

BMJ Open Effectiveness of amoxicillin alone in the treatment of uncomplicated acute otitis media: a systematic review protocol

Emmanuel Choffor-Nchinda,¹ Leonel Christophe Atanga,¹ Jobert Richie Nansseu,² François Djomou^{1,3}

To cite: Choffor-Nchinda E, Atanga LC, Nansseu JR, *et al*. Effectiveness of amoxicillin alone in the treatment of uncomplicated acute otitis media: a systematic review protocol. *BMJ Open* 2018;**8**:e021133. doi:10.1136/bmjopen-2017-021133

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2017-021133>).

Received 12 December 2017

Revised 22 April 2018

Accepted 11 May 2018



¹Department of Otolaryngology-Head and Neck Surgery, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaounde, Cameroon

²Department of Public Health, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon

³Otolaryngology- Head and Neck Surgery unit, Yaoundé University Teaching Hospital, Yaoundé, Cameroon

Correspondence to

Dr Emmanuel Choffor-Nchinda; ecnchinda@yahoo.com

ABSTRACT

Introduction Amoxicillin is the first-line antibiotic recommended by most scientific societies for the treatment of uncomplicated acute otitis media (AOM) in children and adults. In low-income and middle-income countries however, absence of setting-specific recommendations and antibiotic resistance, promoted by higher population density and over-the-counter antibiotic availability, could hamper the effectiveness of amoxicillin. We aim to provide updated information to enable evidence-based decisions for first-line therapy of uncomplicated AOM in our setting.

Methods and analysis We will conduct a systematic review of all randomised controlled trials on the clinical effectiveness of amoxicillin for the treatment of uncomplicated AOM in children above 6 months and adults. The search will include studies published from the generation of the included databases to 31 December 2017. Study selection will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and study quality will be assessed by the Risk of Bias Assessment Tool from the Cochrane Handbook for randomised trials. A meta-analysis will be conducted for homogeneous studies, eventually, using the fixed-effect model. Subgroup analysis will include age groups, amoxicillin dosage, treatment duration, effectiveness criteria, time of trial realisation, study quality and region of the world involved.

Ethics and dissemination Formal ethical approval is not required, as primary data will not be collected. The results will be disseminated through a peer-reviewed publication and presented at scientific meetings.

PROSPERO registration number CRD42017080029.

INTRODUCTION

Otitis media (OM) is the most common specifically treated disease in children, the second most common disease of childhood¹ and a major cause of childhood morbidity.^{2–4} It is the second most important cause of hearing loss which ranked fifth on the global burden of disease and affected 1.23 billion people in 2013.⁵ In low-income and middle-income countries specifically, the incidence of OM in sub-Saharan Africa (SSA), South Asia and Oceania is twofold to eightfold higher than in

Strengths and limitations of this study

- We will carry out a systematic review and meta-analysis of randomised controlled trials only.
- Our study design will provide the highest level of evidence for decision-making regarding the management of uncomplicated acute otitis media.
- Our study will enable harmonisation of practice hence reduce the risk of antibiotic resistance by proposing concrete guidelines for treatment of acute otitis media.
- Secondary outcome analysis will permit clarification of the risk of adverse outcomes with the use of amoxicillin alone.
- Relatively few controlled trials carried out in Africa could be a setback for this study.

developed world regions, with India and SSA accounting for the majority of OM-related deaths.⁴ A systematic review by DeAntonio *et al* reported a prevalence of OM in population-based studies between 6.3% and 10.7%.⁶ Chronic OM, which usually follows untreated or inadequately treated acute OM (AOM), constitutes a major chronic disease in low-income and middle-income countries.⁵

While most low-income and middle-income countries do not have setting-specific guidelines for the treatment of AOM, those that have them show a huge diversity regarding diagnosis and management.⁶ Paediatric societies formulate recommendations in developed countries, while in low-income and middle-income countries the Ministry of Health usually initiates guideline formulation.⁶ Amoxicillin is generally accepted as the first-line antibiotic, both in low-income and middle-income countries, and developed countries, though in different doses (30–100 mg/kg/day).⁷ Conversely, Eholié *et al* recommended amoxicillin–clavulanic acid combination as first-line therapy for AOM in patients living in SSA.⁸ In Cameroon, practitioners theoretically adopt recommendations of the French drug regulatory body, *Haute*

Autorité de Santé which similarly recommends amoxicillin.⁹ Most clinicians however prefer amoxicillin–clavulanic acid as first-line therapy.

Another major issue in resource-limited settings is antimicrobial resistance. Studies provide some disturbing data on extensive unjustified use of antibiotics for AOM, high antibiotic resistance of *Streptococcus pneumoniae* isolated from AOM cases, including multidrug resistance phenotypes, and high complication rates.¹⁰ This situation is accentuated by higher-density populations, automedication and over-the-counter antibiotic availability. As a result, antibiotics are taken abusively and at inappropriate dosages. This could explain the reluctance of many practitioners to prescribe amoxicillin alone as first-line therapy.

The purpose of this review therefore is to find out if amoxicillin alone is effective in treating children and adults with uncomplicated AOM. The ultimate goal is to provide updated information to enable evidence-based decisions for first-line therapy of uncomplicated AOM in our setting, thereby harmonising practice and reducing antibiotic resistance.

METHODS AND ANALYSIS

Recommendations from the Centre for Review and Dissemination will serve as guidance to conduct this review¹¹ which will be subsequently reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹² This protocol was written and presented in compliance with the PRISMA-P 2015 guidelines,¹³ and registered with PROSPERO (ID: CRD42017080029).

Eligibility criteria

Type of studies

We will consider only randomised controlled trials published from inception to 31 December 2017. Studies lacking explicit method description will not be included, for studies published in more than one report, we will consider the most comprehensive and up-to-date version.

Population

Studies must have included patients aged 6 months and above, diagnosed with uncomplicated AOM and treated with amoxicillin alone. Cases considered uncomplicated must not present any of the following: mastoiditis, postauricular abscess, facial nerve paresis, labyrinthitis, temporal abscess, petrositis, intracranial abscess, meningitis, otitic hydrocephalus or sigmoid sinus thrombosis.

Intervention

The intervention will be treatment with amoxicillin in monotherapy, irrespective of dosage or duration of treatment. Amoxicillin may have been compared with any other drug. The comparison will include comparison with a placebo or any other antibiotic.

Outcome of interest

Primary outcome:

- ▶ Clinical effectiveness of amoxicillin in AOM evaluated by effective recovery from the episode. The criteria for effectiveness will be considered as defined by the respective authors.

Secondary outcome:

- ▶ Whether or not there is a recurrent episode of AOM following treatment with amoxicillin, defined as another episode of AOM within 1 month following treatment completion.
- ▶ Whether or not there is a complication of AOM following treatment with amoxicillin.

Search strategy

A comprehensive and exhaustive search of databases will be performed to identify all relevant articles on effectiveness of amoxicillin alone in the treatment of AOM from the generation of the databases to 31 December 2017. The following sources will be searched for published literature: PubMed/MEDLINE, EMBASE, ISI Web of Science, WHO Global Health library, African Journals Online, SciELO database and The Cochrane Library (Cochrane Database of Systematic Reviews). Grey literature will be sought from GreyLit and OpenGray databases, as well as the library of the Faculty of Medicine and Biomedical Sciences of the University of Yaounde 1. Studies published in English and French will be included. The search strategy will comprise text words, keywords and MeSH terms, using the syntax of the respective databases, based on our Population, Intervention, Comparison, Outcome (PICO) framework. The strategy will be developed and made available as the study is carried out. For instance, the search strategy for MEDLINE will include the terms: Amoxicillin OR Amoxycillin AND Otitis OR Otitis Media OR Otitis Media, Suppurative OR Middle Ear Inflammation OR Inflammation, Middle Ear AND Clinical Effectiveness OR Outcome Treatment OR Clinical Effectiveness OR Clinical Effectivenesses.

Study selection

Two reviewers (EC-N and LA) will independently and systematically screen the abstracts of articles found through searching databases. Study characteristics will be studied and evaluated to match eligibility criteria. Subsequently, full-text articles will be retrieved when a study is found suitable, when an abstract is unavailable or when assessment of an abstract is found inconclusive. Moreover, this literature search will be supplemented by scanning the reference lists of relevant studies and other relevant review articles. This process will be reported using the PRISMA flow diagram. Any disagreements will be resolved through discussion and consensus, or arbitration by a third review author (JRN). Agreement between review authors will be measured using the Cohen's κ -statistic.¹⁴

Risk of bias assessment

Studies will be included regardless of their internal validity and results of all included studies will be presented, along with an assessment of their quality. Risk of bias will be classified as 'low', 'high' or 'unclear' according to the Risk of Bias Assessment Tool from the Cochrane Handbook for randomised controlled trials. Two reviewers will independently assess the bias in each study, and the level of agreement between them will be assessed using the Cohen's κ -statistic.

Data extraction

Data extraction will be performed by two independent review authors (EC-N and LA) using a standardised form. Any disagreement will be discussed and resolved by a third reviewer (JRN) if necessary. Information about the following aspects will be extracted: authors, title and other citation information, aims of the study, study setting, inclusion and exclusion criteria, population characteristics (age, gender, clinical characteristics, ie, signs and symptoms recorded), AOM diagnosis criteria, intervention details (dosage of amoxicillin, duration of treatment), control procedure, number of patients per group, study completion rates, outcome measures, adverse effects, times of measurement after intervention, complications and information for assessment of the risk of bias. A code number will be assigned to each study.

Strategy for data synthesis

Data will be analysed and synthesised using the statistical software STATA V.13.0 (Stata Corp 2013). Using a table, we will synthesise the main characteristics of each study retained for this review, including criteria for clinical effectiveness of amoxicillin in AOM as defined by the various authors. Additionally, a summary flow diagram for potentially eligible studies that were subsequently excluded, and reasons for exclusion will be drawn.

For the outcome 'clinical effectiveness', we will calculate whether differences between subgroups (ie, amoxicillin, placebo or another antibiotic) are statistically significant. Evidence concerning recurrence of AOM and complication of AOM following treatment with amoxicillin will also be qualitatively synthesised. Results (frequencies, means, percentages, p values, ORs, relative risk and CIs) given in each study will be reported. A meta-analysis using the fixed-effect model will be done including only studies that present sufficient homogeneity. If no homogeneous studies are found, we will not conduct a meta-analysis. Statistical heterogeneity between and across studies will be assessed using the χ^2 test on Cochrane's Q statistic, quantified by calculating the I^2 statistic (with values of 25%, 50% and 75% being indicative of low, medium and high heterogeneity, respectively).^{15 16} The GRADE system will be used to assess the strength of the body of evidence.

Subgroup analyses will be performed to investigate the possible sources of heterogeneity. The subgroup analyses will comprise the following: amoxicillin dosage, treatment duration, effectiveness criteria, time of trial

realisation, age groups, study quality, region of the world involved. We will use meta-regression analyses to explain the predictors of the effect size. If the included studies are too heterogeneous to be pooled together, they will be summarised in a narrative format. Moreover, funnel plots will serve to assess publication bias, complemented with the Egger's test of bias. Additionally, the trim-and-fill method will be applied to assess the impact of potential publication bias.¹⁷ A p value <0.05 will be considered statistically significant for all analyses.

Potential limitations of our study include the fact that most clinical trials around the world are carried out in developed countries. Given that our goal is to recommend guidelines for the low-income and middle-income setting, this might be a setback. In addition, we plan to include all eligible studies irrespective of the risk of bias and internal validity. This could have a negative impact on the quality of our results. However, we plan to evaluate the risk of bias in each individual study and appraise in a narrative form, with the help of a table.

Patient and public involvement

Our study aims to provide updated information that would enable evidence-based decisions for first-line therapy, thereby harmonising practice for medical personnel and reducing antibiotic resistance. This would be greatly beneficial to patients. Patients will however not be actively involved in the study design. We will involve the National Association of Otolaryngology and Head and Neck Surgery by informing them about the review prior to conduction to obtain their input, given that this body plays a major role in formulating treatment recommendations at the national level. Finally, we will submit our results to a peer-reviewed journal for publication to enable dissemination.

SIGNIFICANCE

This systematic review will provide evidence on the clinical effectiveness of amoxicillin alone in treating children and adults presenting AOM. Our conclusions will be drawn from the results of randomised controlled trials studying this, carried out around the world. To confirm our findings, a meta-analysis will be conducted if sufficient homogeneous studies are identified. This will permit harmonisation of clinical practice concerning this affection, especially in low-income and middle-income countries that critically lack local evidence-based guidelines.

Ethics and dissemination plans

Ethical approval is not required, as primary data will not be collected. The results of this systematic review, in the form of a scientific paper, will be submitted to a peer-reviewed journal for publication consideration and presented at scientific conferences.

Contributors EC-N conceived the study and planned the protocol. EC-N, LCA and JRN designed the study protocol and planned the data extraction and statistical

analysis. JRNN provided critical insights. EC-N, LCA, JRNN and FD reviewed and contributed to the final written manuscript.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

1. Waseem M, Elluru RG. Otitis Media. Medscape. 2016. <http://emedicine.medscape.com/article/99465> (accessed 1 Sep 2017).
2. Bardach A, Ciapponi A, Garcia-Marti S, et al. Epidemiology of acute otitis media in children of Latin America and the Caribbean: a systematic review and meta-analysis. *Int J Pediatr Otorhinolaryngol* 2011;75:1062–70.
3. Roy E, Hasan K, Haque F, et al. Acute otitis media during the first two years of life in a rural community in Bangladesh: a prospective cohort study. *J Health Popul Nutr* 2007;25:414–21.
4. Monasta L, Ronfani L, Marchetti F, et al. Burden of disease caused by otitis media: systematic review and global estimates. *PLoS One* 2012;7:e36226.
5. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;386:743–800.
6. DeAntonio R, Yarzabal JP, Cruz JP, et al. Epidemiology of otitis media in children from developing countries: A systematic review. *Int J Pediatr Otorhinolaryngol* 2016;85:65–74.
7. Ovnat Tamir S, Shemesh S, Oron Y, et al. Acute otitis media guidelines in selected developed and developing countries: uniformity and diversity. *Arch Dis Child* 2017;102:450–7.
8. Eholie SP, Bissagnene E, Cremieux AC, et al. *Du bon usage des antibiotiques en Afrique sub-saharienne*. Paris: DOIN, 2013.
9. Haute Autorité de Santé. Otite moyenne aiguë purulente de l'enfant de plus de 3 mois. https://www.has-sante.fr/portail/upload/docs/application/pdf/2016-11/v1-fm_otite_aigue_enfant_cd-171116.pdf (accessed 17 Oct 2017).
10. Ding Y, Geng Q, Tao Y, et al. Etiology and epidemiology of children with acute otitis media and spontaneous otorrhea in Suzhou, China. *Pediatr Infect Dis J* 2015;34:e102–e106.
11. Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking systematic reviews in health care*: Centre for Reviews and Dissemination, 2017. (accessed 1 Dec 2017).
12. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;6:1006–12.
13. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
14. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. *Fam Med* 2005;37:360–3.
15. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
16. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
17. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56:455–63.