

Critically Appraised Topic (CAT):
Acute Otitis Media (AOM) Low-Dose versus High-Dose Amoxicillin

Specific Care Question

For pediatric patients with acute otitis media, is low-dose amoxicillin versus high-dose amoxicillin equivalent to or better for the outcomes of clinical cure, failure rate, and adverse events?

Recommendations from the AOM Committee

A **conditional** recommendation against the intervention of low-dose versus high-dose amoxicillin. Even though the review found no difference between low-dose and high-dose amoxicillin, the overall certainty in the evidence is very low^a. Only one cohort study (Chu et al., 2014) and one RCT (Bielicki et al., 2021) found lower-dose amoxicillin to be equivalent to high-dose amoxicillin for patients with AOM. When there is a lack of scientific evidence, standard work should be developed, implemented, and monitored.

Literature Summary

Background. Acute otitis media (AOM) is the most common infection in early childhood (Venekamp et al., 2015). Although AOM usually resolves without treatment, it is the most common condition for which antibiotics are prescribed in the United States (Lieberthal et al., 2013). The American Academy of Pediatrics Clinical Practice Guideline (CPG; Lieberthal et al., 2013) recommends providing safety-net antibiotic prescription (SNAP) to parents of children > 6 months of age with mild to moderate unilateral AOM. A dose of 80-90 mg/kg per day of amoxicillin is recommended as first-line therapy for most children with mild to moderate AOM for a duration of 10 days for patients ≤ 23 months of age and 7 days for patients 2-5 years of age (Lieberthal et al., 2013). Alternatively, in a systematic review (Suzuki et al., 2020) of European CPGs, only 7 of 14 CPGs recommended high dose amoxicillin (80-90mg/kg per day) as an option for first-line treatment.

This review aims to synthesize the current literature on the topic of amoxicillin dosing. This review excludes older articles before the pneumococcal vaccine was widely administered due to its effect on the infection rate and causative organisms of AOM (Eskola et al., 2001). Studies that looked at community acquired pneumonia (CAP) were included in this review as this disease is caused by the same organisms (Eskola et al., 2001). This review will summarize identified literature to answer the specific care question.

Study characteristics. The search for suitable studies was completed on July 11, 2022. R. El Feghaly, MD, MSCI and D. Wyly, MSN, RN, APRN, CPNP-AC, PPCNP-BC, ONC reviewed the 127 titles and/or abstracts found in the search and identified^b 12 single studies believed to answer the question. After an in-depth review of the single studies, two single studies (Bielicki et al., 2021; Chu et al., 2014) answered the question.

Summary by Outcome

Retreatment by Day 28

One RCT (Bielicki et al., 2021) measured retreatment by day 28, ($N = 814$). For the outcome of re-treatment by day 28, the *OR* indicated that for patients with CAP the intervention of low dose amoxicillin (35-50 mg/kg/d) was not different to the comparator of high dose amoxicillin (70-90 mg/kg/d), *OR* = 1.03, 95% CI [0.68, 1.56] (see Figure 2 & Table 2)

Certainty Of The Evidence For Retreatment by Day 28. The certainty of the body of evidence was low. The body of evidence was assessed to not have serious risk of bias, but serious indirectness, and serious imprecision. Indirectness was serious as the study population investigated was patients with CAP. Imprecision was serious due to the low number of events ($n = 100$). As only one study (Bielicki et al., 2021) was identified to answer this question, consistency could not be assessed.

Adverse Events

One RCT (Bielicki et al., 2021) measured adverse events, ($N = 814$). For the outcome of adverse events, the *OR* indicated that for patients with CAP, the intervention of low dose amoxicillin (35-50 mg/kg/d) was not different to the comparator of high dose amoxicillin (70-90 mg/kg/d), *OR* = 1.14, 95% CI [0.62, 2.11] (see Figure 3 & Table 2).

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Certainty Of The Evidence For Adverse Events. The certainty of the body of evidence was low. The body of evidence was assessed to not have serious risk of bias, but serious indirectness, and serious imprecision. Indirectness was serious as the study population investigated was patients with CAP. Imprecision was serious due to the low number of events ($n = 100$). As only one study (Bielicki et al., 2021) was identified to answer this question, consistency could not be assessed.

Successful Control (see Chu et al., 2014, for the definition of this outcome on page 13 of this synopsis)

One cohort study (Chu et al., 2014) measured successful control, ($N = 165$). For the outcome of successful control, the *OR* indicated that for patients with AOM, the intervention of low dose amoxicillin (40-50 mg/kg/d) was not different to the comparator of high dose amoxicillin (80-90 mg/kg/d), *OR* = 0.52, 95% CI [0.14, 1.88] (see Figure 3 & Table 2)

Certainty Of The Evidence For Successful Control. The certainty of the body of evidence was very low. The body of evidence was assessed to not have serious indirectness, but serious risk of bias, and serious imprecision. Risk of bias was serious due to the study being a retrospective cohort that was unable to verify compliance for antibiotics. Imprecision was serious due to the low number of subjects ($N = 165$) and low number of events ($n = 121$). As only one study (Chu et al., 2014) was identified to answer this question, consistency could not be assessed.

Failed Control (see Chu et al., 2014, for the definition of this outcome on page 13 of this synopsis)

One cohort study (Chu et al., 2014) measured failed control, ($N = 165$). For the outcome of failed control, the *OR* indicated that for patients with AOM, the intervention of low dose amoxicillin (40-50 mg/kg/d) was not different to the comparator of high dose amoxicillin (80-90 mg/kg/d), *OR* = 1.93, 95% CI [0.53, 7.03] (see Figure 4 & Table 2).

Certainty Of The Evidence For Failed Control. The certainty of the body of evidence was very low. The body of evidence was assessed to not have serious indirectness, but serious risk of bias, and serious imprecision. Risk of bias was serious due to the study being a retrospective cohort that was unable to verify compliance for antibiotics. Imprecision was serious due to the low number of subjects ($N = 165$) and low number of events ($n = 44$). As only one study (Chu et al., 2014) was identified to answer this question, consistency could not be assessed.

Identification of Studies

Search Strategy and Results (see Figure 1)

(**2010**:py OR **2011**:py OR **2012**:py OR **2013**:py OR **2014**:py OR **2015**:py OR **2016**:py OR **2017**:py OR **2018**:py OR **2019**:py OR **2020**:py OR **2021**:py OR **2022**:py) AND ([child]/lim OR [infant]/lim OR [preschool]/lim OR [school]/lim) AND ('article'/it OR 'article in press'/it) 'acute otitis media'/exp OR 'acute otitis media' amoxicillin:ti,ab,kw 'drug dose' OR dosing:ti,ab,kw OR 'low drug dose' OR 'drug megadose' OR 'low dose':ti,ab OR 'high dose':ti,ab OR dosage:ti,ab,kw 'amoxicillin'/exp/dd_do

Records identified through database searching $n = 132$

Additional records identified through other sources $n = 0$

Studies Included in this Review

Citation	Study Type
Chu et al. (2014)	Cohort
Bielicki et al. (2021)	RCT

Studies Not Included in this Review with Exclusion Rationale

Citation	Reason for exclusion
Baig et al. (2017)	Outcome of interest not reported
Garrison et al. (2004)	Older studies prior to pneumococcal vaccine

Heinrichs and Frère (2018)	Non-English
Jung et al. (2019)	Outcome of interest not reported
Kondratieva et al. (2019)	Outcome of interest not reported
Lyttle et al. (2019)	Study Protocol
Peters et al. (2016)	Study on Dosing instructions
Pichichero et al. (2013)	No comparison of low versus high dose
Vilas-Boas et al. (2014)	No comparison of low versus high dose
Wu et al. (2021)	Outcome of interest not reported

Methods Used for Appraisal and Synthesis

- ^aThe GRADEpro Guideline Development Tool (GDT) is the tool used to create the Summary of Findings (SOF) table(s) for this analysis. Using the GDT, the author of this CAT rates the certainty of the evidence based on four factors: *within-study risk of bias*, *consistency among studies*, *directness of evidence*, and *precision of effect estimates*. Each factor is subjectively judged against the author's confidence of the estimated treatment effect. Confidence is assessed as not serious, serious, or very serious. If the attribute of serious or very serious is assessed, the author will provide an explanation.
- ^bRayyan is a web-based software used for the initial screening of titles and / or abstracts for this analysis (Ouzzani, Hammady, Fedorowicz & Elmagarmid, 2017).
- ^cThe Appraisal of Guidelines Research and Evaluation II (AGREE II) is an international instrument used to assess the quality and reporting of clinical practice guidelines for this analysis (Brouwers et al. 2010).
- ^dReview Manager (Higgins & Green, 2011) is a Cochrane Collaborative computer program used to assess the study characteristics as well as the risk of bias and create the forest plots found in this analysis.
- ^eThe Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicts the process in which literature is searched, screened, and eligibility criteria is applied (Moher, Liberati, Tetzlaff, & Altman, 2009).

References to Appraisal and Synthesis Methods

- ^aGRADEpro GDT: GRADEpro Guideline Development Tool (2015). McMaster University, (developed by Evidence Prime, Inc.). [Software]. Available from grade.org.
- ^bOuzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews*, 5(1), 210. Doi:10.1186/s13643-016-0384-4
- ^cBrouwers, M.C. et al. for the AGREE Next Steps Consortium. (2010) AGREE II: Advancing guideline development, reporting and evaluation in healthcare. *Canadian Medical Association Journal*, 182, E839-842. Retrieved from <https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf>
- ^dHiggins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cochrane Collaboration, 2011.
- ^eMoher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. Doi:10.1371/journal.pmed1000097 **For more information, visit www.prisma-statement.org.**

Question Originator

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Acronyms Used in this Document

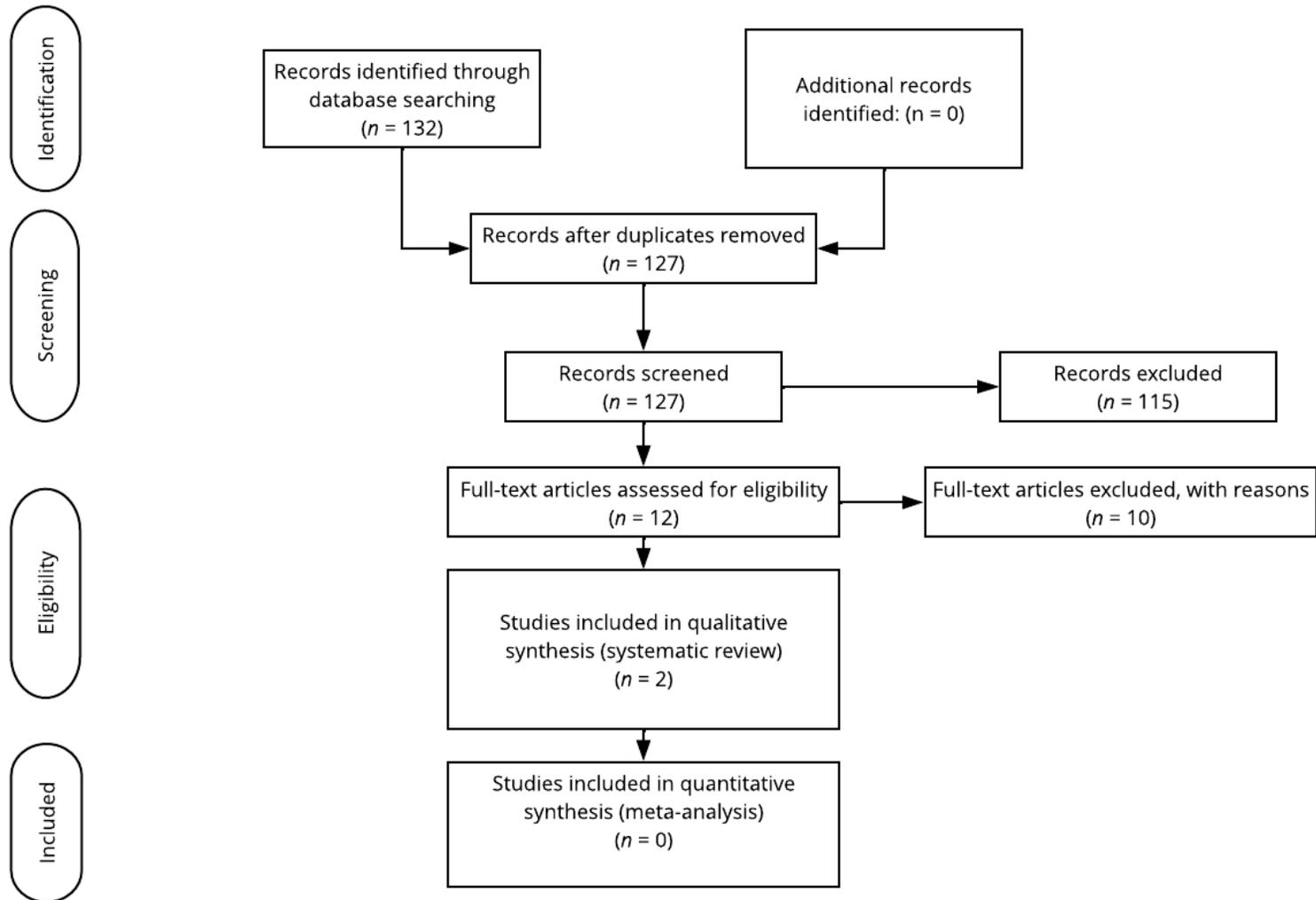
Acronym	Explanation
AGREE II	Appraisal of Guidelines Research and Evaluation II
AOM	Acute Otitis Media
CAP	Community Acquired Pneumonia
CAT	Critically Appraised Topic
CPG	Clinical Practice Guidelines
EBP	Evidence Based Practice
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
OME	Otitis Media with Effusion

Statistical Acronyms Used in this Document

Statistical Acronym	Explanation
CI	Confidence Interval
M or \bar{x}	Mean
n	Number of cases in a subsample
N	Total number in sample
OR	Odds Ratio
P or p	Probability of success in a binary trial
RCT	Randomized controlled trial
SD	Standard deviation
SR	Systematic Review

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Figure 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)^e



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Summary of Findings Table(s)

Table 2

Summary of Findings Table^a

Certainty assessment							Nº of patients		Effect		Certainty
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose	Low dose	Relative (95% CI)	Absolute (95% CI)	
Re-treatment by day 28											
1	randomized trials	not serious	not serious	serious ^d	serious ^e	none	51/410 (12.4%)	49/404 (12.1%)	OR 1.03 (0.68 to 1.56)	3 more per 1,000 (from 35 fewer to 56 more)	⊕⊕○○ Low
Serious adverse event											
1	randomized trials	not serious	not serious	serious ^d	serious ^f	none	23/410 (5.6%)	20/404 (5.0%)	OR 1.14 (0.62 to 2.11)	7 more per 1,000 (from 18 fewer to 50 more)	⊕⊕○○ Low
Successful Control											
1	observational studies	serious ^a	not serious	not serious	serious ^b	none	106/147 (72.1%)	15/18 (83.3%)	OR 0.52 (0.14 to 1.88)	111 fewer per 1,000 (from 422 fewer to 71 more)	⊕○○○ Very low
Failed Control											
1	observational studies	serious ^a	not serious	not serious	serious ^c	none	41/147 (27.9%)	3/18 (16.7%)	OR 1.93 (0.53 to 7.03)	112 more per 1,000 (from 71 fewer to 418 more)	⊕○○○ Very low

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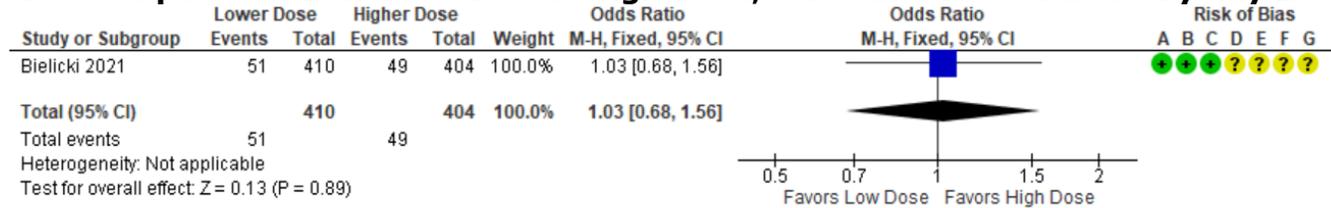
Explanations

- a. A retrospective cohort that was unable to verify compliance for antibiotics
- b. Low number of subjects ($N = 165$) and low number of events ($n = 121$)
- c. Low number of subjects ($N = 165$) and low number of events ($n = 44$)
- d. Study of patients with Community-Acquired Pneumonia
- e. Low number of events ($n = 100$)
- f. Low number of events ($n = 43$)

Meta-analysis(es)

Figure 2

RCT Comparison: Low Dose versus High Dose, Outcome: Retreatment by day 28

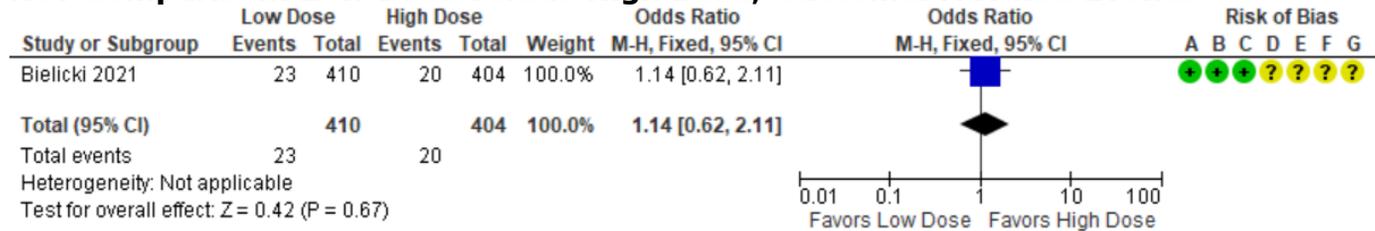


Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Figure 3

RCT Comparison: Low Dose versus High Dose, Outcome: Adverse Events

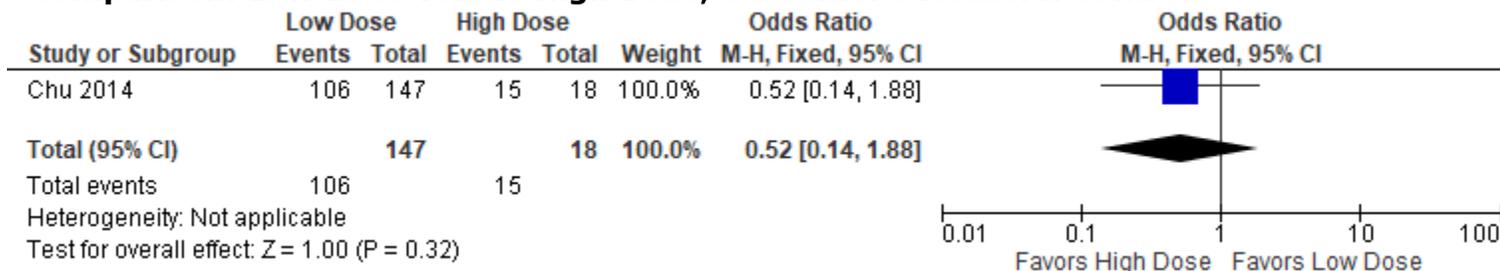


Risk of bias legend

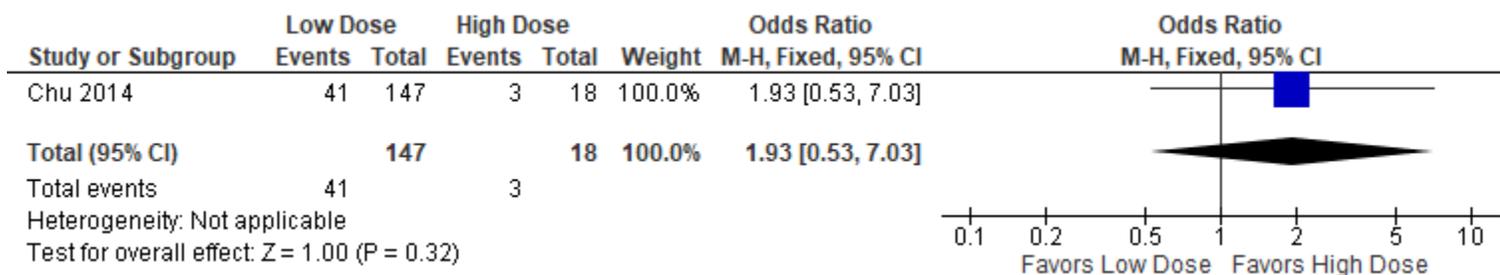
- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

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**Figure 4
Cohort Comparison: Low Dose versus High Dose, Outcome: Successful Control**



**Figure 5
Cohort Comparison: Low Dose versus High Dose, Outcome: Failed Control**



Characteristics of Intervention Studies

Bielicki et al. (2021)

Methods	Randomized Control Trial																														
Participants	<p>Participants: Children with clinically diagnosed CAP and planned treatment with amoxicillin upon discharge</p> <p>Setting: Children discharged from emergency and inpatient wards of 28 hospitals in the UK and 1 in Ireland between February 2017 and April 2019</p> <p>Randomized into study: $N = 824$</p> <ul style="list-style-type: none"> • Group 1, low dose amoxicillin for 3 days: $n = 209$ • Group 2, low dose amoxicillin for 7 days: $n = 203$ • Group 3, high dose amoxicillin for 3 days: $n = 207$ • Group 4, high dose amoxicillin for 7 days: $n = 205$ <p>Completed Study: $N = 814$</p> <ul style="list-style-type: none"> • Group 1: $n = 208$ • Group 2: $n = 202$ • Group 3: $n = 205$ • Group 4: $n = 199$ <p>Gender, males (as defined by researchers):</p> <ul style="list-style-type: none"> • Group 1: $n = 110$ (53%) • Group 2: $n = 100$ (50%) • Group 3: $n = 107$ (52%) • Group 4: $n = 104$ (52%) <p>Race / ethnicity or nationality (as defined by researchers):</p> <table border="1"> <thead> <tr> <th>Race and Ethnicity</th> <th>Group 1 ($n = 208$)</th> <th>Group 2 ($n = 202$)</th> <th>Group 3 ($n = 205$)</th> <th>Group 4 ($n = 199$)</th> </tr> </thead> <tbody> <tr> <td>Asian or British Asian</td> <td>32 (15%)</td> <td>23 (11%)</td> <td>21 (10%)</td> <td>30 (15%)</td> </tr> <tr> <td>Black or British Black</td> <td>20 (10%)</td> <td>20 (10%)</td> <td>20 (10%)</td> <td>16 (8%)</td> </tr> <tr> <td>Multiracial</td> <td>15 (7%)</td> <td>17 (8%)</td> <td>14 (7%)</td> <td>14 (7%)</td> </tr> <tr> <td>White</td> <td>139 (67%)</td> <td>136 (67%)</td> <td>144 (70%)</td> <td>135 (68%)</td> </tr> <tr> <td>Other</td> <td>2 (1%)</td> <td>6 (3%)</td> <td>6 (3%)</td> <td>4 (2%)</td> </tr> </tbody> </table> <p>Age, median in years, (IQR)</p> <ul style="list-style-type: none"> • Group 1: 2.5 (1.7-3.7) • Group 2: 2.6 (1.6-3.9) • Group 3: 2.5 (1.7-3.8) • Group 4: 2.3 (1.4-3.6) <p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • Age 6 months and older • Weight 6 to 24 kilograms • Diagnosis of CAP consistent with British Thoracic Society guidelines: <ul style="list-style-type: none"> ○ Parent- or guardian-reported cough within the previous 96 hours ○ Measured temperature of 38°C or parent- or guardian-reported fever within previous 48 hours ○ Signs of labored or difficult breathing or focal chest sign <p>Exclusion Criteria:</p>	Race and Ethnicity	Group 1 ($n = 208$)	Group 2 ($n = 202$)	Group 3 ($n = 205$)	Group 4 ($n = 199$)	Asian or British Asian	32 (15%)	23 (11%)	21 (10%)	30 (15%)	Black or British Black	20 (10%)	20 (10%)	20 (10%)	16 (8%)	Multiracial	15 (7%)	17 (8%)	14 (7%)	14 (7%)	White	139 (67%)	136 (67%)	144 (70%)	135 (68%)	Other	2 (1%)	6 (3%)	6 (3%)	4 (2%)
Race and Ethnicity	Group 1 ($n = 208$)	Group 2 ($n = 202$)	Group 3 ($n = 205$)	Group 4 ($n = 199$)																											
Asian or British Asian	32 (15%)	23 (11%)	21 (10%)	30 (15%)																											
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	<ul style="list-style-type: none"> • Uninterrupted prior β-lactam antibiotic treatment for more than 48 hours or any prior non-β-lactam treatment • Severe underlying chronic disease • Any contraindications to amoxicillin, including allergy • Complicated pneumonia (defined as signs of sepsis or local parenchymal or pleural complications) • Bilateral wheezing without focal chest signs <p>Power Analysis: The trial was designed to demonstrate noninferiority of lower dose amoxicillin compared with higher dose amoxicillin, and shorter duration (3 days) compared with longer duration (7 days). The sample size of 800 participants was estimated to achieve 90% power.</p>
Interventions	<ul style="list-style-type: none"> • Group 1: Randomized to receive amoxicillin, 35-50 mg/kg/d for 3 days • Group 2: Randomized to receive amoxicillin, 35-50 mg/kg/d for 7 days • Group 3: Randomized to receive amoxicillin, 70-90 mg/kg/d for 3 days • Group 4: Randomized to receive amoxicillin, 70-90 mg/kg/d for 7 days
Outcomes	<p>Primary outcome(s):</p> <ul style="list-style-type: none"> • The primary end point was clinically indicated treatment with systemic antibiotics (other than trial medication) for a respiratory tract infection, including CAP, within 28 days of randomization <ul style="list-style-type: none"> ○ The noninferiority margin was 8% ○ All primary end points were reviewed by an endpoint review committee, blinded to treatment allocation, to adjudicate whether treatment was clinically indicated and prescribed for respiratory tract infection <p>Secondary outcome(s):</p> <ul style="list-style-type: none"> • Severity (graded as not present, slight/little, moderate, bad, severe/very bad) and duration (with the first day the symptom is reported not present defined as resolved) of 9 parent-reported CAP symptoms (fever, cough, phlegm, fast breathing, wheezing, disturbed sleep, eating/drinking less, interference with normal activity, vomiting) • Potential amoxicillin-related clinical adverse events (diarrhea, thrush, skin rash) • Adherence to trial medication • Phenotypic penicillin nonsusceptibility or resistance at 28 days in nasopharyngeal <i>S. pneumoniae</i> isolates <p>Safety outcome(s):</p> <ul style="list-style-type: none"> • Serious adverse events
Notes	<ul style="list-style-type: none"> • Among children with CAP discharged from an ED or hospital ward (within 48 hours), low-dose outpatient oral amoxicillin was noninferior to high dose, and 3-day duration was noninferior to 7 days, with regard to need for further antibiotic retreatment • See comparison tables for serious adverse events <ul style="list-style-type: none"> ○ No participant had more than one serious adverse event, all serious adverse events were hospitalizations (most for respiratory distress), no deaths. The data stratified by randomization groups can be found in Table 10 in Supplement 2. ○ One serious adverse event (hospital admission for intravenous treatment because of vomiting on day 2 in a patient randomized to the higher-dose, shorter-duration group) was classified as related to trial medication. • Findings should not be generalized to patients with very severe disease or underlying comorbidities

Risk of bias table

Bias	EBP Scholars' judgement	Support for judgement
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Random sequence generation (selection bias)	Low risk	A computer-generated randomization list was produced by the trial statistician based on blocks of 8 and containing an equal number of the 4 possible combinations of dose and duration in random order.
Allocation concealment (selection bias)	Low risk	Trial kits were assigned sequential numbers based on the randomization list and delivered ready to dispense to site pharmacies.
Blinding of participants and personnel (performance bias)	Low risk	Blinding was achieved by independent rebottling, packaging, and labeling of 2 amoxicillin brands. To ensure blinding for the duration comparison, a single amoxicillin brand was used for the first 3 days, followed by a different amoxicillin containing suspension (of the same concentration) or a matching placebo suspension for days 4 to 7.
Blinding of outcome assessment (detection bias)	Unclear risk	Primary endpoint was subjectively adjudicated by an endpoint review committee
Incomplete outcome data (attrition bias)	Low risk	Data analyzed per protocol, however very few subjects were excluded from analysis and would be unlikely to impact results
Selective reporting (reporting bias)	Low risk	Data reported as expected
Other bias	Low risk	No concerns: conflicts of interest reported appropriately and unlikely to impact study results

Chu et al. (2014)

Methods	Retrospective Cohort
Participants	<p>Participants: Children with acute otitis media (AOM) Setting: Taiwan, General Hospital, January 2005 to December 2008 Number of medical records with correct diagnosis code: $N = 400$ Number who meet inclusion criteria: $N = 165$</p> <ul style="list-style-type: none"> • Group 1, Antibiotic with recommended amoxicillin component: $n = 18$ • Group 2, Antibiotic with underdosed amoxicillin component $n = 14$ <p>Gender, males</p> <ul style="list-style-type: none"> • 57% (Not specified by group) <p>Race / ethnicity or nationality (as defined by researchers):</p> <ul style="list-style-type: none"> • Not reported <p>Age, mean +/- SD in years:</p> <ul style="list-style-type: none"> • 4.91 +/- 2.52 (Not specified by group) <p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • Children 2 months to 12 years • Diagnosis of AOM ICD-9-CM (diagnosis code 382.00) • Patients treated with amoxicillin-clavulanate <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • Any anatomic or genetic abnormalities such as craniofacial anomalies or Down syndrome • Immune deficiencies • History of recurrent AOM (three or more previous episodes of AOM within 12 months) • Patients with any history of middle ear or inner ear procedure • Patients with only one visit • Patients with missing records • Patients treated with amoxicillin alone or with another antibiotic <p>Covariates Identified:</p> <ul style="list-style-type: none"> • Illness season • Single vs bilateral disease
Interventions	<p>Both: Reassessment performed within 14 days after antibiotic prescription expiry (sic) date Amoxicillin doses based on the AOM Clinical Practice Guidelines: Diagnosis and Management of AOM, published in May 2004 (AAP, 2004)</p> <ul style="list-style-type: none"> • Group 1: Amoxicillin clavulanate antibiotic dose of amoxicillin 80-90 mg/kg/day, 1500 mg/day max (referred to as "High-dose" in tables) • Group 2: Amoxicillin clavulanate antibiotic dose < 10% of recommended amoxicillin dose (referred to as "Underdose" in tables) <ul style="list-style-type: none"> ○ Average dose of amoxicillin component 45.5 mg/kg/day ○ 52.1% of the prescriptions were in the amoxicillin range of 40-50 mg/kg/day
Outcomes	<p>Primary outcome(s):</p> <ul style="list-style-type: none"> • Successful control (defined as a medical record of an eardrum that was either normal or showed otitis media with effusion (OME)) • Failed control, defined as improvement in only one of two affected ears or a change in antibiotics before the end of the treatment period due to failure to control illness rather than side effects
Notes	<p>Results:</p> <ul style="list-style-type: none"> • Control was achieved in 121 patients • Patients given the high dose amoxicillin had generally but not statistically significantly better AOM prognosis • Bilateral AOM was borderline significantly correlated with failed control

***Critically Appraised Topic (CAT):
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Dose Amoxicillin***

- There was no significant correlation between high dose amoxicillin and better disease control in most groups.
- Illness in autumn and winter were strongly associated with a poor prognosis
- In this study, the ratio of boys who failed AOM control was not significant, this is different than other studies referenced
- The correlation between under dosage and failed control were significant in children below 20 kg with bilateral AOM ($OR = 1.63$; 95% CI [1.02, 2.59], $p = .04$)

Limitations:

- No study of amoxicillin as a standalone medication for AOM
- The duration of treatment for both the high dose and the underdose were never specified in this study. The reassessment was performed sometime within 14 days of the prescription but the actual days between diagnosis and reassessment were not specified.

References

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Appendix

Evidence to Decision Assessment

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know 	Acute Otitis Media is the most common infection in early childhood (Venekamp et al., 2015). Although AOM usually resolves without treatment, it is the most common condition for prescribed antibiotics in the United States (Lieberthal et al., 2013).	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know 	<p>Successful Control (see Chu et al., 2014, for the definition of this outcome on page 13 of this synopsis)</p> <p>One cohort study (Chu et al., 2014) measured successful control ($N = 165$). For the outcome of successful control, the <i>OR</i> indicated that for patients with AOM, the intervention of low dose amoxicillin (40-50 mg/kg/d) was not different from the comparator of high dose amoxicillin (80-90 mg/kg/d), $OR = 0.52$, 95% CI [0.14, 1.88].</p>	The desirable effects of a lower dose are fewer adverse drug reactions, medication side effects, and antimicrobial resistance.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

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<ul style="list-style-type: none"> ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know 	<p>Retreatment by Day 28 One RCT (Bielicki et al., 2021) measured retreatment by day 28, (<i>N</i> = 814). For the outcome of re-treatment by day 28, the <i>OR</i> indicated that for patients with CAP the intervention of low dose amoxicillin (35-50 mg/kg/d) was not different to the comparator of high dose amoxicillin (70-90 mg/kg/d), <i>OR</i> = 1.03, 95% CI [0.68, 1.56].</p> <p>Adverse Events One RCT (Bielicki et al., 2021) measured adverse events, (<i>N</i> = 814). For the outcome of adverse events, the <i>OR</i> indicated that for patients with CAP, the intervention of low dose amoxicillin (35-50 mg/kg/d) was not different to the comparator of high dose amoxicillin (70-90 mg/kg/d), <i>OR</i> = 1.14, 95% CI [0.62, 2.11].</p> <p>Failed Control (see Chu et al., 2014, for the definition of this outcome on page 13 of this synopsis) One cohort study (Chu et al., 2014) measured failed control, (<i>N</i> = 165). For the outcome of failed control, the <i>OR</i> indicated that for patients with AOM, the intervention of low dose amoxicillin (40-50 mg/kg/d) was not different to the comparator of high dose amoxicillin (80-90 mg/kg/d), <i>OR</i> = 1.93, 95% CI [0.53, 7.03].</p>	
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Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● Very low ○ Low ○ Moderate ○ High ○ No included studies 	<p>Certainty Of The Evidence For Retreatment by Day 28. The certainty of the body of evidence was low. The body of evidence was assessed to not have serious risk of bias, but serious indirectness, and serious imprecision. Indirectness was serious as the study population investigated was patients with CAP. Imprecision was serious due to the low number of events (<i>n</i> = 100). As only one study (Bielicki et al., 2021) was identified to answer this question, consistency could not be assessed.</p> <p>Certainty Of The Evidence For Adverse Events. The certainty of the body of evidence was low. The body of evidence was assessed to not have serious risk of bias, but serious indirectness, and serious imprecision. Indirectness was serious as the study population investigated was patients with CAP. Imprecision was serious due to the low number of events (<i>n</i> = 100). As only one study (Bielicki et al., 2021) was identified to answer this question, consistency could not be assessed.</p> <p>Certainty Of The Evidence For Successful Control. The certainty of the body of evidence was very low. The body of evidence was assessed to not have serious indirectness, but serious risk of bias, and serious imprecision. Risk of bias was serious due to the study being a retrospective cohort that was unable to verify compliance for antibiotics. Imprecision was serious</p>	<p>Minimal evidence exists on outcomes of lower doses versus higher dose. Only one cohort study on patients with AOM and one RCT on patients with CAP were included.</p>

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due to the low number of subjects ($N = 165$) and low number of events ($n = 121$). As only one study (Chu et al., 2014) was identified to answer this question, consistency could not be assessed.

Certainty Of The Evidence For Failed Control. The certainty of the body of evidence was very low. The body of evidence was assessed to not have serious indirectness, but serious risk of bias, and serious imprecision. Risk of bias was serious due to the study being a retrospective cohort that was unable to verify compliance for antibiotics. Imprecision was serious due to the low number of subjects ($N = 165$) and low number of events ($n = 44$). As only one study (Chu et al., 2014) was identified to answer this question, consistency could not be assessed

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability 		Some providers (e.g. Antimicrobial Stewardship) may weigh more heavily on the risk of adverse drug events, side effects, and antimicrobial resistance. Some parents/families of patients may weigh more heavily the risk of treatment failure.

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know 	Minimal evidence exists on outcomes of lower doses versus higher doses. Only one cohort study on patients with AOM and one RCT on patients with CAP was included.	

Resources required
How large are the resource requirements (costs)?

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JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know 	<p>The mean cost of treatment for the amoxicillin group is \$189.20 (Gaboury et al., 2010)</p> <p>The indirect costs of AOM, accrued primarily by parental time lost are \$1330.58, 95% CI [\$1008.75, \$1652.43] (Alsarraf et al., 1999).</p>	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ● No included studies 	<p>No studies comparing the required resources of low versus high dose.</p>	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies 	<p>Likely lower costs for lower dose. No included studies.</p>	<p>Families would have to travel to pharmacies, obtain prescriptions, and follow written prescription instructions regardless of the dose. However, the cost would be greater for the higher dose.</p>
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Reduced ○ Probably reduced 		

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<ul style="list-style-type: none"> ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know 		
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Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know 		This would be a large change in practice. Would need stronger evidence.

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know 	No issues with feasibility in prescribing lower dose	

SUMMARY OF JUDGEMENTS

PROBLEM	JUDGEMENT						
	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies

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	JUDGEMENT						
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

CONCLUSIONS

Recommendation

Conditional recommendation against the intervention

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