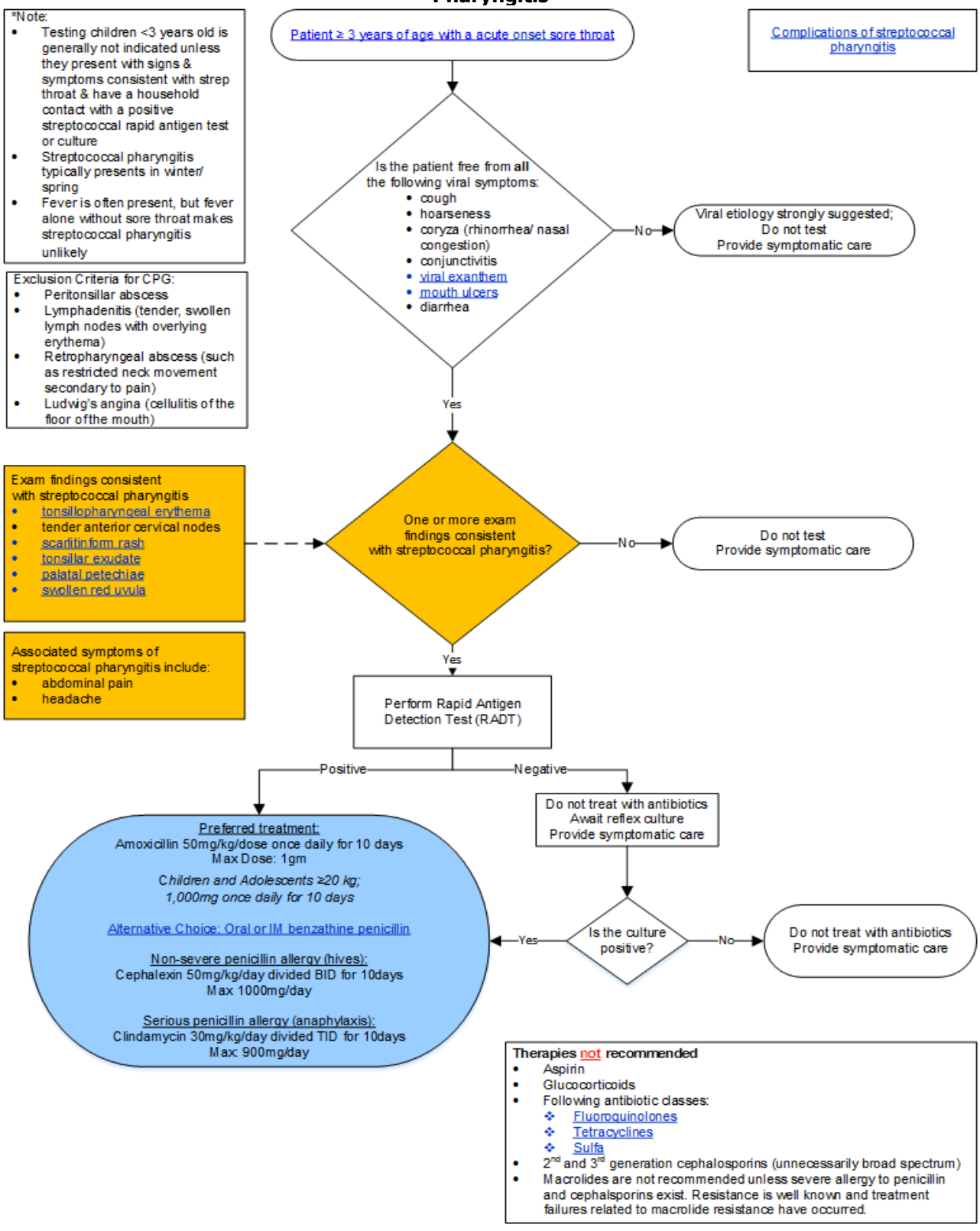
Children's Mercy Hospitals and Clinics
Evidence Based Practice Clinical Practice Guide

Pharyngitis



Epidemiology:

GAS is the most common cause of bacterial pharyngitis in children and adolescents. It accounts for 15 to 30 percent of all cases of pharyngitis in children between the ages of 5 and 15 years (up-to-date, 2016), and peaks at 7 to 8 years of age. The incidence of GAS pharyngitis is highest during the winter and early spring. During these seasons, GAS causes up to 35 to 40 percent of cases of pharyngitis in children and adolescents (Up-to-date, 2016). GAS pharyngitis is most common in school-age children but may occur in younger children, especially if they have close contact with school-age children. Prevalence of GAS among school-aged children who present to an outpatient clinic or emergency department with sore throat is around 37 percent. The prevalence among children <5 years is around 24 percent (Up-to-date, 2016). Up to 70% of patients with sore throats seen in primary care receive prescriptions for antimicrobials, while only 20-30% are likely to have GAS pharyngitis (Shulman, 2012).

Definition: Group A *Streptococcus* (GAS), also known as *Streptococcus pyogenes*, is a gram-positive coccus that grows in chains.

Objective of Guideline: Update providers on appropriate diagnostics and therapy for pediatric patients with streptococcal pharyngitis. The Clinical Practice Guideline will standardize care and improve health outcomes in pediatric patients with streptococcal pharyngitis by establishing care standardization focused on diagnosis, initiation of treatment and proper follow up.

Target population: Pediatric patients

Key stakeholders and users:

- Doctors
- Advanced Practice Nurses
- Direct Care Nurses
- Laboratory
- Patients and Families

Guideline Inclusion Criteria:

- Suspected GABH streptococcus
- ≥Age 3 years

Guideline Exclusion Criteria:

Concern for the following

- Peritonsillar abscess
- Lymphadenitis* (tender, swollen lymph nodes with overlying erythema)
- Viral stomatitis
- Retropharyngeal abscess (such as restricted neck movement secondary to pain)
- Ludwig's angina (cellulitis of the floor of the mouth)

Setting:

- Emergency Department
- Urgent Care
- Primary Care

Measures:

Outcome:

1) Recommended antibiotic (penicillin or amoxicillin; cephalexin for penicillin allergy) utilization and length/dose (Length of enteral antibiotic treatment and dose)
2) Clinically indicated laboratory testing (Decrease the number of unnecessary rapid streptococcal antigen tests)

Process:

1) Power Note utilization
2) Power Plan utilization (CPG Coverage)
3) Family education
4) Provider knowledge

Balance:

1) Readmit with the same diagnosis within 2 weeks

Potential Cost Implications:

1) Decreased lab tests
2) Decreased antibiotic costs

Potential Barriers:

1) Providers grounded in traditional standard of care
2) Parental insistence to obtain rapid strep screen, antibiotics for viral sore throat

Supporting Tools:

- Power Plan (to be completed)
- Algorithm (to be completed)

Existing documents:

- IDSA Guideline 2012
- Judicious Use of Antibiotics for Streptococcal Pharyngitis

For all clinical questions, the Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis: 2012 Updated by the Infectious Disease Society of America (IDSA) was adopted as our "parent" guideline. The Guideline was assessed using the AGREE II Tool by four reviewers. For each domain contains three to eight questions, that are answered on a numeric scale, range [1-7], higher is better.

AGREE II Tool Score:

Domain	Percent Agreement
Domain 1 - SCOPE AND PURPOSE	96%
Domain 2 - STAKEHOLDER INVOLVEMENT	74%
Domain 3 - RIGOR OF DEVELOPMENT	74%
Domain 4 - CLARITY AND PRESENTIATION	76%
Domain 5 - APPLICABILITY	53%
Domain 6 - EDITORIAL INDEPENDENCE	63%
Overall Guideline Assessment	73%

Clinical Questions Answered by Guideline:

1) In pediatric patients, are there any valid and reliable clinical scoring of pharyngitis Centor criteria or other criteria? (Critical) (see Appendix A)
2) In pediatric patients, how often do adverse side effects occur with antibiotic therapy (Rash, nausea, vomiting, & diarrhea)? (Critical) (see Appendix B)
3) In pediatric patients with streptococcal pharyngitis, do oral antibiotics versus intramuscular injections result in faster clinical cure? (Critical) (see Appendix C)
4) In pediatric patients with streptococcal pharyngitis, is amoxicillin versus other antibiotics more efficacious for clinical cure? (Critical) (see Appendix D)
5) In pediatric patients, what is the incidence of streptococcal pharyngitis under three years of age? (Important) (see Appendix E)
6) In pediatric patients with streptococcal pharyngitis, how soon can patients return to school after starting antibiotics? (Important) (see Appendix F)

Practice Recommendations:

Diagnostic Evaluation:

1. Clinical prediction rules for identifying the pediatric patient with group A streptococcal (GAS) pharyngitis are not recommended due to their low diagnostic accuracy (see Appendix A)
2. Do not test patients with viral the following symptoms (if viral etiology strongly suggested; provide symptomatic care and do not test):
    a. Cough

   b. Hoarseness
   c. Coryza (rhinorrhea/nasal congestion)
   d. Conjunctivitis
   e. Viral exanthem
   f. Mouth ulcers
   g. Diarrhea
3. Perform Rapid Antigen Detection Test (RADT) if patient has one or more exam finding consistent with streptococcal pharyngitis
   a. Exam finding consistent with streptococcal pharyngitis:
      i. Tonsillopharyngeal erythema
      ii. Tender anterior cervical nodes
      iii. Scarlitinform rash
      iv. Tonsillar exudate
      v. Palatal petechiae
      vi. Swollen red uvula
   b. Associated symptoms of streptococcal pharyngitis include:
      i. Abdominal pain
      ii. Headache
4. Testing children <3 years old is generally not indicated unless they present with signs and symptoms consistent with strep throat **and** have household contact with an individual with a positive rapid antigen streptococcal test or culture (see Appendix E)
5. Streptococcal pharyngitis typically presents in winter/spring
6. Fever is often present, but fever alone without sore throat makes streptococcal pharyngitis unlikely
7. Exclusion Criteria:
   a. Peritonsillar abscess
   b. Lymphadenitis (tender, swollen lymph nodes with overlying erythema)
   c. Retropharyngeal abscess (such as restricted neck movement secondary to pain)
   d. Ludwig's angina (cellulitis of the floor of the mouth)

Diagnostics:

1. Rapid Antigen Detection Test (RADT)
   a. Start antibiotic treatment if positive
   b. If negative, do not treat with antibiotics and await reflex culture, provide symptomatic care
      i. If reflex culture is negative, provide symptomatic care
      ii. If reflex culture is positive, start antibiotic treatment

Treatment:

1. Preferred treatment:
   a. Amoxicillin 50mg/kg/dose once daily for 10 days, Max Dose: 1gm
   b. Children and adolescents ≥40kg; 1000mg once daily for 10 days
   c. The cure rate of amoxicillin is as high as other antibiotics (see Appendix D)
2. Alternative Choice: Oral or IM benzathine penicillin
   a. Penicillin VK ≤27kg: 250 mg PO every 12 hours, for 10 days
   b. Penicillin VK ≥27kg: 500 mg PO every 12 hours, for 10 days (max single dose 500mg)
   c. Bicillin L-A ≤27 kg: 600,000 units IM x 1
   d. Bicillin L-A >27 kg: 1.2 million units IM x 1
   e. The cure rate for oral and IM penicillin are both equivocal (see Appendix C)
3. Non-severe penicillin allergy (hives)
   a. Cephalexin 50mg/kg/day divided BID for 10day (max 1000mg/day)
4. Serious penicillin allergy (anaphylaxis)
   a. Clindamycin 30mg/kg/day divided TID for 10days (max 900mg/day)
5. The use of antibiotics is not without side effects and clinicians should make parents aware of the harm-to-benefit ratio of taking antibiotics. For every 14 children treated with antibiotics, one child will have an adverse event such as vomiting, diarrhea, or rash (see Appendix B)

6. Therapies **not** recommended
    a. Aspirin
    b. Glucocorticoids
    c. Following antibiotic classes:
        i. Fluoroquinolones
            1. Levofloxacin
            2. Ciprofloxacin
            3. Moxifloxacin
        ii. Tetracyclines
            1. Tetracycline
            2. Minocycline
            3. Doxycycline
        iii. Sulfa
            a. Sulfamethoxazole / Trimethoprim
        iv. 2nd and 3rd generation cephalosporins (unnecessarily broad spectrum)
        v. Macrolides are not recommended unless severe allergy to penicillin and cephalosporins exist. Resistance is well known and treatment failures related to macrolide resistance have occurred.
7. Children can return to School or childcare within 12 to 24 hours after starting antibiotics (see Appendix F)

Complications of:

1. Pharyngitis caused by group A *s*treptococcus (GAS) is usually a self-limited condition; symptoms in untreated patients typically last two to five days. Antimicrobial therapy reduces the duration and severity of symptoms by one to two days and prevents spread of infection (Pichichero, 2017)
2. Potential complications of GAS pharyngitis
    a. Nonsuppurative complication
        i. Acute rheumatic fever (ARF)
            1. The incidence of acute rheumatic fever (ARF) in the United States is ≤2 cases per 100,000 school-aged children (Beaudoin et al., 2015)
        ii. Acute glomerulonephritis
            1. The incidence of clinically detectable glomerulonephritis in children infected during an epidemic is about 5 to 10 percent with pharyngitis (Pichichero, 2017)
        iii. Scarlet Fever
            1. The incidence of scarlet fever is estimated to be 0.3 cases per 1000 per year (Pichcherio, 2017)
        iv. Poststreptococcal arthritis (PSRA)
        v. Streptococcal toxic shock syndrome
    b. Suppurative complications
        i. Peritonsillar abscess
            1. The incidence of pediatric retropharyngeal abscess ranged from .1 case/10,000 in 2000 to .22/10,000 (Van Brusselen et al., 2014)
        ii. Mastoiditis
        iii. Otitis Media
            1. GAS accounts for less than 5 percent of all cases of acute otitis media (Pinchero, 2017).
        iv. Sinusitis
        v. Necrotizing fasciitis
        vi. Streptococcal bacteremia
        vii. Meningitis

Guideline Preparation: This guideline was prepared by The Office of Evidence Based Practice (EBP) in collaboration with content experts at Children's Mercy Hospitals and Clinics. Development of this guideline supports the Department of Clinical Effectiveness's initiative to promote care standardization that builds a culture of quality and safety that is evidenced by measured outcomes. If a conflict of interest is identified the conflict will be disclosed next to the team members name.

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Guideline development funded by:
No external funding was obtained in the development of this guideline.

Development Process:
Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis: 2012 Updated by the Infectious Disease Society of America was identified as a mother guideline. The AGREE II tool was used to determine the quality the guidelines. A further literature search was preformed to look for any new literature that included systematic reviews, meta-analyses, and other published guidelines on the subject of our questions.

The review summary documents the following steps:

1. Review of existing internal and external guidelines and standards
   a. Internal guidelines: Judicious Use of Antibiotics for Streptococcal Pharyngitis
   b. External guidelines: Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis: 2012 Update by the Infectious Disease Society of America
2. Review preparation
   a. PICOT questions established
   b. Team leaders confirmed search terms used
3. Databases searched
   a. AHRQ National Guideline Clearinghouse
   b. Medline
   c. Cochrane
   d. CINAHL
4. Critically analyze the evidence
   a. Guidelines
      i. AGREE criteria were used to analyze published clinical guidelines
   b. Literature
      i. CASP tools were used to analyze the literature (e.g. study limitations, consistency of results, directness of evidence, precision and reporting bias)
      ii. GRADE criteria evaluated the literature based on:
      1.The balance between desirable and undesirable effects
      2.Patient values and preferences
      3.Resource utilization
      The table below defines how the quality of the evidence is rated and how the recommendation is established based on the type of evidence:

Quality	Type of Evidence
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased

	observational studies.
Moderate	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies.
Low	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence.
Very Low	Evidence for at least 1 of the critical outcomes from unsystematic clinical observations or very indirect evidence.
Recommendation	Type of Evidence
Strong	Desirable effects clearly outweigh undesirable effects or vice versa
Weak	Desirable effects closely balanced with undesirable effects

5. Recommendations for the guideline were developed by a consensus process incorporating the three principles of EBP (current literature, content experts, and patient and family preference [when possible])

Approval Process: Guidelines are reviewed and approved by external reviewer Laura Salitros, D.O., Content Expert Team, the Office of EBP, and other appropriate hospital committees as deemed suitable for the guidelines intended use. Guidelines are reviewed and updated as necessary every 5 years within the Office of EBP at CMH&C. Content expert teams will be involved with every review and update.

Disclaimer:
The content experts and the Office of EBP are aware of the controversies surrounding the management of pediatric patients with streptococcal pharyngitis. When evidence is lacking or inconclusive, options in care are provided in the guideline and the power plans that accompany the guideline.

These guidelines do not establish a standard of care to be followed in every case. It is recognized that each case is different and those individuals involved in providing health care are expected to use their judgment in determining what is in the best interests of the patient based on the circumstances existing at the time.

It is impossible to anticipate all possible situations that may exist and to prepare guidelines for each. Accordingly, these guidelines should guide care with the understanding that departures from them may be required at times.

Appendix A:
Question 1: In pediatric patients, are there any valid and reliable clinical prediction rules for of pharyngitis?

Question Originator: Strep Pharyngitis CPG Team

Plain Language Summary:

The Infectious Diseases Society of America (IDSA) guideline recommends rapid antigen detection tests (RADT) and/or cultures because clinical features alone do not reliably discriminate between GAS and viral pharyngitis except when overt viral features like rhinorrhea, cough, oral ulcers, and/or hoarseness are present (Shulman et al., 2012).

Five clinical prediction rules, or scores were reviewed: McIsaac, Breese, Wald, Attia, and Centor. The prediction rules used similar strategies of recommending "no RADT and no antibiotics" for low scores and "antibiotic with no RADT" with high scores. **None of the scores showed significant diagnostic accuracy to recommend their use** (see Tables 1-9)**.** All scores had a high rate of false positive diagnosis for GAS, which would lead to unnecessary antibiotic treatment. The scores would result in a false positive diagnosis for GAS between 6 and 29%. Clinical prediction rules are unable to identify patients at low or high risk in whom testing for GAS could be avoided.

The McIsaac score showed the best ability of ruling patients out for having GAS but would result in a large number of false positive patients (see Table 1-3). The Attia score showed the best ability of ruling patients in for having GAS, although these results were based off one study (see Table 8 & 9).

Literature Summary:

A strong recommendation is made against the use of clinical prediction rules for identifying GAS pharyngitis due to their low diagnostic accuracy. This recommendation is based on very low-quality evidence and further research could influence our confidence in the results.

Fourteen studies were identified for the clinical prediction rules review. From these 14 studies, nine prediction rules were identified, of which five of the rules proved to be validated (Cohen et al., 2015). The five clinical prediction rules, with validated studies, were reviewed. The quality of the overall evidence was very low due to serious risk of bias (Figure 1) along with the body of evidence ranging from serious to very serious for the attributes of indirectness, inconsistency, and imprecision (see Tables 1-9).

The different prediction rules recommended similar interventions based on the outcome of the applied rules: low scores recommended "no RADT and no antibiotics", medium scores "antibiotics with positive test", and high scores "antibiotic treatment with no RADT" (J. F. Cohen et al., 2015). All the studies had high risk of bias for their index tests due to the inherent bias of subjective clinical scoring (Ebell, Smith, Barry, Ives, & Carey, 2000). Only the studies validating the McIsaac score of ≥4 were pooled due to the low number of studies identified for the other prediction rules.

McIsaac Score
Seven diagnostic studies were identified for this clinical prediction rule (Ba-Saddik et al., 2014; J. F. Cohen et al., 2015; Edmonson & Farwell, 2005; Mazur, Bochyńska, Juda, & Kozioł-Montewka, 2014; McIsaac & Goel, 1998; McIsaac, Goel, To, & Low, 2000; Walker, Rimoin, Hamza, & Steinhoff, 2006). McIsaac uses the clinical predictors of: (a) temperature >38 degrees, (b) no cough, (c) tender anterior cervical adenopathy, (d) tonsillar swelling or exudate, and (e) age. Each predictor is given a score of one point. The suggested course of action for the summated scores are: 0-1, no RADT no antibiotic treatment; 2-3, antibiotics with positive test result; ≥4, no testing, antibiotics treatment.

Total Score: Three studies (n=932) reported on the total score (Table 1) (J. F. Cohen et al., 2015; McIsaac & Goel, 1998; McIsaac et al., 2000). The positive predictive value (PPV) ranged from 55-66%, the negative predictive value (NPV) ranged from 94-97%, with the sensitivity ranging from 93-97%, and the specificity ranging from 54-72%. Using the McIsaac score would result in 17.5-29 false positive results per 100 patients. False positive tests would result in unnecessary antibiotic therapy.

Score ≥4: Five studies (n=2646) evaluated diagnostic accuracy for patients with scores ≥4, see Table 2 (Ba-Saddik et al., 2014; Edmonson & Farwell, 2005; Mazur et al., 2014; McIsaac & Goel, 1998; Walker et al., 2006). If a patient had a score ≥4 the PPV was 57%. Pooled sensitivity was 0.66, 95% CI [0.41 to 0.85]. Pooled specificity was 0.70, 95% CI [0.37 to 0.91]. A patient score of ≥4 would result in 18.6 false positive results per 100 patients.

Score <2: Two studies (n=1234) evaluated the sensitivity of patients with scores <2 (J. F. Cohen et al., 2012; Edmonson & Farwell, 2005). Of the two studies only one (n=785) evaluated specificity (Table 3) (J. F. Cohen et al., 2012). The negative predictive value ranged from 82-89%. Patients with scores <2 would result in 7-14 false negative results per 100 patients. False negative tests would result in not providing antibiotic therapy to patients.

Breese Score

Four diagnostic studies were identified that analyzed this clinical prediction rule. (Breese, 1977; J. F. Cohen et al., 2012; J. F. Cohen et al., 2015; Ulukol, Günlemez, Aysev, & Cin, 1999; Walker et al., 2006). Breese uses the clinical predictors of: (a) month in which the patient is seen, (b) age, (c) leukocyte count, (d) fever, (e) sore throat, (f) cough, (g) headache, (h) abnormal pharynx, and (i) abnormal cervical nodes. The suggested course of action for the scores are <25: no RADT, no antibiotic treatment; 26-31: antibiotics with positive RADT results; ≥32: no testing, antibiotics treatment prescribed.

Breese total score: Cohen et al. (2012) (n=676) reported on the total score (see Table 4). The PPV was 74% while the NPV was 92%. The sensitivity was 0.88, 95% CI [0.84 to 0.92] and the specificity was 0.82, 94% CI [0.78 to 0.86]. Use of the Breese score would result in 11.3 false positives results per 100 patients.

Breese >30: Three studies (n=2394) reported scores greater than 30 (see Table 5) (Breese, 1977; Ulukol et al., 1999; Walker et al., 2006). When patients had a Breese score >30 the PPV was 60%. There was a large amount of inconsistency with the sensitivity ranging from 28-83%. This score would also result in 6.9-20.8 false positives results per 100 patients.

Wald Score

Three diagnostic studies were identified for this clinical prediction rule (J. F. Cohen et al., 2015; Wald, Green, Schwartz, & Barbadora, 1998; Walker et al., 2006). Wald uses the clinical predictors of: (a) age, (b) fever, (c) adenopathy, (d) pharyngitis, and (e) no upper respiratory symptoms. The suggested course of action for the scores are ≤1: no rapid antigen detection testing (RADT), no antibiotics treatment; 2-4: antibiotic with positive RADT ≥5: no testing, antibiotic treatment.

Wald total score: One study (n=676) reported on the total score (see Table 6) (J. F. Cohen et al., 2015). The PPV was 60% while the NPV was 95%. The sensitivity was 0.94, 95% CI [0.91 to 0.97] and the specificity was 0.63, 95% CI [0.58 to 0.68]. The use of the Wald score would result in 20.2-26.5 false positive results per 100 patients and 1.1-3.3 false negative results per 100 patients.

Wald ≥5: Two studies (n=775) reported scores greater than or equal to five (see Table 7) (Wald et al., 1998; Walker et al., 2006). When patients had a Wald Score ≥5 the PPV was 43-58%. There was very serious inconsistency with the sensitivity (0.52 to 0.92) and the specificity (0.28 to 0.78) from these studies. This score would result in 14-45 false positive per 100 patients.

Attia Score

Two diagnostic studies were identified for the Attia clinical prediction rule (Attia, Zaoutis, Klein, & Meier, 2001; J. F. Cohen et al., 2015). Attia uses the clinical predictors: of (a) scarlatiniform rash, (b) moderate to severe tonsillar swelling, (c) moderate to severe tenderness and enlargement of cervical lymph nodes, and (d) absence of moderate to severe coryza. The suggested course of action for the scores are: 0, no rapid antigen detection testing, no antibiotics treatment; 1-3, antibiotic with positive test result ≥4, no testing necessary, antibiotic treatment.

Attia total score: Cohen et al. (2015) (n=676) reported on the total score (see Table 8). The PPV was 81% and the NPV was 92%. The sensitivity was 0.87, 95% CI [0.83 to 0.91] and the specificity was 0.88, 95% CI [0.85 to 0.91]. The use of the Attia Score would result in 7.6 false positive results per

100 patients and 4.8 per 100 false negative patients.

Attia Score ≥4: Attia et al. (2001) (n=545) reported scores greater than or equal to four (Table 9) (Attia et al., 2001). When a patient had a score of ≥4 the PPV was 83%. These results are based on very low quality of evidence. This results in 0.6-3.8 false positive results per 100 patients.

Centor Score: Three studies were identified that applied the Centor score to children (Orda et al., 2016; Roggen, van Berlaer, Gordts, Pierard, & Hubloue, 2013; Walker et al., 2006) with suspected GAS. Centor uses the clinical predictors of: (a) temperature >38 degrees, (b) no cough, (c) tender anterior cervical adenopathy, and (d) tonsillar swelling or exudate. Each predictor is given a score of one point. The suggested course of action for the scores are: 0-1, no RADT, no antibiotic treatment; 2-3, antibiotics with positive RADT; 4: no testing, antibiotic treatment prescribed.

The three studies were not combined due to difference in reporting. Sensitivity and specificity for "total score" and "scores of 4" were not reported in the three studies. Roggen et al. (2013) preformed a retrospective cohort study from a tertiary university hospital in Brussels (N=441). They reported that a Centor score of ≥3 was ineffective in ruling in or out GAS (Negative Likelihood ratio 0.67, 95% CI [0.50 to 0.90]; Positive likelihood ratio 1.37, 95% CI [1.04 to 1.79]. Orda et al. (2016) performed a prospective diagnostic study in a remote Australian emergency department on pediatric patients aged 3-15 (N=101). The area under the receiver operating characteristic (ROC) curve was 0.70, 95% CI [0.58 to 0.81]. The study reported that Centor score was inadequate for clinical decision-making for children. Walker et al. (2006) reviewed the different clinical prediction rules with 410 children in Egypt. A Centor score of ≥3 would have resulted in 67 patients (16.3%) with a false positive diagnosis of GAS.

Search Strategy and Results: pharyngitis[tw] AND ("centor"[tw] OR "clinical prediction rule*"[tw] OR "diagnostic criteria"[tw] OR "McIsaac"[tw]) AND (child[tw] OR childr*[tw] OR childh*[tw] OR adolescen*[tw] OR pediatr*[tw] OR paeditr*[tw]) AND ("Comparative Study" [Publication Type] OR "Validation Studies as Topic"[Mesh] OR "Validation Studies" [Publication Type] OR "Evaluation Studies" [Publication Type] OR diagnosis OR valid OR validation OR score OR scale) AND pharyngitis[tw] AND ("centor"[tw] OR "clinical prediction rule*"[tw] OR "diagnostic criteria"[tw] OR "McIsaac"[tw]) AND (child[tw] OR childr*[tw] OR childh*[tw] OR adolescen*[tw] OR pediatr*[tw] OR paeditr*[tw])

Studies included in this review:
Attia et al., 2001
Ba-Saddik et al., 2014
Breese, 1977
J. F. Cohen et al., 2012
J. F. Cohen et al., 2015
Edmonson & Farwell, 2005
Mazur et al., 2014
McIsaac & Goel, 1998
McIsaac et al., 2000
Orda et al., 2016
Roggen et al., 2013
Ulukol et al., 1999
Wald et al., 1998
Walker et al., 2006

Studies <u>not</u> included in this review with rationale for exclusion:

Author	Reason for exclusion

R. Cohen et al., (2004)	No sensitivity and specificity
McIsaac, et al., (2004)	No sensitivity and specificity
Tanz et al., (2009)	Combined scores do not match question
Fine, Nizet, & Mandl., (2012)	No sensitivity and specificity
Shih, Lin, & Lu., (2012)	Low prevalence of 10%

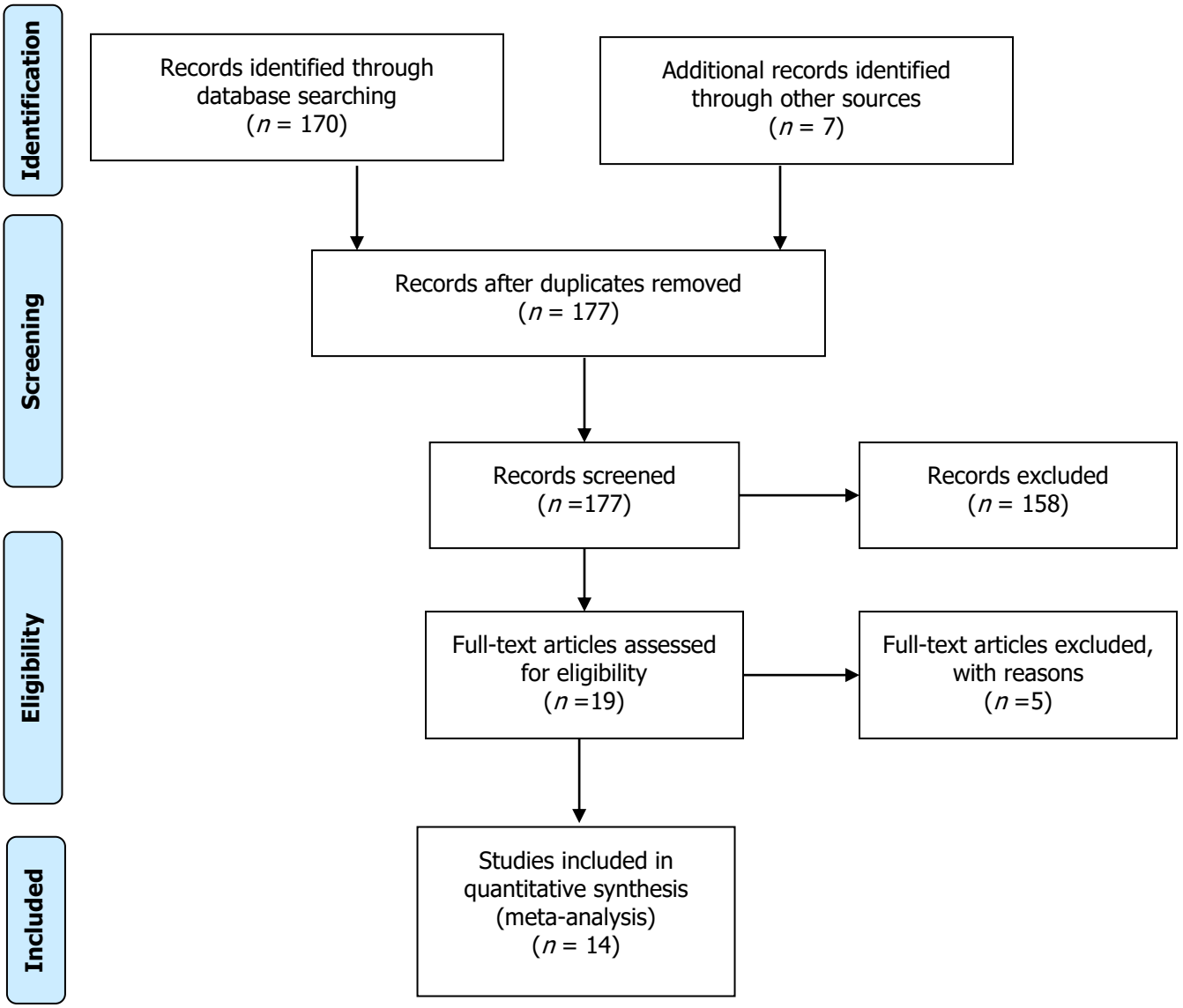
Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program, Review Manager (RevMan 5.3) was used to synthesize the 14 included studies.

Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cohcrane Collaboration, 2011.

EBP team member responsible for reviewing, synthesizing, and developing this literature:
Jarrod Dusin, MS, RD, LD, CNSC

Date Developed: July 2017

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



[b]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.

Table 1
Question: Should McIsaac be used to diagnose streptococcal pharyngitis in pediatric patients?

Sensitivity	0.93 to 0.97
Specificity	0.54 to 0.72

Prevalence	37%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1,000 patients tested	Test accuracy
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 37%	
True positives (patients with Streptococcal Pharyngitis)	3 studies 932 patients	cross-sectional (cohort type accuracy study)	serious [a]	serious [b]	not serious	not serious	none	343 to 359	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having Streptococcal Pharyngitis)								11 to 27	
True negatives (patients without Streptococcal Pharyngitis)	3 studies 932 patients	cross-sectional (cohort type accuracy study)	serious [a]	serious [b]	serious [c]	serious [d,e]	none	340 to 455	⊕◯◯◯ VERY LOW
False positives (patients incorrectly classified as having Streptococcal Pharyngitis)								175 to 290	

Explanations
a. Inherent bias of symptom scoring
b. Assessment scores could be applied differently for the intended populations (patients from different countries than intended guideline)
c. Unexplained inconsistency in sensitivity
d. Wide confidence intervals for specificity 54-72%
e. 17.5% of patients will have a false positive

Table 2

Question: Should McIsaac Score ≥4 be used to diagnose streptococcal pharyngitis in pediatric patients?

Sensitivity	0.66 (95% CI: 0.41 to 0.85)
Specificity	0.70 (95% CI: 0.37 to 0.91)

Prevalence	37%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1,000 patients tested	Test accuracy
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 37%	
True positives (patients with Streptococcal Pharyngitis)	5 studies 2646 patients	cohort & case-control type studies	serious [a,b]	serious [c,d]	serious [e]	serious [f]	none	245 (152 to 313)	⊕◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having Streptococcal Pharyngitis)								125 (57 to 218)	
True negatives (patients without Streptococcal Pharyngitis)	4 studies 2197 patients	cohort & case-control type studies	serious [a,b]	serious [c,d]	serious [g]	serious [f]	none	444 (232 to 571)	⊕◯◯◯ VERY LOW
False positives (patients incorrectly classified as having Streptococcal Pharyngitis)								186 (59 to 398)	

Explanations
a. Patient sampling could have introduced bias
b. Inherent bias of symptom scoring
c. Patient populations are from different countries
d. Assessment scores could be applied differently for the intended populations (patients from different countries than intended guideline)
e. Unexplained inconsistency in sensitivity
f. 35% of patients with a score 4 or greater will have a false positive
g. Unexplained inconsistency in specificity

Table 3
Question: Should McIsaac <2 be used to rule out streptococcal pharyngitis in pediatric patients?

Sensitivity	0.62 to 0.80
Specificity	0.96 to 0.99

Prevalence	37%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1,000 patients tested	Test accuracy
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 37%	
True positives (patients with Streptococcal Pharyngitis)	2 studies 1234 patients	cross-sectional (cohort type accuracy study)	very serious [a,b]	serious [c]	not serious	serious [d]	none	229 to 296	⊕◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having Streptococcal Pharyngitis)								74 to 141	
True negatives (patients without Streptococcal Pharyngitis)	1 studies 785 patients	cross-sectional (cohort type accuracy study)	serious [b]	serious [c]	not serious	not serious	none	605 to 624	⊕⊕◯◯ LOW
False positives (patients incorrectly classified as having Streptococcal Pharyngitis)								6 to 25	

Explanations
a. Edmonson et. al, only used rapid antigen-detection tests as reference standard
b. Inherent bias of symptom scoring
c. Assessment scores could be applied differently for the intended populations (patients from different countries than intended guideline)
d. Wide confidence intervals of 62-80%

Table 4
Question: Should Breese score be used to diagnose streptococcal pharyngitis in pediatric patients?

Sensitivity	0.88 (95% CI: 0.84 to 0.92)
Specificity	0.82 (95% CI: 0.78 to 0.86)

Prevalence	37%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1,000 patients tested	Test accuracy
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 37%	
True positives (patients with Streptococcal Pharyngitis)	1 studies 676 patients	cross-sectional (cohort type accuracy study)	serious [a]	not serious	serious [b]	not serious	none	326 (311 to 340)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having Streptococcal Pharyngitis)								44 (30 to 59)	
True negatives (patients without Streptococcal Pharyngitis)	1 studies 676 patients	cross-sectional (cohort type accuracy study)	serious [a]	not serious	serious [b]	serious [c]	none	517 (491 to 542)	⊕◯◯◯ VERY LOW
False positives (patients incorrectly classified as having Streptococcal Pharyngitis)								113 (88 to 139)	

Explanations
a. Inherent bias of symptom scoring
b. Only one study looked at Breese total score
c. 11% of patients will have a false positive

Table 5
Question: Should Breese Score >30 be used to diagnose streptococcal pharyngitis in pediatric patients?

Sensitivity	0.28 to 0.83

Prevalence	37%

Specificity	0.67 to 0.89

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1,000 patients tested	Test accuracy
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 37%	
True positives (patients with Streptococcal Pharyngitis)	3 studies 2394 patients	cohort & case-control type studies	serious [a]	serious [b,c]	very serious [d]	not serious	none	104 to 307	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having Streptococcal Pharyngitis)								63 to 266	
True negatives (patients without Streptococcal Pharyngitis)	3 studies 2394 patients	cohort & case-control type studies	serious [a]	serious [b,c]	serious [e]	not serious	none	422 to 561	⨁◯◯◯ VERY LOW
False positives (patients incorrectly classified as having Streptococcal Pharyngitis)								69 to 208	

Explanations
a. Inherent bias of symptom scoring
b. Patients populations are from different countries
c. Assessment scores could be applied differently for the intended populations (patients from different countries than intended guideline)
d. Unexplained inconsistency with sensitivity, with wide confidence interval of CI 28-83%
e. Unexplained inconsistency with specificity

Table 6
Question: Should Wald Score be used to diagnose streptococcal pharyngitis in pediatric patients?

Sensitivity	0.94 (95% CI: 0.91 to 0.97)	Prevalence	37%

Specificity	0.63 (95% CI: 0.58 to 0.68)

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1,000 patients tested	Test accuracy
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 37%	
True positives (patients with Streptococcal Pharyngitis)	1 studies 676 patients	cross-sectional (cohort type accuracy study)	serious [a]	not serious	serious [b]	not serious	none	348 (337 to 359)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having Streptococcal Pharyngitis)								22 (11 to 33)	
True negatives (patients without Streptococcal Pharyngitis)	1 studies 676 patients	cross-sectional (cohort type accuracy study)	serious [a]	not serious	serious [b]	serious [c]	none	397 (365 to 428)	⊕◯◯◯ VERY LOW
False positives (patients incorrectly classified as having Streptococcal Pharyngitis)								233 (202 to 265)	

Explanations
a. Inherent bias of symptom scoring
b. Only one study looked at Wald total score
c. 23% of patients will have a false positive result

Table 7
Question: Should Wald Score >5be used to diagnose streptococcal pharyngitis in pediatric patients?

Sensitivity	0.52 to 0.92
Specificity	0.28 to 0.78

Prevalence	37%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1,000 patients tested	Test accuracy
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 37%	
True positives (patients with Streptococcal Pharyngitis)	2 studies 775 patients	cohort & case-control type studies	serious [a]	serious [b,c]	serious [d]	not serious	none	192 to 340	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having Streptococcal Pharyngitis)								30 to 178	
True negatives (patients without Streptococcal Pharyngitis)	2 studies 775 patients	cohort & case-control type studies	serious [a]	serious [b,c]	serious [e]	serious [f]	none	176 to 491	⨁◯◯◯ VERY LOW
False positives (patients incorrectly classified as having Streptococcal Pharyngitis)								139 to 454	

Explanations
a. Inherent bias of symptom scoring
b. Patient populations are from different countries
c. Assessment scores could be applied differently for the intended populations (patients from different countries than intended guideline)
d. Unexplained inconsistency for sensitivity
e. Unexplained inconsistency with specificity
f. 14% of patients will have a false positive

Table 8
Question: Should Attia score be used to diagnose streptococcal pharyngitis in pediatric patients?

Sensitivity	0.87 (95% CI: 0.83 to 0.91)
Specificity	0.88 (95% CI: 0.85 to 0.91)

Prevalence	37%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1,000 patients tested	Test accuracy
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 37%	
True positives (patients with Streptococcal Pharyngitis)	1 studies 676 patients	cross-sectional (cohort type accuracy study)	serious [a]	not serious	serious [b]	not serious	none	322 (307 to 337)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having Streptococcal Pharyngitis)								48 (33 to 63)	
True negatives (patients without Streptococcal Pharyngitis)	1 studies 676 patients	cross-sectional (cohort type accuracy study)	serious [a]	not serious	serious [b]	not serious	none	554 (536 to 573)	⊕⊕◯◯ LOW
False positives (patients incorrectly classified as having Streptococcal Pharyngitis)								76 (57 to 94)	

Explanations
a. Inherent bias of symptom scoring
b. Only once study looked at Attia total score

Table 9

Question: Should Attia Score >4 be used to diagnose streptococcal pharyngitis in pediatric patients?

Sensitivity	0.17 (95% CI: 0.13 to 0.27)
Specificity	0.98 (95% CI: 0.94 to 0.99)

Prevalence	37%

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1,000 patients tested	Test accuracy
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 37%	
True positives (patients with Streptococcal Pharyngitis)	1 studies 545 patients	cross-sectional (cohort type accuracy study)	serious [a]	not serious	serious [b]	serious [c]	none	63 (48 to 100)	⊕◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having Streptococcal Pharyngitis)								307 (270 to 322)	
True negatives (patients without Streptococcal Pharyngitis)	1 studies 545 patients	cross-sectional (cohort type accuracy study)	serious [a]	not serious	serious [b]	not serious	none	617 (592 to 624)	⊕⊕◯◯ LOW
False positives (patients incorrectly classified as having Streptococcal Pharyngitis)								13 (6 to 38)	

Explanations

a. Inherent Bias of symptom scoring

b. Only one study looked at Attia Scores >4

c. 31% of patients would have a false negative with a score greater than 4

Figure 1: Risk of Bias

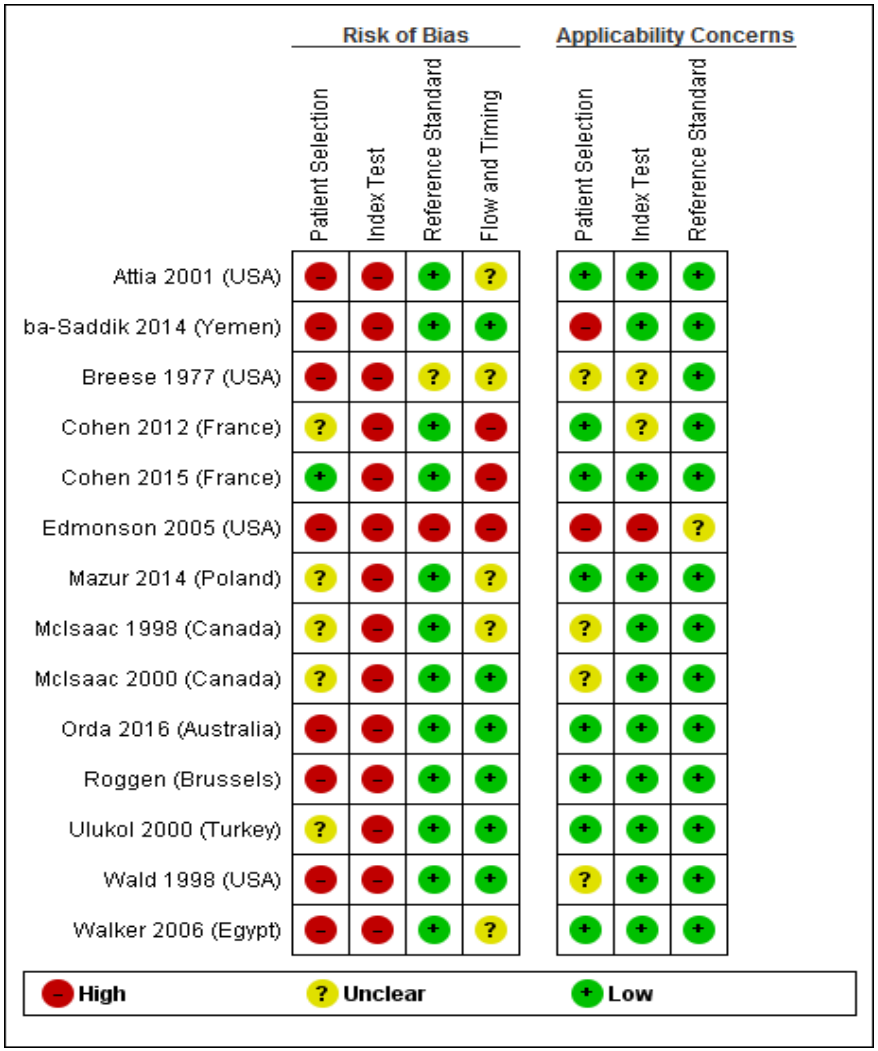


Figure 2: McIsaac Total Score

If you have questions – please contact jmichael@cmh.edu or amyers@cmh.edu

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cohen 2015 (France)	263	182	17	214	0.94 [0.90, 0.96]	0.54 [0.49, 0.59]
McIsaac 1998 (Canada)	31	19	1	39	0.97 [0.84, 1.00]	0.67 [0.54, 0.79]
McIsaac 2000 (Canada)	54	30	4	78	0.93 [0.83, 0.98]	0.72 [0.63, 0.80]

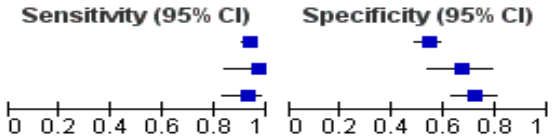


Figure 3: McIsaac ≥4

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
ba-Saddik 2014 (Yemen)	206	28	80	376	0.72 [0.66, 0.77]	0.93 [0.90, 0.95]
Edmonson 2005 (USA)	384	0	65	0	0.86 [0.82, 0.89]	Not estimable
Mazur 2014 (Poland)	37	40	8	5	0.82 [0.68, 0.92]	0.11 [0.04, 0.24]
McIsaac 1998 (Canada)	20	19	12	39	0.63 [0.44, 0.79]	0.67 [0.54, 0.79]
Walker 2006 (Egypt)	20	28	81	281	0.20 [0.13, 0.29]	0.91 [0.87, 0.94]

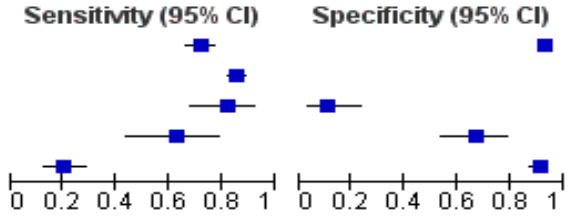


Figure 4: McIsaac ≤2

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cohen 2012 (France)	214	12	71	489	0.75 [0.70, 0.80]	0.98 [0.96, 0.99]
Edmonson 2005 (USA)	301	0	148	0	0.67 [0.62, 0.71]	Not estimable

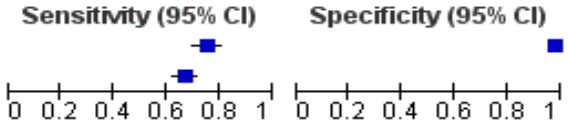


Figure 5: Breese Total Score

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cohen 2012 (France)	246	71	34	325	0.88 [0.83, 0.91]	0.82 [0.78, 0.86]

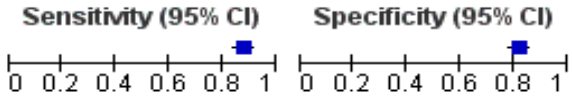


Figure 6: Breese >30

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Breese 1977 (USA)	301	86	62	221	0.83 [0.79, 0.87]	0.72 [0.67, 0.77]
Ulukol 2000 (Turkey)	121	117	38	238	0.76 [0.69, 0.82]	0.67 [0.62, 0.72]
Walker 2006 (Egypt)	28	34	73	275	0.28 [0.19, 0.38]	0.89 [0.85, 0.92]

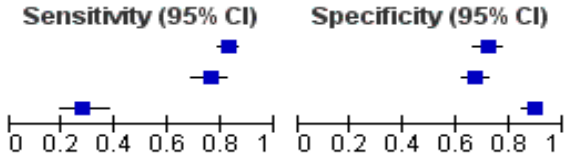


Figure 7: Wald ≥5

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Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wald 1998 (USA)	161	137	14	53	0.92 [0.87, 0.96]	0.28 [0.22, 0.35]		
Walker 2006 (Egypt)	52	68	48	241	0.52 [0.42, 0.62]	0.78 [0.73, 0.82]		

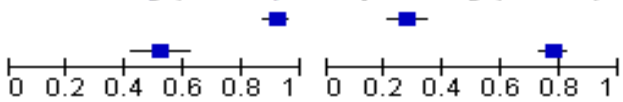


Figure 8: Attia Total Score

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Cohen 2015 (France)	212	52	32	381	0.87 [0.82, 0.91]	0.88 [0.85, 0.91]		

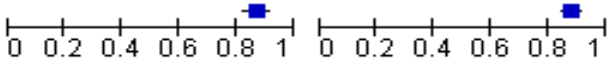
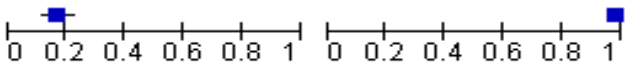


Figure 9: Attia ≥4

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Attia 2001 (USA)	36	7	174	328	0.17 [0.12, 0.23]	0.98 [0.96, 0.99]		



Attia 2001 (USA)
Patient Selection

A. Risk of Bias	
Patient Sampling	**Design:** Prospective Cohort Study **Sampling:** Authors did not disclose how participant sampling occurred **Patient selection:** 0-18 year-old with signs and symptoms of acute pharyngitis. All patients who had received antibiotics therapy within 5 days and those who were previously enrolled were excluded.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample Size:** N = 587 **Mean age in years (SD):** 6.7 years (± 3.9) **Presentation:** Signs and symptoms of acute pharyngitis **Setting:** Emergency Department, Two pediatric outpatient clinics **Exclusions**: N = 27 patients
Are there concerns that the included patients and setting do not match the review question?	Low Concern

Index Test

Index tests	Attia Score: 0-5

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk Inherent bias of symptom scoring

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	streptococcal pharyngitis

	throat culture and RADT
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
C. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Uncertain of flow and timing of reference and index tests
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Group A Streptococcus Prevalence: 37% Clinical Predictors: 1) Scarlatiniform rash 2) Moderate to serve tonsillar swelling 3) Moderate to severe tenderness and enlargement of cervical lymph nodes 4) Absence of moderate to severe coryza No Clear course of action suggested

ba-Saddik 2014 (Yemen)

Patient Selection

A. Risk of Bias	
Patient Sampling	**Design:** Prospective cross-sectional **Sampling:** Authors did not disclose how participant sampling occurred **Patient selection:** Children aged 1-16 years with symptoms of a sore throat with evidence of fever, anterior tonsillar exudates and anterior cervical adenitis. Children who used antibiotics in the 2-weeks prior were excluded.
Was a consecutive or random sample of patients enrolled?	No

Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample Size:** N = 691 **Mean age in years (SD): 11.3 years (**±3.4) **Presentation:** symptoms of a sore throat with evidence of fever, anterior tonsillar exudates and anterior cervical adenitis. **Setting:** Children attending Elementary School **Exclusions**: n = 39
Are there concerns that the included patients and setting do not match the review question?	High concern

Index Test

Index tests	McIsaac Score

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk Inherent bias of symptom scoring

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	streptococcal pharyngitis throat culture and RADT
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias

Flow and timing	Uncertain of flow and timing of reference and index tests
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Group A Streptococcus Prevalence: 41.5% McIsaac Clinical Predictors: 1) Temperature >38 2) No cough 3) Tender anterior cervical adenopathy 4) Tonsillar swelling or exudate 5) Age Course of action: 0-1: No culture or antibiotic required 2-3: culture all; treat only if result is positive ≥ 4: Culture all or treat with penicillin on clinical grounds

Breese 1977 (USA)

Patient Selection

A. Risk of Bias	
Patient Sampling	**Design:** Prospective Cohort **Sampling:** Authors did not disclose how participant sampling occurred **Patient selection:** Authors did not disclose how patients were selected
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Unclear
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample Size:** N = 670 **Mean age in years (SD):** Not reported **Presentation:** Acute respiratory illness **Setting:** Office-based
Are there concerns that the included patients and setting do not match the review question?	Unclear concern

Index Test

Index tests	Breese Score

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk Inherent bias of symptom scoring
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Streptococcal Pharyngitis Throat Culture
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Uncertain of flow and timing of reference and index tests
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Unclear
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**Unclear risk**

Notes

Notes	Group A Streptococcus Prevalence: 54.2% Breese Clinical Predictors: 1) Month patient is seen 2) Age 3) Leukocyte count 4) Fever 5, Sore throat

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	6) Cough 7) Headache 8) Abnormal pharynx 9) Abnormal cervical nodes Course of action: No clear action suggested

Cohen 2012 (France)

Patient Selection

A. Risk of Bias	
Patient Sampling	**Design**: Prospective Cohort Study **Sampling**: Secondary analysis of data from an office based study (unpublished data) **Patient selection**: 3-15 year old with a diagnosis of pharyngitis and did not receive antibiotics for 7 days before inclusion.
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample Size**: N = 785 **Mean age in years (SD)**: 6.1 (2.5) **Presentation:** Diagnosis of pharyngitis **Setting**: Office-based, multicenter **Exclusions:** n = 22
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	McIsaac Score

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk Inherent bias of symptom scoring

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	streptococcal pharyngitis throat culture and RADT
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Some throat swabs were plated >48 hours after collection. Prolonged or inadequate shipping conditions could have resulted in the loss of viability of GAS.
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	High risk

Notes

Notes	Group A Streptococcus Prevalence: 36.3% McIsaac Clinical Predictors: 1) Temperature >38 2) No cough 3) Tender anterior cervical adenopathy 4) Tonsillar swelling or exudate 5) Age Course of action 0-1: No culture or antibiotic required 2-3: culture all; treat only if result is positive ≥ 4: Culture all or treat with penicillin on clinical grounds

Cohen 2015 (France)

Patient Selection

A. Risk of Bias	
Patient Sampling	**Design**: Prospective Cohort Study **Sampling**: Consecutive sampling

	Patient selection: 3-14 year olds with a diagnosis of pharyngitis and did not receive antibiotics for 7 days before inclusion.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Low risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample Size**: N = 676 **Mean age in years (SD)**: 6.1 (2.5) **Presentation:** Diagnosis of pharyngitis **Setting**: Office-based, multicenter **Exclusions:** None reported
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Breese, McIsaac, Wald, and Attia Score

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk Inherent bias of symptom scoring

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	streptococcal pharyngitis throat culture and RADT
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

If you have questions – please contact jmichael@cmh.edu or amyers@cmh.edu

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Some throat swabs were plated >48 hours after collection. Prolonged or inadequate shipping conditions could have resulted in the loss of viability of GAS.
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	High risk

Notes

Notes	Group A Streptococcus Prevalence: 41.4% The study reviewed 8 Prediction Scores. Only four were previously validated. Breese Clinical Predictors: (a) month patient is seen, (b) age, (c) leukocyte count, (d) fever, (e) sore throat, (f) cough, (g) headache, (h) abnormal pharynx, (i) abnormal cervical nodes Wald Clinical Predictors: (a) Age, (b) Fever, (c) adenopathy, (d)Pharyngitis, (e) no upper respiratory symptoms McIsaac Clinical Predictors: (a) temperature >38, (b) no cough, (c) tender anterior cervical adenopathy, (d) tonsillar swelling or exudate, (e) age Attia Clinical Predictors: (a) scarlatiniform rash, (b) moderate to serve tonsillar swelling, (c) moderate to severe tenderness and enlargement of cervical lymph nodes, (d) absence of moderate to severe coryza

Edmonson 2005 (USA)

Patient Selection

A. Risk of Bias	
Patient Sampling	**Design**: Retrospective, cross-sectional **Sampling**: Consecutive patients **Patient selection:** <24 years of age and had a diagnostic test to detect pharyngeal GAS.
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate	Unclear

exclusions?	
Could the selection of patients have introduced bias?	High risk – retrospective chart review and included some adults.
B. Concerns regarding applicability	
Patient characteristics and setting	**Sample Size:** N = 614 **Mean age in years (SD):** Not reported for all 614 patients **Presentation:** Included patients had a diagnostic test to detect pharyngitis **Setting:** Single Pediatric Clinic **Exclusions:** 605 patients excluded or not selected for analysis
Are there concerns that the included patients and setting do not match the review question?	High concern Inherent bias of symptom scoring

Index Test

Index tests	McIssac Score

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk Inherent bias of symptom scoring
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	streptococcal pharyngitis RADT OR throat culture
Is the reference standards likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	High risk
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Not discussed by the authors
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	No
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	High risk

Notes

Notes	Group A Streptococcus Prevalence: Not reported. McIsaac Clinical Predictors: 1) Temperature >38 2) No cough 3) Tender anterior cervical adenopathy 4) Tonsillar swelling or exudate 5) Age Course of action 0-1: No culture or antibiotic required 2-3: culture all; treat only if result is positive ≥ 4: Culture all or treat with penicillin on clinical grounds

Mazur 2014 (Poland)

Patient Selection

A. Risk of Bias	
Patient Sampling	**Design:** Prospective Cohort Study **Sampling**: Author did not disclose how participant sampling occurred **Patient Selection:** 2-15 year old with signs and symptoms suggesting of GAS etiology and had not had pharyngitis for 3 months and were not treated with antibiotics for 2 weeks.
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk
B. Concerns regarding applicability	
Patient characteristics and setting	**Sample Size:** N = 90 **Mean age in years (SD)**: 6.6 (3.4) **Presentation:** symptoms suggesting of GAS etiology **Setting:** Single site outpatient clinic
Are there concerns that the included patients and setting do not match	Low concern

the review question?	

Index Test

Index tests	McIssac Score

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk Inherent bias of symptom scoring
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	streptococcal pharyngitis throat culture and RADT
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Not reported by the author
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	Group A Streptococcus Prevalence: Not reported.

	McIsaac Clinical Predictors: (a) Temperature >38 (b) No cough (c) Tender anterior cervical adenopathy (d) Tonsillar swelling or exudate (e) Age Course of action 0-1: No culture or antibiotic required 2-3: culture all; treat only if result is positive ≥ 4: Culture all or treat with penicillin on clinical grounds

McIsaac 1998 (Canada)
Patient Selection

A. Risk of Bias	
Patient Sampling	**Design**: Prospective Cohort Study **Sampling**: Authors did not report **Patient selection**: All patients >3 with a new upper respiratory tract infection (URTI)/pharyngitis and did not receive antibiotics for 7 days prior or were immunocompromised.
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample Size**: N = 90 (3-14 year olds) **Mean age in years (SD)**: reported only as a range 3-14 year olds. **Presentation:** URTI/Pharyngitis **Setting**: Office-based, single center **Exclusions:** 126 for bronchitis, otitis media, sinusitis, pneumonia, Lower respiratory tract syndrome.
Are there concerns that the included patients and setting do not match the review question?	Unclear concern

Index Test

Index tests	McIsaac Score

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of	High risk

the index test have introduced bias?	

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	streptococcal pharyngitis throat culture
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Not discussed by authors
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Unclear risk

Notes

Notes	Group A Streptococcus Prevalence: 35.5% for Children McIsaac Clinical Predictors: (a) Temperature >38 (b) No cough (c) Tender anterior cervical adenopathy (d) Tonsillar swelling or exudate (e) Age Course of action 0-1: No culture or antibiotic required 2-3: culture all; treat only if result is positive ≥ 4: Culture all or treat with penicillin on clinical grounds

McIsaac 2000 (Canada)

Patient Selection

A. Risk of Bias	
Patient Sampling	**Design**: Prospective cohort study, survey of physicians **Sampling**: Authors did not report **Patient selection**: All patients >3 with a new upper respiratory tract infection (URTI)/Pharyngitis and did not receive antibiotics for 7 days prior or were immunocompromised.
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample Size**: N = 167 (3-14 year olds) **Mean age in years (SD)**: range reported - 3-14 year olds. **Presentation:** URTI/Pharyngitis **Setting**: Multicenter outpatient **Exclusions:** n = 71 because of other conditions
Are there concerns that the included patients and setting do not match the review question?	Unclear concern

Index Test

Index tests	McIsaac Score

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk Inherent bias of symptom scoring

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Streptococcal Pharyngitis Throat Culture
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results	Unclear

interpreted without knowledge of the results of the index tests?	
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Tests done at the same time
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Group A Streptococcus Prevalence: 34.8% for Children McIsaac Clinical Predictors: (a) Temperature >38 (b) No cough (c) Tender anterior cervical adenopathy (d) Tonsillar swelling or exudate (e) Age Course of action 0-1: No culture or antibiotic required 2-3: Culture all; treat only if result is positive ≥ 4: Culture all or treat with penicillin on clinical grounds

Orda 2016 (Australia)

Patient Selection

A. Risk of Bias	
Patient Sampling	**Design**: Prospective Case-Control Study **Sampling**: Convenience sample **Patient selection**: 3-15 year olds presenting with sore throats and already taking antibiotics
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	No
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	High risk
B. Concerns regarding applicability	

Patient characteristics and setting	**Sample Size**: N = 248, n = 101 presenting with sore throat **Mean age in years**: 7.9 **Presentation:** Sore throat **Setting**: Emergency Department **Exclusions:** 2 parents refused cultures
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Centor Score

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk Inherent bias of symptom scoring
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	streptococcal pharyngitis throat culture
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Not reported by authors
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes

Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Group A Streptococcus Prevalence: 26% for Children Centor Score: (a) Absence of Cough (b) Swollen and tender cervical lymph nodes (c) Fever (e) Tonsillar exudate or swelling No clear action recommended

Roggen (Brussels)

Patient Selection

A. Risk of Bias	
Patient Sampling	**Design**: Retrospective Cohort Study **Sampling**: Chart review **Patient selection**: 2-16 years old with diagnosis codes for infectious mononucleosis, nasopharyngitis, tonsillitis, and sore throat. Excluded patients included chronic respiratory illness, cardiac, hematological or immunological diseases, and children you had received antibiotics.
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	High risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample Size**: N = 441 **Mean age in years**: 5 years **Presentation:** 2-16 years old with diagnosis codes for infectious mononucleosis, nasopharyngitis, tonsillitis, and sore throat. **Setting**: University Hospital **Exclusions:** n = 1677
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Centor Score

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear

If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk Inherent bias of symptom scoring
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Streptococcal Pharyngitis Throat Culture
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Not reported by author
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Group A Streptococcus Prevalence: 27.6% for Children Centor Score: (a) Absence of Cough (b) Swollen and tender cervical lymph nodes (c) Fever (d) Tonsillar exudate or swelling No clear action recommended

Ulukol 2000 (Turkey)

Patient Selection

A. Risk of Bias	
Patient Sampling	**Design**: Prospective Cohort **Sampling**: Not reported by authors **Patient selection**: All Children diagnosed with tonsillopharyngitis and excluded otitis media and sinusitis
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk

B. Concerns regarding applicability	
Patient characteristics and setting	**Sample Size**: *N* = 716, *n* = 514 (3 years and older) **Mean age in years (SD)**: 7.4 (1.7) **Presentation:** Tonsillopharyngitis **Setting**: Single site, Hospital Outpatient **Exclusions:** none reported
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Breese Score

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk Inherent bias of symptom scoring

B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Streptococcal Pharyngitis
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results	Unclear

interpreted without knowledge of the results of the index tests?	
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Not reported by authors
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Group A Streptococcus Prevalence: 31.3% Breese Clinical Predictors: (a) Month patient is seen (b) Age (c) Leukocyte count (d) Fever (e) Sore throat (f) Cough (g) Headache (h) Abnormal pharynx (i) Abnormal cervical nodes Course of action: Score 30 or great definitive for positive streptococcal pharyngitis

Wald 1998 (USA)

Patient Selection

A. Risk of Bias	
Patient Sampling	**Design**: Prospective Cohort **Sampling**: Not reported by author **Patient selection**: Children 2-16 years of age with sore throat and **history of fever**. Excluded if they had received antibiotics therapy within the previous 7 days.
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate	Unclear

exclusions?	
Could the selection of patients have introduced bias?	High risk
B. Concerns regarding applicability	
Patient characteristics and setting	**Sample Size**: N = 365 **Mean age in years**: 8.2 years **Presentation:** Sore throat and history of fever **Setting**: ED department or Children's Hospital walk-in clinic **Exclusions:** None reported by author
Are there concerns that the included patients and setting do not match the review question?	Unclear concern

Index Test

Index tests	Wald Score

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	No
Could the conduct or interpretation of the index test have introduced bias?	High risk Inherent bias of symptom scoring
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	streptococcal pharyngitis throat culture
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Not reported by authors
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Notes

Notes	Group A Streptococcus Prevalence: 48% Wald Clinical Predictors: (a) Age (b) Fever (c) Adenopathy (d) Pharyngitis (e) No upper respiratory symptoms No clear action recommended

Walker 2006 (Egypt)

Patient Selection

A. Risk of Bias	
Patient Sampling	**Design**: Retrospective Cohort Study **Sampling**: Patients from previous study **Patient selection**: Children with a history of sore throat and unequivocal erythema of the pharynx, exclusion included a history of rheumatic fever, antibiotic treatment within 7 days, presence of another diagnosis requiring antibiotic treatment or residence outside of Cairo.
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	High risk
B. Concerns regarding applicability	
Patient characteristics and setting	**Sample Size**: N = 410 **Mean age in years**: not reported **Presentation:** history of sore throat and unequivocal erythema of the pharynx **Setting**: Single Site, Outpatient Clinic **Exclusions:** None reported
Are there concerns that the included patients and setting do not match the review question?	Low concern

Index Test

Index tests	Breese, Centor, Wald, McIsaac Score

All tests

A. Risk of Bias	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	High risk Inherent bias of symptom scoring
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

Reference Standard

A. Risk of Bias	
Target condition and reference standard(s)	Streptococcal pharyngitis Throat culture
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

Flow and Timing

A. Risk of Bias	
Flow and timing	Not reported
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	Unclear risk

If you have questions – please contact jmichael@cmh.edu or amyers@cmh.edu

Children's Mercy

Notes

Notes	Group A Streptococcus Prevalence: 24.6% The study reviewed 7 Prediction Scores. Only four were previously validated. Breese Clinical Predictors: (a) month patient is seen, (b) age, (c) leukocyte count, (d) fever, (e) sore throat, (f) cough, (h) headache, (i) abnormal pharynx, (j) abnormal cervical nodes Wald Clinical Predictors: (a) Age, (b) Fever, (c) adenopathy, (d)Pharyngitis, (e) no upper respiratory symptoms McIsaac Clinical Predictors: (a) temperature >38, (b) no cough, (c) tender anterior cervical adenopathy, (d) tonsillar swelling or exudate, (e) age Centor Predictors: (a) Absence of Cough, (b) Swollen and tender cervical lymph nodes, (c) Fever, (d) Tonsillar exudate or swelling No clear action recommended

Appendix B
Question 2: In pediatric patients, how often do adverse side effects occur with antibiotic therapy?

Question Originator: Strep Pharyngitis CPG Team

Plain Language Summary: The purpose of this review is to discuss the potential harm-to-benefit risk of prescribing antibiotics.

Antibiotics are among the most commonly prescribed medication, but up to half the time they are administered when not needed. Antibiotics are used to treat infections, and are generally safe when used as directed. However, like taking any medication, there is risk in taking antibiotics. Few studies have looked at the potential side effects. For example, adverse drug events that occur with amoxicillin (Lexicomp®, 2017) therapy are:

- Commonly-nausea, vomiting, diarrhea, or rash
- Less commonly- abdominal pain and lack of appetite

From a study published on children who were administered penicillin, one in 14 children experienced vomiting, diarrhea, or rash.

Literature Summary: The use of antibiotics is not without side effects and clinicians should make parents aware of the harm-to-benefit ratio of taking antibiotics. For every 14 children treated with antibiotics, one child will have an adverse event such as vomiting, diarrhea, or rash.

Two systematic reviews citation and one retrospective review citation were included in this synopsis.

From a Cochrane systematic review and meta-analysis, children with acute otitis media who were treated with antibiotics had a significant increase in adverse drug events (ADE) *RR* = 34%, 95% CI [16, 55] (see Figure 1). ADEs were defined as vomiting, diarrhea, or rash in this review (Venekamp et al., 2013).

Bourgeois et al. (2009) obtained data from the National Center for Health Statistics, which collects information on patient visits to outpatient clinics and emergency departments throughout the United States. Reporting on children from zero to 18 years of age from 1995-2005 who sought treatment for an adverse drug event (ADE). Antibiotics were implicated in over a quarter of the ADEs, *RR* = 27.5%, 95% CI [21.5%, 34.5%]. Among ADEs related to antimicrobial agents, more than half were the result of a penicillin (40%) or cephalosporin (15%). The most common manifestations were dermatologic conditions (*RR* = 45.4%, 95% CI [36.9, 54.1]) and gastrointestinal symptoms (*RR* = 16.5%, 95% CI [11.1, 23.8])

Kuehn et al. (2015) completed a systematic review evaluating antibiotic associated diarrhea (ADD) in patients treated with penicillin or related antibiotics. Forty-two studies were identified. Antibiotic treatment was for acute otitis media, sinusitis, pharyngitis, and pneumonia. Thirty-three trials reported on amoxicillin/clavulanate, six on amoxicillin, and three on penicillin V (N=7729 children). Data was pooled for each type of penicillin. The overall average for antibiotic associated diarrhea (AAD) was 17.2%. Although a definition of diarrhea was not clearly defined across the studies, the AAD incidence was reported to be 19.8% for amoxicillin/clavulanate, 8.1% for amoxicillin, and 1.2% for penicillin V. A definition of diarrhea was not clearly defined across all studies.

Search Strategy and Results: Search: ("Otitis Media"[Mesh] OR "otitis media"[tw] OR "Sinusitis"[tw] OR "Streptococcus pyogenes"[Mesh] OR "Streptococcal Infections"[Mesh] OR "Streptococcal Infection*"[tw] OR "Streptococcus pyogenes"[tw] OR "group A strep"[tw] OR "group A

streptococcal”[tw] OR “group A streptococcus”[tw] OR "streptococcal pharyngitis"[All Fields] OR "GAS pharyngitis"[All Fields]) AND (Exanthema[tw] OR rash[tw] OR Nausea[tw] OR Vomiting[tw] OR Diarrhea[tw] OR "Drug Eruptions"[Mesh] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR "Adverse Drug Reaction Reporting Systems"[Mesh] OR "adverse effects"[sh] OR "adverse effect*"[tw] OR "adverse reaction*"[tw] OR "Anti-Bacterial Agents/adverse effects"[MAJR]) AND ("Amoxicillin"[tw] OR "Penicillin*"[tw]) AND (infant[tw] OR child[tw] OR childr*[tw] OR childh*[tw] OR adolescen*[tw] OR pediatr*[tw] OR paeditr*[tw]) AND ("2011/12/01"[PDat] : "2017/12/31"[PDat])

Studies included in this review:
Venekamp et al., (2013)
Bourgeois et al. (2009)
Kuehn et al. (2015)

Excluded articles and reason for exclusion:

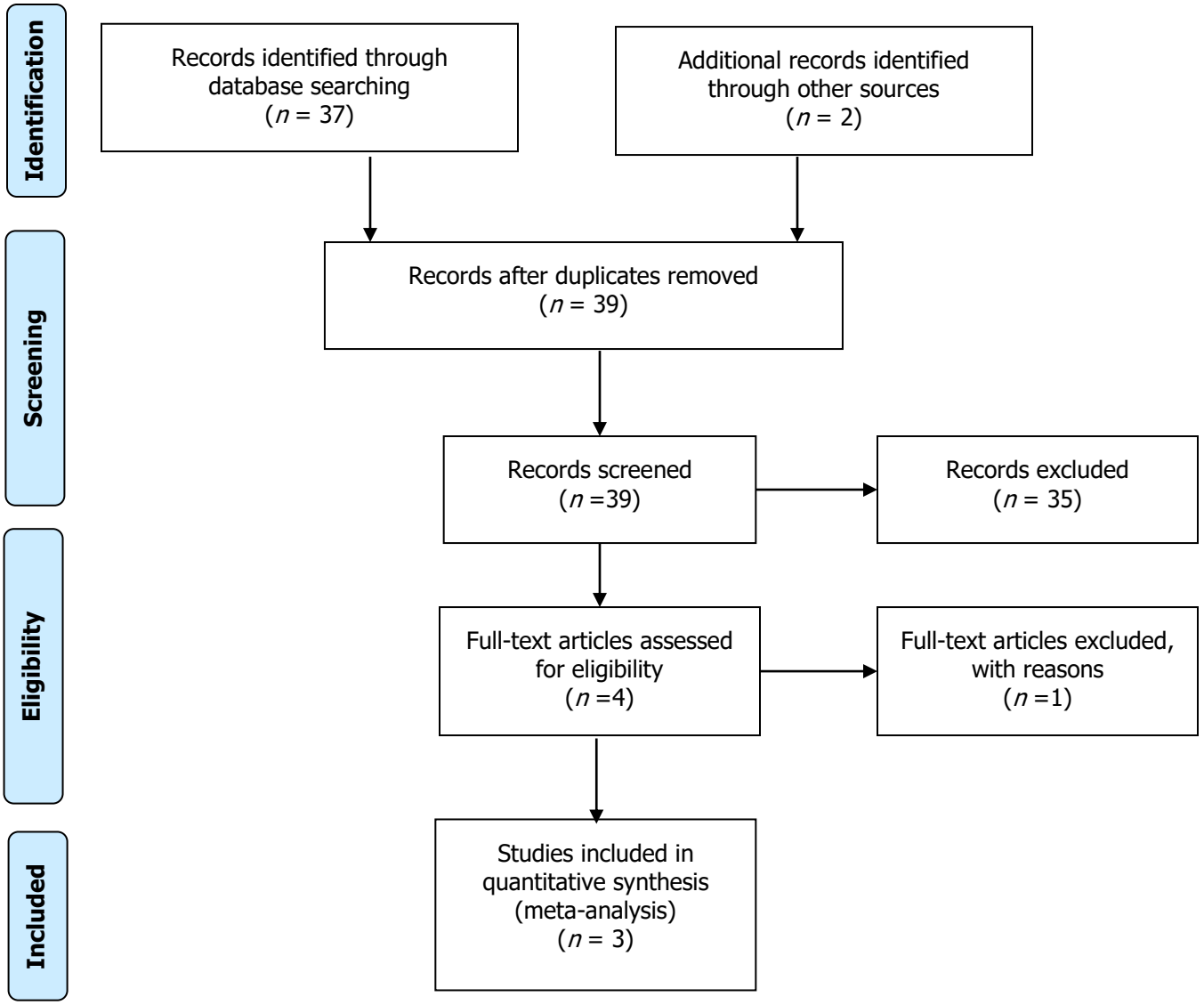
Author	Reason for exclusion
Kaya et al., (2014)	reports on allergies not side effects

Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program, Review Manager (RevMan 5.3) (Higgins & Green, 2011) was used to synthesize the three included studies.

EBP Scholar’s responsible for analyzing the literature:
Hope Scott, RN, CPEN
Kori Hess, PharmD
Jennifer Foley, RT(R)(N), CNMT
Rhonda Sullivan, MS, RD, LD
EBP team member responsible for reviewing, synthesizing, and developing this literature:
Jarrod Dusin, MS, RD, LD, CNSC

Date Developed: August 2017

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



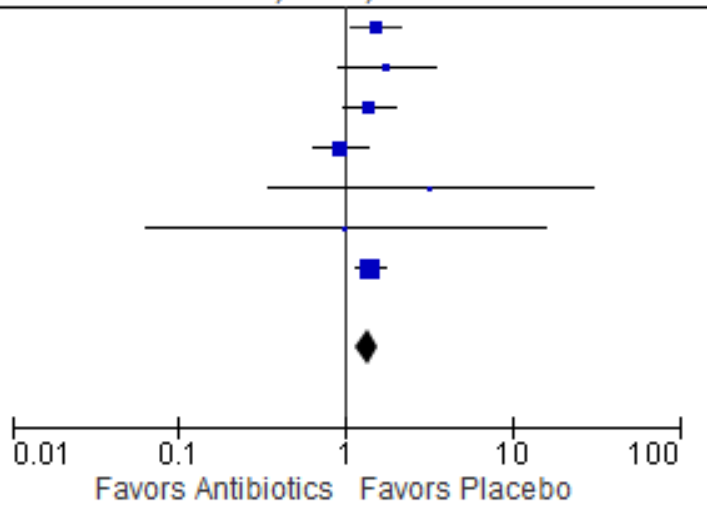
[b]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 1.
Antibiotics versus placebo, adverse events (vomiting, diarrhea, or rash)
(Venekamp et al., 2013)

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burke 1991	53	114	36	118	17.3%	1.52 [1.09, 2.13]
Damoiseax 2000	20	117	12	123	5.7%	1.75 [0.90, 3.42]
Hoberman 2011	49	144	36	147	17.4%	1.39 [0.97, 2.00]
Le Saux 2005	43	235	47	240	22.7%	0.93 [0.64, 1.36]
Mygind 1981	3	72	1	77	0.5%	3.21 [0.34, 30.14]
Tahtinen 2011	1	159	1	158	0.5%	0.99 [0.06, 15.75]
Thalin 1985	105	161	73	158	36.0%	1.41 [1.15, 1.73]
Total (95% CI)		**1002**		**1021**	**100.0%**	**1.34 [1.16, 1.55]**
Total events	274		206			

Heterogeneity: $Chi^2 = 5.68$, $df = 6$ ($P = 0.46$); $I^2 = 0\%$
Test for overall effect: $Z = 4.02$ ($P < 0.0001$)



Kuehn 2015

Methods	Summary of reported rates of diarrhea following oral penicillin therapy in pediatric clinical trials
Background	**Objective:** Determine rate of antibiotic associated diarrhea (AAD). **Secondary Objective:** determine dose and duration, diarrhea severity, age and size of study population, length of post therapy follow up, number of children who discontinued therapy as a result of AAD **Participants:** Children who received oral penicillin therapy for any indicated infection **Completed study:** *N* = 7729 **Gender:** Not reported **Age:** 0-17 years
Methods	**Inclusion criteria:** received oral penicillin therapy for any indicated infection **Exclusion criteria:** treatment related to chronic conditions, concomitant antimicrobial therapy, dose not specified Advanced search conducted in EMBASE and Medline for any article reporting on rates of AAD arising from the use of any oral penicillin to treat an indicated infection in children 0-17 years.

Results	Included Studies: 42 clinical trials from Medline and EMBASE search (33 trials reported on amoxicillin / clavulanate (amox/clav), 6 trials on amoxicillin (amox), 3 trials on penicillin)
	
	Overall rate of AAD across all trials = 17.2%
	• rate of ADD with amox/clav = 19.8%
	  ○ 4:1 formulation = 10.3-36.6%
	  ○ 7:1 formulation = 6.7-47.8%
	  ○ 8:1 formulation = 10-27%
	  ○ 14:1 formulation = 11-30%
	• rate of AAD with amox = 8.1%
	• rate of AAD with pen V = 1.2%
	
	Dose and duration:
	• amox/clav 40-90 mg/kg/day / 5.7-15 mg/kg/day for 5-14 days
	• amoxicillin 40-90 mg/kg/day for 6-10 days
	• penicillin 25-45 mg/kg/day for 10 days
	
	Severity: not consistently defined but overall 55 cases of AAD were reported as severe
	
	Duration of follow-up:
	• amox 10-28 days
	• amox/clav 4-46 days
	• penicillin 14-28 days
	
	Rate of discontinuation due to AAD (from studies specifically reporting reasons for discontinuation):
	• amox = 2 of 940
	• amox/clav = 71 of 2926
	• penicillin = 1 of 417

Discussion	**Sources of bias:** definition of diarrhea not well described across studies

Bourgeois 2009

Methods	Retrospective study on treatment of adverse drug events (ADEs)
Background	**Setting:** • Patient visits to outpatient clinics and emergency departments throughout the United States. • The data was obtained from the National Center for Health Statistics, which collects information on patient visits to outpatient clinics and emergency departments throughout the United States. • They looked at children 0 to 18 years of age seeking medical treatment for an Adverse Drug Events (ADE) between 1995 and 2005. **Number complete:** 585,922 visits **% Male:** 51.5 **Inclusion criteria:** • Visits classified as an ADE with E-code for drugs • medicinal or biological substances causing adverse effects in therapeutic use • diagnosis of anaphylactic shock due to adverse effect of correct medicinal substance properly administered • an unspecified adverse effect to correct medicinal substance properly administered • shock due to anesthesia in which the correct substance was properly administered • aspirin gastritis • drug dermatitis • drug reaction in newborn • drug psychoses • allergic uritcaria • neuropathy due to drugs • accidental poisoning by drugs • poisoning by drugs **Exclusion criteria:** • ADE resulting from administration of wrong medication, • intentional drug overdose, or • use of illicit substance, • drug dependence or abuse, • drug withdrawal, • intentional self-harm • assault by poisoning.
Results	• The medication classes most frequently implicated in an ADE were antimicrobial agents 7.5%, 95% CI [21.5%, 34.5%]. • Among ADEs related to antimicrobial agents, more than half were the result of a penicillin (40%) or cephalosporin (15%). • The most common symptom manifestations were dermatologic conditions 45.4%, 95% CI [36.9%, 54.1%] and gastrointestinal symptoms 16.5%, 95% CI [11.1%, 23.8%].

Appendix C
Question 3: In pediatric patients with group A streptococcal (GAS) pharyngitis, do oral antibiotics versus intramuscular (IM) injections result in faster clinical cure?

Question Originator: Streptococcal Pharyngitis CPG Team

Plan Language Summary: The cure rate for oral and IM penicillin are both equivocal, therefore a strong recommendation is made that antimicrobials for GAS pharyngitis may be given either orally or intramuscular.

Literature Summary: A strong recommendation is made based on strong evidence from a previously published guideline (Shulman et al., 2012). A clinical practice guideline and one randomized control trial were identified related to oral versus intramuscular injections for the treatment of GAS pharyngitis (Eslami et al., 2014; Shulman et al., 2012).

The Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Diagnosis and Management of GAS Pharyngitis, recommends antibiotics be given either orally or intramuscular (Shulman et al., 2012). IDSA also recommended intramuscular benzathine penicillin G (BPG) therapy is preferred for patients deemed unlikely to complete a full 10-day course of oral therapy. The guideline gave a strong recommendation and rated the evidence as strong. An evidence table was not provided for this topic in the guideline.

A randomized control trial by Eslami et al. (2014) compared efficacy of once daily oral amoxicillin versus BPG in relieving various clinical manifestations and the bacteriologic response to pharyngitis in 99 pediatric patients. In the amoxicillin group, 18.9% failed to respond to treatment compared to 6.4% in the BPG group but the difference was not statistically significant (p=.10). Benzathine penicillin G was more effective at reducing cough (p= .01), abdominal pain (p= .01), and reducing exudate (p= .01). There was no significant difference in reducing erythema (p> .05), reducing severity of cervical lymph node tenderness and enlargement (p> .05), and reducing sore throat (p> .05).

Search Strategy and Results: The IDSA parent guideline was identified for this question (Shulman et al., 2012). A literature search was conducted from December 2011-December 2017 to identify any current studies answering the clinical question.

(Pharyngitis[tw] OR Pharyngotonsillitis[tw]) AND (penicillin[tw] OR amoxicillin[tw] OR "drug therapy"[sh] OR "anti-bacterial agent"[tw] OR therapy[tw] OR treatment[tw] OR antibiotic[tw] OR antibiotics[tw]) AND ("Streptococcal Infection*"[tw] OR "Streptococcus pyogenes"[tw] OR ("group A" AND streptoc*)) AND (infant[tw] OR child[tw] OR childr*[tw] OR childh*[tw] OR adolescen*[tw] OR pediatr*[tw] OR paeditr*[tw]) AND ("2011/12/01"[PDat] : "2017/12/31"[PDat])

Studies included in this review:
Shulman et al., (2012)
Eslami et al., (2014)

Studies <u>not</u> included in this review with exclusion rationale:

Author (Year)	Reason for exclusion
Altamimi et al., (2012)	Only oral medications reviewed
Armengol et al., (2012)	Only oral medications studied.

van Driel et al., (2016)	Intramuscular injections not reviewed
Gidengil et al., (2013)	Study did not compare Intramuscular injections versus oral
Kuroki et al., (2013)	Only oral medications studied
Sarrell et al., (2012)	Study did not compare Intramuscular injections versus oral

Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program, Review Manager (Higgins & Green, 2011)[a] was used to synthesize the one included study.

[a]Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cohcrane Collaboration, 2011.

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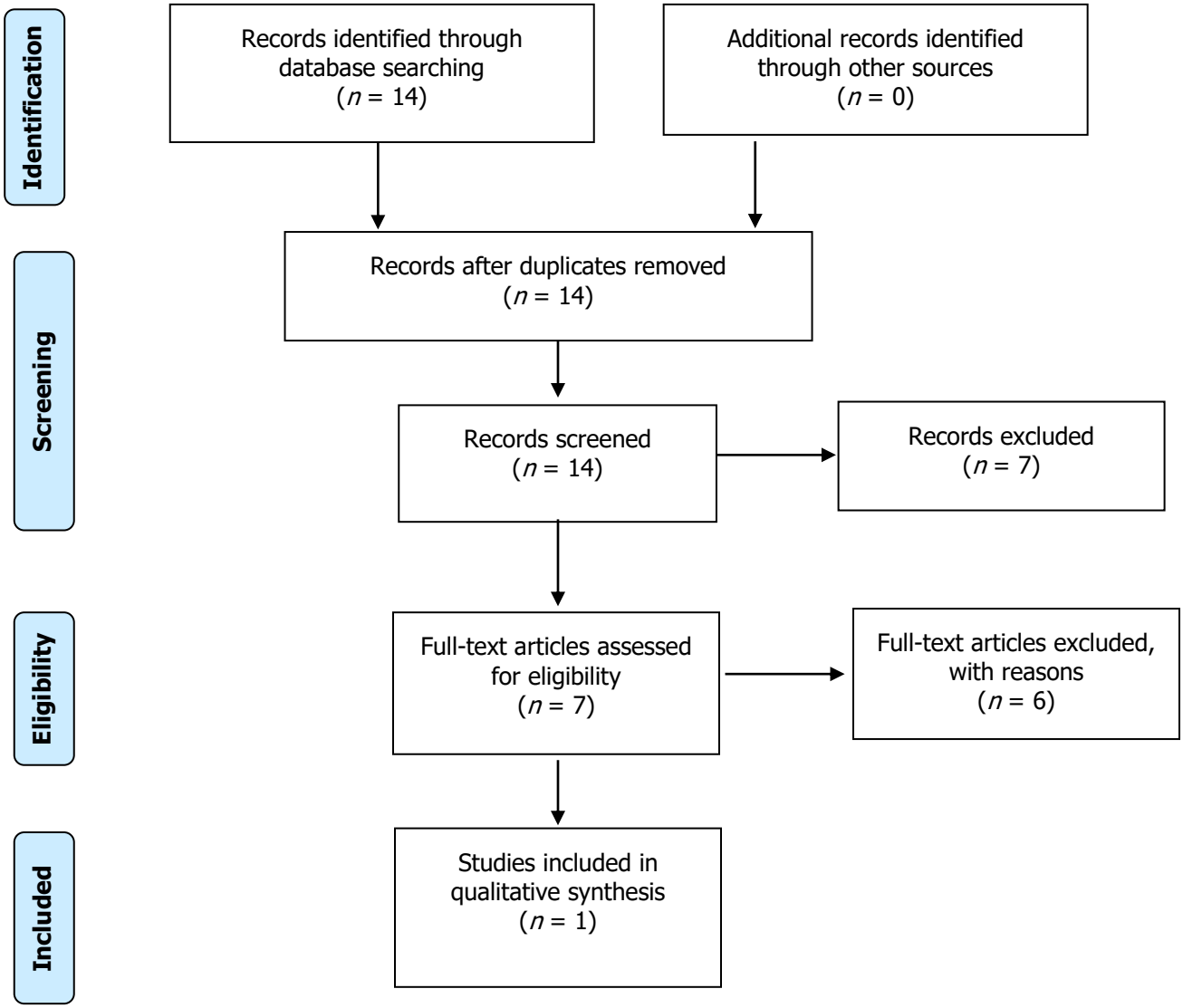
Date Developed: August 2017

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



[b]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.

Elsami 2014

Methods	RTC
Participants	**Setting:** Academic hospital in North-East Iran, Mashhad **Randomized into study: (only positive throat cultures)** :*N*=99 **Group 1:** 750mg orally once-daily amoxicillin (amoxicillin) for 10 days *n*=68 **Group 2:** Single IM injection of benzathine penicillin G (BPG) *n*=31 Five hundred and seventy one children with pharyngitis met the enrollment criteria Four hundred and seventy two had negative throat culture Ninety nine had positive throat cultures **Gender, males:** *n*=51 **Age, years:** **Group 1:** mean 8.4 +/- 1.6 **Group 2:** mean 9.1 +/- 1.5 **Inclusion criteria:** • Children 6-15 years presented with pharyngitis (sore throat, erythema, exudate, tender or enlarged anterior cervical lymph nodes) before the initiation of drug therapy • GAS positive throat culture **Exclusion criteria:** • Reporting of one or more of the following: ○ Oral antibiotic use within preceding week ○ Intramuscularly administered antibiotics within 28 days prior to visit ○ No signs of pharyngitis ○ Negative throat culture for GAS ○ History of allergy to the drugs **Power analysis:** • at least 97 children with GAS positive for *p*-value <0.05, CL 95% and permissible error 1%
Interventions	Both Groups: • Evaluated for inclusion criteria • Randomized into groups • Given treatment • Sent home from school after beginning treatment **Group 1:** 750 mg orally once-daily amoxicillin for 10 days **Group 2:** single shot of BPG 600,000 IU for children ≥ 27 kg and 200.000 IU for children less than 27 kg
Outcomes	**Primary:** Compare efficacy of once-daily oral amoxicillin and BPG in relieving various clinical manifestations and their bacteriologic response to pharyngitis.
Results	▪ In the amoxicillin group, 18.9% failed to respond to treatment compared to 6.4% in the penicillin group. ▪ BCG was more effective at reducing cough and abdominal pain (*p*=.01) ▪ BCG was more effective in reducing exudate (*p*=.01) ▪ No significant difference in reducing erythema was found between the two drugs (*p*> .05) ▪ No significant difference in reducing severity of cervical lymph nodes, tenderness, and enlargement was found between the two drugs (*p*> .05) ▪ No significant difference in reducing sore throat was found between the two drugs (*p*> .05). **Sore throat** **Group 1:** Before: *n*=52, After: *n*=4 **Group 2:** Before: *n*=29, After: *n*=3

	Erythema **Group 1:** Before: *n*=51, After: *n*=31 **Group 2:** Before: *n*=30, After: *n*=12 **Exudate** **Group 1:** Before: *n*=39, After: *n*=18 **Group 2:** Before: *n*=24, After: *n*=0 **Lymph nodes** **Group 1:** Before: *n*=46, After: *n*=13 **Group 2:** Before: *n*=22, After: *n*=15 **Failed to respond** **Group 1:** failed to respond 18.9% **Group 2:** failed to respond 6.4%

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear Risk	States random allocation, but not discussed how it was done.
Allocation concealment (selection bias)	Unclear Risk	Not discussed
Blinding of participants and personnel (performance bias)	High Risk	Physician not blinded, does not discuss if subject blinded
Blinding of outcome assessment (detection bias)	High Risk	Physician not blinded and he assessed symptom outcomes in both groups
Incomplete outcome data (attrition bias)	High Risk	Did not report drop-out
Selective reporting (reporting bias)	Unclear Risk	Clinical manifestations were not clearly defined, not sure if any were not reported. Also, reported on socio economic status but it was not described objectively.
Other bias	Unclear Risk	

Appendix D
Question 4: In pediatric patients with streptococcal pharyngitis, is amoxicillin versus other antibiotics more efficacious for clinical cure?

Question Originator: Streptococcal Pharyngitis GPG Team

Plain Language Summary: Group A streptococcus (GAS), is the most common cause of bacterial pharyngitis, or sore throat, in children and adolescents. While most sore throats are caused by viruses, for some individuals bacteria is the source of the throat infection. When GAS is the cause of a sore throat, penicillin or amoxicillin are the treatments of choice (Shulman et al., 2012)

Literature Summary: Amoxicillin is as efficacious as other antibiotics, therefore a strong recommendation is made that amoxicillin or penicillin be used for group A streptococcus A (GAS) pharyngitis. This recommendation is made based on very low quality evidence.

In the clinical practice guideline by the Infectious Diseases Society of America (Shulman et al., 2012), penicillin and amoxicillin are the recommended treatments for GAS.

Outcome: Clinical cure rate 2 to 13 days follow-up
Six trials (*N* = 1165) report on clinical cure rate, measured between 2 to 13 days post the start of treatment of amoxicillin versus other antibiotics (Cohen et al., 1996; Eslami et al., 2014; Feder, Gerber, Randolph, Stelmach, & Kaplan, 1999; Kuroki et al., 2013; Lennon, Farrell, Martin, & Stewart, 2008; Shvartzman, Tabenkin, Rosentzwaig, & Dolginov, 1993) (see Table 1).

- One study compared amoxicillin versus clavulanate/amoxicillin (*n* = 119) (Kuroki et al., 2013),
- Three studies compared amoxicillin versus penicillin V (*n* = 790) (Cohen et al., 1996; Feder et al., 1999; Lennon et al., 2008),
- One study compared amoxicillin versus phenoxymethylpenicillin (*n* = 157) (Shvartzman et al., 1993), and
- One study compared amoxicillin verses benzathine penicillin G (*n* = 99) (Eslami et al., 2014).

The analysis of the studies showed no difference between treatments, *RR* 1.02, 95% CI [.96 to 1.02], (see Figure 1). A sub-group analysis of amoxicillin versus clavulanate/amoxicillin showed a higher cure rate for amoxicillin at follow-up, *RR* = 1.24, 95% CI [1.04 to 1.48]. A sub-group analysis between the three other antibiotics showed no difference between treatments: (a) amoxicillin versus benzathine penicillin G, *RR* = 0.86, 95% CI [.75 to 1.00]; (b) amoxicillin versus penicillin V, *RR* = 1.01, 95% CI [.96 to 1.06]; (c) amoxicillin versus phenoxymethylpenicillin, *RR* = 1.04, 95% CI [.96 to 1.12]. The studies were very low quality evidence due to the serious risk of bias and very serious inconsistency. Only one study (Lennon et al., 2008) did not have some form of serious bias. There was substantial heterogeneity as evidenced by an I^2 of 53%. The heterogeneity was likely due to different control antibiotics and clinical cure follow-up times.

Outcome: Clinical cure rate 14 to 36 days follow-up
Four trials (*N* = 1300) reported on clinical cure rate for amoxicillin versus other antibiotics (14 to 36 days post start of treatment) (Feder et al., 1999; Lennon et al., 2008; Shvartzman et al., 1993; NCT00643149) (see Table 1).

- Two studies compared amoxicillin versus penicillin V (*n* = 470) (Feder et al., 1999; Lennon et al., 2008),
- One study compared amoxicillin versus phenoxymethylpenicillin (*n* = 157) (Shvartzman et al., 1993), and
- One study compared amoxicillin verses azithromycin (*n* = 673) (NCT00643148).

The analysis of the studies showed no difference between treatments, *RR* = 1.03, 95% CI [.96 to 1.1] (see Figure 2). A sub-group analysis (see Figure 2) between the other antibiotics showed no difference between treatments, amoxicillin versus azithromycin G, *RR* =1.21, 95% CI [.97 to 1.51]; amoxicillin versus penicillin V, *RR* = .99, 95% CI [.93 to 1.04]; amoxicillin versus phenoxymethylpenicillin *RR* = 1.06, 95% CI [1.00 to 1.13]. The studies were very low quality evidence based on the serious risk of bias within the studies and a very serious inconsistency between studies. There was substantial heterogeneity as evidenced by an I^2 of 60%. The heterogeneity was likely due to different control antibiotics and clinical cure? follow-up times.

Outcome: Adverse events
Three trials (*n* = 1077) reported on adverse events for amoxicillin versus other antibiotics (Cohen et al., 1996; Kuroki et al., 2013; NCT00643148) (see Table 1).

- One study compared amoxicillin versus clavulanate/amoxicillin (*n* = 86) (Kuroki et al., 2013),
- One study compared amoxicillin versus penicillin V (*n* = 318) (Cohen et al., 1996), and
- One study compared amoxicillin versus azithromycin (*n* = 318) (NCT00643148).

The analysis of the studies showed less adverse events with amoxicillin when compared to other antibiotics, *OR* = .35, 95% CI [.23 to .52] (see Figure 3). A sub-group analysis showed no difference in adverse events was found between amoxicillin versus penicillin V, *OR* = .48, 95% CI [.14 to 1.63]. A sub-group analysis of amoxicillin versus clavulanate/amoxicillin showed lower adverse events with amoxicillin *OR* = .17, 95% CI [.06 to .50]. Also, amoxicillin versus azithromycin showed lower adverse events with amoxicillin, *OR* = 0.37, 95% CI [.25 to .56]). The studies were very low quality evidence due to the serious risk of bias, inconsistency, and imprecision. The inconsistency was due to the studies measuring adverse events differently and imprecision was based on the low number of events.

Search Strategy and Results: (Pharyngitis[tw] OR Pharyngotonsillitis[tw]) AND (penicillin[tw] OR amoxicillin[tw] OR "drug therapy"[sh] OR "anti-bacterial agent"[tw] OR therapy[tw] OR treatment[tw] OR antibiotic[tw] OR antibiotics[tw]) AND ("Streptococcal Infection*"[tw] OR "Streptococcus pyogenes"[tw] OR ("group A" AND streptoc*)) AND (infant[tw] OR child[tw] OR childr*[tw] OR childh*[tw] OR adolescen*[tw] OR pediatr*[tw] OR paeditr*[tw]) AND ("2011/12/01"[PDat] : "2017/12/31"[PDat])

Studies included in this review:

Cohen et al., (1996)
Eslami et al., (2014)
Feder et al., (1999)
Kuroki et al., (2013)
Lennon et al., (2008)
NCT00643148, (2004)
Shvartzman et al., (1993)

Studies <u>not</u> included in this review with exclusion rationale:

Author (Year)	Reason for exclusion
Swaminathanom et al., (2014)	Amoxicillin not included (cohort)
Schwartz, et al., (2015)	Different outcomes (cohort)
Gidengil, et al., (2013)	Amoxicillin alone (cohort)
Sarrell, et al., (2012)	Amoxicillin alone (cohort)
Armengol et al. (2012)	Amoxicillin alone (cohort)

Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program, Review Manager (Higgins & Green, 2011)[a] was used to synthesize the seven included studies. <u>GRADEpro GDT (Guideline Development Tool)</u> is the tool used to create the Summary of Findings Tables for this analysis.

[a]Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cohcrane Collaboration, 2011.

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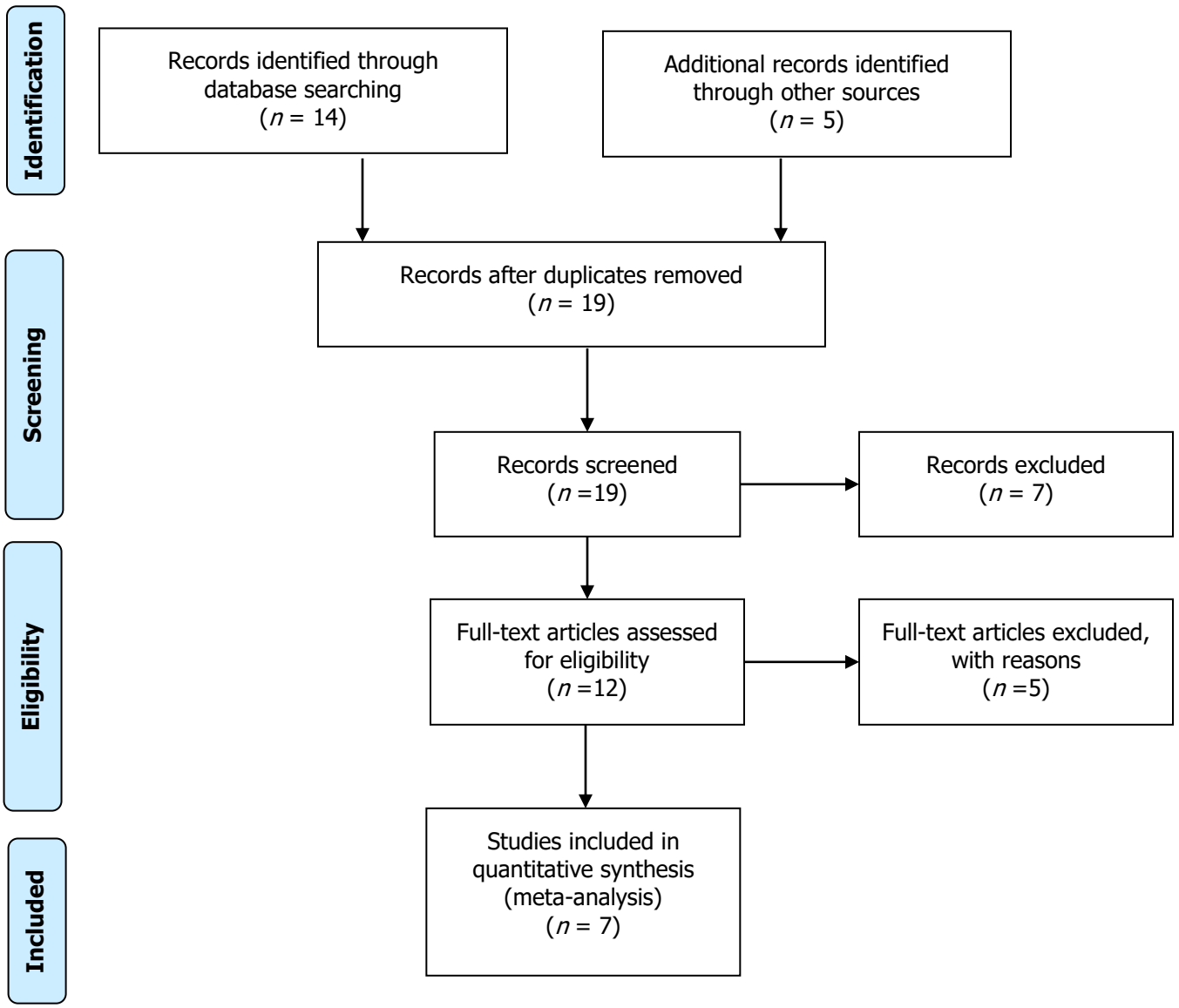
Date Developed/Updated: November 2017

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



[b]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

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Table 1
Summary of Findings

Amoxicillin compared to other antibiotics for pediatric patients with streptococcal pharyngitis											
Certainty assessment							**Summary of findings**				
№ of 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 other antibiotics	**With Amoxicillin**		**Risk with other antibiotics**	**Risk difference with Amoxicillin**
Clinical Cure (follow up: range 2 days to 13 days)											
1165 (6 RCTs)	serious [a]	very serious [b]	not serious	not serious	none	⊕◯◯◯ VERY LOW	480/572 (83.9%)	572/593 (96.5%)	**RR 1.02** (0.96 to 1.02)	839 per 1,000	**17 more per 1,000** (34 fewer to 17 more)
Clinical Cure (follow up: range 14 days to 36 days)											
1300 (4 RCTs)	serious [a]	very serious [c]	not serious	not serious	none	⊕◯◯◯ VERY LOW	382/651 (58.7%)	402/649 (61.9%)	**RR 1.03** (0.93 to 1.10)	587 per 1,000	**18 more per 1,000** (41 fewer to 59 more)
Adverse Events											
1077 (3 RCTs)	serious [d]	serious [f]	not serious	serious [e]	none	⊕◯◯◯ VERY LOW	123/542 (22.7%)	51/535 (9.5%)	**OR 0.35** (0.23 to 0.52)	227 per 1,000	**134 fewer per 1,000** (164 fewer to 95 fewer)

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

Explanations

a. Only one study did not have some form of serious bias.
b. Substantial heterogeneity as evidence by an I^2 of 53%. This is likely due to different control antibiotics and different follow-up times.
c. Substantial heterogeneity as evidence by an 1^2 of 60%. This is likely due to different control antibiotics and different follow-up times.
d. All three studies had high risk of bias and/or unclear risk.
e. Low number of events
f. Adverse events measured differently

Figure 1
Comparison: amoxicillin versus other antibiotics, Outcome: clinical cure at 2 to 13 days

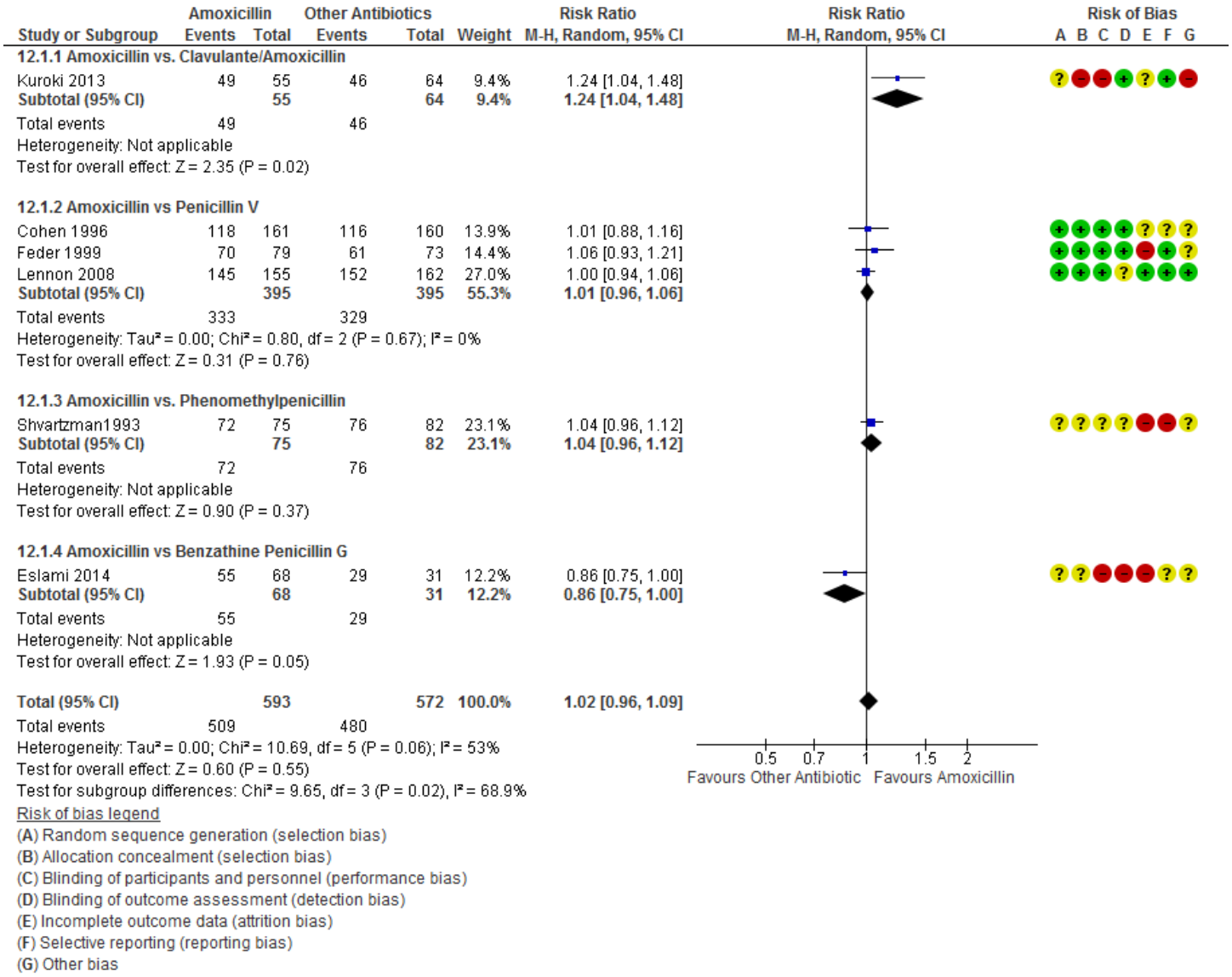


Figure 2
Comparison: amoxicillin versus other antibiotics, Outcome: clinical cure 14 to 36 days

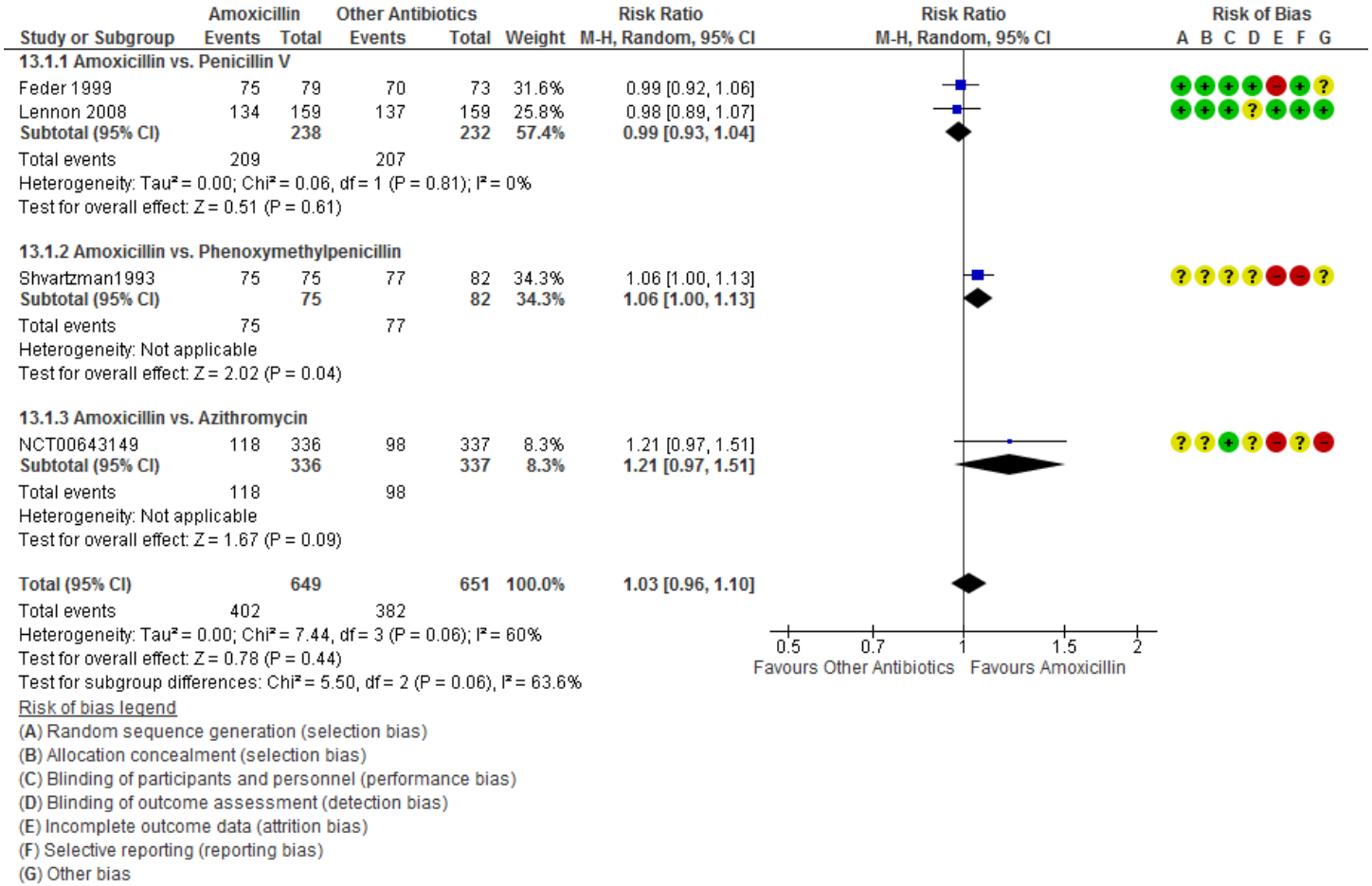


Figure 3
Comparison: amoxicillin versus other antibiotics, Outcome: adverse events

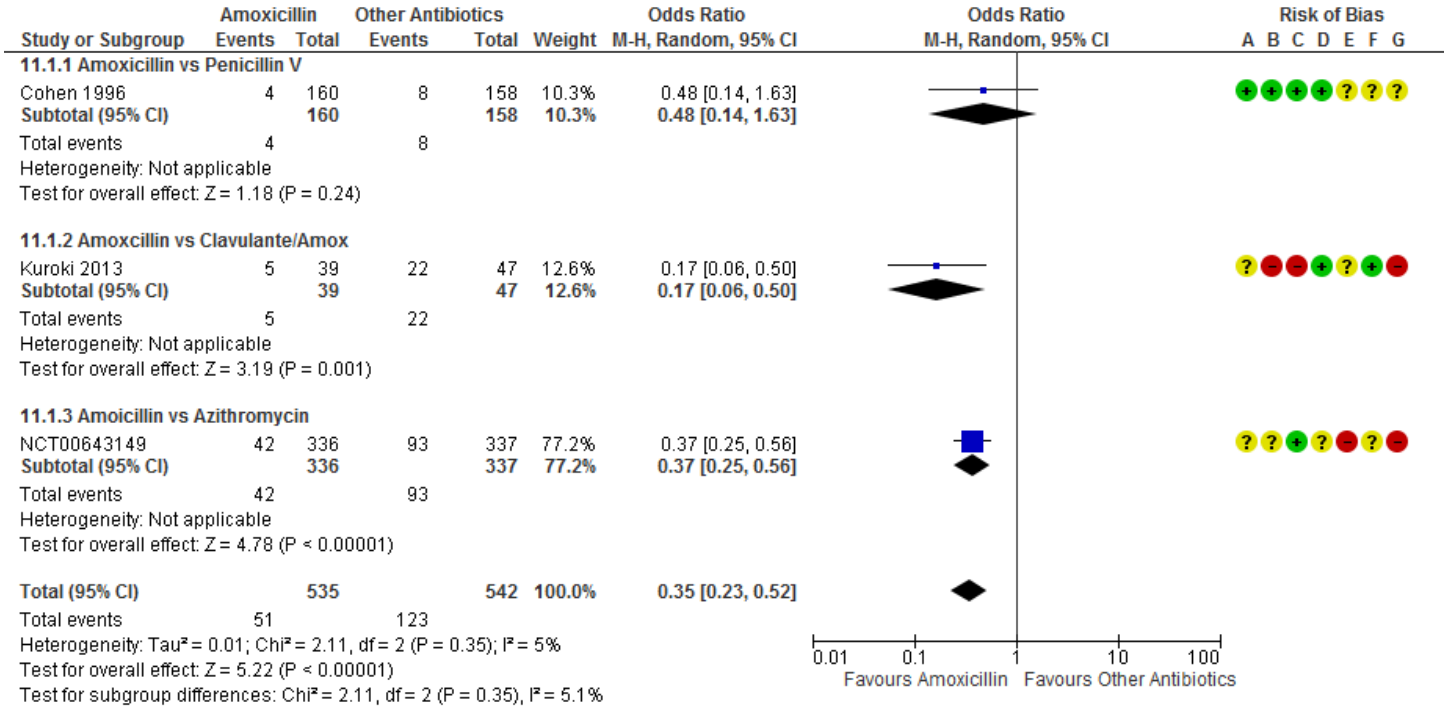
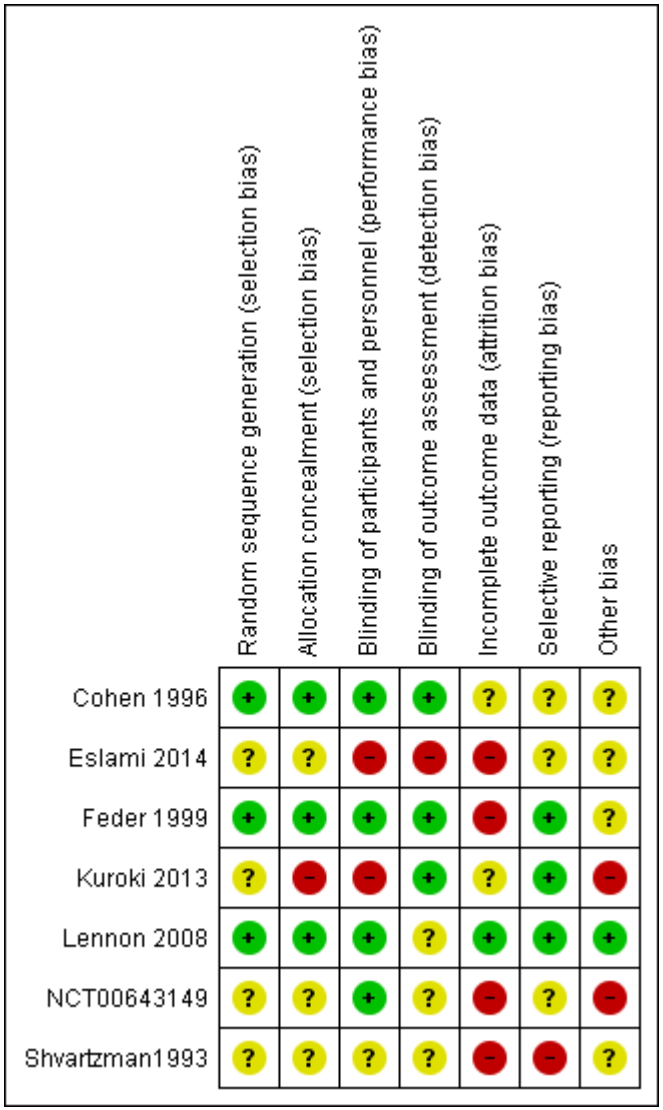


Figure 4
Risk of bias table



Cohen 1996

Methods	Randomized control trial
Participants	**Setting:** Pediatric Physician offices in France between September 1993 and February 1995. **Randomized into study:** *N* = 321 • Group 1 (Amoxicillin): *n* = 161 • Group 2 (Penicillin): *n* =160 **Completed Study (tolerability):** *N* = 318 • Group 1 (Amoxicillin): *n* = 160 • Group 2 (Penicillin): *n* = 158 **Completed Study (efficacy day 4):** *N* = 277 • Group 1 (Amoxicillin): *n* = 141 • Group 2 (Penicillin): *n* = 136 **Completed Study (efficacy day 30):** *N* = 216 • Group 1 (Amoxicillin): *n* = 111 • Group 2 (Penicillin): *n* = 105 **Gender, males:** • Group 1 (Amoxicillin): *n* = 83 (51.9%) • Group 2 (Penicillin): *n* = 70 (44.3%) **Age, years (mean):** • Group 1 (Amoxicillin): 5.9 (SD = 2.1) • Group 2 (Penicillin): 5.9 (SD = 2.3) **Inclusion Criteria:** • Children of both sexes and 3 to 15 years old who had signs of tonsillopharyngitis (tonsillopharyngeal erythema and/or exudate, with sore throat or dysphagia, or fever >=38°C) • A positive result in a rapid test for streptococcal antigen (Testpack Strept®; Abbott Diagnostics, Rungis, France) • A throat culture positive for group A streptococcus **Exclusion Criteria:** • Antibiotic treatment within 7 days before enrollment • History of hypersensitivity to beta-lactams • Severe underlying disease • Previous inclusion in the study **Power Analysis:** The authors did not disclose power analysis
Interventions	• **Group 1:** oral amoxicillin (AMX) suspension, 50 mg/kg/day divided twice daily for 6 days • **Group 2:** oral phenoxymethyl penicillin suspension (PEN V), 45 mg/kg/day divided into three doses/day (75,000 IU/kg/day) for 10 days. • The only other authorized treatment was with antipyretic agents (paracetamol or aspirin). If signs and symptoms persisted or adverse events occurred, an additional visit was scheduled 3 to 5 days after the beginning of treatment. A daily diary card was used by the parents to record temperature, gastrointestinal disorders, compliance with treatment and concomitant

	medications.
Outcomes	**Primary outcome(s):** • Eradication of pretreatment GAS on throat cultures obtained 4 days after the completion of treatment **Secondary outcome(s)** • Efficacy and safety, 30-Day follow up
Notes	Limited information was reported for the outcomes at the 30-Day follow-up

Risk of bias table

Bias	Scholars' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralized telephonic computer program
Allocation concealment (selection bias)	Low risk	Centralized telephonic computer program
Blinding of participants and personnel (performance bias)	Low risk	No blinding mentioned, blinding unlikely to affect the outcome.
Blinding of outcome assessment (detection bias)	Low risk	Microbiologic studies and molecular typing were carried out by personnel unaware of the treatment arm.
Incomplete outcome data (attrition bias)	Unclear risk	Per protocol analysis and no power analysis.
Selective reporting (reporting bias)	Unclear risk	The data from the 30-day visit was limited
Other bias	Unclear risk	The study was supported by a grant from a pharmaceutical company

Eslami 2014

Methods	Randomized control trial
Participants	**Setting:** Education organization in North-East of Iran, Mashhad **Randomized into study:** *N* = 571 Group1: Positive throat culture *n* = 99 Group 2: Negative throat culture *n* = 472 **Completed Study Group 1 (only positive throat cultures)**: *N* = 98 Group 1A: 750mg orally once-daily amoxicillin (amox) for 10 days *n* = 68 Group 2A: Single shot of benzathine penicillin G (BPG) 600.000 IU and 200.000 IU for children less than 27kg *n* = 31 **Gender, males:** 225 Group 1: 51 Group 2: 174 **Age, years: (Mean ± SD)** Group 1: 8.4 + - 1.6 Group 2: 9.1 + - 1.5 **Inclusion criteria:** • Children 6-15 years presented with pharyngitis (sore throat, erythema, exudate, tender or enlarged anterior cervical lymph nodes) before the initiation of drug therapy

	• GAS positive throat culture
	Exclusion criteria:
	• Reports of one or more of the following:
	  ○ Oral antibiotic use within preceding week
	  ○ Intramuscularly administered antibiotics within 28 days prior to visit
	  ○ No signs of pharyngitis
	  ○ Negative throat culture for GAS
	  ○ History of allergy to the drugs
	
	Power analysis:
	• At least 97 children with GAS positive for *p*-value <.05, CL 95% and permissible error 1%

Interventions	Both Groups: • Evaluated for inclusion criteria • Randomized into groups • Given treatment • Sent home from school after beginning treatment Group 1A: 750 mg orally once-daily amoxicillin (amox) for 10 days Group 2A: single shot of benzathine penicillin G (BPG) 600.000 International Units and 200.000 International Units for children less than 27 kg
Outcomes	**Primary:** Compare the efficacy of once-daily orally amoxicillin and BPG in relieving various clinical manifestations and their bacteriologic response to pharyngitis

Notes	**Group 1A:**
	• Sore throat
	  ○ before: 52% (64.2)
	  ○ after: 4% (57.1)
	• Erythema
	  ○ before: 51 % (63)
	  ○ after: 31% (72)
	• Exudate
	  ○ before: 39% (61.9)
	  ○ After: 18% (100)
	• Lymph nodes
	  ○ before: 46% (67.6)
	  ○ after: 13% (46.4)
	• Failed to respond 18.9%
	
	Group 2A:
	• Sore throat
	  ○ before: 29% (35.8)
	  ○ after: 34% (42.9)
	• Erythema
	  ○ before: 30% (37.5)
	  ○ after: 12% (27.9)
	• Exudate
	  ○ before: 24% (38.1)
	  ○ After: 0 (zero)
	• Lymph nodes
	  ○ before: 22% (32.4)
	  ○ after: 15% (53.6)
	• Failed to respond 6.4%

Risk of bias table

Bias	Scholars' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not discussed
Allocation concealment (selection bias)	Unclear risk	States random allocation, but not discussed
Blinding of participants and personnel (performance bias)	High risk	Physician not blinded, does not discuss if subject blinded
Blinding of outcome assessment (detection bias)	High risk	Physician not blinded and he assessed symptom outcomes in both groups
Incomplete outcome data (attrition bias)	High risk	Per protocol
Selective reporting (reporting bias)	Unclear risk	In primary outcome clinical manifestations was not defined, so not sure if any were not reported, reported on socio-economic status
Other bias	Unclear risk	

Feder 1999

Methods	Randomized controlled trial
Participants	**Setting:** Private pediatric office in Danbury, Connecticut during the winter and spring of 1996 to 1997 **Randomized into study:** *N* = 161 • Amoxicillin: *n* = 84 • Penicillin V: *n* = 77 **Completed study:** *N* **=** 152 • Amoxicillin: *n* =79 • Penicillin V: *n* =73 **Gender, males (%) :** Not stated in study • Amoxicillin: 65% • Penicillin V: 62% **Age, years (mean):** 9.9 • Amoxicillin: 9.0 • Penicillin V: 11.4 **Inclusion criteria** • Children between ages of 3-18 years old • Clinical findings suggesting GABHS pharyngitis **Exclusion criteria** • History of hypersensitivity to penicillin or amoxicillin • Patient who had received antimicrobial therapy within the previous week **Power analysis**: Study did not state
Interventions	**Experimental:** Received Amoxicillin 750 mg (250 mg/5 ml suspension) orally once daily for 10 days **Control:** Received Penicillin V 250 mg (250 mg/5 ml suspension) orally three times daily for 10 days *Any participant having a positive throat culture on the follow up cultures after completion of initial therapy was given Penicillin V 250 mg (250 mg/5 ml suspension) orally three times daily for 10 days as a second round of treatment.

Outcomes	**Primary outcomes:** **1)** Eradication of group A, beta-hemolytic streptococcal (GABHS) pharyngitis from the upper respiratory tract 18-24 hours after beginning therapy **2)** Impact on the clinical course at days 4-6 and 14-21 **3)** Bacteriologic treatment failure rate **Secondary outcome:** Newly acquisition GABHS
Notes	Bacteriologic treatment failures were defined as the presence of the same serotype of GABHS on either follow-up cultures (4-6 days or 14-21 days after completing therapy) as on the initial throat culture, regardless of clinical status. Patient with a different serotype of GABHS on follow-up culture than the initial culture were considered to have a newly developed GABHS rather than treatment failure.

Risk of bias table

Bias	Scholars' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used table of random numbers
Allocation concealment (selection bias)	Low risk	Physicians were blinded to which treatment was being dispensed to participants
Blinding of participants and personnel (performance bias)	Low risk	Testing of throat cultures were done at a separate facility. Study did not state where the rapid testing was done.
Blinding of outcome assessment (detection bias)	Low risk	All testing for this study was done at a separate facility.
Incomplete outcome data (attrition bias)	High risk	Per protocol analysis. They assigned 161 into the study but only reported on 152
Selective reporting (reporting bias)	Low risk	Reported on all primary outcomes stated.
Other bias	Unclear risk	

Kuroki 2013

Methods	Randomized control trial
Participants	**Setting:** Multi-center study, Japan. **Randomized into study:** *N* = 119 • Group 1 Clavulanate/amoxicillin (CVA/AMX): *n* = 64 • Group 2 Amoxicillin (AMX) *n* = 55 **Completed Study:** *N* = 93 • Group 1 (CVA/AMX): *n* = 52 • Group 2 (AMX) *n* = 41 **Gender, males:** • Group 1 (CVA/AMX): *n* = 25 (46.3%) • Group 2 (AMX) *n* = 22 (51.2%) **Age, years range (mean):** • Group 1 (CVA/AMX): 2-13y (5.6y) • Group 2 (AMX): 1-9y (5.3y)

	Inclusion Criteria: • Children with pharyngolaryngitis or tonsillitis aged less than 15 years, who tested positive on the instantaneous Group A Streptococcus infection diagnosis kit between November 2009 and May 2011 **Exclusion Criteria:** • None provided **Power Analysis:** The authors did not disclose power analysis.
Interventions	• CVA/AMX group: 3-day treatment with a combined clavulanate/amoxicillin preparation (CVA/AMPC)(Clavamox combination dry syrup for pediatric) at a dose level of 96.4 mg/kg/day (CVA 6.4 mg/kg/day, AMPC90 mg/kg/day) in two divided doses • AMX group: 10-day treatment at a dose level of 30 mg/kg/day in three divided doses Each patient was followed for approximately 1–2 weeks after completion or discontinuation of treatment.
Outcomes	Primary outcome: Bacteriological efficacy Safety outcome: Adverse reactions
Notes	• There was no sign of abnormality or of acute glomerulonephritis in any patient. • Urticaria and eruption (one case each) were noted in the CVA/AMX group, and upper airway inflammation (one case) was seen in the AMX group. • None of these adverse reactions was severe. • Discontinuation of test drug treatment because of an adverse reaction occurred in one patient (urticaria) from the CVA/AMX group and one patient (diarrhea) from the AMX group.

Risk of bias table

Bias	Scholars' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Two groups by simple randomizations.
Allocation concealment (selection bias)	High risk	Concealment was not described by the authors
Blinding of participants and personnel (performance bias)	High risk	Not blinded, open-label.
Blinding of outcome assessment (detection bias)	Low risk	Not blinded, but the outcome measurement is not likely to be influenced by the lack of blinding (temperature, bacterial test, urinalysis)
Incomplete outcome data (attrition bias)	Unclear risk	They used per protocol analysis
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	High risk	The lead author received financial aid from Glaxo- SmithKline K.K.

Lennon 2008

Methods	Randomized, parallel-group, non-inferiority
Participants	**Setting:** single site (school-based clinic) in New Zealand from May 1996 to

	November 1998 **Randomized into Study:** *N* = 353 • Group 1: Amoxicillin QD *n* = 177 • Group 2: Penicillin V BID *n* = 176 **Completed Study:** *N* = 335 • Group 1: *n* = 166 • Group 2: *n* = 169 **Gender, males (%)**: • Group 1: 52% • Group 2: 49% **Age, years (mean)**: • Group 1: 8.7 years • Group 2: 8.5 years **Inclusion criteria**: Children presenting to a sore throat clinic at a primary school and Auckland, New Zealand with signs and symptoms of acute pharyngitis (core temp >38C, headache, nausea or abdominal pain, difficulty in swallowing, inflamed or infected throat, tender glands in neck) AND had throat swab cultures positive for GABHS **Exclusion criteria:** Hypersensitivity to penicillin, were likely to require treatment with other antimicrobials during the study period or had received antimicrobial therapy within 72 h prior to study entry, had a previous history of acute rheumatic fever, cardiac disease or kidney disease, had a rash suggestive of scarlet fever or mononucleosis, were immunocompromised, had a neoplastic disease, a terminal illness or neutropenia (absolute neutrophil count ,1.5610/9 cells/l) or had previously been included in this study within the current school term (approximately 12 weeks in duration) **Power Analysis:** With no difference in treatment effect in the two arms of the trial and assuming 85% eradication, 155 evaluable subjects per treatment group would have 80% power to demonstrate noninferiority.
Interventions	**Group 1**: Amoxicillin 1500 mg by mouth once daily (or 750 mg if ≤ 30 kg) for 10 days **Group 2**: Penicillin V 500 mg by mouth twice daily (or 250 mg if ≤ 20 kg) for 10 days
Outcomes	Eradication of GABHS determined with follow-up throat cultures on days 3-6, 12-16, and 26-36
Notes	Positive follow-up throat cultures were further divided to differentiate between treatment failure, relapse, or new acquisition. Adherence rates were similar between treatment groups (based on direct observation and/or diary analysis) Study was completed at a single site in New Zealand which limits generalizability of results

Risk of bias table

Bias	Scholars' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Computer generated randomization schedule
Allocation concealment (selection bias)	Low risk	Allocation implemented by third party via telephone
Blinding of participants and personnel (performance bias)	Low risk	Groups were not blinded to treatment arm but this is unlikely to affect the primary outcome: eradication of bacterial agent
Blinding of outcome assessment (detection bias)	Unclear risk	No discussion of whether the study personnel reading the culture results were blinded to treatment groups
Incomplete outcome data (attrition bias)	Low risk	Reasons for lost data were reported and were similar between treatment groups
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes were reported as expected
Other bias	Low risk	Funded by New Zealand Heart Foundation (no role in study design, implementation, or interpretation)

NCT00643149

Methods	Randomized control trial, non-inferiority
Participants	**Setting**: Multicenter: 33 centers in North America (6 sites in Canada, 19 in US), Latin America (3 sites in Costa Rica, 1 in Guatemala), and India (4 sites); Pediatric outpatients; May 14, 2003 to May 23, 2004. **Number of participants randomized:** *N* = 693 **Number of evaluated (treated) participants:** *N* = 673 Group 1: Azithromycin *n* = 337 Group 2: Amoxicillin *n* = 336 **Number of participants discontinued:** *N* = 125 Group 1: Azithromycin *n* = 56 Group 2: Amoxicillin *n* = 69 **Age:** Children 2 to 12 years **Gender:** Not reported **Inclusion criteria:** Acute pharyngitis/tonsillitis based on "erythematous pharyngeal mucosa or thick exudate covering the pharynx and tonsillar area, and at least one of the following signs or symptoms: sore/scratchy throat; pain on swallowing; chills and/or fever; cervical adenopathy; scarlet fever rash on the face and skin folds, or red tongue with prominent papillae ("strawberry tongue")." - Positive rapid antigen detection test or positive culture for GABHS - GABHS pharyngitis/tonsillitis (tested for susceptibility to azithromycin and amoxicillin)
Interventions	**Group 1**: Azithromycin SR 60 mg/kg single dose (*n* = 337); bacteriological per protocol population (*n* = 245) **Group 2:** Amoxicillin 45 mg/kg twice daily for 10 days (n = 336); bacteriological per protocol population (n = 237)
Outcomes	- Bacteriological cure (primary outcome) - Clinical success - Compliance - Adverse events - Time points of assessment: "Test of Cure" at 24 to 28 days after starting study drug; and long-term follow-up on days 38 to 45
Notes	Report provided by Pfizer

	- Study supported and conducted by Pfizer - Protocol No: A0661071 - Outcomes only reported for "Bacteriological Per Protocol Population", i.e. positive GABHS culture at recruitment or within 48hrs of starting treatment, at least 8 days of study medication and assessment at baseline

Risk of bias table

Bias	Scholars' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Low risk	Placebo matched to active treatment
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	High risk	In total 693 randomized; 20 were not treated due to insufficient drug supply at study site (no more information given). Of 673 patients treated 125 patients discontinued (56 in azithromycin group and 69 in amoxicillin group); reasons for discontinuation provided (more dropout due to adverse events in azithromycin arm (4.7% versus .9%) and more lack of efficacy in amoxicillin arm (8.3% versus 3.3%)).
Selective reporting (reporting bias)	Unclear risk	All outcomes reported
Other bias	High risk	Study supported and conducted by Pfizer

Shvartzman1993

Methods	Randomized controlled trail
Participants	**Setting:** Five family medicine practices over six months in Israel **Randomized into study:** *N* = 393 presented with symptoms suggesting streptococcal pharyngitis • **Group 1:** Phenoxymethylpenicillin 250 mg x 3-4 daily • **Group 2:** Amoxycillin once daily **Completed Study:** *N* = 157 (Positive throat culture and completed 24-48 hour and 14 day follow-up) • **Group 1:** *n* = 82 • **Group 2:** *n* = 72 (3 patients were treated with penicillin after another positive throat culture after 24 hours) **Gender, males:** • **Group 1:** *n* = 35 • **Group 2:** *n* = 29 **Age, years:** • 0-4: *n* = 11 • 5-10: *n* = 66 • 11-20: *n* = 45 • >20: *n* = 22 • Unknown age: *n* = 13

	Inclusion Criteria: • Patients presented with symptoms suggestive of group A hemolytic streptococcal pharyngitis in whom had a positive throat swab culture **Exclusion Criteria:** • Younger than 3 years old without s/s for group A hemolytic streptococcal pharyngitis AND negative throat swab culture • Patients with a history of hypersensitivity to penicillin • Received antibiotics within the previous 72 hours • Chronic disease • Personal or family history of rheumatic fever **Power Analysis:** Not reported
Interventions	• **Group 1:** Phenoxymethylpenicillin 250 mg x 3-4 daily for 10days • **Group 2:** Amoxycillin once daily for 10days
Outcomes	**Primary outcome:** • Positive throat culture at day 2 • Positive throat culture at day 14 **Secondary outcome(s)** • School or work missed
Notes	

Risk of bias table

Bias	Scholars' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	How patients were randomized was not described.
Allocation concealment (selection bias)	Unclear risk	Not described by authors
Blinding of participants and personnel (performance bias)	Unclear risk	Patients were not blinded and it is unlikely personnel was blinded. Although, the outcome was objective and it is unclear if blinding would have affected the results.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described by authors
Incomplete outcome data (attrition bias)	High risk	Only included patients that completed 14 days of follow-up. Did not address how many or if any patients in amoxycillin group was treated with phenoxymethlypencillin.
Selective reporting (reporting bias)	High risk	Any patient who had received amoxycillin and whose throat culture yielded positive results at 24-48 hours or was not improved within three days was immediately switched to a 10 day course of phenoxymethylpenicillin. This may explain why there were no positive result for amoxycillin group on day 14!
Other bias	Unclear risk	

Appendix E
Question 5: In pediatric patients, what is the incidence of streptococcal A pharyngitis under three years of age?

Question Originator: Strep Pharyngitis CPG Team

Plain Language Summary from The Office of Evidence Based Practice: The Infectious Diseases Society of America (IDSA) guideline recommends that diagnostic tests for GAS are not indicated for children <3 years old because the incidence of GAS is uncommon in this age group, and ARF is rare in children <3 years old (Carapetis, Steer, Mulholland, & Weber, 2005; Shulman et al., 2012). A meta-analysis included in the IDSA guidelines reported children <3 years of age had a low prevalence of GAS pharyngitis (10% to 14%) compared to school-aged children (37%) (Shaikh, Leonard, & Martin, 2010). However, it is reasonable to consider testing children <3 years of age if there is a household contact with a school-aged child with documented streptococcal pharyngitis (Shulman et al., 2012).

Literature Summary: A strong recommendation is made against testing children less three years of age for GAS pharyngitis, based on very low quality evidence.

Further research, if performed is likely to have an important influence on our confidence in the results (Table 1).
Testing for Group A Streptococcal (GAS) pharyngitis in children < 3years of age is not recommended due to the low prevalence of GAS and the low risk of developing acute rheumatic fever (ARF) in this population.

AGREE II (Brouwers et al., 2010) was used to grade and evaluate the IDSA guideline (Shulman et al., 2012). Based on the AGREE II scores, the guideline obtained an overall high quality rating. The IDSA guideline reports the prevalence of GAS pharyngitis is significantly lower for children <3 years of age, ranging from 10% to 14% (Shulman et al., 2012). The GAS pharyngitis prevalence increases to as high as 25% for the <3 years of age population when there is an infection within a family (Shulman et al., 2012). Typically, the IDSA guideline does not recommend testing for children <3 years of age, although, special considerations can be made if there is a close household contact.

A systematic review by Shaikh et al. (2010), included in the IDSA guideline, identified three studies (Feery, Forsell, & Gulasekharam, 1976; Gunnarsson, Holm, & Söderström, 1997; Rimoin et al., 2005) that looked at the prevalence of GAS infection among children <5 years of age (N=964) who presented with a sore throat. Four studies were identified (Edmond et al., 1996; Feery et al., 1976; Ginsburg et al., 1985; Gunnarsson et al., 1997) that looked at prevalence of GAS among asymptomatic children (N=1036). The pooled prevalence of children presenting with sore throat (0 to 5 years of age) with GAS was 24%, 95% CI [21, 26]. The pooled prevalence of asymptomatic children (<5 years of age) with GAS was 4%, 95% CI [1, 7]. The authors of the meta-analysis reported scarcity of studies looking at preschool age children and a high level of heterogeneity ($P < .001$) between the studies. Authors were only interested in the point prevalence of GAS, not the incidence of GAS overtime; longitudinal studies in which the same child was cultured multiple times were excluded.

Vieira et al. (2006) reported on prevalence of *Streptococcus pyogenes.* Children from Sao Paulo and Porto Velho Brazil, including children enrolled in daycare and those not enrolled in daycare (N = 200). In the children ($N = 50$), each from four different settings (nursery school children - Sao Paulo and Porto Velho; non-institutionalized children - Sao Paulo and Porto Velho) had a mean age of 1 year 10 months, 1 year 11 months, 4 years 3 months, and 4 years 3 months, respectively. The prevalence in the youngest groups was 2% and 8%, whereas the prevalence in the older groups was 16% and 24%.

Wu et al. (2016) conducted a three-year GAS surveillance study in pediatric clinics within 36 Beijing hospitals. Compared to children aged 0–4 years, those aged 5–14 years had a higher risk of outpatient visits for GAS culture-positive pharyngitis in each year (2551 vs. 815 cases per 100,000 children in 2012, 976 vs. 304 cases per 100,000 children in 2013, and 3419 vs. 932 cases per 100,000 children in 2014, $p < 0.05$). The GAS culture-positive rate

was 1-3% for children aged 0-4, while the GAS culture-positive rate was 4.6-14.9% for 5-14 year old.

Search Strategy and Results:
((("Pharyngitis"[tw] OR "pharyngitis"[mesh] OR Pharyngotonsillitis) AND ("Streptococcus pyogenes"[Mesh] OR "Streptococcal Infections"[Mesh] OR "Streptococcal Infection*"[tw] OR "Streptococcus pyogenes"[tw] OR "group A strep"[tw] OR "group A streptococcal"[tw] OR "group A streptococcus"[tw])) OR "streptococcal pharyngitis"[All Fields] OR "GAS pharyngitis"[All Fields]) AND Incidence[tw] AND (infant[tw] OR child[tw] OR childr*[tw] OR childh*[tw] OR adolescen*[tw] OR pediatr*[tw] OR paeditr*[tw])

Studies included in this review:

Shaikh, N., et al. (2010). "Prevalence of streptococcal pharyngitis and streptococcal carriage in children: a meta-analysis." Pediatrics **126**(3): e557-e564.

Shulman, S. T., et al. (2012). "Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America." Clinical infectious diseases: cis 629.

Vieira, F. M. J., et al. (2006). "Prevalence of Streptococcus pyogenes as an oropharynx colonizer in children attending daycare: a comparative study of different regions in Brazil." Revista Brasileira de Otorrinolaringologia **72**(5): 587-591.

Wu, S., et al. (2016). "Estimated burden of group a streptococcal pharyngitis among children in Beijing, China." BMC Infectious Diseases **16**(1): 452.

Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program (Higgins et al., 2011), Review Manager (RevMan 5.1.7) was used to synthesize the three included studies. GRADEpro GDT (Guideline Development Tool) (Guyatt et al., 2008) is the tool used to create Summary of Findings Tables for this analysis. AGREE II was used to assess the quality of the one included guideline (Brouwers et al., 2010).

EBP Scholar's responsible for analyzing the literature:
Kim Robertson, MBA, MT-BC
Audrey Snell, MS, RD, CSP, LD

EBP team member responsible for reviewing, synthesizing, and developing this literature:
Jarrod Dusin, MS, RD, LD, CNSC

Developed: June 2017

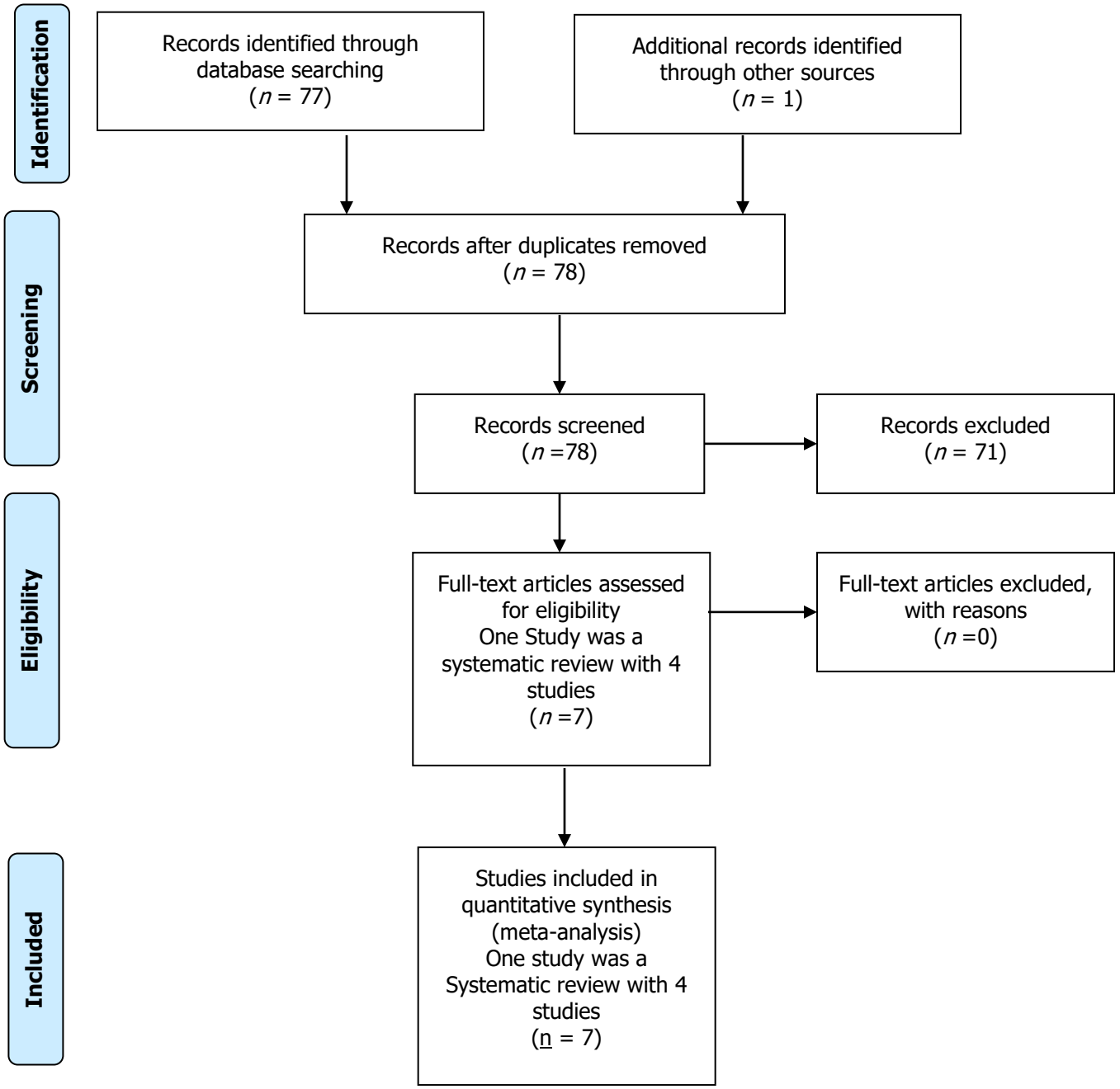
Table 1
Question: In pediatric patients, what is the incidence of streptococcal A pharyngitis under three years of age?
Setting: ED/UCC

Incidence of streptococcal A pharyngitis under three years of age											
Certainty assessment							**Summary of findings**				
№ of 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 >3year old	**With <3year old**		**Risk with >3year old**	**Risk difference with <3year old**
Prevalence/Incidence											
(7 observational studies)	very serious [a]	very serious [b]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	The pooled prevalence of children (n=964) presenting with sore throat (<5 years of age) with GAS was 24%, 95% [21,26]. The pooled prevalence of asymptomatic children (n=1036) (<5 years of age) with GAS was 4%, 95% CI [1,7] (Edmond et al., 1996; Feery et al., 1976; Ginsburg et al., 1985; Gunnarsson et al., 1997; Rimoin et al., 2005). Prevalence in children (mean age 1.8 year -1.9 year) was 2-8% compared to 16-24% of older children (mean age 4 years 3 months) (Vieira et al., 2006). Wu et al. (2016) found children aged 0-4 had lower risks of outpatient visits for GAS culture-positive pharyngitis compared to 5-14 year old (2551 vs. 815 cases per 100,000 children in 2012, 976 vs. 304 cases per 100,000 children in 2013, and 3419 vs. 932 cases per 100,000 children in 2014, $p < 0.05$). The GAS culture-positive rate was 1-3% for children aged 0-4, while the GAS culture-positive rate was 4.6-14.9% for 5-14 year olds.				

CI: Confidence interval
a. 4 of the 7 studies are case series which typically yields very low quality evidence.
b. High level of heterogeneity among patients. Patients are from different countries and different age groups were observed.
c. Results are imprecise when studies include relatively few patients and few events.

Children's Mercy

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



[b]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.

If you have questions regarding this Specific Care Question – jmichael@cmh.edu or amyers@cmh.edu

Shaikh

Methods	Meta-analysis
Participants	Articles on GAS pharyngitis or asymptomatic carriage in children who were younger than 18 years. **Number of Studies:** 29 articles met the inclusion criteria. • 18 References: asymptomatic children • 14 References: children with sore throat • 3 References: both **All Ages Children Presenting with Sore Throat:** N=68,731 **Younger than 5 years Presenting with Sore Throat:** 964 **All Ages Asymptomatic Children:** N=9662 **Younger than 5 years Asymptomatic Children**: N=1036 **Inclusion:** • Article with reported data on the prevalence of GAS in children who presented to a clinician for evaluation of sore throat. • Only studies that used throat cultures as the gold standard were included; • Studies in which rapid antigen tests were used were included only when specimens that were negative on the rapid antigen test were sent for culture confirmation. **Exclusions:** • **Authors were only interested in the point prevalence of GAS, not the incidence of GAS overtime; longitudinal studies in which the same child was cultured multiple times were excluded.** • Did not specifically identify the *Streptococcus* as group A • Included only children who lived in isolated communities or residential homes, • reported on an unusual epidemic of GAS, • Included large proportion (>30%) of children who had received antibiotics before the throat culture • Required children to have signs and symptoms other than sore throat (eg, required fever). • We excluded studies that did not describe the exact signs and symptoms required for patient enrollment.
Results	Prevalence of GAS Infection Among Children Presenting With Sore Throat **All ages:** Pooled prevalence 37%, 95 CI [32,43] **Younger than 5 years:** Pooled prevalence 24%, 95 CI [21,26] Prevalence of GAS carriage Among Asymptomatic Children **All ages:** Pooled prevalence 12% 95 CI [9,14] **Younger than 5 y:** Pooled prevalence 4% 95 CI[1,7] There was significant heterogeneity (P<.001) among the estimates from the 14 studies that reported data on the prevalence of GAS among children with sore throat. Among asymptomatic children who were younger than 18 years there was significant heterogeneity among the estimates from the studies (P <.001).

Vieira 2006

Methods	Prospective study
Participants	**Setting:** Brazil **Participants:** Children from Sao Paulo and Porto Velho Brazil, including children enrolled in daycare and those not enrolled (N = 200). Fifty children each from 4 different settings (3 nursery schools and one pediatric outpatient center) were included. **Number Complete:** 200 **Age:** • Group I: 3months to 3years (mean: 1year 10months) • Group II: 6months to 3years (mean: 1year 11months • Group III: 1year to 8years (mean: 4years 3months) • Group IV: 1year to 8years (mean: 4years 3months) **% Male Subjects:** • Group I (nursery school children - Sao Paulo): 47% • Group II (non-institutionalized children - Sao Paulo): 54% • Group III (nursery school children - Porto Velho): 56% • Group IV (non-institutionalized children - Porto Velho): 54% **Inclusion Criteria:** • Healthy children not older than 10 years old • Normal ear, nose and throat exam **Exclusion Criteria:** • Use of antibiotic therapy in the last 15 days • Previous tonsillectomy • Eating within 2 hours before taking the sample • Congenital or acquired immunodeficiencies • History of persistent tonsillitis (2 or more events in 6 months or 4 events in 1 year)
Interventions	• Four groups were identified (see above), two from nursery schools and two from outpatient children's health centers (non-nursery schools). • Samples of oropharynx material were taken following a microbiologic protocol identified in the study. • Samples in Sao Paulo occurred during the months of June and July (dry winter), and during Sept and Oct in Port Velho (during the hot and humid periods).
Outcomes	Prevalence *Streptococcus pyogenes*

Results	Positive prevalence *Streptococcus pyogenes* Group I: 4 (8%) Group II: 1 (2%) Group III: 12 (24%) Group IV: 8 (16%) • In Sao Paulo, *Streptococcus pyogenes* was present in 8% of cultures in children from the nursery school group, and in 2% in the control group (outpatient health center), demonstrating a significant statistical difference between the groups. • In Porto Velho, *Streptococcus pyogenes* was present in 24% of the nursery school group samples, and in 16% of the control group samples (outpatient health center). No statistical difference was found between these two. • A significant statistical difference was found between the control groups of the two cities and between the nursery school groups as well, with a higher prevalence in both found in Porto Velho. • Analysis of the samples from the two cities was done in separate labs but using the same standardization of processes. • The authors mention that the older age group normally has more colonization by SBHGA due to higher prevalence of social contact than the younger range.

Wu2016

Methods	Prospective study to view the incidence of clinical cases of pharyngitis and GAS culture-positive pharyngitis, and their outpatient visits among children aged 0–14 years in Beijing, China
Participants	**Setting**: 36 hospitals within Beijing districts from 2011-2013 then 17 hospitals in 2014. **Age groups**: age 0-4 age 5-14 Overall 0-14
Outcomes	• Cases of Scarlet Fever from GAS • Cases of Pharyngitis from GAS • Culture-positive rates of GAS
Results	Number of clinical cases of scarlet fever from GAS surveillances Age 0–4: 1158 Age 5-14: 231,007 Age 0-14: 2366 Number of clinical cases of pharyngitis from GAS surveillances Age 0-4: 231,007 Age 5–14: 216,225 Overall(0–14): 447,232 Number of clinical cases of scarlet fever from National Notifiable Infectious Disease Surveillance System (NNIDSS) Age 0-4: 2366 Age 5-14: 6712 Overall (0-14): 9078 • An average of 29,804.6 clinical cases of pharyngitis per 100,000 person-year occurred among children age 0-14 years resulting in correspondingly 19519.0 (95 % CI: 18516.7,20521.2) outpatient visits per 100,000 person-years from 2012 to 2014 in Beijing.

	• On average, there were 2685.1 (95 % CI: 2039.6,3330.6) GAS culture-positive cases of pharyngitis and 1652.7 (95 % CI: 1256.5,2049.0) outpatient visits per 100,000 person-years during the same period. • The estimated burden of GAS pharyngitis was significantly higher than that of scarlet fever. • Compared to children aged 0–4 years, those aged 5–14 years had a higher risk of outpatient visits for GAS culture-positive pharyngitis in all the 3 years (2551.3 vs. 815.8 cases per 100,000 children in 2012, 976.9 vs. 304 cases per 100,000 children in 2013, and 3419.9 vs. 932.6 cases per 100,000 children in 2014, $p < 0.05$). • From 2012 to 2014, 9078 clinical cases of scarlet fever aged 0–14 years were reported from NNIDSS in Beijing, 26.1 % of whom were children aged 0–4 years, and 73.9 % were between the age of 5 and 14 years. • Total of 4093 clinical cases of scarlet fever and 447,232 ones of pharyngitis were reported from GAS surveillances in Beijing. • Of the 4093 clinical cases of scarlet fever, 28.3 % were children aged 0–4 years and 71.7 % were between the age of 5 and 14 years. • Of the 447,232 clinical cases of pharyngitis, 51.7 % were children aged 0–4 years and 48.3 % were between the age of five and fourteen years.

Appendix F
Question 6: In pediatric patients with streptococcal pharyngitis, how soon can patients return to school after starting antibiotics?

Question Originator: Strep Pharyngitis CPG Team

Plain Language Summary: Group A streptococcus (GAS) is the most common cause of bacterial pharyngitis in children and adolescents. Children can return to school or daycare after 12-24 hours of starting antibiotic therapy for a strep throat. Most of the studies identified for this review checked follow-up throat cultures at 18-24 hours. Only one study was found that looked at follow-up throat cultures between 12 to 23 hours but most of the patients (74%), in this study, were tested between 20 to 23 hours (Schwartz, Kim, Martin, & Pichichero, 2015).

The American Academy of Pediatrics recommends that children can return to school or child care after 12 hours of antibiotic treatment (American Academy of Pediatrics, 2017).

The Center for Disease Control and prevention recommends that people with strep throat should stay home from work, school, or daycare until they no longer have a fever and have taken antibiotics for at least 24 hours so they do not spread the infection to others (The Center for Disease Control, 2016).

Literature Summary: Based on very low quality evidence a weak recommendation is made that children can return to school or daycare after 12-24 hours of starting antibiotics.

Outcome: Positive throat culture after starting antibiotics
Due to the inconstancy of the different antibiotic treatments a meta-analysis was not performed for this outcome.

Schwartz et al. (2015) evaluated 111 children with positive streptococci between 12 to 23 hours after receiving a single dose of amoxicillin. Participants were randomized into two groups either to receive a second dose one hour before their return clinic visit on day two, or after their return clinic visit on day two. Eighty-two patients (74%) had a second culture at 18 to 24 hours. Only two patients had throat cultures at 12 hours. Only 10 of 111 participants continued to have a positive rapid antigen detection test (RADT) result, confirmed with an overnight throat culture. In 91%, CI [86, 96%] of the study participants Group A streptococci were not detected on the day two throat specimen by RADT nor by culture. There was no significant different between the positive culture between the two groups (see Table 1, Figure 2).

Randolph, Gerber, DeMeo, and Wright (1985) randomized 194 children with positive throat cultures to receive penicillin V (*n* = 68), cefadroxil (*n* = 70), or placebo (*n* = 56). Throat cultures were checked approximately 18 to 24 hours after starting on medication. Only two patients of the penicillin V group and two patients of the cefadroxil groups were found to have a positive culture 18 to 24 hours after starting either medication (see Table 1, Figure 3).

Feder, Gerber, Randolph, Stelmach, and Kaplan (1999) randomized 152 children with positive throat cultures to receive penicillin V (*n* = 73) or amoxicillin (*n* = 79). Throat cultures were checked at 18 to 24 hours after starting on antibiotics. One patient in the penicillin V group and none in the amoxicillin group were positive at 18 to 24 hours (see Table 1, Figure 4).
Snellman, Stang, Stang, Johnson, and Kaplan (1993) randomized 47 children with a positive throat culture to receive oral erythromycin (*n* = 15), benzathine penicillin (*n* = 15), or penicillin v (*n* = 17). Additional throat cultures were obtained during three home visits within 24 hours after their initial clinic visit. Twenty patients were cultured between 17 to 24 hours after initial treatment with nine (33%) patients found to be still positive. Twenty patients were tested between 12 to 18 hours with eight (40%) continuing to test positive after the initial treatment. The mean time to a negative culture was 14.7 $\pm$ 5.73 hours for oral erythromycin, 18.8 $\pm$ 5.57 hours for benzathine penicillin, and 18.1 ± 5.66 hours for penicillin V. Time to negative culture was not statistically significant between the different antibiotics (see Figures 3, 4, and 5). For The following antibiotic comparisons the mean difference (*MD*) were as follows:

- Oral erythromycin vs. benzathine penicillin, *MD* = -4.10, *P* = .05, 95% CI [-8.23, .03]
- Oral erythromycin vs. penicillin V, *MD* = -3.40, *P* = .09, 95% CI [-7.38, .58]

- Benzathine penicillin vs. penicillin V, *MD* = .70, *P* = .73, 95% CI [-3.26, 4.66]

A cohort study (Gerber, Randolph, & DeMeo, 1987) of 128 children with positive throat cultures were started on penicillin V at the end of their initial visit. Only 115 children had a follow-up culture at 18 to 24 hours. Of the patients cultured, six patients remained positive for GAS at 18 to 24 hours after the start of antibiotic treatment.

Search Strategy and Results: ("strep throat" OR (("Streptococcal Infections"[Mesh] OR "Streptococcus pyogenes"[Mesh]) AND ("Pharyngitis"[Mesh]))) AND ("Schools"[Mesh] OR "Students"[MeSH] OR "return to school") AND ("2011/12/01"[PDat] : "2017/12/31"[PDat]

Studies included in this review:
Gerber et al., (1987)
Feder et al., (1999)
Randolph et al., (1985)
Schwartz et al., (2015)
Snellman et al., (1993)

Studies not included in this review with exclusion rationale:

Author (Year)	Reason for exclusion
Krober et al., (1985)	Follow-up cultures at 2 days

Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program, Review Manager (Higgins & Green, 2011)[a] was used to synthesize five included study. GRADEpro GDT (Guideline Development Tool) is the tool used to create the Summary of Findings Tables for this analysis.

[a]Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cohcrane Collaboration, 2011.

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Date Developed: November 2017

12hours compared to 24hours for returning to school after starting antibiotics											
Certainty assessment							**Summary of findings**				
№ of 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 24hours	**With 12hours**		**Risk with 24hours**	**Risk difference with 12hours**
Positive Cultures after starting antibiotics (follow up: range 12 Hours to 24 Hours)											

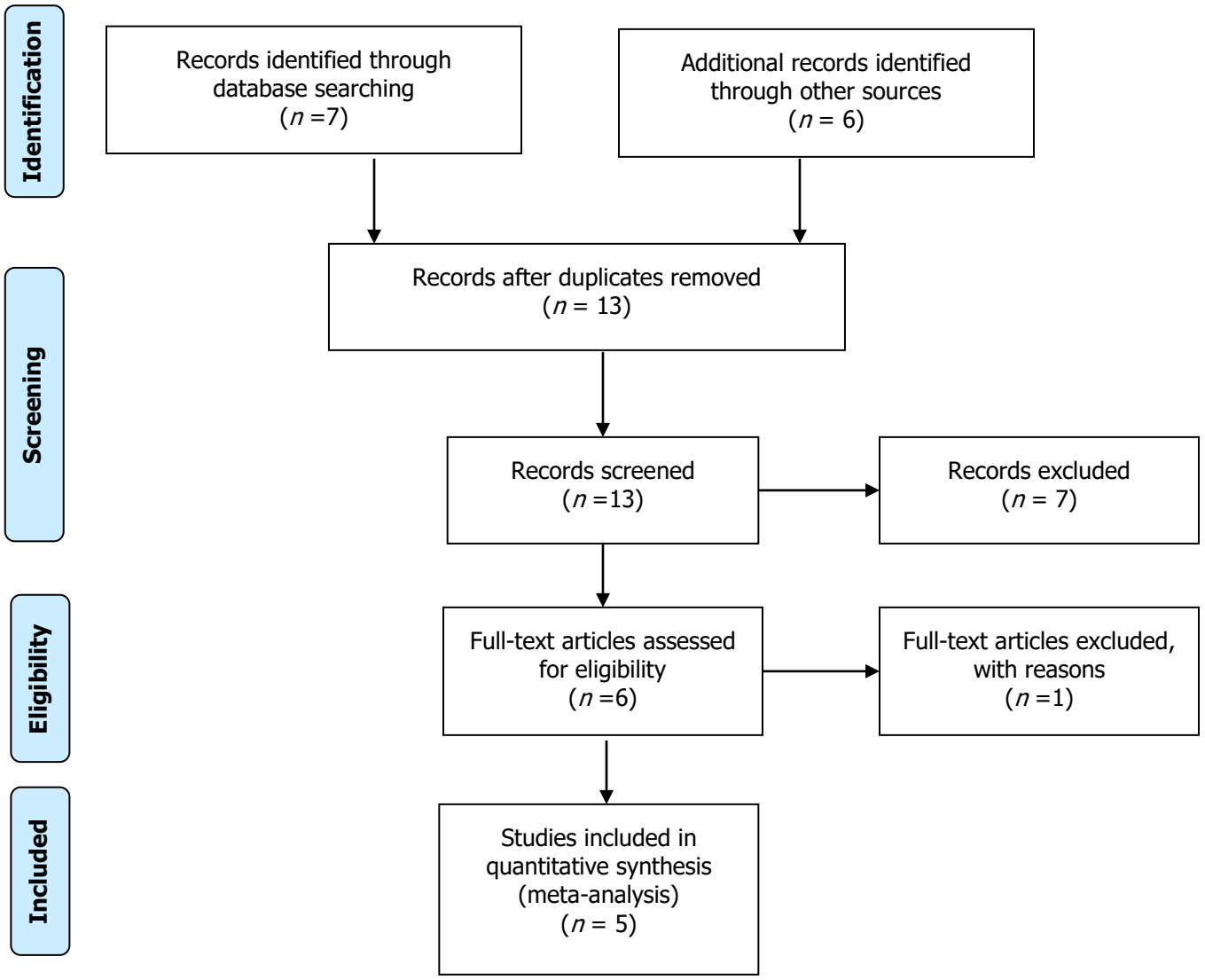
503 (4 RCTs)	serious [a,b]	serious [c]	not serious	serious [d]	none	⊕◯◯◯ VERY LOW	Schwartz et al. (2015) evaluated 111 children with positive streptococci at 12 to 23 hours after receiving a single dose of amoxicillin. Only 10 of 111 participants continued to have a positive rapid antigen detection test (RADT) result, confirmed by overnight throat culture. Eight two patients (74%) had their second culture at 18 to 24hours. Only two patients had throat cultures at 12 hours. Randolph et al. (1985) randomized 194 children with positive throat cultures to receive penicillin V (n=68), cefadroxil (n=70), or placebo (n=56). Throat cultures were checked at approximately 18 to 24hours after starting on medication. Only two patients of the penicillin V group and two patients of the cefadroxil were positive at 18 to 24hours after starting both medications. Feder et al. (1999) randomized 152 children with positive throat cultures to receive penicillin V (n=73) or amoxicillin (n=79). Throat cultures were checked at 18 to 24 hours after starting on antibiotics. One patient in the penicillin V group and none in the amoxicillin group were positive at 12 to 24hours. Snellman et al. (1993) randomized 47 children with pharyngitis and a positive throat culture to receive oral erythromycin (n=15), benzathine penicillin (n=15), or penicillin v (n=17). Additional throat cultures were obtained during three home visits in the 24hours after their initial clinic visit. 27 patients were cultured at 17 to 24 hours after initial treatment and nine were still positive (33%). Twenty patients were tested at 12 to 18 hours. Eight were positive (40%) after initial treatment.
Positive Cultures after starting antibiotics (follow up: range 18 Hours to 24)							
115 (1 observational study)	serious [a]	not serious	not serious	serious [d]	none	⊕◯◯◯ VERY LOW	A cohort study (Gerber et al., 1987) of 115 patients with a positive throat culture were started on penicillin V at the end of their initial visit. A follow-up visit at 18 to 24hours found Six patients still positive for group A streptococci.

Table 1
a. Poor study design
b. Per protocol analysis
c. each study used different antibiotics
d. Studies include relatively few patients and few events

If you have questions regarding this Specific Care Question – jmichael@cmh.edu or amyers@cmh.edu

Children's Mercy

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



[b]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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Figure 2
Forest plot of comparison: Three different antibiotic comparisons
Outcome: Positive cultures at 12 to 24hours

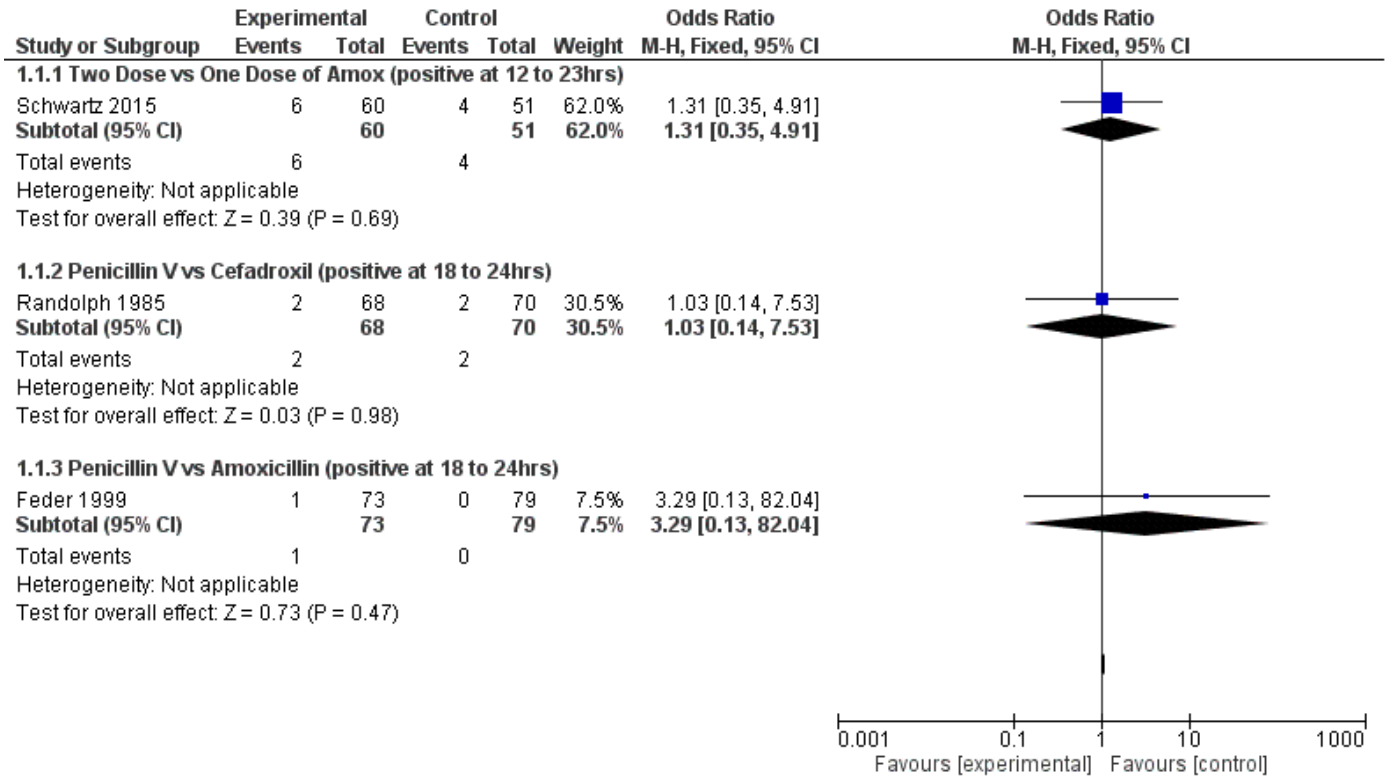

Figure 3
Forest plot comparison: Oral erythromycin vs benzathine penicillin
Outcome: Mean time to negative culture

Study or Subgroup	Oral Erythromycin Mean	SD	Total	Benzathine Penicillin Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Snellman 1993	14.7	5.8	15	18.8	5.75	15	100.0%	-4.10 [-8.23, 0.03]
Total (95% CI)			**15**			**15**	**100.0%**	**-4.10 [-8.23, 0.03]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.94 (P = 0.05)

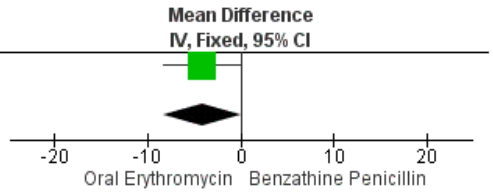

Figure 4
Forest plot comparison: Oral erythromycin vs penicillin V
Outcome: Mean time to negative culture

Study or Subgroup	Oral Erythromycin Mean	SD	Total	Penicillin V Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Snellman 1993	14.7	5.8	15	18.1	5.66	17	100.0%	-3.40 [-7.38, 0.58]
Total (95% CI)			**15**			**17**	**100.0%**	**-3.40 [-7.38, 0.58]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.67 (P = 0.09)

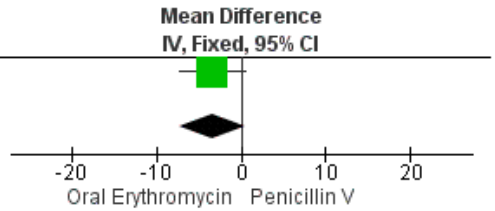

Figure 5
Forest plot comparison: Benzathine penicillin vs penicillin V
Outcome: Mean time to negative culture

Study or Subgroup	Benzathine Penicillin Mean	SD	Total	Penicillin V Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Snellman 1993	18.8	5.75	15	18.1	5.66	17	100.0%	0.70 [-3.26, 4.66]
Total (95% CI)			**15**			**17**	**100.0%**	**0.70 [-3.26, 4.66]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.73)

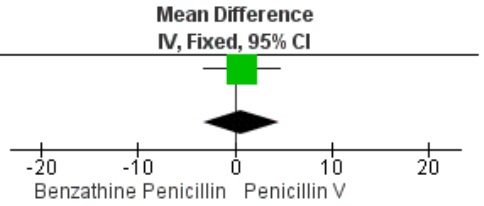

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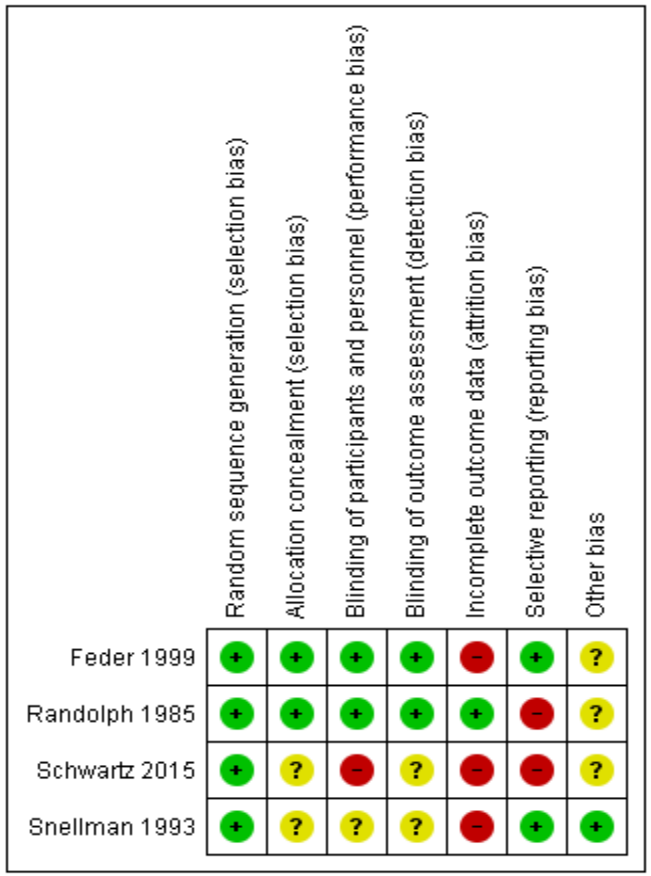
Figure 6
Risk of Bias Table for Randomized Control Trials



Feder 1999

Methods	Prospective, randomized, controlled trial
Participants	**Setting:** Private pediatric office in Danbury, Connecticut during the winter and spring of 1996 to 1997 **Randomized into study:** *N*= 161 • Amoxicillin: *n* = 84 • Penicillin V: *n* = 77 **Completed study:** 152 • Amoxicillin: *n* =79 • Penicillin V: *n* =73 **Gender, males (%):** not stated in study • Amoxicillin: 65% • Penicillin V: 62% **Age, years (mean):** 9.9 • Amoxicillin: 9.0 • Penicillin V: 11.4 **Inclusion criteria** • Children between ages of 3-18 years old • Clinical findings suggesting GABHS pharyngitis **Exclusion criteria** • History of hypersensitivity to penicillin or amoxicillin • Patient who had received antimicrobial therapy within the previous week **Power analysis**: Study did not state
Interventions	**Experimental:** Received Amoxicillin 750 mg (250 mg/5 ml suspension) orally once daily for 10 days **Control:** Received Penicillin V 250 mg (250 mg/5 ml suspension) orally three times daily for 10 days *Any participant having a positive throat culture on the follow up cultures after completion of initial therapy was given Penicillin V 250 mg (250 mg/5 ml suspension) orally three times daily for 10 days as a second round of treatment.
Outcomes	**Primary outcomes:** **1)** Eradication of group A, beta-hemolytic streptococcal (GABHS) pharyngitis from the upper respiratory tract 18-24 hours after beginning therapy **2)** Impact on the clinical course at days 4-6 and 14-21 **3)** Bacteriologic treatment failure rate **Secondary outcome:** Newly acquisition GABHS
Notes	Bacteriologic treatment failures were defined as the presence of the same serotype of GAS on either follow-up cultures (4-6 days or 14-21 days after completing therapy) as on the initial throat culture, regardless of clinical status. Patient with a different serotype of GABHS on follow-up culture than the initial culture were considered to have a newly developed GAS rather than treatment failure.

Risk of bias table

Bias	Scholars' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Used table of random numbers
Allocation concealment (selection bias)	Unclear risk	Physicians were blinded to which treatment was being dispensed to participants
Blinding of participants and personnel (performance bias)	Unclear risk	Testing of throat cultures were done at a separate facility. Study did not state where the rapid testing was done.
Blinding of outcome assessment (detection bias)	Low risk	All testing for this study was done at a separate facility.
Incomplete outcome data (attrition bias)	Unclear risk	Per protocol analysis. They assigned 161 into the study but only reported on 152
Selective reporting (reporting bias)	Unclear risk	Reported on all primary outcomes stated.
Other bias	Unclear risk	

Gerber 1987

Methods	Cohort study
Participants	**Participants:** Patients aged 3 to 21 years old with clinical finding suggestive of GABHS pharyngitis. **Setting:** University of Connecticut Health Center **Number enrolled**: *N* = 188 patients **Number of patients with isolated GABHS**: *N* = 128 **Number of patients with follow-up culture at 18-24 hours**: *N* = 115 **Gender, males**: Not identified in study **Age, years (mean)**: 3 to 21 (10.2) **Inclusion criteria:** Not reported **Exclusion criteria:** Not reported **Covariates Identified:** Not reported
Interventions	• All patients began penicillin V therapy at the end of their initial visit. • Patients were asked to return in18 to 24hours for a second culture. • Patients were instructed to continue for 10 full days. • Patients returned for an additional follow-up visit 14 to 16 days after initial visit.
Outcomes	**Primary outcome:** Number of patients enrolled who had isolated GABHS.
Notes	**Results**: • Of the 188 patients from who throat cultures were obtained at the initial visit, GABHS were isolated from 128 (68%) • 115 of the 128 returned for follow-up cultures at 18 to 24 hours. • 115 patients from whom throat cultures were obtained at the 18 to 24 hour follow-up visit, GABHS were isolated from six (5%).

Randolph 1985

Methods	Randomized control trial

Participants	**Setting:** Private, pediatric office, United States 1983-1984 **Randomized into study:** *N* = 260 • **Group 1 (penicillin):** *n = 87* • **Group 2 (cefadroxil):** *n = 92* • **Group 3 (placebo):** *n = 81* **Completed Study:** *N = 194* • **Group 1 (penicillin):** *n = 68* • **Group 2 (cefadroxil):** *n = 70* • **Group 3 (placebo):** *n = 56* **Gender, males:** • Not reported **Age, years (mean) (SD):** 8.8 • **Group 1:** Not reported • **Group 2:** Not reported • **Group 3:** Not reported The study states that the three treatment groups were comparable with respect to age, sex, race, clinical findings, and duration of illness prior to initiation of treatment. **Inclusion Criteria:** • Children 2-20 years of age • clinical findings suggestive of GABHS pharyngitis **Exclusion Criteria:** • Children with a history of hypersensitivity to either penicillin or cephalosporins • Children who had received antibiotic therapy within the previous 72 hours **Power Analysis:** The authors did not disclose power analysis

Interventions	• **Group 1:** Penicillin V 250 mg/5 ml, orally, three doses over the next 24 hours
	• **Group 2:** Cefadroxil 250 mg/5 ml, orally, three doses over the next 24 hours
	• **Group 3:** Grape syrup placebo, orally, three doses over the next 24 hours
	
	Parents were instructed to:
	• Take the child's temperature every 4 hours during waking hours
	• Note the rate of improvement in the child's clinical status
	• Return in 18 to 24 hours with a fresh urine specimen and the medicine bottle they had been given
	
	All study patients were evaluated for
	• The presence and severity of three objective signs
	  ○ Fever
	  ○ Cervical lymphadenitis as manifested by tender, enlarged lymph nodes
	  ○ Pharyngeal injection
	• Three subjective symptoms
	  ○ Sore throat
	  ○ Headache
	  ○ Abdominal pain

Outcomes	**Primary outcome(s):** • Positive culture at 18-24 hours **Secondary outcome(s)** • Resolution of objective and subjective clinical symptoms
Notes	The study did not list the numbers of the positive cultures for each group at the 18-24 hour

	visit. This prohibited the comparison between the penicillin and cefadroxil. "Approximately 3% of the penicillin-treated and cefadroxil-treated patients had positive throat cultures for GABHS at the 18- to 24-hour follow-up visit, whereas 100% of the placebo-treated patients had positive throat cultures at this visit."

Risk of bias table

Bias	Scholars' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Randomization was performed by a study nurse, provider and parents were not aware of the group to which they were assigned
Blinding of participants and personnel (performance bias)	Low risk	The evaluating physician, parents, and patients were unaware of which agent was dispensed.
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Low risk	All 194 children with positive throat cultures returned for the 18- to 24-hour follow-up evaluation
Selective reporting (reporting bias)	High risk	The authors did not disclose specific data numbers for the individual group outcomes. Unable to compare penicillin vs. cefadroxil for the 18-24 hour follow-up.
Other bias	Unclear risk	

Schwartz 2015

Methods	Randomized control trial
Participants	**Setting:** One private primary care pediatric practice located in Virginia **Randomized into study:** *N* = 135 • They do not disclose the initial randomization into the two groups. Twenty children were excluded, but it does not describe which group they are from. **Completed Study:** *N* = 111 • **Group 1:** Group A (two doses): *n* = 60 • **Group 2:** Group B (Single dose): *n* = 51 **Gender, males:** • **Group 1:** Group A (two doses): *n* = 32 (53.3%) • **Group 2:** Group B (Single dose): *n* = 34 (66.7%) **Age, years (mean):** • **Group 1:** Group A (two doses): mean *n* = 7.0 • **Group 2:** Group B (Single dose): mean *n* = 6.5 **Inclusion Criteria:** • Symptomatic children with sore throat who had pharyngeal erythema and a positive rapid antigen detection test (RADT) result for group A streptococcus (GAS). **Exclusion Criteria:** • Noncompliance with the protocol (*n* = 10) • Critical data not entered on work sheet (*n* = 7) • Miscellaneous reasons (*n* = 7) **Power Analysis:** The authors did not disclose power analysis

Interventions	All study children swallowed the initial dose of amoxicillin in the office immediately after signed informed parental consent and received 1 bottle of amoxicillin suspension (400 mg/5 mL), weight dosage based at 50 mg/kg/d, administered in a single daily dose. **Group A**: On the following morning (day 2 of study), group A subjects were given the day 2 dose by a parent at least 1 hour before arrival at the office. **Group B:** Only received only the day 1 dose of amoxicillin and did not receive the day 2 dose until after the office visit and the throat culture/RADT specimen was taken.
Outcomes	**Primary outcome:** • Evaluating the necessity of the 24 hours of antibiotic treatment before returning to school.
Notes	• 29 patients (26%) had their second culture at 12 to 17 hours • 82 patients (74%) had their second culture at 18 to 24 hours

Risk of bias table

Bias	Scholars' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A table of random numbers divided consecutive enrollees into 2 groups: group A and B
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not discussed
Blinding of participants and personnel (performance bias)	Low risk	It is unlikely that blinding would have affected the outcome of RADT or culture.
Blinding of outcome assessment (detection bias)	Low risk	No blinding of the outcome assessment, but the outcome measurement is not likely influenced by the lack of blinding.
Incomplete outcome data (attrition bias)	High risk	Per protocol analysis performed, 18% of patients were excluded for "miscellaneous reasons" or "critical data not entered on worksheet"
Selective reporting (reporting bias)	High risk	The primary outcome was to evaluate the necessity of 24hour of antibiotics before returning to school. Both groups received an initial dose of amoxicillin and returned the next day. The only difference between the groups was the timing of the second dose.
Other bias	Unclear risk	The author reported: "We cannot exclude the possibility that the morning dose of amoxicillin in group A subjects resulted in a temporary negative throat culture and/or RADT that later reverted to positive on that day, as the peak concentration of the morning amoxicillin dose waned."

Snellman 1993

Methods	Randomized control Trial
Participants	**Setting:** Study was performed October 1988 to April 1989 and September 1989 to May 1990, in the Pediatric department in the White Bear Lake Medical Center of Group Inc., Minnesota. **Randomized into study:** *N* =49 • **Group 1:** Oral Penicillin (OP)=unclear • **Group 2:** Oral Erythromycin Estolate (OE)=unclear • **Group 3:** Intramuscular benzathine Penicillin G (BPG)= unclear **Completed Study:** *N* = 47 • **Group 1:** Oral Penicillin (OP) *n* = 17 • **Group 2:** Oral Erythromycin Estolate (OE) *n* =15 • **Group 3:** Intramuscular benzathine Penicillin G (BPG) *n* = 15 *Data from 2 of the 49 are not included in the analysis because of a technical problem with the

	laboratory incubator rendering the convalescent cultures unevaluable. Did not disclose which group **Gender, males:** • *N* =33 males (did not disclose group breakdown) **Age, years (mean):** • 8.9 years (did not disclose group breakdown) **Inclusion Criteria:** • Children -4 to 17 years of age • Living within a 15-minute drive of the clinic • Being available for three repeat home visits during the 24 hours after enrollment in the study **Exclusion Criteria:** • Concurrent bacterial infection • Allergy to the antibiotics used in the study • Received oral antibiotics within the previous week or benzathine penicillin within the previous month **Power Analysis:** Not reported
Interventions	Group 1: Oral penicillin V, 250mg three times a day for 10 days Group 2: Oral Erythromycin Estolate, 250 mg three times daily for 10 days Group 3: Intramuscular Benzathine Penicillin G, 600,000 units if body weight <60 pounds and 1.2 million units if >60 pounds The study nurse visited the patient at home three times during the subsequent 24 hours. The times were dependent upon time of admission to the study. Home visit involved: throat culture, recording of signs and symptoms, and the ingestion of each oral dose of antibiotic was supervised At 4 weeks, patient returned to clinic for blood specimen collection to measure convalescent antibody studies
Outcomes	1. At what point in the first 24 hours after initiating antibiotic therapy do throat cultures from patients with pharyngitis and positive throat cultures for GAS actually become negative? 2. What percentage of treated children have a negative throat culture by the morning after initiating antibiotic therapy, often before a full 24 hours of therapy? 3. Can the choice of antibiotic affect the time required for conversion to a negative throat culture? 4. Does the presence of specific clinical signs or symptoms at initial examination assist the clinician in deciding how quickly the culture will become negative? 5. Do the presence of signs or symptoms at the time a throat culture is performed help predict the presence of group A streptococci on that specific culture? 6. Does an antibody response to streptococcal extracellular antigens such as streptolysin O or DNase B correlates with the length of time on therapy for conversion to a negative throat culture?
Notes	Culture plates that failed to yield any colonies of group A B-hemolytic streptococci after 72 hours of incubation were considered negative. This does not represent eradication of the streptococci from the upper respiratory tract during the 24-hour period, but it reflects a decreased number of viable organisms in the upper respiratory tract, and thus, suggests decreased "contagiousness" of the patient. The mean time intervals between culture 1 and: • Culture 2: 6.5 $\pm$ 2.9 hours • Culture 3: 15.7 $\pm$ 4.2 hours • Culture 4: 23.2 $\pm$ 1.6 hours

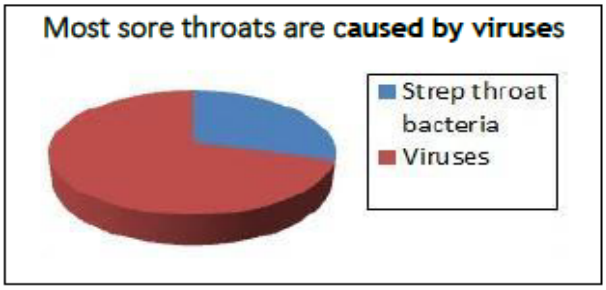
Risk of bias table

Bias	Scholars' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Rolled a three-numbered die
Allocation concealment (selection bias)	Unclear risk	Did not disclose
Blinding of participants and personnel (performance bias)	Unclear risk	Did not disclose
Blinding of outcome assessment (detection bias)	Unclear risk	Examination of all culture plates was performed by the study nurse and also at the streptococcal research laboratory
Incomplete outcome data (attrition bias)	High risk	Data from 2 of the 49 are not included in the analysis because of a technical problem with the laboratory incubator rendering the convalescent cultures unavailable. Did not disclose which group
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	The study appears to be free of other sources

Appendix G
Education handouts

Children's Mercy

Sore Throat



- Children have many viral respiratory illnesses (colds) each year
- Antibiotics do not treat viral infections
- Your child does NOT need testing for strep throat if they have prominent cough, runny nose, hoarseness, red eyes, or diarrhea because these symptoms suggest a virus
- Testing for strep throat is usually not needed for children younger than 3 years old because strep throat is uncommon in very young children
- Some children carry strep bacteria in their throat but it does not cause infection

We can help decide whether testing for strep throat is necessary for your child based on symptoms and examination

- Amoxicillin and penicillin are the recommended antibiotics for strep throat
- ALL strep throat bacteria are killed by amoxicillin or penicillin

Unnecessary antibiotics can be harmful; only children with a positive test for strep throat should receive antibiotics

- We will recommend options to ease symptoms of viral infections
- We can provide a letter for your child's daycare or school regarding your child's illness
- We are committed to providing the best medical care for your child including not testing or giving antibiotics when they are not needed
- If you have any questions from today's visit please ask!

References:
1. Monto AS, Ullman BM. Acute respiratory illness in an American community. JAMA 1974;227:164-169.
2. Shulman ST, Bisno A, et al. Clinical practice guideline for the diagnosis and management of group a streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2012;55(10):e86-e102.
3. Shaikh N, Leonard E, Martin JM. Prevalence of streptococcal pharyngitis and streptococcal carriage in children: a meta-analysis. *Pediatrics*. 2010;126(3):e557-64.

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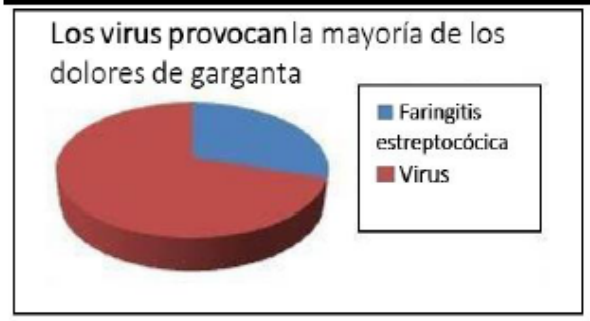
Children's Mercy

DOLOR DE GARGANTA



- Los niños tienen muchas infecciones virales respiratorias (catarro) cada año
- Los antibióticos no combaten las infecciones virales
- No se necesitan realizar pruebas de faringitis estreptocócica a su niño si tiene tos prominente, flujo nasal, ronquera, ojos rojos o diarrea ya que estos síntomas sugieren la presencia de un virus
- Normalmente no se necesitan realizar pruebas de faringitis estreptocócica para los niños menores de 3 años ya que no es común en niños pequeños
- Algunos niños tienen bacteria estreptocócica en sus gargantas, pero no desarrollan una infección

Podemos ayudarle a decidir si es necesario realizar una prueba de faringitis estreptocócica para su niño, basado en síntomas y una evaluación.

- La amoxicilina y la penicilina son los antibióticos recomendados en caso de una faringitis estreptocócica
- La amoxicilina o la penicilina mata a TODAS las bacterias de la faringitis estreptocócica

Los antibióticos innecesarios pueden ser dañinos. Solamente los niños con una prueba positiva por faringitis estreptocócica deberán recibir antibióticos.

- Le recomendaremos opciones para aliviar los síntomas de las infecciones virales
- Podemos brindarle una carta para la guardería o la escuela de su niño que indique la enfermedad de su niño
- Nos comprometemos en darle la mejor atención médica para su niño, incluyendo no realizarle pruebas o darle antibióticos cuando no sea necesario
- Si tiene alguna pregunta sobre su cita de hoy ¡no dude en hacer preguntas!

Referencias:

1. Monto AS, Ullman BM. Acute respiratory illness in an American community. JAMA 1974;227:164-169.
2. Shulman ST, Bisno A, et al. Clinical practice guideline for the diagnosis and management of group a streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2012;55(10):e86-e102.
3. Shaikh N, Leonard E, Martin JM. Prevalence of streptococcal pharyngitis and streptococcal carriage in children: a meta-analysis. *Pediatrics*. 2010;126(3):e557-64.

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Caring for Your Child with Strep Throat

Key Point
Strep throat is a common cause of sore throat in kids. Antibiotics can help your child feel better within a few days.

Your Child's Diagnosis
Strep throat is an infection caused by bacteria (a type of germ). The type of bacteria is called Group A streptococcus – that is why it is called strep throat. Kids with strep throat have a sore throat, and can have trouble swallowing, fever, headache, and swollen glands in the neck. They also might have belly pain, feel sick to their stomach, and throw up.
Strep throat is contagious (can be spread to others). It can spread:

- When someone uses the same fork, spoon, or drinking glass as someone with strep throat.
- When someone with strep throat coughs, sneezes, or touches his or her own mouth or nose and then touches another person.
- If someone with strep throat touches something (such as a doorknob) that others will touch.

Strep throat is most common in school-age kids. However, it can affect people of any age, especially those who have close contact with school-aged kids.
The doctor talked to you and your child and did an examination. Strep throat is usually diagnosed by touching a cotton swab to both tonsils and the back of the throat to test it for strep germs. Some doctors do a rapid strep test. If this test is positive, strep germs are present in the throat. If the rapid strep test is negative, strep germs may not be present in the throat. A regular throat culture is usually sent to the lab when a rapid strep test is negative, or sometimes if a rapid test was not done. The throat culture looks at whether strep germs grow over the next few days.
Strep throat is treated with antibiotics. The antibiotics will help your child feel better within a few days. Antibiotics also keep the infection from spreading to others. Treatment also helps prevent other problems that strep throat can sometimes cause.
After your child has been on antibiotics for at least 12 hours, he or she is no longer contagious.
Home Care Instructions

- Be sure your child takes all of the antibiotic doses as prescribed, even if he or she is feeling better. This is the best way to kill the harmful germs.
- Encourage your child to drink lots of liquids and rest as needed.
- If swallowing is so painful that eating solids is hard to do, try serving liquids and soft foods, like soups, milkshakes, smoothies, ice pops, or ice cream.
- Help your child avoid acidic drinks like orange juice and lemonade, which can irritate the throat.
- If you child has pain or is uncomfortable from fever, a medicine may help your child feel better:
    - For children under 6 months, you may give acetaminophen (brand names include Tylenol, Feverall, and Panadol)
    - For children over 6 months, you may give acetaminophen (brand names include Tylenol, Feverall, and Panadol) OR ibuprofen (brand names include Advil, Motrin, and Q-Profen), if recommended by your doctor.

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- Do not give aspirin to your child or teen, as it has been linked to a rare but serious illness called Reye syndrome.
- If your child is 5 years or older and is not at risk for choking, he or she may find it soothing to suck on hard candy.
- Saltwater gargling may help your child feel more comfortable, but should be used only for kids older than 6 years. Mix ¼ teaspoon of salt in 8 ounces of warm water and have your child gargle and spit 4-6 times per day.
- To prevent the spread of strep throat and other illnesses, remind your child and other family members to:
    - Wash their hands often with soap and water. Be sure to scrub for at least 20 seconds, rinse, and dry thoroughly. If soap and water are not available, a hand sanitizer with at least 60% alcohol can be used.
    - Avoid sharing food, drinks, dishes, eating utensils, napkins, or towels with others. Wash dishes in hot, soapy water.
    - Cover their mouth and nose when coughing or sneezing. A tissue can be used and then thrown away (wash hands afterward). If a tissue is not available, sneeze or cough into the elbow or upper arm, not the hands.

Special Instructions

- If your doctor did a regular throat culture, follow up as recommended.
- As long as your child is feeling better and does not have fever, he or she may return to childcare or school the morning after treatment is started.

Call Your Health Care Professional if….
Your child:

- Can't take the antibiotics as directed.
- Gets worse or does not get better within 3 days of starting antibiotics.
- Can't swallow any food or drinks.
- Develops a rash, ear pain, or other symptoms.
- Still has fever after 2-3 days. Or your child's fever goes away and then comes back.
- Develops neck swelling, difficulty opening and closing the mouth, voice changes, or drooling.
- Has pee that is red or tea-colored.

Go to the ER if…
Your child:

- Appears dehydrated; signs include dizziness, drowsiness, a dry or sticky mouth, sunken eyes, crying with few or no tears, or peeing less often (or having fewer wet diapers).
- Is having trouble breathing.

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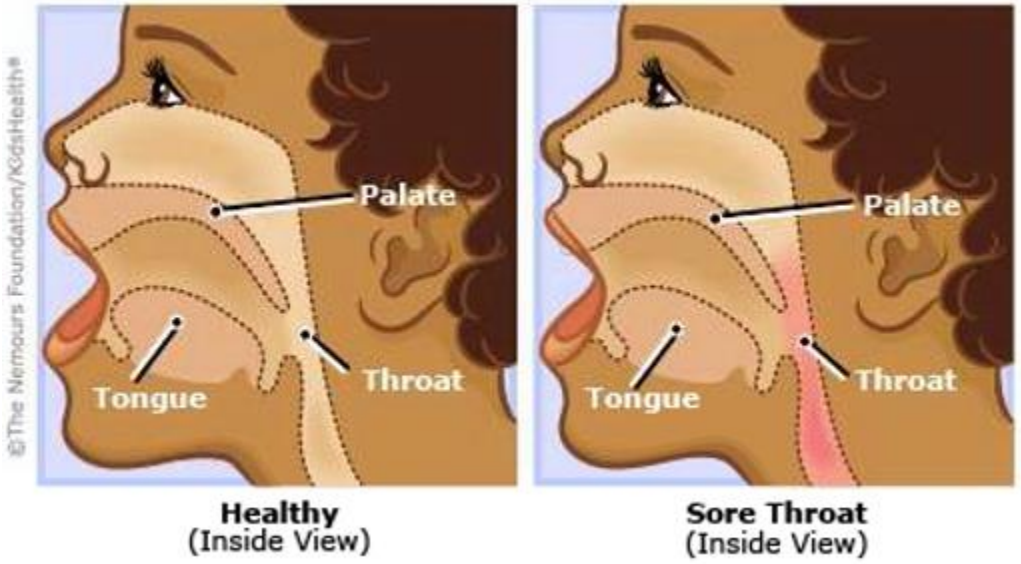
Caring for Your Child with a Sore Throat (Pharyngitis)

Key Point

Sore throats are common in children and rarely serious. Many can be treated with simple methods at home.



Healthy (Inside View)

Sore Throat (Inside View)

Your Child's Diagnosis

Sore throats are usually caused by viruses, but also can be due to bacteria, repeated coughing or vomiting, allergies, secondhand smoke, or other factors.

Your child might have a fever and the neck glands may swell, which is a sign that your child's body is fighting off germs. Sore throats caused by a virus tend to get better by themselves in 4-5 days and can last up to 2 weeks.

Home Care Instructions

- For pain, a medication may help your child feel better:
  - For children under 6 months, you may give acetaminophen.
  - For children over 6 months, you may give acetaminophen OR ibuprofen as directed.
- Do not give aspirin to your child or teen as it has been linked to a rare but serious illness called Reye syndrome.
- Offer your child plenty of warm or cold liquids; both can help to relieve discomfort.
- Children 5 years and older may find relief by sucking on hard candy. Younger children should not be given hard candy or lozenges because they could choke.
- Saltwater gargling may bring some relief, but should be used only for children older than 6 years. Mix ¼ teaspoon of salt in 8 ounces of warm water and have your child gargle 4-6 times a day.
- Offer your child soft foods that are easy to swallow. Avoid salty, spicy, crunchy, or acidic foods (like citrus fruits), which can irritate a sore throat.
- Let your child rest as needed.

Special Instructions

- If your health care provider did a strep throat culture, you will be contacted if the results were positive.

Call Your Health Care Professional if…

Your child:

- Develops pus in the back of the throat.
- Is extremely tired.
- Has throat pain that worsens.
- Develops a rash.
- Is unable to take liquids
- If fever lasts greater than 3 days.

Go to the ER if….

- Has difficulty swallowing or breathing.
- Starts drooling.

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Appendix H
Power Plan

Unique Plan Description: EDP Sore Throat CPG EKM
Plan Selection Display: EDP Sore Throat CPG EKM
PlanType: ED/UCC
Version: 1
Begin Effective Date: 12/31/2100 00:00
End Effective Date: Current
Available at all facilities
Plan Comment: Following Rule Associated to this Plan:PP_FLEX_ED_SORE_THROAT

EDP Sore Throat CPG EKM

Nursing

- ☐ Oral fluid challenge
- ☐ IV placement

Respiratory

- ☐ Oxygen/Pulse oximetry

Laboratory

Testing children <3 years old is generally not indicated, unless signs and symptoms consistent with strep throat and close contact with strep(NOTE)*

- ☐ Rapid Ag Strep Gp A

Continuous Medications/Fluids

- ☐ NS fluid bolus
  10 mL/kg, IV, IV Soln, 1 time only (DEF)*
  20 mL/kg, IV, IV Soln, 1 time only

Medications

- ☐ acetaminophen 160 mg/5 mL oral liquid
  10 mg/kg, PO, 1 time only (DEF)*
  15 mg/kg, PO, 1 time only
- ☐ acetaminophen oral 325 mg tablet
  10 mg/kg, PO, 1 time only (DEF)*
  15 mg/kg, PO, 1 time only
- ☐ ibuprofen 100 mg/5 mL oral suspension
  10 mg/kg, PO, 1 time only
- ☐ ibuprofen 100 mg oral tablet
  10 mg/kg, PO, 1 time only
- ☐ oxyCODONE 5 mg/5 mL oral solution
  0.1 mg/kg, PO, 1 time only (DEF)*
  0.15 mg/kg, PO, 1 time only
- ☐ oxyCODONE 5 mg oral tablet
  5 mg, PO, 1 time only (DEF)*
  10 mg, PO, 1 time only

Preferred treatment for positive Rapid Antigen Detection Test (RADT)-see Pharyngitis CPG(NOTE)*
Alternative choice for positive Rapid Antigen Detection Test (RADT)(NOTE)*

- ☐ penicillin G benzathine
  600,000 unit, IM, 1 time only [Less Than 27 kg] (DEF)*
  1,200,000 unit, IM, 1 time only [Greater Than or Equal To 27 kg]

***Report Legend:**
DEF - This order sentence is the default for the selected order
GOAL - This component is a goal
IND - This component is an indicator

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INT - This component is an intervention
IVS - This component is an IV Set
NOTE - This component is a note
Rx - This component is a prescription
SUB - This component is a sub phase

References

Altamimi, S., Khalil, A., Khalaiwi, K. A., Milner, R. A., Pusic, M. V., & Al Othman, M. A. (2012). Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children. *The Cochrane Library*.

Armengol, C. E., & Hendley, J. O. (2012). Occurrence of Group A β-Hemolytic Streptococcal Pharyngitis in the Four Months After Treatment of an Index Episode With Amoxicillin Once-daily or Twice-daily or With Cephalexin. *The Pediatric infectious disease journal, 31*(11), 1124-1127.

Attia, M. W., Zaoutis, T., Klein, J. D., & Meier, F. A. (2001). Performance of a predictive model for streptococcal pharyngitis in children. *Archives of Pediatrics & Adolescent Medicine, 155*(6), 687-691.

Ba-Saddik, I., Munibari, A., Alhilali, A., Ismail, S., Murshed, F., Coulter, J., . . . Parry, C. M. (2014). Prevalence of Group A beta-haemolytic Streptococcus isolated from children with acute pharyngotonsillitis in Aden, Yemen. *Tropical Medicine & International Health, 19*(4), 431-439.

Beaudoin, A., Edison, L., Introcaso, C. E., Goh, L., Marrone, J., Mejia, A., & Beneden, C. (2015). Acute rheumatic fever and rheumatic heart disease among children—American Samoa, 2011–2012. *MMWR Morb Mortal Wkly Rep, 64*(20), 555-558.

Bourgeois, F. T., Mandl, K. D., Valim, C., & Shannon, M. W. (2009). Pediatric adverse drug events in the outpatient setting: an 11-year national analysis. *Pediatrics, 124*(4), e744-e750.

Breese, B. B. (1977). A simple scorecard for the tentative diagnosis of streptococcal pharyngitis. *American Journal of Diseases of Children, 131*(5), 514-517.

Brouwers, M. C., Kho, M. E., Browman, G. P., Burgers, J. S., Cluzeau, F., Feder, G., . . . Hanna, S. E. (2010). AGREE II: advancing guideline development, reporting and evaluation in health care. *Canadian Medical Association Journal, 182*(18), E839-E842.

Carapetis, J. R., Steer, A. C., Mulholland, E. K., & Weber, M. (2005). The global burden of group A streptococcal diseases. *The Lancet infectious diseases, 5*(11), 685-694

Centers for Disease Control and Prevention (September 8, 2015), About Antimicrobial Resistance. Retrieved from https://www.cdc.gov/drugresistance/about.html

Center for Disease Control and Prevention (2016). *Worried your sore throat may be strep?* Retrieved from https://www.cdc.gov/features/strepthroat

Cohen, R., Levy, C., Doit, C., De La Rocque, F., Boucherat, M., Fitoussi, F., . . . Bingen, E. (1996). Six-day amoxicillin vs. ten-day penicillin V therapy for group A streptococcal tonsillopharyngitis. *The Pediatric infectious disease journal, 15*(8), 678-682.

Cohen, J. F., Chalumeau, M., Levy, C., Bidet, P., Thollot, F., Wollner, A., . . . Cohen, R. (2012). Spectrum and inoculum size effect of a rapid antigen detection test for group A streptococcus in children with pharyngitis. *PLoS One, 7*(6), e39085.

Cohen, J. F., Cohen, R., Levy, C., Thollot, F., Benani, M., Bidet, P., & Chalumeau, M. (2015). Selective testing strategies for diagnosing group A streptococcal infection in children with pharyngitis: a systematic review and prospective multicentre external validation study. *Canadian Medical Association Journal, 187*(1), 23-32.

Cohen, R., Levy, C., Ovetchkine, P., Boucherat, M., Weil-Olivier, C., Gaudelus, J., . . . Bingen, E. (2004). Evaluation of streptococcal clinical scores, rapid antigen detection tests and cultures for childhood pharyngitis. *European Journal of Pediatrics, 163*(4-5), 281-282.

Ebell, M. H., Smith, M. A., Barry, H. C., Ives, K., & Carey, M. (2000). Does this patient have strep throat? *Jama, 284*(22), 2912-2918.

Edmonson, M. B., & Farwell, K. R. (2005). Relationship between the clinical likelihood of group A streptococcal pharyngitis and the sensitivity of a rapid antigen-detection test in a pediatric practice. *Pediatrics, 115*(2), 280-285.

Eslami, S., Nassirian, A., Nassirian, H., Hatami, E., Sobhani, E., & Najibpour, R. (2014). Comparing performance of amoxicillin and intramuscular benzathine penicillin in relieving manifestations of streptococcal pharyngitis in children. *Ghana medical journal, 48*(4), 185-188.

Feder, H. M., Gerber, M. A., Randolph, M. F., Stelmach, P. S., & Kaplan, E. L. (1999). Once-daily therapy for streptococcal pharyngitis with amoxicillin. *Pediatrics, 103*(1), 47-51.

Feery, B., Forsell, P., & Gulasekharam, M. (1976). Streptococcal sore throat in general practice--a controlled study. *The Medical journal of Australia, 1*(26), 989-991.

Fine, A. M., Nizet, V., & Mandl, K. D. (2012). Large-scale validation of the Centor and McIsaac scores to predict group A streptococcal pharyngitis. *Archives of Internal Medicine, 172*(11), 847-852.

Gerber, M., Randolph, M., & DeMeo, K. (1987). Streptococcal antigen in the pharynx after initiation of antibiotic therapy. *The Pediatric infectious disease journal, 6*(5), 489.

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Gidengil, C. A., Kruskal, B. A., & Lee, G. M. (2013). Initial antibiotic choice in the treatment of group a streptococcal pharyngitis and return visit rates. *Journal of the Pediatric Infectious Diseases Society, 2*(4), 361-367.
Ginsburg, C. M., McCracken, G. H., Crow, S. D., Dildy, B. R., Morchower, G., Steinberg, J. B., & Lancaster, K. (1985). Seroepidemiology of the group-A streptococcal carriage state in a private pediatric practice. *American Journal of Diseases of Children, 139*(6), 614-617.
Gunnarsson, R. K., Holm, S. E., & Söderström, M. (1997). The prevalence of beta-haemolytic streptococci in throat specimens from healthy children and adults: implications for the clinical value of throat cultures. *Scandinavian journal of primary health care, 15*(3), 149-155.
Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., & Schunemann, H. J. (2008). GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ: British Medical Journal, 336*(7650), 924.
Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cohcrane Collaboration, 2011.
Kaya, A., Erkoçoğlu, M., Şenkon, O., Ekici, F., Toyran, M., Çetin, İ., & Kocabaş, C. (2014). Confirmed penicillin allergy among patients receiving benzathine penicillin prophylaxis for acute rheumatic fever. *Allergologia et immunopathologia, 42*(4), 289-292.
Kimberlin, D., Brady, M., Jackson, M., & Long, S. (2015). Red book. Report of the Committee on Infectious Diseases. American Academy of Pediatrics.
Kuehn, J., Ismael, Z., Long, P. F., Barker, C. I., & Sharland, M. (2015). Reported rates of diarrhea following oral penicillin therapy in pediatric clinical trials. *The Journal of Pediatric Pharmacology and Therapeutics, 20*(2), 90-104.
Kuroki, H., Ishiwada, N., Inoue, N., Ishikawa, N., Suzuki, H., Himi, K., & Kurosaki, T. (2013). Comparison of clinical efficacy between 3-day combined clavulanate/amoxicillin preparation treatment and 10-day amoxicillin treatment in children with pharyngolaryngitis or tonsillitis. *Journal of Infection and Chemotherapy, 19*(1), 12-19.
Lennon, D. R., Farrell, E., Martin, D. R., & Stewart, J. M. (2008). Once-daily amoxicillin versus twice-daily penicillin V in group A β-haemolytic streptococcal pharyngitis. *Archives of disease in childhood, 93*(6), 474-478.
Lexicomp (June 29, 2017), Amoxicillin (Pediatric and Neonatal Lexi-Drugs). Retrieved from https://online.lexi.com/lco/action/doc/retrieve/docid/pdh_f/129550
Mazur, E., Bochyńska, E., Juda, M., & Kozioł-Montewka, M. (2014). Empirical validation of Polish guidelines for the management of acute streptococcal pharyngitis in children. *International Journal of Pediatric Otorhinolaryngology, 78*(1), 102-106.
McIsaac, W. J., & Goel, V. (1998). Effect of an explicit decision-support tool on decisions to prescribe antibiotics for sore throat. *Medical Decision Making, 18*(2), 220-228.
McIsaac, W. J., Goel, V., To, T., & Low, D. E. (2000). The validity of a sore throat score in family practice. *Canadian Medical Association Journal, 163*(7), 811-815.
McIsaac, W. J., Kellner, J. D., Aufricht, P., Vanjaka, A., & Low, D. E. (2004). Empirical validation of guidelines for the management of pharyngitis in children and adults. *Jama, 291*(13), 1587-1595.
NCT00643149. A multicenter, randomized, double-blind, double-dummy study of azithromycin SR versus amoxicillin for the treatment of strep throat in children. Retrieved from http://clinicaltrials.gov/ct2/show/record/NCT00643149
Orda, U., Mitra, B., Orda, S., Fitzgerald, M., Gunnarsson, R., Rofe, G., & Dargan, A. (2016). Point of Care Testing for group A streptococci in patients presenting with pharyngitis will improve appropriate antibiotic prescription. *Emergency Medicine Australasia*.
Pichichero, M., (2017). Treatment and prevention of streptococcal tonsillopharyngitis. Retrieved from https://www.uptodate.com/contents/treatment-and-prevention-of-streptococcal-tonsillopharyngitis?source=search_result&search=Streptococcal%20Pharyngitis&selectedTitle=1~143
Randolph, M. F., Gerber, M. A., DeMeo, K. K., & Wright, L. (1985). Effect of antibiotic therapy on the clinical course of streptococcal pharyngitis. *The Journal of pediatrics, 106*(6), 870-875.
Rimoin, A. W., Hamza, H. S., Vince, A., Kumar, R., Walker, C. F., Chitale, R. A., . . . Steinhoff, M. C. (2005). Evaluation of the WHO clinical decision rule for streptococcal pharyngitis. *Archives of disease in childhood, 90*(10), 1066-1070.
Roggen, I., van Berlaer, G., Gordts, F., Pierard, D., & Hubloue, I. (2013). Centor criteria in children in a paediatric emergency department: for what it is worth. *BMJ Open, 3*(4), e002712.
Shih, C.-T., Lin, C.-C., & Lu, C.-C. (2012). Evaluation of a streptococcal pharyngitis score in southern Taiwan. *Pediatrics & Neonatology, 53*(1), 49-54.
Sarrell, E. M., & Giveon, S. M. (2012). Streptococcal pharyngitis: a prospective study of compliance and complications. *ISRN pediatrics, 2012*.

Schwartz, R. H., Kim, D., Martin, M., & Pichichero, M. E. (2015). A Reappraisal of the minimum duration of antibiotic treatment before approval of return to school for children with Streptococcal pharyngitis. *The Pediatric infectious disease journal, 34*(12), 1302-1304

Shaikh, N., Leonard, E., & Martin, J. M. (2010). Prevalence of streptococcal pharyngitis and streptococcal carriage in children: a meta-analysis. *Pediatrics, 126*(3), e557-e564.

Shulman, S. T., Bisno, A. L., Clegg, H. W., Gerber, M. A., Kaplan, E. L., Lee, G., . . . Van Beneden, C. (2012). Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*, cis629.

Shvartzman, P., Tabenkin, H., Rosentzwaig, A., & Dolginov, F. (1993). Treatment of streptococcal pharyngitis with amoxycillin once a day. *Bmj, 306*(6886), 1170-1172.

Snellman, L. W., Stang, H. J., Stang, J. M., Johnson, D. R., & Kaplan, E. L. (1993). Duration of positive throat cultures for group A streptococci after initiation of antibiotic therapy. *Pediatrics, 91*(6), 1166-1170.

Strep Throat (Streptococcal Pharyngitis) and Scarlet Fever. (2007). Aronson, S. S., Shope, T.R., (Ed.), *Managing infectious diseases in child care and schools* (4th ed., pp. 159-160). Elk Grove Village, IL: American Academy of Pediatrics.

Swaminathan, A., & Hom, J. (2014). Are short-term late-generation antibiotics equivalent to standard penicillin therapy in the resolution of symptoms in acute strep throat in children? *Annals of emergency medicine, 63*(6), 690-691.

Tanz, R. R., Gerber, M. A., Kabat, W., Rippe, J., Seshadri, R., & Shulman, S. T. (2009). Performance of a rapid antigen-detection test and throat culture in community pediatric offices: implications for management of pharyngitis. *Pediatrics, 123*(2), 437-444.

Ulukol, B., Günlemez, A., Aysev, D., & Cin, S. (1999). Alternative diagnostic method for streptococcal pharyngitis: Breese scoring system. *The Turkish Journal of Pediatrics, 42*(2), 96-100.

Van Brusselen, D., Vlieghe, E., Schelstraete, P., De Meulder, F., Vandeputte, C., Garmyn, K., . . . Van de Voorde, P. (2014). Streptococcal pharyngitis in children: to treat or not to treat? *European journal of pediatrics, 173*(10), 1275-1283.

van Driel, M. L., De Sutter, A. I., Habraken, H., Thorning, S., & Christiaens, T. (2016). Different antibiotic treatments for group A streptococcal pharyngitis. *The Cochrane Library*.

Venekamp, R. P., Sanders, S., Glasziou, P. P., Del Mar, C. B., & Rovers, M. M. (2013). Antibiotics for acute otitis media in children.

Vieira, F. M. J., Figueiredo, C. R., Soares, M. C., Weckx, L. Y., Santos, O., Magalhães, G., . . . Pignatari, S. (2006). Prevalence of Streptococcus pyogenes as an oropharynx colonizer in children attending daycare: a comparative study of different regions in Brazil. *Revista Brasileira de Otorrinolaringologia, 72*(5), 587-591.

Wald, E. R., Green, M. D., Schwartz, B., & Barbadora, K. (1998). A streptococcal score card revisited. *Pediatric Emergency Care, 14*(2), 109-111.

Walker, C. L. F., Rimoin, A. W., Hamza, H., & Steinhoff, M. C. (2006). Comparison of clinical prediction rules for management of pharyngitis in settings with limited resources. *The Journal of Pediatrics, 149*(1), 64-71.

Wu, S., Peng, X., Yang, Z., Ma, C., Zhang, D., Wang, Q., & Yang, P. (2016). Estimated burden of group a streptococcal pharyngitis among children in Beijing, China. *BMC Infectious Diseases, 16*(1), 452.