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Treatment of sore throat (pharyngitis) to prevent rheumatic heart disease – a rapid summary

Plain language summary

Among people with sore throat (pharyngitis) penicillin treatment probably reduces rheumatic fever recurrences and streptococcal throat infections (moderate certainty of evidence).

No studies reported the effects of penicillin treatment on rheumatic heart disease progression, disability, mortality or adverse events among people with sore throat (pharyngitis).

Table. Effectiveness of penicillin treatment among people with sore throat (pharyngitis)

What happens?	No penicillin	Penicillin	Certainty of evidence[1]
Rheumatic fever recurrences Penicillin probably reduces the incidence of acute rheumatic fever within 2 months among people with sore throat (follow up: up to 2 months)	19 per 1 000 people	5 per 1 000 people (3 to 10)*	⊕⊕⊕◯ MODERATE
Streptococcal throat infections after 3 days Penicillin probably reduces the number of people with streptococcal sore throat on day 3 among people with sore throat	710 per 1 000 people	405 per 1 000 people (327 to 504)*	⊕⊕⊕◯ MODERATE
Streptococcal throat infections after 1 week Penicillin probably reduces the number of people with streptococcal sore throat after a week among people with sore throat	126 per 1 000 people	37 per 1 000 people (14 to 95)*	⊕⊕⊕◯ MODERATE
Rheumatic heart disease progression Not reported in the systematic Cochrane review	Not reported in the systematic Cochrane review		
Mortality Not reported in the systematic Cochrane review	Not reported in the systematic Cochrane review		
Adverse events Not reported in the systematic Cochrane review	Not reported in the systematic Cochrane review		
Disability/Quality of Life Not reported in the systematic Cochrane review	Not reported in the systematic Cochrane review		

For more details and information, see the Results of this rapid summary. * The confidence interval (95% CI) reflects the extent to which the play of chance may be responsible for an effect estimate from a study. [1] Indicates the extent to which one can be confident that an estimate of effect is correct.

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Commission

The Norwegian Institute of Public Health, (NIPH) performed a rapid summary commissioned by the Bergen Centre for Ethics and Priority Setting (BCEPS), University of Bergen. The assignment was to systematically summaries evidence on penicillin for the treatment of acute pharyngitis to prevent rheumatic heart disease in children and adolescents.

Background

Acute pharyngitis is hallmarked by acute onset of sore throat; the absence of cough, nasal congestion and discharge suggests a bacterial aetiology. Rapid antigen detection tests allow immediate point-of-care assessment of group A Streptococcus (GAS) pharyngitis. The goal of treatment of GAS is to prevent acute rheumatic fever, reduce the severity and duration of symptoms, and prevent transmission. Acute pharyngitis is generally a self-limited condition with resolution within two weeks. Infected individuals are not, however, immune to reinfection with most aetiological pathogens (BMJ Best Practice (accessed Dec 18 2020)).

Acute rheumatic fever is an autoimmune disease that may occur following group A streptococcal throat infection. It can affect multiple systems, including the joints, heart, brain, and skin. Only the effects on the heart can lead to permanent illness; chronic changes to the heart valves are referred to as chronic rheumatic heart disease. No treatment has been shown to alter the progression of acute rheumatic fever to chronic rheumatic heart disease. Secondary prophylaxis can improve the prognosis of established rheumatic valvular disease. The recommended choice of treatment is long-term penicillin secondary prophylaxis (BMJ Best Practice (accessed Nov 20 2020))

PICO

Population: Children and adolescents with sore throat (pharyngitis)

Intervention: Penicillin treatment (any regimens)

Comparison: No penicillin treatment

Outcomes: Mortality, morbidity (rheumatic heart disease progression, recurrence of rheumatic fever, streptococcal throat infection), disability/ quality of life, adverse events

Setting: All countries and settings

Study design: Systematic review of randomised controlled trials

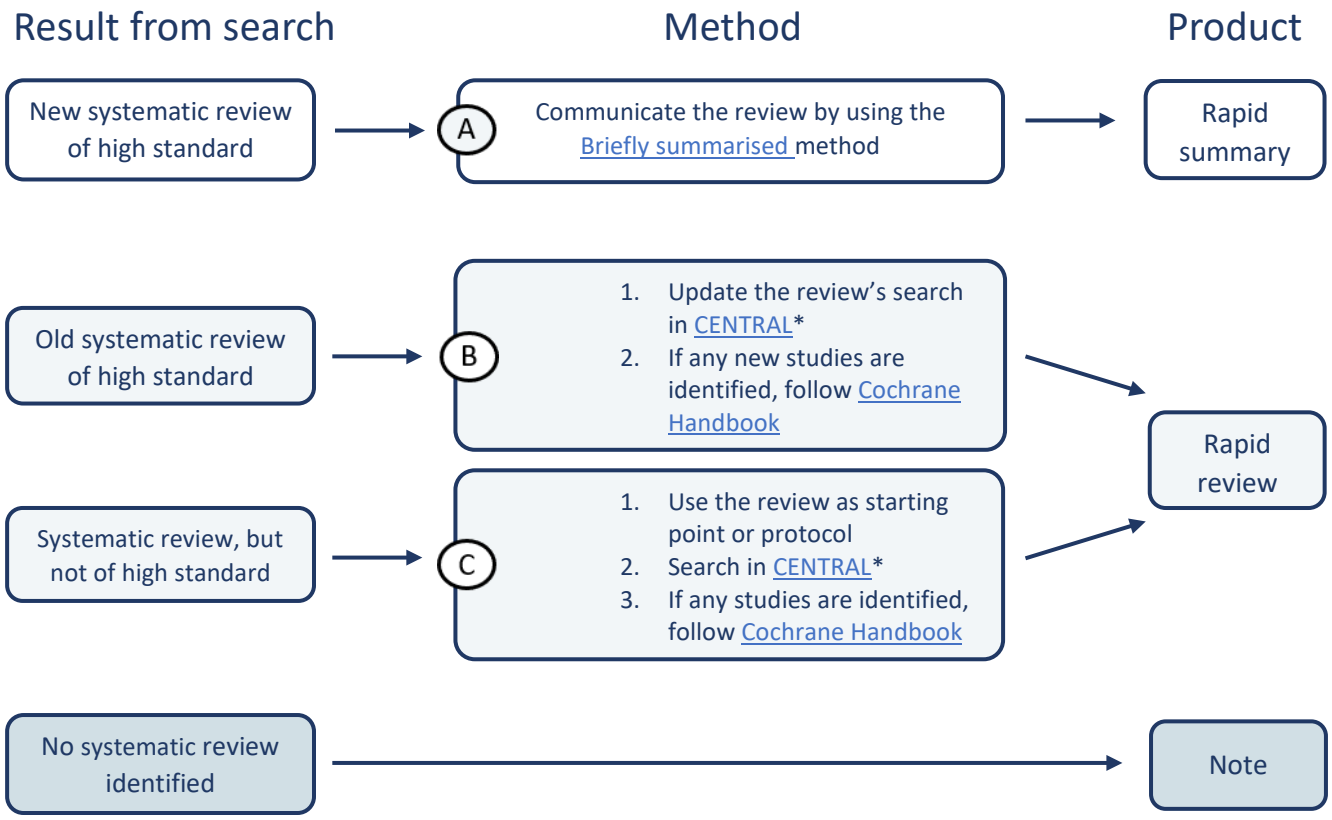
Description of the general methodological approach

For questions about effectiveness of interventions, a natural starting point is to try to find systematic reviews. To find systematic reviews, we here search in Epistemonikos.

As illustrated in figure 1, the method used and product produced will depend on what type of results we have from the search in Epistemonikos. If we identify a relatively new and high standard systematic review, we will make a communication product called a rapid summary. We will follow method A and produce the rapid summary according to Cochrane Norway's Briefly summarised method. If we find a systematic review that for some reason cannot be communicated in its present form as a rapid summary, we will make a rapid review. We will use either method B or C, depending on the type of challenge we find with the review in its present form. If we cannot find any systematic reviews in Epistemonikos, we will write a note describing this research gap so that it can, hopefully, be addressed with a systematic review in the future.

Systematic reviews of randomised controlled studies that evaluate effectiveness of interventions are relevant and we will not search for systematic reviews of observational studies.

Figure 1. Illustration of the general methodological approach



** We will perform searches for randomised controlled studies in CENTRAL only, even in updates of existing systematic reviews that have searched other places in their original search. All steps in a systematic review approach, selecting studies, assessing risk of bias, making analyses and judging the certainty of the evidence (GRADE), is according to Cochrane Handbook for Systematic Reviews of Interventions 2020.*

Description of this rapid summary's method

We searched Epistemonikos for systematic reviews in December 2020. We used the following search strategy:

(title:((penicillin*) OR (antibiotic*)) OR abstract:((penicillin*) OR (antibiotic*))) AND (title:(("sore throat") OR (streptococ*)) OR abstract:(("sore throat") OR (streptococ*)))
Filters: systematic review

One person performed the search and selected relevant systematic reviews and the other double checked.

We selected relevant analyses and sub-analyses for our specific PICO. We extracted the analysis from the review that reported the effect of penicillin on relevant outcomes. We used Review Manager (RevMan) Version 5.4 from 2020. Relevant analyses or sub-analyses where the systematic review authors had not judged the certainty of the evidence (GRADE), we performed GRADE. Two people independently judged the certainty of the evidence (GRADE) by using the software GRADEpro GDT: GRADEpro Guideline Development Tool.

Results

We found 289 systematic reviews of which one was relevant (Spinks 2013) for our PICO question. We assessed this Cochrane review as up-to-date according to the Cochrane Handbook for Systematic Reviews of Interventions 2020. We followed the method A approach and produced the rapid summary according to Cochrane Norway's Briefly summarised method.

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Information about the included studies

PICO	What we searched for	What we found in the systematic review
Study design	Systematic reviews of randomised and quasi-randomised controlled trials	According to the systematic review: Randomised and quasi-randomised controlled trials (17 of which were included in our rapid summary)
Population	Children and adolescents with sore throat (pharyngitis) (5-19 years)	According to the systematic review: **Age:** Age varied from less than 1 year to 60 years. For the 17 studies included in our rapid summary: Four of the relevant studies included only children (El-Daher 1991; Pichichero 1987; Siegel 1961; Zwart 2003), while 5 studies (Bennike 1951; Chapple 1956; Dagnelie 1996; De Meyere 1992; Middleton 1988) included all ages and 8 studies (Brink 1951; Brumfitt 1957; Cantanzaro 1954; Chamovitz 1954; Denny 1950; Denny 1953; Wannamaker 1951; Zwart 2000) included young adults (mainly in the military). **Condition:** All studies included people with sore throat of which 6 studies included only people with strepptococcal thoat infection (Cantanzaro 1954; Dagnelie 1996; De Meyere 1992; El-Daher 1991; Middleton 1988; Pichichero 1987)
Intervention and comparison	Intervention: Penicillin (any regimens) Comparison: No penicillin	According to the systematic review: **Intervention:** Penicillin. Oral penicillin in 7 studies (Chapple 1956; Dagnelie 1996; De Meyere 1992; El-Daher 1991; Pichichero 1987; Zwart 2000; Zwart 2003) and intramuscular injection in 9 studies (Bennike 1951; Brink 1951; Brumfitt 1957; Cantanzaro 1954; Chamovitz 1954; Denny 1950; Denny 1953: Siegel 1961; Wannamaker 1951)) and not described in one study (Middleton 1988). Dose: Not described in the systematic review Duration: 1-10 days. 1-3 days in 2 studies (Pichichero 1987; Wannamaker 1951), 4 days in 3 studies (Brink 1951; Brumfitt 1957; Denny 1950), 5 days in 3 studies (Cantanzaro 1954; Chapple 1956; Denny 1953), 6 days (Bennike 1951), 7 days in 2 studies (Zwart 2000; Zwart 2003), 10 days (El-Daher 1991) and not described in 5 studies (Chamovitz 1954; Dagnelie 1996; De Meyere 1992; Middleton 1988; Siegel 1961) **Comparison:** Nothing in 7 studies (Bennike 1951; Brink 1951; Brumfitt 1957; Cantanzaro 1954; Denny 1950; Siegel 1961; Wannamaker 1951), placebo in 9 studies (Chapple 1956; Dagnelie 1996; De Meyere 1992; Denny 1953; El-Daher 1991; Middleton 1988, Pichichero 1987; Zwart 2000; Zwart 2003) and not described in one study (Chamovitz 1954).
Outcomes	Mortality Morbidity - rheumatic heart disease progression - recurrences of rheumatic fever - streptococcal throat infections Disability/Quality of life Safety	According to the systematic review: Mortality (not reported) Morbidity - rheumatic heart disease progression (not reported) - recurrences of rheumatic fever (14 studies: Bennike 1951; Brink 1951; Brumfitt 1957; Cantanzaro 1954; Chamovitz 1954; Chapple 1956; Dagnelie 1996; De Meyere 1992; Denny 1950; Denny 1953; Pichichero 1987; Siegel 1961; Wannamaker 1951; Zwart 2000) - streptococcal throat infections (Brink 1951; Brumfitt 1957; Chapple 1956; Dagnelie 1996; De Meyere 1992; Denny 1953; El-Daher 1991; Middleton 1988; Zwart 2000; Zwart 2003) Disability/Quality of life (not reported) Safety (not reported)
Setting	All countries and settings	According to the systematic review: **Setting:** The systematic review did not report on setting for all studies. Where reported, 7 studies were in the military (Brink 1951; Brumfitt 1957; Cantanzaro 1954; Chamovitz 1954; Denny 1950; Denny 1953; Wannamaker 1951) and 1 in general practice (Dagnelie 1996). **Countries:** Not reported by the systematic review
Follow-up	All follow-up times (might be divided into short, medium and long follow-up time)	The systematic review did not describe the length of the studies, nor their follow-up time. The follow-up time for the outcomes were reported and are shown in the Summary of findings table

All the references to the primary studies are listed in the Spinks 2013 systematic review

Analyses

We report three meta-analyses of which one was directly extracted from the Spinks 2013 systematic review (analysis 4.2) and two meta-analysis (analysis 1.4.1 and 1.7.1) were adjusted to include studies examining the effect of penicillin versus no penicillin. The adjustment we did was to remove one study that did not use penicillin from the meta-analysis.

Meta-analyses

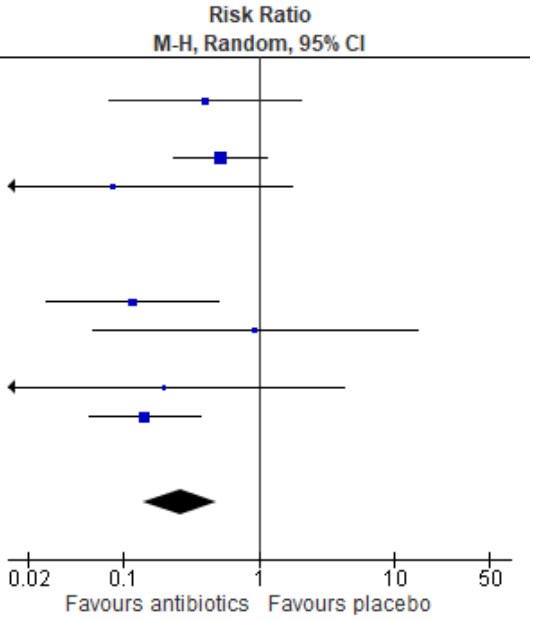
Morbidity: Recurrence of rheumatic fever

Random effect model

Meta-analysis by Spinks 2013.

Study or Subgroup	Antibiotics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bennike 1951	0	238	0	268		Not estimable
Brink 1951	2	197	5	198	12.2%	0.40 [0.08, 2.05]
Brumfitt 1957	0	62	0	59		Not estimable
Catanzaro 1954	12	420	12	220	33.2%	0.52 [0.24, 1.15]
Chamovitz 1954	0	257	2	109	4.0%	0.09 [0.00, 1.76]
Chapple 1956	0	99	0	97		Not estimable
Dagnelie 1996	0	121	0	118		Not estimable
De Meyere 1992	0	87	0	94		Not estimable
Denny 1950	2	798	17	804	14.5%	0.12 [0.03, 0.51]
Denny 1953	1	53	1	50	4.8%	0.94 [0.06, 14.68]
Pichichero 1987	0	59	0	58		Not estimable
Siegel 1961	0	605	2	608	4.0%	0.20 [0.01, 4.18]
Wannamaker 1951	5	978	35	996	27.3%	0.15 [0.06, 0.37]
Zwart 2000	0	358	0	164		Not estimable
Total (95% CI)		**4332**		**3843**	**100.0%**	**0.27 [0.14, 0.50]**
Total events	22		74			

Heterogeneity: Tau² = 0.15; Chi² = 7.61, df = 6 (P = 0.27); I² = 21%
Test for overall effect: Z = 4.16 (P < 0.0001)

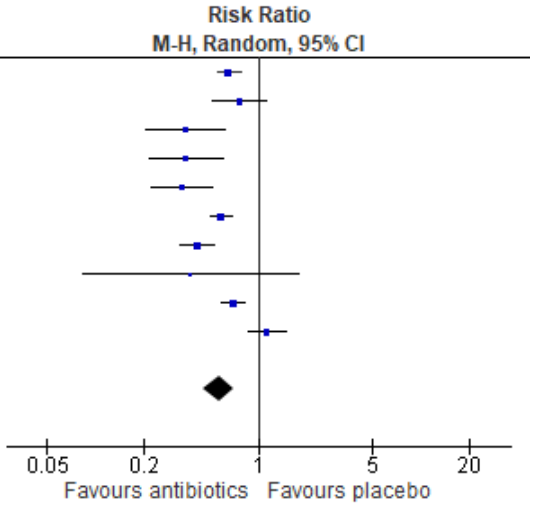


Morbidity: Streptococcal throat infection (clinical symptoms + strep A positive test) after 3 days

Random effect model (reanalysed to include penicillin only)

Study or Subgroup	Penicillin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Brink 1951	119	277	129	198	13.3%	0.66 [0.56, 0.78]
Brumfitt 1957	21	42	26	40	10.0%	0.77 [0.53, 1.12]
Chapple 1956	13	68	22	41	7.2%	0.36 [0.20, 0.63]
Dagnelie 1996	13	55	36	55	7.9%	0.36 [0.22, 0.60]
De Meyere 1992	18	82	59	91	9.0%	0.34 [0.22, 0.52]
Denny 1953	89	157	48	50	13.6%	0.59 [0.51, 0.68]
El-Daher 1991	42	111	106	118	12.2%	0.42 [0.33, 0.54]
Middleton 1988	2	24	5	23	1.7%	0.38 [0.08, 1.78]
Zwart 2000	102	178	68	83	13.4%	0.70 [0.59, 0.82]
Zwart 2003	39	53	28	43	11.8%	1.13 [0.86, 1.48]
Total (95% CI)		**1047**		**742**	**100.0%**	**0.57 [0.46, 0.71]**
Total events	458		527			

Heterogeneity: Tau² = 0.08; Chi² = 51.18, df = 9 (P < 0.00001); I² = 82%
Test for overall effect: Z = 5.18 (P < 0.00001)

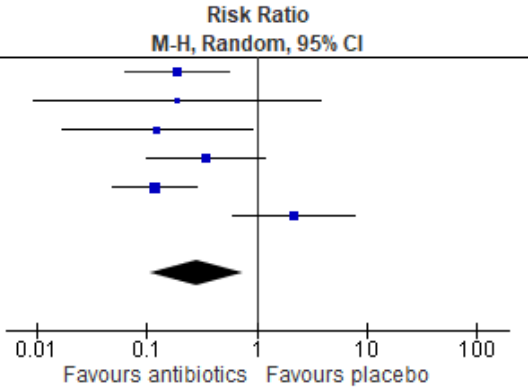


Morbidity: Streptococcal throat infection (clinical symptoms + strep A positive test) after 1 week

Random effect model (reanalysed to include penicillin only)

Study or Subgroup	Antibiotics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Brink 1951	4	277	15	198	20.3%	0.19 [0.06, 0.57]
Brumfitt 1957	0	42	2	40	7.5%	0.19 [0.01, 3.85]
Dagnelie 1996	1	34	10	42	12.5%	0.12 [0.02, 0.92]
De Meyere 1992	3	61	10	70	18.8%	0.34 [0.10, 1.19]
Denny 1953	6	157	16	50	22.2%	0.12 [0.05, 0.29]
Zwart 2003	8	53	3	43	18.6%	2.16 [0.61, 7.66]
Total (95% CI)		**624**		**443**	**100.0%**	**0.29 [0.11, 0.75]**
Total events	22		56			

Heterogeneity: Tau² = 0.89; Chi² = 14.89, df = 5 (P = 0.01); I² = 66%
Test for overall effect: Z = 2.54 (P = 0.01)



Summary of findings table (GRADE)

Penicillin compared to placebo/control/no penicillin for the treatment of sore throat (acute pharyngitis)

Patient or population: People presenting to primary care facilities with symptoms of sore throat.
Setting: Primary care
Intervention: Penicillin
Comparison: Placebo/control/no penicillin

Outcomes	Anticipated absolute effects* (95% CI) Risk with no penicillin	Risk with penicillin	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Incidence of acute rheumatic fever within 2 months. (analysis 4.2)	19 per 1 000	**5 per 1 000** (3 to 10)	**RR 0.27** (0.14 to 0.50)	8175 (14 RCTs)	⨁⨁⨁◯ MODERATE [a]	Penicillin probably reduces the incidence of acute rheumatic fever within 2 months among people with sore throat
Streptococcal throat infection at 3 days (Analysis 1.4.1. Removed one study that did not use penicillin (MacDonnal1951))	710 per 1 000	**405 per 1 000** (327 to 504)	**RR 0.57** (0.46 to 0.71)	1789 (10 RCTs)	⨁⨁⨁◯ MODERATE [b]	Penicillin probably reduces the number of people with streptococcal sore throat on day 3 among people with sore throat
Streptococcal throat infection at 1 week Analysis 1.7.1. Removed one study that did not use penicillin (MacDonnal1951))	126 per 1 000	**37 per 1 000** (14 to 95)	**RR 0.29** (0.11 to 0.75)	1067 (6 RCTs)	⨁⨁⨁◯ MODERATE [a]	Penicillin probably reduces the number of people with streptococcal sore throat after a week among people with sore throat

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

Explanations

a. Mostly old studies where it is unclear whether it is a true RCT resulting in quite unclear risk of bias (downgraded 1 point for risk of bias)
b. I2 is high (over 60%) thus downgraded one point

GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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Reference to the systematic review

Spinks 2013

Spinks A, Glasziou PP, Del Mar CB. Antibiotics for sore throat. Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD000023. DOI: 10.1002/14651858.CD000023.pub4. Accessed 21 December 2020.

Suggested citation

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