Adverse Events of Antibiotics Used to Treat Acute Otitis Media in Children: A Systematic Meta-Analysis

Stephanie W. Hum, BS[1], Kai J. Shaikh[2], Samar S. Musa, BS[2], and Nader Shaikh, MD, MPH[1,2]

Objective To characterize the incidence of adverse events (AEs) associated with antibiotics used to treat acute otitis media in children.

Study design We searched MEDLINE for studies conducted between January 1, 1966, and August 25, 2018. Two authors independently assessed potential studies and extracted the data. We included published randomized controlled trials, cross-sectional studies, and cohort studies that evaluated the incidence of diarrhea, generalized rash, diaper rash, and candidal diaper dermatitis associated with the use of amoxicillin, amoxicillin/clavulanate, azithromycin, cefdinir, and placebo in children with acute otitis media.

Results We included 82 studies in the meta-analysis. The incidence of diarrhea, listed from lowest to highest, was azithromycin (2.2%), placebo (6.9%), low-dose amoxicillin (8.7%), cefdinir (13.0%), high-dose amoxicillin (13.8%), and high-dose amoxicillin/clavulanate (18.9%). The incidence of generalized rash, listed from lowest to highest, was azithromycin (1.4%), placebo (2.3%), low-dose amoxicillin (2.9%), high-dose amoxicillin/clavulanate (4.9%), and high-dose amoxicillin (6.5%). In studies of low-dose amoxicillin, we found a higher incidence of diarrhea in studies that used daily diaries to collect information about diarrhea and a lower incidence of generalized rash in studies that reported only rashes judged to be secondary to antibiotic use.

Conclusions The incidence of AEs varies widely depending on which antibiotic is used and how the information on AEs was collected or reported. The AEs rates reported here may be helpful to clinicians when choosing an antibiotic to treat acute otitis media. *(J Pediatr 2019;215:139-43)*.

Of all the medication classes prescribed to children, antibiotics are responsible for the majority of adverse events (AEs) in both hospital and community settings,[1] and acute otitis media (AOM) is the most frequent reason antibiotics are prescribed.[1,2] Clinicians' choice of antibiotic is influenced largely by their perception of patient adherence, which is largely driven by the antibiotic's common AE profile.[3,4] For example, even though the efficacy of cefdinir at eradicating pathogens responsible for AOM is relatively low,[5,6] it is the second most frequently prescribed antibiotic for AOM primarily because it is perceived to cause less diarrhea.[7] Accordingly, a thorough understanding of the common AEs associated with the use of antibiotics used to treat children with AOM is essential; only then can informed decisions be made regarding antibiotic choice and the risks and benefits of prescribing antibiotics. Although many systematic reviews have been conducted comparing the efficacy of the antibiotics used to treat AOM in children, to our knowledge, no systematic reviews have evaluated the incidence of AEs in these patients.

One systematic review evaluated the AEs of amoxicillin and amoxicillin/clavulanate prescribed for any indication compared with placebo and found that diarrhea did not occur significantly more than placebo with amoxicillin, but did occur significantly more with amoxicillin/clavulanate.[8] This review also evaluated rash, nausea, itching, vomiting, and abnormal liver function tests, but none of these entities were significantly increased compared with placebo. However, this study was not exclusive to children, did not quantify the pooled prevalence for each AE, and did not differentiate between dosing regimens of amoxicillin or amoxicillin/clavulanate, which can significantly affect the reported incidence of AEs.

The objective of this study was to characterize the incidence of common AEs associated with the 4 most frequently used antibiotics for treating AOM (amoxicillin, amoxicillin/clavulanate, azithromycin, and cefdinir) and placebo. We chose to focus on common rather than severe AEs because severe AEs associated with the considered antibiotics are exceedingly rare, trials to date evaluating these antibiotics have been relatively small, and meta-analysis of rare events is fraught with difficulties.[9]

AE	Adverse event
AOM	Acute otitis media

From the [a]Department of Pediatrics, University of Pittsburgh School of Medicine, and the [b]Division of General Academic Pediatrics, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA

The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2019.08.043

Methods

We considered published randomized controlled trials, cross-sectional studies, and cohort studies that reported the incidence of diarrhea, generalized rash, diaper rash, or candida diaper dermatitis in children 0-19 years of age receiving oral antibiotics for uncomplicated AOM. We only considered studies that evaluated the 4 most frequently used antibiotics for treating AOM (amoxicillin, amoxicillin/clavulanate, azithromycin, and cefdinir)[7] and on placebo for comparison. We excluded case-control studies and studies that included fewer than 30 children because these studies may distort results of meta-analyses.[10,11]

We searched MEDLINE for studies conducted between January 1, 1966, and August 25, 2018. We limited the search to human studies published in English. Additional studies were identified by reviewing the reference lists of important review articles retrieved from the search (see **Appendix** [available at www.jpeds.com] for the complete search strategy). The review protocol was not published online before study completion.

Two authors independently assessed the titles, abstracts, and, if necessary, the full text of studies found using the search strategy to determine whether they satisfied the inclusion criteria.

Data extraction was carried out by 2 authors using standardized data extraction forms. Uncertainties in data extraction were resolved by discussion. When possible, we contacted study authors for clarification. When more than 1 publication of a study existed, we used the publication with the most complete data in the analyses. We also extracted data on whether diaries were used to collect data on AEs and whether authors reported all observed AEs or only those judged to be attributable to the antibiotic being studied.

Amoxicillin was subdivided into low-dose (<80 mg/kg/day) and high-dose (≥80 mg/kg/day) formulations. We only included the high-dose formulation of amoxicillin/clavulanate (90/6.4 mg/kg/day) and the low-dose formulation of azithromycin (<10 mg/kg/day) because these formulations are the only ones currently available for AOM. Because short courses of antibiotics are less efficacious in treating AOM,[12] we only included studies in which antibiotics were administered for at least 7 days in the main analysis with 1 exception; we chose to include studies that used 5 days of azithromycin because of the relatively long half-life of this antibiotic. We report data for shorter antibiotic courses in the **Appendix**.

For studies reporting prevalence of diarrhea, we only included those that used the term "diarrhea"; articles that used other terms (eg, "loose stool," "gastrointestinal side effects," "stool changes,") were not included. Similarly, we only included studies in which we could discern whether the rash reported was generalized or in the diaper area. We did not include articles that described rash using the terms "eczema," "atopic dermatitis," "skin scaly," "infection skin," or "skin allergy."

We calculated the incidence of each AE by dividing the number of children with the AE by the total number of children assessed for that AE. In 10 studies, the population of children assessed for the AE was not reported; in these studies, we used the enrollment population, or if this was not reported, the population used for the efficacy analysis, as the denominator. We excluded studies in which the reported data was unclear or inconsistent.

We performed this meta-analysis using random effects models (Dersimonian and Laird) and used I^2 values to assess heterogeneity. We used random effects meta-regression to identify whether the use of diaries or treatment attribution influenced the reported incidence of AEs. To allow us to include studies in which prevalence of AEs were 0%, we performed a double arcsine transformation before pooling and an arcsine transformation after.[13]

We also used meta-regression to evaluate whether or not studies with a high risk of bias influenced the reported incidence of AEs. We assessed the risk of bias using the ROBINS-I tool, which is suitable for assessing both randomized and nonrandomized studies in the same review.[14] Overall, we considered the study to have a low risk of bias if all of the criteria were judged to be low risk and a high risk of bias if any of the criteria were judged to be high risk.

Owing to the low power of meta-regression,[15] we performed meta-regression only for comparisons that included at least 15 studies. STATA version 14.0 (StataCorp, College Station, Texas) and R studio version 1.1 (The R Foundation, Vienna, Austria) was used to perform all analyses.

Results

The results of the search strategy are shown in **Figure 1**. Of the 1087 articles found through the search strategy, we retrieved and reviewed 206 full-text articles; of these, 82 articles (**Table I** [available at www.jpeds.com] lists the characteristics of included studies) reported incidence of diarrhea, generalized rash, diaper rash, and/or candidal diaper dermatitis for the 4 frequently used antibiotics and placebo.

The incidence of diarrhea, generalized rash, diaper rash, and candidal diaper dermatitis for the 4 frequently used antibiotics and placebo are reported in **Table II**. The incidence (CI) of diarrhea, listed in order from lowest to the highest, was: 2.2% (1.4%-3.0%) for azithromycin, 6.9% (2.8%-12.4%) for placebo, 8.7% (6.2%-11.6%) for low-dose amoxicillin, 13.0% (11.2%-14.7%) for cefdinir, 13.8% (4.7%-22.9%) for high-dose amoxicillin, and 18.9% (14.7%-23.1%) for high-dose amoxicillin/clavulanate. The incidence of generalized rash listed in order from lowest to highest was: 1.4% (0.2%-3.2%) for azithromycin, 2.3% (0.3%-5.5%) for placebo, 2.9% (1.7%-4.4%) for low-dose amoxicillin, 4.9% (2.4%-7.4%) for high-dose amoxicillin/clavulanate, and 6.5% (0.0%-15.3%) for high-dose amoxicillin. The amount of heterogeneity was generally large (76% of analyses had I^2 values of >50%). Data regarding incidence of AEs when using shorter courses than is customary is presented in **Table III** (available at www.jpeds.com).

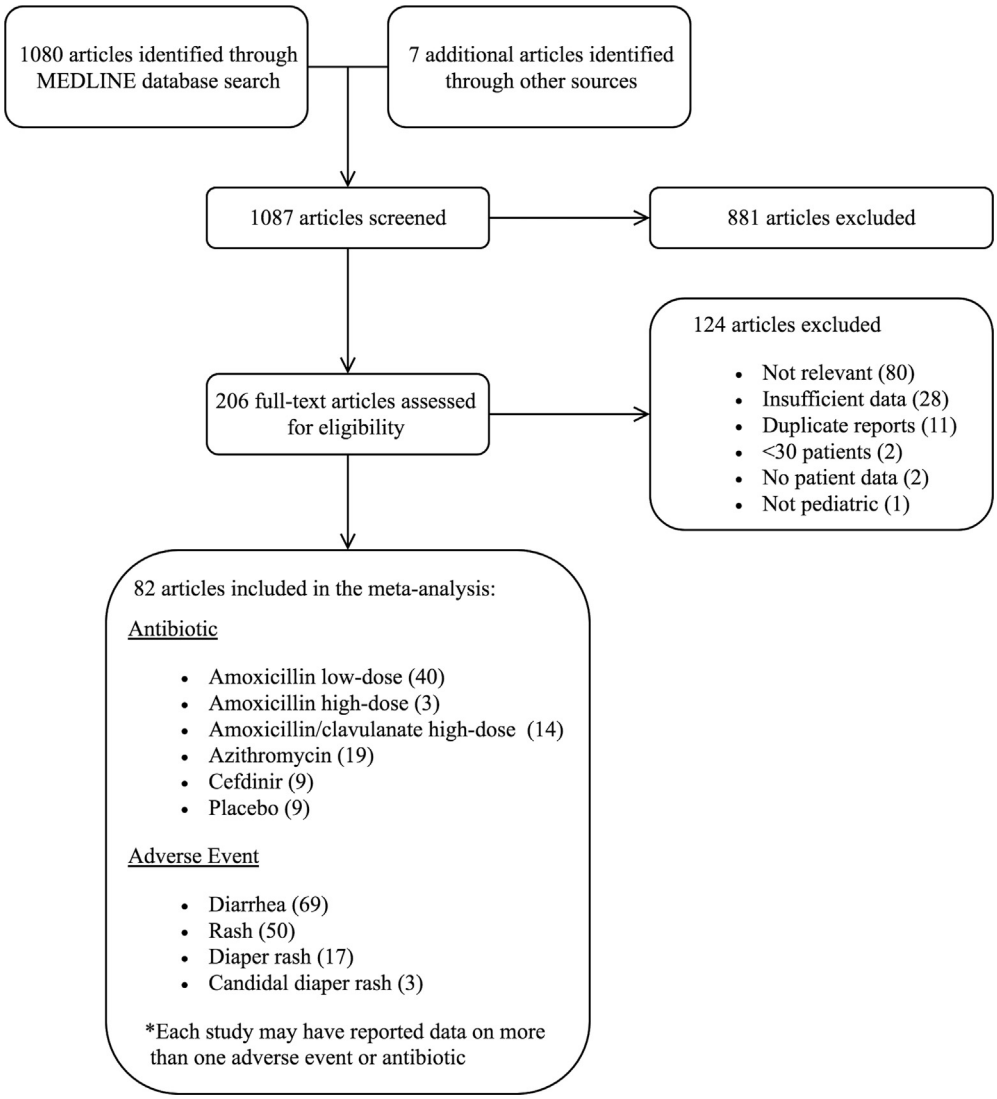

Figure 1. Study flow diagram.

For low-dose amoxicillin, which was the only antibiotic for which meta-regression was possible, the reported incidence of diarrhea was significantly higher ($P = .006$) in studies that used diaries to collect data on diarrhea (**Figure 2**). The incidence of generalized rash was similar in studies that used diaries and studies that did not ($P = .34$). The incidence of generalized rash was lower in studies that only reported rashes attributed to the antibiotic treatment compared with studies that reported all observed rashes ($P = .01$; **Figure 2**). The number of studies was insufficient to explore relationships between diarrhea and selective reporting.

The risk of bias was generally high; 61 studies (74%) were judged to be at high risk of bias on at least 1 domain on the ROBINS-I risk of bias tool. The main issues (**Figure 3** and **Figure 4**; available at www.jpeds.com) were reporting bias (ie, only AEs judged to be related to the study product were reported) and measurement bias (ie, participants and their parents were not blinded). On the positive side, no studies used co-interventions that could plausibly affect the incidence of reported AEs and the amount missing data was negligible in most studies included. The risk of bias did not explain heterogeneity between studies.

Discussion

The incidence of diarrhea associated with the use of antibiotics used to treat AOM ranged from 2.2% to 18.9%. The incidence of diarrhea was lowest in children receiving azithromycin and highest in children receiving high-dose amoxicillin/clavulanate. The incidence of generalized rash associated with the use of antibiotics used to treat AOM ranged from 1.4% to 6.5%. The incidence of generalized rash was lowest in children receiving azithromycin and highest in children receiving high-dose amoxicillin. The incidence of diarrhea and generalized rash for high-dose amoxicillin, which is currently the first-line therapy for

Table II. Prevalence of AEs for frequently used antibiotics compared to placebo in the treatment of children with uncomplicated AOM

AEs/antibiotics*	No. of studies	No. of children with finding/total	Pooled prevalence % (CI)	I^2 (%)
Diarrhea				
Azithromycin	8	38/1443	2.2 (1.4-3.0)	10.1
Placebo	9	112/1022	6.9 (2.8-12.4)	88.0
Amoxicillin LD	29	251/2582	8.7 (6.2-11.6)	80.1
Cefdinir	7	184/1388	13.0 (11.2-14.7)	0.0
Amoxicillin HD	2	29/179	13.8 (4.7-22.9)	57.3
Amoxicillin/clavulanate HD	14	649/3519	18.9 (14.7-23.1)	91.0
Generalized rash				
Azithromycin	2	5/285	1.4 (0.2-3.2)	–
Placebo	6	32/782	2.3 (0.3-5.5)	79.4
Amoxicillin LD	26	82/2093	2.9 (1.7-4.4)	60.4
Amoxicillin/clavulanate HD	7	80/1631	4.9 (2.4-7.4)	87.2
Amoxicillin HD	2	13/231	6.5 (0.0-15.3)	81.8
Diaper Rash				
Placebo	2	24/305	4.6 (2.4-7.3)	–
Amoxicillin LD	4	20/251	6.4 (1.2-14.7)	77.3
Cefdinir	1	16/159	10.1 (5.4-14.7)	–
Amoxicillin/clavulanate HD	8	359/2673	14.8 (8.7-20.9)	97.2
Candidal diaper rash				
Amoxicillin/clavulanate HD	1	15/452	3.3 (1.7-5.0)	–
Amoxicillin LD	2	6/82	5.8 (1.3-12.3)	–

–, I^2 was not calculable; *HD*, high-dose (amoxicillin ≥80 mg/kg/day); *LD*, low-dose (amoxicillin <80 mg/kg/day).
*All given for ≥7 days except for azithromycin, which was given for 5 days.

uncomplicated AOM,[16] was 13.8% and 6.5%, respectively. The corresponding numbers for high-dose amoxicillin/clavulanate, currently the second-line therapy, were 18.9% and 4.9%, respectively.

The incidence of diarrhea in children on placebo was relatively high (6.9%). However, children in the included studies invariably had upper respiratory infections, which may partly explain this high incidence. Accordingly, a significant proportion of AEs observed in clinical trials may be unrelated to the antibiotic being evaluated. The high incidence of AEs associated with the use of placebo may be important to consider when evaluating the costs and benefits of antibiotic treatment.

Few studies to date have systematically explored whether differences in the methods of obtaining or reporting data on AEs can significantly influence the reported incidence of AEs. One previous study of analgesics suggested that studies using daily

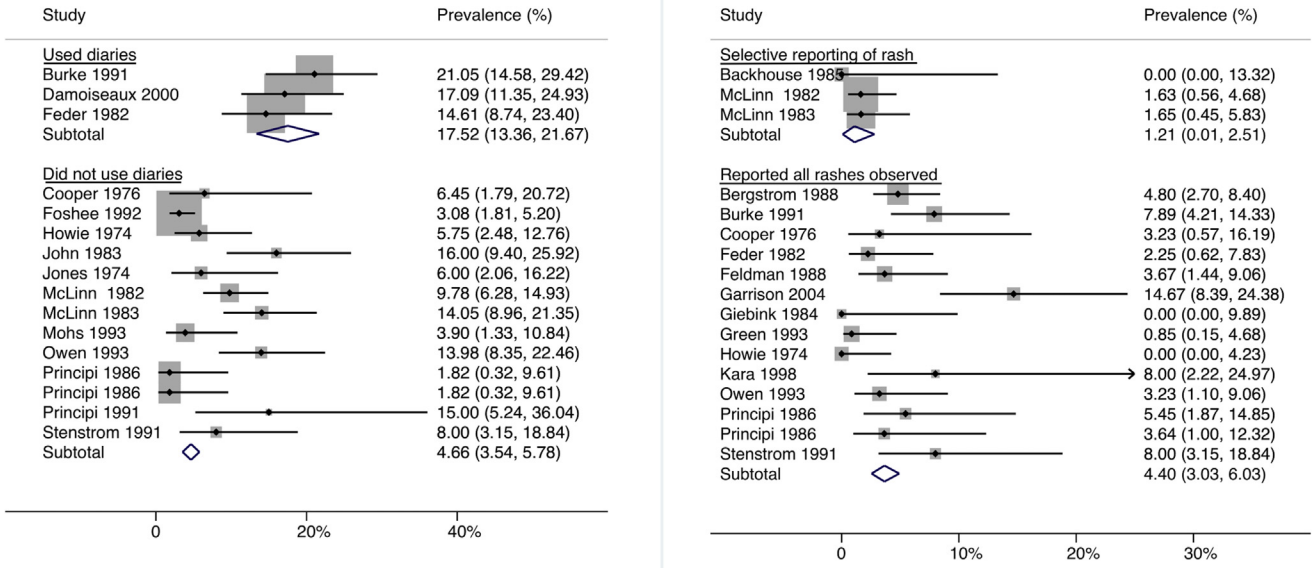

Figure 2. Effect of using diaries on rates of diarrhea (P = .006; *left*) and effect of selective reporting on rates of generalized rash (P = .01; *right*) in children with AOM treated with low-dose amoxicillin.

diaries to collect information about AEs improved AEs reporting.[17] We found some evidence to support this notion; studies of low-dose amoxicillin that used diaries to collect AEs data reported a significantly higher incidence of diarrhea than studies that did not use diaries. We found no significant difference in the incidence of generalized rash between studies that used diaries and studies that did not. We hypothesize that diarrhea, which usually occurs in the first 5 days of therapy, would not likely have been reported at study visits (which generally occur at the end of therapy) were it not for daily data collection using a diary. In contrast, the occurrence of a ash, is unlikely to be forgotten quickly, and thus reporting at study visits would likely capture the same information as a diary. Based on these findings, we suggest that authors explicitly report how the data on AEs were collected (ie, written questionnaire, interview, diary), which is consistent with the recommendation of the CONSORT extension for harms reporting.[18]

We also found that, in studies of low-dose amoxicillin, the incidence of generalized rash was lower in studies that only reported rashes attributed to treatment compared with studies that reported all observed rashes. We hypothesize that, whereas most episodes of diarrhea would be attributed to antibiotics by the investigators, episodes of rash could have more frequently been attributed to other causes. Based on these findings we feel that it is important for authors to explicitly state whether reported AEs include all observed AEs or only those attributed to the study product; reporting both incidences would facilitate between-study comparisons. The 2004 CONSORT extension for harms reporting recommends that, if the authors decide to report only a subset of AEs observed, they should specify the definitions used, the qualifications of the investigator making the decision, and whether the decision maker was blinded to treatment allocation.[18]

The high level of heterogeneity in the pooled values and the high-risk of bias in some of the included studies are limitations. Heterogeneity notwithstanding, the analysis presented can provide practitioners with a better overall understanding of the incidence of AEs associated with the use of antibiotics used to treat children with AOM and will help practitioners to weigh the overall risks of antibiotic treatment when making clinical decisions. The high variability between studies allowed us to conclude that differences in methodology (ie, use of diaries and selective reporting) did influence the incidence of the AEs being reported.

We encourage authors of randomized controlled trials to follow the guidelines in the CONSORT extension for harms reporting, as this will aid in the interpretation of the study findings and facilitate between-study comparisons. A sample form that investigators can use to record AEs in future trials of children with AOM is shown in **Figure 5** (available at www.jpeds.com). ■

Submitted for publication May 31, 2019; last revision received Jul 17, 2019; accepted Aug 21, 2019.

Reprint requests: Nader Shaikh, MD, MPH, Children's Hospital of Pittsburgh, General Academic Pediatrics, 4401 Penn Avenue, Pittsburgh, PA 15224. E-mail: nader.shaikh@chp.edu

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Table I. Characteristic of 82 included studies evaluating AEs of antibiotics used to treat acute otitis media in children

First Author	Year	Article title	Antibiotics evaluated	No. of patients evaluated for AEs	Age range	Randomized trial
Adler	1997	Cefdinir vs amoxicillin/clavulanic acid in the treatment of suppurative acute otitis media in children	Amoxicillin/clavulanate, Cefdinir	752	6 months-12 years	Yes
Arguedas	1996	Comparative trial of 3-day azithromycin vs 10-day amoxycillin/clavulanate potassium in the treatment of children with acute otitis media with effusion	Amoxicillin/clavulanate, Azithromycin	92	6 months-12 years	Yes
Arguedas	1997	Comparative trial of 3 days of azithromycin vs 10 days of clarithromycin in the treatment of children with acute otitis media with effusion	Azithromycin, Clarithromycin	97	6 months-12 years	Yes
Arguedas	2003	A pilot study of single-dose azithromycin vs three-day azithromycin or single-dose ceftriaxone for uncomplicated acute otitis media in children	Azithromycin, Ceftriaxone	132	6 months-5 years	Yes
Arguedas	2005	A randomized, multicenter, double blind, double dummy trial of single dose azithromycin vs high dose amoxicillin for treatment of uncomplicated acute otitis media	Amoxicillin	154	6-30 months	Yes
Arguedas	2006	A multicenter, open label, double tympanocentesis study of high dose cefdinir in children with acute otitis media at high risk of persistent or recurrent infection	Cefdinir	447	6 months-4 years	Yes
Arguedas	2011	Single-dose extended-release azithromycin vs a 10-day regimen of amoxicillin/clavulanate for the treatment of children with acute otitis media	Amoxicillin/clavulanate, Azithromycin	902	No age listed	Yes
Aronovitz	1974	Middle ear infections in pediatric patients: treatment with amoxicillin	Amoxicillin, Ampicillin	67	2-15 years	No
Aronovitz	1996	A multicenter, open label trial of azithromycin vs amoxicillin/clavulanate for the management of acute otitis media in children	Amoxicillin/clavulanate, Azithromycin	169	2-15 years	Yes
Arrieta	2003	High-dose azithromycin vs high-dose amoxicillin-clavulanate for treatment of children with recurrent or persistent acute otitis media	Amoxicillin/clavulanate, Azithromycin	300	6 months-6 years	Yes
Backhouse	1985	Trimethoprim and amoxycillin in acute otitis media	Amoxicillin	25	12 months-12 years	Yes
Bergstrom	1988	Clinical evaluation of rectally administered ampicillin in acute otitis media	Amoxicillin	229	6 months-12 years	Yes
Berman	1983	A controlled trial of cefaclor vs amoxicillin for treatment of acute otitis media in early infancy	Amoxicillin, Cefaclor	40	<3 months	Yes
Biner	2007	The comparison of single-dose ceftriaxone, five-day azithromycin, and ten-day amoxicillin/clavulanate for the treatment of children with acute otitis media	Amoxicillin/clavulanate, Azithromycin, Ceftriaxone	104	6 months-10 years	Yes
Block (Comparative)	2000	Comparative safety and efficacy of cefdinir vs amoxicillin/clavulanate for treatment of suppurative acute otitis media in children	Amoxicillin/clavulanate, Cefdinir	384	6 months-12 years	Yes
Block (Five-day cefdinir)	2000	Five-day cefdinir course vs ten-day cefprozil course for treatment of acute otitis media	Cefdinir, Cefprozil	435	6 months-12 years	Yes
Block (Five-day twice)	2000	Five-day twice daily cefdinir therapy for acute otitis media: microbiologic and clinical efficacy	Cefdinir	177	6 months-12 years	No
Block	2004	Comparison of five-day cefdinir treatment with ten-day low dose amoxicillin/clavulanate treatment for acute otitis media	Amoxicillin/clavulanate, Cefdinir	425	6 months-6 years	Yes
Block	2005	A comparison of 5 days of therapy with cefdinir or azithromycin in children with acute otitis media: a multicenter, prospective, single-blind study	Azithromycin, Cefdinir	357	6 months-6 years	Yes
Block	2006	Efficacy, tolerability, and parent reported outcomes for cefdinir vs high-dose amoxicillin/clavulanate oral suspension for acute otitis media in young children	Amoxicillin/clavulanate, Cefdinir	318	6 months-6 years	Yes

(*continued*)

Table I. Continued

First Author	Year	Article title	Antibiotics evaluated	No. of patients evaluated for AEs	Age range	Randomized trial
Bottenfield	1998	Safety and tolerability of a new formulation (90 mg/kg/day divided every 12 h) of amoxicillin/clavulanate (Augmentin) in the empiric treatment of pediatric acute otitis media caused by drug-resistant Streptococcus pneumoniae	Amoxicillin/clavulanate	408	3 months-12 years	Yes
Brook	2002	Effect of amoxicillin and co-amoxiclav on the aerobic and anaerobic nasopharyngeal flora	Amoxicillin/clavulanate, Amoxicillin	50	9 months-5 years	No
Brook	2005	Effects of amoxicillin and cefdinir on nasopharyngeal bacterial flora	Amoxicillin, Cefdinir	50	7-64 months	No
Burke	1991	Acute red ear in children: controlled trial of non-antibiotic treatment in general practice	Amoxicillin, Placebo	232	3-10 years	Yes
Coles	1993	A comparative study of clarithromycin and amoxycillin suspensions in the treatment of pediatric patients with acute otitis media	Amoxicillin, Clarithromycin	259	1-12 years	Yes
Cooper	1976	A comparison between co-trimoxazole and amoxycillin in the treatment of acute otitis media in general practice	Amoxicillin, Trimethoprim-Sulfamethoxazole	61	>6 months	Yes
Dagan	2000	Bacteriologic and clinical efficacy of amoxicillin/clavulanate vs azithromycin in acute otitis media	Amoxicillin/clavulanate, Azithromycin	238	6-48 months	Yes
Dagan	2001	Bacteriologic and clinical efficacy of high dose amoxicillin/clavulanate in children with acute otitis media	Amoxicillin/clavulanate	521	3-48 months	No
Damoiseaux	2000	Primary care based randomised, double blind trial of amoxicillin vs placebo for acute otitis media in children aged under 2 years	Amoxicillin, Placebo	240	6-24 months	Yes
Dohar	2006	Topical ciprofloxacin/dexamethasone superior to oral amoxicillin/clavulanic acid in acute otitis media with otorrhea through tympanostomy tubes	Amoxicillin/clavulanate	41	6 months-12 years	Yes
Dunne	2003	Randomized, double-blind study of the clinical efficacy of 3 days of azithromycin compared with co-amoxiclav for the treatment of acute otitis media	Amoxicillin/clavulanate, Azithromycin	373	6 months-12 years	Yes
Engelhard	1989	Randomised study of myringotomy, amoxycillin/clavulanate, or both for acute otitis media in infants	Amoxicillin/clavulanate, Placebo/Myringotomy	90	3-12 months	Yes
Feder	1982	Comparative tolerability of ampicillin, amoxicillin, and trimethoprim-sulfamethoxazole suspensions in children with otitis media	Amoxicillin	263	2 months-7 years	Yes
Feldman	1988	Trimethoprim-sulfamethoxazole v. amoxicillin in the treatment of acute otitis media	Amoxicillin, Trimethoprim-Sulfamethoxazole	221	1-14 years	Yes
Foshee	1992	Comparative United States and European trials of loracarbef in the treatment of acute otitis media	Amoxicillin/clavulanate, Loracarbef	472	6 months-12 years	Yes
Garrison	2004	High-dose vs standard-dose amoxicillin for acute otitis media	Amoxicillin	152	>3 months	Yes
Gehanno	1999	Eradication by ceftriaxone of Streptococcus pneumoniae isolates with increased resistance to penicillin in cases of acute otitis media	Amoxicillin	186	5 months-5 years	No
Ghaffar	2002	Effects of large dosages of amoxicillin/clavulanate or azithromycin on nasopharyngeal carriage of Streptococcus pneumoniae, Haemophilus influenzae, nonpneumococcal alpha-hemolytic streptococci, and Staphylococcus aureus in children with acute otitis media	Amoxicillin/clavulanate, Azithromycin	115	6 months-6 years	Yes
Giebink	1984	Cefaclor v amoxicillin in treatment of acute otitis media	Amoxicillin, Cefaclor	72	3 months-17 years	Yes
Green	1993	Single-dose intramuscular ceftriaxone for acute otitis media in children	Amoxicillin, Ceftriaxone	233	5 months-5 years	Yes
Guven	2006	Bacterial etiology of acute otitis media and clinical efficacy of amoxicillin-clavulanate vs azithromycin	Amoxicillin/clavulanate, Azithromycin	174	6 months-12 years	Yes
Hedrick	2001	Cefprozil vs high-dose amoxicillin/clavulanate in children with acute otitis media	Amoxicillin/clavulanate, Cefprozil	303	6 months-7 years	Yes
Hoberman	2005	Large dosage amoxicillin/clavulanate, compared with azithromycin, for the treatment of bacterial acute otitis media in children	Amoxicillin/clavulanate, Azithromycin	730	6-30 months	Yes

(*continued*)

Table I. Continued

First Author	Year	Article title	Antibiotics evaluated	No. of patients evaluated for AEs	Age range	Randomized trial
Hoberman	2011	Treatment of acute otitis media in children under 2 years of age	Amoxicillin/clavulanate, Placebo	291	6-23 months	Yes
Hoberman	2016	Shortened antimicrobial treatment for acute otitis media in young children	Amoxicillin/clavulanate	515	6-23 months	Yes
Honig	1988	Amoxicillin and diaper dermatitis	Amoxicillin	57	2-24 months	No
Howie	1974	Comparison of ampicillin and amoxicillin in the treatment of otitis media in children	Amoxicillin, Ampicillin	123	1-76 months	Yes
John	1983	Treatment of otitis media in children. A comparison between cefaclor and amoxycillin	Amoxicillin, Cefaclor	150	6 months-6 years	Yes
Johnson	1991	Cefixime compared with amoxicillin for treatment of acute otitis media	Amoxicillin, Cefixime	110	2 months-13 years	Yes
Jones	1974	Treatment of otitis media in pediatric practice: amoxicillin vs ampicillin	Amoxicillin, Ampicillin	75	2 months-10 years	No
Kara	1998	Comparison of amoxicillin with second and third generation cephalosporins in the treatment of acute otitis media	Amoxicillin, Ceftriaxone, Cefuroxime axetil	75	6 months-6 years	Yes
Khurana	1996	A multicenter, randomized, open label comparison of azithromycin and amoxicillin/clavulanate in acute otitis media among children attending day care or school	Amoxicillin/clavulanate, Azithromycin	526	6 months-12 years	Yes
Le Saux	2005	A randomized, double-blind, placebo-controlled noninferiority trial of amoxicillin for clinically diagnosed acute otitis media in children 6 months to 5 years of age	Amoxicillin, Placebo	475	6 months-6 years	Yes
Leigh	1989	A general practice comparative study of a new third-generation oral cephalosporin, cefixime, with amoxycillin in the treatment of acute paediatric otitis media	Amoxicillin, Cefixime	325	6 months-16 years	Yes
Little	2001	Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media	Amoxicillin	185	6 months-10 years	Yes
Mandel	1993	A comparative evaluation of cefaclor and amoxicillin in the treatment of acute otitis media	Amoxicillin, Cefaclor	157	7 months-12 years	Yes
McCarty	1996	A multicenter, open label trial of azithromycin for the treatment of children with acute otitis media	Azithromycin	200	1-15 years	No
McLinn	1980	Cefaclor in treatment of otitis media and pharyngitis in children	Amoxicillin, Cefaclor	173	1 months-11 years	Yes
McLinn	1982	Double-blind multicenter comparison of cyclacillin and amoxicillin for the treatment of acute otitis media	Amoxicillin	184	2 months-14 years	Yes
McLinn	1983	Cyclacillin vs amoxicillin as treatment for acute otitis media	Amoxicillin	121	2 months-11 years	Yes
McLinn	1987	Randomized, open label, multicenter trial of cefixime compared with amoxicillin for treatment of acute otitis media with effusion	Amoxicillin, Cefixime	120	6 months-11 years	Yes
McLinn	1996	A multicenter, double blind comparison of azithromycin and amoxicillin/clavulanate for the treatment of acute otitis media in children	Amoxicillin/clavulanate, Azithromycin	674	1-15 years	Yes
Mohs	1993	A comparative study of azithromycin and amoxycillin in paediatric patients with acute otitis media	Amoxicillin, Azithromycin	154	2-12 years	No
Mygind	1981	Penicillin in acute otitis media: a double-blind placebo-controlled trial	Penicillin V, Placebo	149	1-10 years	Yes
Neumark	2007	Evaluation of phenoxymethylpenicillin treatment of acute otitis media in children aged 2-16	Penicillin V, Placebo	179	2-16 years	Yes
Noel	2008	A randomized comparative study of levofloxacin vs amoxicillin/clavulanate for treatment of infants and young children with recurrent or persistent acute otitis media	Amoxicillin/clavulanate	810	6 months-5 years	Yes
Oguz	2003	Etiology of acute otitis media in childhood and evaluation of two different protocols of antibiotic therapy: 10 days cefaclor vs 3 days azithromycin	Azithromycin, Cefaclor	78	6 months-12 years	Yes
Owen	1993	Efficacy of cefixime in the treatment of acute otitis media in children	Amoxicillin, Cefixime	184	2 months-6 years	Yes

(*continued*)

Table I. Continued

First Author	Year	Article title	Antibiotics evaluated	No. of patients evaluated for AEs	Age range	Randomized trial
Principi	1986	Amoxicillin twice daily in the treatment of acute otitis media in infants and children.	Amoxicillin	110	6 months-12 years	Yes
Principi	1991	Cefixime vs amoxicillin in the treatment of acute otitis media in infants and children	Amoxicillin, Cefixime	40	6 months-12 years	Yes
Principi	1995	Multicentre comparative study of the efficacy and safety of azithromycin compared with amoxicillin/clavulanic acid in the treatment of paediatric patients with otitis media.	Amoxicillin/clavulanate, Azithromycin	483	6 months-12 years	Yes
Puhakka	1989	Clinical efficacy and tolerance of bacampicillin and amoxycillin suspensions in children with acute otitis media	Amoxicillin	49	6 months-8 years	No
Pukander	1993	Clarithromycin vs amoxicillin suspensions in the treatment of pediatric patients with acute otitis media	Amoxicillin, Clarithromycin	79	1-12 years	Yes
Rodriguez	1985	Erythromycin-sulfisoxazole vs amoxicillin in the treatment of acute otitis media in children. A double-blind, multiple-dose comparative study	Amoxicillin	127	2 months-17 years	Yes
Rodriguez	1990	Sultamicillin (sulbactam/ampicillin) vs amoxycillin in the treatment of acute otitis media in children	Amoxicillin, Sultamicillin	86	2 months-17 years	Yes
Rodriguez	1996	An open study to compare azithromycin with cefaclor in the treatment of children with acute otitis media	Azithromycin, Cefaclor	259	6 months-12 years	Yes
Schaad	1993	Multicentre evaluation of azithromycin in comparison with co-amoxiclav for the treatment of acute otitis media in children	Amoxicillin/clavulanate, Azithromycin	389	2-12 years	Yes
Sher	2005	Randomized, investigator-blinded, multicenter, comparative study of gatifloxacin vs amoxicillin/clavulanate in recurrent otitis media and acute otitis media treatment failure in children	Amoxicillin/clavulanate, Gatifloxacin	349	6 months-7 years	Yes
Stenstrom	1991	Amoxycillin/clavulanate vs amoxycillin in recurrent otitis media and therapeutic failure in children	Amoxicillin/clavulanate, Amoxicillin	100	6 months-10 years	Yes
Syrogiannopoulos	1992	Cefuroxime axetil in the treatment of acute otitis media in children	Amoxicillin, Cefuroxime axetil	55	5-11 years	Yes
Tahtinen	2011	A placebo-controlled trial of antimicrobial treatment for acute otitis media	Amoxicillin/clavulanate, Placebo	319	6-35 months	Yes
Tapiainen	2014	Effect of antimicrobial treatment of acute otitis media on the daily disappearance of middle ear effusion: a placebo-controlled trial	Amoxicillin/clavulanate, Placebo	84	6 months-15 years	Yes

Table III. Prevalence of AEs for short-course (<7 days) antibiotics for uncomplicated AOM

AEs/antibiotics*	No. of studies	No. of children with finding/total	Pooled prevalence % (CI)	I^2 (%)
Diarrhea				
Azithromycin (3 days)	7	25/784	2.5 (1.0-4.6)	51.8
Amoxicillin LD	3	15/478	3.0 (1.5-4.6)	0.0
Cefdinir	4	62/783	7.7 (5.8-9.5)	0.0
Amoxicillin/clavulanate HD	1	75/258	29.1 (23.5-34.6)	–
Generalized rash				
Azithromycin (3 days)	7	6/959	0.2 (0.0-0.9)	29.2
Cefdinir	2	3/396	0.7 (0.0-1.5)	0.0
Amoxicillin LD	3	15/580	2.1 (0-4.3)	76.1
Diaper rash				
Cefdinir	3	26/607	3.8 (0.9-6.7)	75.7
Amoxicillin/clavulanate HD	1	87/258	33.7 (28.0-29.5)	–

–, No data available; *HD*, high-dose (amoxicillin/clavulanate, 90/6.4 mg/kg/day); *LD*, low-dose (amoxicillin <80 mg/kg/day).
*All given for <7 days (azithromycin given for 3).

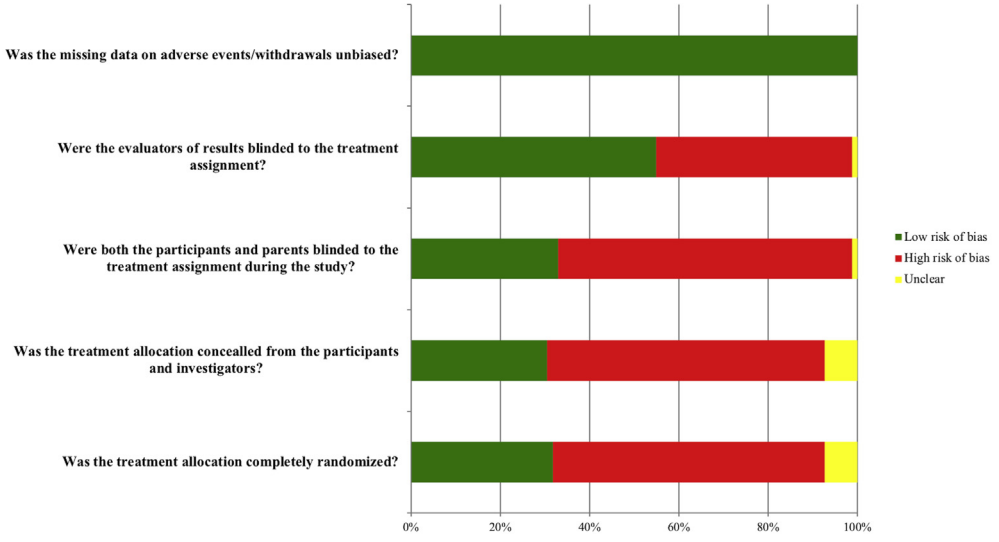

Figure 3. Overall risk of bias analysis of 82 studies of antibiotic treatment in children with AOM.

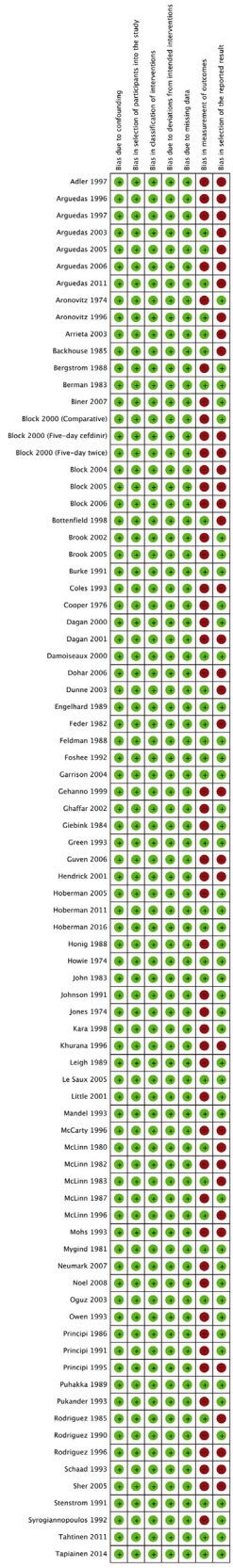

Figure 4. Individual risk of bias assessment of 82 studies of antibiotic treatment in children with uncomplicated AOM.

ADVERSE EVENTS FORM

Date: [Date]		ID Number: [ID Number]
Diagnosis/Symptom: (If more than one AE occurred, complete a separate form for each)	☐ Protocol Defined Diarrhea (3 or more watery stools per day or 2 or more watery stools for 2 consecutive days) ☐ Diaper Rash	☐ Rash (generalized rash, uticaria, or exanthema not including eczema or rash on the diaper area ☐ Other
If other please specify:		
Date of Onset: [Date]	Date of Resolution: [Date]	
Collection Method: ☐ Diary ☐ Patient Recall ☐ Other		
If other please specify:		
Treatment given for adverse event (if indicated): [Medication, Dose]		
Date study product last taken prior to event: [Date]		
Action taken with study product:	☐ No action taken ☐ Stopped temporarily ☐ Permanently discontinued	
Action taken with the subject:	☐ No action taken ☐ Withdrawn from study ☐ Treatment given ☐ Other	
If other please specify:		
Causality: ☐ Associated ☐ Not Associated	Attributed by: [Name/Title]	

Figure 5. Sample AEs data collection form.