (41/199) / 16.3% (31/190) / 4% (-3.4, 12) Outcome: Other infections at days 28-42: Amox-clav / Ceftriaxon / Diff (95%CI) Per Protocol: 9.1% (17/187) / 11.5% (21/183) / -2% (-9, 3.8) Intent-to-treat: 8.0% (16/199) / 10.5% (20/190) / -2.5% (-8, 3) Outcome: Adverse events Amox-clav / Ceftriaxon / Diff (95%CI) Any: 31% (79/258) / 14% (36/255) / 16%(9, 24) Diarrhea: 27% (70/258) / 14% (36/255) / 13%(6, 20) The article also publishes data on the carriage of Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis before treatment and at Days 12 to 14.

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Cohen 2000[100]	Jadad quality score[1] (0-5):5 [1,1,1,1,1] Definition: Presence of MEE, S&S of MEI	Cefpodoxime 8 mg/kg/day / bid for 10 days vs. Cefpodoxime 8 mg/kg/day / bid for 5 days	Enrollment Time: 10/1996-4/1997 Place: France Multicenter Inclusion: 4-30 mo, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Erythematous TM, Otalgia, Otoscopy (distinct TM erythema), Fever Exclusion: Penicillin/beta-lactams, Antibiotic within 7 days, TM perforation/Otorrhea, PE tubes/history of PE tubes, Major Systemic disease/ condition, medical problem	Influencing factors: Age, Parent/caretaker Entering: N=450 N=223 Cefpodoxime 10 day N=227 Cefpodoxime 5 day Completing: N=418 N=210 Cefpodoxime 10 day N=208 Cefpodoxime 5 day Analyzed: N=448 N=222 Cefpodoxime 10 day N=226 Cefpodoxime 5 day	Treatment failure; Presence of MEE [also persistent effusion, OME]; Signs or symptoms of MEI; Other symptoms: fever; Disease recurrence; Adverse effects of treatment	Outcome: Clinical success (cure or improve) on day 12-14 per protocol population CPD 5d / CPD 10d / Diff (95%CI) Total 84.1% (175/208) / 92.4% (194/210) / -8% (-14, -2.1) Data by age group not reported. Multivariable analysis showed the response to treatment was significantly influenced by the treatment duration, the day-care modality, age, and a history of otitis media with effusion. Outcome: Clinical success (cure or improve) on day 28-42 per protocol population CPD 5d / CPD 10d / Diff (95%CI) Total 85.4% (134/157) / 83.7% (144/172) / -2% (-6, 9) Outcome: Relapse or recurrence CPD 5d / CPD 10d / Diff (95%CI) Total 14.6% (23/157) / 16.3% (28/172) / -2% (-9, 6.1) Outcome: clinical success (cure or improve) per protocol population by day-care modality CDP 5d / CDP 10d / Diff (95%CI) Home 88.1% (74/84) / 92.2% (95/103) / -4.1%(-13, 4) Caretaker 81.4% (101/124) / 92.5% (99/107) / -11%(-20, -2) Sitter 86.8% (66/76) / 100%(47/47) / -13%(-23, -3) Day-care 72.9% (35/48) / 86.7% (52/60) / -14%(-29, 1) Outcome: Adverse events CDP 5d / CDP 10d / Diff (95%CI) Any 12% (26/224) / 16% (36/222) / 3% (-11, 1.8)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Dagan 2000[7]	Jadad quality score[1] (0-5):2 [1,0,1,0,0] Definition: Presence of MEE, S&S of MEI	Amoxicillin-clavulanate 45/6.4 mg/kg/day / bid for 10 days vs. Azithromycin 10 mg/kg/day = qd for 1 day, --- 5 mg/kg/day = qd for 4 days	Enrollment Time: 12/1997-8/1998 Place: United States, Israel, Dominican Republic Multicenter: 12 centers Inclusion: 6-48 mo, <41 kg, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Cloudy TM, Loss of landmarks, Otorrhea, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), S&S of middle ear inflammation (MEI), Otalgia within last 24 hours, Otoscopy (distinct TM erythema), Ear fullness Exclusion: Allergic to other medication NOS, Penicillin/beta-lactams, Macrolides, Antibiotic within 72 hours, OME (serous OM, nonsuppurative OM, mucoid OM secretory OM, glue ear), TM perforation/Otorrhea 24 hours, PE tubes/history of PE tubes, GI disorders/Liver, Renal Disorders, Immunosuppressed /compromised/deficient, Other Infectious diseases (meningitis), On other medication/treatment	Influencing factors: Pathogen Entering: N=238 N=118 Amoxicillin-clavulanate N=120 Azithromycin Completing: N=169 N=84 Amoxicillin-clavulanate N=85 Azithromycin Analyzed: N=136 N=65 Amoxicillin-clavulanate N=71 Azithromycin	Treatment failure; Signs or symptoms of MEI; Bacteriologic cure/failure; Adverse effects of treatment	Outcome: Clinical success at days 12-14 Pathogen — Amox-clav — Azithromycin — Diff (95%CI) All type — 86% (60/70) — 70% (51/73) — 16%(2, 30) HF — 91% (30/33) — 65% (22/34) — 26% (6, 46) SP — 86% (18/21) — 80% (16/20) — 6% (-17, 29) Others — 75% (12/16) — 68% (13/19) — 7% (-23, 37) Outcome: Clinical success at days 22-28 Pathogen — Amox-clav — Azithromycin — Diff (95%CI) All type — 71% (46/65) — 66% (44/67) — 5%(-11,21) HF — 81% (25/31) — 58% (18/31) — 23%(0.1, 46) SP — 62% (13/21) — 72% (13/18) — -10%(-40,20) Others — 62% (8/13) — 72% (13/18) — -10%(-43,23) Outcome: Bacteriologic success at days 4-6 Pathogen — Amox-clav — Azithromycin — Diff (95%CI) All type — 83% (64/65) — 49% (35/71) — 34%(18, 50) HF — 87% (26/30) — 39% (13/33) — 48%(24, 72) SP — 90% (18/20) — 68% (13/19) — 22%(-3.4, 47) Others — 67% (10/15) — 47% (9/19) — 20%(-14, 54) Outcome: Adverse events — Amox-clav — Azithromycin — Diff (95%CI) Any — 27% (32/118) — 22% (26/120) — 3% (-11, 1.8) Related to treatment — 10% (12/118) — 2% (2/120) — 8% (2.5, 14) Diarrhea — 8% (9/118) — 4% (5/120) — 3% (-2.6, 9) Vomiting — 8% (10/118) — 0% (0/120) — 8% (3.4, 14)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Dagan 2000[81]	Jadad quality score[1] (0-5):2 [1,0,1,0,0] Definition: Presence of MEE, S&S of MEI	Cefaclor 40 mg/kg/day / tid for 10 days vs. Azithromycin 10 mg/kg/day = qd for 3 days	Place: Israel Emergency room Inclusion: 3-36 mo, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Erythematous TM, S&S of middle ear inflammation (MEI), Otalgia, Otoscopy (distinct TM erythema), Fever, Onset of AOM symptoms within 7 days before entry, Tympanocentesis preformed Fluid obtained, Irritability, Other constitutional symptoms NOS Exclusion: Antibiotic within 72 hours, Concomitant/Concurrent infection needing antibiotic treatment, Chronic suppurative OM, OME (serous OM, nonsuppurative OM, mucoid OM secretory OM, glue ear), Lack of effusion on tympanocentesis, TM perforation/Otorrhea, Endocrine disorders (diabetes), Immunosuppressed /compromised/deficient	Influencing factors: Pathogen Entering: N=138 N=68 Cefaclor N=70 Azithromycin Completing: N=122 N=59 Cefaclor N=63 Azithromycin Analyzed: N=122 N=59 Cefaclor N=63 Azithromycin	Treatment failure; Presence of MEE [also persistent effusion, OME]; Signs or symptoms of MEI; Bacteriologic cure/failure; Adverse effects of treatment	Outcome: Clinical success Cefaclor / Azithromycin / Diff (95%CI) Day 10: 85% (50/59) / 82% (51/62) / 3%(-10, 16) Outcome: Bacteriologic success in initially culture-positive cases Cefaclor / Azithromycin / Diff (95%CI) SP: 63% (17/27) / 71% (12/17) / -8%(-37, 21) HF: 48% (12/25) / 47% (14/30) / 1%(-26, 28) Others: 100% (4/4) / 100% (4/4) / 0% (0, 0) Outcome: Bacteriologic success in initially culture-negative cases Cefaclor / Azithromycin / Diff (95%CI) SP: 81% (26/32) / 98% (45/46) / -17%(-30, -4) HF: 88% (30/34) / 85% (28/33) / 3%(-13, 19) Others: 95% (52/55) / 98% (58/59) / -3%(-10, 4) Adverse events not reported by drug arm.

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Damoiseaux 2000[88]	Jadad quality score[1] (0-5):5 [1,1,1,1,1] Definition: Acute onset of S&S, S&S of MEI	Placebo vs. Amoxicillin 40 mg/kg/day / tid for 10 days	Study Time: 2/1996-5/1998 Place: Netherlands Multicenter: 53 centers Office setting/ private practice, General/ family practice Inclusion: 6-24 mo, Acute onset S&S (parent/guardian report), Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Erythematous TM, Otorrhea, S&S of middle ear inflammation (MEI), Otalgia, Fever, Irritability, Other constitutional symptoms NOS Exclusion: Penicillin/beta-lactams, Antibiotic within 4 weeks, Cranio-facial, Immunosuppressed /compromised/deficient	Entering: N=240 N=123 Placebo N=117 Amoxicillin Completing: N=235 N=120 Placebo N=115 Amoxicillin Analyzed: N=235 N=120 Placebo N=115 Amoxicillin	Treatment failure; Presence of MEE [also persistent effusion, OME]; Signs or symptoms of MEI; Other symptoms: fever; Adverse effects of treatment	Outcome: Clinical outcome at day 4 Amoxicillin / Placebo / Diff (95% CI) No persistent symptoms: 41% (48/117) / 28% (34/123) / 13% (1, 25) Improvement in eardrum: 23% (26/114) / 17% (21/120) / 6% (-4, 16) Outcome: Clinical success at day 11 Amoxicillin / Placebo / Diff (95% CI) 36% (40/112) / 30% (36120) / 6% (-6, 18) Outcome: Middle ear effusion present at 6 weeks Amoxicillin / Placebo / Diff (95% CI) 64% (69/107) / 67% (70/105) / 3% (-10, 16) Outcome: Adverse effects - Diarrhea Amoxicillin / Placebo / Diff (95% CI) Day 4: 17% (20/117) / 10% (12/123) / -7% (-16, 2) Day 10: 12% (14/117) / 8% (10/123) / -4% (-12, 4) Outcome: Duration of symptoms in days Amoxicillin Median / Placebo Median / p-value Fever: 2 / 3 / 0.004 Pain/crying: 8 / 9 / 0.43

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Damrikarnlert 2000[6]	Jadad quality score[1] (0-5):3 [1,0,1,1,0] Definition: Presence of MEE, S&S of MEI	Amoxicillin-clavulanate 40/10 mg/kg/day / tid for 7-10 days vs. Amoxicillin-clavulanate 45/6.4 mg/kg/day / bid for 7-10 days	Study Time: 8/1996-3/1998 Place: Multicenter: 18 centers Inclusion: 2 mo-12 yr, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Loss of landmarks, Erythematous TM, Otorrhea, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), S&S of middle ear inflammation (MEI), Otalgia, Otoscopy (distinct TM erythema), Decreased hearing, Ear fullness Exclusion: Penicillin/beta-lactams, Antibiotic within 10 days, Concomitant/Concurrent infection needing antibiotic treatment, OME (serous OM, nonsuppurative OM, mucoid OM secretory OM, glue ear), TM perforation/Otorrhea 24 hours, PE tubes/history of PE tubes, GI disorders/Liver, Renal Disorders, Investigational drug within 30 days	Entering: N=415 N=206 Amoxicillin-clavulanate 40/10 TID N=209 Amoxicillin-clavulanate 45/6.4 BID Completing: N=324 N=151 Amoxicillin-clavulanate 40/10 TID N=173 Amoxicillin-clavulanate 45/6.4 BID Analyzed: N=386 N=187 Amoxicillin-clavulanate 40/10 TID N=199 Amoxicillin-clavulanate 45/6.4 BID	Treatment failure; Signs or symptoms of MEI; By symptoms (otalgia, ear fullness); By otoscopy (distinct TM erythema); Bacteriologic cure/failure; Adverse effects of treatment; Other antibiotic: No new abx Rx/no change in abx Rx	Outcome: Clinical success at the end of therapy on day 7-12 A-C BID: 94.0% (187/199); A-C TID: 94.1% (175/186); Diff (95%CI): 0.1%(-4.8,4.6) Outcome: Clinical success at follow-up on day 38-42 A-C BID: 93.3% (168/180); A-C TID: 87.9% (153/174); Diff (95%CI): 5.4%(-0.7, 12) Outcome: Bacteriological success at end of therapy on day 7-12 A-C BID: 77.8% (7/9); A-C TID: 84.6% (11/13); Diff (95%CI): -7%(-40, 26) Outcome: Adverse events A-C BID / A-C TID / Diff (95%CI) At least 1 treatment related: 12% (25/209) / 18% (37/206) / -6%(-13, 0.9) Abdominal pain or enteritis or fever or rash: 0.5% (1/209) / 0% (0/206) / 0.5%(-0.5,1.5) Constipation or ear disorder or enlarged abdomen or enterocolitis or erythematous rash or somnolence or stomatitis (ulcerative): 0% (0/209) / 0.5% (1/206) / -0.5%(-1.5,0.5) Dermatitis: 0.5% (1/209) / 1.9% (4/206) / -1.4%(-3.5,0.7) Diarrhea: 7% (15/209) / 11% (22/206) / -3.5%(-9, 2.8) Nervous: 1% (2/209) / 0% (0/206) / -0.5%(-0.4,2.4) Otitis media: 0.5% (1/209) / 1% (2/206) / -0.5%(-2.2,1.2) Urticaria: 0% (0/209) / 1.5% (3/206) / -1.5%(-3.2,0.2) Vomiting: 2% (4/209) / 0.5% (1/206) / 1.4%(-0.7,3.5)

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
De Diego 2001[128]	Jadad quality score[1] (0-5):2 [1,0,1,0,0] Definition: Not specified	Amoxicillin 20 mg/kg/day = qd for 12 weeks vs. Azithromycin 10 mg/kg/day = q week for 12 weeks	Study Time: 1/1998-5/1999 Inclusion: Recurrent AOM	Entering: N=71 N=40 Amoxicillin N=31 Azithromycin Completing: N=69 N=38 Amoxicillin N=31 Azithromycin Analyzed: N=69 N=38 Amoxicillin N=31 Azithromycin	Disease recurrence; Adverse effects of treatment	Outcome: Effective rate (#AOM episodes dropped to <50% after prophylaxis) in 6-27 months Amoxicillin: 89% (34/38); Azithromycin: 81% (25/31); Diff (95%CI): 9% (-8, 26) Outcome: Adverse events GI: Amoxicillin 2.5% (1/40); Azithromycin 0% (0/31); Diff (95%CI) 2.5%(-3. 8)

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Dohar 2006[80]	Jadad quality score[1] (0-5):2 [1,0,0,1,0] Definition: Not specified	Amoxicillin-clavulanate 90 mg/kg/day / bid for 10 days vs. Ciprodex drops 4 drops = bid for 7 days	Enrollment Time: 5/2003-5/2004 Inclusion: 6 mo-12 yr, Otorrhea, AOM < 3 weeks, Patent tympanostomy tubes Exclusion: Any antibiotic, Antibiotic within 3 days, Any complications requiring antibiotics, Concomitant/Concurrent infection needing antibiotic treatment, Topical antibiotic drops prior to study, Otitis externa, TM perforation/Otorrhea >3 weeks, Complication of OM, History of otic/ME surgery (excluding tubes), Cranio-facial, Endocrine disorders (diabetes), GI disorders/Liver, Renal Disorders, Immunosuppressed /compromised/deficient, On other medication/treatment, Menarche	Entering: N=80 N=41 Amoxicillin-clavulanate N=39 Ciprodex Analyzed: N=80 N=41 Amoxicillin-clavulanate N=39 Ciprodex	Treatment failure; By otoscopic findings:; Otorrhea; Bacteriologic cure/failure; Adverse effects of treatment	Outcome: Clinical cure or absence of otorrhea at test-of-cure visit on day 18-21 Amox-clav: 58.5% (24/41); Ciprodex: 84.6% (33/39); Diff (95%CI): -26%(-46, -6) Outcome: Adverse events Any: Amox-clav 29% (12/41); Ciprodex 13% (5/39); Diff (95%CI) 16%(-1.4,34) Dermatitis: 7% (3/41); 0% (0/39); 7%(-1,16) Device block or taste perversion: 0% (0/41); 3% (1/39); -3%(-8,2.3) Diarrhea: 20% (8/41); 0% (0/39); 20%(6.4,33) Ear pain: 0% (0/41); 5% (2/39); -5%(-12,1.7) Gastroenteritis: 5% (2/41); 0% (0/39); 5%(-2,12) Infection skin or nausea or oral moniliasis: 2.4% (1/41); 0% (0/39); 2.4%(-2.4,7) Vomiting: 2.4% (1/41); 2.6% (1/39); -0.2%(-7, 7)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Dunne 2003[70]	Jadad quality score[1] (0-5):5 [1,1,1,1,1] Definition: Presence of MEE, S&S of MEI	Amoxicillin-clavulanate 45 mg/kg/day / bid for 10 days vs. Azithromycin 10 mg/kg/day = qd for 3 days	Study Time: 1/2000-3/2000 Place: Multicenter: 28 centers Inclusion: 6 mo-12 yr, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Loss of landmarks, Erythematous TM, Otorrhea, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), Presence of MEF by acoustic reflectometry, S&S of middle ear inflammation (MEI), Otalgia, Otoscopy (distinct TM erythema), Decreased hearing, Ear fullness, Fever Exclusion: Penicillin/beta-lactams, Macrolides, Any antibiotic, Antibiotic within 30 days, Other antibiotic Tx, AOM of more than 4 weeks duration, Metabolic/Inborn Errors of metabolism	Influencing factors: Age Entering: N=373 N=185 Amoxicillin-clavulanate N=188 Azithromycin Completing: N=362 N=180 Amoxicillin-clavulanate N=182 Azithromycin Analyzed: N=362 N=180 Amoxicillin-clavulanate N=182 Azithromycin	Treatment failure; Presence of MEF by otoscopic findings; Bulging tympanic membrane [TM]; Loss of landmarks; Impaired TM mobility; Presence of MEF by acoustic reflectometry; Adverse effects of treatment	Outcome: Clinical success (cure+improvement) at day 10 Amox-clav / Azithro / Diff (95%CI) All ages 88% (159/181 / 83% (153/183) / 5%(-2, 12) <=2 yrs 85% (44/52) / 76% (45/59) / 9% (-6, 24) >2 yrs 73% (94/129) / 86% (108/126) / -13%(-23, -3) Outcome: Clinical success (cure+improvement) at day 24-28 Amox-clav / Azithro / Diff (95%CI) All ages 69% (124/180) / 74% (134/182) / -5%(-14, 4.3) <=2 yrs 58% (30/52) / 60% (35/58) / -2%(-20, 16) >2 yrs 73% (94/128) / 80% (99/124) / -7% (-18, 3.5) Outcome: Signs of tympanic membrane disease at day 10 Amox-clav / Azithro / Diff (95%CI) Bulging 13% (23/178) / 22% (40/183) / -9%(-17, -1.1) Loss of landmarks 20% (36/178) / 31% (56/183) / -11%(-20, -2) Impaired mobility 28% (46/162) / 39% (67/170) / -11%(-21,-0.8) Outcome: Signs of tympanic membrane disease at day 24-28 Amox-clav / Azithro / Diff (95%CI) Bulging 16% (29/176) / 10% (17/177) / 6% (-1, 13) Loss of landmarks 22% (38/176) / 11% (20/178) / 11% (3.3, 19) Impaired mobility 26% (42/160) / 18% (29/164) / 8%(-1, 17) Outcome: Abnormal acoustic reflectometry Amox-clav / Azithro / Diff (95%CI) Day 10 63% (109/174) / 61% (108/176) / 2%(-8, 12) Day 24-28 59% (100/170) / 45% (77/170) / 14%(3.4, 25) Outcome: Adverse events Amox-clav / Azithro / Diff (95%CI) Any 20% (37/185) / 11% (21/188) / 9% (1.4, 16) Diarrhea 15% (27/185) / 6% (11/188) / 9% (2.6, 15) Rash 4% (8/185) / 0% (0/188) / 4% (1.4, 7) Vomiting 1% (2/185) / 2% (4/188) / -1%(-3.5,1.5)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Garrison 2004[96]	Jadad quality score[1] (0-5):2 [1,1,0,0,0] Definition: Not specified	Amoxicillin 40-45 mg/kg/day for 5-10 days vs. Amoxicillin 80-90 mg/kg/day for 5-10 days	Study Time: 12/1999-12/2002 Place: United States Office setting/ private practice, Pediatric practice Inclusion: >3 mo, <18 kg, AOM, AOM requiring antibiotic, Age of child Upper age limit not specified, Weight of child Lower weight limit not specified Exclusion: Penicillin/beta-lactams, Concomitant/Concurrent infection needing antibiotic treatment, Other antibiotic Tx, Unable/unlikely to return to follow-up	Entering: N=162 N=80 Amoxicillin 40-45 N=82 Amoxicillin 80-90 Completing: N=151 N=76 Amoxicillin 40-45 N=75 Amoxicillin 80-90 Analyzed: N=151 N=76 Amoxicillin 40-45 N=75 Amoxicillin 80-90	Treatment failure; Disease recurrence; Adverse effects of treatment; Other antibiotic: No new abx Rx/no change in abx Rx	Outcome: Clinical success at 3-4 day visit Amox-low dose: 95% (68/76) Amox-high dose: 88% (66/75) Diff (95%CI): 7%(-2, 16) Outcome: Adverse events Amox-low dose / Amox-high dose / Diff (95%CI) Skin rash: 15% (11/75) / 12% (9/77) / 3%(-8, 14) GI distress: 30% (22/74) / 33% (25/76) / -3%(-18, 12)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Guven 2006[52]	Jadad quality score[1] (0-5):2 [1,0,1,0,0] Definition: Presence of MEE, S&S of MEI	Amoxicillin-clavulanate 45/6.4 mg/kg/day / bid for 10 days vs. Azithromycin 10 mg/kg/day = qd for 3 days	Study Time: 6/2002-4/2004 Place: Turkey Hospital clinic/ outpatient Inclusion: 6 mo-12 yr, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Loss of landmarks, Erythematous TM, Otorrhea, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), S&S of middle ear inflammation (MEI), Otalgia, Fever Exclusion: Penicillin/beta-lactams, Macrolides, Antibiotic within 2 weeks, Chronic suppurative OM, TM perforation/Otorrhea 24 hours, GI disorders/Liver, Renal Disorders, Immunosuppressed /compromised/deficient, Major Systemic disease/ condition, medical problem	Influencing factors: Pathogen Entering: N=180 N=86 Amoxicillin-clavulanate N=94 Azithromycin Completing: N=174 N=84 Amoxicillin-clavulanate N=90 Azithromycin Analyzed: N=174 N=84 Amoxicillin-clavulanate N=90 Azithromycin	Treatment failure; Disease recurrence; Adverse effects of treatment	Outcome: Clinical cure (complete resolution of signs and symptoms Amox-clav / Azithromycin / Diff (95%CI) Day2-4 37% (32/86) / 36% (32/90) / 1%(-13, 15) Day11-13 81% (68/84) / 78% (70/90) / 3%(-9, 15) Day26-28 88% (74/80) / 78% (70/78) / 10%(-2, 22) Outcome: Clinical cure (complete resolution of signs and symptoms Culture / Amox-clav / Azithromycin / Diff (95%CI) Negative 80% (24/30) / 100% (38/38) / -20%(-34,-6) SP 100% (10/10) / 67% (20/30) / 33% (2, 64) Others 88% (28/32) / 71% (10/14) / 17% (-7, 41) Outcome: Reinfection rate Amox-clav / Azithromycin / Diff (95%CI) Day26-28 5% (4/84) / 13% (12/90) / -8%(-17, 0.6) Outcome: Persistence of MEE Amox-clav / Azithromycin / Diff (95%CI) Day11-13 19% (16/84) / 22% (20/90) / -3%(-15, 9) Day26-28 8% (6/80) / 10% (8/78) / -2%(-11, 7) Outcome: Side effects Amox-clav / Azithromycin / Diff (95%CI) Any 5% (4/84) / 4% (4/90) / 1%(-5.2, 7) Abd pain 5% (4/84) / 0% (0/90) / 5%(0.3, 9) Diarrhea 0% (0/84) / 4% (4/90) / 4%(-9, 0)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Hammaren-Malmi 2005[132]	Jadad quality score[1] (0-5):2 [1,0,1,0,0] Definition: Acute onset of S&S, S&S of MEI	Tympanostomy tubes vs. Adenoidectomy, Tympanostomy tubes	Study Time: 3/2001-12/2002 Place: Hospital Inclusion: 1-4 yr, Recurrent AOM, OME Exclusion: PE tubes/history of PE tubes, Respiratory Illness, Cranio-facial, Endocrine disorders (diabetes), Adenoidectomy and/or tonsillectomy	Influencing factors: Recurrent otitis media/ otitis prone Entering: N=217 N=108 Tubes N=109 Tubes & Adenoid Completing: N=207 N=103 Tubes N=104 Tubes & Adenoid Analyzed: N=198 N=96 Tubes N=102 Tubes & Adenoid	Disease recurrence; Adverse effects of treatment	Outcome: Number of otitis media episodes during 1-year follow-up Mean±SD (n) Mean±SD (n) Adeno+Tympan: Tympan only: Diff (95%CI) 1.9 ± 1.9 (74) 1.6 ± 1.6 (72) 0.3(-0.9, 0.9) Outcome: Adverse events Adeno+Tympan: Tympan only: Diff (95%CI) Neck abscess or type 1 diabetes 0% (0/109) 1% (1/108) -1%(-3, 1)
Hatakka 2007[91]	Jadad quality score[1] (0-5):5 [1,1,1,1,1] Definition: Presence of MEE, S&S of MEI	Placebo vs. Probiotic bacteria 1 capsule = qd for 24 weeks	Study Time: 9/2001-4/2002 Place: Finland Inclusion: 10 mo-6 yr, Recurrent AOM Exclusion: OME (serous OM, nonsuppurative OM, mucoid OM secretory OM, glue ear), History of otic/ME surgery (excluding tubes), PE tubes/history of PE tubes, Cranio-facial, Major Systemic disease/ condition, medical problem	Entering: N=309 N=154 Placebo N=155 Probiotic bacteria Completing: N=269 N=134 Placebo N=135 Probiotic bacteria Analyzed: N=269 N=134 Placebo N=135 Probiotic bacteria	Disease recurrence; Duration of AOM	Outcome: Success rate (% <4 URI) during 6-month intervention Probiotic Placebo Diff (95%CI) 28% (38/135) 18% (24/134) 10% (0.2, 20) Outcome: Success rate (%<6URI) during 6-month intervention Probiotic Placebo Diff (95%CI) 80% (108/135) 70% (94/134) 10% (-0.5, 20) Adverse events not reported

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Hedrick 2001[76]	Jadad quality score[1] (0-5):2 [1,0,1,0,0] Definition: Presence of MEE, S&S of MEI	Amoxicillin-clavulanate 90/6.4 mg/kg/day / bid for 10 days vs. Cefprozil 30 mg/kg/day / bid for 10 days	Place: United States, Costa Rica Multicenter Inclusion: 6 mo-7 yr, Bulging tympanic membrane [TM], Cloudy TM, Loss of landmarks, Air fluid level behind TM, Otorrhea, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), Otalgia, Decreased hearing, Ear fullness Exclusion: Penicillin/beta-lactams, Antibiotic within 7 days, Concomitant/Concurrent infection needing antibiotic treatment, Recurrent AOM (>2 episodes in 6 months), Otitis externa, OME (serous OM, nonsuppurative OM, mucoid OM secretory OM, glue ear), TM perforation/Otorrhea 48 hours, Complication of OM, PE tubes/history of PE tubes, Respiratory Illness, Cranio-facial, GI disorders/Liver, Renal Disorders, Major Systemic disease/ condition, medical problem, Metabolic/Inborn Errors of metabolism, Investigational drug within 1 month	Influencing factors: Hearing deficit and severity, Laterality, Age Completing: N=303 N=153 Amoxicillin-clavulanate N=150 Cefprozil Analyzed: N=292 N=146 Amoxicillin-clavulanate N=146 Cefprozil	Treatment failure; Adverse effects of treatment	Outcome: Clinical success (cure or improved) at day 4-7 after treatment by Age A-C / Cefprozil / Diff (95%CI) Total 89% (116/130) / 87% (110/127) / 2% (-6, 10) <2 yrs 86% (55/64) / 80% (47/59) / 6% (-7, 19) 2-7yrs 92% (61/66) / 93% (63/68) / -1% (-10, 8) Outcome: Clinical success (cure or improved) at day 4-7 after treatment by Laterality A-C / Cefprozil / Diff (95%CI) Total 89% (116/130) / 87% (110/127) / 2% (-6, 10) Unilateral 93% (66/71) / 89% (73/82) / 4% (-5.2, 13) Bilateral 85% (50/59) / 82% (37/45) / 3% (-11, 17) Outcome: Clinical success (cure or improved) at day 4-7 after treatment by Severity A-C / Cefprozil / Diff (95%CI) Total 89% (116/130) / 87% (110/127) / 2% (-6, 10) Moderate 92% (83/90) / 85% (64/75) / 7% (-2.7, 17) Severe 82% (32/39) / 88% (45/51) / -6% (-21, 9) Outcome: Adverse events A-C / Cefprozil / Diff (95%CI) Any 32% (49/153) / 19% (28/150 / 13%(3.5, 23) Diarrhea 19% (29/153) / 9% (14/150) / 10%(1.8,18) Rash 11% (16/153) / 6% (9/150) / 5%(-1.7,11) Vomiting 6% (9/153) / 2% (3/150) / 4%(-0.5, 8)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Jacobs 2001[92]	Jadad quality score[1] (0-5):4 [1,1,1,0,1] Definition: Presence of MEE, S&S of MEI	Placebo vs. Homeopathic NOS 3 pellets = tid for 5 days	Study Time: 1/1996-1/1997 Place: United States Office setting/ private practice, Pediatric practice Inclusion: 18 mo-6 yr, Presence of middle ear effusion (MEE), Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), Otalgia, Fever Exclusion: Antibiotic within 1 week, TM perforation/Otorrhea, History of otic/ME surgery (excluding tubes), PE tubes/history of PE tubes, Cranio-facial, Major Systemic disease/ condition, medical problem, On other medication/treatment, Adenoidectomy and/or tonsillectomy, Prolonged ear pain	Influencing factors: Middle ear effusion Entering: N=75 N=39 Placebo N=36 Homeopathic Completing: N=72 N=38 Placebo N=34 Homeopathic Analyzed: N=75 N=39 Placebo N=36 Homeopathic	Treatment failure; Presence of MEE [also persistent effusion, OME]; Adverse effects of treatment	Outcome: Clinical success at different time points Homeopathic / Placebo / Diff (95%CI) 5-day 81% (29/36) 69% (27/39) 11%(-8, 31) 2-wk 69% (25/36) 51% (20/39) 18%(-4, 40) 6-wk 58% (21/36) 38% (15/39) 20%(-3, 42) Outcome: Absence of MEE Homeopathic / Placebo / Diff (95%CI) 2-wk 28% (10/36) 23% (9/39) 5%(-15, 24) 6-wk 44% (16/36) 59% (23/39) -14%(-37, 8) Outcome: Adverse events Homeopathic / Placebo / Diff (95%CI) Any 0% (0/36) 0% (0/39) 0% (0, 0)

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Koivunen 2004[130]	Jadad quality score[1] (0-5):3 [1,0,1,1,0] Definition: Not specified	Sulfa alone 50 mg/kg/day = qd for 24 weeks vs. Placebo vs. Adenoidectomy	Study Time: 4/1994-4/1997 Place: Finland Hospital clinic/ outpatient Inclusion: 10-24 mo, Recurrent AOM Exclusion: Any antibiotic during present illness, History of otic/ME surgery (excluding tubes), PE tubes/history of PE tubes, Cranio-facial, Immunosuppressed /compromised/deficient	Entering: N=180 N=60 Placebo N=60 Sulfa alone N=60 Adenoidectomy Completing: N=174 N=59 Placebo N=56 Sulfa alone N=59 Adenoidectomy Analyzed: N=180 N=60 Placebo N=60 Sulfa alone N=60 Adenoidectomy	Disease recurrence; Adverse effects of treatment; Healthcare utilization	Outcome: Success rate (<=1 in 2 months or <=2 in 6 months of AOM or <2 months of MEE) at 6 months Sulfafurazole / Placebo / Diff (95%CI) 63% (29/46) / 45% (21/47) / 18% (-2, 39) Outcome: Success rate (<=1 in 2 months or <=2 in 6 months of AOM or <2 months of MEE) at 2 years Sulfafurazole / Placebo / Diff (95%CI) 34% (14/41) / 22% (10/45) / 12% (-7, 31) Outcome: Success rate (<=1 in 2 months or <=2 in 6 months of AOM or <2 months of MEE) at 6 months Sulfafurazole / Adenoidectomy / Diff (95%CI) 63% (29/46) / 58% (34/59) / 5% (-14, 24) Outcome: Success rate (<=1 in 2 months or <=2 in 6 months of AOM or <2 months of MEE) at 2 years Sulfafurazole / Adenoidectomy / Diff (95%CI) 34% (14/41) / 28% (16/58) / 6% (-12, 25) Outcome: Success rate (<=1 in 2 months or <=2 in 6 months of AOM or <2 months of MEE) at 6 months Adenoidectomy / Placebo / Diff (95%CI) 58% (34/59) / 45% (21/47) / 13% (-6, 32) Outcome: Success rate (<=1 in 2 months or <=2 in 6 months of AOM or <2 months of MEE) at 2 years Adenoidectomy / Placebo / Diff (95%CI) 28% (16/58) / 22% (10/45) / 5% (-12, 22) Outcome: Adverse events Sulfafurazole / Placebo / Diff (95%CI) Any 8% (5/60) / 3% (2/60) / 5%(-3.4, 13) Diarrhea 3% (2/60) / 2% (1/60) / 2%(-4.8,7.2) Skin rash 3% (2/60) / 0% (0/60) / 3%(-1.3,7.9) Unknown 2% (1/60) / 2% (1/60) / 0%(-4.6, 4.6) Sulfafurazole / Adenoidectomy / Diff (95%CI) Any 8.3% (5/60) / 0% (0/60) / 8%(1.2,15) Diarrhea 3% (2/60) / 0% (0/60) / 3%(-1.3, 8) Skin rash 3% (2/60) / 0% (0/60) / 3%(-1.3, 8) Unknown 2% (1/60) / 0% (0/60) / 2%(-1.6,5.0) Adenoidectomy / Placebo / Diff (95%CI) Any 0% (0/60) / 3% (2/60) / -3%(-8, 1.3) Diarrhea 0% (0/60) / 2% (1/60) / -2%(-5.0,1.6) Skin rash 0% (0/60) / 0% (0/60) / 0%(0, 0) Unknown 0% (0/60) / 2% (1/60) / -2%(-5.0,1.6)

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Le Saux 2005[89]	Jadad quality score[1] (0-5):5 [1,1,1,1,1] Definition: Acute onset of S&S, Presence of MEE, S&S of MEI	Placebo vs. Amoxicillin 60 mg/kg/day / tid for 10 days	Study Time: 12/1999-3/2002 Place: Canada Multicenter: 3 centers Emergency room, Pediatric practice Inclusion: 6 mo-5 yr, Acute onset S&S (parent/guardian report), Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Cloudy TM, Erythematous TM, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), Otalgia, Fever, Onset of AOM symptoms within 4 days before entry Exclusion: Allergic to other medication NOS, Penicillin/beta-lactams, Antibiotic within 2 weeks, Recurrent AOM (>4 episodes in 12 months), TM perforation/Otorrhea, Complication of OM, History of otic/ME surgery (excluding tubes), PE tubes/history of PE tubes, Respiratory Illness, Cranio-facial, Immunosuppressed /compromised/deficient, Major Systemic disease/ condition, medical problem	Influencing factors: Middle ear effusion, Age Entering: N=512 N=254 Placebo N=258 Amoxicillin Completing: N=490 N=240 Placebo N=250 Amoxicillin Analyzed: N=490 N=240 Placebo N=250 Amoxicillin	Treatment failure; Presence of MEE [also persistent effusion, OME]; Other symptoms: fever; Invasive infections, e.g., mastoiditis, bacteremia; Adverse effects of treatment; Duration of AOM	Outcome: Cumulative clinical resolution rates at 14 days-ALL Amox / Placebo / Diff (95%CI) All ages 92.8% (232250) / 84.2% (202/240) / -9% (-14,-3) 6-23 mo 85.4% (76/89) / 79.3% (73/92) / -6% (-17, 5.2) 2-5 yrs 96.9% (156/161) / 87.2% (129/148) / -10% (-16,-4) Outcome: Cumulative clinical resolution rates at 14 days-Among Children with MEE Amox / Placebo / Diff (95%CI) All ages 93.2% (150/161) / 83.0% (112/135) / -10% (-18,-3) 6-23 mo 87.1% (54/62) / 83.3% (45/54) / -4% (-17, 9) 2-5 yrs 99.0% (96/99) / 82.7% (67/81) / -14% (-24,-6) Outcome: Presence of middle ear fluid Amox / Placebo / Diff (95%CI) At 1-mo 29.2% (68/233) / 34.7% (77/222) / -5%(-14, 3.1) At 3-mo 25.4% (58/228) / 22.4% (47/210) / 3%(-5, 11) Outcome: Occurrence of adverse events - 6 to 23 months Amox / Placebo / Diff (95%CI) Diarrhea 22.5% (20/89) / 18.5% (17/92) / 4%(-8, 16) Rash 14.6% (13/89) / 9.8% (9/92) / 5%(-4.7, 14) Outcome: Occurrence of adverse events - 2-5 years Amox / Placebo / Dif(95%CI) Diarrhea 4.1% (6/146) / 6.8% (10/148) / -3%(-8, 2.5) Rash 2.7% (4/146) / 7.4% (11/148) / -5%(-10, 0.3) The article also published results for Days 1, 2, and 3 for: fever, pain, irritability, vomiting, No. of analgesic doses, No. of codeine doses, and able to do usual activities.

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Little 2001[2]	Jadad quality score[1] (0-5):3 [1,1,0,1,0] Definition: Presence of MEE, S&S of MEI	Amoxicillin tid for 7 days vs. Prescription to Hold	Place: United Kingdom Multicenter Office setting/ private practice, General/ family practice Inclusion: 6 mo-10 yr, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Cloudy TM, Erythematous TM, Air fluid level behind TM, S&S of middle ear inflammation (MEI), Otalgia, Otoscopy (distinct TM erythema) Exclusion: Antibiotic within 2 weeks, Strong indication of antibiotics (bulging eardrum, perforation, pus, tubes), Chronic suppurative OM, OME (serous OM, nonsuppurative OM, mucoid OM secretory OM, glue ear), Complication of OM, Major Systemic disease/ condition, medical problem	Entering: N=315 N=151 Amoxicillin N=164 Prescription to hold Completing: N=285 N=135 Amoxicillin N=150 Prescription to hold Analyzed: N=285 N=135 Amoxicillin N=150 Prescription to hold	Signs or symptoms of MEI; Adverse effects of treatment; Quality of life or functional outcome; Parent satisfaction; Cost outcomes	Outcome: Success rate at day 3 after first visit Antibiotic: 86% (116/135); RxHold: 70% (105/150); Diff (95%CI): 16%(6.3, 26) Outcome: Duration of symptoms (days), mean (range) Earache: Antibiotic 2.6(0-10); RxHold 3.6 (0-11); Diff (95% CI) -1.1 (-0.5, -1.5); p-value <0.01 Discharge: Antibiotic 0.6 (0-7); RxHold 1.2 (0-14); Diff (95% CI) -0.7 (-0.2, -1.1); p-value <0.01 Night dist: Antibiotic 1.6 (0-8); RxHold 2.4 (0-11); Diff (95% CI) -0.7 (-0.3, -1.1); p-value <0.01 Crying: Antibiotic 1.5 (0-7); RxHold 2.2 (0-11); Diff (95% CI) -0.7 (-0.3, -1.1); p-value <0.01 Pain score: Antibiotic 2.3 (1-5); RxHold 2.4 (1-6); Diff (95% CI) -0.2 (-0.4, 0.1); p-value 0.24 Outcome: Side effects Rash: Antibiotic 5% (6/133); RxHold 5% (8/149); Diff (95%CI) -1%(-6, 4.2) Diarrhea: Antibiotic 19% (25/133); RxHold 9% (14/149); Diff (95%CI) 9%(1, 18) Outcome: Healthcare utilization, mean (range) School days missed: Antibiotic 2.0 (0-8); RxHold 2.2 (0-13); Diff (95% CI) -0.2 (-0.8, 0.4); p-value 0.56 Daily No. of spoons of paracetamol consumed: Antibiotic 1.7 (0-6); RxHold 2.3 (0-8); Diff (95% CI) -0.5 (-0.8, -0.3); p-value <0.01 Outcome: Parents' belief and satisfaction Belief that antibiotics are very effective: Antibiotic 76% (100/131); RxHold 46% (64/140); Diff (95% CI) 31%(19, 42) Very satisfied with treatment approach: Antibiotic 94% (123/131); RxHold 77% (115/150); Diff (95% CI) 17%(9, 26) Very likely to consult doctor in future: Antibiotic 83% (109/132); RxHold 63% (92/147); Diff (95% CI) 20%(9, 31)

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Little 2006[93]	Jadad quality score[1] (0-5):3 [1,0,1,1,0] Definition: S&S of MEI	Amoxicillin vs. Prescription to Hold	Place: United Kingdom Inclusion: 6 mo-10 yr, S&S of middle ear inflammation (MEI), Otalgia, Otoscopy (distinct TM erythema) Exclusion: Antibiotic within 2 weeks, Strong indication of antibiotics (bulging eardrum, perforation, pus, tubes), AOM within 2 weeks, Chronic suppurative OM, OME (serous OM, nonsuppurative OM, mucoid OM secretory OM, glue ear), Complication of OM, Major Systemic disease/ condition, medical problem	Influencing factors: Symptoms and signs, Prior episodes of otitis media, Child care setting Entering: N=315 N=151 Amoxicillin N=164 Prescription to Hold Completing: N=219 N=99 Amoxicillin N=120 Prescription to Hold Analyzed: N=219 N=99 Amoxicillin N=120 Prescription to Hold	By symptoms (otalgia, ear fullness); Quality of life or functional outcome	Outcome: Earache Amox RxHold OR (95% CI) At 3 mos 0.89 (0.48, 1.65) At 1 yr 1.03 (0.60, 1.78) Outcome: Poor scores on the function scale Amox RxHold OR (95% CI) At 3 mos 1.37 (0.72, 2.60) At 1 yr 1.16 (0.61, 2.23) Data by influencing factor could not be abstracted by treatment groups.

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Marchisio 2010[133]	Jadad quality score[1] (0-5):2 [1,0,0,1,0] Definition: Presence of MEE, S&S of MEI ROM - ≥3 AOM in preceding 6 months or ≥4 episodes in preceding 12 months with most recent in previous 2-8 weeks	Elimination of environmental risk factors vs. 30% hydroglyceric extract of propolis; 1.2% zinc sulfate 0.3 ml/kg/d = QD for 3 months Plus Elimination of environmental risk factors	Study Time: 12/2004-3/2005 Place: Italy University/ academic Inclusion: 1-5 yr, Otoscopy (distinct TM erythema), Recurrent AOM, Free of AOM currently, OME, >= 2 episodes documented with symptoms, otoscopy, tympanometry Exclusion: Antibiotic within 2 weeks, Persistent TM perforation/Otorrhea, Tympanostomy tubes, Cleft palate, Immunosuppressed /compromised/deficient, Received blood products recently, Severe atopy, Obstructive adenoids, Sleep apnea	Entering: N=122 N=61 Envt Analyzed: N=122 N=61 Envt	Treatment failure; By Pneumatic otoscopy/tympanometry; By otoscopy (distinct TM erythema); Disease recurrence; Adverse effects of treatment; Quality of life or functional outcome; Parent satisfaction; Bacteriologic outcomes by nasopharyngeal cultures; Episodes of AOM (prevention study); Compliance; Any respiratory, relaspe defined as reappearance of any s or s <= 4 days after treatment ended; recurrence: 5-14 days	Outcome: ≥1 episode during 3-month study period Propolis+Zinc Controls Diff (95%CI) AOM 50.8% (31/61) 70.5% (43/61 -19.7% (-36.7, -2.7) RTI* 73.8% (45/61) 77.0% (47/61) -3.3% (-18.5, 12.1) *febrile respiratory tract infection (RTI) Outcome: ≥1 antibiotic course during 3-month study period Propolis+Zinc Controls Diff (95%CI) AOM 49.2% (30/61) 75.4% (46/61) -26.2% (-42.8, -9.6) RTI* 75..4% (46/61) 81.9% (50/61) -6.5% (-21.0, 8.0) *febrile respiratory tract infection (RTI) Outcome: Parent satisfaction Degree satisfaction Propolis+Zinc Controls Diff (95%CI) Unsatisfied 0.0% (0/61) 27.4% (17/61) -27.9% (-38, -16) Satisfied 65.6% (40/61) 62.3% (38/61) -3.3% (-13, 20) Very satisfied 34.4% (21/61) 9.8% (6/61) 24.6% (10, 39) Outcome: adverse events Adverse event Propolis+Zinc Controls Diff (95%CI) Vomiting 1.6% (1/61) 1.6% (1/61) 0% (-5, 5) Rash 1.6% (1/61) 0.0% (0/61) 1.6% (-2, 5) Outcome: mean number of episodes per child/month during 3-month study period Propolis+Zinc Controls Diff (95%CI) p-value AOM 0.23 (±0.26) 0.34 (±0.29) 0.11 (0.01, 0.21) 0.3 RTI* 1.20 (±0.94) 1.36 (±1.26) 0.43 (-0.23, 0.55) 0.43 *febrile respiratory tract infection (RTI) Outcome: mean number of antibiotic course for AOM during 3-month study period Propolis+Zinc Controls Diff (95%CI) p-value AOM 0.64 (±0.69) 0.98 (±0.73) 0.34 (0.09, 0.59) 0.005 RTI* 1.29 (±1.15) 1.31 (±0.96) 0.92 (-0.36, 0.40) 0.92 *febrile respiratory tract infection (RTI) Outcome: mean duration in months of bilateral OME per child Propolis+Zinc Controls Diff (95%CI) p-value 8.62 (±3.73) 9.50 (±4.06) 0.88 (-0.50, 2.26) 0.24

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
McCormick 2005[3]	Jadad quality score[1] (0-5):3 [1,0,1,1,0] Definition: Presence of MEE, S&S of MEI	Amoxicillin 90 mg/kg/day / bid for 10 days vs. Wait and see	Enrollment Time: 5/2000-3/2003 Place: Hospital clinic/ outpatient, University/ academic Inclusion: 6 mo-12 yr, Presence of middle ear effusion (MEE), S&S of middle ear inflammation (MEI), Non-severe AOM at onset Exclusion: Penicillin/beta-lactams, Concomitant/Concurrent infection needing antibiotic treatment, TM perforation/Otorrhea, PE tubes/history of PE tubes, Cranio-facial, Immunosuppressed /compromised/deficient, Major Systemic disease/ condition, medical problem	Influencing factors: Age Entering: N=223 N=112 Amoxicillin N=111 Wait and see Completing: N=218 N=110 Amoxicillin N=108 Wait and see Analyzed: N=218 N=110 Amoxicillin N=108 Wait and see	Treatment failure; Invasive infections, e.g., mastoiditis, bacteremia; Disease recurrence; Adverse effects of treatment; Quality of life or functional outcome; Parent satisfaction; Cost outcomes; Bacteriologic outcomes by nasopharyngeal cultures	Outcome: Success rate at Day 12 Age — Amoxicillin — Wait-and-see — Diff (95%CI) 0.5-12yrs — 95.3% (102/107) — 80.4% (86/107) — 15%(6, 24) <2yrs — 93.8% (60/64) — 77.8% (42/54) — 16% (4, 28) >=2yrs — 97.7% (42/43) — 83.0% (44/53) — 15% (2, 27) Outcome: Cure rate before Day 30 Age — Amoxicillin — Wait-and-see — Diff((95%CI) 0.5-12yrs — 77.1% (84/109) — 66.0% (66/100) — 11%(-1, 23) <2yrs — 76.9% (50/65) — 56% (28/50) — 21%(4, 38) >=2yrs — 77.3% (34/44) — 76% (38/50) — 1.3%(-16, 18) Outcome: Parent/Child Quality of Life Measure — Amoxicillin — Wait-and-see — Diff (95%CI) AOM-related extra office visit 13% (14/111) — 20% (22/108) — -7%(-17, 3) AOM-related emergency department visit 1% (1/111) — 4% (4/108) — -3%(-7, 1) AOM-related extra phone calls 23% (26/111) — 24% (26/108) — -1%(-12, 10) Parent missed work or school 14% (14/111) — 9% (10/108) — 5%(-3.5, 14) Doses of pain medicine [Mean±SD (n)] — p-value 3.4± 4.0 (105) — 7.7±7.5 — <0.01 Outcome: Adverse events Amoxicillin — Wait-and-see — Diff (95%CI) ABX-related adverse events 12% (13/111) — 5% (5/108) — 7%(-0.4, 14) Serious adverse events related to AIM 0% (0/111) — 0% (0/108) — 0% (0, 0) [The article also reported ABX-Resistance patterns of S. Pneumoniae strains isolated from the nasopharynx of subjects at enrollment and day 12.]

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Morris 2010[67]	Jadad quality score[1] (0-5):3 [1,1,1,0,0] Definition: AOM without perforation any tympanic membrane bulging and type B tympanogram; AOM with perforation - middle ear discharge observed and perforation recently healed or present for < 6 weeks or covering < 2% of the pars tensa	Azithromycin 30 mg/kg as a single dose plus Amoxicillin Placebo vs. Amoxicillin 50 mg/kg/day / BID for 7 days, plus Azithromycin Placebo = QD for 1 day	Study Time: 3/2003-7/2005 Place: Australia Multicenter: 16 centers Hospital clinic/ outpatient, Setting rural and remote communities Inclusion: Aboriginal children, 6 mos-6 y, New/first episode of AOM, Willingness of parents to bring child for follow-up visit Exclusion: Antibiotic within 7 days, Prior assignment to another arm of study, Allergy to penicillin or azithromycin, Other major illness requiring IV or IM antibiotics, Perforation covering >2% of the tympanic membrane	Influencing factors: Carriers/non carriers of Sp or NCHI - resistant or sensitive to antibiotic Entering: N=320 Completing: N=306 Analyzed: N=306	Treatment failure; Bulging tympanic membrane [TM]; Otorrhea; By symptoms (otalgia, ear fullness); Disease recurrence; Bacteriologic outcomes by nasopharyngeal cultures; Failure of a TM perforation to heal	**Outcome: Clinical success between day 6 and day 11** Azithromycin / Amoxicillin / Diff (95%CI) Intention to treat: 50% (83/165) / 46% (72/155) / 4% (-7, 15) Per protocol: 53% (74/140) / 47% (63/135) / 6% (-6, 18) Age / Azithromycin / Amoxicillin / Diff (95%CI) <2 years old: 51% (64/125) / 46% (57/125) / 6% (-7, 18) ≥2 years old: 47% (19/40) / 50% (15/30) / -3% (-26, 21) Diff (95%CI): 4% (-14, 21) / -4% (-24, 15) Baseline Diagnosis* / Azithromycin / Amoxicillin / Diff (95%CI) AOMwoP: 60% (81/134) / 54% (68/125) / 6% (-6, 18) AOMwiP: 8% (2/24) / 17 % (4/23) / -9% (-28, 10) *AOMwoP=without perforation; AOMwiP=with perforation Nasal Pathogen* / Azithromycin / Amoxicillin / Diff (95%CI) (+) SP: 50% (21/42) / 43% (40/92) / 7% (-12, 24) (-) SP: 54% (62/115) / 57 % (30/53) / -3% (-19, 13) (+) NCHi: 46% (40/86) / 44% (55/124) / 2% (-12, 16) (-) NCHi: 61% (43/71) / 71% (15/21) / -11% (-33, 12) * S pneumoniae (SP) or non-capsular Haemophilus influenzae (NCHi) Outcome: Improvement by end of therapy Azithromycin / Amoxicillin / Diff (95%CI) Intention to treat: 55% (87/158) / 51% (76/148) / 4% (-7, 15) Per protocol: 56% (78/140) / 50% (67/135) / -6% (-6, 18) Outcome: Other clinical outcomes Azithromycin / Amoxicillin / Diff (95%CI) No new pain: 99% (155/156) / 98% (144/147) / 1% (-1, 4) Runny nose: 35% (55/158) / 46% (67/146) / -11% (-22, 0.1) Skin sores: 4% (7/158) / 3% (4/146) / 2% (-3, 6) Nasal carriage of S. pneumonia, non-capsular H. influenzae, resistant S. pneumoniae, beta-lactamase-posituve non-capsular H. influenzae: See article. Ear discharge cultures positive for S. pneumoniae or non-capsular H. influenzae: See article.

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Neumark 2007[87]	Jadad quality score[1] (0-5):3 [1,0,1,1,0] Definition: Presence of MEE, S&S of MEI	Wait and see vs. Phenoxymethyl-penicillin 25 mg/kg/day = bid for 5 days	Place: Sweden Multicenter: 32 centers Public health center/ clinic/CHC Inclusion: 2-16 yr, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Erythematous TM, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), S&S of middle ear inflammation (MEI) Exclusion: Penicillin/beta-lactams, Concomitant/Concurrent infection needing antibiotic treatment, Recurrent AOM (>2 episodes in 6 months), Chronic suppurative OM, TM perforation/Otorrhea, Neurological disease/impairment, Immunosuppressed /compromised/deficient, Major Systemic disease/ condition, medical problem	Completing: N=179 N=92 Wait & See N=87 Phenoxymethylpenicillin Analyzed: N=179 N=92 Wait & See N=87 Phenoxymethylpenicillin	Treatment failure; Signs or symptoms of MEI; By symptoms (otalgia, ear fullness); Other symptoms: fever; Cost outcomes; Otologic complications, i.e., cholestetoma; Healthcare utilization	Outcome: Success (recovery) PcV / Wait-and-see / Diff (95% CI) Day2-7 100% (76/76) 95% (83/87) 5% (0, 10) Day14 82% (71/87) 85% (70/82) -4%(-15, 7) 3Months 85% (73/86) 84% (63/75) 1%(-10, 12) Outcome: Long-term outcome at 3 months PcV / Wait-and-see / Diff (95% CI) Perforation 0% (0/86) 0% (0/75) 0% Serous OM 12% (10/86) 11% (8/75) 1% (-9, 11) Outcome: Signs or symptoms at Day3-7 PcV / Wait-and-see / Diff (95%CI) Pain severity 2-3 2% (2/76) 5% (4/87) -3% (-9, 3) Analgesics use 3% (3/76) 10% (8/87) -7%(-15, 1) Fever>38ºC 3% (3/76) 6% (5/87) -3%(-9, 3) Outcome: Economic PcV / Wait-and-see / Diff (95%CI) Parents at home 56% (49/76) 53% (42/87) 3%(-12, 18) Days at home from work (median, range) 1.2 (0-7) 1.2 (0-7) 0.90

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Noel 2008[123] Page 1 of 2	Jadad quality score[1] (0-5):3 [1,0,1,1,0] Definition: Presence of MEE, S&S of MEI	Amoxicillin-clavulanate 45 mg/kg/day = bid for 10 days vs. Levofloxacin 10 mg/kg/day = bid for 10 days	Study Time: 10/2002-5/2005 Place: Multicenter: 66 centers Inclusion: >6 mo, Bulging tympanic membrane [TM], Cloudy TM, Erythematous TM, Otorrhea, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), Otalgia within last 24 hours, Otoscopy (distinct TM erythema), Recurrent AOM, Persistent AOM Exclusion: Penicillin/beta-lactams, Any antibiotic, Any antibiotic during present illness, Concomitant/Concurrent infection needing antibiotic treatment, PE tubes/history of PE tubes, Major Systemic disease/ condition, medical problem, On other medication/treatment	Influencing factors: Age Entering: N=1650 N=823 Amoxicillin-clavulanate N=827 Levofloxacin Completing: N=1435 N=721 Amoxicillin-clavulanate N=714 Levofloxacin Analyzed: N=1305 N=675 Amoxicillin-clavulanate N=630 Levofloxacin	Treatment failure; By Pneumatic otoscopy/tympanometry; Signs or symptoms of MEI; By symptoms (otalgia, ear fullness); By otoscopy (distinct TM erythema); Other symptoms: fever; Adverse effects of treatment	Outcome: Clinical success (cure and improved) at 2-5 days Age / Levofloxacin / Amox-clav / Diff (95%CI) 0.5-<5yr 94% (592/630) 91% (613/675) -3.2 (-6.0,-0.3) 0.5-2yr 92% (327/357) 88% (347/394) -3.5 (-7.3, 0.8) >2-<5yr 97% (265/273) 95% (266/281) -2.4 (-5.7, 0.9) Outcome: Clinical success (cure and improved) at 10-17 days Age / Levofloxacin / Amox-clav / Diff (95%CI) 0.5-<5yr 84% (585/700) 80% (578/719) -3.2 (-7.2, 0.8) 0.5-2yr 79% (318/404) 76% (315/417) -3.2 (-8.9, 2.6) >2-<5yr 90% (267/296) 87% (263/302) -3.1 (-8.2, 2.0) Outcome: Clinical cure (not including improved) at 2-5 days Age / Levofloxacin / Amox-clav / Diff (95%CI) 0.5-<5yr 72% (456/630) 70% (472/675) -2.5 (-7.4, 2.5) 0.5-2yr 69% (246/357) 66% (261/394) -2.7 (-9.4, 4.0) >2-<5yr 77% (210/273) 75% (211/281) -1.8 (-8.9, 5.3) Outcome: Clinical cure (not including improved) at 10-17 days Age / Levofloxacin / Amox-clav / Diff (95%CI) 0.5-<5yr 75% (524/700) 74% (531/719) -1.0 (-5.6, 3.5) 0.5-2yr 70% (284/404) 70% (291/417) -0.5 (-6.7, 5.8) >2-<5yr 81% (240/296) 80% (240/302) -1.6 (-8.0, 4.8) Outcome: Adverse events Levofloxacin / Amox-clav / Diff (95%CI) 1 or more up to visit 4 54% (448/827) 58% (475/823) -4%(-8,1.3) Arthralgia 1.5% (12/827) 0.7%(6/823) 0.8%(-0.2,1.8) Arthralgia disorder 1.2% (10/827) 0.6% (5/823) 0.6%(-0.3,1.5) Arthritis disorder 0.2% (2/827) 0% (0/823) 0.2%(-0.1,0.5) Arthropathy 0% (0/827) 0.2% (2/823) -0.2%(-0.5,0.1) Dermatitis 13% (108/827) 16% (129/823) -3%(-6, 0.8) Diarrhea 13% (108/827) 20% (161/823) -7%(-10, -3) Fever 7% (60/827) 8% (64/823) -1%(-3, 2) Gait abnormality disorder 0.1% (1/827) 0% (0/823) 0.1%(-0.1,0.3) Muscle weakness 0% (0/827) 0.1% (1/823) -0.1%(-0.3,0.1) Otitis media not related to treatment failure 5% (45/827) 4% (34/823) 1% (-0.8, 3.4) Pathologic fracture 0% (0/827) 0.5% (4/823) -0.5%(-1, 0)

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Noel 2008[123] Page 2 of 2						Levofloxacin / Amox-clav / Diff (95%CI) Musculoskeletal disorder (DSMC) 1.5% (12/827) / 0.6% (5/823) / 1%(-0.1, 1.9) Muscoskeletal adverse events 2.8% (23/827) / 2.3% (19/823) / 0.5%(-1, 2) Rhinitis 5% (43/827) / 5% (39/823) / 0.5%(-1.6,2.6) Synovitis 0.1% (1/827) / 0% (0/823) / 0.1%(-0.1,0.3) URI 6% (53/827) / 9% (78/823) / -3%(-5.7,-0.5) Vomiting 10% (81/827) / 7% (61/823) / 2%(-0.3, 5.1)
Oguz 2003[82]	Jadad quality score[1] (0-5):3 [1,0,1,1,0] Definition: Presence of MEE	Cefaclor 40 mg/kg/day / tid for 10 days vs. Azithromycin 10 mg/kg/day = qd for 3 days	Study Time: 1/1998-5/2000 Place: Turkey, Turkey Hospital clinic/ outpatient Inclusion: 6 mo-12 yr, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Cloudy TM, Erythematous TM, Otorrhea, Diagnosis by ENT Exclusion: Any antibiotic, Antibiotic within 2 weeks, Long acting antibiotic within 6 weeks, Chronic suppurative OM, TM perforation/Otorrhea, Respiratory Illness, Renal Disorders, Immunosuppressed /compromised/deficient, Major Systemic disease/ condition, medical problem	Entering: N=78 N=37 Cefaclor N=41 Azithromycin Completing: N=73 N=33 Cefaclor N=40 Azithromycin Analyzed: N=73 N=33 Cefaclor N=40 Azithromycin	Treatment failure; Presence of MEE [also persistent effusion, OME]; Disease recurrence; Antibiotic resistance; Adverse effects of treatment	Outcome: Clinical success (cure + improvement) Cefaclor / Azithromycin / Diff (95%CI) Day3-5 100% (33/33) / 98% (39/40) / 2%(-2.8, 6.8) Day10 97% (32/33) / 97% (38/39) / 0%(-8, 8) Day30 91% (30/33) / 94% (33/35) / -3%(-15, 10) Outcome: Clinical cure Cefaclor / Azithromycin / Diff (95%CI) Day3-5 36% (12/33) / 32% (13/40) / 4%(-18, 26) Day10 85% (28/33) / 77% (30/39) / 8%(-10, 26) Day30 82% (27/33) / 91% (32/35) / -9%(-25, 7) Outcome: Persistence of MEF Cefaclor / Azithromycin / Diff (95%CI) Day10 12% (4/33) / 21% (8/39) / -9%(-26, 8) Day30 3% (1/33) / 9% (3/35) / -6%(-17, 5) Outcome: Adverse events Cefaclor / Azithromycin / Diff (95%CI) Diarrhea and vomiting 3% (1/37) / 2% (1/41) / 1%(-5.9, 8)

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Paradise 1999[26] Page 1 of 2	Jadad quality score[1] (0-5):3 [1,0,1,1,0] Definition: Other	Placebo vs. Adenoidectomy vs. Adenoidectomy and/or tonsillectomy	Study Time: 4/1980-4/1994 Place: United States Hospital Inclusion: 3-15 yr, Recurrent AOM Exclusion: PE tubes/history of PE tubes, Cranio-facial	Entering: N=461 N=181 Placebo N=100 Adenoid N=180 Adenoid/tonsil Completing: N=410 N=177 Placebo N=79 Adenoid N=154 Adenoid/tonsil	Disease recurrence; Adverse effects of treatment; PE tube placement; Days of ear pain; Days of Abx Tx; Duration of AOM	Outcome: Success rate (% with no AOM episode) in 1 year in patients with no tonsil-related indications Adenoidectomy: 31% (19/61); Placebo: 22% (17/79); Diff (95%CI): 10% (-5, 24) Outcome: Success rate (% with<=1 AOM episode) in 1 year in patients with no tonsil-related indications Adenoidectomy: 48% (29/61); Placebo: 51% (40/79); Diff (95%CI): -3% (-20, 14) Outcome: Success rate (% with no AOM episode) in 1 year in patients with no tonsil-related indications Adenoidectomy: 31% (19/61); Adenotonsillectomy: 37% (26/71); Diff (95%CI): -6% (-22, 11) Outcome: Success rate (% with<=1 AOM episode) in 1 year in patients with no tonsil-related indications Adenoidectomy: 48% (29/61); Adenotonsillectomy: 59% (42/71); Diff (95%CI): -12% (-29, 5) Outcome: Success rate (% with no AOM episode) in 1 year in patients with no tonsil-related indications Adenotonsillectomy: 37% (26/71); Placebo: 22% (17/79); Diff (95%CI): 15% (0.6, 30) Outcome: Success rate (% with<=1 AOM episode) in 1 year in patients with no tonsil-related indications Adenotonsillectomy: 59% (42/71); Placebo: 51% (40/79); Diff (95%CI): 9% (-7, 25) Outcome: Adverse events Adenoidectomy: Placebo: Diff (95%CI) Erythematous rashes during treatment 7.2% (6/83); 3.9% (7/181); 3%(-2.3,9) Adenoidectomy: Adenotonsillectomy: Diff (95%CI) Erythematous rashes during treatment 7.2% (6/83); 2.2% (4/178); 5%(0,10) Hemorrhage after hospital discharge 0% (0/83); 2.2% (4/178); -2%(-5.4,1) Incipient malignant hyperthermia 1.2% (1/83); 0.6% (1/178); 0.6%(-1.7,1) Perioperative and postoperative complications 4.8% (4/83); 14.6% (26/178); -10%(-18,-1.5) Postoperative pneumonia 1.2% (1/83); 0% (0/178); 1.2%(-0.4,2.8) Postoperative velopharyngeal insufficiency - persistent (9mo) 0% (0/83); 0.6% (1/178); -0.6%(-2.3,1.1)

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Paradise 1999[26] Page 2 of 2						Adenoidectomy Adenotonsillectomy: Diff (95%CI) Postoperative velopharyngeal insufficiency-transient (<=43 d) 2.4% (2/83) 5.1% (9/178) -2.7%(-8,2.6) Retained in hospital 1 additional day and/or readmitted to hospital due to fever, poor fluid intake orally, vomiting, and/or dehydration 0% (0/83) 6% (11/178) -6%(-11,-0.8) Serum sickness during antimicrobial treatment 0% (0/83) 0.6% (1/178) -0.6%(-2.3,1.1) Adenotonsillectomy Placebo Diff (95%CI) Erythematous rashes during treatment 2.2% (4/178) 3.9% (7/181) -1.7%(-5.3,1.9)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Pessey 1999[79]	Jadad quality score[1] (0-5):2 [1,0,1,0,0] Definition: Presence of MEE, S&S of MEI	Amoxicillin-clavulanate 40 mg/kg/day / tid for 10 days vs. Amoxicillin-clavulanate 80 mg/kg/day / tid for 8 days vs. Cefuroxime 30 mg/kg/day / bid for 5 days	Place: France Multicenter: 50 centers Inclusion: 6-36 mo, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Cloudy TM, Loss of landmarks, Erythematous TM, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), Otalgia, Decreased hearing, Fever, Tympanocentesis preformed Not Specified Exclusion: Penicillin/beta-lactams, Antibiotic within 72 hours, Concomitant/Concurrent infection needing antibiotic treatment, TM perforation/Otorrhea, PE tubes/history of PE tubes, GI disorders/Liver, Renal Disorders, Immunosuppressed /compromised/deficient, Major Systemic disease/ condition, medical problem, Investigational drug within 3 months	Influencing factors: Age Entering: N=716 N=255 Amoxicillin-clavulanate 40 mg 10 days N=209 Amoxicillin-clavulanate 80 mg 8 days N=252 Cefuroxime	Treatment failure; Signs or symptoms of MEI; Bacteriologic cure/failure; Adverse effects of treatment	Outcome: Satisfactory clinical response post-treatment - A-C10d vs. CAE A-C10d: Total 88% (181/205); <1.5 yrs 89% (116/131); 1.5-3yrs 88% (65/74) CAE: Total 86% (175/203); <1.5 yrs 83% (111/134); 1.5-3yrs 93% (64/69) Diff (95%CI): Total 2% (-4.5, 8.5); <1.5 yrs 6% (-2.4, 14); 1.5-3yrs -5% (-15, 4.7) Outcome: Satisfactory clinical response post-treatment - A-C8d vs. CAE A-C8d: Total 88% (145/165); <1.5 yrs 84% (83/99); 1.5-3yrs 94% (62/66) CAE: Total 86% (175/203); <1.5 yrs 83% (111/134); 1.5-3yrs 93% (64/69) Diff (95%CI): Total 2% (-4.9, 9); <1.5 yrs 1% (-9, 11); 1.5-3yrs 1% (-7, 9) Outcome: Satisfactory clinical response post-treatment - A-C10d vs. A-C8d Outcome: Adverse events A-C10d: Total 88% (181/205); <1.5 yrs 89% (116/131); 1.5-3yrs 88% (65/74) A-C8d: Total 88% (145/165); <1.5 yrs 84% (83/99); 1.5-3yrs 94% (62/66) Diff (95%CI): Total 0% (-7, 7); <1.5 yrs 5% (-3.8, 14); 1.5-3yrs -6% (-16, 4) Outcome: Adverse events A-C10d: Any 22% (57/255); Diarrhea 18% (46/255) CAE: Any 15% (37/252); Diarrhea 10% (25/252) Diff (95%CI): Any 8%(1,14); Diarrhea 8%(2, 14) A-C8d: Any 16% (33/209); Diarrhea 10% (21/209) CAE: Any 15% (37/252); Diarrhea 10% (25/252) Diff (95%CI): Any 1%(-5.5,8); Diarrhea 0.1%(-5.4,5.6) A-C10d: Any 22% (57/255); Diarrhea 18% (46/255) A-C8d: Any 16% (33/209); Diarrhea 10% (21/209) Diff (95%CI): Any 7%(-0.6,14); Diarrhea 8%(1.6,14)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Roland 2003[126]	Jadad quality score[1] (0-5):3 [1,0,1,1,0] Definition: Not specified	Cipro otic 3% 3 drops = bid for 7 days vs. Ciprodex drops 3 drops = bid for 7 days	Study Time: 3/2000-2/2001 Place: Multicenter: 18 centers Inclusion: 6 mo-12 yr, Otorrhea, AOM < 3 weeks, Patent tympanostomy tubes Exclusion: Antibiotic within 2 days, Long acting antibiotic within 2 weeks, Complication of OM, Cranio-facial, Endocrine disorders (diabetes), GI disorders/Liver, Renal Disorders, Immunosuppressed /compromised/deficient, Other Infectious diseases (meningitis), Major Systemic disease/ condition, medical problem	Influencing factors: Age Entering: N=201 N=98 Cipro otic N=103 Ciprodex Completing: N=167 N=80 Cipro otic N=87 Ciprodex Analyzed: N=167 N=80 Cipro otic N=87 Ciprodex	Treatment failure; Bacteriologic cure/failure; Adverse effects of treatment	Outcome: Clinical success (cure and improve) on day 8 (post-therapy) Cipro alone / Cipro+Dex / Diff (95%CI) Total 91.2% (73/80) / 94.2% (82/87) / -3% (-11, 4.9) No data by age groups were reported. Outcome: Clinical success (cure and improve) on day 14 (test-of-cure) Cipro alone / Cipro+Dex / Diff (95%CI) Total 93.8% (75/80) / 98.9% (86/87) / -5% (-11, 0.5) No data by age groups were reported. Outcome: Adverse event Cipro alone / Cipro+Dex / Diff (95%CI) Excessive crying 1% (1/98) / 1% (1/103) / 0% (-2.8, 2.8) Burning 1% (1/98) / 2% (2/103) / -1%(-4.2,2.4) Pain 1% (1/98) / 2% (2/103) / -1%(-4.2,2.4) Precipitate 3% (3/98) / 0% (0/103) / 3%(-0.3,6.5) Pruritus 1% (1/98) / 1% (1/103) / 0%(-2.8,2.8) Taste perversion 0% (0/98) / 1% (1/103) / -1%(-3, 1)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Roland 2004[127]	Jadad quality score[1] (0-5):1 [1,0,0,0,0] Definition: Not specified	Ciprodex drops 4 drops = bid for 7 days vs. Ofloxacin drops 5 drops = bid for 10 days	Place: United States, Canada Multicenter: 39 centers Inclusion: 6 mo-12 yr, Otorrhea, Onset of AOM symptoms within 21 days before entry, Patent tympanostomy tubes Exclusion: Any antibiotic, Concomitant/Concurrent infection needing antibiotic treatment, Other antibiotic Tx, Topical antibiotic drops prior to study, Otitis externa, TM perforation/Otorrhea >3 weeks, Complication of OM, History of otic/ME surgery (excluding tubes), Respiratory Illness, Cranio-facial, Endocrine disorders (diabetes), GI disorders/Liver, Renal Disorders, Immunosuppressed /compromised/deficient, Other Infectious diseases (meningitis), On other medication/treatment, Menarche	Entering: N=599 N=297 Ciprodex N=302 Ofloxacin Completing: N=423 N=207 Ciprodex N=216 Ofloxacin Analyzed: N=423 N=207 Ciprodex N=216 Ofloxacin	Treatment failure; By otoscopic findings:; Otorrhea; Other symptoms: decreased hearing; Bacteriologic cure/failure; Adverse effects of treatment; Other antibiotic: No new abx Rx/no change in abx Rx	Outcome: clinical cure at test-of-cure visit day 18-21 Ciprodex / Ofloxacin / Diff (95%CI) Total: 90% (162/180) / 78.2% (133/170) / 12%(4.2, 19) Outcome: Clinical success (cured or improved) Ciprodex / Ofloxacin / Diff (95%CI) Day 3: 93.7% (194/207) / 79.6% (172/216) / 14%(7.6, 21) Day 11: 96.1% (199/207) / 89.8% (194/216) / 6%(1.4, 11) Day 18: 93.7% (194/207) / 88.4% (191/216) / 5%(-0.2, 11) Outcome: Absence of otorrhea Ciprodex / Ofloxacin / Diff (95%CI Day 3: 32.2% (67/207) / 18.5% (40/216) / 14%(5.4, 22) Day 11: 84.6% (176/207) / 63.4% (137/216) / 21%(13, 30) Day 18: 85.0% (176/206) / 70.8% (153/216) / 14%(6, 22) Outcome: Adverse events Ciprodex / Ofloxacin / Diff (95%CI Cough or crying or diarrhea or ear debris or edema eardrum or headache or hyperemia eardrum: 0% (0/297) / 0.3% (1/302) / -0.3%(-0.9,0.3) Discomfort ear: 3.4% (10/297) / 1% (3/302) / 2.4%(0.1,4.7) Dizziness or erythema or tinnitus or tympanostomy tube blockage: 0.3% (1/297) / 0%(0/302) / 0.3%(-0.3,0.9) Infection super ear or irritation ear or pruritus ear: 0% (0/297) / 0.7% (2/302) / -0.7%(-1.6,0.2) Irritability: 0.7% (2/297) / 0% (0/302) / 0.7%(-0.2,1.6) Monilia oral: 0.3% (1/297) / 0.3% (1/302) / 0%(-0.9,0.9) Pain ear: 2.4% (7/297) / 3.0% (9/302) / -0.6%(-3.2,2) Precipitate ear: 0.7% (2/297) / 1.0% (3/302) / -0.3%(-1.8,1.2) Serious Tx related: 0% (0/297) / 0% (0/302) / 0% (0, 0) Taste perversion: 0.3% (1/297) / 1% (3/302) / -0.7%(-2,0.6)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Roos 2000[131]	Jadad quality score[1] (0-5):2 [1,0,1,0,0] Definition: Presence of MEE, S&S of MEI	Ceftibuten 9 mg/kg/day = qd for 10 days vs. Ceftibuten 9 mg/kg/day = qd for 5 days	Enrollment Time: 6/1995-6/1996 Place: Sweden Multicenter: 6 centers Inclusion: 6 mo-8 yr, <45 kg, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Erythematous TM, Otalgia, Recurrent AOM, Weight of child Lower weight limit not specified Exclusion: Penicillin/beta-lactams, Complication of OM, PE tubes/history of PE tubes, Immunosuppressed /compromised/deficient	Entering: N=180 N=90 Ceftibuten 10 days N=90 Ceftibuten 5 days Completing: N=178 N=89 Ceftibuten 10 days N=89 Ceftibuten 5 days Analyzed: N=178 N=89 Ceftibuten 10 days N=89 Ceftibuten 5 days	Disease recurrence; Adverse effects of treatment; Bacteriologic outcomes by nasopharyngeal cultures	Outcome: Success rate (no recurrence after treatment) up to day 14 from start of treatment Age — Ceftibuten 5d — Ceftibuten 10d — Diff (95%CI) All — 79% (70/89) — 96% (85/89) — -16.8(-26.7,-7.0) Outcome: Success rate (no recurrence after treatment) up to day 40 from start of treatment Age — Ceftibuten 5d — Ceftibuten 10d — Diff (95%CI) All — 65% (58/89) — 70% (62/89) — -5.0 (-18.8, 8.8) Outcome: Percent patients with adverse events Ceftibuten 5d — Ceftibuten 10d — Diff (95%CI) All — 7% (6/90) — 17% (15/90) — -10.0(-19.4, -0.6) Outcome: Adverse events Ceftibuten 5d — Ceftibuten 10d — Diff (95%CI) GI disturbance 6.7% (6/90) — 16.7% (15/900 — -10%(-19,-0.6)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Saez-Llorens 2005[121] Page 1 of 2	Jadad quality score[1] (0-5):2 [1,0,1,0,0] Definition: Presence of MEE, S&S of MEI	Amoxicillin-clavulanate 45/6.4 mg/kg/day / bid for 10 days vs. Gatifloxacin 10 mg/kg/day = qd for 10 days	Enrollment Time: 5/2001-5/2002 Place: Multicenter: 20 centers Inclusion: 6 mo-7 yr, Recurrent AOM, Failed previous antibiotic Exclusion: Penicillin/beta-lactams, Any antibiotic, Antibiotic within 7 days, Concomitant/Concurrent infection needing antibiotic treatment, Otitis externa, TM perforation/Otorrhea, PE tubes/history of PE tubes, Cranio-facial, GI disorders/Liver, Renal Disorders, Major Systemic disease/ condition, medical problem, Metabolic/Inborn Errors of metabolism, Investigational drug within 1 month, On other medication/treatment	Influencing factors: Hearing deficit and severity, Laterality, Age, Recurrent otitis media/ otitis prone Entering: N=419 N=139 Amoxicillin-clavulanate N=280 Gatifloxacin Analyzed: N=413 N=136 Amoxicillin-clavulanate N=277 Gatifloxacin	Treatment failure; Presence of MEE [also persistent effusion, OME]; Signs or symptoms of MEI; Disease recurrence; Adverse effects of treatment	Outcome: Success rate at day 3-10- all type of diagnoses Age / Amox-clav / Gatifloxacin / Diff (95%CI) All / 84% (102/121) / 90% (222/246) / -6%(-13, 1) <2yrs / 80% (36/45) / 92% (81/88) / -12%(-24,-0.3) 2-7yrs / 87% (66/76) / 89% (141/158) / -2%(-11, 7) Outcome: Success rate at day 3-10- Recurrent OM only Age / Amox-clav / Gatifloxacin / Diff (95%CI) All / 81% (35/43) / 89% (67/75) / -8%(-21, 5.0) <2yrs / 88% (14/16) / 94% (30/32) / -6%(-22, 10) 2-7yrs / 78% (21/27) / 86% (37/43) / -8%(-26, 10) Outcome: Success rate at day 3-10- AOM treatment failures only Age / Amox-clav / Gatifloxacin / Diff (95%CI) All / 85% (62/73) / 91% (140/154) / -6%(-15, 2.7) <2yrs / 73% (19/26) / 89% (41/46) / -16%(-34, 2) 2-7yrs / 92% (43/47) / 92% (99/108) / 0%(-9.3, 9.3) Outcome: Success rate at day 3-10- both ROM and AOM tx failures Age / Amox-clav / Gatifloxacin / Diff (95%CI) All / 100% (5/5) / 88% (15/17) / 12% (-17, 41) <2yrs / 100% (3/3) / 100% (10/10) / 0% 2-7yrs / 100% (2/2) / 71% (5/7) / 29%(-37, 95) Outcome: Success rate at day 3-10- Unilateral cases Age / Amox-clav / Gatifloxacin / Diff (95%CI) All / 91% (49/54) / 92% (109/118) / -1%(-10, 8) <2yrs / 86% (12/14) / 98% (40/41) / -12%(-25, 1.3) 2-7yrs / 92% (37/40) / 90% (69/77) / 2%(-9, 13) Outcome: Success rate at day 3-10- Bilateral cases Age / Amox-clav / Gatifloxacin / Diff (95%CI) All / 79% (53/67) / 88% (113/128) / -9%(-20, 1.6) <2yrs / 77% (24/31) / 87% (41/47) / -10%(-27, 7) 2-7yrs / 81% (29/36) / 89% (72/81) / -8%(-21, 5.4) Outcome: Success rate at day 3-10- Mild/Moderate Severity cases Age / Amox-clav / Gatifloxacin / Diff (95%CI) All / 80% (33/41) / 89% (83/93) / -9%(-22, 4) <2yrs / 67% (10/15) / 87% (20/23) / -20%(-46, 6) 2-7yrs / 88% (23/26) / 90% (63/70) / -2%(-16, 12) Outcome: Success rate at day 3-10- Severe Severity cases Age / Amox-clav / Gatifloxacin / Diff (95%CI) All / 86% (69/80) / 91% (139/153) / -5%(-13, 3.4) <2yrs / 87% (26/30) / 94% (61/65) / -7%(-19, 4.9) 2-7yrs / 86% (43/50) / 89% (78/88) / -3%(-14, 8)

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Saez-Llorens 2005[121] Page 2 of 2						Outcome: Success rate (sustained cure) at day 21-28 Age — Amox-clav — Gatifloxacin — Diff (95%CI) All — 73% (88/121) — 74% (183/246) — -1%(-11, 9) <2yrs — 64% (29/45) — 70% (62/88) — -6%(-23, 11) 2-7yrs — 78% (59/76) — 77% (121/158) — 1%(-10, 12) Outcome: Adverse events Amox-clav — Gatifloxacin — Diff (95%CI) Any — 59% (81/136) — 55% (153/277) — 4%(-6, 14) Arthralgia — 2% (2/136) — 2% (6/277) — 0%(-2.9, 2.9) Drug-related — 15% (20/136) — 18% (49/277) — -3%(-11,4.7) Vomiting — 5% (7/136) — 8% (23/277) — -3%(-8, 2.2) Diarrhea — 7% (10/136) — 3% (8/277) — 4%(-0.2, 8) Abd pain — 2% (2/136) — 4% (11/277) — -2%(-5.7, 1.7) Diaper rash — 2% (3/136) — 1% (2/277) — 1%(-1.4,3 .4) Serious* — 2% (2/136) — 0% (0/277) — 2%(0.3, 3.7) * one was generalized seizure

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Sarrell 2001[102]	Jadad quality score[1] (0-5):3 [1,1,1,0,0] Definition: Presence of MEE, S&S of MEI	Topical anesthetic nos 5 drops = tid vs. Otikon drops 5 drops = tid	Study Time: 1/1998-10/1999 Place: Office setting/ private practice, Pediatric practice Multicenter Inclusion: 6-18 yr, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Cloudy TM, Erythematous TM, Air fluid level behind TM, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), S&S of middle ear inflammation (MEI), Otalgia, Otoscopy (distinct TM erythema), Ear fullness Exclusion: Allergic to other medication NOS, AOM within 2 weeks, TM perforation/Otorrhea, Complication of OM, PE tubes/history of PE tubes, Immunosuppressed /compromised/deficient, On other medication/treatment, Inability to do visual scale	Completing: N=103 N=42 Anesthetic drops N=61 Otikon drops Analyzed: N=103 N=42 Anesthetic drops N=61 Otikon drops	Treatment failure; Signs or symptoms of MEI; By symptoms (otalgia, ear fullness); Adverse effects of treatment	Outcome: Improvement in ear pain score (use the measurements at 30 minutes) Anesthetic (n=42) Otikon (n=61) Mean+/-SD Mean+/-SD Diff (95%CI) p-value Day 1 4.3+/-2.2 3.1+/-2.0 1.2 (0.37, 2.03) 0.005 Day 2 2.1+/-1.0 1.4+/-0.8 0.7 (0.35, 1.05) 0.000 Day 3 1.4+/-0.6 1.1+/-0.5 0.3 (0.08, 0.52) 0.007 Outcome: Adverse events Anesthetic Otikon Diff (95%CI) Any 0% (0/42) 0% (0/61) 0% (0,0)

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Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Sarrell 2003[103]	Jadad quality score[1] (0-5):5 [1,1,1,1,1] Definition: Presence of MEE, S&S of MEI	Amoxicillin 80 mg/kg/day / tid, Topical anesthetic nos 5 drops = tid vs. NHED 5 drops = tid vs. Amoxicillin 80 mg/kg/day / tid, NHED 5 drops = tid vs. Topical anesthetic nos 5 drops = tid NHED=Naturopathic Herbal Extract Ear Drops	Study Time: 1/1999-1/2001 Place: Public health center/ clinic/CHC Inclusion: 5-18 yr, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Erythematous TM, Air fluid level behind TM, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), S&S of middle ear inflammation (MEI), Otalgia Exclusion: TM perforation/Otorrhea, Complication of OM, PE tubes/history of PE tubes, Cranio-facial, Immunosuppressed /compromised/deficient, On other medication/treatment, Allergy to other medications, A or B on Tympanogram, Inability to do visual scale	Entering: N=180 N=45 Anesthetic with Amoxicillin N=45 NHED N=45 NHED with Amoxicillin N=45 Anesthetic Completing: N=171 N=43 Anesthetic with Amoxicillin N=44 NHED N=42 NHED with Amoxicillin N=42 Anesthetic Analyzed: N=171 N=43 Anesthetic with Amoxicillin N=44 NHED N=42 NHED with Amoxicillin N=42 Anesthetic	By symptoms (otalgia, ear fullness); Adverse effects of treatment	Outcome: Improvement in ear pain score (use the measurements at 30 minutes) NHED (n=44) vs. NHED+Amox (n=42) Day 1: 3.0+/-2.0 vs. 3.5+/-2.5; Diff (95%CI) -0.5(-1.5, 0.5); p-value 0.31 Day 2: 1.3+/-2.3 vs. 1.8+/-2.3; Diff (95%CI) -0.5(-1.5, 0.5); p-value 0.32 Day 3: 0.3+/-0.6 vs. 0.8+/-2.1; Diff (95%CI) -0.5(-1.2, 0.2); p-value 0.13 NHED (n=44) vs. Anesthetic (n=42) Day 1: 3.0+/-2.0 vs. 2.9+/-1.6; Diff (95%CI) 0.1(-0.7, 0.9); p-value 0.80 Day 2: 1.3+/-2.3 vs. 1.4+/-0.8; Diff (95%CI) -0.1(-0.8, 0.6); p-value 0.79 Day 3: 0.3+/-0.6 vs. 1.2+/-0.5; Diff (95%CI) -0.9(-1.1, -0.7); p-value 0.000 NHED (n=44) vs. Anesthetic+Amox (n=43) Day 1: 3.0+/-2.0 vs. 5.6+/-2.6; Diff (95%CI) -2.6(-3.6, -1.6); p-value 0.000 Day 2: 1.3+/-2.3 vs. 2.7+/-2.6; Diff (95%CI) -1.4(-2.4, -0.4); p-value 0.009 Day 3: 0.3+/-0.6 vs. 2.0+/-2.0; Diff (95%CI) -1.7(-2.3, -1.1); p-value 0.000 NHED+Amox (n=42) vs. Anesthetic (n=42) Day 1: 3.5+/-2.5 vs. 2.9+/-1.6; Diff (95%CI) 0.6(-0.3, 1.5); p-value 0.19 Day 2: 1.8+/-2.3 vs. 1.4+/-0.8; Diff (95%CI) 0.4(-0.4, 1.2); p-value 0.29 Day 3: 0.8+/-2.1 vs. 1.2+/-2.0; Diff (95%CI) -0.4(-1.3, 0.5); p-value 0.37 NHED+Amox (n=42) vs. Anesthetic+Amox (n=43) Day 1: 3.5+/-2.5 vs. 5.6+/-2.6; Diff (95%CI) -2.1(-3.2, -1.0); p-value 0.000 Day 2: 1.8+/-2.3 vs. 2.7+/-2.6; Diff (95%CI) -0.9(-2.0, 0.2); p-value 0.10 Day 3: 0.8+/-2.1 vs. 2.0+/-2.0; Diff (95%CI) -1.2(-2.1, -0.3); p-value 0.008 Anesthetic (n=42) vs. Anesthetic+Amox (n=43) Day 1: 2.9+/-1.6 vs. 5.6+/-2.6; Diff (95%CI) -2.7(-3.6, -1.8); p-value 0.000 Day 2: 1.4+/-0.8 vs. 2.7+/-2.6; Diff (95%CI) -1.3(-2.1, -0.5); p-value 0.003 Day 3: 1.2+/-2.0 vs. 2.0+/-2.0; Diff (95%CI) -0.8(-1.7, 0.06); p-value 0.07 Outcome: Adverse events All treatment options had 0 adverse events: Diff (95%CI): 0%(0,0)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Scholz 1998[4]	Jadad quality score[1] (0-5):5 [1,1,1,1,1] Definition: Presence of MEE, S&S of MEI	Amoxicillin 50 mg/kg/day / bid for 10 days vs. Erythromycin 40 mg/kg/day / bid for 10 days	Study Time: 9/1995-1/1996 Place: Germany Multicenter: 19 centers Pediatric practice Inclusion: 6 mo-11 yr, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Cloudy TM, Erythematous TM, Otorrhea, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), S&S of middle ear inflammation (MEI), Otalgia, Otoscopy (distinct TM erythema), Decreased hearing, Ear fullness, Fever, Onset of AOM symptoms within 4 days before entry Exclusion: Penicillin/beta-lactams, Macrolides, Antibiotic within 7 days, Long acting antibiotic within 4 weeks, AOM within 4 weeks, Chronic suppurative OM, OME (serous OM, nonsuppurative OM, mucoid OM secretory OM, glue ear), TM perforation/Otorrhea 24 hours, PE tubes/history of PE tubes, Cranio-facial, Immunosuppressed /compromised/deficient, Major Systemic disease/ condition, medical problem	Influencing factors: Otorrhea, Laterality, Age Entering: N=302 N=151 Amoxicillin N=151 Erythromycin Completing: N=280 N=139 Amoxicillin N=141 Erythromycin Analyzed: N=280 N=139 Amoxicillin N=141 Erythromycin	Treatment failure; Presence of MEE [also persistent effusion, OME]; Signs or symptoms of MEI; Other symptoms: fever; Other symptoms: decreased hearing; Invasive infections, e.g., mastoiditis, bacteremia; Disease recurrence; Adverse effects of treatment	Outcome: Clinical success on day 9-11 Amoxicillin / Erythromycin / Diff (95%CI) By drugs: 96% (133/139) / 94% (132/141) / 2% (-3, 7) Age<=2years / Age>2years / Diff (95%CI) By Age: 89.7% (35/39) / 95.4% (230/241) / -5.7%(-13, 2) Otorrhea at entry / No Otorrhea at entry / Diff (95%CI) By otorrhea: 94.7% (36/38) / 94.6% (229/242) / 0.1%(-8, 8) Bilateral / Unilateral / Diff (95%CI) By Laterality: 87.3% (69/79) / 97.5% (196/201) / -10%(-16, -4) Outcome: Free of recurrence Amoxicillin / Erythromycin / Diff (95%CI) All pts: 95.0% (132/139) / 94.3% (133/141) / 0.7%(-4.6, 6) 31-40 d: 97.8% (136/139) / 97.2% (137/141) / 0.6 %(-3, 4) Outcome: Adverse events Amoxicillin / Erythromycin / Diff (95%CI) Tx-related or possibly tx-related 7% (11/151) / 5% (8/151) / 2% (-3.7,7.5)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Sher 2005[122]	Jadad quality score[1] (0-5):2 [1,0,1,0,0] Definition: Presence of MEE, S&S of MEI	Amoxicillin-clavulanate 90/6.4 mg/kg/day / bid for 10 days vs. Gatifloxacin 10 mg/kg/day = qd for 10 days	Enrollment Time: 3/2001-6/2002 Place: United States, Costa Rica Multicenter: 27 centers Inclusion: 6 mo-7 yr, Presence of middle ear effusion (MEE), S&S of middle ear inflammation (MEI), AOM treated with antibiotic at least 2 days, Recurrent AOM Exclusion: Antibiotic within 7 days, Other antibiotic Tx, Otitis externa, TM perforation/Otorrhea, PE tubes/history of PE tubes, Major Systemic disease/ condition, medical problem, Failed previous antibotic	Influencing factors: Laterality, Age, Severity Entering: N=349 N=173 Amoxicillin-clavulanate N=176 Gatifloxacin Completing: N=328 N=164 Amoxicillin-clavulanate N=164 Gatifloxacin Analyzed: N=241 N=117 Amoxicillin-clavulanate N=124 Gatifloxacin	Treatment failure; Presence of MEE [also persistent effusion, OME]; Signs or symptoms of MEI; Bacteriologic cure/failure; Adverse effects of treatment	Outcome: Success rate on day 10 (test of day visit) by age group Amox-clav / Gatifloxacin / Diff (95%CI) Total 79% (92/117) 85% (105/124) -6%(-16, 3.7) <2yrs 78% (45/58) 79% (49/62) -1%(-16, 14) >=2yrs 80% (47/59) 90% (56/62) -11%(-23,2.7) Outcome: Success rate on day 10 (test of day visit) by laterality Amox-clav / Gatifloxacin / Diff (95%CI) Unilateral 82% (40/49) 84% (48/57) -3%(-17, 12) Bilateral 76% (52/68) 85% (57/67) -9%(-22, 4.7) Outcome: Success rate on day 10 (test of day visit) by SEVERITY Amox-clav / Gatifloxacin / Diff (95%CI) Mild/Mod 85% (45/53) 84% (47/56) 1%(-13, 15) Bilateral 73% (47/64) 85% (58/68) -12(-26, 2) Outcome: Adverse events Amox-clav / Gatifloxacin / Diff (95%CI) Any 27% (46/173) 24% (42/176) 3%(-6, 12) Abd pain or diarrhea (severe in intensity) 0.6% (1/173) 0% (0/176) 0.6(-0.4,1.7) Anorexia 0% (0/173) 0.6% (1/176) -0.6%(-1.8,0.6) Arthralgia event unrelated to treatment 1.2% (2/173) 0.5% (1/176) 0.6%(-1.4,2.6) Deaths or Serious drug related events 0% (0/173) 0% (1/173) 0% (0, 0) Diaper rash 6.4% (11/173) 5.1% (9/176) 1.3%(-3.6,6) Diarrhea 18% (31/173) 10% (17/176) 8% (1, 15) Vomiting 6% (10/173) 7% (12/176) -1%(-6, 4)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Spiro 2006[94]	Jadad quality score[1] (0-5):3 [1,0,1,1,0] Definition: Not specified	Antibiotic vs. Prescription to Hold	Enrollment Time: 7/2004-7/2005 Place: Emergency room Inclusion: 6 mo-12 yr, AOM Exclusion: Antibiotic within 1 week, Concomitant/Concurrent infection needing antibiotic treatment, TM perforation/Otorrhea, PE tubes/history of PE tubes, Immunosuppressed /compromised/deficient, Hospitalization/need for admission, In other studies/trials, Unable/unlikely to return to follow-up, No telephone, Language barrier	Entering: N=283 N=145 Antibiotic N=138 Prescription to hold Completing: N=265 N=133 Antibiotic N=132 Prescription to hold Analyzed: N=265 N=133 Antibiotic N=132 Prescription to hold	Treatment failure; Adverse effects of treatment; Parent satisfaction; Cost outcomes; Healthcare utilization	Outcome: Healthcare utilization at day 4-6 Antibiotic Rx / RxHold / Diff (95%CI) Not fill Rx 13% (17/133) / 62% (82/132) / -49%(-61, -37) No analgesic 90% (120/133) / 93% (123/132) / -3%(-10, 3.7) No MD visit 92% (125/133) / 90% (110132) / 2%(-4.9, 8.9) Outcome: Presence of symptoms and signs at day 4-6 Antibiotic Rx / RxHold / Diff (95% CI) Otalgia 67% (89/133) / 64% (85/132) / 3%(-8, 14) Fever 35% (46/133) / 32% (42/132) / 3%(-8, 14) Diarrhea 23% (31/133) / 8% (10/132) / 15%(6, 24) Vomiting 11% (15/133) / 11% (15/132) / 0%(-7.5, 7.5) Outcome: Healthcare utilization at day 11-14 Antibiotic Rx / RxHold / Diff (95%CI) No analgesic 11% (13/123) / 5% (6/124) / 6%(-18, 6) No MD visit 89% (109/123) / 85% (106124) / 4%(-4.4, 12) Outcome: Presence of symptoms and signs at day 11-14 Antibiotic Rx / RxHold / Diff (95% CI) Otalgia 61% (75/123) / 67% (83/124) / -6%(-18, 6) Fever 31% (38/123) / 32% (40/124) / -1%(-13, 11) Diarrhea 24% (29/123) / 12% (15/124) / 12%(2.4, 22) Vomiting 10% (12/123) / 9% (11/124) / 1%(-6, 8) Outcome: Adverse event at 4-6 day follow-up Antibiotic Rx / RxHold / Diff (95%CI) Diarrhea 21% (31/145) / 7% (10/138) / 14%(6, 22) Otalgia 61% (89/145) / 62% (85/138) / -0.2%(-11,11) Vomiting 10% (15/145) / 11% (15/138) / -1%(-8, 7) Outcome: Adverse event at 11-14 day follow-up Diarrhea 20% (29/145) / 11% (15/138) / 9% (0.7, 18) Otalgia 52% (75/145) / 60% (83/138) / -8%(-20,3.2) Vomiting 8% (12/145) / 8% (11/138) / 0.3%(-6, 7)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Subba Rao 1998[5]	Jadad quality score[1] (0-5):3 [1,0,1,1,0] Definition: Presence of MEE, S&S of MEI	Amoxicillin-clavulanate 250 mg for > 6 y = tid for 7 days, --- 125 mg for < 6 y = tid for 7 days vs. Cefaclor 125 or 250 mg = tid for 7 days	Study Time: 9/1995-12/1996 Place: India, United Arab Emirates Multicenter: 6 centers Hospital clinic/ outpatient Inclusion: 1-12 yr, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Loss of landmarks, Erythematous TM, Otorrhea, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), S&S of middle ear inflammation (MEI), Otalgia, Decreased hearing, Fever Exclusion: Penicillin/beta-lactams, Antibiotic within 7 days, Concomitant/Concurrent infection needing antibiotic treatment, OME (serous OM, nonsuppurative OM, mucoid OM secretory OM, glue ear), TM perforation/Otorrhea 24 hours, PE tubes/history of PE tubes, GI disorders/Liver, Renal Disorders, Major Systemic disease/ condition, medical problem, Bowel function-altering meds, Concurrent use of antihistamine, On other medication/treatment	Entering: N=233 N=114 Amoxicillin-clavulanate N=119 Cefaclor Completing: N=183 N=93 Amoxicillin-clavulanate N=90 Cefaclor Analyzed: N=217 N=105 Amoxicillin-clavulanate N=112 Cefaclor	Treatment failure; Presence of MEE [also persistent effusion, OME]; Signs or symptoms of MEI; Other symptoms: fever; Other symptoms: decreased hearing; Bacteriologic cure/failure; Disease recurrence; Adverse effects of treatment	Outcome: Success at end of study day 28-34 Amox-clav / Cefaclor / Diff(95%CI) Total 91.4% (96/105) / 78.6%(88/112) / 13%(3.2, 22) Outcome: Success at end of treatment on day 7 Amox-clav / Cefaclor / Diff(95%CI) Total 97.1% (102/105) / 83.9% (94/112) / 13%(5.3, 21) Outcome: Absence of tympanic membrane indicators (redness, bulging, loss of light reflex, rupture) Amox-clav / Cefaclor / Diff(95%CI) Day7 62.9% (66/105) / 44.6% (50/112) / 18%(5.0, 32) Day10-12 90.0%(90/100) / 84.2% (85/101) / 6%(-3.5, 15) Day28-34 93.8%(90/96) / 91.6% (87/95) / 2%(-5.2, 10) Outcome: Absence of signs and symptoms (ear pain, ear discharge, hearing loss) Amox-clav / Cefaclor / Diff(95%CI) Day7 99.0% (104/105) / 83.9% (94/112) / 15%(7.6, 23) Day10-12 97.0% (97/100) / 92.1% (93/101) / 5%(-1.4, 11) Day28-34 97.9% (94/96) / 94.7% (90/95) / 3% (-2.1, 8) Outcome: Adverse events Amox-clav / Cefaclor / Diff(95%CI) Diarrhea 7% (8/114) / 8.4% (10/119) / -1.4%(-8,5.5) Fever 0% (0/114) / 1.7% (2/119) / -1.7%(-4, 0.7) Headache 0% (0/114) / 2.5% (3/119) / -2.5%(-5.4,0.4) Vomiting 2.6% (3/114) / 5% (6/119) / -2.4%(-7.3,2.5)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Teele 2000[129]	Jadad quality score[1] (0-5):3 [1,1,0,1,0] Definition: Acute onset of S&S, Presence of MEE, S&S of MEI	Placebo vs. Sulfa alone 50 mg/kg/day = qd vs. Amoxicillin 20 mg/kg/day = qd	Place: United States Multicenter: 2 centers Inclusion: Recurrent AOM	Entering: N=117 N=41 Placebo N=36 Sulfa N=40 Amoxicillin Completing: N=117 N=41 Placebo N=36 Sulfa N=40 Amoxicillin Analyzed: N=117 N=41 Placebo N=36 Sulfa N=40 Amoxicillin	Treatment failure; Presence of MEE [also persistent effusion, OME]; Disease recurrence	Outcome: Success rate (none or 1 AOM episode in 6 months) Amoxicillin / Sulfisoxazole / Diff (95%CI) 90% (36/40) / 78% (28/36) / 12% (-4, 29) Outcome Success rate (none or 1 AOM episode in 1 year) Amoxicillin / Sulfisoxazole / Diff (95%CI) 68% (27/40) / 64% (23/36) / 4% (-18, 25) Outcome: Success rate (none or 1 AOM episode in 6 months) Amoxicillin / Placebo / Diff (95%CI) 90% (36/40) / 71% (29/41) / 19% (2, 37) Outcome: Success rate (none or 1 AOM episode in 1 year) Amoxicillin / Placebo / Diff (95%CI) 68% (27/40) / 66% (27/41) / 2% (-19, 22) Outcome: Success rate (none or 1 AOM episode in 6 months) Sulfisoxazole: / Placebo / Diff (95%CI) 78% (28/36) / 71% (29/41) / 7% (-12, 27) Outcome: Success rate (none or 1 AOM episode in 1 year) Sulfisoxazole / Placebo / Diff (95%CI) 64% (23/36) / 66% (27/41) / -2% (-23, 20)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Tsai 1998[86]	Jadad quality score[1] (0-5):1 [1,0,1,0,0] Definition: Presence of MEE, S&S of MEI	Cefpodoxime 10 mg/kg/day = qd for 10 days vs. Cefaclor 45 mg/kg/day / tid for 10 days	Study Time: 1/1996-7/1997 Inclusion: 3 mo-15 yr, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Cloudy TM, Loss of landmarks, Air fluid level behind TM, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), Otalgia, Fever Exclusion: Penicillin/beta-lactams, Antibiotic within 48 hours, TM perforation/Otorrhea, Immunosuppressed /compromised/deficient, Major Systemic disease/ condition, medical problem, Investigational drug within 2 weeks, Unable/unlikely to return to follow-up	Entering: N=57 N=23 Cefpodoxime N=34 Cefaclor Completing: N=51 N=21 Cefpodoxime N=30 Cefaclor Analyzed: N=51 N=21 Cefpodoxime N=30 Cefaclor	Treatment failure; Presence of MEE [also persistent effusion, OME]; Signs or symptoms of MEI; Other symptoms: fever; Disease recurrence; Adverse effects of treatment	Outcome: Success (cured or improved) at end of treatment day 10-14 Cefaclor: 90.0% (27/30); Cefpodoxime: 95.2% (20/21); Diff (95%CI): -5%(-20, 10) Outcome: Absence of middle ear effusion day 10-14 Cefaclor: 35.0% (7/20); Cefpodoxime: 26.7% (4/15); Diff (95%CI): 8%(-23, 39) Outcome: Adverse events Any: Cefaclor 15% (5/34); Cefpodoxime 30% (7/23); Diff (95%CI): -16(-37,5.9) Abdominal discomfort: Cefaclor 3% (1/34); Cefpodoxime 9% (2/23); Diff (95%CI): -6%(-18,6) Diarrhea: Cefaclor 3% (1/34); Cefpodoxime 17% (4/23); Diff (95%CI): -14%(-30,0.5) Intolerable abd discomfort or intolerable urticaria leading to being switched to other tx group: Cefaclor 3% (1/34); Cefpodoxime 0% (0/23); Diff (95%CI): 3%(-4, 10) Pruritis: Cefaclor 0% (0/34); Cefpodoxime 4% (1/23); Diff (95%CI): -4%(-11, 3) Skin rash: Cefaclor 6% (2/34); Cefpodoxime 0% (0/23); Diff (95%CI): 6%(-4,16) Sweating: Cefaclor 3% (1/34); Cefpodoxime 0% (0/23); Diff (95%CI): 3% (-4, 10)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Turik 1998[125]	Jadad quality score[1] (0-5):2 [1,0,1,0,0] Definition: Presence of MEE, S&S of MEI	Cefuroxime 30 mg/kg/day / bid for 10 days vs. Cefaclor 40 mg/kg/day / bid for 10 days	Study Time: 2/1996-12/1996 Place: Multicenter: 13 centers Inclusion: 3 mo-12 yr, >5.5 kg, Presence of middle ear effusion (MEE), Bulging tympanic membrane [TM], Cloudy TM, Loss of landmarks, Erythematous TM, Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), S&S of middle ear inflammation (MEI), Decreased hearing, Ear fullness, Fever, AOM treated with antibiotic 2-10 days Exclusion: Penicillin/beta-lactams, Concomitant/Concurrent infection needing antibiotic treatment, OME (serous OM, nonsuppurative OM, mucoid OM secretory OM, glue ear), TM perforation/Otorrhea 24 hours, Complication of OM, PE tubes/history of PE tubes, GI disorders/Liver, Renal Disorders, Other Infectious diseases (meningitis), Major Systemic disease/ condition, medical problem, Investigational drug within 28 days, Menarche	Entering: N=205 N=101 Cefuroxime N=104 Cefaclor Completing: N=189 N=91 Cefuroxime N=98 Cefaclor Analyzed: N=205 N=101 Cefuroxime N=104 Cefaclor	Treatment failure; Adverse effects of treatment	Outcome: Clinical success (cured or improved) Cefaclor / Cefuroxime axetil / Diff (95%CI) Day 10 93.6% (73/78) 92.9% (65/70) 0.7%(-7, 9) Day20-26 85.9% (67/78) 87.1% (61/70) -1.2%(-12, 10) Outcome: Adverse events Cefaclor / Cefuroxime axetil / Diff (95%CI) Any 31% (32/104) 36% (36/101) -5%(-18, 8) Asthma or Bronchospasm unrelated to study drug or respiratory disorder or vomiting 0% (0/104) 1% (1/101) -1%(-2.9, 0.9) Diarrhea 2% (2/104) 1% (11/101) -9%(-16,-2.3) Diarrhea during treatment 0% (0/104) 8% (8/101) -8%(-13,-2.5) Increased cough 7% (7/104) 0% (0/101) 7% (1.7,12) Rhinitis 9% (9/104) 10% (10/101) -1%(-9, 7)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Wang 2004[78]	Jadad quality score[1] (0-5):2 [1,0,1,0,0] Definition: Presence of MEE, S&S of MEI	Amoxicillin-clavulanate 45 mg/kg/day / tid for 10 days vs. Ceftriaxone 50 mg/kg/day = qd for 1 day	Enrollment Time: 2/2000-4/2002 Place: China Inclusion: 3 mo-6 yr, Presence of middle ear effusion (MEE), Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), S&S of middle ear inflammation (MEI), Otalgia, Otoscopy (distinct TM erythema), Decreased hearing, Fever >38 C Exclusion: Antibiotic within 7 days, TM perforation/Otorrhea, PE tubes/history of PE tubes	Entering: N=109 N=55 Amoxicillin-clavulanate N=54 Ceftriaxone Completing: N=78 N=35 Amoxicillin-clavulanate N=43 Ceftriaxone Analyzed: N=73 N=32 Amoxicillin-clavulanate N=41 Ceftriaxone	Treatment failure; Disease recurrence; Adverse effects of treatment	Outcome: Clinical cure rate on day 11 after 10-day treatment (per protocol) Amox-clav: 78.1% (25/32); Ceftriaxon: 75.6% (31/41); Diff (95%CI): 2.5%(-22, 17) Outcome: Clinical cure rate on day 11 after 10-day treatment (intent to treat) Amox-clav: 60.0% (27/45); Ceftriaxon: 62.8% (32/51); Diff (95%CI): 3% (-17, 22) Outcome: Adverse events Any: Amox-clav 36% (20/55); Ceftriaxon 24% (13/54); Diff (95%CI) 12%(-5.0,30) Diarrhea: Amox-clav 31% (17/55); Ceftriaxon 17% (9/54); Diff (95%CI) 14%(-1.8,30) GI: Amox-clav 34% (19/55); Ceftriaxon 22% (12/54); Diff (95%CI) 12%(-4.6,29) Skin & appendages or rash: Amox-clav 11% (6/55); Ceftriaxon 7% (4/54); Diff (95%CI) 4%(-7, 14)

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Zhang 2003[68]	Jadad quality score[1] (0-5):1 [1,0,1,0,0] Definition: Acute onset of S&S	Amoxicillin 40 mg/kg/day tid for 10 vs. Ceftriaxone 50 mg/kg/day for 1 day	Study Time: 11/2001-4/2002 Place: China Multicenter: 3 centers Hospital, University/ academic, Children's Inclusion: 1-12 yr, Acute onset S&S (parent/guardian report), Bulging tympanic membrane [TM], Erythematous TM, S&S of middle ear inflammation (MEI), Otoscopy (distinct TM erythema), Decreased hearing, Fever >38 C, Tympanocentesis preformed Not Specified, Weight of child Lower weight limit not specified, Weight of child Upper weight limit not specified Exclusion: Allergic to other medication NOS, Antibiotic within 7 days, AOM within 3 days, Recurrent AOM (>1 episodes in 6 months), Otitis externa, TM perforation/Otorrhea, Renal Disorders, Major Systemic disease/ condition, medical problem	Entering: N=236 N=118 Ceftriaxone N=118 Amoxicillin Completing: N=212 N=106 Ceftriaxone N=106 Amoxicillin Analyzed: N=212 N=106 Ceftriaxone N=106 Amoxicillin	Treatment failure; By otoscopic findings:; Bulging tympanic membrane [TM]; Erythematous TM; By Pneumatic otoscopy/tympanometry; By symptoms (otalgia, ear fullness); Other symptoms: fever; Other symptoms: decreased hearing	Outcome: Success rate at 10-14 days (cured or improved): Amox: 90.6% (96/106); Ceftriaxon: 97.2% (103/106); Diff (95%CI): -7%(-13, -0.2) Outcome: Adverse effects Amox: 1.9% (2/106) 2/106; Ceftriaxon: 1.9% (2/106) 2/106; Diff (95%CI): 0% Adverse events not reported by drug arm.

Appendix C. Evidence Tables For Randomized Controlled Trials

Author Year	Quality & AOM definition	Intervention	Time, Place, Inclusion, Exclusion Criteria	Influencing Factors and Sample Size	Outcomes	Findings
Zielnik-Jurkiewicz 2005[65]	Jadad quality score[1] (0-5):4 [1,1,1,1,0] Definition: Not specified	Amoxicillin 80 mg/kg/day / tid for 10 days vs. Amoxicillin 80 mg/kg/day / tid for 10 days, Fenspiride 2 ml / tid for 10 days	Place: Poland Inclusion: Pneumatic otoscopy/tympanometry (limited or absent mobility of TM), AOM, Age of child Children, age not specified Exclusion: Any antibiotic, GI disorders/Liver, Adenoid hypertrophy	Entering: N=40 N=20 Amoxicillin N=20 Amoxicillin/Fenspiride Completing: N=40 N=20 Amoxicillin N=20 Amoxicillin/Fenspiride Analyzed: N=40 N=20 Amoxicillin N=20 Amoxicillin/Fenspiride	Otorrhea; Signs or symptoms of MEI; By symptoms (otalgia, ear fullness); Other symptoms: fever; Other symptoms: decreased hearing	In Polish. Adverse events not reported

Appendix D. List of Excluded studies

References	Reason for Exclusion
Legros JM, Hitoto H, Garnier F, Dagorne C, Parot-Schinkel E, Fanello S. Clinical qualitative evaluation of the diagnosis of acute otitis media in general practice. *Int J Pediatr Otorhinolaryngol.* Jan 2008;72(1):23-30.	Design: Single cohort study (Before-After, Time series)
Steinbach WJ, Sectish TC, Benjamin Jr DK, Chang KW, Messner AH. Pediatric residents' clinical diagnostic accuracy of otitis media. *Pediatrics.* Jun 2002;109(6):993-998.	Design: Cross-sectional study
Palmu A, Syrjanen R, Kilpi T, et al. Negative pressure tympanograms in children less than 2 years of age--different bacterial findings in otitis media by tympanometric results. *Int J Pediatr Otorhinolaryngol.* Oct 19 2001;61(1):61-69.	Published before 2002
Johansen EC, Lildholdt T, Damsbo N, Eriksen EW. Tympanometry for diagnosis and treatment of otitis media in general practice. *Fam Pract.* Aug 2000;17(4):317-322.	Published before 2002
Palmu A, Puhakka H, Rahko T, Takala AK. Diagnostic value of tympanometry in infants in clinical practice. *Int J Pediatr Otorhinolaryngol.* Aug 20 1999;49(3):207-213.	Published before 2002
Jensen PM, Lous J. Criteria, performance and diagnostic problems in diagnosing acute otitis media. *Fam Pract.* Jun 1999;16(3):262-268.	Published before 2002
Kontiokari T, Koivunen P, Niemela M, Pokka T, Uhari M. Symptoms of acute otitis media. *Pediatr Infect Dis J.* Aug 1998;17(8):676-679.	Design: Cross-sectional study
Hemlin C, Hassler E, Hultcrantz M, Papatziamos G, Krakau I. Aspects of diagnosis of acute otitis media. *Fam Pract.* Apr 1998;15(2):133-137.	Published before 2002
McCormick DP, Lim-Melia E, Saeed K, Baldwin CD, Chonmaitree T. Otitis media: can clinical findings predict bacterial or viral etiology? *Pediatr Infect Dis J.* Mar 2000;19(3):256-258.	Published before 2002
Rodriguez WJ, Schwartz RH. Streptococcus pneumoniae causes otitis media with higher fever and more redness of tympanic membranes than Haemophilus influenzae or Moraxella catarrhalis. *Pediatr Infect Dis J.* Oct 1999;18(10):942-944.	Published before 2002
Gonzalez-Vallejo C, Sorum PC, Stewart TR, Chessare JB, Mumpower JL. Physicians' diagnostic judgments and treatment decisions for acute otitis media in children. *Med Decis Making.* Apr-Jun 1998;18(2):149-162.	Published before 2002

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References	Reason for Exclusion
Pichichero ME, Casey JR, Hoberman A, Schwartz R. Pathogens Causing Recurrent and Difficult-to-Treat Acute Otitis Media, 2003-2006. *Clin Pediatr (Phila).* Jun 16 2008.	Reject no kq or not valid pre/post vaccine datar data
Benninger MS. Acute bacterial rhinosinusitis and otitis media: changes in pathogenicity following widespread use of pneumococcal conjugate vaccine. *Otolaryngol Head Neck Surg.* Mar 2008;138(3):274-278.	Design
Pichichero ME, Casey JR. Emergence of a multiresistant serotype 19A pneumococcal strain not included in the 7-valent conjugate vaccine as an otopathogen in children. *JAMA.* Oct 17 2007;298(15):1772-1778.	Not valid pre/post vaccine study
Pichichero ME, Casey JR. Evolving microbiology and molecular epidemiology of acute otitis media in the pneumococcal conjugate vaccine era. *Pediatr Infect Dis J.* Oct 2007;26(10 Suppl):S12-16.	Design
Oosterhuis-Kafeja F, Beutels P, Van Damme P. Immunogenicity, efficacy, safety and effectiveness of pneumococcal conjugate vaccines (1998-2006). *Vaccine.* Mar 8 2007;25(12):2194-2212.	Design
Brunton S. Current face of acute otitis media: microbiology and prevalence resulting from widespread use of heptavalent pneumococcal conjugate vaccine. *Clin Ther.* Jan 2006;28(1):118-123.	Design
Arguedas A, Dagan R, Guevara S, et al. Middle ear fluid Streptococcus pneumoniae serotype distribution in Costa Rican children with otitis media. *Pediatr Infect Dis J.* Jul 2005;24(7):631-634.	Design
Zissis NP, Syriopoulou V, Kafetzis D, et al. Serotype distribution and antimicrobial susceptibility of Streptococcus pneumoniae causing invasive infections and acute otitis media in children. *Eur J Pediatr.* Jul 2004;163(7):364-368.	Design
Straetemans M, Sanders EA, Veenhoven RH, Schilder AG, Damoiseaux RA, Zielhuis GA. Pneumococcal vaccines for preventing otitis media. *Cochrane Database Syst Rev.* 2004(1):CD001480.	Design
Kamiya H, Kato T. [Epidemiological survey of pneumococcus serotypes in pediatric patients with acute suppurative otitis media]. *Kansenshogaku Zasshi.* 2007;81(1):59-66.	Not valid pre/post vaccine study

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References	Reason for Exclusion
Straetemans M, Sanders EA, Veenhoven RH, Schilder AG, Damoiseaux RA, Zielhuis GA. Review of randomized controlled trials on pneumococcal vaccination for prevention of otitis media. *Pediatr Infect Dis J.* Jun 2003;22(6):515-524.	Design
McEllistrem MC, Adams J, Mason EO, Wald ER. Epidemiology of acute otitis media caused by Streptococcus pneumoniae before and after licensure of the 7-valent pneumococcal protein conjugate vaccine. *J Infect Dis.* Dec 1 2003;188(11):1679-1684.	Reject at Duplicate data
Hausdorff WP, Yothers G, Dagan R, et al. Multinational study of pneumococcal serotypes causing acute otitis media in children. *Pediatr Infect Dis J.* Nov 2002;21(11):1008-1016.	Design
Kilpi T, Herva E, Kaijalainen T, Syrjanen R, Takala AK. Bacteriology of acute otitis media in a cohort of Finnish children followed for the first two years of life. *Pediatr Infect Dis J.* Jul 2001;20(7):654-662.	Not valid pre/post vaccine study
Joloba ML, Windau A, Bajaksouzian S, Appelbaum PC, Hausdorff WP, Jacobs MR. Pneumococcal conjugate vaccine serotypes of Streptococcus pneumoniae isolates and the antimicrobial susceptibility of such isolates in children with otitis media. *Clin Infect Dis.* Nov 1 2001;33(9):1489-1494.	Design
Dagan R, Givon-Lavi N, Shkolnik L, Yagupsky P, Fraser D. Acute otitis media caused by antibiotic-resistant Streptococcus pneumoniae in southern Israel: implication for immunizing with conjugate vaccines. *J Infect Dis.* Apr 2000;181(4):1322-1329.	Design
Satran R, Leibovitz E, Raiz S, et al. Clinical/otologic score before and during treatment of acute otitis media. *Acta Paediatr.* Dec 2007;96(12):1814-1818.	Design
Bulut Y, Guven M, Otlu B, et al. Acute otitis media and respiratory viruses. *Eur J Pediatr.* Mar 2007;166(3):223-228.	Design
Williams JV, Tollefson SJ, Nair S, Chonmaitree T. Association of human metapneumovirus with acute otitis media. *Int J Pediatr Otorhinolaryngol.* Jul 2006;70(7):1189-1193.	Design
Sakran W, Makary H, Colodner R, et al. Acute otitis media in infants less than three months of age: clinical presentation, etiology and concomitant diseases. *Int J Pediatr Otorhinolaryngol.* Apr 2006;70(4):613-617.	Design

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Yano H, Suetake M, Endo H, et al. Isolation of measles virus from middle ear fluid of infants with acute otitis media. *J Infect.* Nov 2005;51(4):e237-240.	Design
Sagai S, Suetake M, Yano H, et al. Relationship between respiratory syncytial virus infection and acute otitis media in children. *Auris Nasus Larynx.* Dec 2004;31(4):341-345.	Design
Huebner RE, Wasas AD, Hockman M, Klugman KP. Bacterial aetiology of non-resolving otitis media in South African children. *J Laryngol Otol.* Mar 2003;117(3):169-172.	Design
Dagan R, Leibovitz E, Cheletz G, Leiberman A, Porat N. Antibiotic treatment in acute Otitis Media promotes superinfection with resistant Streptococcus pneumoniae carried before initiation of treatment. *J Infect Dis.* Mar 15 2001;183(6):880-886.	Design
Yano H, Okitsu N, Hori T, et al. Detection of respiratory viruses in nasopharyngeal secretions and middle ear fluid from children with acute otitis media. *Acta Otolaryngol.* Jun 13 2008:1-6.	Design
Yano H, Okitsu N, Watanabe O, et al. Acute otitis media associated with cytomegalovirus infection in infants and children. *Int J Pediatr Otorhinolaryngol.* Sep 2007;71(9):1443-1447.	Design
Ruohola A, Meurman O, Nikkari S, et al. Microbiology of acute otitis media in children with tympanostomy tubes: prevalences of bacteria and viruses. *Clin Infect Dis.* Dec 1 2006;43(11):1417-1422.	Not valid pre/post vaccine study
Harimaya A, Takada R, Somekawa Y, Fujii N, Himi T. High frequency of Alloiococcus otitidis in the nasopharynx and in the middle ear cavity of otitis-prone children. *Int J Pediatr Otorhinolaryngol.* Jun 2006;70(6):1009-1014.	Design
Zielnik-Jurkiewicz B, Kolczynska M. [Bacterial flora in children with recurrent acute otitis media]. *Pol Merkur Lekarski.* Feb 2005;18(104):146-150.	Design
Segal N, Givon-Lavi N, Leibovitz E, Yagupsky P, Leiberman A, Dagan R. Acute otitis media caused by Streptococcus pyogenes in children. *Clin Infect Dis.* Jul 1 2005;41(1):35-41.	Design
Hoberman A, Paradise JL, Greenberg DP, Wald ER, Kearney DH, Colborn DK. Penicillin susceptibility of pneumococcal isolates causing acute otitis media in children: seasonal variation. *Pediatr Infect Dis J.* Feb 2005;24(2):115-120.	Not valid pre/post vaccine study

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Hoberman A, Dagan RL, E. , Rosenblut A, et al. Large dosage amoxicillin/clavulanate, compared with azithromycin, for the treatment of bacterial acute otitis media in children. *Pediatr Infect Dis J.* Jun 2005;24(6):525-532.	Design
Shinogami M, Ishibashi T. Presence of human herpesviruses in young children with acute otitis media. *Int J Pediatr Otorhinolaryngol.* Feb 2004;68(2):205-210.	Design
Sakakura K, Chikamatsu K, Furukawa M, et al. Acute otitis media caused by drug-resistant bacteria: correlation with antibiotic treatment. *Acta Otolaryngol.* Nov 2004;124(9):1008-1014.	Design
Leskinen K, Hendolin P, Virolainen-Julkunen A, Ylikoski J, Jero J. Alloiococcus otitidis in acute otitis media. *Int J Pediatr Otorhinolaryngol.* Jan 2004;68(1):51-56.	Not valid pre/post vaccine study
Gene A, Garcia-Garcia JJ, Domingo A, Wienberg P, Palacin E. [Etiology of acute otitis media in a children's hospital and antibiotic sensitivity of the bacteria involved]. *Enferm Infecc Microbiol Clin.* Aug-Sep 2004;22(7):377-380.	Design
Monobe H, Ishibashi T, Nomura Y, Shinogami M, Yano J. Role of respiratory viruses in children with acute otitis media. *Int J Pediatr Otorhinolaryngol.* Jul 2003;67(7):801-806.	Not valid pre/post vaccine study
Leibovitz E, Greenberg D, Piglansky L, et al. Recurrent acute otitis media occurring within one month from completion of antibiotic therapy: relationship to the original pathogen. *Pediatr Infect Dis J.* Mar 2003;22(3):209-216.	Not valid pre/post vaccine study
Arguedas A, Dagan R, Soley C, et al. Microbiology of otitis media in Costa Rican children, 1999 through 2001. *Pediatr Infect Dis J.* Dec 2003;22(12):1063-1068.	Not valid pre/post vaccine study
Ako-Nai AK, Oluga FA, Onipede AO, Adejuyigbe EA, Amusa YB. The characterization of bacterial isolates from acute otitis media in Ile-Ife, southwestern Nigeria. *J Trop Pediatr.* Feb 2002;48(1):15-23.	Design
Wald ER, Mason Jr. EO, Bradley JS, Barson WJ, Kaplan SL. Acute otitis media caused by Streptococcus pneumoniae in children's hospitals between 1994 and 1997. *Pediatr Infect Dis J.* Jan 2001;20(1):34-39.	Design
Sih TM. Acute otitis media in Brazilian children: analysis of microbiology and antimicrobial susceptibility. *Ann Otol Rhinol Laryngol.* Jul 2001;110(7 Pt 1):662-666.	Design

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Rosenblut A, Santolaya ME, Gonzalez P, et al. Bacterial and viral etiology of acute otitis media in Chilean children. *Pediatr Infect Dis J.* May 2001;20(5):501-507.	Not valid pre/post vaccine study
Li WC, Chiu NC, Hsu CH, Lee KS, Hwang HK, Huang FY. Pathogens in the middle ear effusion of children with persistent otitis media: implications of drug resistance and complications. *J Microbiol Immunol Infect.* Sep 2001;34(3):190-194.	Design
Husson MO, Pierreti A, Quelquejay J, Vaneecloo FM, Courcol RJ, Vincent C. [Bacterial epidemiological study of acute otitis media in children observed at home in the Nord Pas-de-Calais region]. *Pathol Biol (Paris).* Dec 2001;49(10):789-793.	Design
Gehanno P, Panajotopoulos A, Barry B, et al. Microbiology of otitis media in the Paris, France, area from 1987 to 1997. *Pediatr Infect Dis J.* Jun 2001;20(6):570-573.	Design
Block SL, Hedrick JA, Tyler RD, Smith RA, Harrison CJ. Microbiology of acute otitis media recently treated with aminopenicillins. *Pediatr Infect Dis J.* Nov 2001;20(11):1017-1021.	Design
Commisso R, Romero-Orellano F, Montanaro PB, Romero-Moroni F, Romero-Diaz R. Acute otitis media: bacteriology and bacterial resistance in 205 pediatric patients. *Int J Pediatr Otorhinolaryngol.* Nov 30 2000;56(1):23-31.	Design
Brook I, Gober AE. Reliability of the microbiology of spontaneously draining acute otitis media in children. *Pediatr Infect Dis J.* Jun 2000;19(6):571-573.	Design
Heikkinen T, Thint M, Chonmaitree T. Prevalence of various respiratory viruses in the middle ear during acute otitis media. *N Engl J Med.* Jan 28 1999;340(4):260-264.	Design
Haddad Jr. J, Saiman L, Chin NX, Della-Latta P. Penicillin-nonsusceptible pneumococcus in acute otitis media in New York City. *Otolaryngol Head Neck Surg.* Jul 1999;121(1):27-30.	Design
Jacobs MR, Dagan R, Appelbaum PC, Burch DJ. Prevalence of antimicrobial-resistant pathogens in middle ear fluid: multinational study of 917 children with acute otitis media. *Antimicrob Agents Chemother.* Mar 1998;42(3):589-595.	Design
Gehanno P, N'Guyen L, Derriennic M, Pichon F, Goehrs JM, Berche P. Pathogens isolated during treatment failures in otitis. *Pediatr Infect Dis J.* Oct 1998;17(10):885-890.	Not valid pre/post vaccine study

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Brook I, Gober AE. Microbiologic characteristics of persistent otitis media. *Arch Otolaryngol Head Neck Surg.* Dec 1998;124(12):1350-1352.	Design
Arguedas A, Loaiza C, Perez A, et al. Microbiology of acute otitis media in Costa Rican children. *Pediatr Infect Dis J.* Aug 1998;17(8):680-689.	Design
Zielnik-Jurkiewicz B, Bielicka A. [Evaluation of antibiotic resistance in material isolated from the middle ear in children with acute otitis media not responding to standard antibiotic treatment]. *Otolaryngol Pol.* 2007;61(5):892-897.	Design
Zielnik-Jurkiewicz B, Kolczynska M. [Nasopharyngeal and middle ear flora in children with acute otitis media]. *Otolaryngol Pol.* 2005;59(4):537-542.	Design
Prymula R, Motlova J, Kriz P. Comparison of Streptococcus pneumoniae serotypes causing acute otitis media & invasive disease in young children in the Czech Republic. *Indian J Med Res.* May 2004;119 Suppl:168-170.	Design
Porat N, Barkai G, Jacobs MR, Trefler R, Dagan R. Four antibiotic-resistant Streptococcus pneumoniae clones unrelated to the pneumococcal conjugate vaccine serotypes, including 2 new serotypes, causing acute otitis media in southern Israel. *J Infect Dis.* Feb 1 2004;189(3):385-392.	Design
Nokso-Koivisto J, Raty R, Blomqvist S, et al. Presence of specific viruses in the middle ear fluids and respiratory secretions of young children with acute otitis media. *J Med Virol.* Feb 2004;72(2):241-248.	Not valid pre/post vaccine study
del Castillo F, Baquero-Artigao F, Garcia-Perea A. Influence of recent antibiotic therapy on antimicrobial resistance of Streptococcus pneumoniae in children with acute otitis media in Spain. *Pediatr Infect Dis J.* Feb 1998;17(2):94-97.	Not valid pre/post vaccine study
Shibata M. [Infant case of acute otitis media due to PISP not eradicated with double-dose of CDTR]. *Jpn J Antibiot.* May 2001;54 Suppl B:99.	Design
Hotomi M, Billal DS, Kamide Y, et al. Serotype distribution and penicillin resistance of Streptococcus pneumoniae isolates from middle ear fluids of pediatric patients with acute otitis media in Japan. *J Clin Microbiol.* Nov 2008;46(11):3808-3810.	Design

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References	Reason for Exclusion
Mahjoub-Messai F, Doit C, Mariani-Kurkdjian P, Francois M, Bingen E. [Epidemiology of acute otitis media caused by Streptococcus pneumoniae: emergence of serotype 19A]. *Arch Pediatr.* Nov 2008;15(11):1713-1716.	Reject no kq or not valid pre/post vaccine datar data
Lopez-Enriquez C, Blanco-Montero A, Espinosa-Monteros LE, Rodriguez R, De la Torre C, Gomez-Barreto D. Middle-ear fluid Streptococcus pneumoniae susceptibility and serotype and distribution in mexican children with acute otitis media. *Pediatrics.* Jan 2008;121:S129-S129.	Design
Papavasileiou K, Papavasileiou H, Makri A, Varzakakos I, Nika E, Voyatzi A. Laboratory investigation of acute otitis media in children. *International Journal of Antimicrobial Agents.* Mar 2007;29:S431-S431.	Design
Casey JR, Adlowitz DG, Pichichero ME. New patterns in the otopathogens causing acute otitis media six to eight years after introduction of pneumococcal conjugate vaccine. *Pediatr Infect Dis J.* Apr 2010;29(4):304-309.	Reject at long for for no KQ
Erramouspe J, Heyneman CA. treatment and prevention of otitis media. *Ann Pharmacother.* Dec 2000;34(12):1452-1468.	Not RCT
Foxlee R, Johansson A, Wejfalk J, Dawkins J, Dooley L, Del Mar C. Topical analgesia for acute otitis media. *Cochrane Database Syst Rev.* 2006;3:CD005657.	Not RCT
Degenhardt BF, Kuchera ML. Osteopathic evaluation and manipulative treatment in reducing the morbidity of otitis media: a pilot study. *J Am Osteopath Assoc.* Jun 2006;106(6):327-334.	Not RCT
Valtonen H, Tuomilehto H, Qvarnberg Y, Nuutinen J. A 14-year prospective follow-up study of children treated early in life with tympanostomy tubes: Part 2: Hearing outcomes. *Arch Otolaryngol Head Neck Surg.* Apr 2005;131(4):299-303.	Not RCT
Nomura Y, Ishibashi T, Yano J, et al. Effect of myringotomy on prognosis in pediatric acute otitis media. *Int J Pediatr Otorhinolaryngol.* Jan 2005;69(1):61-64.	Not RCT
Marchetti F, Ronfani L, Nibali SC, Tamburlini G. Delayed prescription may reduce the use of antibiotics for acute otitis media: a prospective observational study in primary care. *Arch Pediatr Adolesc Med.* Jul 2005;159(7):679-684.	Not RCT

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Esposito S, Novelli A, Noviello S. [Treatment of acute otitis media in paediatrics: a meta-analysis]. *Infez Med.* Jun 2005;13(2):63-71.	Not RCT
Al-Shawwa BA, Wegner D. Trimethoprim-sulfamethoxazole plus topical antibiotics as therapy for acute otitis media with otorrhea caused by community-acquired methicillin-resistant Staphylococcus aureus in children. *Arch Otolaryngol Head Neck Surg.* Sep 2005;131(9):782-784.	Not RCT
Aggarwal M, Sinha R, Murali MV, Trihan P, Singhal PK. Comparative efficacy and safety evaluation of cefaclor vs amoxycillin + clavulanate in children with Acute Otitis Media (AOM). *Indian J Pediatr.* Mar 2005;72(3):233-238.	Not RCT
Wustrow TP. Alternative versus conventional treatment strategy in uncomplicated acute otitis media in children: a prospective, open, controlled parallel-group comparison. *Int J Clin Pharmacol Ther.* Feb 2004;42(2):110-119.	Not RCT
Gupta N, Bagga V, Parmar BJ, et al. Efficacy and tolerability assessment of cefprozil in children with acute otitis media. *Indian J Pediatr.* Apr 2004;71(4):319-324.	Not RCT
Siegel RM, Kiely M, Bien JP, et al. Treatment of otitis media with observation and a safety-net antibiotic prescription. *Pediatrics.* Sep 2003;112(3 Pt 1):527-531.	Not RCT
Piglansky L, Leibovitz E, Raiz S, et al. Bacteriologic and clinical efficacy of high dose amoxicillin for therapy of acute otitis media in children. *Pediatr Infect Dis J.* May 2003;22(5):405-413.	Not RCT
Gryczynska D, Grzegorowski M, Hassman-Poznanska E, Niedzielska G. [Multicenter, open clinical investigation on using cefprozil in therapy of otitis media in children]. *Otolaryngol Pol.* 2003;57(1):99-101.	Not RCT
Arguedas A, Sher L, Lopez E, et al. Open label, multicenter study of gatifloxacin treatment of recurrent otitis media and acute otitis media treatment failure. *Pediatr Infect Dis J.* Nov 2003;22(11):949-956.	Not RCT
Richards M, Giannoni C. Quality-of-life outcomes after surgical intervention for otitis media. *Arch Otolaryngol Head Neck Surg.* Jul 2002;128(7):776-782.	Not RCT

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Mgbor NC, Umeh RE. A blind parallel comparative study of the efficacy and safety of rovamycin versus augmentin in the treatment of acute otitis media. *West Afr J Med.* Apr-Jun 2002;21(2):117-120.	Not RCT
Leiberman A, Leibovitz E, Piglansky L, et al. Bacteriologic and clinical efficacy of trimethoprim-sulfamethoxazole for treatment of acute otitis media. *Pediatr Infect Dis J.* Mar 2001;20(3):260-264.	Not RCT
Frei H, Thurneysen A. Homeopathy in acute otitis media in children: treatment effect or spontaneous resolution? *Br Homeopath J.* Oct 2001;90(4):180-182.	Not RCT
Dagan R, Hoberman A, Johnson C, et al. Bacteriologic and clinical efficacy of high dose amoxicillin/clavulanate in children with acute otitis media. *Pediatr Infect Dis J.* Sep 2001;20(9):829-837.	Not RCT
Block SL, Hedrick JA, Kratzer J, Nemeth MA, Tack KJ. Five-day twice daily cefdinir therapy for acute otitis media: microbiologic and clinical efficacy. *Pediatr Infect Dis J.* Dec 2000;19(12 Suppl):S153-158.	Not RCT
Sox CM, Finkelstein JA, Yin R, Kleinman K, Lieu TA. Trends in otitis media treatment failure and relapse. *Pediatrics.* Apr 2008;121(4):674-679.	Not RCT
Heslop A, Ovesen T. Severe acute middle ear infections: microbiology and treatment. *Int J Pediatr Otorhinolaryngol.* Oct 2006;70(10):1811-1816.	Not RCT
Arguedas A, Dagan R, Pichichero M, et al. An open-label, double tympanocentesis study of levofloxacin therapy in children with, or at high risk for, recurrent or persistent acute otitis media. *Pediatr Infect Dis J.* Dec 2006;25(12):1102-1109.	Not RCT
Starostecka B. [Assessment of therapeutic effectiveness of Cefprozil in a short 5-day course of empirical antibiotic therapy in ambulatory patients with bacterial infections of the upper respiratory tract and otitis media]. *Otolaryngol Pol.* 2005;59(1):147-148.	Not RCT
Takenaka M, Morikawa Y, Nakagawa T, Takashima T, Haruta T, Tsuji T. [Causative organisms of acute otitis media and acute sinusitis in children and their susceptibility of oral beta-lactam antibiotics]. *Jpn J Antibiot.* Feb 1999;52(2):162-171.	Not RCT
Roger G, Carles P, Pangon B, et al. Management of acute otitis media caused by resistant pneumococci in infants. *Pediatr Infect Dis J.* Jul 1998;17(7):631-638.	Not RCT

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Quach C, Collet JP, LeLorier J. Effectiveness of amoxicillin, azithromycin, cefprozil and clarithromycin in the treatment of acute otitis media in children: a population-based study. *Pharmacoepidemiol Drug Saf.* Mar 2005;14(3):163-170.	Not RCT
Maruyama Y, Hoshida S, Furukawa M, Ito M. Effects of Japanese herbal medicine, Juzen-taiho-to, in otitis-prone children - a preliminary study. *Acta Otolaryngol.* Jun 12 2008:1-5.	Not RCT
Coleman C, Moore M. Decongestants and antihistamines for acute otitis media in children. *Cochrane Database Syst Rev.* 2008(3):CD001727.	Not RCT
Sugita R, Yamanaka N, Kudo F, et al. [Efficacy and safety of potassium clavulanate/amoxicillin (CLAVAMOX) dry syrup in children with otitis media]. *Jpn J Antibiot.* Aug 2007;60(4):221-241.	Not RCT
Soley C, Arguedas A, Guevara S, et al. An open-label, double tympanocentesis, single-center study of trimethoprim sulfametoxasole in children with acute otitis media. *Pediatr Infect Dis J.* Mar 2007;26(3):273-274.	Not RCT
Chow Y, Wabnitz DA, Ling J. Quality of life outcomes after ventilating tube insertion for otitis media in an Australian population. *Int J Pediatr Otorhinolaryngol.* Oct 2007;71(10):1543-1547.	Not RCT
Prim Espada MP, Perez Mora R, de Diego Sastre JI. [Comparative analysis of the therapeutic costs to control the recurrent acute otitis media]. *An Otorrinolaringol Ibero Am.* 2006;33(5):505-512.	Not RCT
Wustrow TP. [Naturopathic therapy for acute otitis media. An alternative to the primary use of antibiotics]. *Hno.* Aug 2005;53(8):728-734.	Not RCT
Valtonen H, Tuomilehto H, Qvarnberg Y, Nuutinen J. A 14-year prospective follow-up study of children treated early in life with tympanostomy tubes: Part 1: Clinical outcomes. *Arch Otolaryngol Head Neck Surg.* Apr 2005;131(4):293-298.	Not RCT
Pichichero ME, Arguedas A, Dagan R, et al. Safety and efficacy of gatifloxacin therapy for children with recurrent acute otitis media (AOM) and/or AOM treatment failure. *Clin Infect Dis.* Aug 15 2005;41(4):470-478.	Not RCT

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Mui S, Rasgon BM, Hilsinger Jr. RL, Lewis B, Lactao G. Tympanostomy tubes for otitis media: quality-of-life improvement for children and parents. *Ear Nose Throat J.* Jul 2005;84(7):418, 420-412, 424.	Not RCT
Garashchenko TI, Denisova OA, Kotov RV. [Initial antibiotic therapy in acute otitis media and acute sinusitis in children]. *Vestn Otorinolaringol.* 2005(3):62-63.	Not RCT
Cotter CS, Kosko JR. Effectiveness of laser-assisted myringotomy for otitis media in children. *Laryngoscope.* Mar 2004;114(3):486-489.	Not RCT
Dunne MW, Khurana C, Mohs AA, et al. Efficacy of single-dose azithromycin in treatment of acute otitis media in children after a baseline tympanocentesis. *Antimicrob Agents Chemother.* Aug 2003;47(8):2663-2665.	Not RCT
Dasgupta KS, Deshpande AS, Vedi JN, Patel S. Evaluation of efficacy of nizer versus nimesulide tablets in otitis media. *J Indian Med Assoc.* Oct 2002;100(10):619.	Not RCT
Pichichero ME, Marsocci SM, Murphy ML, Hoeger W, Francis AB, Green JL. A prospective observational study of 5-, 7-, and 10-day antibiotic treatment for acute otitis media. *Otolaryngol Head Neck Surg.* Apr 2001;124(4):381-387.	Not RCT
Uno Y. [Retrospective studies of penicillin-resistant pneumococcal acute otitis media in infants and children--the treatment of tympanostomy tube insertion]. *Kansenshogaku Zasshi.* Sep 2000;74(9):703-708.	Not RCT
Reilly JS, Deutsch ES, Cook S. Laser-assisted myringotomy for otitis media: a feasibility study with short-term followup. *Ear Nose Throat J.* Aug 2000;79(8):650-652, 654-657.	Not RCT
Glasziou PP, Hayem M, Del Mar CB. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev.* 2000(2):CD000219.	Not RCT
Valtonen H, Qvarnberg Y, Nuutinen J. Tympanostomy in young children with recurrent otitis media. A long-term follow-up study. *J Laryngol Otol.* Mar 1999;113(3):207-211.	Not RCT
Thompson D, Oster G, McGarry LJ, Klein JO. Management of otitis media among children in a large health insurance plan. *Pediatr Infect Dis J.* Mar 1999;18(3):239-244.	Not RCT
Sugita R, Harada S, Deguchi K, et al. [A clinicobacteriologic study on clavulanic acid/amoxicillin in pediatric acute otitis media]. *Jpn J Antibiot.* Oct 1999;52(10):595-612.	Not RCT

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Hueston WJ, Ornstein S, Jenkins RG, Pan Q, Wulfman JS. Treatment of recurrent otitis media after a previous treatment failure. Which antibiotics work best? *J Fam Pract.* Jan 1999;48(1):43-46.	Not RCT
Gehanno P, Nguyen L, Barry B, et al. Eradication by ceftriaxone of Streptococcus pneumoniae isolates with increased resistance to penicillin in cases of acute otitis media. *Antimicrob Agents Chemother.* Jan 1999;43(1):16-20.	Not RCT
Leibovitz E, Piglansky L, Raiz S, et al. Bacteriologic efficacy of a three-day intramuscular ceftriaxone regimen in nonresponsive acute otitis media. *Pediatr Infect Dis J.* Dec 1998;17(12):1126-1131.	Not RCT
Franklin JH, Marck PA. Outcome analysis of children receiving tympanostomy tubes. *J Otolaryngol.* Oct 1998;27(5):293-297.	Not RCT
Kim CW, Jin JW, Rho YS. Tuberculous otitis media developing as a complication of tympanostomy tube insertion. *Eur Arch Otorhinolaryngol.* Mar 2007;264(3):227-230.	Not RCT
Steppberger K, Adams I, Deutscher J, Muller H, Kiess W. Meningitis in a girl with recurrent otitis media caused by Streptococcus pyogenes--otitis media has to be treated appropriately. *Infection.* Oct 2001;29(5):286-288.	Not RCT
Garcia-Lopez M, Martinez-Blanco M, Martinez-Mir I, Palop V. Amoxycillin-clavulanic acid-related tooth discoloration in children. *Pediatrics.* Sep 2001;108(3):819.	Not RCT
Spandow O, Gothefors L, Fagerlund M, Kristensen B, Holm S. Lateral sinus thrombosis after untreated otitis media. A clinical problem--again? *Eur Arch Otorhinolaryngol.* 2000;257(1):1-5.	Not RCT
Little JP, Tunkel DE, Marsh BR. Foreign body aspiration: an unusual complication of antibiotic therapy. *Arch Pediatr Adolesc Med.* Mar 2000;154(3):313-314.	Not RCT
Vega C, Quinby PM, Aspy CB. Hepato-biliary abnormalities secondary to ceftriaxone use: a case report. *J Okla State Med Assoc.* Aug 1999;92(8):432-434.	Not RCT
Grouhi M, Hummel D, Roifman CM. Anaphylactic reaction to oral cefaclor in a child. *Pediatrics.* Apr 1999;103(4):e50.	Not RCT
Benjamin S, Mueller BA. Erythema multiforme secondary to amoxicillin/clavulanic acid exposure. *Ann Pharmacother.* Jan 1999;33(1):109-110.	Not RCT

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Beghetti M, Wilson GJ, Bohn D, Benson L. Hypersensitivity myocarditis caused by an allergic reaction to cefaclor. *J Pediatr.* Jan 1998;132(1):172-173.	Not RCT
Kawalec P, Cel M, Glogowski C. Cost-effectiveness of augmentin esovs azithromycin forthetreatment of paediatric acute otitis media (AOM) in Poland. *Value in Health.* Nov-Dec 2007;10(6):A440-A440.	Not RCT
Leach AJ, Morris PS. Antibiotics for the prevention of acute and chronic suppurative otitis media in children. *Cochrane Database Syst Rev.* 2006(4):CD004401.	Not RCT
McDonald S, Langton Hewer CD, Nunez DA. Grommets (ventilation tubes) for recurrent acute otitis media in children. *Cochrane Database Syst Rev.* 2008(4):CD004741.	Not RCT
Williams RL, Chalmers TC, Stange KC, Chalmers FT, Bowlin SJ. Use of antibiotics in preventing recurrent acute otitis media and in treating otitis media with effusion. A meta-analytic attempt to resolve the brouhaha. *JAMA.* Sep 15 1993;270(11):1344-1351.	Not RCT
Thanaviratananich S, Laopaiboon M, Vatanasapt P. Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. *Cochrane Database Syst Rev.* 2008(4):CD004975.	Not RCT
Wall GM, Stroman DW, Roland PS, Dohar J. Ciprofloxacin 0.3%/dexamethasone 0.1% sterile otic suspension for the topical treatment of ear infections: a review of the literature. *Pediatr Infect Dis J.* Feb 2009;28(2):141-144.	Not RCT
Bonati M, Marchetti F, Pistotti V, et al. Metaanalysis of antimicrobial prophylaxis for recurrent acute otitis-media. *Clinical Trials and Meta-Analysis.* 1992;28(1):39-50.	Not RCT
Rovers MM, Glasziou P, Appelman CL, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet.* Oct 21 2006;368(9545):1429-1435.	Not RCT
Spurling GK, Del Mar CB, Dooley L, Foxlee R. Delayed antibiotics for respiratory infections. *Cochrane Database Syst Rev.* 2007(3):CD004417.	Not RCT
Kozyrskyj AL, Hildes-Ripstein GE, Longstaffe SE, et al. Short course antibiotics for acute otitis media. *Cochrane Database Syst Rev.* 2000(2):CD001095.	Not RCT
Takata GS, Chan LS, Shekelle PG, Morton SC, Mason W, Marcy SM. Evidence assessment of management of acute otitis media: I. The role of antibiotics in treatment of uncomplicated acute otitis media. *Pediatrics.* Aug 2001;108(2):239-247.	}Not RCT

Appendix D. List of Excluded studies

References	Reason for Exclusion
Bezakova N, Damoiseaux RA, Hoes AW, Schilder AG, Rovers MM. Recurrence up to 3.5 years after antibiotic treatment of acute otitis media in very young Dutch children: survey of trial participants. *BMJ.* 2009;338:b2525.	Rejected, does not answer KQ
Abba K, Garner P. Zinc supplements for preventing otitis media [Protocol]. *Cochrane Database of Systematic Reviews(3).*	Not RCT
Azarpazhooh A, Lawrence HP. Xylitol for preventing acute otitis media in children up to 12 years of age [Protocol]. *Cochrane Database of Systematic Reviews(3).*	Not RCT
Kay ES, Ng K. "Influenza vaccine for preventing acute otitis media in infants and children [Protocol]." *Cochrane Database of Systematic Reviews(3).*	Not RCT
Koopman L, Hoes AW, Glasziou PP, et al. Antibiotic therapy to prevent the development of asymptomatic middle ear effusion in children with acute otitis media: a meta-analysis of individual patient data. *Arch Otolaryngol Head Neck Surg.* Feb 2008;134(2):128-132.	Not RCT
Rahlfs VW. Brodimoprim in upper respiratory tract infections: two meta-analyses of randomised, controlled clinical trials in acute sinusitis and otitis media (Structured abstract). *Clin Drug Invest.* 1996;11(2):65-.	Not RCT
Sanders S, Glasziou P. Antibiotics for acute otitis media in children [Systematic Review]." *Cochrane Database of Systematic Reviews(3).*	Not RCT
Vouloumanou EK, Karageorgopoulos DE, Kazantzi MS, Kapaskelis AM, Falagas ME. Antibiotics versus placebo or watchful waiting for acute otitis media: a meta-analysis of randomized controlled trials. *J Antimicrob Chemother.* Jul 2009;64(1):16-24.	Not RCT
Gunasekera H, Morris PS, Daniels J, Couzos S, Craig JC. Management of children with otitis media: a survey of Australian Aboriginal Medical Service practitioners. *J Paediatr Child Health.* Jul-Aug 2009;45(7-8):457-463.	Not RCT
Abba K, Gulani A, Sachdev HS. Zinc supplements for preventing otitis media. *Cochrane Database Syst Rev.* 2010;2:CD006639.	Not RCT
Courter JD, Baker WL, Nowak KS, et al. Increased clinical failures when treating acute otitis media with macrolides: a meta-analysis. *Ann Pharmacother.* Mar 2010;44(3):471-478.	Not RCT

Appendix D. List of Excluded studies

References	Reason for Exclusion
Gulani A, Sachdev HP, Qazi SA. Efficacy of short course (<4 days) of antibiotics for treatment of acute otitis media in children: a systematic review of randomized controlled trials. *Indian Pediatr.* Jan 7 2010;47(1):74-87.	Not RCT

Appendix E. List of Peer Reviewers

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Appendix E. List of Peer Reviewers

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Appendix F. Technical Expert Panel Composition and Meeting Summaries

Table F-1. Technical Expert Panel Composition

Name, Affiliation,	Contact information/ Nominating Organization
Margaretha Casselbrant, MD, PhD Chair, Dept of Pediatric Otolaryngology University of Pittsburgh	Childrens Hospital of Pittsburgh Dept of Pediatric Otolaryngology 3705 5th Ave Ste 1650 Pittsburgh, PA 15213-2524 **Email: cassml@chp.edu** Society for Ear Nose Throat Advances in Children
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Appendix F. Technical Expert Panel Composition and Meeting Summaries

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AOM TEP Meeting 9/26/08

Attendance: Tasnee Chonmaitree, Katherine Finn Davis, Ted Ganiats, Mary Goessler, Lawrence Kleinman, Linda Landry, Allan Lieberthal, Richard Rosenfeld, Pauline Thomas, Caryn Davidson, Paul Shekelle, Glen Takata, Linda Chen, Tumaini Coker, Mary Ann Limbos, Sydne Newberry, Tina Murray)

Paul Shekelle introduced the role of the EPC and its responsibility for THE 2001 REPORT: The EPC team includes some clinicians, methodologists. However, the TEP consists of subject matter experts, consumers (and other end users), and representatives of the sponsoring

organization/partner (AAP). The TEP's role today is to help clarify key questions and enunciate the sponsoring organization's and others' needs.

Tina Murray described the role of the Task Order Officer (TOO):
The TOO's role is to try to maintain timeliness, address administrative issues. The TOO tries to make sure the TEP is broadly representative, including end-users. AHRQ looks to TEP to help ensure report is useful to them.

Allan Lieberthal (representing AAP)
This TEP includes many veterans of the original EPC AOM report in 2001.
Following publication of that report, it took over four years to develop and approve new guidelines (2004).There were many controversies, including the right definition, the guideline regarding observation, first line antibiotics (AB), and dose. For the 2001 report, they were just beginning to get data on Prevnar. Now there are many more data on its efficacy as well as the role of viruses in OM. An important and final point to make is that AAP requested that AHRQ add recurrent AOM to the scope. This was a gap in the 2001 report.

Discussion of the Definition of AOM
The definition of AOM was something the research team wrestled with in the 2001 report.
The definitions proposed by the research team were distributed for the TEP's consideration (see attached file or insert as footnote). The team also wanted to know how the TEP would operationalize the definitions and what to do about studies that provide little or no information on how they defined AOM for enrollment.

Rosenfeld said that part of accepting a definition is whether it is more inclusive or exclusive. . For our purposes, we want to err on the side of a few false positives rather than avoiding all false negatives. Thus a tight definition is better.

Three criteria should be considered individually: Time course, rapidity of onset, middle ear effusion (MEE).
But having said that, we can't restrict the literature search to those that meet all three criteria. We can evaluate a study's quality based on how closely it adheres to our definition, but don't exclude studies on this basis. Paul rephrased: "So basically include any studies but conduct a sensitivity analysis that considers the number of criteria adhered to."

Rosenfeld pointed out that a big problem is documenting MEE. How well is it documented? This is an overwhelming cause of false positives.

Lieberthal pointed out that a minimum criterion should be that authors define what THEY considered AOM

Shekelle asked if we want to be stricter regarding diagnosis questions, especially given that there is a gold standard diagnostic method, but be more inclusive and relaxed regarding treatment questions.

Kleinman responded that if our aim is to guide practice, we need to consider the implications for practice, especially in the inner city. Considering only AOM, in isolation, is fine, but if we are guiding practice, we need to consider the spectrum of otitis, and once we propose a definition, we need to consider the implications for other ME disease.

Ganiats said that an issue that came up last time (and was the subject of a minority report) was that studies that show the disease remits spontaneously did not have a good definition of AOM. The implication is that these spontaneous remissions didn't really have the disease in the first place. He proposed the possibility of dividing evidence by studies that fulfill two criteria vs.. studies that fulfill all 3.

Thus, basically the TEP agreed with the following approach: "…accept any study purporting to study AOM or ROM and compare the trial definition to our study definition, report that analysis, and attempt to analyze results by adherence to our study definition, if sufficient data are available" and sensitivity analysis based on definition quality.

KQ1. Validity of clinical symptoms…
What is the validity of clinical symptoms and otoscopic findings such as a bulging tympanic membrane to diagnose AOM? Do these clinical findings aid physicians in distinguishing AOM from OME?

a. What should be the gold standard? E.g. tympanocentesis for middle ear effusion (MEE), microbiologic agent isolation, rectal temperature as opposed to oral or axillary temperature, etc. **Rosenfeld stated there is no gold standard. He also stated that if a child had a tympanocentesis that showed an infectious agent but had no clinical symptoms, he would not call that AOM. Consensus by a panel of MDs would be the only gold standard. Someone suggested developing a composite gold standard (a set of criteria).**

Again, tympanometry (as well as acoustic reflectometry) are useful in research but not the doctor's office. Tympanometers used by general clinicians are not the same quality as those used in the research setting. Chonmaitree pointed out that the *studies* reviewed will have to have a definition of AOM and they may use tympanometry. Another issue is that instruments don't always work well in very young children, the most important group.

It was felt that it should be noted whether a study included tympanometry. The team noted they have already been noting this.

b. Which clinical symptoms and otoscopic findings are of particular interest that we should make every effort to report on, even if data are not available or already known to refute their use?

The discussion did not reach this level of detail.

c. Should any other diagnostic tests other than otoscopy be included in the review? E.g. tympanometry, acoustic reflectometry, oto-acoustic emissions, et cetera

The TEP agreed that clinical symptoms and otoscopic findings should be the focus. The focus should be on diagnostic criteria that must include MEE but differentiate AOM from OME. The TEP agreed that the review could include tympanometry for diagnosis

of MEE. The TEP did not feel acoustic reflectometry was worth evaluating; in particular published studies were lacking.

d. In a prior systematic review, the TEP for the otitis media with effusion (OME) panel decided that diagnosing MEE in a child with OME was different from diagnosing MEE in a child with AOM, so we did not use AOM MEE studies for the OME review of MEE diagnosis. Should the same logic apply to this AOM review if MEE is decided by the TEP to be an integral component of diagnosing AOM?

The TEP did not discuss this issue.

e. Other specifications?

None were discussed.

KQ2. What organisms (bacterial and viral) are associated with otitis media since the introduction of PNC7?

What are the patterns of antimicrobial resistance since the introduction of PNC7?

- New infections
- Recurrent infections

a. Should KQ2 include the effectiveness of the vaccine for preventing AOM?
In general, the TEP felt we should address vaccine effectiveness *only* if time is available.

b. Are "New infections" initial episodes of AOM?
No, they are generally regarded as episodes of AOM that occur after some elapsed period of time since the previous episode. The question is whether the bacteriology of the "new" infection is distinct from the previous infection.

c. Are "Recurrent infections" episodes of ROM? If so, which episode?
The TEP seemed to want to re-phrase "New infections" and "Recurrent infections" to something related to the "antibiotic milieu," i.e., whether or not the child had ever been exposed to an antibiotic, whether for AOM or any other condition. Some TEP members also expressed the desire to retain the concept of recurrent infection with the addition of *persistent* AOM and AOM *relapse*. See KQ4 for further discussion.

d. If possible, we will analyze by antibiotic use pattern in the trial region. Are there any other factors apart from PNC7 and antibiotic use patterns that should be included in the analysis?
This issue was not discussed.

e. Other specifications?
See "c".

KQ3. What is the comparative effectiveness of different treatment options (defined below) for treating AOM in average risk children ages <2 years, ages 2 years to <5years and ages ≥ 5 years?

Treatment options include but not limited to:

- Amoxicillin (including high dose versus low dose)
- Amox-clav (including high dose versus low dose)
- Cephalosporins (e.g. ceftriaxone, cefdinir, cefixime)
- "Wait and see approach"
- Placebo
- Duration of treatment

Outcomes to consider but not limited to:

- Parent satisfaction
- Duration of symptoms/illness
- Treatment failure, mastoiditis, bacteremia, clinical cure, bacteriologic cure
- Disease recurrence

a. Any other antibiotics should be included that we should make every effort to report on, even if data are not available or already known to refute their use??
The TEP was amenable to adding any FDA-approved antibiotic (especially erythromycin).

b. What is the definition of the "Wait and see approach"? e.g. AAP/AAFP Guidelines, Dutch guidelines, et cetera?
Use the AAP/AAFP AOM guideline for observational treatment. Rosenfeld felt most of the new AOM studies would be on this issue: the "delayed treatment" approach, which is distinct from the "wait and see" approach. The delayed treatment approach is in contrast to immediate treatment.

c. Should analgesics be separated as an intervention? Oral versus topical?
Initially there seemed to be a divergence of opinion, but the TEP seemed to be interested in studying analgesics.

d. Are we interested in dual treatment? E.g. antibiotic plus analgesic?
This issue was not addressed.

e. What specific durations of treatment are of interest that we should make every effort to report on, even if data are not available or already known to refute their use?
Rosenfeld believes no new studies of significance on short-duration therapy have been published since the Kozyrskyj (1998) publication of their systematic review. He treats children <2 years old for 7-10 days and children >5 years old for 3-5 days. He stated that for 2-5 years of age, some controversy exists.

f. Any other outcomes that we should make every effort to report on, even if data are not available?
Lieberthal stated he was interested in bacteriologic as well as clinical outcomes. Ganiats stated that clinical outcomes were more important, especially for guideline development.

Kleinman brought up the need for quality of life and functional status outcomes.

Cost outcomes were also discussed, including days of school or daycare missed and days of parental work missed. Landry noted that parents need to pay for daycare regardless of whether child attends, which makes cost an even more compelling issue.

g. What is the definition of disease recurrence? E.g. is this in relation to the otitis-prone child? The TEP agreed that recurrence is defined as AOM relapse within 30 days. Kleinman recommended that we gather specific time to relapse information, as most relapse may actually occur much earlier than 30 days (might be worth assessing whether it should be 15 days).

KQ4. What is the comparative effectiveness of different management options for recurrent otitis media?

Management options include but not limited to:

- Amox-clav
- Cephalosporins (e.g. ceftriaxone, cefuroxime)
- Quinolones
- Antibiotic prophylaxis

Outcomes to consider but not limited to:

- Parent satisfaction
- Duration of symptoms/illness
- Treatment failure, mastoiditis, bacteremia/Cure rates

a. Same questions as for KQ3.

In essence "yes;" however, the major issue is discussed in "c".

b. Are there any procedural interventions we should include that we should make every effort to report on, even if data are not available or already known to refute their use?

Tympanostomy tubes were mentioned. Rosenfeld stated that antibiotic prophylaxis is already known not to be effective, though Kleinman stated the opposite later in the discussion.

c. KQ4 currently addresses ROM? What definitions of chronic suppurative and/or persistent OM should be used to differentiate from ROM?

Lieberthal stated that the AAP intended KQ4 to address ROM, i.e. the otitis-prone child. However, many of the TEP members voiced uncertainty over the present usefulness of the terms ROM and otitis prone The TEP seemed to agree that KQ4 should address ROM but also *acute recurrence* of AOM within 30-60 days, i.e. *persistent* AOM or AOM relapse (Rosenfeld and Chonmaitree mentioned that Dagan and Arguedas are doing interesting studies on persistent AOM in South America).

Coker noted that the definition and distinction (between recurrent, persistent/relapse, and otitis prone) has not been clear among the studies they have reviewed so far. Shekelle recommended determining how big a problem it would pose in analyzing the literature and then going back to the TEP. (Kleinman noted that OME and AOM can present in the same kids, that management may differ when kids show up acutely. He said this is something they need to consider).

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KQ5: What is the evidence that the comparative effectiveness of different treatment options in KQ #3 differs in subpopulations of patients?

Subpopulations to include (but not limited to):

- Bilateral disease
- Comorbidities (e.g. asthma –will need to define further)
- Age groups (e.g., <1 month, 1-<2 months, 2-<6 mos, 6mos-<2 years, 2-5 years)
- Race/Ethnicity
- Day care attendance

a. What are other comorbidities in addition to asthma? Will any subpopulations be excluded such as those with craniofacial anomalies, immunodeficiencies, genetic disorders, et cetera? The TEP felt that most studies would exclude these comorbidities but did not state if we should a priori exclude studies on certain populations. They recommended referring to the Guidelines. [Bilateral disease was also mentioned as a comorbidity but it was unclear whether it should be excluded]

b. Are the proposed age intervals appropriate?
Rosenfeld proposed not studying <6 month olds.

c. What is meant by race and ethnicity? Will we analyze the interaction?
This issue was not discussed.

d. What are thresholds of daycare attendance the review should focus upon?
This issue was not discussed.

e. What additional subpopulations should be considered for KQ5? E.g., AOM with perforation or otorrhea versus no perforation or no otorrhea, et cetera?
Rosenfeld proposed analyzing by severity rating, e.g., the AAP/AAFP AOM Guideline severity rating.

f. Should a similar subpopulation analysis be done for KQ4 on ROM?
This issue was not discussed.

KQ6. What are the comparative harms of different treatment options?

Outcomes to consider (but not limited to):

- Antibiotic resistance
- Diarrhea/vomiting

a. What other harm outcomes should be included that we should make every effort to report on, even if data are not available or are already known not to be significant issues?
Shekelle explained the research team would list all harms reported but wondered if we need to consider any in particular. Kleinman wondered if we need to consider the harms of withholding treatment (e.g., increased risk of suppurative complications);

however this question was assessed in the first report. Only one study, a Dutch study, assessed it and it was done poorly.

Responses to Query Regarding Nasopharyngeal Swabs as Proxy for Ear Fluid
November 18, 2008

Lieberthal: NP swabs do not accurately identify the organisms in the middle ear. They may reflect organisms that the child carries and may or may not be the same as the organism causing AOM.

Studies have looked at both clinical cure and bacteriologic cure. If there is bacteriologic cure there is more certainty of clinical cure. However clinical cure-the practical end point for providers-can occur without having sterilized the middle ear at the time of follow-up.

Rosenfeld:

1. Nasopharyngeal (NP) culture: This has been used as a surrogate for middle ear (ME) aspirates in some studies but the accuracy is poor. A negative NP culture for a particular pathogen has good predictive value for a negative ME culture for the same pathogen, but the value of a positive NP culture is no better than a coin toss at predicting ME results. The main value of NP cultures in OM studies has been to track changes in susceptibility of host organisms after antimicrobial therapy or vaccination.
2. Bacteriologic vs.. clinical efficacy: The primary endpoint relevant to clinical decision making for AOM is clinical response, since about 70-80% of bacteriologic "failures" are nonetheless clinical "successes." The value of bacteriologic endpoints is in assessing new antimicrobials, or in teasing out subtle differences in comparative efficacy of existing antimicrobials for specific pathogens. We can certainly use this as a secondary endpoint if enough data exist, but it takes a distant second place to clinical efficacy for everyday management decisions.

Kleinman: I agree with Allan and would add that I am unaware of evidence that suggests that N-P eradication improves long or short term course.

Goessler: I also concur.

Casselbrant: I have no further comments.

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AOM TEP Meeting 2 Summary

TEP Discussants: Tasnee Chonmaitree; Katherine Finn Davis; Diane Sabo; Allan Lieberthal; Richard Rosenfeld; Pauline Thomas
AAP Staff Representative: Caryn Davidson
AHRQ Representative: Lt. Commander Carmen Kelly
SCEPC Staff Discussants: Linda Chan; Tumaini Coker; Mary Ann Limbos; Sydne Newberry; Paul Shekelle; Glenn Takata

Date/Time: Tuesday 3/10/2009, 11:30 am to 12:40 pm

1. **Project Update**:
   a. KQ1 Diagnosis: Identified recent systematic review and updated search. Screening titles.
   b. KQ2 Microbiology: Identified 70 articles. Conducted second level of screening.
   c. KQ3-6 Treatment and adverse effects: Screening and abstraction complete for original search and updated search; beginning pooling and data analysis.

2. **Additional feedback on the list of articles included for treatment and adverse event questions: Anything we've omitted?**
   The panel was asked to review the lists of articles reviewed for the treatment questions to let us know if we have missed anything important. The searches date from 1998 (when the last AHRQ systematic review ended, allowing for some overlap, although older articles are being considered for recurrent/persistent OM). The search strategy builds on that of THE 2001 REPORT with the addition of new terms, e.g., watchful waiting. PubMed and Web of Science were searched for the update, as well as reference mining systematic reviews and accepted articles.

   Dr. Chonmaitree noted that she had identified several more articles (including back-to-back articles by Hoberman in the January 2009 PID) in addition to a couple by her group (McCormick et al) that seemed to be missing from our lists. The panel suggested we try to determine how we had missed these articles.[1] [Dr. Chonmaitree had also sent an email the previous day regarding Hotomi, Cates, and two Vernacchio articles.]

3. **Including Observational Studies?**
   We also presented the strategy of including observational studies on treatment issues only when controlled trial data were lacking as recommended by current systematic review guidelines. Paul Shekelle clarified that we are focusing on clinical trial comparisons of antibiotics and other treatments. We're now in the pooling stage. If we find cells with no data, we will look to observational studies or we will ask the panel if observational studies will be of use in this analysis. The panel briefly reviewed the frequency table.

[1] It turns out the McCormick et al article pertaining to treatment was identified but then inadvertently excluded when duplicate articles were being eliminated from a list of titles.

There was a discussion of whether to examine each antibiotic separately or to pool. Dr. Rosenfeld suggested doing two sets of analysis: 1) drug a vs.. drug b (specific agents) and 2) combine all antibiotics, i.e. drug A vs.. all comparators. For the immediate vs.. deferred question, it is all right to pool different antibiotics for that comparison. Also, for the primary empiric decision - to treat or not – it is all right to pool. But when looking at treatment failures, we want to look separately.

4. Overall Scope

Finally, we asked for comments on the overall scope for this review: are we missing anything crucial? There was general agreement that it was a good summary.

Clarification was requested for the difference between practitioner and examiner in influencing factors. Several participants noted that sometimes the examiner in a study is not the patient's practitioner, and sometimes the examiner is blinded, whereas the practitioner may not be blinded.

It was suggested we add the cost of antibiotics to the cost of outcomes, although there was discussion about the recent development that Walmart now carries an inexpensive generic amoxicillin-clavulanate. Someone mentioned that the amoxicillin-clavulanate ratio is lower in the generics, which can result in diarrhea.

Should we include cholesteatoma development as an otological complication? Other panel members felt the incidence was too low and the onset time too long. The term "ear fullness" needs to be corrected.

As a result of this discussion, the research team will provide definitions for each of the scope items.

Other Business

AOM Definition. Are we devising a definition of AOM? Paul Shekelle noted that we're documenting elements of definitions used in articles for potential sensitivity analysis. More restrictive definitions result in smaller numbers of trials.

Timeline. The panel asked about the timeline for the report (draft due week of April 12). The AAP expressed interest in having the report available for a June 30 meeting of the AAP AOM Guideline panel. Although the report may not be final by then, the panel should at least have the information they need.

Considering generalizability of findings. Richard Rosenfeld recommended that the generalizability of results needs to be emphasized in the write-up. For example, with respect to pneumatic otoscopy, the concern is that it has to be done with fairly well trained otoscopists and that the validity in trials is not applicable to the average primary care physician, who may be more skilled at other diagnostic techniques. It will be useful to document and comment on the circumstances to which the findings apply with respect to characteristics of the examiner. Also, with regard to the concept of watchful waiting/deferred antibiotic observation and management

options, there is concern with the types of children involved in the clinical trials of this treatment option and the potentially poor quality of studies. The research team was advised to be attentive to studies that propose a reductionist approach: we need to define which patients these results can be extrapolated to. He emphasized that generalizability may be even more important than effect size.

Report format. A question was raised about the report's format. The report will include text as well as evidence tables and flow charts. The link was sent to the panel.

Reporting effect sizes as risk ratios or odds ratios? The question was raised about how effect sizes were expressed in the first report. Dr. Shekelle responded that we mostly report RRs, which can be converted to the number needed to treat (NNT) or the number needed to harm. RR provides relative risk. According to Dr. Rosenfeld, Cochrane prefers to use odds ratios. Dr. Shekelle said that RRs are preferred, and Linda Chan noted that one can be converted to the other. Dr. Rosenfeld reported that risk ratios result in small differences in NNT, and that it is sometimes helpful to see absolute differences as well as relative differences. Dr. Takata noted that THE 2001 REPORT reported rate differences. Dr. Shekelle assured the panel that we can be flexible, but that we tend to avoid reporting odds ratios because of the tendency to overestimate what they mean.

Reporting failure rates or success rates*?* Dr. Rosenfeld asked whether we would report failure rates or success rates. Cochrane reports failure rates. The problem is that with self-limiting conditions, failure rates are fairly small. Doubling still produces a small failure rate, so it is deceptive. Reporting success rates may be preferable if one is anticipating a robust success rate. Dr. Lieberthal noted that the first AOM report used NNT. For the clinician, NNT is one of the easier statistics to understand. Also, success rate is preferable for clinicians, as differences are not inflated. There was general agreement that success rates are simpler to understand. Dr. Takata suggested that maybe this distinction of reporting failure versus success should be made in the guideline discussions. The front-line clinician is more likely to read the guideline than the technical report.

Zone of Indifference. Dr. Chan then raised the issue of the zone of indifference. *A difference may be statistically significant but not clinically important.* There are confidence intervals for failure rates as well as success rates. D r. Rosenfeld agreed that the zone of indifference is an important concept, equally so for adverse events, especially since AOM is a self-limiting disease. Thus adverse effects (AEs) may be the driving force in many treatment decisions. Much harm is done with well-meaning therapies and not enough has been done in previous reports to highlight AEs of treatment. Some discussion ensued about the degree to which AOM is self-limiting and the risk for severe complications like mastoiditis. (Dr. Rosenfeld cited a recent article by Thompson out of the UK in Pediatrics that showed a very low incidence of acute mastoiditis in AOM.) Regardless, the panel wants to see the same clarity and thoroughness in AE reporting as in the reporting of disease-related outcomes.

Definition of persistent OM: AOM or OME? Dr. Davis asked whether persistent OM (as defined in the scope) refers to AOM or OME. Dr. Takata said it is AOM and that we will clarify

the definitions. Dr. Davis also noted that the definition should include middle ear *inflammation,* not *infection* (however Pichicero's definition of "persistent" specifies infection, not inflammation).

This discussion raised questions about the definitions of recurrence and persistence. Is persistence relapse within a month or failure of symptoms to resolve within a month: These are two different conditions. Dr. Thomas asked "At what point is something a new episode as opposed to a continuation of the original episode?" Dr. Chonmaitree noted that Pichicero has apparently studied this question. In fact, it is his definition (from Pediatric Infectious Disease (2000) that we have adopted (the term is Persistent Otitis Media/Relapse of Acute Otitis Media)[2]. Dr. Lieberthal noted that recurrence would be characterized by clear evidence of prior resolution.

Wrap-up

We may be contacting the panel before the report draft is sent out, for resolution of the need for including observational studies.

[2] Pichicero ME. Recurrent and persistent otitis media. Pediatr Infect Dis J 2000;19:911-916

APPENDIX G. Summary Tables for Studies Included in Comparisons

Table G.1 Comparisons for AOM1 Key Question 3 and AOM2 Key Question 3 on Antibiotics versus No Antibiotics

The general principle agreed upon was to separate amoxicillin-clavulanate, penicillin G, penicillin V, erythromycin estolate, triple sulfonamide, and erythromycin estolate-triple sulfonamide from ampicillin/amoxicillin and each other. Penicillin G is oxidized in the stomach and not well absorbed. Penicillin V does not cover Haemophilus influenza well. Erythromycin estolate is quite different from the other antibiotics. Triple sulfonamide is no longer in common usage.

Treatment A	Treatment B	# Studies in AOM1	# Studies in AOM2	Total
Ampicillin or amoxicillin	Placebo	5	2	**7**
Amoxicillin-clavulanate	Placebo	1		
Penicillin G plus sulfisoxazole	Placebo	1		
Penicillin V	Placebo	2		
Erythromycin estolate	Placebo	1		
Triple sulfonamide	Placebo	1		
Erythromycin estolate-triple sulfonamide	Placebo	1		

Table G.2 Comparisons for AOM1 Key Question 4a and AOM2 Key Question 3 on Amoxicillin or Trimethoprim-Sulfamethoxazole versus Other Antibiotics

The general principle agreed upon was to compare by individual antibiotic rather than by antibiotic class, spectrum, or pharmacokinetics.

Treatment A	Treatment B	# Studies in AOM1	# Studies in AOM2	Total
Amoxicillin or ampicillin	Penicillin	**3**		
Amoxicillin or ampicillin	Amoxicillin-clavulanate	0		
Amoxicillin or ampicillin	Cephalexin	2		

Amoxicillin or ampicillin	Cephradine	1		
Amoxicillin or ampicillin	Cefuroxime axetil	2		
Amoxicillin or ampicillin	Cefaclor	**5**		
Amoxicillin or ampicillin	Loracarbef	1		
Amoxicillin or ampicillin	Cefixime	**5**		
Amoxicillin or ampicillin	Ceftriaxone	3	1	**4**
Amoxicillin or ampicillin	Erythromycin estolate	2		
Amoxicillin or ampicillin	Clarithromycin	2		
Amoxicillin or ampicillin	Clindamycin	1		
Amoxicillin or ampicillin	Penicillin V and sulfisoxazole	2		
Amoxicillin or ampicillin	Triple sulfonamide	1		
Amoxicillin or ampicillin	Penicillin G plus triple sulfonamide	1		
Amoxicillin or ampicillin	Erythromycin ethylsuccinate-sulfisoxazole	1		
Amoxicillin or ampicillin	Oxytetracycline and procaine penicillin plus benzathine penicillin G injection plus sulfisoxazole	1		

Treatment A	**Treatment B**	**# Studies in AOM1**	**# Studies in AOM2**	**Total**
Trimethoprim-sulfamethoxazole	Amoxicillin-clavulanate	1		
Trimethoprim-sulfamethoxazole	Cephalexin	0		
Trimethoprim-sulfamethoxazole	Cephradine	0		
Trimethoprim-sulfamethoxazole	Cefuroxime axetil	0		

Trimethoprim-sulfamethoxazole	Cefaclor	**3**		
Trimethoprim-sulfamethoxazole	Loracarbef	0		
Trimethoprim-sulfamethoxazole	Cefixime	0		
Trimethoprim-sulfamethoxazole	Ceftriaxone	1		
Trimethoprim-sulfamethoxazole	Erythromycin estolate	0		
Trimethoprim-sulfamethoxazole	Erythromycin ethylsuccinate	0		
Trimethoprim-sulfamethoxazole	Clarithromycin	0		
Trimethoprim-sulfamethoxazole	Clindamycin	0		
Trimethoprim-sulfamethoxazole	Penicillin-sulfasoxazole	0		
Trimethoprim-sulfamethoxazole	Erythromycin ethylsuccinate-sulfisoxazole	0		
Trimethoprim-sulfamethoxazole	Erythromycin ethylsuccinate-acetyl sulfafurazole	0		

Table G.3 Comparisons for AOM1 Key Question 4e and AOM2 Key Question 3 on Short-term versus Long-term Antibiotic Therapy

The general principle agreed upon was to compare by individual antibiotic stratified by therapy duration, <5days versus 5days.

Treatment A	**Treatment B**	**# Studies in AOM1**	**# Studies in AOM2**	**Total**
Amoxicillin (<5d)	amoxicillin (7-10d)	**3**		
Penicillin V (<5d)	penicillin V (7-10d)	1		
Penicillin V (5d, either 25mg/kg/d or 50mg/kg/d)	penicillin V (7-10d)	1 (two 5-day arms)		
Benthazine penicillin G/procaine penicillin G/potassium penicillin G (Bicillin) (1 dose)	tetracycline (7-10d)	1		

Benthazine penicillin G/procaine penicillin G/potassium penicillin G (Bicillin) (1 dose)	benthazine penicillin/procaine penicilliln G/potassium penicillin G (Bicillin) (1 dose) plus triple sulfonamide (7d)	2		
Amoxicillin-clavulanate (5d, either 45mg/kg/d or 80 mg/kg/d)	amoxicillin-clavulanate (7-10d, either 40mg/kg/d or 45mg/kg/d or 80mg/kg/d)	2		
Cefaclor (<5d)	cefaclor (7-10d)	1		
Cefaclor (5d)	amoxicillin (7-10d)	1		
Cefaclor (5d)	cefaclor (7-10d)	1		
Cefuroxime axetil (5d)	amoxicillin-clavulanate (7-10d)	1	1	2
Cefuroxime axetil (5d)	cefixime (7-10d)	1		
Cefpodoxime proxetil (5d)	amoxicillin-clavulanate (7-10d)	2		
Cefpodoxime proxetil (5d)	cefaclor (7-10d)	1		
Cefpodoxime proxetil (5d)	cefixime (7-10d)	1		
Cefprozil (5d)	cefprozil (7-10d)	1		
Ceftibuten (5d)	ceftibuten (10d)	1		
Ceftriaxone (1 dose)	amoxicillin (7-10d)	**3**		
Ceftriaxone (1 dose)	amoxicillin-clavulanate (7-10d)	2	3	**5**
Ceftriaxone (1 dose)	cefaclor (7-10d)	1		
Ceftriaxone (1 dose)	cefuroxime axetil (7-10d)	1		
Ceftriaxone (1 dose)	trimethroprim-sulfamethoxazole (7-10d)	1		
Azithromycin (<5d)	amoxicillin-clavulanate (7-10d, either 40mg/kg/d or 45mg/kg/d)	5	4	**9**
Azithromycin (<5d)	cefaclor (7-10d)	2	2	**4**
Azithromycin (<5d)	clarithromycin (7-10d)	1		

Azithromycin (5d)	amoxicillin-clavulanate (7-10d)	**3**		
Cefdinir (5d)	amoxicillin-clavulanate (10d)	0	2	2
Cefprozil (10d)	cefdinir (5d)	0	1	1
Cefpodoxime (5d)	cefpodoxime (10d)	0	1	1

Table G.4 Comparisons for AOM2 Key Question 3 But Not in AOM1

(i) For Uncomplicated Acute Otitis Media

Treatment A	Treatment B	# Studies in AOM1	# Studies in AOM2	Total
Amoxicillin-clavulanate	Amoxicillin Sulbactam	0	1	1
Amoxicillin-clavulanate	Cefaclor	0	1	1
Amoxicillin-clavulanate	Cefdinir: 14 mg	0	2	2
Amoxicillin-clavulanate	Cefdinir: 7 mg	0	2	2
Amoxicillin-clavulanate	Cefprozil	0	1	1
Amoxicillin-clavulanate	Ciprodex drops	0	1	1
Amoxicillin-clavulanate: 40 mg 10 d	Amoxicillin-clavulanate: 80 mg 8 d	0	1	1
Amoxicillin-clavulanate: 40/10 mg	Amoxicillin-clavulanate: 45/6.4 mg	0	1	1
Amoxicillin-clavulanate: 45/6.4 mg 10 d	Amoxicillin-clavulanate: 90/6.4 mg 10 d	0	1	1
Amoxicillin-clavulanate: 80 mg	Cefuroxime	0	1	1
Amoxicillin	Azithromycin	0	1	1
Amoxicillin	Prescription to Hold	0	2	2
Amoxicillin	Wait and see	0	1	1
Amoxicillin/NHED	Amoxicillin/Topical anesthetic nos	0	1	1
Amoxicillin/NHED	NHED	0	1	1
Amoxicillin/NHED	Topical anesthetic nos	0	1	1
Amoxicillin/Topical anesthetic nos	NHED	0	1	1
Amoxicillin/Topical anesthetic nos	Topical anesthetic nos	0	1	1
Amoxicillin: 40-45 mg	Amoxicillin: 80-90 mg	0	1	1
Amoxicillin: 80 mg	Amoxicillin: 80 mg/Fenspiride	0	1	1

Antibiotic	Prescription to Hold	0	1	1
Antihistamine/Ceftriaxone	Antihistamine/Ceftriaxone/Prednisolone	0	1	1
Antihistamine/Ceftriaxone	Ceftriaxone	0	1	1
Antihistamine/Ceftriaxone	Ceftriaxone/Prednisolone	0	1	1
Antihistamine/Ceftriaxone/Prednisolone	Ceftriaxone	0	1	1
Antihistamine/Ceftriaxone/Prednisolone	Ceftriaxone/Prednisolone	0	1	1
Aqueous lidocaine	Placebo	0	1	1
Azithromycin	Cefdinir	0	1	1
Azithromycin	Ceftriaxone	0	1	1
Cefaclor	Cefpodoxime	0	1	1
Cefaclor	Cefprozil	0	1	1
Cefaclor	Cefuroxime	0	1	1
Cefdinir: 14 mg	Cefdinir: 7 mg	0	2	2
Ceftriaxone	Ceftriaxone/Prednisolone	0	1	1
Ciprofloxacin otic 3%	Ciprodex drops	0	1	1
Ciprodex drops	Ofloxacin drops	0	1	1
Homeopathic NOS	Placebo	0	1	1
NHED	Topical anesthetic nos	0	1	1
Otikon drops	Topical anesthetic nos	0	1	1
Phenoxymethylpenicilin	Wait and see	0	1	1
Prescription to Hold	Wait and see	0	1	1

(ii) For Treatment of Acute Otitis Media in Recurrent Otitis Media

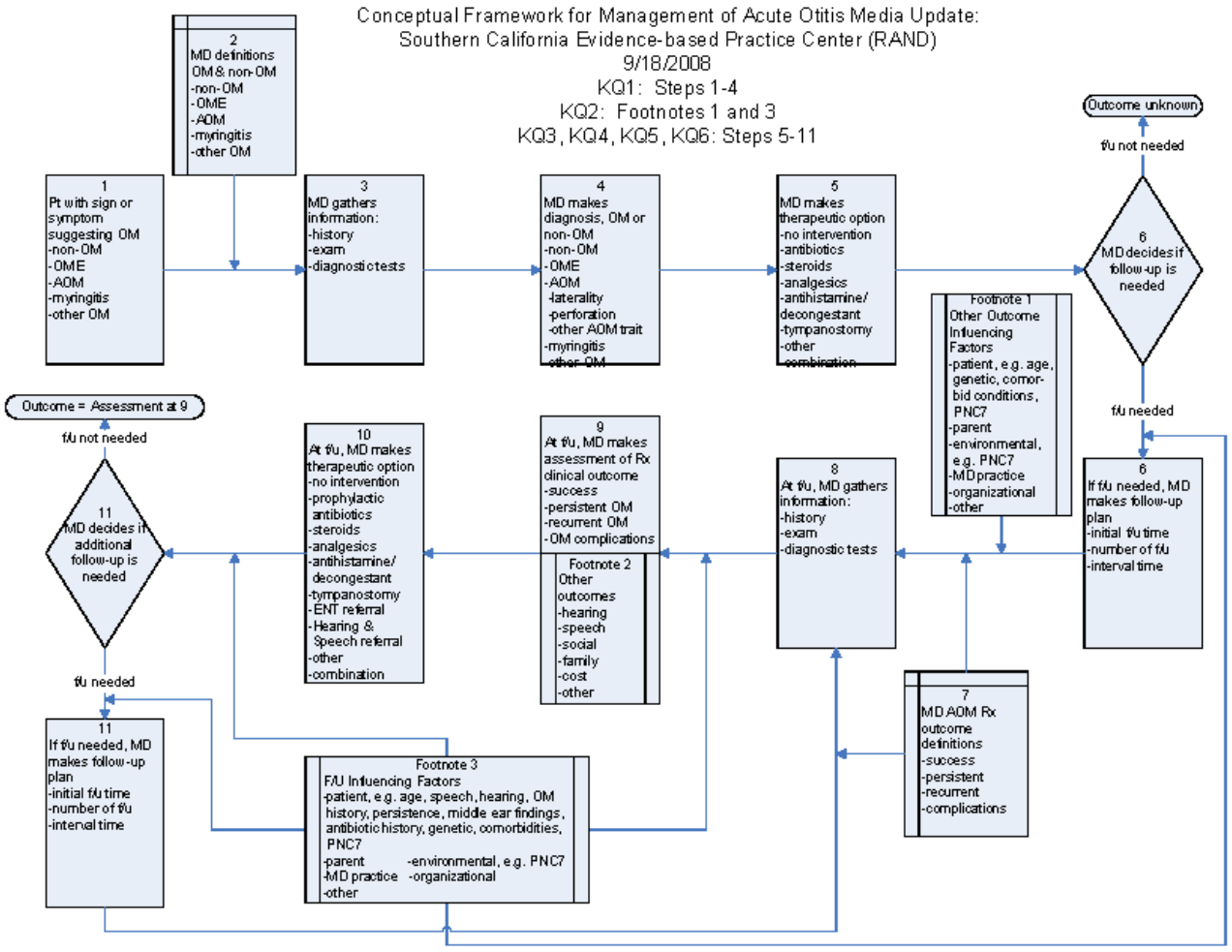
Treatment A	Treatment B	# Studies in AOM1	# Studies in AOM2	Total
Amoxicillin-clavulanate	Azithromycin	0	1	1
Amoxicillin-clavulanate	Gatifloxacin	0	2	2
Amoxicillin-clavulanate	Levofloxacin	0	1	1

(iii) For Prevention of Acute Otitis Media in Recurrent Otitis Media

Treatment A	Treatment B	# Studies	# Studies	Total

		in AOM1	in AOM2	
Adenoidectomy	Adenoidectomy and/or tonsillectomy	0	1	1
Adenoidectomy	Placebo	0	2	2
Adenoidectomy	Sulfa alone	0	1	1
Adenoidectomy and/or tonsillectomy	Placebo	0	1	1
Adenoidectomy/Tympanostomy tubes	Tympanostomy tubes	0	1	1
Amoxicillin	Azithromycin	0	1	1
Amoxicillin	Placebo	0	1	1
Amoxicillin	Sulfa alone	0	1	1
Ceftibuten: 9 mg - 10 days	Ceftibuten: 9 mg - 5 days	0	1	1
Probiotic bacteria	Placebo	0	1	1
Sulfa alone	Placebo	0	2	2

Appendix H. Conceptual Framework for the Report



Appendix I. Summaries of Systematic Reviews Included in Analyses

Appendix I. Summaries of Systematic Reviews Included in Analyses

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 9/25/2008

The document is a summary of the systematic reviews that have relevance to any of the key questions in the present Workplan. It consists of 3 parts: Part 1 contains the characteristics of the systematic reviews and the highlighted conclusions; Part 2 contains our assessment of the quality of the systematic reviews using AMSTAR quality indicators; and Part 3 provides representative quantitative outcomes of the comparisons contained in the systematic reviews. Finally, we include references and the AMSTAR instrument.

We searched Medline and the Cochrane review database from 1998 through the present and identified reviews that have relevance to any of the key questions for the AOM update. We also included one review from 1994.

Based on the general conclusions of these reviews, we would say that we are well justified in re-doing systematic reviews for KQ3-KQ6. In addition, since we did not identify any systematic review relevant to KQ1 or KQ2, those must be addressed, as well.

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 9/25/2008

Part 1. Relevance to Management of Acute Otitis Media Update[1]

Author (year)	Content category by KQ	Review focus	Databases and included dates	Study design, inclusion criteria	Target population	Setting	Outcomes	Cost analysis	Number of trials, participants, and comparisons	Author's highlight conclusion
Marcy (2001)[2] **(initial AHRQ Management of AOM systematic review)**	KQ3 KQ5 KQ6	natural hx ab *vs* no ab ab regimen	CENTRAL (TCL, through Mar 1999), MEDLINE (1966-Mar 1999), HlthSTAR (1975-Mar 1999), IPAInternational Pharmaceutical Abstracts (1970-Mar 1999), CINAHL (1982-Mar 1999), BIOSIS (1970-Mar 1999), and EMBASE (1980-Mar 1999); hand search	RCT; Cohort, for natural hx	AOM 4wk-18y exclude patients with immunodeficiencies or craniofacial deficiencies, including cleft palate	Any setting	Clinical failure; adverse effects	No	80 trials total: 74 addressed ab *vs* no ab & ab regimen See Comparison Table for specific trial and participant numbers 7 primary comparisons & 16 analyses reported (only analyses with ≥3 trials were conducted)	Rx with amp/amox ↓ clinical failure by 12% ***vs*** no ab; ab regimen outcomes not different; cefixime & amoxillin-clavulanate ↑ adverse effects

[1] For quality score of each systematic review, see next table.
[2] Also, reference Takata, Chan, Shekelle, et al. (2001)

Appendix I. Summaries of Systematic Reviews Included in Analyses

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 9/25/2008

Author (year)	Content category by KQ	Review focus	Databases and included dates	Study design, inclusion criteria	Target population	Setting	Outcomes	Cost analysis	Number of trials, participants, and comparisons	Author's highlight conclusion
Rosenfeld (1994)	KQ3 KQ5	ab *vs* no ab ab regimen	MEDLINE (Jan 1966-Jun 1992); Current Contents (3 months through Jun 29, 1992); hand search	RCT	AOM 4wk-18y exclude myrin-gotomy, OM not described, mostly treat-ment failure or otitis prone	Not specified a priori	Clinical response, MEE presence	No	33 trials total See Comparison Table for specific trial and participant numbers	ab effect modest but significant; no significant difference between ab regimens studied
Damoiseaux (1998)	KQ3 KQ5	ab *vs* no ab	MEDLINE (1966-Jan 1997); EMBASE (1974-Jan 1997); hand search	RCT	AOM <2 years old	Not specified a priori	Clinical resolution within 7d	No	4 trials 416 children 1 comparison & analysis	No signifi-cant dif-ference be-tween ab and no ab in <2y olds
Kozyrskyj (2000)	KQ3 KQ5 KQ6	ab <7 d *vs* ≥7d	MEDLINE (Jan 1966-Jul 1997); EMBASE (Jan 1966-Jul 1997); Science Citation Index (Mar 1998);	RCT	AOM 4wk-18y Subgroups: ab ≤2d; oral short-acting ab; oral azithromycin;	Not specified a priori	Clinical resolution 31d & 1-3m; relapse; recurrence	No	32 trials total See Comparison Table for specific trial and participant numbers	ab 5d→ effective Rx for AOM

Appendix I. Summaries of Systematic Reviews Included in Analyses

Author (year)	Content category by KQ	Review focus	Databases and included dates	Study design, inclusion criteria	Target population	Setting	Outcomes	Cost analysis	Number of trials, participants, and comparisons	Author's highlight conclusion
			Current Contents (Mar 1998); hand search		intramuscular ceftriaxone; <2 years old; perforated TM				45 primary comparisons & 54 analyses (several utilizing 1 trial)	
Glasziou (2004)	KQ3 KQ6	ab *vs* no ab	CENTRAL (1966-Jan 2000; TCL, issue 1, 2003); Current Contents (1966- Jan 2000); Index Medicus (1958-1965); MEDLINE (Jan 2000-Mar 2003); EMBASE (Jan 1990-Mar 2003); hand search	RCT	AOM Children, age not specified	Any setting	Severity and duration of pain; mid- to long-term hearing problems; adverse effects; recurrent attacks	No	8 trials total See Comparison Table for specific trial and participant numbers 1 comparison & 6 analyses	ab of small benefit for AOM Rx
Foxlee (2006)	KQ3	topical analgesia	CENTRAL (TCL, issue 2, 2006); MEDLINE (1966-May 2006);	RCT or quasi-RCT	AOM without perforation in Adults and children Subgroups:	Primary care setting	Pain severity and duration; parental satisfaction	No	4 trials total See Comparison Table for specific trial	evidence insufficient to make conclusions on topical

Appendix I. Summaries of Systematic Reviews Included in Analyses

Author (year)	Content category by KQ	Review focus	Databases and included dates	Study design, inclusion criteria	Target population	Setting	Outcomes	Cost analysis	Number of trials, participants, and comparisons	Author's highlight conclusion
			EMBASE (1990-Dec 2005); LILACS (1982-Sep 2005); hand search		<24mws≥24m -<18y *vs*≥18y; topical analge-sic type; concurrent ab use exclude perforation		; days missed from school or work; adverse events		and participant numbers	analgesia effectiveness
Rovers (2006)	KQ3 KQ5 KQ6	ab *vs* no ab	CENTRAL; PubMed; EMBASE (dates not specified)	RCT	AOM 0-12 years Subgroups: <2y *vs* ≥2y; bilateral AOM; otorrhoea	Not specified a priori	Pain &/or fever 3-7d	No	6 trials total [3,4] (10 trials identified & 6 investigators agreed to share data) 1 comparison & 21 analyses	ab beneficial for <2 year old with bilat AOM & AOM with otorrhea See Comparison Table for specific trial and participant numbers

[3] individual patient data meta-analyses
[4] Ten trials identified; investigators of only six of the trials agreed to share their data.

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 9/25/2008

Author (year)	Content category by KQ	Review focus	Databases and included dates	Study design, inclusion criteria	Target population	Setting	Outcomes	Cost analysis	Number of trials, participants, and comparisons	Author's highlight conclusion
Spurling (2007)	KQ3	Delayed (>48 hrs) ab **vs** immediate ab	CENTRAL (TCL, issue 1, 2004; TCL, issue 4, 2006); MEDLINE (Jan 1966-Jan 2007); EMBASE (1990-Jan 2007); Current Contents (1998-Jan 2007)	RCT	Respiratory tract infections All ages (For identified AOM studies 6m-12y)	Not specified a priori	Clinical outcomes; ab use; patient satis-faction; health-seek-ing beha-viors; alter-native thera-pies (For identified AOM studies pain, malaise, and fever)	No	reported 2 trials total for AOM in children See Comparison Table for specific trial and participant numbers 3 comparisons & 9 analyses (all utilizing 1 trial)	immediate ab→ improved pain and malaise on day 3; delayed ab →diarrhea reduced (thought not an a priori outcome of this review)

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 9/25/2008

Coleman (2008)	KQ3 KQ6	decongestant &/or antihistamine	CENTRAL (TCL, issue 2, 2001; TCL, issue 3, 2003; TCL, issue 2, 2007); MEDLINE (Jan 1966-May 2007); EMBASE (Jan 1990-May 2007); hand search	RCT	<18 years old	Any setting	Clinical resolution at 2wk, 1wk, 4wk; symptom resolution; medication side effects; AOM complications	No	15 trials total See Comparison Table for specific trial and participant numbers 5 comparisons & 52 analyses	lack of benefit for decongestant &/or antihistamine; increased risk of side effects

ab=antibiotic; amp/amox=ampicillin or amoxicillin; CENTRAL=Cochrane Central Register of Controlled Trials; CINAHL=Cumulative Index to Nursing & Allied Health Literature CI=confidence interval; Contra Otitis=contralateral otitis; HitkTAR=HealthSTAR; IPA=International Pharmaceutical Abstracts; KQ=key question for Management of AOM Update; MEE=middle ear effusion; R,r=treatment; TCL=The Cochrane Library

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 9/25/2008

Part 2. Systematic Reviews Quality (AMSTAR: See Appendix)

Author (year)	a priori design	duplicate data extraction	comprehensive literature search	publication status	list of studies	provision of study characteristics	study quality assessed	study quality used	findings combined appropriately	publication bias assessed	conflict of interest
Marcy (2001)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[5]
Rosenfeld (1994)	Yes	Yes	No[6]	Yes	No[7]	Yes[8]	Yes	Yes	Yes	No	No[9]
Damoiseaux (1998)	Yes	No[10]	Yes	Yes	No[6]	Yes	Yes	Yes	No	No	No
Kozyrskyj (2000)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[5]
Glasziou (2004)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes[11]	Yes	No	No[5]
Foxlee (2006)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No[5]
Rovers (2006)	Yes	n/a[12]	No[13]	No	No[14]	Yes	Yes	Yes	Yes	Yes	No[5]
Spurling (2007)	Yes	Yes	Yes[15]	No[16]	Yes	Yes	Yes	Yes	Yes	Yes	No[5]
Coleman (2008)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[5]

AMSTAR=Assessment of Multiple Systematic Reviews (Shea, Grimshaw, Wells, et al, 2007)

[5] Conflict of interest was addressed in the systematic review but not in all the included studies.
[6] Searched Medline, three months of Current Contents, and extensive hand search
[7] Excluded studies were not listed.
[8] Study characteristics were summarized in the narrative but characteristics of individual studies were not given in a table.
[9] Percent of studies funded in whole or in part was reported, though not clear if all studies reported conflict of interest.
[10] Study inclusion was scored by four investigators, but the number of data extractors was not reported.
[11] Quality was measured but not used in formulating conclusions or recommendations.
[12] This meta-analysis utilized individual patient data.
[13] Dates searched were not reported, and the hand search was limited to one symposia series.
[14] Excluded studies were not listed
[15] Reported hand search was not as extensive as might be expected.
[16] Unlike most Cochrane reviews this review does not explicitly state if publications were excluded based on language.

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 9/18/2008

Part 3. Comparison Table: Representative Comparisons from Systematic Reviews

Study	Comparison primary subgroup	Outcome	Trials	Participants	OR, RD, RR, or WMD	95% CI
Marcy[17] (2001)	**amp/amox *vs* no ab**	Rx failure 2-7d	5	1518	RD -12.3%	-21.8 % to -2.8%
	pcn *vs* amp/amox	Rx failure 7-14d	3	491	RD 4.5%	-1.8% to 10.7%
	cefaclor *vs* amp/amox	Rx failure 3-7d	4	185	RD -5.4%	-15.2% to 4.4%
		Rx failure 5-21d	5	315	RD 0.5%	-5.7% to 6.8%
	cefixime *vs* amp/amox	Rx failure 10-15d	4	519	RD -0.1%	-4.2% to 3.9%
		recurrence 3-5wk	3	144	RD 1.6%	-5.1% to 8.4%
		diarrhea	5	754	RD 8.4%	3.8% to 13.1%
		vomiting	5	754	RD 2 %	0% to 4%
		rash	4	714	RD 5.8%	-2.4% to 13.9%
	ceftriaxone *vs* amox	Rx failure 5-10d	3	306	RD 3.4%	-1.6% to 8.5%
	azith *vs* amox-clav	Rx failure 10-14d	5	1045	RD 2.1%	-0.6% to 4.8%
		any adverse effect	3	1366	RD -19.2%	-29.2% to -9.2%
		GI adverse effect	3	1366	RD -18.0%	-28.0% to -8.0%
Rosenfeld[18] (1994)	**pcn *vs* no ab**	Rx failure 7-14d	2	242	RD -15.7%	-26.7% to -4.7%
	aminopcn *vs* no ab	Rx failure 7-14d	3	386	RD -12.9%	-19.0% to -6.8%
	any ab *vs* no ab	Rx failure 7-14d	4	535	RD -13.7%	-19.2% to -8.2%
	amp *vs* pcn	Rx failure 7-14d	3	497	RD -6.8%	-15.2% to 1.5%
	amp *vs* pcn/ssx	Rx failure 7-14d	3	462	RD 0.9%	-7.6% to 9.4%
	aminopcn *vs* ery	Rx failure 7-14d	3	525	RD 3.1%	-3.9% to 10.2%
	aminopcn *vs* tmp-smx	Rx failure 7-14d	2	275	RD 0.2%	-8.8% to 9.2%
	amox *vs* cefaclor	Rx failure 7-14d	4	453	RD 6.4%	-10.2 to 22.9%
	amox *vs* cefixime	Rx failure 7-14d	3	404	RD -3.9%	-10.4 to 2.6%
		MEE 30d	Not reported	Not reported	RD -15.0%	-35.5% to 5.5%
	cefaclor *vs* ery/ssx	Rx failure 7-14d	2	222	RD -7.0%	-6.5% to 20.4%
	cefaclor *vs* amox-clav	Rx failure 7-14d	5	776	RD 2.8%	-1.3% to 6.8%
		MEE 30d	Not reported	Not reported	RD 1.6%	-5.1% to 8.3%

[17] Sensitivity analyses deleting or including problematic articles were also reported but are not listed in this table.
[18] Sensitivity analysis by AOM diagnostic specificity was also reported but is not listed in this table.

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 9/18/2008

Study	Comparison primary subgroup	Outcome	Trials	Participants	OR, RD, RR, or WMD	95% CI
	cefaclor *vs* cefixime	Rx failure 7-14d	4	966	RD 1.2%	-2.4% to 4.7%
		MEE 30d	Not reported	Not reported	RD 1.8%	-19.0% to 22.6%
Damoiseaux (1998)	**ab *vs* no ab** <2y old	clinical resolution	4	416	OR 1.31	0.83 to 2.08
Kozyrskyj[19] (2000)	**≤48* ab *vs* >7d ab**	Rx failure ≤1m	2	118	OR 2.99	1.04 to 8.54
	>48*≤7d ab *vs* >7d ab	Rx failure ≤1m	12	3118	OR 1.38	1.15 to 1.66
		Rx failure 8-19d	5	1524	OR 1.52	1.17 to 1.98
		Rx failure 20-30d	9	2115	OR 1.22	0.98 to 1.54
		Rx failure ≤3m	5	1054	OR 1.16	0.90 to 1.50
		Rx failure 90d	2	207	OR 1.16	0.65 to 2.06
		Rx failure 30-40d	3	847	OR 1.16	0.87 to 1.55
	<2y old	Rx failure ≤1m	3	118	OR 0.71	0.30 to 1.64
	≥2y old	Rx failure ≤1m	3	235	OR 1.01	0.53 to 1.94
	perforated TM	Rx failure ≤1m	1	27	OR 3.62	0.81 to 16.1
	non-perforated TM	Rx failure ≤1m	1	101	OR 1.06	0.40 to 2.75
	include chronic OM	Rx failure ≤1m	9	2220	OR 1.39	1.15 to 1.70
	exclude chronic OM	Rx failure ≤1m	3	898	OR 1.29	0.76 to 2.20
	include chronic OM	Rx failure 20-30d	7	1459	OR 1.19	0.93 to 1.51
	exclude chronic OM	Rx failure 20-30d	2	656	OR 1.55	0.79 to 3.04
	only "cured"	Rx failure ≤1m	11	3062	OR 1.35	1.14 to 1.59
	only "cured"	Rx failure 20-30d	8	2059	OR 1.24	1.01 to 1.54
		GI adverse effects	10	3576	OR 0.54	0.43 to 0.66
	excluding amox-clav	GI adverse effects	7	2131	OR 1.13	0.81 to 1.57
	ceftriaxone	Rx failure ≤1m	3	671	OR 1.25	0.90 to 1.72
		Rx failure ≤3m	2	312	OR 0.91	0.57 to 1.47
		GI adverse effects	1	402	OR 2.89	1.70 to 4.91
	azithromycin 3-5d	Rx failure ≤1m	11	2593	OR 1.09	0.86 to 1.38
		Rx failure 8-19d	10	2569	OR 1.11	0.82 to 1.51
		Rx failure 20-30d	6	1254	OR 1.02	0.78 to 1.34

[19] Subgroup analyses by quality and sensitivity analyses excluding trials comparing different antibiotics were also reported but are not listed in this table.

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 9/18/2008

Study	Comparison primary subgroup	Outcome	Trials	Participants	OR, RD, RR, or WMD	95% CI
	<2y old	Rx failure ≤1m	2	138	OR 1.92	0.73 to 5.04
	≥2y old	Rx failure ≤1m	2	656	OR 1.34	0.61 to 2.94
	Rx 3d	Rx failure ≤1m	8	1558	OR 1.17	0.71 to 1.92
	include chronic OM	Rx failure ≤1m	7	1688	OR 0.96	0.70 to 1.31
	exclude chronic OM	Rx failure ≤1m	4	905	OR 1.29	0.89 to 1.85
	include chronic OM	Rx failure 20-30d	4	740	OR 0.83	0.57 to 1.21
	exclude chronic OM	Rx failure 20-30d	2	514	OR 1.27	0.86 to 1.86
Kozyrskyj (2000)	only "cured"	Rx failure 20-30d	4	728	OR 0.83	0.59 to 1.16
	only "cured"	Rx failure ≤1m	9	2067	OR 0.70	0.57 to 0.87
		GI adverse effects	9	2818	OR 0.26	0.19 to 0.37
Glasziou (2004)	**ab *vs* no ab**	pain 24h	4	717	OR 1.03	0.76 to 1.39
		pain 2-7d	9	2287	OR 0.57	0.45 to 0.73
		abnl tympanogram 1m	3	472	OR 0.91	0.62 to 1.32
		abnl tympanogram 3m	2	370	OR 0.75	0.47 to 1.21
		perforation	2	381	OR 0.51	0.20 to 1.26
		vomiting, diarrhea, rash	4	938	OR 1.94	1.28 to 2.94
		contralateral otitis	3	666	OR 0.45	0.16 to 1.23
		late recurrence	5	1669	OR 1.00	0.78 to 1.26
Foxlee[20] (2006)	**top anaesth *vs* placebo**	25% ↓ pain 10min	1	27	RR 1.18	0.65 to 2.15
		25% ↓ pain 20min	1	27	RR 1.24	0.87 to 1.76
		25% ↓ pain 30min[21]	1	27	RR 1.37	1.06 to 1.77
Rovers[22,23] (2006)	**ab *vs* no ab**	pain &/or fever 3-7d	6	1643	RD -13%	-17% to -9%
	<2y old	pain &/or fever 3-7d	6	567	RD -15%	-23% to -7%
	≥2y old	pain &/or fever 3-7d	6	1076	RD -11%	-16% to -6%

[20] Results for analyses comparing topical anaesthetic and naturopathic drops were also reported but apparently the studies showed significant heterogeneity and are not included in this table.
[21] Measuring 50% pain reduction at 10, 20, and 30 minutes showed no difference.
[22] individual patient data meta-analyses
[23] Results of analyses for pain alone at 3-7 days with subgroup analyses and fever alone at 3-7 days without subgroups analyses were also reported but are not included in this table.

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 9/18/2008

Study	Comparison primary subgroup	Outcome	Trials	Participants	OR, RD, RR, or WMD	95% CI
	unilateral	pain &/or fever 3-7d	6	872	RD -6%	-12% to 0%
	bilateral	pain &/or fever 3-7d	6	456	RD –20%	-28% to -11%
	<2y old & bilateral	pain &/or fever 3-7d	6	273	RD –25%	-36% to -14%
	<2y old & unilateral	pain &/or fever 3-7d	6	261	RD –5%	-17% to 7%
	≥2y old & bilateral	pain &/or fever 3-7d	6	183	RD –12%	-25% to 1%
	≥2y old & unilateral	pain &/or fever 3-7d	6	611	RD –7%	-14% to 0%
	otorrhea	pain &/or fever 3-7d	6	116	RD –36%	-53% to -19%
	no otorrhea	pain &/or fever 3-7d	6	439	RD –14%	-23% to -5%
Spurling (2007)	**delayed ab *vs* imm ab**	pain 3d	1	212	OR 1.93	0.96 to 3.88
		pain 4-6d	1	265	OR 0.89	0.54 to 1.48
		pain 7d	1	212	OR 6.55	0.33 to 128.35
		pain severity 3d	1	213	WMD 0.75	0.26 to 1.24
		pain severity 7d	1	212	WMD 0.12	-0.04 to 0.28
		malaise 3d	1	285	OR 2.62	1.44 to 4.76
		malaise severity 3d	1	284	WMD 0.43	-0.11 to 0.75
		malaise severity 7d	1	285	WMD 0.69	0.31 to 1.07
		fever 4-6d	1	265	OR 0.88	0.53 to 1.47
Coleman[24] (2008)	**decong/antihist *vs* none**	persisting AOM 2wk	12	2300	OR 0.80	0.63 to 1.00
		persisting AOM <7d	2	143	OR 0.83	0.36 to 1.91
		persisting AOM >2wk	3	378	OR 1.39	0.69 to 2.80
		otalgia	2	287	OR 0.79	0.43 to 1.47
		fever	1	98	OR 3.90	0.05 to 330.46
		hearing loss	2	976	OR 1.45	0.58 to 3.61
		drowsy	2	567	OR 8.68	0.53 to 143.30
		hyperactivity	3	251	OR 0.79	0.10 to 5.94
		other side effect	3	416	OR 5.00	1.73 to 14.48
		prolonged OM 8-12wk	1	106	OR 0.83	0.25 to 2.74
		recurrent AOM <2wk	5	997	OR 0.95	0.57 to 1.57
		required surgery	4	1172	OR 1.28	0.67 to 2.46

[24] Analyses for decongestant and antihistamine alone and for decongestant and antihistamine together as well as subgroup analyses by primary outcome by various quality criteria, route of medication, and method to diagnose AOM resolution were also reported but are not included in this table.

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 9/18/2008

Study	Comparison primary subgroup	Outcome	Trials	Participants	OR, RD, RR, or WMD	95% CI
		mastoiditis or meningitis	2	662	OR not estimable	not estimable

ab=antibiotic; abnl=abnormal; amox-clav=amoxicillin-clavulanate; amp/amox=ampicillin or amoxicillin; azith=azithromycin; CI=confidence interval; ery=erythromycin; GI=gastrointestinal; imm=immediate; OM=otitis media; OR=odds ratio; pcn=penicillin; RD=rate difference; RR=relative risk; ssx=sulfisoxazole; TM=tympanic membrane; TMP-SMX=trimethoprim-sulfamethoxazole; top=topical; WMD=weighted mean difference

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

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Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 9/18/2008

Appendix: AMSTAR Quality Indicators (Shea, Grimshaw, Wells, et al, 2007)

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	□ Yes □ No □ Can't answer □ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	□ Yes □ No □ Can't answer □ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	□ Yes □ No □ Can't answer □ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	□ Yes □ No □ Can't answer □ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	□ Yes □ No □ Can't answer □ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	□ Yes □ No □ Can't answer □ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	□ Yes □ No □ Can't answer □ Not applicable

8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	□ Yes □ No □ Can't answer □ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	□ Yes □ No □ Can't answer □ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	□ Yes □ No □ Can't answer □ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	□ Yes □ No □ Can't answer □ Not applicable

Appendix I. Summaries of Systematic Reviews Included in Analyses

Review of Acute Otitis Media Diagnosis Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND)

This document is a summary of the systematic reviews that have relevance to Key Question 1 (KQ1) regarding diagnosis of acute otitis media in the present Workplan. It consists of 3 parts: Part 1 contains the characteristics of the systematic reviews and the highlighted conclusions; Part 2 contains our assessment of the quality of the systematic reviews using AMSTAR quality indicators; and Part 3 provides representative quantitative outcomes of the comparisons contained in the systematic reviews. Finally, we include references and the AMSTAR instrument.

We searched Medline from 1998 through the present and identified reviews that have relevance to KQ1 for the AOM update. We searched the Cochrane Review database to the present. We also searched the Web of Science 1980-1997 and did hand searches of reference lists of study articles identified for inclusion in the AOM update.

Based on the general conclusions of these reviews we believe that we are justified in doing a systematic review for KQ1. We have also noted the studies included in these systematic reviews for possible inclusion in the present systematic review.

Review of Acute Otitis Media Diagnosis Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND)

Part 1. Relevance to Key Question 4 of the Management of Acute Otitis Media Update[1]

Author (year)	Content category by KQ	Review focus	Databases and included dates	Study design, inclusion criteria	Target population	Setting	Outcomes	Cost analysis	Number of trials, participants, and comparisons	Author's highlight conclusion
Rothman (2003)	KQ1	Precision and accuracy of history taking and physical exam in diagnosing AOM in children	MEDLINE for English-language articles (1966 through May 2002); hand searches including bibliographies of retrieved articles and textbooks	Included: 1. studies that examined symptoms & signs directly relevant to diagnosis of AOM 2. studies that used tympanocentesis as standard. 3. studies that used a standardized clinical definition of AOM as standard Excluded: 1. Studies on persistent OME 2. studies that used non-independent comparison of symptoms to a standard of uncertain validity	Children, age not defined	not specified a priori	Accuracy of symptoms and accuracy of signs as measured by likelihood ratios, sensitivity and specificity.	No	4 studies on accuracy of symptoms included 965 subjects, 0-15y 1 study on accuracy of signs included 2911 subjects, 6 mo-2.5y.	1.Dx of AOM can be very difficult. 2. Studies examining this condition are limited. 3. A cloudy, bulging or clearly immobile tympanic membrane is most helpful for detecting AOM 4. The degree of erythema may also be useful

Part 1 Abbreviations and Acronyms: ab=antibiotic; amp/amox=ampicillin or amoxicillin; CENTRAL=Cochrane Central Register of Controlled Trials; CINAHL=Cumulative Index to Nursing & Allied Health Literature CI=confidence interval; Contra Otitis=contralateral otitis; CSOM=chronic suppurative otitis media; ENT=ear, nose, and throat; HlthSTAR=HealthSTAR; IPA=International Pharmaceutical Abstracts; KQ=key question for Management of AOM Update; MEE=middle ear effusion; mRCT=*metaRegister*, NRR=National Research Register; Rx=treatment; PCV=pneumococcal conjugated vaccines; PPV=pneumococcal polysaccharide vaccines; ROM=recurrent otitis media; TCL=The Cochrane Library

[1] For quality score of each systematic review, see next table.

Appendix I. Summaries of Systematic Reviews Included in Analyses

Review of Acute Otitis Media Diagnosis Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND)

Part 2. Systematic Reviews Quality (AMSTAR: See Appendix)

Author (year)	a priori design	duplicate data extraction	comprehensive literature search	publication status	list of studies	provision of study characteristics	study quality assessed	study quality used	findings combined appropriately	publication bias assessed	conflict of interest
Rothman (2003)	Yes	Yes	No[1]	Yes	No[2]	No[3]	Yes	Yes	No[4]	No	No

AMSTAR=Assessment of Multiple Systematic Reviews (Shea, Grimshaw, Wells, et al. 2007)

[1] Only one electronic database was searched.

[2] List of excluded studies not provided.

[3] Only limited demographic or clinical characteristics were provided in the table.

[4] Pooled analyses of multiple studies were not performed because of small number and heterogeneity of studies available.

Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 2/24/2009

Part 3. Comparison Table: Representative Comparisons from Systematic Reviews

Study	Source	Trials (Citations)	# Participants	Symptom	Sensitivity in %	Specificity in %	Pos LR (95% CI)	Neg LR (95% CI)
Rothman (2003)	Niemela (1994)	1	354	Ear pain	54	82	3.0 (2.1-4.3)	0.6 (0.5-0.7)
				Ear rubbing	42	87	3.3 (2.1-5.1)	0.7 (0.6-0.8)
				Fever	40	48	0.8 (0.6-1.0)	1.2 (1.0-1.5)
				Cough	47	45	0.9 (0.7-1.1)	1.2 (0.9-1.4)
				Rhinitis	75	43	1.3 (1.1-1.5)	0.6 (0.4-0.8)
				Excessive crying	55	69	1.8 (1.4-2.3)	0.7 (0.5-0.8)
				Poor appetite	36	66	1.1 (0.8-1.4)	1.0 (0.8-1.1)
				Vomiting	11	89	1.0 (0.6-1.8)	1.0 (0.9-1.1)
				Soar throat	13	74	0.5 (0.3-0.8)	1.2 (1.1-1.3)
				Headache	9	76	0.4 (0.2-0.7)	1.2 (1.1-1.3)
	Heikkinen (1995)	1	302	Ear pain	60	92	7.3 (4.4-12.1)	0.4 (0.4-0.5)
				Fever	69	23	0.9 (0.8-1.0)	1.4 (0.9-2.0)
				Cough	84	17	1.0 (0.9-1.1)	1.0 (0.6-1.6)
				Rhinitis	96	8	1.0 (1.0-1.1)	0.5 (0.2-1.4)
				Restless sleep	64	51	1.3 (1.1-1.6)	0.7 (0.5-0.9)
	Ingvarsson (1982)	1	171	Ear pain	100	NA	NA	NA
				Fever	79	70	2.6 (1.9-3.6)	0.3 (0.2-0.5)
				Upper respiratory tract infection	96	29	1.4 (1.2-1.6)	0.3 (0.2-0.5)
	Kontiokari (1998)	1	138	Parental suspicion of acute otitis media	70	80	3.4 (2.8-4.2)	0.4 (0.3-0.5)
	Source	**Trials (Citations)**	**# Participants**	**Sign**			**Unadjusted Pos LR**	**Adjusted Pos LR (95% CI)**
	Karma (1989)	1	2911	Color – Cloudy			11.0	34.0 (28.0-42.0)
				Color – Distinctly red			2.6	8.4 (6.7-11.0)
				Color – Slightly red			0.4	1.4 (1.1-1.8)
				Color – Normal			0.1	0.2 (0.19-0.21)
				Position – Bulging			20.0	51.0 (36.0-73.0)
				Position – Retracted			1.3	3.5 (2.9-4.2)

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Study	Source	Trials (Citations)	# Participants	Symptom	Sensitivity in %	Specificity in %	Pos LR (95% CI)	Neg LR (95% CI)
				Position – Normal			0.4	0.50 (0.49-0.51)
				Mobility – Distinctly impaired			8.4	31.0 (26.0-37.0)
				Mobility – Slightly impaired			1.1	4.0 (3.4-4.7)
				Mobility – Normal			0.04	0.2 (0.19-0.21)

Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 2/24/2009

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Appendix I. Summaries of Systematic Reviews Included in Analyses

Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 2/24/2009

Appendix: AMSTAR Quality Indicators (Shea, Grimshaw, Wells, et al, 2007)

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	□ Yes □ No □ Can't answer □ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	□ Yes □ No □ Can't answer □ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	□ Yes □ No □ Can't answer □ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	□ Yes □ No □ Can't answer □ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	□ Yes □ No □ Can't answer □ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	□ Yes □ No □ Can't answer □ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	□ Yes □ No □ Can't answer □ Not applicable

8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	□ Yes □ No □ Can't answer □ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	□ Yes □ No □ Can't answer □ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	□ Yes □ No □ Can't answer □ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	□ Yes □ No □ Can't answer □ Not applicable

Appendix I. Summaries of Systematic Reviews Included in Analyses

Systematic Reviews Relevant to Management of Acute Otitis Media Update:

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This document is a summary of the systematic reviews that have relevance to Key Question 3 (KQ3) regarding treatment of acute otitis media in the present Workplan. It consists of 3 parts: Part 1 contains the characteristics of the systematic reviews and the highlighted conclusions; Part 2 contains our assessment of the quality of the systematic reviews using AMSTAR quality indicators; and Part 3 provides representative quantitative outcomes of the comparisons contained in the systematic reviews. Finally, we include references and the AMSTAR instrument.

We searched Medline from 1998 through the present and identified reviews that have relevance to KQ3 for the AOM update. We searched the Cochrane Review database to the present. We also searched the Web of Science 1980-1997 and did hand searches of reference lists of study articles identified for inclusion in the AOM update.

Based on the general conclusions of these reviews we believe that we are justified in doing a systematic review for KQ3. We have also noted the studies included in these systematic reviews for possible inclusion in the present systematic review.

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND)

Part 1. Relevance to Management of Acute Otitis Media Update[1]

Author (year)	Content category by KQ	Review focus	Databases and included dates	Study design, inclusion criteria	Target population	Setting	Outcomes	Cost analysis	Number of trials, participants, and comparisons	Author's highlight conclusion
Marcy (2001)[2] **(initial AHRQ Management of AOM systematic review)**	KQ3 KQ5 KQ6	natural hx ab *vs* no ab ab regimen	CENTRAL (TCL, through Mar 1999), MEDLINE (1966-Mar 1999), HlthSTAR (1975-Mar 1999), IPAInternational Pharmaceutical Abstracts (1970-Mar 1999), CINAHL (1982-Mar 1999), BIOSIS (1970-Mar 1999), and EMBASE (1980-Mar 1999); hand search	RCT; Cohort, for natural hx	AOM 4wk-18y exclude patients with immunodeficiencies or craniofacial deficiencies, including cleft palate	Any setting	Clinical failure; adverse effects	No	80 trials total: 74 addressed ab *vs* no ab & ab regimen See Comparison Table for specific trial and participant numbers 7 primary comparisons & 16 analyses reported (only analyses with ≥3 trials were conducted)	Rx with amp/amox ↓ clinical failure by 12% ***vs*** no ab; ab regimen outcomes not different; cefixime & amoxillin-clavulanate ↑ adverse effects

[1] For quality score of each systematic review, see next table.

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND)

Author (year)	Content category by KQ	Review focus	Databases and included dates	Study design, inclusion criteria	Target population	Setting	Outcomes	Cost analysis	Number of trials, participants, and comparisons	Author's highlight conclusion
Rosenfeld (1994)	KQ3 KQ5	ab *vs* no ab ab regimen	MEDLINE (Jan 1966-Jun 1992); Current Contents (3 months through Jun 29, 1992); hand search	RCT	AOM 4wk-18y exclude myringotomy, OM not described, mostly treatment failure or otitis prone	Not specified a priori	Clinical response, MEE presence	No	33 trials total See Comparison Table for specific trial and participant numbers 3 primary comparisons & 16 analyses reported	ab effect modest but significant; no significant difference between ab regimens studied
Damoiseaux (1998)	KQ3 KQ5	ab ***vs*** no ab	MEDLINE (1966-Jan 1997); EMBASE (1974-Jan 1997); hand search	RCT	AOM <2 years old	Not specified a priori	Clinical resolution within 7d	No	4 trials 416 children 1 comparison & analysis	No significant difference between ab and no ab in <2y olds
Kozyrskyj (2000)	KQ3 KQ5 KQ6	ab <7d ***vs*** ≥7d	MEDLINE (Jan 1966-Jul 1997); EMBASE (Jan 1966-Jul 1997);	RCT	AOM 4wk-18y Subgroups: ab ≤2d; oral short-	Not specified a priori	Clinical resolution 31d & 1-3m; relapse; recurrence	No	32 trials total See Comparison Table for specific trial	ab 5d→ effective Rx for AOM

[2] Also, reference Takata, Chan, Shekelle, et al. (2001)

Appendix I. Summaries of Systematic Reviews Included in Analyses

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND)

Author (year)	Content category by KQ	Review focus	Databases and included dates	Study design, inclusion criteria	Target population	Setting	Outcomes	Cost analysis	Number of trials, participants, and comparisons	Author's highlight conclusion
			Science Citation Index (Mar 1998); Current Contents (Mar 1998); hand search		acting ab; oral azithromycin; intramuscular ceftriaxone; <2 years old; perforated TM				and participant numbers	
									45 primary comparisons & 54 analyses (several utilizing 1 trial)	
Abes (2003)	KQ3	effectiveness of ofloxacin otic solution for treatment of suppurative otitis media. Incidence of side-effects or adverse events during course of treatment	Medline through PubMed (1966 to 2000); CD version of the Cochrane Library; Centerwatch Clinical Trial Listing Service; Trial Banks; Research and Researcher Registry; Manual searches.	RCT and non-randomized clinical trial	Adults and/or children who had clinical manifestations associated with acute or chronic suppurative otitis media.	Not specified a priori	cure rate resolution of otalgia resolution of otorrhea bacterial eradication	No	11 studies 1484 adults and children	0.3% ofloxacin otic solution is better than other otic antibiotic drops and other oral antibiotics in terms of overall cure rate and resolution of secondary outcome parameters.

Appendix I. Summaries of Systematic Reviews Included in Analyses

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND)

Author (year)	Content category by KQ	Review focus	Databases and included dates	Study design, inclusion criteria	Target population	Setting	Outcomes	Cost analysis	Number of trials, participants, and comparisons	Author's highlight conclusion
Glasziou (2004)	KQ3 KQ6	ab *vs* no ab	CENTRAL (1966-Jan 2000; TCL, issue 1, 2003); Current Contents (1966- Jan 2000); Index Medicus (1958-1965); MEDLINE (Jan 2000-Mar 2003); EMBASE (Jan 1990-Mar 2003); hand search	RCT	AOM Children, age not specified	Any setting	Severity and duration of pain; mid- to long-term hearing problems; adverse effects; recurrent attacks	No	8 trials total See Comparison Table for specific trial and participant numbers	ab of small benefit for AOM Rx
Foxlee (2006)	KQ3	topical analgesia	CENTRAL (TCL, issue 2, 2006); MEDLINE (1966-May 2006); EMBASE (1990-Dec 2005); LILACS (1982-Sep 2005);	RCT or quasi-RCT	AOM without perforation in Adults and children Subgroups: <24mvs≥24m -<18y*vs*≥18y; topical analge-sic type;	Primary care setting	Pain severity and duration; parental satisfaction; days missed from school or work; adverse events	No	4 trials total See Comparison Table for specific trial and participant numbers 4 comparisons	evidence insufficient to make conclusions on topical analgesia effectiveness

Appendix I. Summaries of Systematic Reviews Included in Analyses

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND)

Author (year)	Content category by KQ	Review focus	Databases and included dates	Study design, inclusion criteria	Target population	Setting	Outcomes	Cost analysis	Number of trials, participants, and comparisons	Author's highlight conclusion
			hand search		concurrent ab use exclude perforation				& 15 analyses	
Rovers (2006)	KQ3 KQ5 KQ6	ab *vs* no ab	CENTRAL; PubMed; EMBASE (dates not specified)	RCT	AOM 0-12 years Subgroups: <2y *vs* ≥2y; bilateral AOM; otorrhoea	Not specified a priori	Pain &/or fever 3-7d	No	6 trials total [3,4] (10 trials identified & 6 investigators agreed to share data) See Comparison Table for specific trial and participant numbers	ab beneficial for <2 year old with bilat AOM & AOM with otorrhea
Spurling (2007)	KQ3	Delayed (>48 hrs) ab *vs* immediate ab	CENTRAL (TCL, issue 1, 2004; TCL, issue 4, 2006);	RCT	Respiratory tract infections All ages (For identified	Not specified a priori	Clinical outcomes; ab use; patient satis-	No	1 comparison & 21 analyses reported 2 trials total for AOM in children See	immediate ab→ improved pain and malaise on

[3] individual patient data meta-analyses

[4] Ten trials identified; investigators of only six of the trials agreed to share their data.

Appendix I. Summaries of Systematic Reviews Included in Analyses

Author (year)	Content category by KQ	Review focus	Databases and included dates	Study design, inclusion criteria	Target population	Setting	Outcomes	Cost analysis	Number of trials, participants, and comparisons	Author's highlight conclusion
			MEDLINE (Jan 1966-Jan 2007); EMBASE (1990-Jan 2007); Current Contents (1998-Jan 2007)		AOM studies 6m-12y)		faction; health-seek-ing beha-viors; alter-native thera-pies (For identified AOM studies pain, malaise, and fever)		Comparison Table for specific trial and participant numbers 3 comparisons & 9 analyses (all utilizing 1 trial)	day 3; delayed ab →diarrhea reduced (thought not an a priori outcome of this review)
Coleman (2008)	KQ3 KQ6	deconges-tant &/or antihista-mine	CENTRAL (TCL, issue 2, 2001; TCL, issue 3, 2003; TCL, issue 2, 2007); MEDLINE (Jan 1966-May 2007); EMBASE (Jan 1990-May 2007); hand search	RCT	AOM <18y	Any setting	Clinical resolution at 2wk, 1wk, 4wk; symptom resolution; medication side effects; AOM com-plications	No	15 trials total See Comparison Table for specific trial and participant numbers 5 comparisons & 52 analyses	lack of benefit for deconges-tant &/or antihista-mine; increased risk of side effects
Thanavirata nanich (2008)	KQ3 KQ6	amox or amox-clav once or twice daily vs three	CENTRAL (TCL, isuue 1, 2008); MEDLINE (Jan 1950-	RCT	AOM ≤12y	Not specified a priori	Clinical cure at end of antibiotic therapy, i.e. 7d and	No	6 trials total See Comparison Table for	evidence appears biased so no data pooling

Appendix I. Summaries of Systematic Reviews Included in Analyses

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND)

Author (year)	Content category by KQ	Review focus	Databases and included dates	Study design, inclusion criteria	Target population	Setting	Outcomes	Cost analysis	Number of trials, participants, and comparisons	Author's highlight conclusion
		times daily	Mar 2008); EMBASE (1974-Mar 2008); Science Citation Index (2001-Mar 2008); NLM Gateway (HSR Project) (Mar 2008); hand search				14 d, with respect to otalgia, fever, bacteriologic cure; also, clinical cure during therapy and post-treatment, recurrent OM, acute mastoiditis, adverse reactions		specific trial and participant numbers	performed; no firm conclusions
		ciprodex otic suspension vs "a comparator "which included ciprofloxacin, ofloxacin, amox-clav							1 comparison & 8 analyses	
Wall (2009)	KQ3 KQ6	MEDLINE; hand search	Not specified a priori RCTs identified	AOM & acute otitis externa Otherwise bot specified a priori	Not specified a priori	Not specified a priori	No		3 trials total	topical fluoroquinolones safe and efficacious in treatment of ear infections
				Identified studies included children 6m-12y			Identified studies included clinical outcome "per protocol" and bacteriologic cure		See Comparison Table for specific trial and participant numbers	

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

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Part 1 Abbreviations and Acronyms: ab=antibiotic; amp/amox=ampicillin or amoxicillin; amox=amoxicillin; amox-clav=amoxicillin-clavulanate; CENTRAL=Cochrane Central Register of Controlled Trials; CINAHL=Cumulative Index to Nursing & Allied Health Literature CI=confidence interval; ciprodex=ciprofloxacin 0.3%/dexmethasone 0.1%; Contra Otitis=contralateral otitis; HItK TA R=Health TAR; IPA=International Pharmaceutical Abstracts; KQ=key question for Management of AOM Update; MEE=middle ear effusion; Rx=treatment; TCL=The Cochrane Library

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND)

Part 2. Systematic Reviews Quality (AMSTAR: See Appendix)

Author (year)	a priori design	duplicate data extraction	comprehensive literature search	publication status	list of studies	provision of study characteristics	study quality assessed	study quality used	findings combined appropriately	publication bias assessed	conflict of interest
Marcy (2001)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[5]
Rosenfeld (1994)	Yes	Yes	No[6]	Yes	No[7]	Yes[8]	Yes	Yes	Yes	No	No[9]
Damoiseaux (1998)	Yes	No[10]	Yes	Yes	No[6]	Yes	Yes	Yes	No	No	No
Kozyrskyj (2000)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[5]
Abes (2003)	Yes	Yes	Yes	Yes	Yes[9]	Yes	Yes	No	Yes	Yes	No
Glasziou (2004)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes[11]	Yes	No	No[5]
Foxlee (2006)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No[5]
Rovers (2006)	Yes	n/a[12]	No[13]	No	No[14]	Yes	Yes	Yes	Yes	Yes	No[5]
Spurling (2007)	Yes	Yes	Yes[15]	No[16]	Yes	Yes	Yes	Yes	Yes	Yes	No[5]
Coleman (2008)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[5]
Thanaviratananich (2008)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wall (2009)	No	?	No	No	No	Yes	Yes	No	n/a	n/a	No[5]

AMSTAR=Assessment of Multiple Systematic Reviews (Shea, Grimshaw, Wells, et al, 2007)

[5] Conflict of interest was addressed in the systematic review but not in all the included studies.
[6] Searched Medline, three months of Current Contents, and extensive hand search
[7] Excluded studies were not listed.
[8] Study characteristics were summarized in the narrative but characteristics of individual studies were not given in a table.
[9] Percent of studies funded in whole or in part was reported, though not clear if all studies reported conflict of interest.
[10] Study inclusion was scored by four investigators, but the number of data extractors was not reported.
[11] Quality was measured but not used in formulating conclusions or recommendations.
[12] This meta-analysis utilized individual patient data.
[13] Dates searched were not reported, and the hand search was limited to one symposia series.
[14] Excluded studies were not listed
[15] Reported hand search was not as extensive as might be expected.
[16] Unlike most Cochrane reviews this review does not explicitly state if publications were excluded based on language.

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Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 9/18/2008

Part 3. Comparison Table: Representative Comparisons from Systematic Reviews

Study	Comparison primary subgroup	Outcome	Trials	Participants	OR, RD, RR, or WMD	95% CI
Marcy[17] (2001)	**amp/amox *vs* no ab**	Rx failure 2-7d	5	1518	RD -12.3%	-21.8 % to -2.8%
	pcn *vs* amp/amox	Rx failure 7-14d	3	491	RD 4.5%	-1.8% to 10.7%
	cefaclor *vs* amp/amox	Rx failure 3-7d	4	185	RD -5.4%	-15.2% to 4.4%
		Rx failure 5-21d	5	315	RD 0.5%	-5.7% to 6.8%
	cefixime *vs* amp/amox	Rx failure 10-15d	4	519	RD -0.1%	-4.2% to 3.9%
		recurrence 3-5wk	3	144	RD 1.6%	-5.1% to 8.4%
		diarrhea	5	754	RD 8.4%	3.8% to 13.1%
		vomiting	5	754	RD 2 %	0% to 4%
		rash	4	714	RD 5.8%	-2.4% to 13.9%
	ceftriaxone *vs* amox	Rx failure 5-10d	3	306	RD 3.4%	-1.6% to 8.5%
	azith *vs* amox-clav	Rx failure 10-14d	5	1045	RD 2.1%	-0.6% to 4.8%
		any adverse effect	3	1366	RD -19.2%	-29.2% to -9.2%
		GI adverse effect	3	1366	RD -18.0%	-28.0% to -8.0%
Rosenfeld[18] (1994)	**pcn *vs* no ab**	Rx failure 7-14d	2	242	RD -15.7%	-26.7% to -4.7%
	aminopcn *vs* no ab	Rx failure 7-14d	3	386	RD -12.9%	-19.0% to -6.8%
	any ab *vs* no ab	Rx failure 7-14d	4	535	RD -13.7%	-19.2% to -8.2%
	amp *vs* pcn	Rx failure 7-14d	3	497	RD -6.8%	-15.2% to 1.5%
	amp *vs* pcn/ssx	Rx failure 7-14d	3	462	RD 0.9%	-7.6% to 9.4%
	aminopcn *vs* ery	Rx failure 7-14d	3	525	RD 3.1%	-3.9% to 10.2%
	aminopcn *vs* tmp-smx	Rx failure 7-14d	2	275	RD 0.2%	-8.8% to 9.2%
	amox *vs* cefaclor	Rx failure 7-14d	4	453	RD 6.4%	-10.2 to 22.9%
	amox *vs* cefixime	Rx failure 7-14d	3	404	RD -3.9%	-10.4 to 2.6%
		MEE 30d	Not reported	Not reported	RD -15.0%	-35.5% to 5.5%
	cefaclor *vs* ery/ssx	Rx failure 7-14d	2	222	RD -7.0%	-6.5% to 20.4%
	cefaclor *vs* amox-clav	Rx failure 7-14d	5	776	RD 2.8%	-1.3% to 6.8%
		MEE 30d	Not reported	Not reported	RD 1.6%	-5.1% to 8.3%

[17] Sensitivity analyses deleting or including problematic articles were also reported but are not listed in this table.
[18] Sensitivity analysis by AOM diagnostic specificity was also reported but is not listed in this table.

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Study	Comparison primary subgroup	Outcome	Trials	Participants	OR, RD, RR, or WMD	95% CI
	cefaclor *vs* cefixime	Rx failure 7-14d	4	966	RD 1.2%	-2.4% to 4.7%
		MEE 30d	Not reported	Not reported	RD 1.8%	-19.0% to 22.6%
Damoiseaux (1998)	**ab *vs* no ab** <2y old	clinical resolution	4	416	OR 1.31	0.83 to 2.08
Kozyrskyj[19] (2000)	**≤48° ab *vs* >7d ab**	Rx failure ≤1m	2	118	OR 2.99	1.04 to 8.54
	>48°≤7d ab *vs* >7d ab	Rx failure ≤1m	12	3118	OR 1.38	1.15 to 1.66
		Rx failure 8-19d	5	1524	OR 1.52	1.17 to 1.98
		Rx failure 20-30d	9	2115	OR 1.22	0.98 to 1.54
		Rx failure ≤3m	5	1054	OR 1.16	0.90 to 1.50
		Rx failure 90d	2	207	OR 1.16	0.65 to 2.06
		Rx failure 30-40d	3	847	OR 1.16	0.87 to 1.55
	<2y old	Rx failure ≤1m	3	118	OR 0.71	0.30 to 1.64
	≥2y old	Rx failure ≤1m	3	235	OR 1.01	0.53 to 1.94
	perforated TM	Rx failure ≤1m	1	27	OR 3.62	0.81 to 16.1
	non-perforated TM	Rx failure ≤1m	1	101	OR 1.06	0.40 to 2.75
	include chronic OM	Rx failure ≤1m	9	2220	OR 1.39	1.15 to 1.70
	exclude chronic OM	Rx failure ≤1m	3	898	OR 1.29	0.76 to 2.20
	include chronic OM	Rx failure 20-30d	7	1459	OR 1.19	0.93 to 1.51
	exclude chronic OM	Rx failure 20-30d	2	656	OR 1.55	0.79 to 3.04
	only "cured"	Rx failure ≤1m	11	3062	OR 1.35	1.14 to 1.59
	only "cured"	Rx failure 20-30d	8	2059	OR 1.24	1.01 to 1.54
		GI adverse effects	10	3576	OR 0.54	0.43 to 0.66
	excluding amox-clav	GI adverse effects	7	2131	OR 1.13	0.81 to 1.57
	ceftriaxone	Rx failure ≤1m	3	671	OR 1.25	0.90 to 1.72
		Rx failure ≤3m	2	312	OR 0.91	0.57 to 1.47
		GI adverse effects	1	402	OR 2.89	1.70 to 4.91
	azithromycin 3-5d	Rx failure ≤1m	11	2593	OR 1.09	0.86 to 1.38
		Rx failure 8-19d	10	2569	OR 1.11	0.82 to 1.51
		Rx failure 20-30d	6	1254	OR 1.02	0.78 to 1.34

[19] Subgroup analyses by quality and sensitivity analyses excluding trials comparing different antibiotics were also reported but are not listed in this table.

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

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Study	Comparison primary subgroup	Outcome	Trials	Participants	OR, RD, RR, or WMD	95% CI
Kozyrskyj (2000)	<2y old	Rx failure ≤1m	2	138	OR 1.92	0.73 to 5.04
	≥2y old	Rx failure ≤1m	2	656	OR 1.34	0.61 to 2.94
	Rx 3d	Rx failure ≤1m	8	1558	OR 1.17	0.71 to 1.92
	include chronic OM	Rx failure ≤1m	7	1688	OR 0.96	0.70 to 1.31
	exclude chronic OM	Rx failure ≤1m	4	905	OR 1.29	0.89 to 1.85
	include chronic OM	Rx failure 20-30d	4	740	OR 0.83	0.57 to 1.21
	exclude chronic OM	Rx failure 20-30d	2	514	OR 1.27	0.86 to 1.86
	only "cured"	Rx failure 20-30d	4	728	OR 0.83	0.59 to 1.16
	only "cured"	Rx failure ≤1m	9	2067	OR 0.70	0.57 to 0.87
		GI adverse effects	9	2818	OR 0.26	0.19 to 0.37
Abes (2003)	Ofloxacin otic solution vs other medical treatment	Cure rate	9	1290	OR 2.67	2.04, 3.50
		Otalgia resolution rate	4	231	OR 2.41	1.20, 4.82
		Otorrhea resolution rate	11	1266	OR 2.78	2.12, 3.65
		Any adverse event	4	647	OR 0.28	0.19, 0.42
		Bacterial eradication rate	6	488	OR 3.86	2.54, 5.87
	Ofloxacin otic solution vs otic solutions containing antibiotics and steroids	Cure rate	4	322	OR 2.73	1.52, 4.90
	Ofloxacin otic solution vs oral systemic antibiotics	Otorrhea resolution rate	3	421	OR 2.78	2.12, 3.65
Glasziou (2004)	**ab *vs* no ab**	pain 24h	4	717	OR 1.03	0.76 to 1.39
		pain 2-7d	9	2287	OR 0.57	0.45 to 0.73
		abnl tympanogram 1m	3	472	OR 0.91	0.62 to 1.32
		abnl tympanogram 3m	2	370	OR 0.75	0.47 to 1.21
		perforation	2	381	OR 0.51	0.20 to 1.26
		vomiting, diarrhea, rash	4	938	OR 1.94	1.28 to 2.94
		contralateral otitis	3	666	OR 0.45	0.16 to 1.23

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 9/18/2008

Study	Comparison primary subgroup	Outcome	Trials	Participants	OR, RD, RR, or WMD	95% CI
		late recurrence	5	1669	OR 1.00	0.78 to 1.26
Foxlee[20] (2006)	**top anaesth *vs* placebo**	25% ↓ pain 10min	1	27	RR 1.18	0.65 to 2.15
		25% ↓ pain 20min	1	27	RR 1.24	0.87 to 1.76
		25% ↓ pain 30min[21]	1	27	RR 1.37	1.06 to 1.77
Rovers[22,23] (2006)	**ab *vs* no ab**	pain &/or fever 3-7d	6	1643	RD -13%	-17% to -9%
	<2y old	pain &/or fever 3-7d	6	567	RD -15%	-23% to -7%
	≥2y old	pain &/or fever 3-7d	6	1076	RD -11%	-16% to -6%
	unilateral	pain &/or fever 3-7d	6	872	RD -6%	-12% to 0%
	bilateral	pain &/or fever 3-7d	6	456	RD –20%	-28% to -11%
	<2y old & bilateral	pain &/or fever 3-7d	6	273	RD –25%	-36% to -14%
	<2y old & unilateral	pain &/or fever 3-7d	6	261	RD –5%	-17% to 7%
	≥2y old & bilateral	pain &/or fever 3-7d	6	183	RD –12%	-25% to 1%
	≥2y old & unilateral	pain &/or fever 3-7d	6	611	RD –7%	-14% to 0%
	otorrhea	pain &/or fever 3-7d	6	116	RD –36%	-53% to -19%
	no otorrhea	pain &/or fever 3-7d	6	439	RD –14%	-23% to -5%
Spurling (2007)	**delayed ab *vs* imm ab**	pain 3d	1	212	OR 1.93	0.96 to 3.88
		pain 4-6d	1	265	OR 0.89	0.54 to 1.48
		pain 7d	1	212	OR 6.55	0.33 to 128.35
		pain severity 3d	1	213	WMD 0.75	0.26 to 1.24
		pain severity 7d	1	212	WMD 0.12	-0.04 to 0.28
		malaise 3d	1	285	OR 2.62	1.44 to 4.76
		malaise severity 3d	1	284	WMD 0.43	-0.11 to 0.75
		malaise severity 7d	1	285	WMD 0.69	0.31 to 1.07
		fever 4-6d	1	265	OR 0.88	0.53 to 1.47
Coleman[24] (2008)	**decong/antihist *vs* none**	persisting AOM 2wk	12	2300	OR 0.80	0.63 to 1.00

[20] Results for analyses comparing topical anaesthetic and naturopathic drops were also reported but apparently the studies showed significant heterogeneity and are not included in this table.
[21] Measuring 50% pain reduction at 10, 20, and 30 minutes showed no difference.
[22] individual patient data meta-analyses
[23] Results of analyses for pain alone at 3-7 days with subgroup analyses and fever alone at 3-7 days without subgroups analyses were also reported but are not included in this table.

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 9/18/2008

Study	Comparison primary subgroup	Outcome	Trials	Participants	OR, RD, RR, or WMD	95% CI
		persisting AOM <7d	2	143	OR 0.83	0.36 to 1.91
		persisting AOM >2wk	3	378	OR 1.39	0.69 to 2.80
		otalgia	2	287	OR 0.79	0.43 to 1.47
		fever	1	98	OR 3.90	0.05 to 330.46
		hearing loss	2	976	OR 1.45	0.58 to 3.61
		drowsy	2	567	OR 8.68	0.53 to 143.30
		hyperactivity	3	251	OR 0.79	0.10 to 5.94
		other side effect	3	416	OR 5.00	1.73 to 14.48
		prolonged OM 8-12wk	1	106	OR 0.83	0.25 to 2.74
		recurrent AOM <2wk	5	997	OR 0.95	0.57 to 1.57
		required surgery	4	1172	OR 1.28	0.67 to 2.46
		mastoiditis or meningitis	2	662	OR not estimable	not estimable
Thanaviratananich (2008)	once or twice *vs* thrice daily	clinical cure at end of therapy	5	1601	RR 0.96 to 1.21 (not combined)	n/a
		clinical cure at follow-up	3	1362	RR 0.93 to 1.00 (not combined)	n/a
		overall adverse effects	2	878	RR 0.67 and 1.19 (not combined)	n/a
		specific adverse effects				
		diarrhea	2	878	RR 0.63 and 0.80 (not combined)	n/a
		skin adverse effects	1	575	RR 0.77	0.46 to 1.29
		Compliance rate	4	1520	RR 0.0 to 1.14 (not combined)	n/a
		persistent middle ear effusion at follow-up, 30d	1	100	RR 0.93	0.73 to 1.19
		persistent middle ear effusion at follow-up, 60d	1	100	RR 0.98	0.98 to 1.35

[24] Analyses for decongestant and antihistamine alone and for decongestant and antihistamine together as well as subgroup analyses by primary outcome by various quality criteria, route of medication, and method to diagnose AOM resolution were also reported but are not included in this table.

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 9/18/2008

Study	Comparison primary subgroup	Outcome	Trials	Participants	OR, RD, RR, or WMD	95% CI
		persistent middle ear effusion at follow-up, 90d	1	100	RR 0.82	0.54 to 1.25
Wall (2009)	ciprodex *vs* "comparator"	clinical outcome	3	880	(not combined)	n/a
		bacteriologic cure	3	880	(not combined)	n/a

Part 3 Abbreviations and Acronyms: ab=antibiotic; ab nl=ab normal; amox-clav=amoxicillin-clavulanate; amp/amox=ampicillin or amoxicillin; azith=azithromycin; CI=confidence interval; ciprodex=ciprofloxacin 0.3%/desmethasone 0.1%; ery=erythromycin; GI=gastrointestinal; imm=immediate; OM=otitis media; OR=odds ratio; pen=penicillin; RD=rate difference; RR=relative risk; sx=sulfisoxazole; TM=tympanic membrane; TMP-SMX=trimethoprim-sulfamethoxazole; top=topical; WMD-weighted mean difference

Appendix I. Summaries of Systematic Reviews Included in Analyses

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

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Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 9/18/2008

Appendix: AMSTAR Quality Indicators (Shea, Grimshaw, Wells, et al, 2007)

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	□ Yes □ No □ Can't answer □ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	□ Yes □ No □ Can't answer □ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	□ Yes □ No □ Can't answer □ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	□ Yes □ No □ Can't answer □ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	□ Yes □ No □ Can't answer □ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	□ Yes □ No □ Can't answer □ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	□ Yes □ No □ Can't answer □ Not applicable

8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	□ Yes □ No □ Can't answer □ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	□ Yes □ No □ Can't answer □ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	□ Yes □ No □ Can't answer □ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	□ Yes □ No □ Can't answer □ Not applicable

Appendix I. Summaries of Systematic Reviews Included in Analyses

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 9/18/2008

This document is a summary of the systematic reviews that have relevance to Key Question 4 (KQ4) in the present Workplan. It consists of 3 parts: Part 1 contains the characteristics of the systematic reviews and the highlighted conclusions; Part 2 contains our assessment of the quality of the systematic reviews using AMSTAR quality indicators; and Part 3 provides representative quantitative outcomes of the comparisons contained in the systematic reviews. Finally, we include references and the AMSTAR instrument.

We searched Medline from 1998 through the present and identified reviews that have relevance to KQ4 for the AOM update. We searched the Cochrane Review database to the present. We also searched the Web of Science 1980-1997 and did hand searches of reference lists of study articles identified for inclusion in the AOM update.

Based on the general conclusions of these reviews we believe that we are justified in doing a systematic review for KQ4. We have also noted the studies included in these systematic reviews for possible inclusion in the present systematic review

Review of Recurrent Otitis Media (ROM) and Persistent Otitis Media or Relapse of AOM (POMR) Systematic Reviews

Relevant to Management of Acute Otitis Media Update: Southern California Evidence-based Practice Center (RAND)

Part 1. Relevance to Key Question 4 of the Management of Acute Otitis Media Update[1]

Author (year)	Content category by KQ	Review focus	Databases and included dates	Study design, inclusion criteria	Target population	Setting	Outcomes	Cost analysis	Number of trials, participants, and comparisons	Author's highlight conclusion
Straetemans (2004)	KQ4	PPV & PCV to prevent AOM	CENTRAL (TCL, Issue2, 2003); MEDLINE (Jan 1966-Jun 2003; EMBASE (Jan 1990-June 2003); hand search	RCT	0-12y exclude follow-up <6m after vaccination	not specified a priori	AOM total number; proportion of children with AOM; bacterial culture results	No	8 trials on PPV &4 trials on PCV	PPV makes a small difference in AOM for children >2y or with AOM history; PCV reduces number of children with ROM; pneumococcal vaccine does not benefit children with ROM <1y old

[1] For quality score of each systematic review, see next table.

Appendix I. Summaries of Systematic Reviews Included in Analyses

Review of Recurrent Otitis Media (ROM) and Persistent Otitis Media or Relapse of AOM (POMR) Systematic Reviews

Relevant to Management of Acute Otitis Media Update: Southern California Evidence-based Practice Center (RAND)

Author (year)	Content category by KQ	Review focus	Databases and included dates	Study design, inclusion criteria	Target population	Setting	Outcomes	Cost analysis	Number of trials, participants, and comparisons	Author's highlight conclusion
Leach (2008)	KQ4	long-term* ab **vs** placebo or no treatment to prevent any AOM, AOM with perforation, CSOM	CENTRAL (TCL, Issue 1, 2006); MEDLINE (Jan 1966-March week 3 2006); OLD MEDLINE (1950-1965); EMBASE (1990-Dec 2005); hand search	RCT long-term ab ≥6-weeks ab	0-18y at increased risk for future AOM episodes* exclude immunodeficiency, craniofacial abnormalities, undergoing tympanostomy tube insertion, or other ENT surgery *otitis prone ≥3 AOM in 6 months or ≥4 AOM in 1 year; high-risk children with history of AOM with	not specified a priori	Primary outcomes: 1. Any AOM/CSOM during intervention 2. # episodes of AOM/CSOM during intervention per child-year Secondary outcomes: 1. recurring AOM/CSOM during intervention; 2. any AOM/CSOM at the end of intervention; 3. any SOM/CSOM following cessation of intervention;	No	Primary outcome #1: 13 studies 1358 children Primary outcome #2: 12 studies, 1112 children Secondary outcome #1: 5 studies, 329 children Secondary outcome #2: 0 studies Secondary outcome #3: 1 study, 117 children Secondary outcome #4: 0 studies. Secondary outcome #5: 11 studies, 715 children Secondary	Long-term ab reduce AOM probability while on treatment

Appendix I. Summaries of Systematic Reviews Included in Analyses

Review of Recurrent Otitis Media (ROM) and Persistent Otitis Media or Relapse of AOM (POMR) Systematic Reviews

Relevant to Management of Acute Otitis Media Update: Southern California Evidence-based Practice Center (RAND)

Author (year)	Content category by KQ	Review focus	Databases and included dates	Study design, inclusion criteria	Target population	Setting	Outcomes	Cost analysis	Number of trials, participants, and comparisons	Author's highlight conclusion
					perforation; children in high-risk populations with CSOM prevalence ≥4%		4. episodes of illness during intervention, 5. any clinical side effects during intervention 6. any antibiotic resistance during intervention.		outcome #6: 2 studies, 181 children	
McDonald (2008)	KQ4	ventilation tube **vs** non-surgical treatment* to reduce ROM and ear disease symptoms *antibiotics/ other treatment/no treatment	CENTRAL (TCL, Issue 1, 2008); MEDLINE (1950-March 2008); EMBASE (1974-March 2008); CINAHL; mRCT; NRR; LILACS; KoreaMed; IndMed; PakMediNet; Zetoc; ISI Proceedings;	RCT	0-16y with ROM* ≥3 AOM in 6 months or ≥4 AOM in 1 year	not specified a priori	Primary outcome #1: AOM frequency following treatment Primary outcome #2: proportion of children with ROM following treatment Secondary outcome #1: change in symptom scores for otalgia and otorrhoea Secondary outcome #2:	No	2 studies 148 children	Ventilation tube plays significant role to maintain a disease-free state in the first six months after tube insertion.

Review of Recurrent Otitis Media (ROM) and Persistent Otitis Media or Relapse of AOM (POMR) Systematic Reviews

Relevant to Management of Acute Otitis Media Update: Southern California Evidence-based Practice Center (RAND)

Author (year)	Content category by KQ	Review focus	Databases and included dates	Study design, inclusio n criteria	Target population	Setting	Outcomes	Cost anal- sis	Number of trials, parti- cipants, and comparison s	Author's highlight conclusio n
			Cambridge Scientific Abstracts; hand search (last search date Mar 2008)				alteration in frequency of otalgia and otorrhoea Secondary outcome #3: # days at nursery/school lost secondary to AOM			

Appendix I. Summaries of Systematic Reviews Included in Analyses

Review of Recurrent Otitis Media (ROM) and Persistent Otitis Media or Relapse of AOM (POMR) Systematic Reviews

Relevant to Management of Acute Otitis Media Update: Southern California Evidence-based Practice Center (RAND)

Author (year	Content category by KQ	Review focus	Databases and included dates	Study design, inclusion criteria	Target population	Setting	Outcomes	Cost analysis	Number of trials, participants, and comparisons	Author's highlight conclusion
Bonati (1992)	KQ4	Assess the efficacy of antibiotic prophylaxis in reducing Recurrent Acute Otitis Media (RAOM)	MEDLINE (1966 through 1991) and bibliographies of the articles	RCT English language	Patients with 3 or more documented episodes of RAOM; Diagnosed on the basis of tympanic membrane exam, and who had received continued antimicrobial prophylaxis.	Not specified	Acute otitis media rate	No	8 studies 420 children	Established the effectiveness of chemoprophylaxis in reducing the episodes of acute otitis media during the winter and spring months
Williams (1993)	KQ4	Use of antibiotics in preventing recurrent acute otitis media and in treating otitis media with effusion. (We will review only	MEDLINE (1966 through April 1993) Current Contents (1990 through 1992) Textbooks, monographs.	RCT	Recurrent acute otitis media or Otitis media with effusion	Not specified	Number of episodes of AOM per patient-month while under treatment	None	9 studies 958 subjects	Antibiotics appear to have beneficial but limited effect on recurrent otitis media

Review of Recurrent Otitis Media (ROM) and Persistent Otitis Media or Relapse of AOM (POMR) Systematic Reviews

Relevant to Management of Acute Otitis Media Update: Southern California Evidence-based Practice Center (RAND)

		the studies on recurrent acute otitis media)						

Part 1 Abbreviations and Acronyms: ab=antibiotic; amp/amox=ampicillin or amoxicillin; CENTRAL=Cochrane Central Register of Controlled Trials; CIN AHL=Cumulative Index to Nursing & Allied Health Literature CI=confidence interval; Contra Otitis=contralateral otitis; CSOM=chronic suppurative otitis media; ENT=ear, nose, and throat; HithSTAR=HealthSTAR; IPA=International Pharmaceutical Abstracts; KQ=key question for Management of AOM Update; MEE=middle ear effusion; mRCT=*meta*Register; NRR=National Research Register; Rx=treatment; PCV=pneumococcal conjugated vaccines; PPV=pneumococcal polysaccharide vaccines; ROM=recurrent otitis media; TCL=The Cochrane Library

Review of Recurrent Otitis Media (ROM) and Persistent Otitis Media or Relapse of AOM (POMR) Systematic Reviews

Relevant to Management of Acute Otitis Media Update: Southern California Evidence-based Practice Center (RAND)

Part 2. Systematic Reviews Quality (AMSTAR: See Appendix)

Author (year)	a priori design	duplicate data extraction	comprehensive literature search	publication status	list of studies	provision of study characteristics	study quality assessed	study quality used	findings combined appropriately	publication bias assessed	conflict of interest
Straetemans (2004)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes[2]	Yes	No[3]
Leach (2008)	Yes	Yes	Yes	Yes[4]	Yes	Yes	Yes	Yes	Yes[5]	Yes	No[6]
McDonald (2008)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes[7]	No	No[8]
Bonati (1992)	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No	No
Williams (1993)	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No

AMSTAR=Assessment of Multiple Systematic Reviews (Shea, Grimshaw, Wells, et al, 2007)

[2] Sensitivity analyses by study quality
[3] Conflict of interest was addressed for the systematic review but not for the included studies.
[4] Language was not a restriction; other publication issues not stated
[5] Sensitivity analyses by study quality
[6] Conflict of interest was addressed for the systematic review but not for the included studies.
[7] Excluded studies from analysis based on quality component scores.
[8] Conflict of interest was addressed for the systematic review but not for the included studies.

Appendix I. Summaries of Systematic Reviews Included in Analyses

Part 3. Comparison Table: Representative Comparisons from Systematic Reviews

Study	Comparison primary subgroup	Outcome	Trials (Citations)	# Participants or Person-months	IRR, OR, RD, RR, or WMD	95% CI
Straetemans (2004)	**PPV *vs* control**	Proportion children with AOM	7 (6)	5,495	RR 0.94	0.86 to 1.03
	<24m	Proportion children with AOM	4	3,578	RR 0.98	0.87 to 1.11
	>24m	Proportion children with AOM	2	759	RR 0.84	0.65 to 1.09
	6-54m	Proportion children with AOM	1	1,158	RR 0.90	0.77 to 1.06
		AOM episodes due to vaccine type per person month	3	47,905	RR 0.72	0.43 to 1.21
		AOM episodes due to non-vaccine type per person month	3	47,905	RR 0.91	0.60 to 1.39
		AOM episodes per person month	12 (8)	80,115	RR 0.88	0.79 to 0.97
	<24m	AOM episodes per person month	7	56,575	RR 0.93	0.84 to 1.04
	>24m	AOM episodes per person month	5	23,540	RR 0.77	0.67 to 0.89
	without previous AOM	AOM episodes per person month	4 (3)	59,333	RR 0.91	0.82 to 1.01
	<24m	AOM episodes per person month	2	45,003	RR 0.94	0.87 to 1.02
	>24m	AOM episodes per person month	2	14,330	RR 0.74	0.47 to 1.17
	with previous AOM	AOM episodes per person month	5	17,512	RR 0.80	0.69 to 0.93
	<24m	AOM episodes per person month	3	9,004	RR 0.85	0.71 to 1.02
	>24m	AOM episodes per person month	3	8,508	RR .074	0.59 to 0.93
	PCV *vs* control	Proportion children with frequent AOM	1	1,662	RR 0.91	0.75 to 1.10
		AOM episodes per	4	1,282,598	RR 0.97	0.87 to 1.08

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Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update: Southern California Evidence-based Practice Center (RAND) 9/18/2008

Study	Comparison primary subgroup	Outcome	Trials (Citations)	# Participants or Person-months	IRR, OR, RD, RR, or WMD	95% CI
		person month				
	AOM episodes due to vaccine-type per person month		2	32,353	RR 0.43	0.34 to 0.54
	AOM episodes due to non-vaccine type per person month		2	32,353	RR 1.22	0.84 to 1.75
	AOM episodes per person month in specific population		2	11,441	RR 1.05	0.66 to 1.67
Leach (2008)	ab vs control	any AOM or CSOM during intervention	13	1,358	RR 0.62	0.52 to 0.75
	<12m	"	1	117	RR 0.60	0.42 to 0.84
	>12m	"	1	21	RR 0.06	0.00 to 0.99
	Age not separated	"	11	1190	RR 0.70	0.59 to 0.84
	otitis prone	"	7	636	RR 0.72	0.62 to 0.84
	non-otitis prone	"	1	117	RR 0.60	0.42 to 0.84
	Otitis proneness not separated	"	5	603	RR 0.49	0.38 to 0.63
	high- risk population	"	1	364	RR 0.61	0.44 to 0.84
	not high- risk population	"	12	994	RR 0.62	0.51 to 0.76
	high quality randomization and allocation concealment	"	7	677	RR 0.71	0.56 to 0.89
	not high quality randomization and allocation concealment	"	6	681	RR 0.53	0.40 to 0.69
	high quality of blinding outcome assessment	"	11	1,277	RR 0.65	0.55 to 0.77
	high quality for all six criteria	"	3	389	RR 0.61	0.50 to 0.76
	<100 participants	"	7	339	RR 0.49	0.30 to 0.81
	>100 participants	"	6	1,019	RR 0.66	0.56 to 0.77
	Excluded age >36m	"	3	391	RR 0.66	0.55 to 0.78
	included age >36m	"	10	967	RR 0.58	0.43 to 0.77

Appendix I. Summaries of Systematic Reviews Included in Analyses

Study	Comparison primary subgroup	Outcome	Trials (Citations)	# Participants or Person-months	IRR, OR, RD, RR, or WMD	95% CI
	otitis prone at entry (2/6 or 3/12)	"	6	595	RR 0.68	0.54 to 0.85
	less otitis prone at entry (2/6 or 3/18; 1 before 6m age or 2/12)	"	5	293	RR 0.50	0.29 to 0.88
	free of MEE at entry	"	3	332	RR 0.53	0.35 to 0.80
free of MEE at entry not required		"	5	225	RR 0.57	0.33 to 0.99
	excluded congenital anomalies	"	8	695	RR 0.60	0.42 to 0.86
exclusion not described		"	5	681	RR 0.61	0.51 to 0.71
conducted in USA		"	8	1,021	RR 0.65	0.52 to 0.81
not conducted in USA		"	4	296	RR 0.50	0.35 to 0.71
	amox, pcn	"	8	1086	RR 0.61	0.50 to 0.74
	ssx, tmp-smx	"	8	363	RR 0.58	0.40 to 0.84
not placebo controlled		"	2	129	RR 0.28	0.02 to 3.69
	once daily	"	8	1131	RR 0.61	0.52 to 0.72
	twice daily	"	6	286	RR 0.68	0.43 to 1.06
	>3m therapy	"	2	190	RR 0.67	0.26 to 1.72
	3-6m therapy	"	8	532	RR 0.59	0.45 to 0.79
	>6m therapy	"	3	636	RR 0.62	0.50 to 0.76
monthly active surveillance		"	8	997	RR 0.67	0.57 to 0.79
4-6 weekly or 3 monthly surveillance		"	5	311	RR 0.45	0.28 to 0.72
	1970s	"	4	474	RR 0.56	0.34 to 0.94
	1980s	"	4	411	RR 0.68	0.53 to 0.87
	1990s	"	3	324	RR 0.57	0.29 to 1.11
	high compliance	"	1	171	RR 0.47	0.29 to 0.76
	not high compliance	"	1	193	RR 0.77	0.50 to 1.19
		episodes of AOM or CSOM during intervention	12	1,112	IRR 0.48	0.37 to 0.62
	<12m	"	1	33	IRR 1.53	0.68 to 3.48
	>12m	"	2	12	IRR 0.12	0.01 to 2.18
Age not separated		"	10	1046	IRR 0.45	0.35 to 0.57

Appendix I. Summaries of Systematic Reviews Included in Analyses

Study	Comparison primary subgroup	Outcome	Trials (Citations)	# Participants or Person-months	IRR, OR, RD, RR, or WMD	95% CI
	otitis prone	"	8	796	IRR 0.52	0.37 to 0.73
	Otitis proneness not separated	"	4	316	IRR 0.37	0.23 to 0.61
	high- risk population	"	1	224	IRR 0.52	0.39 to 0.70
	not high- risk population	"	11	888	IRR 0.51	0.30 to 0.87
	high quality randomization and allocation concealment	"	5	452	IRR 0.58	0.39 to 0.86
	not high quality randomization and allocation concealment	"	7	660	IRR 0.43	0.31 to 0.59
	high quality of blinding outcome assessment	"	9	821	IRR 0.55	0.43 to 0.70
	high quality for all six criteria	"	2	284	IRR 0.41	0.20 to 0.83
	<100 participants	"	8	548	IRR 0.42	0.30 to 0.61
	>100 participants	"	4	564	IRR 0.56	0.38 to 0.83
	excluded >36m	"	2	294	IRR 0.59	0.47 to 0.75
	included >36m	"	10	818	IRR 0.41	0.31 to 0.61
	otitis prone at entry (2/6 or 3/12)	"	6	627	IRR 0.47	0.30 to 0.72
	less otitis prone at entry (2/6 or 3/18; 1 before 6m age or 2/12)	"	4	171	IRR 0.59	0.38 to 0.91
	free of MEE at entry	"	3	306	IRR 0.39	0.22 to 0.67
	free of MEE at entry not required	"	7	526	IRR 0.44	0.30 to 0.65
	excluded congenital anomalies	"	7	507	IRR 0.53	0.37 to 0.76
	exclusion not described	"	5	605	IRR 0.41	0.27 to 0.64
	conducted in USA	"	8	946	IRR 0.50	0.36 to 0.70
	not conducted in USA	"	3	97	IRR 0.33	0.20 to 0.52
	amox, pcn	"	6	631	IRR 0.50	0.36 to 0.70
	ssx, tmp-smx	"	7	503	IRR 0.52	0.28 to 0.96
	not placebo controlled	"	2	269	IRR 0.27	0.19 to 0.39
	once daily	"	7	701	IRR 0.53	0.39 to 0.71

Appendix I. Summaries of Systematic Reviews Included in Analyses

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update: Southern California Evidence-based Practice Center (RAND) 9/18/2008

Study	Comparison primary subgroup	Outcome	Trials (Citations)	# Participants or Person-months	IRR, OR, RD, RR, or WMD	95% CI
	twice daily	"	6	467	IRR 0.49	0.27 to 0.87
	>3m therapy	"	2	86	IRR 0.62	0.15 to 2.53
	3-6m therapy	"	5	189	IRR 0.47	0.33 to 0.68
	>6m therapy	"	5	837	IRR 0.45	0.32 to 0.63
	monthly active surveillance	"	7	698	IRR 0.55	0.41 to 0.72
	4-6 weekly or 3 monthly surveillance	"	5	414	IRR 0.32	0.19 to 0.56
	1970s	"	1	43	IRR 0.50	0.26 to 0.98
	1980s	"	3	338	IRR 0.55	0.42 to 0.71
	1990s	"	3	138	IRR 0.47	0.16 to 1.35
	high compliance	"	2	140	IRR 0.36	0.24 to 0.54
	not high compliance	"	2	153	IRR 0.87	0.62 to 1.22
		any rAOM or CSOM during intervention	5	329	RR 0.45	0.20 to 1.01
		episodes of illness during intervention	1	730	RR 0.84	0.72 to 0.97
		any clinical side effects during intervention	11	714	RR 1.99	0.25 to 15.89
		any antibiotic resistance during intervention	2	181	RR 1.37	0.83 to 2.26
McDonald (2008)	grommets vs control	>1 episode of AOM	2	148	OR 0.18	0.08, 0.42
Bonati (1992)	Antimicrobial prophylaxis vs placebo	Recurrence of acute otitis media	8	420	OR 0.23	0.16 to 0.34
Williams (1993)	Antibiotics vs placebo	Recurrence rate (as defined above)	9	958	RD 0.11	0.03 to 0.19

Part 3 Abbreviations and Acronyms: ab=antibiotic; abnl=abnormal; amox-clav=amoxicillin-clavulanate; amp/amox=ampicillin or amoxicillin; azith=azithromycin; CI=confidence interval; ery=erythromycin; GI=gastrointestinal; imm=immediate; IRR=incidence rate ratio; OM=otitis media; OR=odds ratio; pcn=penicillin; RD=rate difference; Risk=Risk Ratio; RR=relative risk; sulfisox=sulfisoxazole; TM=tympanic membrane; TMP-SMX=trimethoprim-sulfamethoxazole; top=topical; WMD=weighted mean difference

Appendix I. Summaries of Systematic Reviews Included in Analyses

Review of Acute Otitis Media (AOM) Systematic Reviews Relevant to Management of Acute Otitis Media Update:

Southern California Evidence-based Practice Center (RAND) 9/18/2008

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Appendix I. Summaries of Systematic Reviews Included in Analyses

Appendix: AMSTAR Quality Indicators (Shea, Grimshaw, Wells, et al, 2007)

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	□ Yes □ No □ Can't answer □ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	□ Yes □ No □ Can't answer □ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	□ Yes □ No □ Can't answer □ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	□ Yes □ No □ Can't answer □ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	□ Yes □ No □ Can't answer □ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	□ Yes □ No □ Can't answer □ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	□ Yes □ No □ Can't answer □ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	□ Yes □ No □ Can't answer □ Not applicable

9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	□ Yes □ No □ Can't answer □ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	□ Yes □ No □ Can't answer □ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	□ Yes □ No □ Can't answer □ Not applicable

Appendix J. Comparison of Original Research Studies Included in Systematic Reviews

Incl=Included
Ref=In reference list, but not specifically included
excl=Excluded

	Damoiseaux 1998 - "Antibiotic treatment of acute otitis media in children under 2 years of age" Br.J.Gen.Prac. 48(437): 1861-1864	Foxlee 2006 - "Topical analgesia for acute otitis media" Cochr. Database Syst Revs (3)	Glasziou 2004 - "Antibiotics for acute otitis media in children" Cochr. Database Syst Revs (1)	Kozyrskyj 2000 - "Short course antibiotics for acute otitis media" Cochr. Database Syst Revs (2)	Rosenfeld 1994 - "Clinical efficacy of antimicrobial drugs for acute otitis media: metaanalysis..." J. Pediatrics 124:355-367	Rovers 2006 - "Antibiotics for acute otitis media: a meta-analysis..." Lancet 368(9545): 1429-1435	Spurling 2007 - "Delayed antibiotics for respiratory infections" Cochr. Database Syst Revs (3)	Takata 2001 - "Evidence assessment of management of acute otitis media: I. The role of antibiotics..." Pediatrics 108:239-247	AHRQ Report No. 15 - "Management of Acute Otitis Media" - References	Bonati 1992 -"Metaanalysis of antimicrobial prophylaxis for recurrent acute otits-media" Clinical Trials and Meta-Analysis 28(1):39-50	Leach 2006 - "Antibiotics for the prevention of acute and chronic suppurative otitis media in children" Cochrane Collaboration 2009, Issue 1	McDonald 2008 - "Grommets (ventilation tubes) for recurrent acute otitis media in children (Review)." The Cochrane Collaboration, 2009, Issue 1	Straetemans 2004 - "Pnemococcal vaccines for preventing otitis media (Review)", Cochrane Collaboration 2008(3).	Williams 2003 - " Use of antibiotics in preventing recurrent otitis media and in treating otitis media with effusion: A meta-analytic attempt to resolve the brouhaha," JAMA 270(11):1344-1351.	Rothman 2003 - "Does this child have acute otitis media?" JAMA 2003; 290(12):1633-1640	Abes 2003 - "A systematic review of the effectiveness of ofloxaxin[sic] for the treatment of suppurative otitis media," ORL J Otorhinolaryngol Relat Spec. 2003;65:106-116.	Thanavirataananich 2008 - "Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media (Review)." Cochrane Collaboration 2009	Wall 2009 -"Ciprofloxacin 0.3%/Dexamethasone 0.1% Sterile Otic Suspension for the Topical treatment of ear infections: A review of the literature." Pediatric Infectious Disease Journal, 28(2):141-144.
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