10-2022

# Acute Otitis Media: Low Dose Versus High Dose Amoxicillin

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Evidence Based Practice

# *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 a., 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).

**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**

[a]The 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.

[b]Rayyan is a web-based software used for the initial screening of titles and / or abstracts for this analysis (Ouzzani, Hammady, Fedorowicz & Elmagarmid, 2017).

[c]The 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).

[d]Review 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.

[e]The 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**

[a]GRADEpro GDT: GRADEpro Guideline Development Tool (2015). McMaster University, (developed by Evidence Prime, Inc.). [Software]. Available from gradepro.org.

[b]Ouzzani, 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

[c]Brouwers, 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

[d]Higgins, 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.

[e]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PloS Med 6(7): e1000097. Doi:10.1371/journal.pmed1000097 **For more information, visit www.prisma-statement.org.**

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

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*Acronyms Used in this Document*

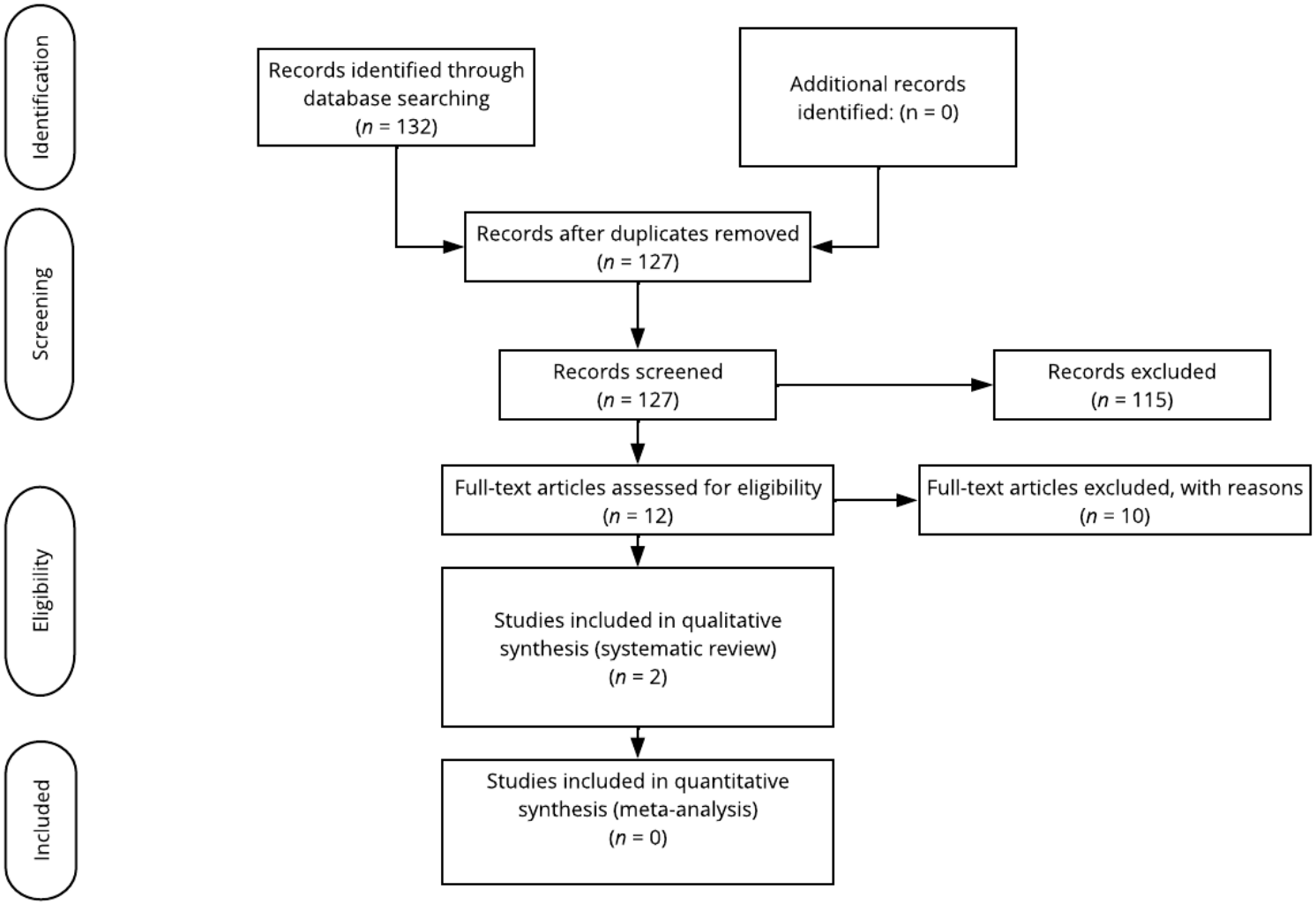
| Acronym | Explanation |
|---|---|
| AGREE II | Appraisal of Guidelines Research and Evaluation II |
| AOM | Acute Otitis Media |
| CAP | Community Acquired Pneumonia |
| CAT | Critically Appraised Topic |
| CPG | Clinical Practice Guidelines |
| EBP | Evidence Based Practice |
| PRISMA | Preferred 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 |

**Figure 1**

*Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)*[e]



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**Summary of Findings Table(s)**
**Table 2**
***Summary of Findings Table[a]***

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ 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 |

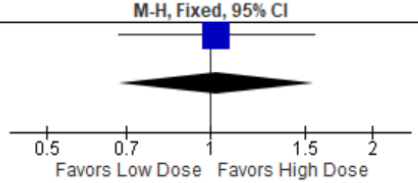
*Explanations*

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**

| Study or Subgroup | Lower Dose Events | Total | Higher Dose Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Bielicki 2021 | 51 | 410 | 49 | 404 | 100.0% | 1.03 [0.68, 1.56] |
| **Total (95% CI)** | | **410** | | **404** | **100.0%** | **1.03 [0.68, 1.56]** |
| Total events | 51 | | 49 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.13 (P = 0.89)



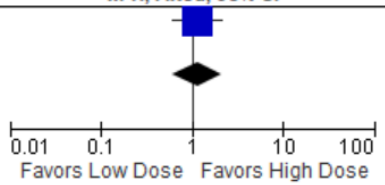


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

**Figure** *3*
**RCT Comparison: Low Dose versus High Dose, Outcome: Adverse Events**

| Study or Subgroup | Low Dose Events | Total | High Dose Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Bielicki 2021 | 23 | 410 | 20 | 404 | 100.0% | 1.14 [0.62, 2.11] |
| **Total (95% CI)** | | **410** | | **404** | **100.0%** | **1.14 [0.62, 2.11]** |
| Total events | 23 | | 20 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.67)





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** *4*

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

| | Low Dose | | High Dose | | | Odds Ratio |
|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI |
| Chu 2014 | 106 | 147 | 15 | 18 | 100.0% | 0.52 [0.14, 1.88] |
| **Total (95% CI)** | | **147** | | **18** | **100.0%** | **0.52 [0.14, 1.88]** |
| Total events | 106 | | 15 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.00 (P = 0.32) | | | | | | |

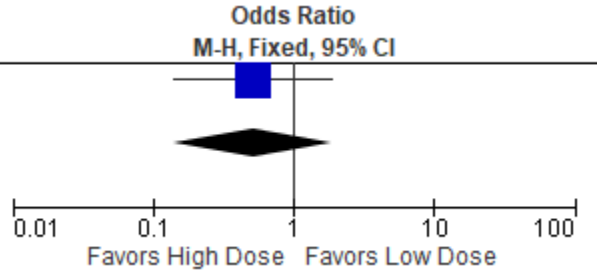
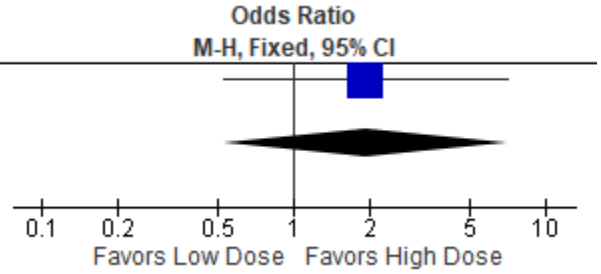



**Figure** *5*

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

| | Low Dose | | High Dose | | | Odds Ratio |
|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI |
| Chu 2014 | 41 | 147 | 3 | 18 | 100.0% | 1.93 [0.53, 7.03] |
| **Total (95% CI)** | | **147** | | **18** | **100.0%** | **1.93 [0.53, 7.03]** |
| Total events | 41 | | 3 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.00 (P = 0.32) | | | | | | |



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

*Characteristics of Intervention Studies*
**Bielicki et al. (2021)**

| **Methods** | **Randomized Control Trial** |
|---|---|
| **Participants** | **Participants:** Children with clinically diagnosed CAP and planned treatment with amoxicillin upon discharge<br><br>**Setting:** Children discharged from emergency and inpatient wards of 28 hospitals in the UK and 1 in Ireland between February 2017 and April 2019<br><br>**Randomized into study:** *N* = 824<br>• **Group 1, low dose amoxicillin for 3 days:** *n* = 209<br>• **Group 2, low dose amoxicillin for 7 days:** *n* = 203<br>• **Group 3, high dose amoxicillin for 3 days:** *n* = 207<br>• **Group 4, high dose amoxicillin for 7 days:** *n* = 205<br><br>**Completed Study:** *N* = 814<br>• **Group 1:** *n* = 208<br>• **Group 2:** *n* = 202<br>• **Group 3:** *n* = 205<br>• **Group 4:** *n* = 199<br><br>**Gender, males (as defined by researchers):**<br>• **Group 1:** *n* = 110 (53%)<br>• **Group 2:** *n* = 100 (50%)<br>• **Group 3:** *n* = 107 (52%)<br>• **Group 4:** *n* = 104 (52%)<br><br>**Race / ethnicity or nationality (as defined by researchers):** |

| Race and Ethnicity | Group 1 (*n* = 208) | Group 2 (*n* = 202) | Group 3 (*n* = 205) | Group 1 (*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%) |

**Age, median in years, (IQR)**
- **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)

**Inclusion Criteria:**
- Age 6 months and older
- Weight 6 to 24 kilograms
- Diagnosis of CAP consistent with British Thoracic Society guidelines:
  - 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

**Exclusion Criteria:**

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

| | |
|---|---|
| | • Uninterrupted prior β-lactam antibiotic treatment for more than 48 hours or any prior non-β-lactam treatment<br>• Severe underlying chronic disease<br>• Any contraindications to amoxicillin, including allergy<br>• Complicated pneumonia (defined as signs of sepsis or local parenchymal or pleural complications)<br>• Bilateral wheezing without focal chest signs<br>**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. |
| **Interventions** | • **Group 1:** Randomized to receive amoxicillin, 35-50 mg/kg/d for 3 days<br>• **Group 2:** Randomized to receive amoxicillin, 35-50 mg/kg/d for 7 days<br>• **Group 3:** Randomized to receive amoxicillin, 70-90 mg/kg/d for 3 days<br>• **Group 4:** Randomized to receive amoxicillin, 70-90 mg/kg/d for 7 days |
| **Outcomes** | **Primary outcome(s):**<br>• 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<br>  ○ The noninferiority margin was 8%<br>  ○ 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<br>**Secondary outcome(s):**<br>• 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)<br>• Potential amoxicillin-related clinical adverse events (diarrhea, thrush, skin rash)<br>• Adherence to trial medication<br>• Phenotypic penicillin nonsusceptibility or resistance at 28 days in nasopharyngeal S. pneumoniae isolates<br>**Safety outcome(s):**<br>• Serious adverse events |
| **Notes** | • 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<br>• See comparison tables for serious adverse events<br>  ○ 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.<br>  ○ 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.<br>• 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 |
|---|---|---|

| | | |
|---|---|---|
| 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 |

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

**Chu et al. (2014)**

| **Methods** | **Retrospective Cohort** |
|---|---|
| **Participants** | **Participants:** Children with acute otitis media (AOM)<br>**Setting:** Taiwan, General Hospital, January 2005 to December 2008<br>**Number of medical records with correct diagnosis code:** *N* = 400<br>**Number who meet inclusion criteria:** *N* = 165<br>• **Group 1,** Antibiotic with recommended amoxicillin component: *n* = 18<br>• **Group 2,** Antibiotic with underdosed amoxicillin component *n* = 14<br>**Gender, males**<br>• 57% (Not specified by group)<br>**Race / ethnicity or nationality (as defined by researchers):**<br>• Not reported<br>**Age, mean +/- SD in years:**<br>• 4.91 +/- 2.52 (Not specified by group)<br>**Inclusion Criteria:**<br>• Children 2 months to 12 years<br>• Diagnosis of AOM ICD-9-CM (diagnosis code 382.00)<br>• Patients treated with amoxicillin-clavulanate<br>**Exclusion Criteria:**<br>• Any anatomic or genetic abnormalities such as craniofacial anomalies or Down syndrome<br>• Immune deficiencies<br>• History of recurrent AOM (three or more previous episodes of AOM within 12 months)<br>• Patients with any history of middle ear of inner ear procedure<br>• Patients with only one visit<br>• Patients with missing records<br>• Patients treated with amoxicillin alone or with another antibiotic<br>**Covariates Identified:**<br>• Illness season<br>• Single vs bilateral disease |
| **Interventions** | **Both:** Reassessment performed within 14 days after antibiotic prescription expiry (sic) date<br>Amoxicillin doses based on the AOM Clinical Practice Guidelines: Diagnosis and Management of AOM, published in May 2004 (AAP, 2004)<br>• **Group 1:** Amoxicillin clavulanate antibiotic dose of amoxicillin 80-90 mg/kg/day, 1500 mg/day max (referred to as "High-dose" in tables)<br>• **Group 2:** Amoxicillin clavulanate antibiotic dose < 10% of recommended amoxicillin dose (referred to as "Underdose" in tables)<br>  ○ Average dose of amoxicillin component 45.5 mg/kg/day<br>  ○ 52.1% of the prescriptions were in the amoxicillin range of 40-50 mg/kg/day |
| **Outcomes** | **Primary outcome(s):**<br>• Successful control (defined as a medical record of an eardrum that was either normal or showed otitis media with effusion (OME))<br>• 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** | **Results:**<br>• Control was achieved in 121 patients<br>• Patients given the high dose amoxicillin had generally but not statistically significantly better AOM prognosis<br>• Bilateral AOM was borderline significantly correlated with failed control |

| | |
|---|---|
| | • There was no significant correlation between high dose amoxicillin and better disease control in most groups.<br>• Illness in autumn and winter were strongly associated with a poor prognosis<br>• In this study, the ratio of boys who failed AOM control was not significant, this is different than other studies referenced<br>• 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)<br>**Limitations:**<br>• No study of amoxicillin as a standalone medication for AOM<br>• 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. |

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

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

**Appendix**

Evidence to Decision Assessment

| **Problem**<br>Is the problem a priority? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ 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**<br>How substantial are the desirable anticipated effects? | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| ○ Trivial<br>● Small<br>○ Moderate<br>○ Large<br>○ Varies<br>○ Don't know | **Successful Control** (see Chu et al., 2014, for the definition of this outcome on page 13 of this synopsis)<br>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 from the comparator of high dose amoxicillin (80-90 mg/kg/d), *OR* = 0.52, 95% CI [0.14, 1.88]. | The desirable effects of a lower dose are fewer adverse drug reactions, medication side effects, and antimicrobial resistance. |
| **Undesirable Effects**<br>How substantial are the undesirable anticipated effects? | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |

| | | |
|---|---|---|
| ○ Large<br>○ Moderate<br>● Small<br>○ Trivial<br>○ Varies<br>○ Don't know | ***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].<br><br>***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].<br>**Failed Control** (see Chu et al., 2014, for the definition of this outcome on page 13 of this synopsis)<br>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]. | |

| **Certainty of evidence**<br>What is the overall certainty of the evidence of effects? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | **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.<br>**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.<br>**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 | 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. |

| | | |
|---|---|---|
| | 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.<br>**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 |
|---|---|---|
| ○ Important uncertainty or variability<br>● Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ 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 |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>● Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ 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 |
|---|---|---|
| ○ Large costs<br>○ Moderate costs<br>● Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>○ Don't know | The mean cost of treatment for the amoxicillin group is $189.20 (Gaboury et al., 2010)<br>The indirect costs of AOM, accrued primarily by parental time lost are $1330.58, 95% CI [$1008.75, $1652.43] (Alsarraf et al., 1999). | |

**Certainty of evidence of required resources**
What is the certainty of the evidence of resource requirements (costs)?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Very low<br>○ Low<br>○ Moderate<br>○ High<br>● No included studies | No studies comparing the required resources of low versus high dose. | |

**Cost effectiveness**
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | Likely lower costs for lower dose. No included studies. | 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. |

**Equity**
What would be the impact on health equity?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ Reduced<br>○ Probably reduced | | |

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| | | |
|---|---|---|
| ● Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | | |

**Acceptability**
Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| ○ No<br>● Probably no<br>○ Probably yes<br>○ Yes<br>○ Varies<br>○ 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 |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | No issues with feasibility in prescribing lower dose | |

SUMMARY OF JUDGEMENTS

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM** | 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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