Office of Evidence Based Practice (EBP) – Critically Appraised Topic (CAT): Community-Acquired Pneumonia (CAP) Antibiotic Treatment Length

Specific Care Question

In pediatric patients with uncomplicated community-acquired pneumonia (CAP), what is the optimal antibiotic duration for clinical cure?

Recommendations Based on Current Literature (Best Evidence) Only

A strong recommendation is made for 5 to 7 days of antibiotic for uncomplicated CAP, based on the Summary of Findings Table[a]. The overall certainty in the evidence is very low[a] (see Summary by Outcome for substantiation of recommendations).

One randomized control trial (Greenberg et al., 2014) compared 5 versus 10 days and 3 versus 10 days of amoxicillin in children with uncomplicated pneumonia. There was no difference in treatment failure for 5 to 10 day treatment. The study stopped the 3-day treatment arm of the study due to high failure rates. One respective cohort (Same et al., 2020) reviewed 5-7 days versus 8-14 day of antibiotics treatment in children with uncomplicated pneumonia. Antibiotics were not identified in the study. There was no difference in treatment failure between the two groups. Treatment failure was 3.0% and 5.9% for 5-7 days and 8-14 days, respectively. Two randomized control trials (Agarwal et al., 2004; MASCOT 2002) compared 3 days versus 5 days of amoxicillin treatment in children with uncomplicated pneumonia. There was no difference in treatment failure between the two groups. Treatment failure was 11.4% and 10.3% for 3 days and 5 days, respectively.

The overall certainty of the evidence is very low. There was very serious imprecision for all the outcomes due to low number of events. When there is a lack of scientific evidence, standard work should be developed, implemented, and monitored.

Literature Summary

Background. Globally, CAP accounts for 15% of deaths in children under 5 years old (WHO, 2015). CAP is defined as a clinical diagnosis of pneumonia caused by a community-acquired infection in a previously healthy child. Uncomplicated pneumonia is the absence of significant effusion, empyema, severe or impending respiratory failure, and/or signs and symptoms of sepsis or shock (Barnson, 2018).

Streptococcus pneumoniae is the most common bacterial cause of pneumonia in children of all ages (Barnson, 2018). Other bacterial pathogens that may be included for hospitalized children include *Staphylococcus. aureus* (including *Methicillin-resistant staphylococcus aureus*), *Streptococcus pyogenes* (group A *Streptococcus*), *Haemophilus* influenzae type b (if unimmunized), non-typeable *H. influenzae*, and *Moraxella catarrhalis* (Branson, 2018).

The Pediatric Infectious Disease Society and the Infectious Disease Society of America (PIDS/IDSA) and the British Thoracic Society (BTS) are the governing guidelines used for this question (Bradley et al., 2011; Harris et al., 2011). The PIDS/IDSA and the BTS recommended amoxicillin as the first choice for oral antibiotic therapy in all children because it is effective against most pathogens that cause uncomplicated CAP, is well tolerated, and inexpensive (Bradley et al., 2011; Harris et al., 2011). In fiscal year 2018, Children's Mercy Hospital providers in the emergency department or urgent care prescribed amoxicillin 75% of the time for patients seen with the diagnosis of CAP.

The PIDS/IDSA guideline discusses that a shorter course of therapy may be as effective as longer courses, especially in patients with milder disease (Bradley et al., 2011). The authors recommended a 10-day course of antibiotics for CAP, but no cited studies were identified within the evidence review. The guideline also recommends treating for the shortest effective duration to minimize resistance to antimicrobials (Bradley et al., 2011).

Study characteristics. The search for suitable studies was completed on August 11, 20202. A. Burns, PharmD and J. Markham, MD reviewed the 98 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[e], five answered the question. Three systematic reviews (SR) (Ben-Shimol et al., 2014; Dawson-Hahn et al., 2017; Lassi et al., 2014), one randomized control trial (RCT) (Greenberg et al., 2014), and one cohort study (Same et al., 2020) (see Figure 1). The three SR's included only three studies that answered the question of this review (Agarwal et al., 2004; MASCOT, 2002; Peltola et al., 2001).

While there was a limited number of studies that answered this question, there are currently two protocols (Lyttle et al., 2019; Pernica et al., 2018) that have not been completed that will increase the knowledge in this area.

Summary by Outcome

Treatment Failure of Amoxicillin 5 days versus Amoxicillin 10 days. One study (Greenberg et al., 2014) measured treatment failure in children aged age 6-59 months with uncomplicated pneumonia, (*N* = 115). The OR indicated the intervention (5 days amoxicillin) was not different to the comparator (10 days amoxicillin) (see *Table 2*). There was no treatment failure in either group at 30-days*, OR* = 0, 95% CI [-0.03, 0.03].

Treatment Failure of Amoxicillin 5 days versus Amoxicillin 10 days. The certainty of the body of evidence was very low based on four factors[c]: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*. The body of evidence was assessed to have serious risk of bias and very serious imprecision. Risk of bias was assessed as serious as the study revised its power analysis, after 40 participants were enrolled, to lower the number needed in the study. The study was assessed as having very serious imprecision as there was only one study with no events. As only one study (Greenberg et al., 2014) was identified to answer this question, consistency could not be assessed.

Treatment Failure of Amoxicillin 3 days versus Amoxicillin 10 days. One study (Greenberg et al., 2014) measured treatment failure in children aged 6-59 months with uncomplicated pneumonia, (*n* = 66). The OR indicated the intervention (3 days amoxicillin) was unfavorable to the comparator (10 days amoxicillin) (see Figure 3 & *Table 2*). The three-day treatment arm of the study was stopped after 4 of the 10 patients had treatment failure, OR = 78.23, 95% CI [3.77, 1623].

Treatment Failure of Amoxicillin 3 days versus Amoxicillin 10 days. The certainty of the body of evidence was very low based on four factors[c]: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*. The body of evidence was assessed to have serious risk of bias and very serious imprecision. Risk of bias was assessed as serious as the study revised its power analysis to lower the participant number needed for the study. The study was assesses as having very serious imprecision as the study was stopped as four participants in the 3-day study arm experienced treatment failure. As only one study (Greenberg et al., 2014) was identified to answer this question, consistency could not be assessed

Treatment Failure of Amoxicillin 3 days versus Amoxicillin 5 days. Two studies (Agarwal et al., 2004; MASCOT, 2002) measured treatment failure in children with uncomplicated pneumonia (*n* = 4012). The OR of 1.13, 95% CI [0.93, 1.39] indicated the intervention (3 days amoxicillin) was not different to the comparator (5 days amoxicillin) (see Figure 5 & *Table 3*). Treatment failure was 11.4% and 10.3% for 3 days and 5 days, respectively.

Treatment Failure of Amoxicillin 3 days versus Amoxicillin 5 days) The certainty of the body of evidence was low based on four factors[c]: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*. The body of evidence was assessed to have very serious imprecision. The study was assessed as having very serious imprecision as there were a low number of events.

Treatment Failure of Antibiotics 5-7 days versus 8-14 days. One study (Same et al., 2020) measured treatment failure of children with uncomplicated pneumonia (*n* = 439). The OR of 0.49, 95% CI [0.18, 1.36] indicated the intervention (5–7 day antibiotics) was not different to the comparator (8-14 day antibiotics) (see Figure 4 & *Table 4*). Treatment failure was 3.0% and 5.9% for 5-7 days and 8-14 days, respectively.

Treatment Failure of Antibiotics 5-7 days versus 8-14 days. The certainty of the body of evidence was very low based on four factors[c]: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*. The body of evidence was assessed to have serious risk of bias and very serious imprecision. Risk of bias was assessed as serious due to inability of the study to reliably verify the duration of the antibiotics and which antibiotics were used. The study was assessed as having very serious imprecision as there was only one study with a lower number of events. As only one study (Same et al., 2020) was identified to answer this question, consistency could not be assessed.

Treatment Failure Penicillin or Cefuroxime 4 days versus 7 days. One study (Peltola et al., 2001) measured treatment failure of hospitalized children with uncomplicated pneumonia (*n* = 154). The OR of 1.69, 95% CI [0.27, 10.43] indicated the intervention (4 days penicillin or cefuroxime)

was not different to the comparator (7-day penicillin or cefuroxime) (see Figure 6 & *Table 5*). Treatment failure was 4.1% and 2.5% for 4-days and 7-days, respectively.

Treatment Failure Penicillin or Cefuroxime 4 days versus 7 days. The certainty of the body of evidence was low based on four factors[c]: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*. The body of evidence was assessed to have very serious imprecision. The study was assessed as having very serious imprecision as there was only one study with a lower number of events. As only one study (Peltola et al., 2001) was identified to answer this question, consistency could not be assessed.

Identification of Studies

Search Strategy and Results (see Figure 1)

("community acquired pneumonia" OR "community-acquired pneumonia" OR ("Community-Acquired Infections"[Mesh] AND ("Pneumonia"[Mesh] OR "Respiratory Tract Infections"[Mesh]))) AND ("Anti-Bacterial Agents/administration and dosage"[Mesh] OR antibiotic) AND ("Time Factors"[Mesh] OR "short course" OR short-course OR long-course OR "long course" OR prolonged-course OR duration OR "length of therapy") AND (child OR children OR pediatr* OR paediatr*) Filters: in the last 10 years. Records identified through database searching *n* = 98. Additional records identified through other sources *n* = 9.

Studies Included in this Review

Citation	Study Type
Ben-Shimol et al. (2014)	SR
*Agarwal et al. (2004)	RCT
*MASCOT (2002)	RCT
Dawson-Hahn et al. (2017)	SR
*Agarwal et al. (2004)	RCT
*MASCOT (2002)	RCT
Lassi et al. (2014)	SR
*Peltola et al. (2001)	RCT
Greenberg et al. (2014)	RCT
Same et al. (2020)	Cohort

Studies Not Included in this Review with Exclusion Rationale

Citation	Reason for exclusion
Hanretty and Gallagher (2018)	Adult Studies
Esposito et al. (2012)	Review Article
Lassi et al. (2017)	SR found no studies
Lyttle et al. (2019)	Protocol
Pernica et al. (2018)	Protocol
Tamma and Cosgrove (2012)	Review Article
López-Alcalde et al. (2018)	SR found no studies

Methods Used for Appraisal and Synthesis

[a]The GRADEpro Guideline Development Tool (GDT) is the tool used to create the Summary of Findings table(s) for this analysis.

[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]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.

[d]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).

[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).

[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]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.

[d]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

[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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Acronyms Used in this Document

Acronym	Explanation
AGREE II	Appraisal of Guidelines Research and Evaluation II
CAT	Critically Appraised Topic
CAP	Community-acquired pneumonia
EBP	Evidence Based Practice
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SR	Systematic Review
RCT	Randomized Control Trial
UTI	Urinary tract infection
WHO	World Health Organization

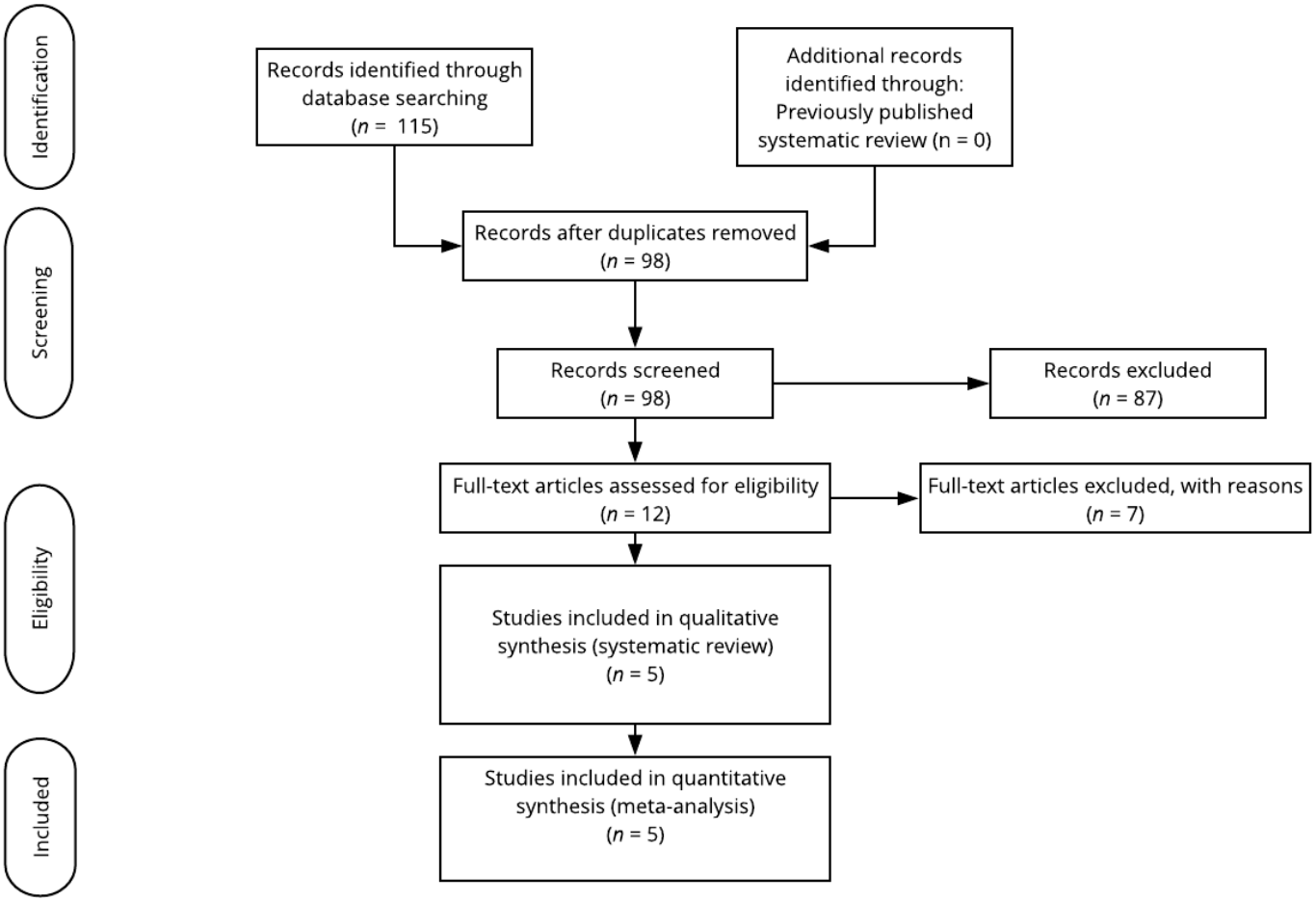

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)[e]

Table 1

AGREE II [d] Summary for the IDSA Guideline (Bradley et al., 2011) and British Thoracic Society Guideline (BTS) (Harris et al., 2011)

Domain	Percent Agreement IDSA Guideline	Percent Agreement BTS Guideline
Scope and purpose	96%	100%
Stakeholder involvement	65%	57%
Rigor of development	56%	83%
Clarity and presentation	94%	86%
Applicability	38%	55%
Editorial independence	65%	73%
Overall guideline assessment	82%	82%
Team's recommendation for guideline use	Yes	Yes

Note: Four EBP Scholars completed the AGREE II on both guidelines.

[d] 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

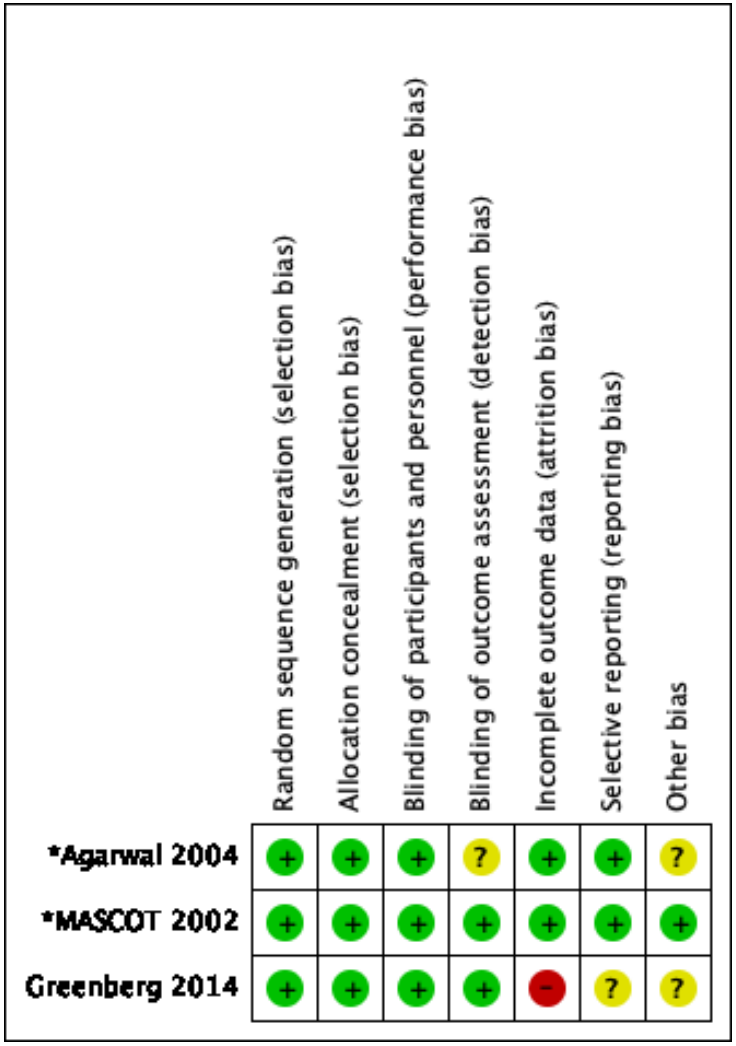

Figure 2. Risk of Bias Summary

Summary of Findings Table

Table 2

Summary of Findings Table[a]: Amoxicillin 3 days or 5 days compared to Amoxicillin 10 days

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Amoxicillin 10 days	With Amoxicillin 3 days	Relative effect (95% CI)	Risk with Amoxicillin 10 days	Risk difference with Amoxicillin 3 days
Treatment Failure 3 days versus 10 days											
66 (1 RCT)	serious [a]	not serious	not serious	very serious [b]	none	⨁◯◯◯ VERY LOW	0/56 (0.0%)	4/10 (40.0%)	OR 78.23 (3.77 to 1623.08)	0 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)
Treatment Failure 5 days versus 10 days											
115 (1 RCT)	serious [a]	not serious	not serious	very serious [b]	none	⨁◯◯◯ VERY LOW	0/59 (0.0%)	0/56 (0.0%)	**OR 0.00** (-0.03 to 0.03)	0 per 1,000	**-- per 1,000** (from 0 fewer to 0 fewer)

Notes

a. Power analysis changed during study to reduce number of subjects needed
b. Only one study, low number of events

Table 3

***Summary of Findings Table*[a]: Treatment Amoxicillin 3 days compared to Amoxicillin 5 days**

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**With Amoxicillin 5 days**	**With Amoxicillin 3 days**	**Relative effect (95% CI)**	**Risk with Amoxicillin 5 days**	**Risk difference with Amoxicillin 3 days**
Treatment Failure 3 days versus 5 days											
4012 (2 RCTs)	not serious	not serious	not serious	very serious [a]	none	⨁⨁◯◯ LOW	205/1999 (10.3%)	230/2013 (11.4%)	**OR 1.13** (0.93 to 1.39)	103 per 1,000	**12 more per 1,000** (from 6 fewer to 35 more)

Notes

a. Low number of subjects

Table 4

***Summary of Findings Table[a]:* Treatment Length 5-7 days compared to 8-14 days**

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With 8-14 days	With 5-7 days		Risk with 8-14 days	Risk difference with 5-7 days
Treatment Failure											
439 (1 observational study)	serious [a]	not serious	not serious	very serious [b]	none	⨁◯◯◯ VERY LOW	16/271 (5.9%)	5/168 (3.0%)	**OR 0.49** (0.18 to 1.36)	59 per 1,000	**29 fewer per 1,000** (from 48 fewer to 20 more)

Notes

a. Unable to reliably verify the duration of antibiotics administered before hospitalization, Specific antibiotics not reported

b. Only study with limited number of subjects

Table 5

***Summary of Findings Table*[a]: Penicillin or Cefuroxime Treatment 4 days compared to 7 days**

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With 7 days	With Penicillin or Cefuroxime 4	Relative effect (95% CI)	Risk with 7 days	Risk difference with Penicillin or Cefuroxime 4
Treatment Failure											
154 (1 RCT)	not serious	not serious	not serious	very serious [a]	none	⨁⨁◯◯ LOW	2/81 (2.5%)	3/73 (4.1%)	**OR 1.69** (0.27 to 10.43)	25 per 1,000	**16 more per 1,000** (from 18 fewer to 184 more)

Notes

a. Only one study with limited number of participants

Meta-analysis(es)

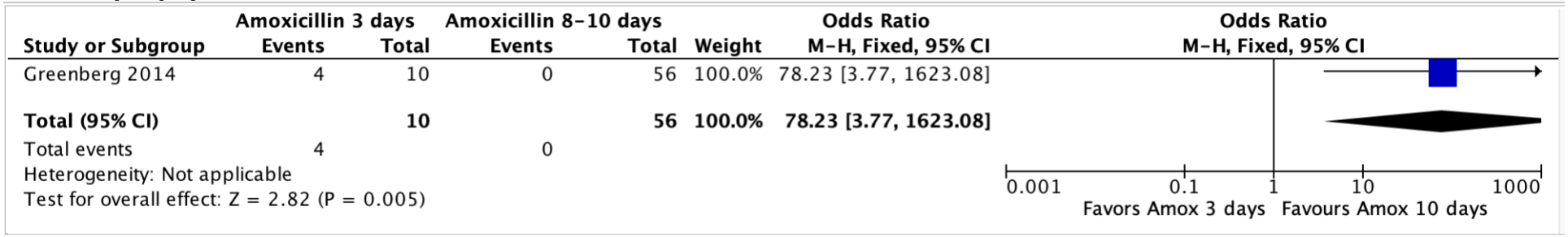

Figure 3. **Comparison: 3 days Amoxicillin versus 8-10 days Amoxicillin, Outcome: Treatment Failure**

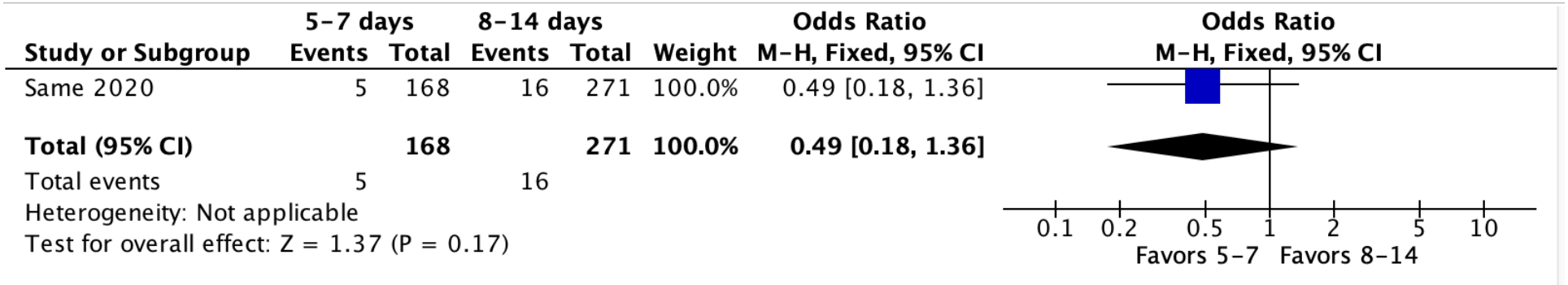

Figure 4. **Comparison: 5-7 days Antibiotic versus 8-14 days Antibiotic, Outcome: Treatment Failure**

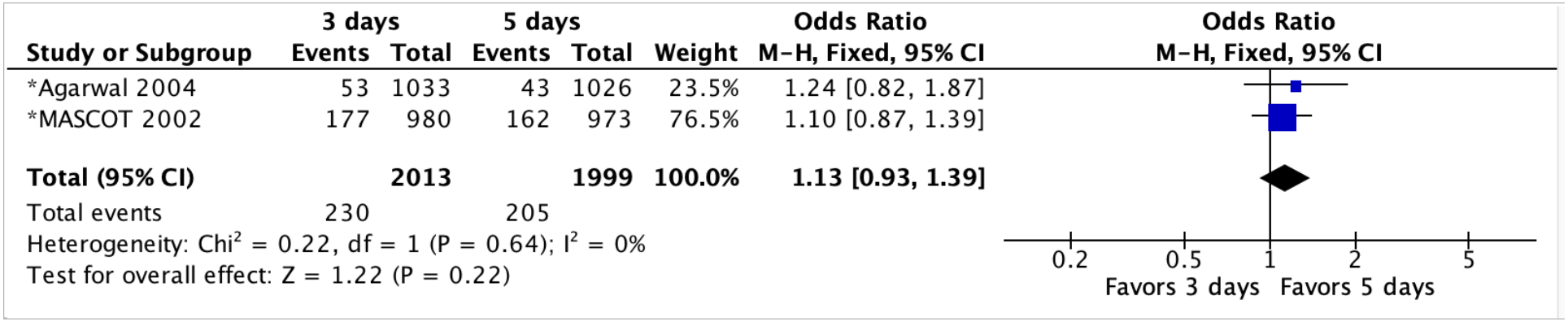

Figure 5. **Comparison: 3 days Amoxicillin versus 8-10 days Amoxicillin, Outcome: Treatment Failure**

Study or Subgroup	4 days Treatment Events	Total	7 days Treatment Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Peltola 1999	3	73	2	81	100.0%	1.69 [0.27, 10.43]
Total (95% CI)		**73**		**81**	**100.0%**	**1.69 [0.27, 10.43]**
Total events	3		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)

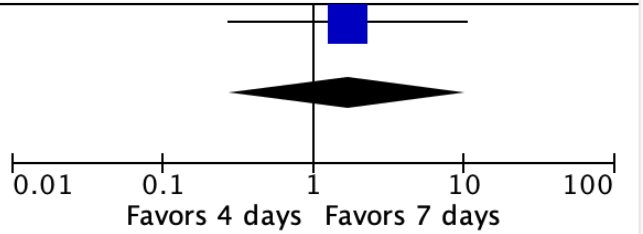

Figure 6. **Comparison: Penicillin or Cefuroxime 4 days versus 7days, Outcome: Treatment Failure**

Characteristics of Intervention Studies

Ben-Shimol et al, 2014

Design	Diagnostic Qualitative Synthesis
Objective	To evaluate randomized controlled trials that assessed the efficacy of short duration oral antibiotic treatment against non-severe childhood Community acquired pneumonia (CAP) and whether the current evidence allows a similar approach to be used in populations in developed countries
Methods	**Protocol and registration.** Not specified **Types of studies.** Randomized controlled trials **(**RCT) **Participants.** **Study inclusion criteria:** • Pediatric patients, aged 2 months-12 years (search was up to 18 years, articles used included up to 12 years) • RCT's evaluating duration of oral antibiotic treatment <7 days in children with non severe CAP • Studies comparing different treatment durations of the same antibiotic regimen • Studies comparing different drugs or comparing antibiotic regimen with placebo • English articles only • Studies that included the outcome measures of treatment failure and/or cure rate **Study Exclusion criteria:** • All non-RCT publications, including meta analysis • RCTs on adults only • RCTs where non-oral antibiotic treatment was given **Index tests.** Not specified **Target Condition (s).** Not specified **Reference Standards.** Not specified **Information sources.** • PubMed database • PRISMA reporting guidelines were followed **Search.** Studies were limited to those published between January 1, 1996 and May 1, 2013 Various combinations of the following key words were used in 5 literature searches: • Pneumonia • Treatment • Duration • Child • Children • Days • Short • Respiratory infection

	• Non-severe
	
	Study Selection.
	• All articles were screened independently for relevancy by three of the authors
	• Articles were screened by preformed questionnaire to extract study population data:
	  ○ Age
	  ○ Ambulatory vs hospital setting
	  ○ Sample size
	  ○ Randomization
	  ○ Case definition of CAP
	  ○ Disease severity
	  ○ Antibiotic treatment (type, dose, administration method, duration of treatment)
	  ○ Outcome
	• Relevant articles evaluated for inconsistencies by three authors
	• Disagreements were resolved by discussion
	
	Data collection process. Information extracted from each selected RCT:
	• Study location (developed vs developing country)
	• Case definition of pneumonia (World Health Organization (WHO) definition vs Chest X-ray (CXR)/clinical signs)
	• Characteristics of trial participants, including number and age
	• Antibiotic regimens
	  ○ Type of drug
	  ○ administration method
	  ○ Duration of treatment
	• Outcome (cure/failure rate)
	
	Methodological quality (Risk of Bias). Not reported
	
	Synthesis of results. Done in paragraph format

Results	**Study Selection.** **Number of articles identified:** *N* = 643 • This number is the total of five keyword combinations, one of which differentiated between the use of a hyphen in the word "non-severe" • It is unclear if there are duplicates between the five combinations **Full-text articles assessed for eligibility:** *n* = 42 **Studies included in qualitative synthesis:** *n* = 8 • 7 from developing countries • 1 from developed country **Synthesis of results.** **Outcome (cure/failure rate):** • For the 7 studies from developing populations ○ Four studies concluded that 3 days of oral amoxicillin are sufficient treatment for non-severe CAP

	○ Two articles found 5 days of treatment with co-trimozazole or amoxicillin to be sufficient for non-severe CAP ○ One article found no difference between 3 days of amoxicillin and placebo for non-severe CAP • For the 1 study from a developed country, 3 days of azithromycin is as effective as 10 days of co-amoxiclav **Methodological quality of included studies (Risk of Bias)**. Authors considered that the following could affect bias: • Settings of studies were different: outpatient vs inpatient vs community studies • Identification of pathogen was only included in one study • Duration of follow-up varied from 7-30 days • Children with asthma were excluded in the 7 studies from developing countries • No validated instrument was used to assess the quality of the RCTs
Discussion	• The studies are heterogeneous, and include the following compared regimens: ○ 3 days standard dose vs 3 days high dose amoxicillin ○ 3 days vs 5 days amoxicillin (2 studies) ○ 3 days amoxicillin vs placebo ○ 3 days amoxicillin vs 5 days co-trimoxazole ○ 5 days amoxicillin vs 5 days co-trimoxazole ○ 5 days standard dose co-trimoxazole vs 5 days high dose co-trimoxazole ○ 3 days azithromycin vs 10 days co-amoxiclav • The 7 studies from developing countries included the following criteria: ○ Case definition: WHO guidelines ○ Patient age 2-59 months • The 1 study from a developed country included the following criteria: ○ Case definition: CXR or Clinical signs ○ Patient age 3 months-12 years
Funding	Authors report "No support or funding"

Dawson-Hahn et al., 2017

Design	Diagnostic Quantitative Synthesis and Meta-analysis
Objective	To evaluate and summarize the evidence from systematic reviews that compared short courses of oral antibiotics to long courses for the clinical resolution of bacterial infections commonly encountered by adults and children in primary care settings.
Methods	**Protocol and registration.** Not specified **Types of studies.** Systematic reviews (SR) of randomized controlled trials (RCT) **Participants.** **Study inclusion criteria:** • Systematic reviews of RCTs for children and adults with bacterial infections commonly treated in outpatient or primary care settings • Trials comparing antibiotic prescriptions described as short course (duration 2 or more days shorter than longer course treatments) with longer courses based on disease specific standards of care **Study exclusion criteria:** • Reviews that included the following: o Infections that were exclusively or routinely treated in hospitalized patients o Parasitic, fungal, viral, or mixed etiology infections o Those involving patients who were immunocompromised o Any that included combination, topical or intravenous administration of antibiotics o Reviews of strategies to reduce uptake of antibiotics (use of delayed prescriptions for example) • Individual articles or abstracts not included in systematic reviews **Index tests.** Not specified **Target Condition (s).** Not specified initially. After included studies were identified, the following conditions were investigated: Pediatric: • Streptococcal Tonsillopharyngitis • Community Acquired Pneumonia (CAP) • Acute Otitis Media • Urinary Tract Infection (UTI) Adult: • Acute Bacterial Sinusitis • Uncomplicated UTI in non-pregnant women • Acute Pyelonephritis • CAP • Acute Uncomplicated Lower UTI in Elderly Women **Reference Standards.** Not specified **Information sources.** • Medline (OvidSP) [1946-present]

- Embase (OvidSP) [1974-April 4, 2016]
- CINAHL (OvidSP) [1982-present]
- Cochrane Database of Systematic Reviews [Issue 4 of 12, April 2016]
- The Database of Abstracts of Review of Effects [Issue 2 of 4, April 2015)

Search.

- Detailed search strategy was developed in collaboration with an information specialist (full search strategy found online in supplementary tables).
- Searches were not restricted by country of origin or language, but only systematic reviews published in English were eligible.
- Search was completed April 6, 2016.

Study Selection.

- Initial screening included title and abstract, then full text of potentially eligible articles were screened for inclusion.
- Two pairs of authors performed the initial screening.
- If eligibility continued to be uncertain, consensus was used to decide final eligibility.
- In cases where two or more reviews were considered on the same infection and/or had same participants, one review was selected for inclusion based on the following criteria evaluated by 2 authors independently: higher quality, and published more recently.
- The Assessment of Multiple Systematic Reviews (AMSTAR) scale was used to assess quality of the included systematic reviews by the same pairs of authors.
    - AMSTAR scale is based on 11 points. Quality is low if score is 0-3, medium if score is 4-7, and high if score is 8-11.

Data collection process.

- A two-person technique was used where one author extracted data using a pre-specified form and accuracy was checked by the second author.
- Consensus was used to resolve disagreements.
- Information extracted included:
    - Year of publication
    - Patient population
    - Clinical setting
    - Antibiotic regimens compared (antibiotic type, dosing schedule, definitions of short and long or standard courses)
    - Measures for predefined primary and secondary outcomes and how those were defined
- Countries where studies took place were grouped based on income levels using World Bank criteria.

Methodological quality (Risk of Bias).

One of two risk of bias tools was used when describing the overall quality of the studies included in each systematic review.

- Jadad score – used to define the quality of an RCT
- Assessment for risk of bias

Synthesis of results.

- Results were reported descriptively in paragraph form, including information on differences between studies and any heterogeneity.
- Results for primary and secondary outcomes of interest were summarized separately for children and adults.

Results

Study Selection.

- **Number of articles identified:** *N* = 504
- **Full-text articles assessed for eligibility:** *n* = 30
- **Studies included in qualitative synthesis:** *n* = 9
  - **Adult studies:** *n* = 5
  - **Pediatric studies:** *n* = 3
  - **Adult and pediatric studies:** *n* = 1 (data for adults and children were extracted separately)

Synthesis of results.

Outcome for CAP:

Children:

- One systematic review of 4 studies was included.
- No significant difference was found in clinical cure rate between those receiving 3 days of antibiotics versus those receiving 5 days.
- Subgroup analyses revealed no significant differences in clinical cure with 3 days of antibiotic treatments versus 5 days with either Amoxicillin or Cotrimoxazole.
- No significant difference was found in rates of treatment failure and relapse after 3 days versus 5 days of treatment.

Adults:

- One systematic review of 8 studies was included.
- No significant differences in the rates of clinical improvement when antibiotics were given 3-7 days versus 7 days or longer.
- After sensitivity analysis of only the high-quality studies there was no significant difference in clinical improvement rates between short versus long courses of treatment.
- No significant differences were found in mortality rates between the short versus long courses of treatment.

Children					
Primary Outcome	**Definition, course of treatment**	**# of SRs/# of Studies**	**Age Range**	**# of Patients**	**Relative effect of short vs long (95%CI)**
Clinical cure	3 versus 5 days of treatment	1/4	2-59 months	6177	0.99 (0.97, 1.01)
Adults					
Clinical Failure	≤7 versus >7 days of treatment	1/8	≥12 years old	1540	0.96 (0.74, 1.26)

(RR > 1 supports long course of treatment.)

Methodological quality of included studies (Risk of Bias) – CAP only.

- Hader, 2011 (children): 75% of included studies reported adequate sequence generation, allocation concealment, blinding, and addressing incomplete outcome data
- Li *et al.*, 2007 (adults): All studies had overall quality of moderate/good with Jadad scores ≥3.

Discussion

Regarding CAP:

	Children: • The one included systematic review included studies published between 1999 and 2004. All were conducted in lower to middle income countries. • Overall quality of studies was considered moderate to good. • This review found 3 days of antibiotic treatment acceptable in treating children with mild to moderate CAP. Adults: • The one included systematic review included studies published between 1981 and 2005. All were conducted in upper middle and high income countries. • Overall quality of studies was considered moderate to good. • Results of this review concluded that shorter courses of antibiotic treatment produced similar clinical cure rates when compared to longer courses of treatment in adults treated in outpatient settings with mild to moderate CAP. **Limitations:** • Due to poor reporting quality about the effect of antibiotic resistance across included studies, this review could not generate evidence about that topic. • This study cannot comment on the effectiveness of short versus long duration antibiotic treatment for rare outcomes, such as hospitalization for CAP. • Only limited age ranges were considered in the included studies for particular diagnoses such as CAP. It was suggested that additional study via a new systematic review be undertaken for children with pneumonia that would include a wider age range and in high-income countries.
Funding	**Funding.** Acknowledgement was given about funding sources for two authors. No conflicts of interest were reported.

Greenberg et al., 2014

Methods	Single-center, randomized, double-blind, 1:1 placebo-controlled study
Participants	**Setting:** Soroka University Medical Center (SUMC) Pediatric Emergency Room in Beer-Sheva, Israel. **Randomized into study:** *N* = 115 • **Group 1:** Oral Amoxicillin (10-day course of amoxicillin) *n* = 59 • **Group 2:** Oral Amoxicillin + Placebo Powder (5-day course of amoxicillin followed by 5-day course of placebo powder) *n* = 56 **Completed Study:** *n* = 91 • **Group 1:** Oral Amoxicillin *n* = 49 • **Group 2:** Oral Amoxicillin + Placebo Powder *n* = 42 **Gender, males:** • **Group 1:** Oral Amoxicillin *n* = *35* (59.3%) • **Group 2:** Oral Amoxicillin + Placebo Powder *n* = 32 (57.1%) **Age, months** (mean ± SD): • **Group 1:** Oral Amoxicillin 27.9 ± 15.5 • **Group 2:** Oral Amoxicillin + Placebo Powder 27.5 ± 14.4 **Inclusion Criteria:** • Age 6-59 months • Alveolar pneumonia based on chest radiography • Disease symptoms began < 7 days prior to presentation • Temperature ≥ 38.5°C • WBC ≥ 15,000/mm^3 • Community-acquired disease • Patient judged to be manageable as outpatient • Informed consent obtained from parents or legal guardian **Exclusion Criteria:** • Antimicrobial drug received within ≤14 days • Need of parenteral treatment (ie, impaired perfusion, hypotension, oliguria, lactic acidosis, impaired consciousness, presence of pleural effusion, vomiting) • Oxygen saturation < 94% • Known impaired immunity • ≥ 2 pneumonia episodes in last year • Chronic illness (i.e., cystic fibrosis or cerebral palsy) potentially influencing current illness • Presence of an additional infection necessitating a longer or different antibiotic treatment • Unavailability for follow up • Known β-lactam hypersensitivity • Known allergy to soy milk **Power Analysis:** • The probability of cure was assumed to be 95% with an α value of 0.05 and a power of 80%. The noninferiority margin was 10% and the test was 2 sided. Using these parameters, the calculated sample size of 59 in each group. After achieving > 40 evaluable patients in both groups (5-day and 10-day arms with no failures), the sample size

	needed was recalculat ed against the probability of success of 99%, 98%, or 97%. This recalculation led to a sample size of 12 subjects (3-day), 14 subjects (5-day), and 36 subjects (10-day).

Interventions	• **Intervention arms:**
	  ○ **Group 1:** Received oral amoxicillin (80mg/kg/day divided to 3 doses) for 10 days (30 total doses).
	  ○ **Group 2:** Received oral amoxicillin (80mg/kg/day divided to 3 doses) for 5 days (15 total doses) then Placebo powder (Vitamed, Binyamina, Israel) reconstituted with soy milk for 5 days (15 total doses)
	• **Both arms:**
	  ○ Each participant received 1 kit each including 2 packages at enrollment.
	  ○ All participants received amoxicillin for 5 days in their first package (15 doses).
	  ○ On the sixth day, all participants opened their second package which either contained:
	  ▪ amoxicillin for an additional 5 days to complete a 10-day treatment (30 doses altogether) or
	  ▪ placebo powder.
	  ○ To minimize the chance of distinguishing between amoxicillin and the placebo powder in the second package, the amoxicillin used in the second package looked different than that used in the first package. The first package contained Moxypen powder syrup (Teva Pharmaceutical Industry, Israel) whereas the second package contained either Moxyvit suspension (Vitamed, Bynyamina, Israel) or placebo powder.
	  ○ Compliance measured by:
	  ▪ Parents were asked daily about the number of administered doses
	  ▪ Returned empty bottles were counted
	  ○ Evaluation occurred via daily phone calls for the first 14 days and at the end of the study on day 30-35
	  ○ Patients evaluated by study physician on days 5-7 and 10-14 who:
	  ▪ Performed a physical exam
	  ▪ Obtained a blood sample for WBC count, absolute neutrophil count (ANC) and CRP concentration determination

Outcomes	**Primary outcome:**
	• Absence of treatment failure within 30 days
	Secondary outcome(s)
	• Clinical parameters such as:
	  ○ Temperature
	  ○ Difficult breathing
	  ○ Restlessness
	  ○ Coughing
	  ○ Loss of appetite
	  ○ Sleep disturbances
	• Laboratory Values (WBC and CRP)

Notes	*Patients diagnosed with asthma were not considered as meeting exclusion criteria Stage 1: Compared 3- to 10- day arms. Four patients had treatment failure between days 4 and 10 (all of these patients were in the 3-day arm). Stage 1 was discontinued and replaced with Stage 2. Stage 2: Compared 5-day to 10-day treatment regimens.

Bias	Scholars' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The random allocation sequence was done with a computerized random-number generator by the epidemiologist (N.L.G.). The block length was 10 and the code was known only to the epidemiologist.
Allocation concealment (selection bias)	Low risk	The allocation numbers were random 4 digit numbers which were in nonconsecutive order in the allocation list. The epidemiologist handled the allocation list to the pharmacist who concealed the allocation by labeling the identical opaque study drug containers with allocation numbers. Another allocation list without the randomization code was given to the investigators. An unblinded research coordinator provided each patient with the amount of study drug for the first 5 days (depending on the study stage).
Blinding of participants and personnel (performance bias)	Low risk	Both parents and study researcher (excluding the person in charge of preparing the study drug) were blinded to the content of the treatment kits.
Blinding of outcome assessment (detection bias)	Low risk	Study drugs were not handled by physician who collected data and assessed outcomes.
Incomplete outcome data (attrition bias)	High risk	The power analysis and sample size needed was changed from needing 59 subjects in each arm to 24 subjects in the 5-day arm and 36 subjects needed in the 10-day arm.
Selective reporting (reporting bias)	Unclear risk	The study did not disclose data for all secondary outcomes. They only mentioned that the proportions were similar between the two arms of the study.
Other bias	Unclear risk	The study protocol changed from a 3-day and 10-day amoxicillin course to a 5-day and 10-day amoxicillin course due to study treatment failure for the 3-day arm.

Lassi et al., 2013

Design	Diagnostic Quantitative Synthesis and Meta-analysis
Objective	To determine the most suitable antibiotic therapy for treating pediatric pneumonia: • very severe, severe, and non-severe • Children, 2-59 months old with Community Acquired Pneumonia (CAP)

Methods	**Protocol and registration.** The protocol was not registered.
	
	Types of studies. Randomized Controlled Trials (RCT)
	
	Inclusion Criteria:
	• Studies that assessed the route, dose, combination and duration of antibiotics in the management of WHO defined non-severe/severe/very severe CAP
	• Children aged 2-59 months with CAP
	• Studies that used standard World Health Organization definition and/or classification for CAP
	• Studies that analyzed outcomes including:
	  ○ Clinical cure rate
	  ○ Treatment failure
	  ○ Relapse rate
	  ○ Change in antibiotic required
	  ○ Mortality rate
	• Studies that compared any intervention:
	  ○ Single drug vs combination
	  ○ Single drug with different dose/duration/route
	
	Target Condition (s). Cure rate or failure rate around length of treatment
	Information sources.
	• PubMed
	• Cochrane Library
	• Science Direct
	• Lilac
	• JOLIS
	• Google Scholar
	Search
	Last performed on 15 March 2013
	
	Medical subject headings/keywords:
	• Pneumonia
	• Very severe pneumonia
	• Severe pneumonia
	• Non-severe pneumonia
	• Acute respiratory illness
	• Community acquired pneumonia
	• Child
	• Infant

<table>
<tr><td></td><td>

Preschool
Schoolchild
School age
Preschool
Kid
Toddler
Treatment
Anti-infective agent
Anti-bacterial agents
Antibiotic
Management

All bibliographies of relevant RCTs and reviews were cross checked
Clinical trial registries were browsed for on-going trials
Study Selection.

All available titles and abstracts screened for inclusion by two review authors independently
Where trial eligibility could not be assessed by screening title/abstract, full test was retrieved to judge relevance
Any differences were resolved by discussion or conferring with a third review author

Data collection process.

Standard extraction forms used to extract data from included studies by two independent reviewers
Errors corrected by comparison of extracted data and in differences in interpretation of data were resolved by contacting the trial author
All data entered and analyzed using Review Manager 5 software

Methodological quality (Risk of Bias).

Cochrane methods for risk of bias assessment to assess the quality of included studies

Synthesis of results. Completed
</td></tr>
<tr><td>Results</td><td>
Study Selection.
Number of articles identified: N = 8122
Full-text articles assessed for eligibility: n = 83

Studies included in qualitative synthesis: n = 22

Very severe pneumonia n = 3
Severe pneumonia n = 6
Non severe pneumonia n = 1

Very severe pneumonia:

All antibiotics administered parenterally

Failure rates:
<table>
<tr><td></td><td>Outcome</td><td>Summary estimate</td><td>Number of studies (n=participants)</td><td>Heterogeneity</td></tr>
<tr><td>Ampicillin and gentamycin vs chloramphenicol</td><td>Failure rate, day 5</td><td>RR 0.70
95% CI: 0.51 to 0.97</td><td>1 (n = 958)</td><td>n/a</td></tr>
</table>
</td></tr>
</table>

	Failure rate, day 10	RR 0.73 95% CI: 0.55 to 0.97	1 (*n* = 958)	n/a
	Failure rate, day 21	RR 0.75 95% CI: 0.57 to 0.98	1 (*n* = 952)	n/a
	Failure rates	RR 0.79 95% CI 0.66 to 0.94	2 (*n* = 2074)	X^2 p = .36 I^2 = 0%
Penicillin and gentamicin vs amoxicillin-clavulanic acid	Failure rates	RR 0.87 95% CI: .06 to 13.35	1 (*n* = 71)	n/a

Severe pneumonia (chest indrawing pneumonia):

Failure rates/cure rates

	Outcome	Summary Estimate	Number of studies (n=participants)	Heterogeneity
Chloramphenicol plus penicillin vs ceftriaxone	Cure rate, day 10	RR:1.05 95% CI: 0.88 to 1.27	1 (*n* = 97)	n/a
Co-trimoxazole vs amoxicillin	Failure rate	RR: 1.79 95% CI:1.13 to 2.84	1 (*n* = 302)	n/a
Parenteral penicillin vs oral amoxicillin	Treatment failure at 48 hours	RR: 0.98 95% CI: 0.80 to 1.19	1 (*n* = 1702)	n/a
Ampicillin (IV) plus oral amoxicillin vs oral amoxicillin	Treatment failure by 3 days	RR: 1.66 95% CI: 1.11 to 2.49	1 (*n* = 2037)	n/a
Oral co-trimoxazole vs IM procaine penicillin	Treatment failure at day 7	RR: 0.01 95% CI: 0.11 to 0.09	1 (*n* = 134)	n/a
Penicillin or cefuroxime	4 days vs 7 days	RR: 3.28 95% CI: 0.14 to 79.36	1 (*n* = 134)	n/a

Non severe pneumonia:

Clinical or Treatment Failure/Cure rate

	Outcome	Summary estimate	Number of studies (n=participants)	Heterogeneity
Oral co trimoxazole vs oral amoxicillin	Clinical failure	RR: 1.09 95% CI: 0.93 to 1.27	3 (*n* = 3759)	X^2 p = .007 I^2 = 80%
Oral co trimoxazole vs oral amoxicillin	Cure rate	RR: 0.99 95% CI: 0.96 to 1.01	2 (*n* = 3468)	X^2 p = .004 I^2 = 88%
Oral levofloxacin vs oral co-amoxiclavulanic acid	Cure rate	RR: 1.02 95% CI: 0.93 to 1.11	1 (*n* = 3759)	n/a
Oral azithromycin vs oral co-amoxiclavulanic acid	Treatment failure (2 weeks)	RR: 1.20 95% CI: 0.45 to 3.21	2 (*n* = 276)	X^2 p = .55 I^2 = 0%
Amoxicillin vs co-amoxiclavulanic acid	Cure rate	OR: 10.44 95% CI: 2.85 to 38.21	1 (*n* = 100)	n/a
Parenteral ampicillin vs penicillin plus chloramphenicol	Clinical cure	RR: 0.90 95% CI: 0.76 to 1.06	1 (*n* = 101)	n/a
Parenteral ampicillin vs penicillin plus chloramphenicol	Treatment failure	RR: 1.88 95% CI: 0.69 to 5.12	1 (*n* = 101)	n/a

Methodological quality of included studies (Risk of Bias).

- Cochrane methods for risk of bias assessment done
- For each study the level of attrition was noted along with its impact on overall treatment effect via sensitivity analysis
- Analysis for all outcomes was done as far as possible on an intention to treat basis
- Fixed effect meta-analysis model was used
- Where heterogeneity was high, data was analyzed in a random effect model

Discussion	• A summary table is included
Funding	**Funding:** Not specified

Same et al., 2020

<table>
<tr><td>Methods</td><td>Retrospective Cohort</td></tr>
<tr><td>Participants</td><td>
Participants: 6 months-21 years of age admitted to The Johns Hopkins Hospital with pneumonia.
Setting: The Johns Hopkins Hospital from January 2012 through December 2018.
Number enrolled into study: 439
Gender, males (as defined by researchers):
• Group 1 (short course): 85
• Group 2 (prolonged course): 129
Race / ethnicity or nationality (as defined by researchers):
<table>
<tr><th>Race, n (%)</th><th>Short Course</th><th>Prolonged Course</th></tr>
<tr><td>White</td><td>58 (34.5)</td><td>104 (38.4)</td></tr>
<tr><td>Black</td><td>77 (45.8)</td><td>125 (46.1)</td></tr>
<tr><td>Asian</td><td>5 (3)</td><td>10 (3.7)</td></tr>
<tr><td>Latino</td><td>16 (9.5)</td><td>23 (8.5)</td></tr>
<tr><td>Unreported</td><td>12 (7.1)</td><td>9 (3.3)</td></tr>
</table>
Age in years, median (interquartile range [IQR]):
• Group 1: 4 (2-8)
• Group 2: 4 (2-7)
Inclusion Criteria:
• ICD-9/ICD-10 codes for pneumonia on discharge diagnosis list as well as both clinical and radiographic criteria considered to be consistent with CAP based on the adjudication of 2 infectious disease physicians.
• Clinical criteria included fever plus at least 1 of the following:
  ○ cough, chest pain, increased work of breathing, or hypoxia.
• Radiographic criteria required a radiologist interpretation to include findings of an "opacity, density, infiltrate, or consolidation".
Exclusion Criteria:
• Presence of a loculated or moderate to large pleural effusion or pulmonary abscess
• Tracheostomy dependency
• Healthcare-associated, hospital-acquired, or ventilator-associated pneumonia
• Intensive care unit stay >48 hours
• Sickle cell disease
• Cystic fibrosis or bronchiectasis
• Severe immunosuppression from chemotherapy, hematopoietic stem cell transplant, or solid organ transplant within the last 6 months
• Receipts of >48 hours of antipseudomonal beta-lactams
• Children that received less than 5 or more than 14 days of antibiotic therapy
Covariates Identified:
• n/a
</td></tr>
<tr><td>Interventions</td><td>
• Group 1: Short course (5-7 days) duration of antibiotics.
• Group 2: Prolonged-course (8-14 days) duration of antibiotics.

• Day 1 being the first day antibiotics were administered in the hospital for treatment of CAP.
• Duration included antibiotics administered in the hospital and those prescribed after hospital discharge.
</td></tr>
</table>

Outcomes	**Primary outcome:** • Treatment failure*; a composite of unanticipated emergency department visits, outpatient visits, hospital readmissions, or death within 30 days after completing antibiotic therapy. **Secondary outcome:** • n/a **Safety outcome:** • n/a *Outcomes of interest to the CMH CPG /CAT development team
Results	**Results:** • In the propensity-weighted cohort, 20 children (4%) experienced treatment failure within 30 days of discontinuing antibiotics • There was no difference in treatment failure between patients who received short-course (3%) vs prolonged-course (6%) antibiotic therapy. • Three patients in the short course compared with eight patients in the prolonged course experienced an unplanned emergency department or outpatient visit. • Two patients in the short course compared with seven patients in the prolonged course required hospital readmission for pneumonia. • There were no deaths. **Limitations:** • Possibility of bias in favor of short courses of therapy due to the inclusion of children with viral pneumonia who would have improved without antibiotic therapy (subgroup analysis excluding all patients with any positive respiratory viral test was done which included 312 patients, 14 children experienced treatment failure. • Single-center study at a tertiary care center. • Unable to reliably verify the duration of antibiotics administered before hospitalization, which may have underestimated treatment duration for some children. • Some locations within and outside of the John Hopkins Health System do not sure EPIC electronic health record system, so if patients sought care at these locations, some healthcare visits would have been missed to identify failure of treatment.

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References marked with an asterisk indicate studies included the meta-analysis. Citations are marked with an asterisk.

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