

Efficacy of antimicrobials or placebo compared to amoxicillin-clavulanate in children with acute otitis media: a systematic review

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ABSTRACT

Background. Acute otitis media (AOM) is the inflammation of the middle ear. It constitutes one of the most frequent infections which affects children and usually occurs between 6 to 24 months of age. AOM can emerge due to viruses and/or bacteria. The aim of the current systematic review is to assess in children between 6 months and 12 years of age with AOM, the efficacy of any antimicrobial agent or placebo compared with amoxicillin-clavulanate, to measure the resolution of AOM or symptoms.

Methods. The medical databases PubMed (MEDLINE) and Web of Science were used. Data extraction and analysis were performed by two independent reviewers. Eligibility criteria were set, and only randomised control trials (RCTs) were included. Critical appraisal of the eligible studies was performed. Pooled analysis was conducted using the Review Manager v. 5.4.1 software (RevMan).

Results. Twelve RCTs were totally included. Three (25.0%) RCTs studied the impact of azithromycin, two (16.7%) investigated the impact of cefdinir, two (16.7%) investigated placebo, three (25.0%) studied quinolones, one (8.3%) investigated cefaclor and one (8.3%) studied penicillin V, compared to amoxicillin-clavulanate. In five (41.7%) RCTs, amoxicillin-clavulanate proved to be superior to azithromycin, cefdinir, placebo, cefaclor and penicillin V, while in seven (58.3%) RCTs its efficacy was comparable with other antimicrobials or placebo. The rates of AOM relapse after treatment with amoxicillin-clavulanate were comparable to those of other antimicrobials or placebo. However, amoxicillin-clavulanate was more effective in eradicating *Streptococcus pneumoniae* from the culture, when compared to cefdinir. The results of the meta-analysis were not evaluated due to substantial heterogeneity between studies.

Conclusions. Amoxicillin-clavulanate should be the treatment of choice for children between 6 months and 12 years of age with AOM.

Key words: child, otitis media, amoxicillin-clavulanic acid, antimicrobial agents, recurrence.

Acute otitis media (AOM) is the inflammation of the middle ear. It constitutes one of the most frequent infections that affect children and usually occurs between 6 to 24 months of age.¹ Around 80% of children are expected to suffer from an episode of AOM before entering school age^{1,2}, as the disease mainly

appears in children aged between 6 and 24 months.³ AOM can emerge due to viruses (coronaviruses, respiratory syncytial virus, and influenza viruses), as well as due to Gram-positive (*Streptococcus pneumoniae*) and Gram-negative (*Haemophilus influenzae*, and *Moraxella catarrhalis*) bacteria. Concurrent infection with both viral and bacterial factors have also been recorded.^{4,5}

The main symptoms of AOM include mainly pain and/or fever, possibly combined with loss of appetite or vomiting. On the contrary, middle-

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ear effusion, which is called the accumulation of fluid in the middle ear, is not usually associated with the presence of any symptoms.⁶ AOM may be persistent for a long time, leading often to surgical procedures. Notably, the most frequent complication is a reduction in the mobility of the tympanic membrane, leading to hearing disorders, even hearing loss. This condition in children is so severe that it can have a negative impact on their psychological development, their speech development and their educational future.^{6,7}

The appearance and spread of resistant bacteria, either through enzymatic mechanisms (production of β -lactamase) or through diminished susceptibility to penicillin, have crucially influenced the effective antimicrobial cure of AOM.⁸ The goal of the current systematic review was to assess in children between 6 months and 12 years of age with AOM, the efficacy of any antimicrobial agent or placebo compared with amoxicillin-clavulanate and to measure the resolution of AOM or symptoms.

Methods

Search databases

To track all available data and information concerning the subject of this review, the medical databases PubMed (MEDLINE) and Web of Science were used. To secure full-literature tracking, a hand-search of references to related publications was also conducted.

Search plan

The search plan of the online medical databases mentioned above were comprised of Medical Subject Heading (MeSH) terms and 'free text' terms. Different spellings, synonyms, and terminology alterations over time were also considered. The final search was performed on December 3, 2021. The structured query for PubMed (MEDLINE) was:

A. Search terms for the status of AOM

- #1 otitis media
- #2 otitis media [MeSH Terms]
- #3 middle ear inflam*
- #4 middle ear inflammation [MeSH Terms]
- #5 middle ear infect*
- #6 #1 OR#2 OR#3 OR#4 OR#5

B. Search terms for the treatment with amoxicillin-clavulanate

- #7 amoxicillin
- #8 amoxicillin [MeSH Terms]
- #9 amoxicillin clav*
- #10 amoxi clavulanate [MeSH Terms]
- #11 amoxicillin clavulanic acid [MeSH Terms]
- #12 amox clav [MeSH Terms]
- #13 acids, clavulanic [MeSH Terms]
- #14 #7 OR#8 OR#9 OR#10 OR#11 OR#12 OR#13

C. Amoxicillin-clavulanate in AOM

- #15 #6 AND #14

For Web of Science the search query was the following:

A. Search terms for the condition of AOM

Query #1:

acute media otitis (Topic) or acute media otitis (Title) or acute media otitis (Conference)

B. Search terms for the intervention amoxicillin-clavulanate

Query #2:

amoxicillin clavulanate (Topic) or amoxicillin clavunate (Title) or amoxicillin clavunate (Conference) or amoxicillin clavulanic acid (Topic) or amoxicillin clavulanic acid (Title) or amoxicillin clavulanic acid (Conference)

C. Amoxicillin-clavulanate in acute otitis media

(#1) AND #2

The filter with the term “English” was applied to both search engines to retrieve exclusively search results with publications in the English language.

Management of search results and study selection

Initially, all retrieved studies were introduced into the reference management software EndNote Version X7 (Clarivate, London, United Kingdom), where duplicates were deleted. Afterwards, for the selection of relevant studies all titles and abstracts were screened from the retrieved search results. In case it was not feasible to judge the potential suitability of the studies according to their title and/or abstract, full-text documents were assessed. Management of search results and study selection were performed independently by KT and NK. Any potential disagreements were arbitrated by TK.

Data extraction

The extraction of data was organised in Excel (Microsoft Corp., Redmond, WA, USA) format. The information retrieved from the remaining studies were: the first author of the publication, country, year of publication, journal of publication, the aim of the study, study population characteristics, study design, setting, sample size, intervention, comparator, measures used, analysis, primary and secondary outcomes of interest. Data extraction was conducted independently by KT and NK. Any probable disagreements were resolved by TK.

Data analysis

All data were summarised using basic descriptive statistics. The summary measure used was the distribution of frequency, expressed as a percentage of the total frequency

(relative frequency, %). All descriptive statistics were conducted through the Statistical Package for Social Sciences (SPSS, 22nd version, IBM). The statistical significance was determined at $p < 0.05$.

Eligibility criteria

Studies fulfilling the following criteria were eligible: Population: Studies on children between 6 months and 12 years of age, with AOM as defined in each study. A minimum sample size of 200 individuals was used to increase the power of the studies. There was no constraint regarding sex, race, or setting.

Intervention: All studies examining the impact of antimicrobials or placebos.

Comparator: Amoxicillin-clavulanate. There was no constraint on the days of treatment or the dosage used.

Outcomes: The main outcome was the disappearance of AOM otoscopic signs (bulging of the tympanic membrane, redness) or relief from its symptoms (pain or hearing disorders). The secondary outcomes included absence of middle ear fluid, microbiological eradication of the bacterial pathogen in culture, and relapse of AOM.

The types of studies included were exclusively randomised controlled trials (RCTs) which constitute the cornerstone of evidence-based medicine. The minimum study duration was set at 12 months. The publication date was set up to November 30, 2021. All publications written in languages other than English were excluded, as well as publications with no full-text available.

Assessment of methodological quality

The Critical Appraisal Skills Programme (CASP) for RCTs was used for the assessment of the methodological quality of the studies.⁹ All RCTs fulfilling at least seven out of the 11 criteria set by the corresponding questions of the checklist were classified as being high-quality.

Statistical and pooled analysis

A separate pooled analysis was performed for each outcome. The 95% Confidence Intervals (CIs) and the pooled Odds Ratios (ORs) were calculated through the Cochran-Mantel-Haenszel test using the DerSimonian and Laird random effect model (since possible variability in the population of effects was assumed), as previously described.¹⁰ Statistical heterogeneity of the study was assessed through poor overlap of 95% CIs at visual inspection, Higgin's and Thompson's I^2 , tau-squared, and chi-square statistic. A value of $I^2 > 50\%$ was used to define substantial heterogeneity.¹¹ A p-value < 0.1 was used to define statistical significance in heterogeneity. Pooled analysis was conducted through the Review Manager v. 5.4.1 software (RevMan). The level of statistical significance was set at $p < 0.05$. For the outcomes of clinical success, microbiological eradication, and

relapse, ORs > 1 favoured antimicrobials or placebo, while ORs < 1 favoured amoxicillin-clavulanate.

Results

Study basic retrieval and eligibility results

A total of 1086 unique records were initially retrieved. These studies were investigated for relatedness by title, abstract and availability of full-text. Ninety-one studies were reviewed for eligibility, identified as potentially relevant. Out of 91 studies, 79 were excluded: 21 as not being RCTs, 38 did not match the Population, Intervention, Comparator, Outcomes (PICO) question, and 20 were excluded due to a duration of less than 12 months. Finally, 12 studies were eligible for the CASP checklist. The PRISMA flow diagram of study retrieval and eligibility is shown in Figure 1.

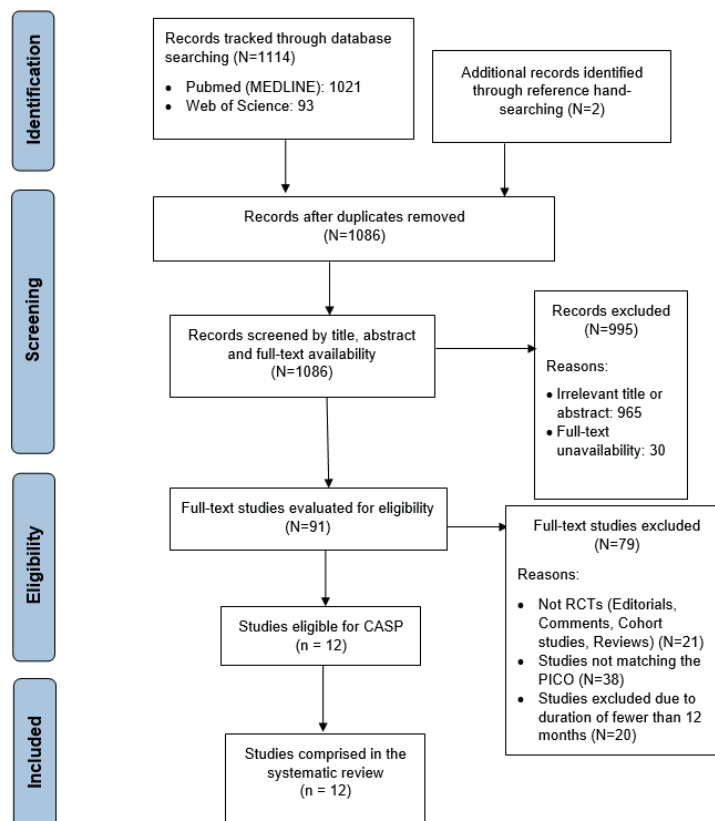


Fig. 1. PRISMA flow diagram of study retrieval and eligibility.

Assessment of methodological quality

Out of the 12 studies included, 10 were characterised as high-quality RCTs as they fulfilled more than seven out of 11 criteria.¹²⁻²¹ Two of them displayed poor quality as they fulfilled only four and five criteria, respectively (Table I).^{22,23}

Study characteristics

Out of 12 studies included, five (41.7%) were double-blind RCTs^{12,14,16,21,23}, while seven (58.3%) were investigator-blind RCTs^{13,15,17-20,22}, conducted mainly in the United States of America (USA) and South America (Table II). The study sample sizes ranged from 233 to 1586, with a median of 347.5 children (IQR = 99).^{18,19} Out of 5577 children participating in all studies, 691 (12.4%) received azithromycin, 419 (7.5%) received cefdinir, 280 (5%) received placebo, 786 (14.1%) received levofloxacin, 453 (8.1%) received gatifloxacin, 119 (2.1%) received cefaclor and 171 (3.1%) received penicillin. A total of 2658 (47.7%) children received amoxicillin-clavulanate (Table II). Only two out of 12 (16.7%) included RCTs that applied to the administration of high-dose amoxicillin-clavulanate.^{12,18} Nine out of 12 (75%) RCTs

utilised amoxicillin-clavulanate in a 10-day treatment regimen.^{12-18,20,22} Other RCTs utilised amoxicillin-clavulanate in 7-day¹⁹ and 28-day courses.^{21,23}

Main outcome

Three RCTs studied the impact of azithromycin compared to amoxicillin-clavulanate. Effective treatment with high- or single-dose azithromycin was comparable to treatment with amoxicillin-clavulanate^{12,14}, while amoxicillin-clavulanate displayed a higher rate of clinical success when compared with azithromycin (91.6% vs 73.7%, respectively, $p < 0.01$), pertaining only to AOM cases caused by *Haemophilus influenzae*.¹⁵ One study showed relevant clinical efficacy of cefdinir compared to amoxicillin-clavulanate¹³, while another showed significantly higher rates of clinical success for amoxicillin-clavulanate compared to cefdinir (86.5% vs 71.0%, respectively, $p < 0.001$).²² One study displayed the non-inferiority of placebo compared to amoxicillin-clavulanate¹⁶, while another revealed clear superiority of amoxicillin-clavulanate compared to placebo (61.0% vs 30.0%, respectively, $p < 0.001$).²³ Regarding quinolones, which were studied through three different RCTs, gatifloxacin and levofloxacin

Table I. Randomized controlled trials eligible for Critical Appraisal Skills Programme (CASP).

	Arrieta A et al. ¹²	Block SL et al. ¹³	Block SL et al. ¹⁴	Casey JR et al. ²²	Hoberman A et al. ¹⁵	Hoberman A et al. ¹⁶	Sáez-Llorens X et al. ¹⁷	Noel GJ et al. ¹⁸	Subba-Rao SD et al. ¹⁹	Sher L et al. ²⁰	Thomsen J et al. ²³	Thomsen J et al. ²¹
Focused	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Randomisation	✓	?	?	X	?	?	✓	✓	✓	X	X	?
Dropout	?	✓	?	X	✓	✓	?	?	?	✓	?	X
Blinding	✓	X	✓	?	?	✓	?	?	?	?	✓	✓
Baseline similar	✓	✓	✓	X	✓	✓	✓	?	✓	✓	?	✓
Equal treatment	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	✓	✓
Treatment effect	✓	✓	✓	✓	✓	✓	?	✓	✓	X	?	✓
Precise	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	X	✓
Generalisable	?	X	?	?	?	✓	?	✓	✓	✓	?	✓
Outcome	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	✓	✓
Benefit vs harm	✓	?	?	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table II. Selected studies with their basic results – Primary outcome.

Author (Year)	Population age range	Study place	Sample size (Intervention/ Comparator)	Intervention	Comparator	Clinical success (%) Intervention/AMC	p-value (95% CI)
Arrieta A et al. ¹²	6 months to 6 years with recurrent or persistent AOM	USA, South America	296 (151/145)	High-dose azithromycin	High-dose AMC	79.0/81.0	0.846 (-14.3 – 10.4)
Block SL et al. ¹³	6 months to 6 years with AOM	USA	384 (256/128)	Cefdinir	AMC	83.3/86	>0.05 (N/A)
Block SL et al. ¹⁴	6 months to 6 years with AOM	USA	346 (173/173)	Single-dose azithromycin	AMC	87.0/88.0	>0.05 (-9.2 – 6.5)
Casey JR et al. ²²	6 to 24 months with AOM	USA	325 (163/162)	Cefdinir	AMC	71.0/86.5	0.001 (N/A)
Hoberman A et al. ¹⁵	6 to 30 months with AOM	USA, Europe, South America	730 (367/363)	Azithromycin	AMC	73.7/91.6*	<0.01 (6.37 – 29.42)
Hoberman A et al. ¹⁶	6 to 23 months with AOM	USA	291 (147/144)	Placebo	AMC	74.0/80.0	0.14 (N/A)
Sáez-Llorens X et al. ¹⁷	6 to 7 years with AOM	South America, Asia	413 (277/136)	Gatifloxacin	AMC	74.4/72.7	>0.05 (-8.3 – 10.7)
Noel GJ et al. ¹⁸	6 to 5 years with AOM	USA, South America	1586 (786/800)	Levofloxacin	AMC	83.6/80.4	>0.05 (-7.18 – 0.81)
Subba Rao SD et al. ¹⁹	1 to 12 years with AOM	South America, Asia	233 (119/114)	Cefaclor	AMC	78.6/91.4	0.008 (3.5 – 22.1)
Sher L et al. ²⁰	6 months to 7 years with AOM	USA, Central America	349 (176/173)	Gatifloxacin	AMC	84.7/78.6	>0.05 (-2.8 – 16.4)
Thomsen J et al. ²³	1 to 10 years with secretory AOM	Denmark	264 (133/131)	Placebo	AMC	30.0/61.0	<0.0001 (N/A)
Thomsen J et al. ²¹	1 to 10 years with secretory AOM	Denmark	360 (171/189)	Penicillin V	AMC	19.0/44.0	<0.001 (N/A)

*Clinical success for the treatment of AOM caused by *Haemophilus influenzae*
AOM: acute otitis media, AMC: amoxicillin-clavulanate, N/A: not available, USA: United States of America

proved to have non-inferior cure rates when compared with amoxicillin-clavulanate.^{17,18,20} Finally, amoxicillin-clavulanate displayed higher clinical success rates compared to cefaclor (91.4% vs 78.6%, $p=0.008$, respectively) and penicillin V (44.0% vs 19.0%, $p<0.001$, respectively).^{19,21} The basic results of the 12 selected studies are summarised in Table II. Overall, the clinical success was 2111/2658 (79.4%) in the amoxicillin-clavulanate arm and 2154/2919 (73.8%) in the antimicrobials or placebo arm, with a statistically significant difference (OR=0.61, 95% CI 0.41 – 0.91, $p=0.02$, $I^2=87\%$).

Secondary outcomes

Regarding the secondary outcomes of the study, Sher et al.²⁰ revealed similar microbiological eradication rates of the pathogens causing AOM

between children treated with gatifloxacin and children treated with amoxicillin-clavulanate (81.2% vs 82.0%, respectively). Block et al.¹³ disclosed higher rates of microbiological eradication in children treated with amoxicillin-clavulanate compared to cefdinir administered twice daily, in cases of AOM caused by *Streptococcus pneumoniae* (89.5% vs 55.2%, respectively, $p=0.0019$) (Table III). Overall, comparable microbiological eradication rates were observed between patients in the amoxicillin-clavulanate arm (256/301, 85.0%) and the antimicrobials or placebo arm (284/432, 65.7%) (OR=0.38, 95% CI 0.06 – 2.33, $p=0.29$, $I^2=95\%$). As far as the secondary outcome of relapse is concerned, three out of 12 (25.0%) RCTs provided data and showed no significant differences between azithromycin and amoxicillin-clavulanate by day 28-32¹⁴, similar rates of relapse between placebo and

Table III. Studies reporting microbial eradication of the pathogen.

Author (Year)	Population age range	Study place	Sample size (Intervention/Comparator)	Intervention	Comparator	Microbiological eradication rate (%) Intervention/AMC	p-value (95% CI)
Block SL et al. ¹³	6 months to 6 years with AOM	USA	384 (256/128)	Cefdinir	AMC	55.2/89.5*	0.0019 (N/A)
Sher L et al. ²⁰	6 months to 7 years with AOM	USA, Central America	349 (176/173)	Gatifloxacin	AMC	81.2/82.0	(N/A)

* AMC compared to cefdinir administered twice daily, for cases of AOM caused by *Streptococcus pneumoniae*
AOM: acute otitis media, AMC: amoxicillin-clavulanate, N/A: not available, USA: United States of America

Table IV. Studies reporting recurrence of AOM after treatment.

Author (Year)	Population age range	Study place	Sample size (Intervention/Comparator)	Intervention	Comparator	Recurrence rate (%) Intervention/AMC	p-value (95% CI)
Block SL et al. ¹⁴	6 months to 6 years with AOM	USA	346 (173/173)	Single-dose azithromycin	AMC	N/A	N/A*
Hoberman A et al. ¹⁶	6 to 23 months with AOM	USA	291 (147/144)	Placebo	AMC	16.0/19.0	0.056
Sáez-Llorens X et al. ¹⁷	6 to 7 years with AOM	South America, Asia	413 (277/136)	Gatifloxacin	AMC	11.4/6.6	N/A*

* The authors claim that there were no significant differences between intervention and AMC without providing exact p-values
AOM: acute otitis media, AMC: amoxicillin-clavulanate, N/A: not available, USA: United States of America

amoxicillin-clavulanate before the day 21-25 visit (16.0% vs 19.0%, respectively, $p=0.56$)¹⁶ and between gatifloxacin and amoxicillin-clavulanate (11.4% vs 6.6%) (Table IV).¹⁷ Overall, the relapse rates were statistically comparable between patients in the amoxicillin-clavulanate arm (36/280, 12.9%) and the antimicrobials or placebo arm (54/424, 12.7%) (OR=1.15, 95% CI 0.53 – 2.50, $p=0.72$, $I^2=60\%$).

Discussion

This study highlights the comparison of amoxicillin-clavulanate compared to other antimicrobials or a placebo in the treatment of AOM in children between 6 months and 12 years of age. This study revealed the superiority of amoxicillin-clavulanate compared to the other most commonly used antimicrobials for treating AOM, such as cefaclor and penicillin.^{19,21} Out of three RCTs comparing azithromycin with amoxicillin-clavulanate, two of them revealed equal clinical success between the two antimicrobials.^{12,14} The third one revealed the superiority of amoxicillin/clavulanate against azithromycin only when treating AOM cases caused by *H. influenzae*.¹⁵ These findings are in accordance with a recently published meta-analysis focusing exclusively on amoxicillin/clavulanate and azithromycin highlighting the latter as compared to the former in treating AOM in children.²⁴ One study showed the non-inferiority of cefdinir compared to amoxicillin-clavulanate.¹⁴ On the contrary, another study revealed the superiority of amoxicillin-clavulanate compared to cefdinir, despite being assigned as a poor quality RCT.²² A previous study revealed that cefdinir is generally an effective antimicrobial showing clinical results faster than amoxicillin in children, focusing on the treatment of pharyngo-tonsillitis caused by group A beta-hemolytic *Streptococcus*, and including a small number of children.²⁵

Three RCTs showed similar clinical success rates between amoxicillin-clavulanate and

gatifloxacin, and amoxicillin-clavulanate and levofloxacin.^{17,18,20} However, this finding is of minor clinical importance, as gatifloxacin has been withdrawn by the Food and Drug Administration (FDA) from sale due to reasons of safety and effectiveness in 2008.²⁶ In addition, the use of quinolones in children is controversial, and these antimicrobials should not be used in pediatric patients for routine infections.²⁷ One RCT showed clear superiority of amoxicillin-clavulanate vs placebo²³, while another displayed no statistical difference between them.¹⁶ However, Hoberman et al.¹⁶ underline that despite the comparable primary outcome between amoxicillin-clavulanate and placebo, children using the latter displayed higher rates of clinical failure. In any case, the use of a placebo in the control group in RCTs is a topic that raises severe ethical issues, and several considerations should be taken into account before deciding to use a placebo in them.²⁸

Regarding the secondary outcomes of our review, despite the fact that no statistical differences were found regarding recurrence of AOM between amoxicillin-clavulanate and azithromycin, a placebo or gatifloxacin^{14,16,17}, amoxicillin-clavulanate proved to be more efficient in eradicating *S. pneumoniae* from the culture.¹³ This is very important, as *S. pneumoniae* is the most common cause of AOM in children²⁹, and its rates of resistance to amoxicillin-clavulanate are relatively low.³⁰

However, the robustness of our findings could not be strengthened through meta-analysis due to high heterogeneity between studies regarding both main and secondary outcomes. Thus, the results of quantitative synthesis could not be evaluated.

Our study presents several limitations. Initially, only studies in the English language were included. In addition, the initial search was performed using only two databases, instead of including others as well (e.g Cochrane Library

or EMBASE). Moreover, the NIH ClinicalTrials.gov (<http://www.clinicaltrials.gov/>) was not assessed to track terminated RCTs or those in progress. Furthermore, no actions were taken to resolve the observed heterogeneity when attempting to perform the meta-analysis. Finally, our systematic review did not take into consideration the importance of the duration of treatment, as underlined in previous RCTs.³¹

In conclusion, from the present systematic review, it can be concluded that amoxicillin-clavulanate should be the treatment of choice for children between 6 months and 12 years of age, with AOM. Although the effects of several antimicrobials or even placebos were proved to be comparable with that of amoxicillin-clavulanate according to several studies, none of them revealed any statistical superiority compared to amoxicillin-clavulanate.

Ethical approval

This study is a systematic review. As such, no ethical approval was required.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: KT, TK; data collection: KT, NK; analysis and interpretation of results: KT, NK, TK; draft manuscript preparation: KT, NK, TK. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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