Addis Ababa University-College of Health Sciences

CDT-Africa

Azithromycin versus amoxicillin-clavulanate for treatment of otitis media in children: a systematic review and meta-analysis of randomized controlled trials

By

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SIGNATURE FORM

This thesis paper is prepared under my supervision by Gabriel Dawit entitled '**Azithromycin versus amoxicillin-clavulanate for treatment of otitis media in children: a systematic review and meta-analysis of randomized controlled trials'** and submitted in partial fulfillment of the requirement of the degree of Masters of Science (MSc) in Clinical trials.

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DECLARATION

I, the undersigned, declare that this thesis entitled "Azithromycin versus amoxicillin-clavulanate for treatment of otitis media in children: a systematic review and meta-analysis of randomized controlled trials", is my original work and has not been presented for degree in any other university or organization, and that all sources of materials used for the thesis have been duly acknowledged. Declared by:

Name: Gabriel Dawit

Date: 22/07/2020

Signature: _____

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Abbreviations

Abbreviations	Explanation
AOM	Acute Otitis Media
CDT-Africa	Center for innovative Drug Development and Therapeutic Trials for Africa
CSOM	Chronic Supportive Otitis Media
DNA	Deoxyribonucleic Acid
OME	Otitis Media with effusion
OM	Otitis Media
OR	Odd Ratio
PROSPERO	International Prospective Register of Systematic Reviews
RCT	Randomized Clinical Trials
tRNA	transfer Ribonucleic Acid

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Abstract

Background: Otitis media is an ear infection middle that caused by bacteria or a viruses, which affects more children. Amoxicillin/clavulanate is the drug of choice for otitis media currently. However emergency of resistance, long duration of treatment and more adverse reactions make amoxicillin to be a less valuable choice for treating otitis media.

Objective: The aim of this study is to compare the efficacy and safety of azithromycin against amoxicillin/clavulanate for the treatment of otitis media in children.

Methodology: Two databases PubMed and Cochrane library were searched systematically and from Google scholar manually searched. The articles were screened by two review authors, duplicates were removed by Mendeley reference manager software. Remained search results was screened for fulfillment of PICOs and inclusion criteria. Articles which did not fulfill the PICO and inclusion criteria were excluded from the study. Data extracted by the first review author and checked by second author. For analysis, all the included studies for review are provide on a table with relevant findings. Meta-analysis was performed using STATA software version 16, and Mantel-Haenszel method and effect measure odds ratio was employed for data analysis, data synthesis and creating forest plot.

Result: Seven hundred fifty one records were identified and fourteen studies have fulfilled the inclusion criteria. In twelve studies azithromycin had equivalent clinical efficacy and in the remaining two studies the bacteriologic efficacy of azithromycin is lower than amoxicillin/clavulante. Meta-analysis results showed a small statistical difference on efficacy in favor of amoxicillin/clavulanate after completion of treatment and there was no statistical significant difference on efficacy on follow up. There was statistically significant difference of clinical adverse events more in amoxicillin/clavulanate group than in azithromycin.

Conclusion: Efficacy of azithromycin is not inferior to amoxicillin/clavulanate to treat otitis media in children, and it is more safe and tolerable in children than amoxicillin/clavulanate.

Recommendations: Azithromycin can be a possible first line treatment option of otitis media. More up to date well controlled clinical trial researches are required to replace amoxicillin/clavuluanate.

1. Introduction

1.1. Background

Otitis media is a middle ear infection, caused by bacteria or virus and exists in acute or chronic state and occur with or without symptoms [1]. About 80% of children have acute otitis media (AOM) once before age of three years, and about 40% have six or more recurrences by the age of seven years [2,3]. The prevalence is high among children less than two year and also higher in children living in rural than in urban areas [4]. Developing countries have high burden of otitis media compared to developed countries [5]. In US children experiences attack of AOM in more than 70% before age one [6]. A research on prevalence of otitis media in Australian indigenous children showed (7.1-18.8%) with AOM and (10.5-30.3%) with active chronic otitis media [7]. The incidence of acute otitis media across Europe is 160.7 cases (95 % CI: 144.7–177.9) per 1000 person years [8]. In sub-Saharan West Africa the incidence of otitis media found to be 43.3% [9]. A systematic review by DeAntonio *et al*. reported the incidence of otitis media under 6 years olds from five countries; 9.2% in Nigeria, 10% in Egypt, 6.7% in China, 9.2% in India, 9.1% in Iran and 7.8% in Russia [10]. In Ethiopia a study conducted in Dessie referral hospital revealed, the frequency of otitis media below age of fifteen was 45.0% [11].

Bacteria isolates 50% to 90% from middle ear fluid culture with cases of acute otitis media and otitis media with effusion [12]. The three most common bacteria causes of otitis media are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* [13,14,15]. The etiology of otitis media can vary geographically. In sub-Saharan African countries the most prevalent bacteria causes otitis media are *Pseudo aeruginosa* and *Staphylococcus aureus* [16] and in Ethiopia the most dominant bacteria cause otitis media are *Proteus species*, *staphylococcus aureus Escherchia coli Enterobacter*, *Citrobacter* and *Klebsiella species* [11].

Otitis media can be further classified by its associated clinical symptoms, otoscopic findings, duration, frequency, and complications into acute otitis media, otitis media with effusion (residual or persistent effusion), unresponsive otitis media, recurrent otitis media, otitis media with complications, and chronic suppurative otitis media. Acute otitis media is commonly defined as inflammation of the middle ear presenting with rapid onset of symptoms such as otalgia, fever, irritability, anorexia, or vomiting. AOM is the most common otitis media

occurred. Recurrent acute otitis media can be defined as three new acute otitis media episodes within six months or four times during one year [17]. Otitis media with effusion is defined as an asymptomatic middle ear effusion which may be associated with a 'plugged ear' feeling [18]. Otitis media with residual effusion is characterized by the presence of an asymptomatic middle ear effusion without otoscopic signs of inflammation from three to fifteen weeks following the diagnosis of acute otitis [18]. Unresponsive acute otitis media is characterized by clinical signs and symptoms associated with otoscopic findings of inflammation which continue beyond forty eight hours of therapy [3]. Otitis media with complications involves damage to the middle ear structures such as tympanosclerosis, retraction pockets, adhesions, ossicular erosion, cholesteatonia, and perforations, as well as other intratemporal and intracranial complications [19]. Chronic suppurative otitis media is defined as persistent otorrhea present longer than 6 weeks [20].

The most common complication of otitis media is conductive hearing loss. Conductive hearing loss occurs as a direct result of otitis media, particularly when there has been either an early onset of the disease or chronic otitis media [21]. The early effects of conductive hear loss on children's social, behavioral and intellectual development can have an impact throughout an individual's lifetime. The major impacts of OM are; Medical consequences: Severe otitis media can cause many medical complications, like mastoiditis, sub periosteal abscess, facial nerve palsy brain abscesses, meningitis, and chronic sinus infection [22,23]. Impact on early childhood development: frequent occurrence of conductive hearing loss in less than two years of life, has a negative effect on the development of the central auditory nerve pathway. This effect results deficits in auditory skills like attention, sound discrimination, the ability to listen in competing noise, and auditory memory [24]. These problems are results in delays of verbal language, intellectual development and social skills. Impact on educational attainment: If a child has otitis media during preschool years, it affects auditory processing skills then children will be unable to process auditory information and if the speech perception affects, the child faces problems in reading and spelling [25,26].

Selection of an antibacterial for the treatment of otitis media is based on the antibacterial spectrum, pharmacokinetic properties, safety and overall cost of treatment. The increased prevalence of β-lactamase-producing strains of *H. influenzae, S. aureus S. pneumoniae* and

M. catharhalis responsible for otitis media, has raised concern about the efficacy due to resistance to the traditional antibacterial. The established antibacterial therapy for otitis media as a first line treatment is amoxicillin (45mg/kg/day), amoxicillin- clavulanate (45mg/kg/day); second line ceftriaxone (50 mg / kg / day), clindamycin (10 mg/kg/day) with or without Cefdinir, cefdinir (14 mg / kg / dose). If a patient is allergic to penicillin first line, a second line therapy ceftriaxone (50 mg / kg / day) or cefdinir (14 mg/kg/day) and clindamycin (10mg/ kg / day) is given [27]. Currently all the recommended therapy for otitis media are penicillins. However, problems with drug compliance, more after symptomatic improvement occurs, and drug-related side-effects have been noted. Macrolides are also effective in the management of otitis media. Azithromycin is with good in vitro activity against common pediatric middle ear pathogens. In an animal model, the 50% effective dose for azithromycin is lower than for clarithromycin and amoxicillin in the treatment of experimental otitis media due to *S. pneumoniae* [23]. In addition to that, the half-life of azithromycin exceeds 60 hours suggests for once-daily dosing and a shorter duration of treatment compared with established therapy for ten days twice or three times a day [28].

Amoxicillin is a broad spectrum semi synthetic antibacterial drug that belongs to class of penicillin (beta lactam antibiotics). It has a wide range of activity against both gram negative and gram positive bacteria. Since the production of amoxicillin to the market there are many uses of amoxicillin to treat bacterial infections. The conditions where amoxicillin is recommended are otitis media, tonsillitis, pneumonia, bronchitis, urinary tract infection, cervicitis, gastritis (*H.pylori*), meningitis, typhoid fever and others [29,30,31]. Pharmacokinetics profile of amoxicillin is well understood, its absorption depends on rate and site of the gastrointestinal tract. It is well absorbed in the duodenum and jejunum, but less in ileum. It has high bioavailability (75-90%) after oral absorption, more resistant to acid in activation than other penicillin [32]. The peak plasma level reaches within one to two hours (7.2mg/l) [33]. The volume of distribution of amoxicillin is approximately 0.26 – 0.31L/kg [34] and It distributes to liver lungs, muscles, bile, pleural and synovial fluids, ocular fluids and it also presents in amniotic fluid and crosses the placenta but with poor penetration to central nervous system [31, 35]. The binding of amoxicillin to human plasma protein and albumin is 17-20% [34]. About 10-25% of amoxicillin metabolized by liver microsomes in to penicilloic acid [36]. The half-life ($t_{1/2}$) of amoxicillin is 60 to 90 minutes. The most predominant excretory system is renal, more

than 80% [34] and about 50-70% excrete unchanged and it also present in milk [37]. Activity of amoxicillin against susceptible micro-organisms is bactericidal through the inhibition of biosynthesis of cell wall, it acts by binding to penicillin binding protein 1A (PBP.1A) located inside the bacterial cell wall [38].

Amoxicillin is well tolerable for all age group, but there are reports of adverse drug effect from different clinical studies in human. The adverse effects are allergic reaction, diarrhea, nausea, fever, loose stools, anorexia, abnormal laboratory finding of hepatic function and hematology [29,39]. Few years after discovery of penicillin β-lactamase bacteria had emerged. Amoxicillin is catalyzed by β-lactamase producing bacteria for that reason it started to be given with β-lactamase inhibitor such as clavulanic acid [40]. Clavulanic acid is potent inhibitor of β-lactamase enzymes, produced from *Streptomyces clavuligerus* [42]. Thus amoxicillin in combination with clavulanic acid is effective for β-lactam antibacterial. The pharmacokinetics of clavulanic acid is similar with amoxicillin and they do not affect Pharmacokinetic parameter of each other [42,43] and the dose given is always constant 125mg.

Azithromycin is a 15 ring semisynthetic subclass of macrolide (an azalide) antibiotics approved by united state FDA in 1991 [44] which is similar to erythromycin but with superior pharmacokinetic characteristics, less adverse effects, and broader spectrum of antimicrobial activity (active against both bacteria and virus) [45,46]. Azithromycin is used for treatment of various range of infections of diseases like upper and lower respiratory tract infections, middle ear infections (otitis media), sexually transmitted infections and trachoma [19]. It is active in vitro against a variety of microorganisms, including *S. aureus, Streptococcus pyogenes, H. influenzae, Neisseria gonorrhoeae, Legionella pneumophila, Escherichia coli, Klebsiella pneumoniae*, and *Borrelia burgdorferi* [47,48]. Azithromycin is more stable at gastric pH and has good absorption with bioavailability of 37% compared to other macrolides. Despite its low concentration, it is rapidly and highly concentrated in white blood cells and macrophages and it undergoes extensive tissue distribution with an apparent steady-state volume of distribution of 31.1 L/kg and achieves high concentrations in infection site and other body parts [49]. Protein binding increases with decreasing serum concentration, [50]. Azithromycin not much metabolizes in humans but in snake after given azithromycin it produced four metabolite (3'-desamine-3-ene-azithromycin, descladinose dehydroxy-2-ene-azithromycin, 3'-desamine-3-ene

descladinose-azithromycin, and 3'-N-nitroso,9a-N-desmethyl-azithromycin) [51]. In humans this drug is eliminated by biliary (50%) and kidney (6%) excretion method largely unchanged and also eliminates unchanged by fecal route. Rapid distribution of the drug into tissue and its subsequent slow elimination from tissues leads to have polyphasic elimination. A terminal serum elimination half-life ranges from 2-4 days has been reported for azithromycin [52, 53].

The mechanism of action of azithromycin is by binding in the 50s subunit of bacteria ribosome to inhibit the protein synthesis [54] and it has time dependent killing of bacteria. It reaches the infection site either by direct distribution to tissues or carried by macrophages and phagocytes. The most common side effects of azithromycin are gastro intestinal disorders (vomiting, diarrhea abdominal pain), fever and some laboratory abnormality of hepatic function and hematology [55].

Table 1. Pharmacological comparison of azithromycin and amoxicillin antibacterial drugs

S.no	Characteristics	Azithromycin	Amoxicillin
01	Bioavailability per oral route	37%	75-90%
02	Distribution	31.1L/kg	0.26 - 0.31L/kg
03	Protein binding	12%	17-20%.
04	Metabolite	Four metabolites: (3′-desamine-3-ene, descladinose dehydroxy-2-ene, 3′-desamine-3-ene descladinose, and 3′-*N*-nitroso,9a-*N*-desmethyl)-azithromycin	Penicilloic acid
05	Excretion	Biliary, Renal	Renal
06	Elimination Half life	57-77 hours	60-90 min
07	Action	Bacteriostatic	Bactericidal

Sources: [34,36,43,49,51,52,53].

The aim of this study was to compare the efficacy and safety of azithromycin and amoxicillin/clavulanate for treatment of otitis media in children from comparative randomized clinical trials through systematic review and meta-analysis.

1.2 Problem statement

Otitis media is one of a major problem among children caused by multiple bacteria pathogens and viruses. It is with high prevalence in developed and developing countries. More than 80% of children are affecting once before three years old. Otitis media is a fifth burden of diseases and a second that cause of hearing loss in developing countries [56, 8] In addition to hearing loss otitis media can cause many medical complications like mastoiditis, sub periosteal abscess, facial nerve palsy brain abscesses, meningitis, and chronic sinus infection [22,23]. More bacterial pathogens are becoming resistant to currently available drugs for treatment of Otitis media. A study conducted in sub-Sharan African countries revealed that the responsible bacteria for otitis media are highly resistant for ampicillin, amoxicillin, amoxicillin-clavulante cefuroxime and cotrimoxazole [16] In a study conducted in Ethiopia, the isolated bacteria found to be 100% resistant to amoxicillin [11]. Amoxicillin is the drug of choice for longtime for treatment of otitis media but due to emerging of resistance by beta-lactamase enzyme and other mechanisms, long duration of treatment and more adverse events, its efficacy and compliance is decreasing. Despite all this facts that affect the efficacy of amoxicillin/clavuluanate, it is still a first line treatment otitis. Therefore there must be antibacterial drug that is more safe and effective in treating otitis media and replaces Amoxicillin/clavuluanate.

1.3 Significance of the study

The objective of this systematic review and meta-analysis is to compare the efficacy and safety of azithromycin and amoxicillin/clavulanate for treatment of otitis media in children. Amoxicillin and other beta-lactam antibiotics considered standard treatments for otitis media are becoming less effective due to resistance emergence. Bacteria and viruses are responsible for otitis media and beta-lactams have activity against only bacteria, but Azithromycin has both antibacterial, antiviral and anti-inflammatory activity. Azithromycin is a broad spectrum antibiotic for most of bacterial pathogens that can cause for otitis media and can also fight against the viruses susceptible to it. In many individual comparative clinical trial studies on efficacy, azithromycin is equivalent to amoxicillin/clavulanate for treatment OM, except in few studies where azithromycin is inferior in bacteriologic efficacy. Regarding safety, azithromycin is more tolerable by children. Azithromycin is given for maximum five days but amoxicillin/clavulanate is given for ten days. But still azithromycin is not yet recommended for

otitis media treatment. Therefore this systematic review and meta-analysis will provide us more evidence for the efficacy and safety of azithromycin in children with otitis media.

2. Objectives

2.1 General objective

To compare the efficacy and safety of azithromycin and amoxicillin/clavulanate for treatment of otitis media in children.

2.2 Specific Objectives

1. To compare the efficacy of azithromycin and amoxicillin/clavulanate for treatment of otitis media in children ≥ six month and ≤ 2 years.
2. To compare the efficacy of azithromycin and amoxicillin/clavulanate for treatment of otitis media in children greater than 2 years old and ≤ 15 years
3. To compare the safety of azithromycin and amoxicillin/clavulanate for treatment of otitis media in children.
4. To identify the most common bacteria that cause otitis media.
5. To compare the compliance of treatment between azithromycin and amoxicillin/clavulanate

3. Methodology

3.1. PICOS

The study population are Children with any type of otitis media (OM) at age range of six months up to 15 years. Azithromycin is the study drugs comparing its efficacy with Amoxicillin/clavulanate combination. The outcome to be assessed is the cure rate and improvement rate from otitis media.

3.2. Search strategy and sources

This review is designed according the preferred reporting items for systematic reviews and meta-analysis protocols (PRISMA) guideline [57]. Published research papers are systematically and comprehensively searched.

3.2.1. Searching study articles

Two databases (PubMed and Cochrane library) and manual search from Google scholar are used to search the studies.

3.2.2. Searching terms

(Azithromycin) AND (Amoxicillin-Clavuluanate) AND (otitis media or acute otitis media) AND (children or Pediatrics), search terms are used in PubMed database and Google scholar search. Azithromycin AND Otitis media search terms are used in Cochrane library search.

3.3. Eligibility criteria

3.3.1 Inclusion criteria

1. RCT studies for comparison of azithromycin and amoxicillin/clavulanate for treating children with any type of otitis media.
2. RCT with outcome cure and improve or failure response from otitis media.
3. Participant of the study are children age ranged from six month up to fifteen years.
4. Children with clinical evidence of bilateral or unilateral infection of the middle ear (OM).
5. Publication of article from inception of the database up to 30-09-2019.
6. A full text article for review.
7. Articles written in English.

3.3.2. Exclusion criteria

1. Researches articles on azithromycin and amoxicillin/clavuluanate for indication other than otitis media.

3.4 Search Result Management

All the search results from PubMed, Cochrane library and Google scholar were stored in Mendeley reference management software.

3.5 Screening of Search Results

When all the results of search were stored in Mendeley reference management software, duplicates were removed by the software. After removing the duplicate studies, the two reviewers screened the title and abstract of each article depending on the PICOs criteria independently. After title and abstract screening, both reviewers had checked the selected studies if they met the eligibility criteria. One review author was extracting the data from the included studies and the second author checked the extracted data. All disagreements were resolved by discussion between the two authors

3.6. Data Extraction

Data extraction form was developed with the help of guide from the Cochrane collaboration data extraction form for interventional review for RCTs and non-RCTs. All the available data were extracted with the data extraction form (Appendix 1.). The data was extracted by one author and in mean whiles was checked by the second author. This was helpful in facilitating reliability of data extraction between reviewers. Then the extracted data were stored in a Microsoft excel spreadsheet.

3.7. Outcomes

The primary outcome of this research is a satisfactory response i.e. cure and improved rate and adverse reaction rate is the secondary outcome.

3.8 Data Quality Assessment

For each article the following were critically appraised independently by two reviewers.

Whether the study design or approach was appropriate to the research question.

Outcome measure was valid and appropriate to the research question.

The risk of bias in the study design and results were assessed by Cochrane risk of bias tool.

3.9 Data Synthesis and analysis plan

This study was conducted according to PRISMA statement. The findings of individual eligible and quality-assured studies were collated, combined and summarized. Meta-analysis was performed using STATA software version 16, and Mantel-Haenszel method and effect measure odds ratio was employed for data analysis, data synthesis and creating tables (forest plot). Studies with similar design on the same intervention and assessing the same outcome and where sufficient data was available, meta-analyses was performed. The results were reported in odd ratio with 95% CI in studies. Heterogeneity I^2 were analyzed from the forest plot result and publication bias also assessed by creating funnel plot. We have used a random and fixed effects model depending on the degree of heterogeneity between studies. Results, together with the associated interpretations and conclusions were generated from narrative and quantitative synthesis and the review were presented on a tables.

4. Results

4.1. Search results

From the three databases seven hundred fifty one records were identified, five hundred thirty nine were from PubMed, eight five from Cochrane library, hundred twenty seven (manual search) from Google scholar. All search results were stored in Mendeley reference management software. Sixty-seven duplicates were removed from the identified records. In the first phase of title and abstract screening, six hundred fifty eight studies were excluded for not meeting PICOs criteria of the study. Twenty four full text articles full-filled the PICOs criteria out of which only fourteen full filled the eligibility criteria were included in the systematic review. All the included studies were comparative randomized studies on azithromycin and amoxicillin/clavulanate of age range almost from six months to fifteen years children. These fourteen comparative RCTs were conducted in four continents (Europe, North America, Asia and South America) and more than twenty two countries with two hundred twenty six centers of total sample size of five thousand six hundred children. None of them was conducted in Africa and Australia and most were conducted in the US. The flowchart is shown in Figure 1.

PRISMA flow diagram of study selection

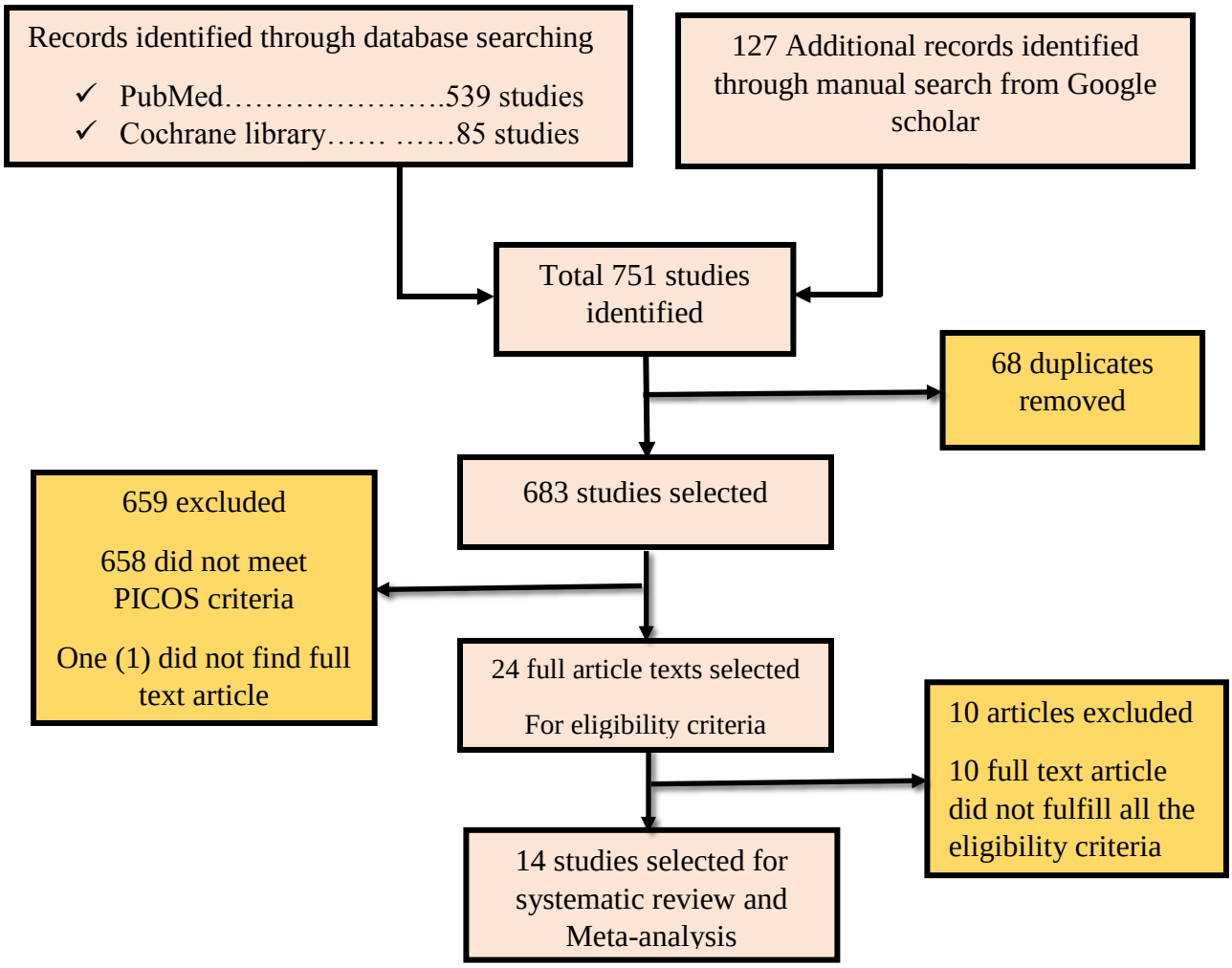

Figure 1**.** Study selection

4.2. Study appraisal of included studies (Data quality assessment)

All the fourteen studies were critically appraised by the two reviewers independently. In all fourteen eligible RCTs, the study design and outcome measure were valid and appropriate to the research questions. The risk of bias in the study design and results were assessed by the revised tool to asses Cochrane risk of bias in randomized trials (RoB 2) latest version 22 August 2019. The overall risk of bias of individual study is displayed in Table 3**.** Eight studies were found to be low risk of bias and six studies were with some concern of bias but none of the studies was with high risk of bias.

Table 2. Risk of bias assessment for included studies by Cochrane risk-of-bias tool for randomized trials (RoB-2).

Domain of the ROB-2.0	Signal questions	Judgment													
		AR-1	**AR-2**	**AR-3**	**AR-4**	**AR-5**	**AR-6**	**AR-7**	**AR-8**	**AR-9**	**AR-10**	**AR-11**	**AR-12**	**AR-13**	**AR-14**
1. Bias arising from the randomization process.	1.1 Was the allocation sequence random?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	NI	NI	PY	NI	NI	Y	PY	Y	Y	PY	PY	NI	Y
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	N	PN	N	N	N	NI	N	N	N	N	N	N	N
	Risk of bias judgment	SC	SC	SC	LR	SC	SC	LR	LR	LR	LR	LR	LR	SC	LR
2. Bias due to deviations from intended interventions.	2.1. Were participants aware of their assigned intervention during the trial?	Y	PY	Y	Y	Y	Y	N	PN	N	N	N	PN	PY	N
	2.2. Were careers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	PY	Y	Y	Y	Y	N	N	N	N	N	N	PN	N
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention beyond what would be expected in usual practice.	N	N	N	N	N	N	NA	NA	NA	NA	NA	NA	N	NA
	2.4 If Y/PY to 2.3: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	2.5. Were any participants analyzed in a group different from the ones to which were assigned.	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	2.6 If Y/PY/NI to 2.5 Was there potential for a	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

	substantial impact (on the estimated effect of intervention) of analyzing participants in the wrong group														
	Risk-of-bias judgment	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR
3. Bias due to missing outcome data.	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Y	Y	Y	N	Y	Y	N	N	Y	Y	N	Y	N
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA	NA	NA	NA	Y	NA	NA	PY	Y	NA	NA	Y	NA	Y
	3.3 If N/PN/NI to 3.2: Could missing in the outcome depend on its true value?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	3.4 If Y/PY/NI to 3.3: Is it likely that missing in the outcome depended on its true value?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Risk-of-bias judgment	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR
4. Bias in measurement of the outcome.	**4**.1 Was the method of measuring the outcome inappropriate?	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Y	PY	PY	PY	PY	Y	N	N	N	N	N	N	PN	N
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN	PN	PN	PN	PN	PN	NA	NA	NA	NA	NA	NA	NA	NA
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Risk-of-bias judgment	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR

5. Bias in selection of the reported result.	5.1 Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Risk-of-bias judgment	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR
6.Over all bias		**SC**	**SC**	**SC**	**LR**	**SC**	**SC**	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**	**SC**	**LR**

Daniel. (1993) = **AR-1,**

Schaad. (1993) = **AR-2,**

Principi. (1995) = **AR-3,**

Arguedasa.*et.al*.(1996)=**AR-4,**

Gerson. (1996) = **AR-5**,

Mohini. (1996) = **AR-6**,

Samuel (1996) = **AR-7,**

Dagan. (2000) = **AR-8,**

Arrieta.*et.al*. (2003) = **AR-9,**

Block.*et.al*. (2003) = **AR-10**

Dune.*et.al*. (2003) = **AR-11**

Hoberma.*et.al*. (2005) = **AR-12**

Guven.et.al. (2006) = **AR-13,**

Arguedas.et.al (2011) = **AR-14.**

Y= Yes, **PY**= probably yes, **PN**= probably no, **N**= No, **NI**= No information, **NA**= Not applicable.

LR= Low risk, **HR**= High risk, **SC**= Some Concern

Table 3. Summary risk of bias of studies

S.no	Author (year)	Bias due to deviations from intended interventions	Bias from missing outcome data	Bias in the measurement of the outcome	Bias in selection of the reported results	Overall risk of bias
01	Daniel. (1993)	Some concern	Lower risk	Lower risk	Lower risk	Some concerns
02	Schaad. (1993)	Some concern	Lower risk	Lower risk	Lower risk	Some concerns
03	Principi. (1995)	Some concern	Lower risk	Lower risk	Lower risk	Some concerns
04	Arguedasa.*et.al.*(1996)	Lower risk	Lower risk	Lower risk	Lower risk	Low risk of bias
05	Gerson. (1996)	Some concern	Lower risk	Lower risk	Lower risk	Some concerns
06	Mohini.(1996)	Some concern	Lower risk	Lower risk	Lower risk	Some concerns
07	Samuel. (1996)	Lower risk	Lower risk	Lower risk	Lower risk	Low risk of bias
08	Dagan.(2000)	Lower risk	Lower risk	Lower risk	Lower risk	Low risk of bias
09	Arrieta.et.al. (2003)	Lower risk	Lower risk	Lower risk	Lower risk	Low risk of bias
10	Block.*et.al.* (2003)	Lower risk	Lower risk	Lower risk	Lower risk	Low risk of bias
11	Dune.*et.al. (*2003)	Lower risk	Lower risk	Lower risk	Lower risk	Low risk of bias
12	Hoberma.*et.al.(*2005)	Lower risk	Lower risk	Lower risk	Lower risk	Low risk of bias
13	Guven.*et.al.* (2006)	Some concern	Lower risk	Lower risk	Lower risk	Some concerns
14	Arguedas.et.al.(2011)	Lower risk	Lower risk	Lower risk	Lower risk	Low risk of bias

4.3. Efficacy of azithromycin and amoxicillin/clavulanate for otitis media.

The efficacy assessment was conducted for fourteen studies after completion of treatment between tenth to sixteenth days following initiation of treatment. The second assessment on long term follow-up was done in eleven studies between three to five weeks. Sub-group analysis was done for children less or equal to two years and greater than two years. Out of the included fourteen studies for systematic review, in the twelve studies the efficacy of azithromycin in treating otitis media was with no statistical significant difference to amoxicillin/clavulanate. The final included studies for systematic review is presented in Table 4 with their relevant findings. In the six studies 10mg/kg azithromycin was given for three days and 40-45 mg/kg amoxicillin/clavulanate for ten days [29,55,58,59,60,61]. There was no statistically significant difference in the efficacy of both drugs at these doses. In the remaining four studies, the doses given was 10mg/kg on the 1st day then 5mg/kg/day of azithromycin for the next four days and 40-45mg/kg of amoxicillin /clavulanate for ten days, and there was no statistical significant difference in their clinical efficacy (two studies) [55,59] and bacteriologic efficacies (one study) [39], In one study, however, bacteriologic activity of azithromycin was inferior to amoxicillin/clavulanate [62]. Doubling the dose of both drugs in the two studies, i.e., 20mg/kg for three days and 60mg/kg of azithromycin and 90mg/kg for ten days of amoxicillin/clavulanate had no statistical significant difference in their clinical [63] and bacteriologic [64] efficacies, respectively. Single dose 30mg/kg of Azithromycin and 45mg/kg amoxicillin/clavulanate for ten days in one study also had shown equivalent efficacy in treating otitis media [65]. In another study, the bacteriologic efficacy of azithromycin was inferior at the dose of 10mg/kg on the 1st day then 5mg/kg for the next four days to 90mg/kg for ten days of Amoxicillin/clavulanate [66]. The efficacy of azithromycin was more than 90% (92.3-100%) in five studies, more than 80% (80.2-87.7%) in seven study and more than 70% (70-73.5%) in two studies. Similarly the efficacy of amoxicillin/clavulanate was more than 90% (93.9-100%) in six studies and more than 80% (80.7-88.3%) seven studies and more than 70% (78.9%) one study [Table 5].

In children less than or equal to two years old, there was no statistical significant difference between azithromycin and amoxicillin/clavulanate groups in clinical [58,60,63,65] and bacteriologic [64] efficacy reported in five of the studies [Table 6]. In five of the studies, there was no statistically significant difference between azithromycin and amoxicillin/clavulanate

otitis media treated children greater than two years old, in both the bacteriologic [64] and clinical [58,60,63,65] efficacies [Table 7].

The clinical and bacteriologic efficacies of azithromycin and amoxicillin/clavulanate on long term follow-up were reported in eleven of the studies. The clinical [29,55,58,59,61,63,65] and bacteriological [39,62,64] efficacies were comparable with no statistical significant difference in ten of the studies though the bacteriological efficacy of azithromycin was inferior to amoxicillin/clavulanate in one of the studies [66]. Both clinical and bacteriological efficacies of both treatments have decreased in all studies in comparing to the first efficacy assessment. The percentage efficacy during the follow up period ranged from 30 to 91% for azithromycin and from 29 to 95% for amoxicillin/clavulanate [Table 8].

Table 4. Final studies included for analysis.

Author (year)	Title	Study drugs	Condition	Target population	countries	Sample size	Study design	Relevant findings
Daniel. (1993)	Comparison of azithromycin and amoxicillin/clavulanate in the treatment of otitis media in children	Azithromycin (10mg/kg) and amoxicillin-clavulanate (40mg/kg)	Otitis media	Children (2-8 year)	Europe Multi center (Munich, Mannheim, Geneva, Fribourg, Munchenstein, Basel, Pratteln)	159	RCT	Clinical efficacy of azithromycin once daily for three days is equivalent to amoxicillin/ clavulanate three times a day for ten days to treat otitis media.
Schaad. (1993)	Multicenter evaluation of azithromycin in comparison with amoxicillin/clavulanate for the treatment of acute otitis media in children	Azithromycin (10mg/kg) and amoxicillin-clavulanate (40mg/kg)	Acute otitis media	6 months to 12 years	Switherland (Monthey, Epalinges, Nyon, Fribourg, Bern Lausanne, Lugano Munchenbuchsee massagnoWabern , Fontana Ostermundigen	389	RCT	Clinical efficacy of azithromycin once daily for three days is equivalent to amoxicillin/clavulanate three times a day for ten days for acute otitis media.

Principi. (1995)	Multicenter comparative study of the efficacy and safety of azithromycin compared with amoxicillin/clavulanic acid in the treatment of pediatric patients with otitis media.	Azithromycin (10mg/kg) and amoxicillin-clavulanate (40mg/kg)	Otitis media	Children (6-months to 12 years)	Brazil, Chile, Germany, Italy, Korea, Spain, Turkey and Venezuela	483	RCT	Clinical efficacy of azithromycin once daily for three days is equivalent to amoxicillin /clavulanate three times a day for ten days to treat otitis media.
Arguedas a *et al.* (1996)	Comparative trial of 3-day azithromycin versus 10-day amoxicillin-clavulanate potassium in the treatment of children with otitis media with effusion	Azithromycin (10mg/kg) and amoxicillin-clavulanate (40mg/kg)	Otitis media with effusion	Children 6-months to 12 years	San Jose Costa Rica -National Children's Hospital. (1 center)	100	RCT	Clinical efficacy of azithromycin once daily for three days is equivalent to amoxicillin /clavulanate three times a day for ten days for acute otitis media.
Gerson. (1996)	A multicenter, open label trial of azithromycin versus amoxicillin/clavulanate for the management of AOM in children.	Azithromycin (10mg/kg and 5mg/kg) and amoxicillin-clavulanate (40mg/kg)	Acute otitis media	Children 2 to 15 years	USA (3 centers)	169	RCT	Bacteriologic efficacy of amoxicillin/clavulanate three times a day for ten days is equivalent to azithromycin once daily for 5 days for treating acute otitis media.
Mohini. (1996)	A multi-center randomized open label comparison of	Azithromycin (10mg/kg	Acute otitis media	Children (6-months to	USA (21 centers)	527	RCT	Clinical efficacy of azithromycin once daily

	azithromycin and amoxicillin/clavulanate in acute otitis media among children attending day care or school.	and 5mg/kg) and amoxicillin-clavulanate (40mg/kg)		12 years)				for 5 days is equivalent to amoxicillin/clavulanate three times a day for ten days to treat acute otitis media.
Samuel (1996)	A multicenter double blind comparison of azithromycin and amoxicillin/clavulanate for the treatment of Acute otitis media in children.	Azithromycin (10mg/kg and 5mg/kg) and amoxicillin-clavulanate (40mg/kg)	Acute otitis media	Children 1 to 15 years	USA 12 centers	677	RCT	Clinical efficacy of azithromycin once daily for 5 days is equivalent to amoxicillin/clavulanate three times a day for ten days for acute otitis media.
Dagan. (2000)	Bacteriologic and clinical efficacy of amoxicillin/clavulanate vs. azithromycin in acute otitis media	Amoxicillin-clavulanate (45mg/kg). and azithromycin (10mg/kg and 5mg/kg)	Acute otitis media	Children 6 months to 2 years	Israel USA and Dominican Republic (12 center)	238	RCT	Bacteriologic and clinical efficacy of amoxicillin /clavulanate twice a day for ten days is superior to azithromycin once daily for 5 days for acute otitis media.
Arrieta *et al.* (2003)	High-dose azithromycin versus high-dose amoxicillin-clavulanate for treatment of children with recurrent or persistent	Azithromycin (20mg/kg) and amoxicillin-clavulanate	Recurrent or Persistent Acute Otitis	Children 6-months to 6 years	U.S.A, Latin American centers (18 centers)	304	RCT	Clinical efficacy of high dose of azithromycin once daily for three days is equivalent to high dose of amoxicillin/clavulanate

	acute otitis media	(90mg/kg)	Media					twice a day for ten days for persistent and recurrent acute otitis media.
Block *et al.* (2003)	Single-dose (30 mg/kg) azithromycin compared with 10-day amoxicillin/clavulanate for the treatment of uncomplicated acute otitis media: a double-blind, placebo-controlled, RCT.	Azithromycin (30mg/kg) and amoxicillin-clavulanate (45/6.4 mg/kg).	Acute otitis media	Children (6-months to 12 years)	USA (9 centers)	350	RCT	Clinical efficacy of single dose (30mg/kg) azithromycin for one day is equivalent to amoxicillin clavulanate twice a day for ten days for acute otitis media.
Dune *et al.* *(*2003)	Randomized, double-blind study of the clinical efficacy of 3 days of Azithromycin compared with amoxicillin/clavulanate for the treatment of acute otitis. media	Azithromycin (10mg/kg) and amoxicillin-clavulanate (45mg/kg)	Acute otitis media	Children (6-months to 12 years)	USA 28 centers	373	RCT	Clinical efficacy of azithromycin once daily for three days is equivalent to amoxicillin clavulanate three times a day for ten days for acute otitis media.
Hoberman.*et al.* (2005)	Large dosage amoxicillin/clavulaanate compared with azithromycin, for the treatment of bacterial Acute Otitis Media in	Amoxicillin-clavulanate (90/6.4 mg/kg). and Azithromycin (10mg/kg	Acute otitis media	Children 6 month to 30 month	Bulgaria, Chile, Domenica Republic, Guatemala, Israel, Peru, Romania Lativa Mexico,	731	RCT	Bacteriologic efficacy of amoxicillin/clavulanate twice a day for 10 days is superior to azithromycin once daily for five days for treating bacterial acute

	Children	and 5mg/kg)			USA (34 centers)			otitis media.
Guven *et al.* (2006)	Bacterial etiology of acute otitis media and clinical efficacy of amoxicillin-clavulanate versus azithromycin	Amoxicillin-clavulanate (45/6.4 mg/kg) and azithromycin (10mg/kg)	Acute otitis media	Children (6-months to 12 years)	Turkey (1 center)	180	RCT	Clinical efficacy of amoxicillin/clavulanate twice a day for ten days is equivalent to azithromycin once daily for three days for acute otitis media.
Argueda s *et al.* *(*2011)	Single-dose extended-release azithromycin versus a 10-day regimen of Amoxicillin/clavulanate for the treatment of children with acute otitis media.	Azithromycin (60mg/kg) and amoxicillin-clavulanate (90mg/6.4kg)	Acute otitis media	Children 3 months - 4 years	North America, Europe, and Latin America. (60 centers)	923	RCT	Bacteriologic efficacy of high single dose (60mg/kg) azithromycin for one day is equivalent to high dose of amoxicillin clavulanate twice a day for ten days for acute otitis media.

Table 5. Clinical and bacteriologic efficacies of study drugs for treatment of otitis media in children (10-16 days).

S.no	Author (year)	Azithromycin group	Amox-clav group	95% CI	P-value
01	Daniel. (1993)	97/ 98 (99%)	54/54 (100%)	N/A	NS
02	Schaad. (1993)	179/192 (93.2%)	184/189 (97.4%)	N/A	NS
03	Principi (1995)	199/215 (92.6%)	186/198 (93.9%)	N/A	NS
04	Arguedasa *et.al.*(1996)	33/40 (82.5%)	30/38 (78.9%)	N/A	NS
05	*Gerson. (1996)	43/49 (87.7%)	43/43 (100%)	N/A	0.102
06	Mohini.(1996)	215/233 (92.3%)	207/230 (90%)	N/A	0.417
07	Samuel. (1996)	245/280 (87.6%)	240/273 (87.9%)	N/A	0.636
08	*Dagan.(2000)	51/73 (70%)	60/70 (85.7%)	(2,30)	0.023
09	Arrieta *et al*. (2003)	128/149 (85.9%)	122/145 (84.1%)	(-6.4, 10)	0.744
10	Block *et al.* (2003)	139/ 160 (86.9%)	142/162 (87.7%)	-9.2 to 6.5	NS
11	Dune *et al.* (2003)	153/185 (82.7%)	159/180 (88.3%)	(-13, 3)	0.186
12	*Hoberman *et.al. (*2005)	165/204(80.9%)	181/200 (90.5%)	(2.37–16.9)	<0.01
13	Guven *et al.* (2006).	90/90 (100%)	84/84 (100%)	N/A	NS
14	*Arguedas *et al.* (2011)	207/258 (80.2%)	202/239 (84.5%)	(-10.4, 2.6)	0.24

* Bacteriologic efficacy, ** Bacteriological and Clinical efficacy. NS=not significant, N/A= Not available.

Meta-analysis of the overall efficacy of azithromycin and amoxicillin/clavulanate on day 10-16 after treatment initiation, there was small statistical difference with OR= 0.75; 95% CI [0.62-0.91]. Heterogeneity of the included studies is I^2 = 22.5%. The meta-analysis result is summarized in Figure 2.

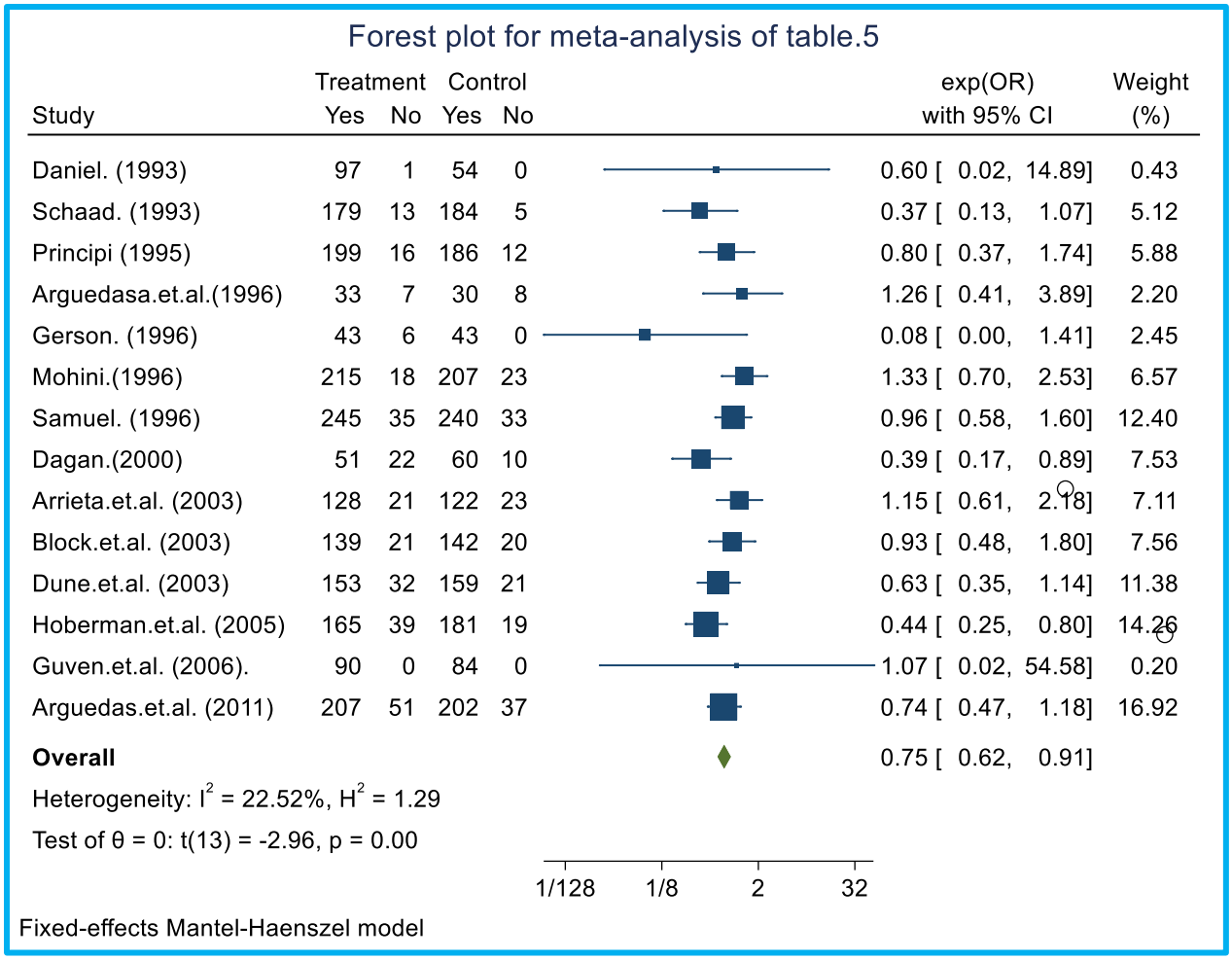

Figure 2. Forest plot for meta-analysis of table.5

Table 6 Clinical and bacteriologic efficacy of study drugs for otitis media treatment in children ≤2 years

S.no	Author (year)	Azithromycin group	Amox-clav group	95% CI	P-Value
01	Principi. (1995)	50/61 (81.91%)	45/49 (91.8%)	N/A	NS
02	Arrieta *et al*. (2003)	82/85 (96.5%)	73/92 (79.4%)	(-4.9, 17.)	0.339
03	Block *et al.* (2003)	53/68 (77.94%)	45/56 (80.4%)	(-18 to 13.7)	NS
04	Dune *et al.*(2003)	45/59 (76.3%)	44/52 (84.6%)	(-23, 5)	0.343
05	*Arguedas *et al.*(2011)	139/180 (77.2%)	133/162 (82.1%)	(-13.4, 3.9)	0.285

* Bacteriologic efficacy; NS=not significant, N/A= not available

Meta-analysis for children less than or equal to two years old, showed no statistical significance between the two treatment groups with overall OR= 0.96; 95% CI [0.41, 2.29]. Heterogeneity (I^2) of the included studies was I^2 = 77.6%. The meta-analysis result is summarized in Figure 3.

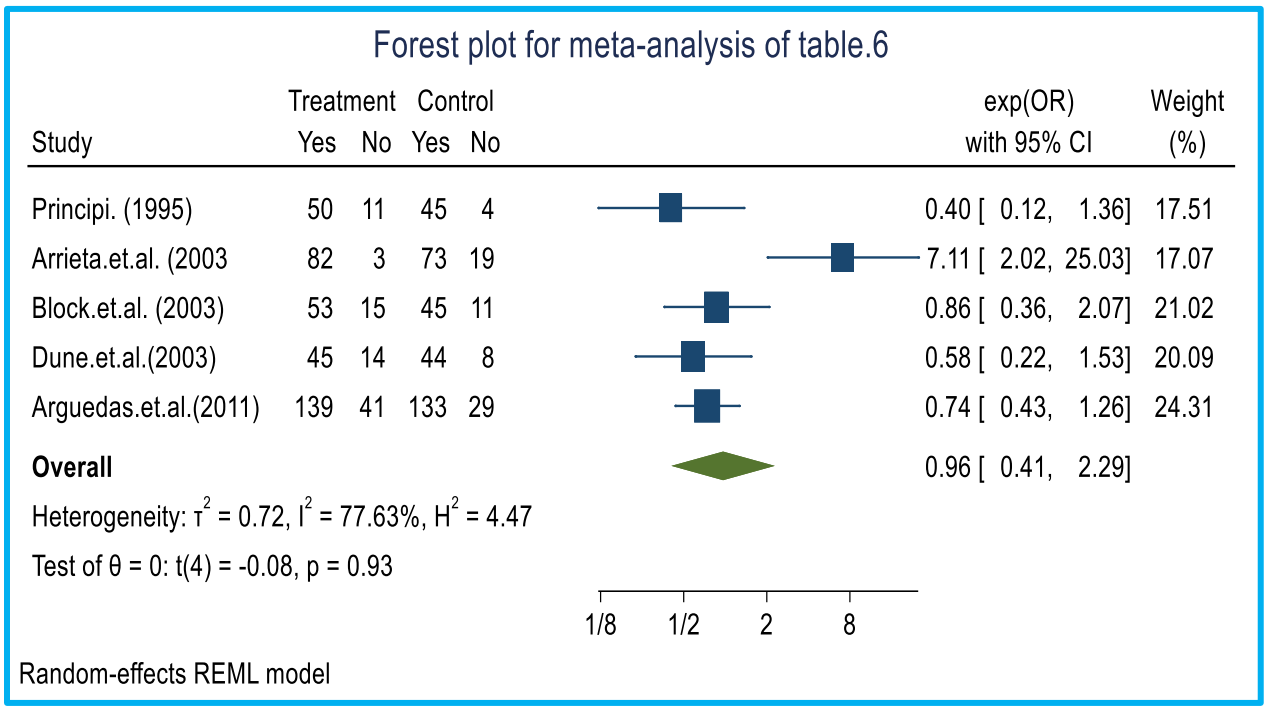

Figure 3. Forest plot for meta-analysis of table.6

Table 7. Clinical and bacteriologic efficacy of study drugs for otitis media treatment in children ≥ 2 years

S.no	Author (year)	Azithromycin group	Amox-clav group	95% CI	P-Value
01	Principi. (1995)	149/154 (96.8%)	141/149 (94.6%)	N/A	NS
02	Arrieta *et al*. (2003)	46/53 (86.8%)	49/53 (92.45%)	N/A	NS
03	Block *et al.*(2003)	86/92 (93%)	97/105 (92.38%)	(-7.1 to 9.3)	NS
04	Dune *et al.*(2003)	108/126 (86%)	94/129 (72.87%)	(-12, 6)	0.453
05	*Arguedas *et al.*(2011)	68/78 (87.2%)	69/77 (89.6%)	(-13.1, 8.2)	0.803

* Bacteriologic efficacy **NS**=not significant, **N/A**= Not available.

Meta-analysis for the sub-group analysis in children greater than two years old, there is no statistical significant difference between tow treatment groups with the overall OR= 1.40, 95% CI [0.63, 2.11]. Heterogeneity of the included studies was I^2 = 29.9%. The meta-analysis result is summarized on Figure 4.

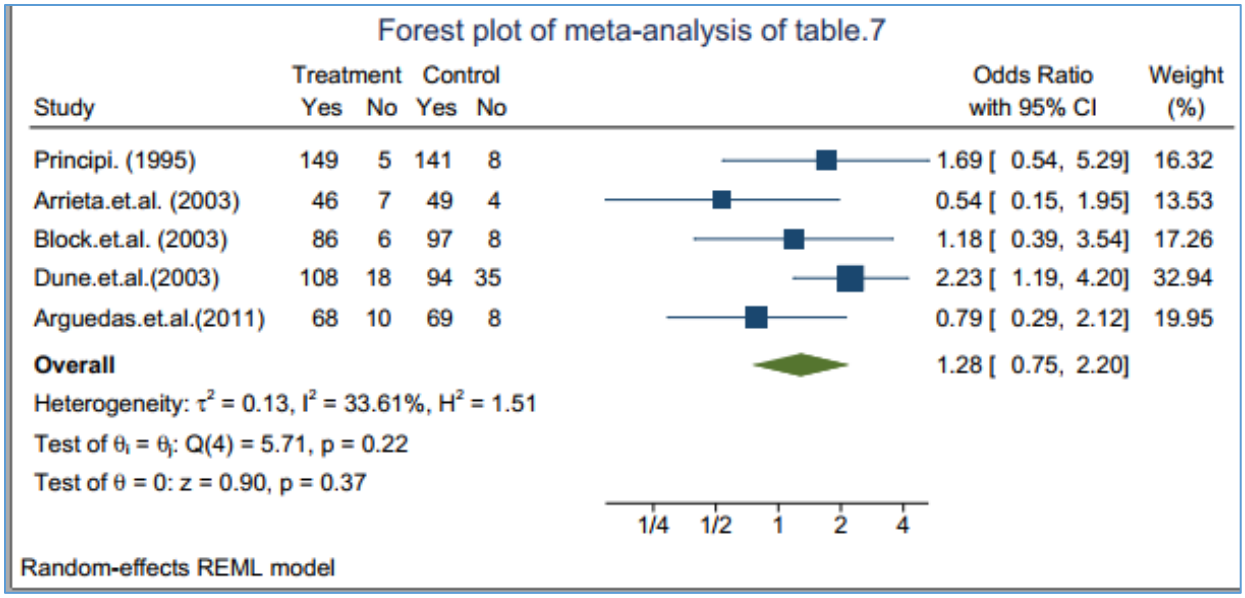

Figure 4. Forest plot for meta-analysis of table.7

Table 8. The clinical and bacteriologic efficacy of study drugs for otitis media treatment on follow-up (21-35) days.

S.no	Author (Year)	Azithromycin group	Amox-clav Group	95% CI	P-Value
01	Arguedasa *et al.*1996	12/40 (30%)	11/38 (28.9%)	N/A	NS
02	*Gerson. 1996	37/45 (82.2%)	28/35 (80%)	N/A	0.949
03	Mohini. 1996	150/225 (66.7%)	152/209 (72.7%)	N/A	0.102
04	Samuel. 1996	194/264 (73.5%)	183/257 (71.2%)	N/A	0.314
05	*Dagan.2000	44/67 (66%)	46/65 (71%)	(-11, 21)	0.53
06	Arrieta *et al.* 2003	107/148 (72%)	88/144 (61%)	(0.4, 22)	0.047
07	Block *et al.* 2003	114/151 (75%)	116/154 (75%)	(-10.2 to 10.5)	NS
08	Dune *et al.*2003	134/182 (74%)	124/180 (69%)	(-5, 15)	0.353
09	*Hoberman *et al.*2005	135/190(71.1%)	155/193(80.3 %)	(0.19–18.33)	<0.05
10	Guven *et al.* 2006.	78/90 (86.7%)	80/84 (95.3%)	N/A	0.087
11	*Arguedas *et al.*2011	184/202 (91.1%)	170/190 (89.5%)	(-4.5, 7.8)	0.612

* Bacteriologic efficacy, NS=not significant, N/A= Not available.

In meta-analysis the overall efficacy of azithromycin and amoxicillin/clavuluanate on follow up 21-35 has no statistical significant difference with OR= 0.97: 95% CI [0.7542; 1.3337]. Heterogeneity of the included studies is I^2 = = 35.64%. The meta-analysis result is summarized on Figure 5.

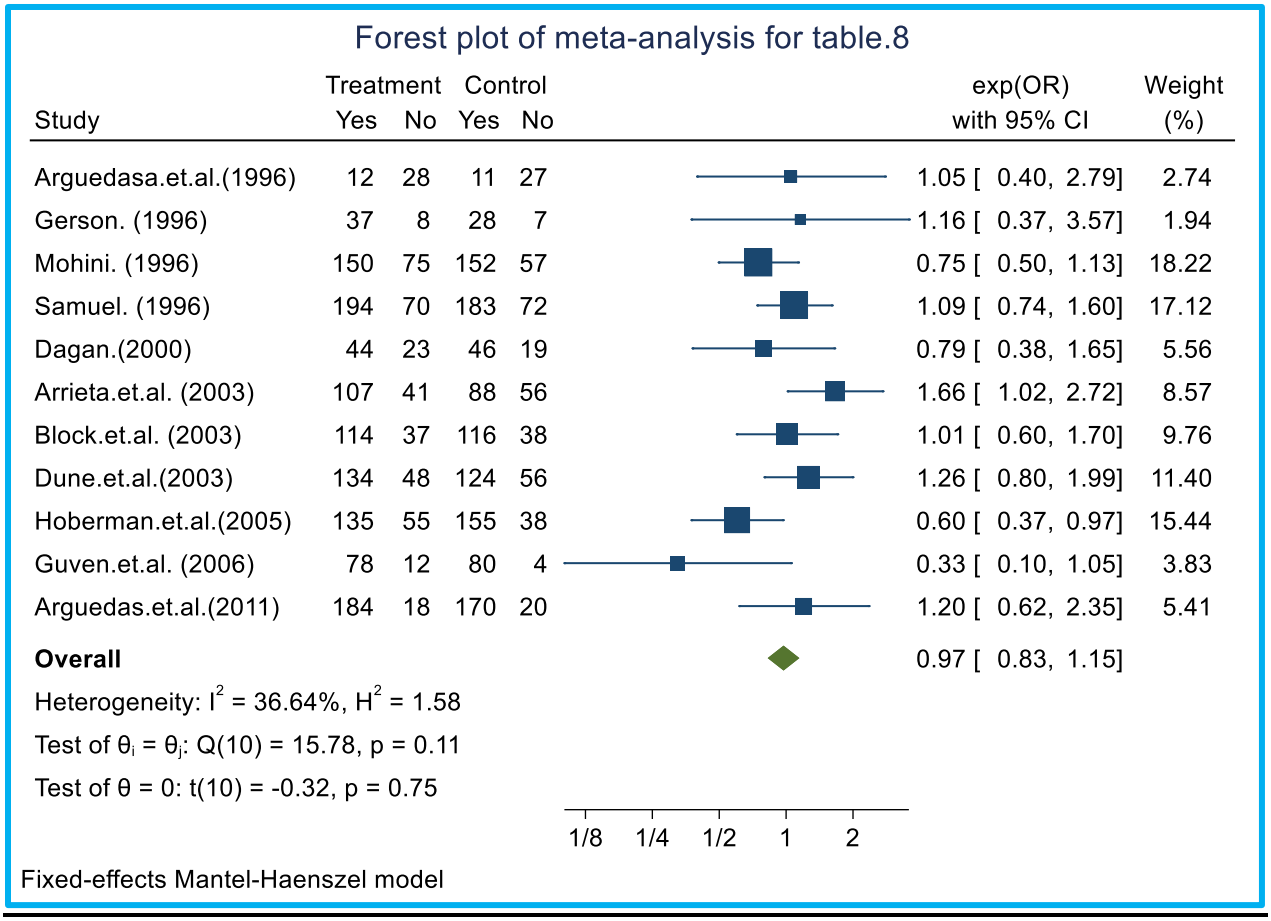

Figure 5. Forest plot for meta-analysis of table.8

4.4. Safety of azithromycin and amoxicillin/clavulanate in children

Adverse effects of study drugs were reported as clinical findings and laboratory abnormalities. Clinical adverse effects refer to the observable symptoms that occur after taking the medication. The incidence of clinical adverse effects of amoxicillin-clavulanate are significantly higher than those of azithromycin [Table 9].The most common adverse effects occurred with both drugs were gastrointestinal disorders (diarrhea, vomiting, nausea, abdominal pain and loose stool), skin rash and fever. The clinical adverse effects mean percentage and range of azithromycin and amoxicillin-clavulanate was 20% (3.5 - 45.6%) vs 32.05% (3.7 – 64.2%), respectively.

Table 9**.** Clinical adverse effects of study drugs in children.

S.no	Author (year)	Azithromycin group	Amox-clav group	P-Value
01	Daniel. (1993)	8/103 (7.77%)	2/54 (3.7%)	N/A
02	Schaad. (1993)	23/197 (11.68%)	43/192 (22.4%)	<0.002
03	Principi (1995)	11/243 (4.53 %)	20/ 240 (8.3 %)	0.0146
04	Arguedas.*et al.* (1996)	8/47 = 17.02%	30/45 (66.7%)	N/A
05	Gerson.(1996)	3/85 (3.53%)	26/84 (31%)	<0.001
06	Mohini.(1996)	19/263 (7.22%)	45/263 (17.11%)	<0.001
07	Samuel. (1996)	30/340 (8.82%)	109/334 (32.64)	<0.0001
08	Dagan.(2000)	26/120 (21.67%)	32/118 (27.12%)	0.327
09	Arrieta *et al*. (2003)	48/151(31.79%)	61/145 (42.07%)	0.095
10	Block *et al*. (2003)	29/173 (16.8%)	39/173(22.54%)	NS
11	Dune *et al*.(2003)	21/188 (11.2%)	37/185 (20%)	0.014
12	Hoberman *et al*.(2005)	128/363 (35.26%)	139/367 (37.9%)	NS
13	Guven*et et al*. (2006)	4/90 (4.44%)	4/84 (4.76%)	NS
14	Arguedas *et al.(*2011)	205/450 (45.6%)	290/452 (64.16%)	N/A

N/A= Not available, **NS=** Not significant

The meta-analysis on clinical adverse effects of the study drugs, azithromycin has found to be more safe and tolerable than amoxicillin/clavuluanate with OR= 0.46: 95% CI [0.33, 0.64]. Heterogeneity of the included studies is I^2 = 80.37%. The meta-analysis result is summarized on Figure 6.

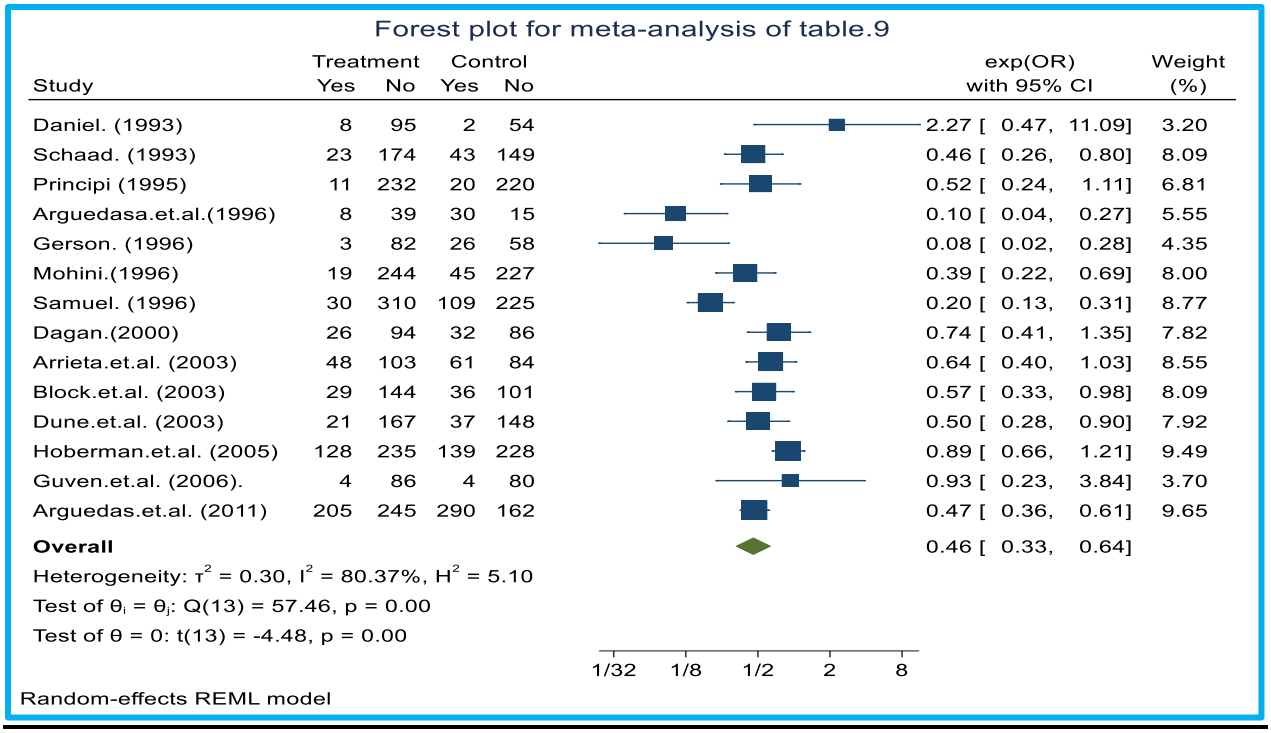

Figure 6. Forest plot for meta-analysis of table.9

The laboratory abnormality results occurred in both azithromycin and amoxicillin-clavulanate treated patients. The most abnormal results in both treatment groups were change in liver function values, increased and decreased white blood cells count, decreased neutrophils, increased eosinophils, blood urea. There was no significant difference in laboratory abnormality results between the two treatment groups of children [Table 10].

Table 10. Laboratory abnormalities of study drugs in children

S.no	Author (Year)	Azithromycin group	Amox-Clav group	P-Value
01	Daniel. (1993)	9/100 (9%)	8/54 (15%)	N/A
02	Schaad. (1993)	1/100 (1%)	6/101 (5.9%)	N/A
03	Principi (1995)	15/243 (6.17%)	10/240 (4.17%)	NS
04	Arguedas *et al.* (1996)	6/47 (12.77%)	9/45 (19.4%)	NS
05	Gerson.(1996)	7/79 (8.86%)	8/76 (10.5%)	NS
06	Mohini.(1996)	18/246 (7.3%)	21/238 (8.8%)	NS
07	Samuel. (1996)	18/305 (5.9%)	21/321 (6.5%)	NS

N/A= Not available, NS= Not significant

The meta-analysis on laboratory abnormality of the study drugs shows that there is no statistical Significant difference on the occurrence of laboratory abnormality between both study groups with OR= 0.83; 95%CI [0.60, 1.15]. Heterogeneity (I^2) of the included studies is I^2 = -21.38%. The meta-analysis result is summarized on Figure 7.

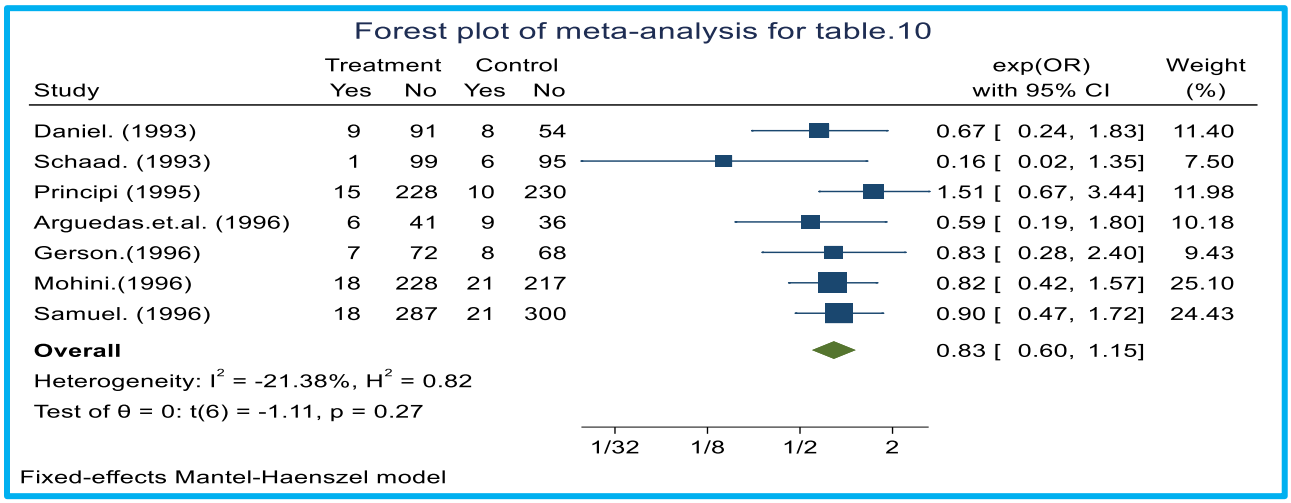

Figure 7. Forest plot for meta-analysis of table.10

4.5. Publication bias assessment

There is no publication bias for this study, depending on the funnel plot report below Figure 8, the studies are symmetrically distributed shows absence of bias within the studies. Three studies have small size widely scattered at the bottom of the graph with less treatment effect estimation.

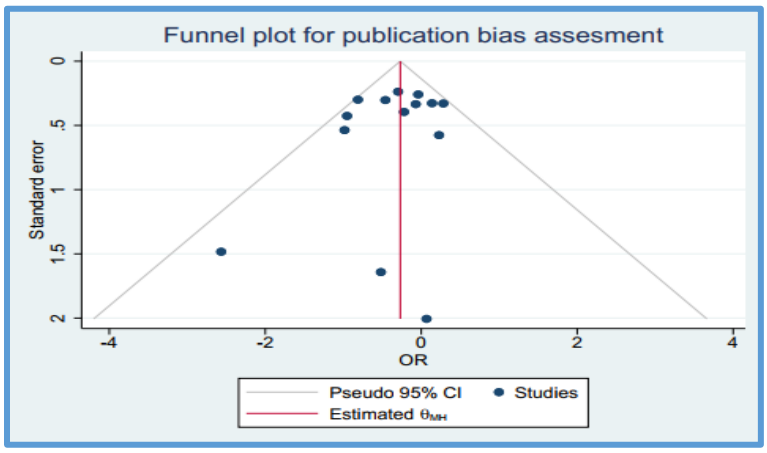

Figure 8. Funnel plot for publication bias assessment

4.6. Culture positive for otitis media pathogens and top five identified bacteria

The total sample taken from patients for culture test of bacteria from eight studies were 3020. The mean of positive culture of otitis media pathogens in children with otitis media from is

1695/3020 (56.1 %). The percentage frequency of the otitis media pathogens in the studies are 13.8 % [60], 51% [29], 54.4% [39], 55% [63], 60% [59], 62.6% [64], 67.7% [63] [66] and 71.1% [62] [Table 11]. Out of 1695 bacteriologic evaluable patients 1753 pathogens was isolated. The top five identified bacteria were *H.influenzae* 737 (42%), *S. pneumoniae* 721 (41.1%), *M. catarrhalis* 140 (8%), *S.pyogens A* 72 (4.1%), *S.aureus*59 (3.4%) and others 24 (1.37%).

4.7. Medication compliance

Three studies was included for assessing medication compliance. The medication compliance is significantly higher with azithromycin than amoxicillin/clavuluanate treatment group. The percentage frequency of compliance between azithromycin and amoxicillin/clavuluanate group is 99 vs 93% [63], 99 vs 89% [58] and 91.3 vs 85.2% [66] respectively. The percentage mean of compliance in the three studies is 94.9% vs 88.05% respectively [Table 12].

Table 11. Patients culture positive and top five identified bacteria

Culture for +ve bacteria	A-1	A-2	A-3	A-4	A-5	A-6	A-7	A-8	Total (%)
Total patients with Positive culture.	57/413 13.8%	47/92 51.1%	92/169 54.4%	169/238 71.1%	163/296 (55%)	494/730 (67.7%	108/180 (60%)	565/902 (62.6%)	1695/3020 (56.13%)
H.influenzae	15	17	20	82	75	245	24	259	737(42%)
S.pneumonae	20	20	53	49	73	229	46	231	721 (41.1%)
M. catarrhalis	0	3	12	5	22	20	18	60	140 (8%)
St. pyogenes A	14	0	7	4	10	0	6	31	72 (4.1%)
S.aureus	7	5	0	4	0	0	16	27	59 (3.4%)
others	10	8	0	0	0	0	6	0	24 (1.37%)
Total isolated bacteria	66	53	92	144	180	494	116	608	1753 (100%)

Principi 1995 = **A-1,** Arguedasa.*et.al*.1996 = **A-2,** Gerson 1996 = **A-3,** Dagan.2000 = **A-4,** Arrieta.*et.al*.2003 =**A-5,** Hoberman.*et.al*.2005 = **A-6,** Guven.*et.al*.2006. = **A-7,** Arguedas.*et.al*.2011 = **A-8.**

Table 12. Medication compliance of azithromycin and amoxicillin-clavulanate in children

S.no	Author (Year)	Azithromycin group	Amox-Clav group	P-Value
01	Arrieta *et al.* 2003	151/153 (99%)	138/147 (93%).	0.018
02	Dune *et al*.2003	183/185 (99%)	161/181 (89%)	N/A
03	Hoberman *et al*.2005	335/367 (91.3%)	313/367 (85.2%)	N/A
Mean of percentage		669/705 (94.9%)	612/ 695 (88.05%)	---

5. Discussion

The overall clinical efficacy of azithromycin and amoxicillin/clavulanate is equivalent to treat otitis media in children. The efficacy evaluation was either clinical efficacy or bacteriological efficacy. The clinical efficacy of both study drugs is equivalent with no statistically significant difference in all eleven studies [Table 5]. The bacteriological efficacy evaluation of amoxicillin/clavulanate is superior to azithromycin [59,66] but in one of these studies the dose of amoxicillin was doubled to 90mg/kg whereas the dose of azithromycin did not and in children with no otitis media pathogens there is no significant difference in the clinical efficacy of both drugs [66]. In two studies for all the patients with positive bacteriological culture test there is no difference in bacteriologic efficacy of both treatment groups [39,66] Meta-analysis result of a similar study on the bacteriologic efficacy azithromycin had more significant effect on the treatment of some bacterial respiratory infections in children (OR=0.78, 95%CI (0.65-0.93), P=0.007) more than amoxicillin/ clavulanate [68]. Azithromycin has both antibacterial, antiviral, anti-inflammatory activity, this can be the reason that makes clinical efficacy of azithromycin to be equivalent with amoxicillin/clavulanate. In similar studies that was comparing azithromycin (10 mg/kg on day 1, then 5 mg/kg daily on days 2-5) with single intramuscular dose of ceftriaxone 50mg/kg, and 10 days at dose of 90/6.4mg/kg amoxicillin/clavulanate in two divided dose for treating acute otitis media all have equivalent efficacy of 87.1%, 85.3% and 87.2% respectively [69]. Comparing failure rate of amoxicillin alone (50mg/kg BID for 7 days) and azithromycin (single dose 30mg/kg) for treating acute otitis media is 54% (83/155) and 50% (82/165) respectively [70]. In meta-analysis by Wang.PX.*et.al* from 20 RCT with 4980 children included for assessing the clinical efficacy of azithromycin and amoxicillin/clavulanate on the treatment of upper respiratory infection (acute otitis media and so on) in children, azithromycin has significant effect with OR=0.75 95%CI (0.62 0.91) P-value 0.003 than amoxicillin/clavulanate [68], but in our meta-analysis the efficacy of both study drugs is with small statistical difference OR= 0.75 95%CI (0.62-0.91) in favor of amoxicillin/clavulanate.

The follow up efficacy analysis on (21-35 days) was done in eleven studies. In nine study the clinical efficacy is not with statistical significant difference in both treatment groups. The bacteriological efficacy is amoxicillin/clavuluanate in single study is more significant but there is no significant difference in the other three studies [Table 5]**.** The difference is much narrower than on day10-16 efficacy assessment after finishing treatment. There is a decrease in efficacy

percentage in both groups the efficacy of azithromycin is more in six study**,** less in four studies and equal in one study compare with amoxicillin/clavuluanate. The meta-analysis shows efficacy of azithromycin and amoxicillin/clavuluanate on day 21-35 is equivalent with OR= 0.97; 95%CI (0.83-1.15)

The subgroup analysis for the efficacy on treating otitis media was evaluated in less or equal to two years old there is no any significant difference in all five studies. The same for children greater than two years old the efficacy is comparable in the same groups. Both study drugs have more percentage of efficacy in children greater than two years old. The meta-analysis result for both sub group in less than two years children is OR= 0.96; 95% CI [0.41-2.29] and in greater than two years old children. OR= 1.40 95% CI [0.93-2.11]. The efficacy is little high in children greater than two years old in both study drugs.

Azithromycin is more safe and tolerable than amoxicillin/ clavuluanate. The clinical findings of adverse events found in both groups is similar, but the difference is in frequency. In our meta-analysis from fourteen studies the clinical finding adverse events is higher in amoxicillin/clavuluanate with OR=0.46 95% CI (0.33- 0.64). In similar meta-analysis from thirteen RCT study by Wang.PX.*et.al* for clinical safety assessment shows, the difference between azithromycin and amoxicillin/clavuluanate is statistical significant in the treatment of some bacterial respiratory infections in children (OR=0.49, 95%CI (0.40, 0.60), P<0.000 01) [68]. A comparative study in US on the efficacy amoxicillin/clavuluanate and azithromycin and to treat acute bacterial sinusitis in adults the incidence of adverse events was 31.1% and 51.1% p <0.001 respectively [71]. In other studies conducted in Australia and New Zealand hospitals the adverse events in children within azithromycin group 17 (21%) of 82 versus 23 (24%) of 97 in the amoxicillin–clavuluanate group (RR= 0·9, 95% CI 0·5 to 1·5) [72]. Also a study done by Ferwerda.*et.al* reported a significant higher adverse events in amoxicillin/clavuluanate than azithromycin 43% versus 19% in children [73]. In both study groups the most clinical findings are gastro intestinal problem (vomiting, diarrhea, nausea and abdominal cramp) and there is no significant difference in laboratory abnormality findings from meta-analysis results OR=0.83; 95%CI [0.60, 1.15]. In most comparative study, the adverse events reported from both study groups are similar and moderate in severity.

The children with otitis media that are positive for bacteria culture test, in the included 7 study are ranged from 13.8% to 71.1% with mean of 56.1% and more than one bacteria was identified in some patients. The top five bacteria responsible for otitis media infection are *H.influenzae* (42%), *S.pnuemoniae* (41.1%), *M.catarhlis* (8%), *S.pyogens A* (4%), *S.aureus* (3.4%) and others (1.37%). In many studies the first dominant bacteria is *S.pnuemoniae* but in this study both *H.influenzae* and *S.pnuemoniae* have accounted similar percentage. The top three bacteria are the same in other studies [13,14, 15].

The pharmacokinetic benefits of azithromycin over amoxicillin/clavuluanate are long half-life, well distribution inside macrophages and neutrophils high concentration in infected site. The short period (1-5 days) of treatment of azithromycin make the patients to have more adherence than with long period (10 days) of treatment of amoxicillin/clavuluanate. From the included three studies the mean compliance of treatment with azithromycin and amoxicillin/clavuluanate is 95% and 88% respectively. In a study done by Auersperg. DM.*et.al* comparing efficacy of azithromycin and amoxicillin for treating otitis media, 53% and 86% patients respectively completed their medication [74].

6. Conclusion

Efficacy of azithromycin is comparable with amoxicillin-clavuluanate for the treatment otitis media and it is with more safe and tolerable by children. In children greater than two years efficacy of azithromycin is better than amoxicillin/clavulanate. Therefore azithromycin can be a drug of choice in treatment of otitis media.

7. Recommendations

Azithromycin should be introduced in the guideline of otitis media treatment in children at least as a second-line treatment of otitis media for amoxicillin/clavulanate eligible patients and first line for amoxicillin/clavulanate ineligible patients.

More research is required on the efficacy and safety of high dose of azithromycin (20mg/kg) and amoxicillin/clavuluanate (90mg/kg) in treating otitis media.

More researches on efficacy and safety of azithromycin for treating otitis media in children should be done in Africa.

There must be an up-to-date information on the resistance status of azithromycin and amoxicillin against the bacteria responsible for otitis media

References

1. Scottish intercollegiate guidelines network (2003), diagnosis and management of childhood otitis media in primary care, a National clinical guideline. ISBN 1899893482
2. World Health Organization (2006). Primary ear and hearing care training resource; http://www.who.int.pbd. (Accessed 2020)
3. Penido N.O *et al.* (2016). Complications of otitis media -a potentially lethal problem still present. Brazil Journal Otorhinolaryngology; 82:253-262. doi.org/10.1016/j.bjorl.2015.04.007.
4. Anggraeni *et al*. (2014). Otitis Media in Indonesian Urban and Rural School Children, Pediatric Infectious Diseases Journal. 33 (10):1010-1016.
5. Bluestone C.D (1998). Epidemiology and pathogenesis of chronic suppurative otitis media: implications for prevention and treatment. International Journal of Pediatric Otorhinolaryngology. 42:207–223.
6. Brady J.J *et al.* (2014). Otitis media in Indigenous Australian children: review of epidemiology and risk factors. Journal of laryngology and otolaryngology. 128 (1):16-27. doi: 10.1017/S0022215113003083.
7. Paradise J.L *et al.* (1997). Otitis media in 2253 Pittsburgh-area infants; prevalence and risk factors during the first two years life. Pediatrics, 99(3): 318-333.
8. Usonis, V *et al.* (2016). Incidence of acute otitis media in children below six years of age seen in medical practices in five East European countries.
9. Monasta L *et al.* (2012). Burden of diseases caused by otitis media: a systematic review and global estimate. Plos ONE. 7 (4): e36226. doi.10.1371/journal.pone.0036226.
10. DeAntonio *et.al.* (2016). Epidemiology of otitis media in children from developing countries: A systematic review; International Journal of Pediatric Otorhinolaryngology 8:565–74.
11. Abdurrahman, S *et al.* (2013). Bacterial otitis media in all age group of patients seen at Dessie referral hospital, North East Ethiopia. Egyptian Journal of Ear Nose Throat and Allied Science; 14 (2) 73-78doi.org/10.1016/j.ejenta.2013.02.005.
12. Harmes *et al.* (2013). Otitis Media: Diagnosis and Treatment, American family physicians, Volume 88, (7) 435-531.

13. Jacobs M.R *et al.* (1998). Prevalence of antimicrobial-resistant pathogens in middle ear fluid. Antimicrobial Agents Chemotherapy; 42 (3):589-595.
14. Arrieta A and Singh J. (2004). Management of recurrent and persistent acute otitis media: new options with familiar antibiotics. Pediatric Infectious Diseases Journal; 23 (2):115-124.
15. Schilder G.M *et al*. (2016). Otitis media: Nature reviews | disease primer, volume 2:1-18 Doi:10.1038/nrdp.2016.63.
16. Tesfa T *et al.* (2020). Bacterial otitis media in sub-Saharan Africa: a systematic review and meta-analysis; Biomed Central Infectious Diseases, 20:225.
17. Lieberthal, A.S *et al.* (2013).The diagnosis and management of acute otitis media. Pediatrics 131, 964–999.
18. Rosenfeld R.M (2016). Clinical Practice Guideline: Otitis Media with Effusion (Update). Otolaryngology–Head and Neck Surgery,154(1) 1–41 DOI: 10.1177/0194599815623467
19. Hirsch *et al.* (2011). Azithromycin in periodontal treatment: more than an antibiotic, Journal of Periodontics Research 2012; 47: 137–148.
20. Verhoeff M *et al*. (2006).Chronic suppurative otitis media: a review. International Journal of Pediatric Otorhinolaryngology. 70, 1–12.
21. Vernon-Feagans L *et al*. (2007). Quality of childcare and otitis media: relationship to children's language during naturalistic interactions at 18, 24 and 36 months. Journal of Applied Development Psychology; 28: 115-133.
22. Klein J.O (2000). The burden of otitis media. Vaccine. 19 (1):2-8.
23. Pechère J.C (1991).The activity of azithromycin in animal models of infection. European Journal of Clinical Microbiology of Infectious Diseases. 10(10):821-7. DOI: 10.1007/bf01975834.
24. Baldwin R.L (1993). Effects of otitis media on child development. American Journal of Otolaryngology. 14(6):601-4
25. Nittrouer S (1996). The relation between speech perception and phonemic awareness: evidence from low-SES children and children with chronic OM. Journal of Speech Hearing Research. 39: 1059-1070.
26. Williams C.J (2009). The impact of otitis media on cognitive and educational outcomes. Medical Journal Australia. 191 (9):69-72. DOI: 10.5694/j.1326-5377.2009.tb02931.x.

27. Intermountain Healthcare's (2019). Diagnosis and management of Pediatric Acute Otitis Media (Ear Infection), Care Process Models (CPM).update (2019).
28. Foulds G *et al.* (1990).The pharmacokinetics of azithromycin in human serum and tissues. Journal of Antimicrobial Chemotherapy; 25(A):73-82.
29. Arguedas A *et al*. (1996) Comparative trial of 3-day azithromycin versus 10-day Amoxicillin/Clavuluanate potassium in the treatment of children with otitis media with effusion. International Journal of Antimicrobial Agents 6; 233-238.
30. Pukander J.S *et.al.* (1993). Clarithromycin vs amoxicillin suspensions in the treatment of pediatric patients with acute otitis media. Pediatric Infectious Diseases Journal; 1993; 12 (3): 118-121.
31. Eppes S.C and Childs J.A. (2002). Comparative study of cefuroxime acetyl versus amoxicillin in children with early Lyme disease. Pediatrics. 109(6); 1173-1177.
32. Tong D.C and Rothwell B.R. (2000). Antibiotic prophylaxis in dentistry: a review and practice recommendations. Journal of American Dentistry Association. 131: 366-374.
33. Weber, D.J *et al.* (1984). Amoxicillin and potassium clavuluanate: an antibiotic combination. Pharmacotherapy 4; 122–36.
34. Amin A.S *et al.* (1994). Colorimetric determination of amoxicillin in pure form and in pharmaceutical preparations. Atlanta. 41(5): 691-694.
35. Shah S.H *et al*. (1994). Cefuroxime acetyl in the treatment of bronchitis: comparison with amoxicillin in a multicenter study in general practice patients. British of Journal of Clinical Practice. 48(4): 185-189.
36. Bush K *et al.* (2010). β-lactam antibiotics: Penicillin, and other β-lactamase inhibitors. Expert opinion therapy patients.20 (10). 1277-93. Doi: 10.1517/13543776.2010.515588.
37. Brodie D.P *et al*. (1990) Comparative study of cefuroxime acetyl suspension and amoxicillin syrup in the treatment of acute otitis media in general practice. International Journal of Medical Research. 18(3): 235-239.
38. Dousa M and Hosmanova R (2005). Rapid determination of amoxicillin in premixes by HPLC. Journal of Pharmacy and Biomedical Analysis. 37: 373-377.
39. Gerson A (1996). A multicenter open label trial of azithromycin versus amoxicillin/clavulanate for the management of acute otitis media in children. Pediatric Infectious Diseases Journal.15 (6) 15-19.

40. Levy S.B (1992). Active efflux mechanisms for antimicrobial resistance. Antimicrobial. Agents Chemotherapy. 36: 695–703.
41. Neto.A.B. *et al.* (2005) A study on clavulanic acid production by *streptomyces clavuligerus* in batch, fed-batch and continuous processes. Beijing Jingneng Clean Energy: 22 (4); 557 – 563.
42. Reed M.D (1998). The clinical pharmacology of amoxicillin and clavulanic acid. Pediatric Infectious Disease Journal.17:957-962.
43. Adam D *et al.* (1982) Pharmacokinetics of amoxicillin and Clavulanic acid administered alone and in combination. Antimicrobial Agents and Chemotherapy. 22:353-357.
44. Fohner A.E *et al.* (2017). Summary: Macrolide antibiotic pathway, pharmacokinetics/ pharmacodynamics. Pharmacogenetics Genomics. 27(4):164-167. doi:10.1097/FPC.0000000000000270.
45. Tran D.H *et al*. (2019). Azithromycin, a 15-membered macrolide antibiotic, inhibits influenza A (H1N1) pdm09 virus infection by interfering with virus internalization process. Journal of Antibiotics (Tokyo). 72 (10):759-768.
46. Retsema J *et al.* (1987). Spectrum and mode of action of azithromycin (CP-62, 993), a new 15-membered-ring macrolide with improved potency against Gram-negative organisms. Antimicrobial Agents Chemotherapy 31:1939-1947.
47. Kirst H.A. and Sides G.D (1989). New directions for macrolide antibiotics: structural modifications and in vitro activity. Antimicrobial Agents Chemotherapy: 33(9) 1413-1418. Doi: 101128/aac.33.9.1413.
48. Atkinson *et al.* (2015). Acute otitis media. Postgraduate Medicine 127:386–390. doi.10.1111/j.1600-0765. 2011.01418.x.
49. Cheng *et al*. (2016). Antimicrobial drugs in fighting against antimicrobial resistance. Front Microbiology. 7:470. doi: 10.3389/fmicb.2016.00470.
50. Lode H (1991). The pharmacokinetics of azithromycin and their clinical significance. European Journal of Microbiology and Infectious Diseases. 10 (10); 807- 812. Doi: 10.1007/BF01975832.
51. Hunter, R.P *et al.* (2003). Azithromycin metabolite identification in plasma, bile, and tissues of the ball python (Python regius) Journal of Veterinary Pharmacology and Therapeutics. 26 (2):117-21. doi: 10.1046/j.1365-2885.2003.00464.x

52. Salman *et al.* (2010). Pharmacokinetic Properties of Azithromycin in Pregnancy. Antimicrobial Agents and Chemotherapy. 54 (1)360–366. Doi:10.1128/AAC.00771-09.
53. Dunn.C.J (1996). Azithromycin A Review of its Pharmacological Properties and Use as 3-Day Therapy in Respiratory Tract Infections. Drugs: 51 (3): 483-505.
54. Singlas E (1995). Clinical pharmacokinetics of azithromycin. Pathologie Biologie (Paris). 43(6):505-11.
55. Samuel (1996). A multi-center double blind comparison of azithromycin and Amoxicillin- Clavuluanate for the treatment of acute otitis media in children. Pediatric infectious diseases journal. 15 (9):20-23.
56. Morris, P.S *et al.* (2009). Acute and chronic otitis media. Pediatric Clinics of North America.56 (6):1383–99.
57. Liberati *et al.* (2009).The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLoS Medicine 6 (7) e1000100.
58. Dunne M.W *et al.* (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. Journal of Antimicrobial Chemotherapy. 52.469–472 DOI: 10.1093/jac/dkg358.
59. Guven *et al*. (2006) Bacterial etiology of acute otitis media and clinical efficacy of amoxicillin—clavuluanate versus azithromycin. International Journal of Pediatric Otorhinolaryngology: 70: 915—923.
60. Principi (1995). Multicenter comparative study of the efficacy and safety of azithromycin compared with amoxicillin/clavulanic acid in the treatment of pediatric patients with otitis media. European Journal of Clinical Microbiology and Infectious diseases. 14(8):669-676.
61. Schaad U.B (1993). Multicenter evaluation of azithromycin in comparison with co-amoxi-clav for the treatment of acute otitis media in children. Journal of Antimicrobial Chemotherapy: 31: 81-88.
62. Dagan *et al.* (2000). Bacteriologic and clinical efficacy of amoxicillin/clavuluanate *vs.* azithromycin in acute otitis media. Pediatric Infectious Disease Journal.19 (2):95–104.

63. Arrieata *et al. (*2003). High-dose azithromycin versus high-dose amoxicillin-clavulanate for treatment of children with recurrent or persistent acute otitis media. Antimicrobial Agents chemotherapy. 47 (10). 3179–3186.
64. Arguedas *et al*. (2011). Single-dose extended-release azithromycin versus a 10-day regimen of amoxicillin/clavuluanate for the treatment of children with acute otitis media International Journal of Infectious Diseases 15; 240–248 doi:10.1016/j.ijid.2010.12.003.
65. Block S.L *et al.* (2003) Single-Dose (30 mg/kg) azithromycin compared with 10-day amoxicillin/clavuluanate for the treatment of uncomplicated acute otitis media: A double-blind, placebo-controlled, randomized clinical trial. Current Therapeutic Research 6 4: A30-A40. doi:10.1016/j.curtheres.2003.09.006.
66. Hoberman *et al*. (2005). Large dosage amoxicillin/clavuluanate, compared with azithromycin, for the treatment of bacterial acute otitis media in children. Pediatric Infectious Diseases Journal. 24 (6): 525-532. doi 10.1097/01.inf.0000164794.50281.1a.
67. Mohini K.C (1993). A Multicenter randomized open label comparison of azithromycin and amoxicillin/clavuluanate in acute otitis media among children attending day care or school. Pediatric Infectious Diseases Journal. 15 (09): 24-29.
68. Wang P.X *et al.* (2016) clinical efficacy and safety of azithromycin versus amoxicillin-clavulanic acid in the treatment of some acute respiratory infections in children. International Journal of Cardiology. DOI:10.13220/j.cnki.jipr.2016.04.011.
69. Morris P.S *et al.* (2010). Single-dose azithromycin versus seven days of amoxicillin in the treatment of acute otitis media in aboriginal children (AATAAC): a double blind, randomized controlled trial**.** Medical Journal. 192(1):24-9.
70. Henry D.H *et al.* (2003). Randomized double-blind study comparing 3- and 6-day regimens of azithromycin with a 10-day amoxicillin-clavuluanate regimen for treatment of acute bacterial sinusitis. Antimicrobial Agent Chemotherapy. 47 (9): 2770–2774. DOI: 10.1128/AAC.47.9.2770–2774.2003.
71. Henry D.H *et al.* (2003). Randomized double-blind study comparing 3- and 6-day regimens of azithromycin with a 10-day amoxicillin-clavuluanate regimen for treatment of acute bacterial sinusitis. Antimicrobial Agent Chemotherapy. 47 (9): 2770–2774. DOI: 10.1128/AAC.47.9.2770–2774.2003.

72. Goyal *et al.* (2019) Efficacy of oral amoxicillin/clavuluanate or azithromycin for non-severe respiratory exacerbation in children with bronchiectasis (BEST-1): a multicenter, three arm, double blind randomized placebo-controlled trial. Lancet Respiratory Medicine. 7 (9): 791-801. doi: 10.1016/S2213 – 2600(19)30254-1.
73. Ferwerda *et al.* (2001) Efficacy safety and tolerability 3-day azithromycin versus 10-day co-amoxiclav in the treatment of children with acute lower respiratory tract infection. Journal of Antimicrobial Therapy: 47: 441-446.
74. Auersperg D.M *et al.* (2001). Amoxicilina versus azitromicina en el tratamiento de otitis media aguda. Archivos de Pediatria del Uruguay 72, (1): 1688—1249.

Appendix 1.

Data extraction form

01	Review title or ID _____.
02	Study ID Author Name: _____ Publication year_____.
03	Report IDs of other reports of this study
04	Date form completed
05	Name/ID of person extracting data: _____.
06	Report title _____.
07	Report author contact details Authors Name: 1. _____ 2._____. 3. _____ 4. _____. 5. _____ 6. _____.
08	Publication type: _____.
09	Funding source: _____.
10	Declaration of Conflict of Interest _____.
11	Type of study _____.
12	Participants _____.
13	Types of intervention _____.
14	Types of outcome variable
15	Population description _____.
16	Setting _____.
17	Inclusion criteria _____. _____. _____.
18	Method of participants recruitment _____.
19	**Objective of the study**

20 Study design
_____.

21 Start date: _____ End date: _____

22 Duration of treatment period
- Study drug for _____ days.
- Comparison drug for _____days.

23 Timing of daily dose
- Study drug _____ per day.
- Comparison drug _____ per day.

24 Follow up _____.

25 **Result**

Patient Demography

Characteristics	Azithromycin treated	Amoxicillin clavuluanate treated
Female n (%)		
Male n (%)		
Total		
Age mean and range (years)		

Clinical response analysis results at date _____.

	Azithromycin N (%) (n=)		Amoxicillin clavuluanate N (%) (n=)		95% CI	P= value
Cured						
Improved						
Failed						

Adverse events (clinical findings)

	Azithromycin N (%) (n=)		Amoxicillin clavuluanate N (%) (n=)		95% CI	P= value
Clinical findings						

Adverse events (clinical findings)

	Azithromycin N (%) (n=)		Amoxicillin clavuluanate N (%) (n=)		95% CI	P= value
Clinical findings						

26 **Conclusion**