NIPH
Norwegian Institute of Public Health

Secondary prophylaxis with penicillin for rheumatic fever or established rheumatic heart disease - a rapid review

Plain language summary

Prophylactic penicillin probably reduces rheumatic fever recurrences and streptococcal throat infections among children and adolescents with rheumatic fever or rheumatic heart disease (moderate certainty of evidence).

The effect of prophylactic penicillin on mortality and adverse events among children and adolescents with rheumatic fever or rheumatic heart disease is uncertain (very low certainty of evidence).

No studies reported the effects on rheumatic heart disease progression and disability among children and adolescents with rheumatic fever or rheumatic heart disease.

Table. Effectiveness of prophylactic penicillin among children and adolescents with rheumatic fever of heart disease

What happens?	No prophylactic penicillin	Prophylactic penicillin	Certainty of evidence[1]
Rheumatic fever recurrences Prophylactic penicillin probably reduces rheumatic fever recurrences among children and adolescents with rheumatic fever or rheumatic heart disease (follow up: range 6 months to 5 years)	83 per 1 000 children	25 per 1 000 children (10 to 60)*	⊕⊕⊕◯ MODERATE
Streptococcal throat infections Prophylactic penicillin probably reduces streptococcal throat infections among children and adolescents with rheumatic fever or rheumatic heart disease (follow up: range 6 months to 2 years)	126 per 1 000 children	29 per 1 000 children (11 to 79)*	⊕⊕⊕◯ MODERATE
Rheumatic heart disease progression Not reported in the included studies (1 ongoing study will report on this)	Not reported in the included studies		
Mortality – all cause The evidence is very uncertain about the effect of prophylactic penicillin on all-cause mortality among children and adolescents with rheumatic fever or rheumatic heart disease (follow up: range 1 years to 5 years)	We do not report numbers of results of very low certainty		⊕◯◯◯ VERY LOW
Mortality – due to heart failure or carditis The evidence is very uncertain about the effect of prophylactic penicillin on mortality due to heart failure or carditis among children and adolescents with rheumatic fever or rheumatic heart disease (follow up: range 1 years to 5 years)	We do not report numbers of results of very low certainty		⊕◯◯◯ VERY LOW
Adverse events The evidence is very uncertain about the effect of prophylactic penicillin on adverse events among children and adolescents with rheumatic fever or rheumatic heart disease (follow up: range 6 months to 5 years)	We do not report numbers of results of very low certainty		⊕◯◯◯ VERY LOW
Disability/Quality of Life Not reported in the included studies	Not reported in the included studies		

For more details and information, see the Results of this rapid review. * 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.

Commission

The Norwegian Institute of Public Health, (NIPH) performed a rapid review commissioned by the Bergen Centre for Ethics and Priority Setting (BCEPS), University of Bergen. The assignment was to systematically summaries evidence on secondary prophylaxis with penicillin for rheumatic fever or established rheumatic heart disease.

Background

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)).

The clinical support tool from BMJ Best Practice provides a complete clinical decision tool about rheumatic fever and a list of existing clinical guidelines (both international, regional and national). Among the listed guidelines, the following cover the secondary prevention of rheumatic fever:

- South African Guidelines
- Australian Guidelines
- Saudi Arabian Guidelines
- Fiji Guidelines
- New Zealand Guidelines
- Indian Guidelines
- Statement from American Heart Association
- WHO Technical Report

BMJ Best Practice also has one section about secondary prevention of rheumatic fever states that (accessed January 2021):

"The main priority of long-term management is to ensure secondary prophylaxis is adhered to. Secondary prophylaxis is clinically effective and cost-effective…. The World Health Organization (WHO) defines secondary prophylaxis for rheumatic fever as "the continuous administration of specific antibiotics to patients with a previous attack of rheumatic fever, or well-documented rheumatic heart disease…. The most effective antibiotic is penicillin and the most effective method of delivery of penicillin is by intramuscular injection of long-acting benzathine benzylpenicillin every 3 to 4 weeks… "

PICO

Population: Children and adolescents with rheumatic fever or rheumatic heart disease

Intervention: Prophylactic penicillin (any regimens)

Comparison: No prophylactic penicillin

Outcomes: Mortality, Morbidity (rheumatic heart disease progression, recurrence of rheumatic fever, streptococcal throat infection), Disability/QoL, Adverse events

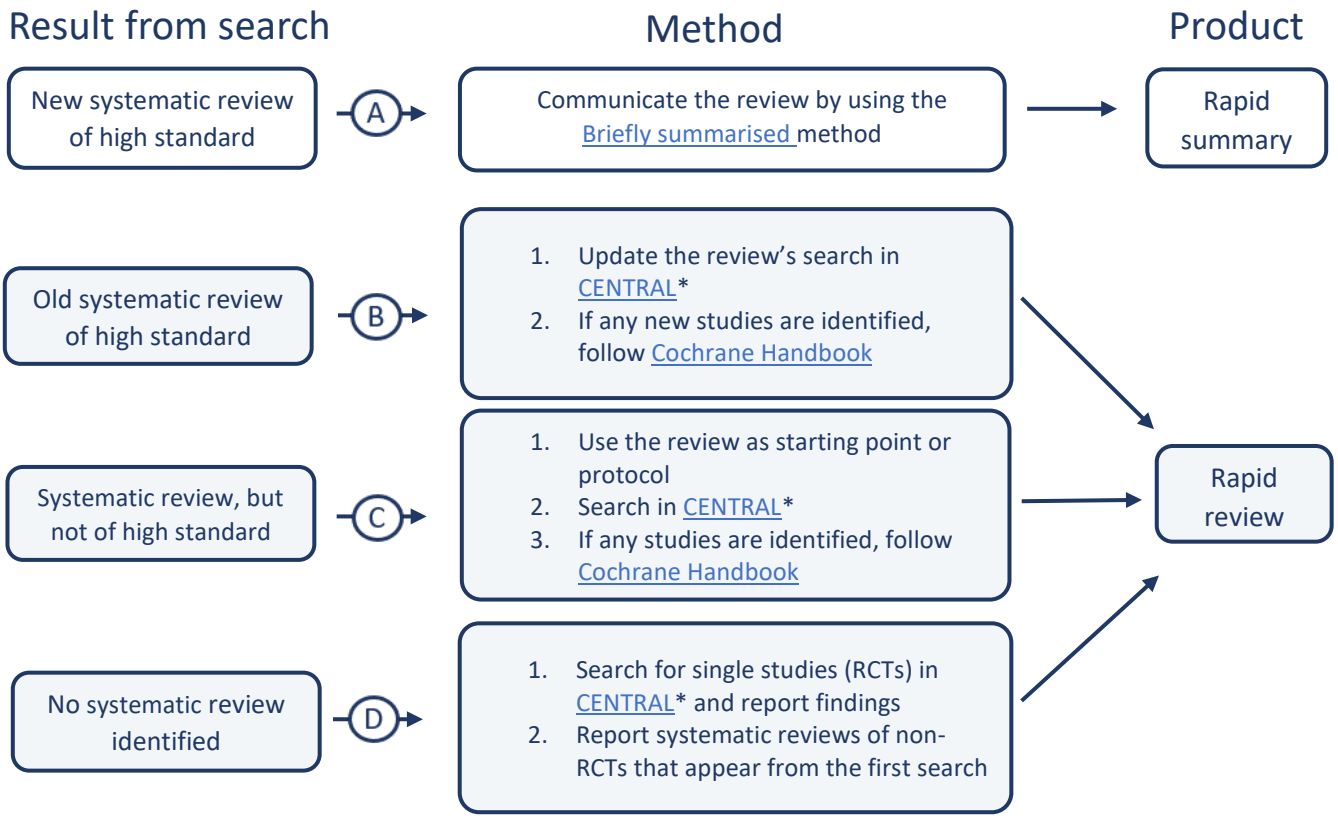
Setting: All countries and settings, **Study design:** Randomised and quasi-randomised controlled trials

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 rapid review where we seek to find single studies that are randomised controlled trials (RCTs). Also, other systematic reviews of non-RCT will be reported from the initial search for systematic reviews. 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, is according to Cochrane Handbook for Systematic Reviews of Interventions 2020.*

Description of this rapid review's method

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

(title:(("rheumatic fever") OR ("rheumatic heart disease") OR (acute rheumatic fever") OR (carditis)) OR abstract:(("rheumatic fever") OR ("rheumatic heart disease") OR (acute rheumatic fever") OR (carditis))) AND (title:(penicillin) OR abstract:(penicillin))
Filters: systematic review

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

Results

We searched for systematic reviews in Epistemonikos in October 2020. We found six systematic reviews and one was relevant (Manyemba 2002) for our PICO question. We assessed this Cochrane review as not up-to-date according to the Cochrane Handbook for Systematic Reviews of Interventions 2020. We followed the method C approach and produced the rapid review according to the Cochrane Handbook for Systematic Reviews of Interventions 2020.

The steps and results in the method C approach

Based on the Manyemba 2002 Cochrane systematic review we performed a new literature search in Cochrane Central Register of Controlled Trials (CENTRAL).

We used the following search strategy:

ID	Search	Hits
#1	MeSH descriptor: [Rheumatic Fever] explode all trees	183
#2	rheumatic*	7837
#3	chorea*	410
#4	rhd	117
#5	rheumatism	4229
#6	#1 or #2 or #3 or #4 or #5	10885
#7	MeSH descriptor: [Penicillins] explode all trees	5678
#8	(penicillin* or ultracillin or phenoxymethylpenicillin* or penicilium* or penicillium* or orapen*)	3834
#9	MeSH descriptor: [Antibiotic Prophylaxis] explode all trees	1280
#10	(prophylaxis or prophylactic)	37348
#11	antibiotic*	32767
#12	(secondary and prevent*)	47323
#13	#7 or #8 or #9 or #10 or #11 or #12	107838
#14	#6 and #13 in Trials	480

Our search, carried out in November 2020, resulted in 480 hits of studies of which six primary studies (Brick 1950, Evans 1950, Feinstein 1966, Gale 1952, Kohn 1953, and Padmavati 1973) were included and 1 ongoing study (Beaton 2019) was relevant to report.

We selected relevant studies, retrieved information from the studies, assessed risk of bias, and made analyses by using the Review Manager (RevMan) Version 5.4 from 2020. Two people independently judged the certainty of the evidence (GRADE) by using the software GRADEpro GDT: GRADEpro Guideline Development Tool.

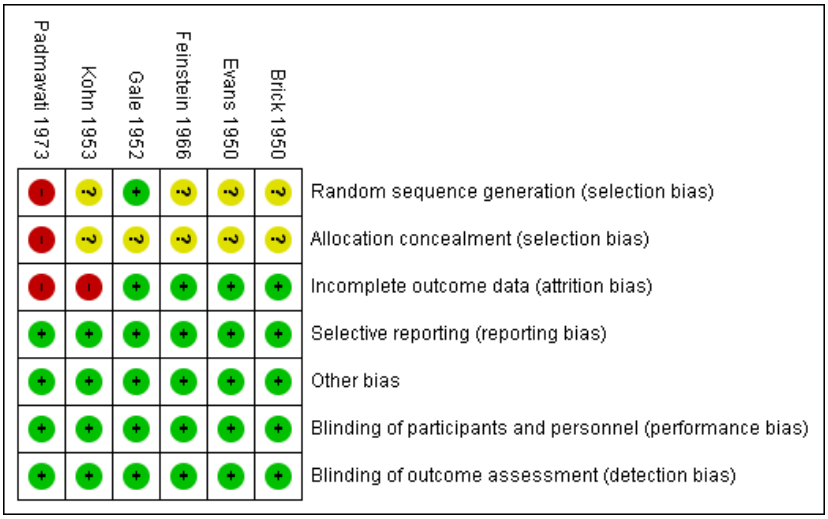
Information about the included studies

PICO	What did we search for?	What did we find?
Study design	Randomised and quasi-randomised controlled trials	Quasi-randomised controlled trials (not enough description to clearly judge, but we believe they were not truly randomised).
Population	Children and adolescents with rheumatic fever or rheumatic heart disease (5-19 years)	**Age:** The age varied in the studies from 5 to 24 years. One study (Brick 1950) reported average age (11 years), one study (Kohn 1953) did not report the age of the children, and four studies reported age range (5-13 years (Evans 1950), 14-24 years (Feinstein 1966), and 5-15 years (Gale 1952), and 5-19 years (Padmavati 1973)). **Rheumatic fever episode:** had occurred 3-5 years (Feinstein 1966), 2 years (Kohn 1953) prior to study enrolment and was not reported in 4 studies (Brick 1950, Evans 1950, Gale 1952, Padmavati 1973) **Rheumatic heart disease:** was not established in any of the participants in one study (Feinstein 1966), was established in all participants in two studies (Gale 1952, Padmavati 1973) and not reported in 3 studies (Brick 1950, Evans 1950, Kohn 1953). However, we assume that a significant number had established rheumatic heart disease in at least two of these studies (Brick 1950, Evans 1950). The children and adolescents were inpatients (Evans 1950), outpatients (Brick 1950, Feinstein 1966, Padmavati 1973), or both inpatients and outpatients (Gale 1952), or followed through the school-setting at home (Kohn 1953).
Intervention and comparison	Intervention: Prophylactic penicillin (any regimens) Comparison: No prophylactic penicillin	**Intervention:** Prophylactic penicillin (5 studies oral (Brick 1950; Evans 1950; Feinstein 1966; Gale 1952; Kohn 1953), 1 study injection (Padmavati 1973)). Dose: 100,000 U per day (Brick 1950; Evans 1950), 200,000 U per day (Feinstein 1966; Gale 1952). 800,000 U per day (Kohn 1953), dose not specified for injection (Padmavati 1973) Frequency: Daily with no further information provided (Evans 1950; Feinstein 1966; Gale 1952) daily, but with summer months stop period (Evans 1950), for 7 consecutive days of the first week of each month (Kohn 1953), once a month for injection (Padmavati 1973). **Comparison:** Nothing (Evans 1950, Kohn 1953), vitamin B injection (Padmavati 1973), placebo tablet (Feinstein 1966), lactose tablet (Gale 1952) or "control" (Brick 1950).
Outcomes	Mortality Morbidity - rheumatic heart disease progression - recurrences of rheumatic fever - streptococcal throat infections Disability/Quality of life Safety	Mortality (Kohn 1953; Padmavati 1973) Morbidity - rheumatic heart disease progression (no studies) - recurrences of rheumatic fever (Brick 1950; Evans 1950; Feinstein 1966; Gale 1952; Kohn 1953; Padmavati 1973). One study (Padmavati 1973) not included in meta-analysis. - streptococcal throat infections (Brick 1950; Evans 1950; Feinstein 1966; Gale 1952; Kohn 1953; Padmavati 1973). Two studies not included in meta-analysis (Kohn 1953; Padmavati 1973) Disability/Quality of life (no studies) Safety (Brick 1950; Gale 1952; Kohn 1953)
Setting	All countries and settings	**Setting:** hospital (Brick 1950, Evans 1950, Gale 1952, Padmavati 1973), clinic (Feinstein 1966), or at home (Kohn 1953). The children and adolescents were inpatients (Evans 1950), outpatients (Brick 1950, Feinstein 1966, Padmavati 1973), or both inpatients and outpatients (Gale 1952), or followed through the school-setting at home (Kohn 1953). **Countries:** Canada (Brick 1950), India (Padmavati 1973), UK (Evans 1950, Gale 1952), and USA (Feinstein 1966, Kohn 1953)
Follow-up	All follow-up times (might be divided into short, medium and long follow-up time)	Follow-up time ranged from 6 months (Evans 1950, Gale 1952), up to 2 years (Brick 1950, Feinstein 1966, Padmavati 1973), and up to 5 years (Kohn 1953).

Information about the ongoing study

We found one relevant ongoing study, Beaton 2019 (ClinicalTrials.gov Identifier: NCT03346525). The name of the study is "Determining the Impact of Penicillin in Latent RHD: The GOAL Trial (GOAL)". The intervention is intramuscular benzathine penicillin G (BPG) prophylaxis and the comparison is no prophylaxis. The population is children from 5 to 17 years with rheumatic heart disease. Their main outcome is regression of valvular changes. The trial is set in Uganda.

Risk of bias assessment

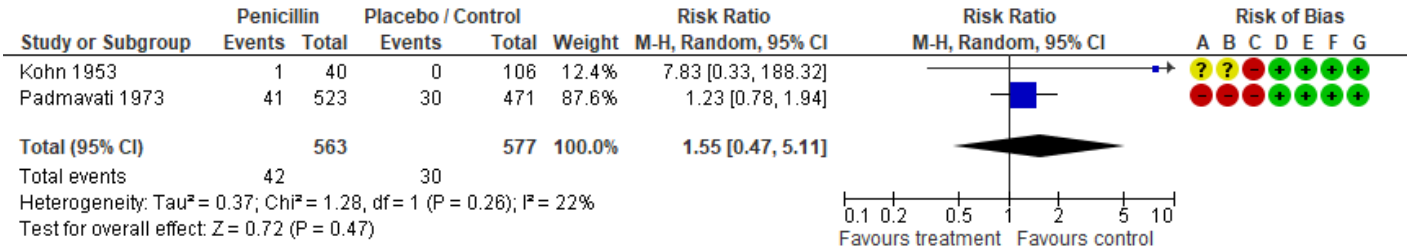


Analyses

Meta-analyses

Mortality: All-cause mortality

Random effect model



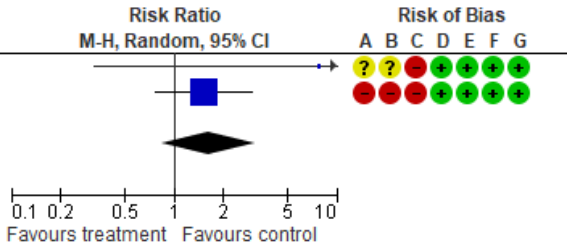
Fixed effect model

Mortality: Due to heart failure or carditis

Random effect model

Study or Subgroup	Penicillin Events	Penicillin Total	Placebo / Control Events	Placebo / Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Kohn 1953	1	40	0	106	4.3%	7.83 [0.33, 188.32]
Padmavati 1973	22	523	13	471	95.7%	1.52 [0.78, 2.99]
Total (95% CI)		**563**		**577**	**100.0%**	**1.64 [0.85, 3.16]**
Total events	23		13			

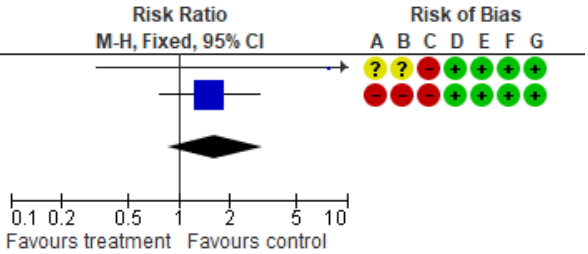
Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 1 (P = 0.32); I² = 0%
Test for overall effect: Z = 1.46 (P = 0.14)



Fixed effect model

Study or Subgroup	Penicillin Events	Penicillin Total	Placebo / Control Events	Placebo / Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kohn 1953	1	40	0	106	2.0%	7.83 [0.33, 188.32]
Padmavati 1973	22	523	13	471	98.0%	1.52 [0.78, 2.99]
Total (95% CI)		**563**		**577**	**100.0%**	**1.65 [0.86, 3.16]**
Total events	23		13			

Heterogeneity: Chi² = 0.97, df = 1 (P = 0.32); I² = 0%
Test for overall effect: Z = 1.51 (P = 0.13)

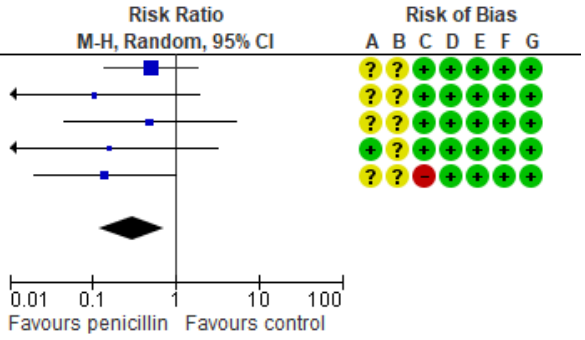


Morbidity: Recurrence of rheumatic fever

Random effect model

Study or Subgroup	Penicillin Events	Penicillin Total	Placebo / Control Events	Placebo / Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Brick 1950	3	38	6	38	46.8%	0.50 [0.13, 1.85]
Evans 1950	0	155	4	145	9.5%	0.10 [0.01, 1.91]
Feinstein 1966	1	82	2	79	14.2%	0.48 [0.04, 5.21]
Gale 1952	0	41	2	32	8.9%	0.16 [0.01, 3.16]
Kohn 1953	1	40	19	106	20.6%	0.14 [0.02, 1.01]
Total (95% CI)		**356**		**400**	**100.0%**	**0.30 [0.12, 0.73]**
Total events	5		33			

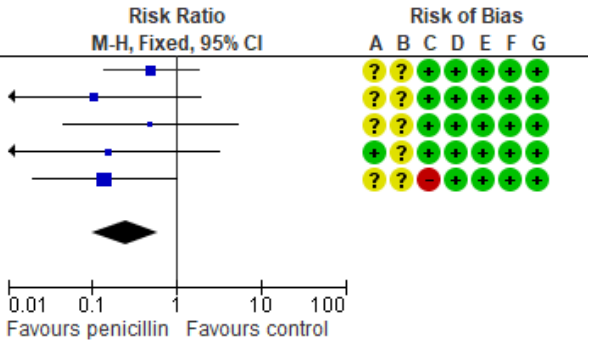
Heterogeneity: Tau² = 0.00; Chi² = 2.17, df = 4 (P = 0.70); I² = 0%
Test for overall effect: Z = 2.65 (P = 0.008)



Fixed effect model

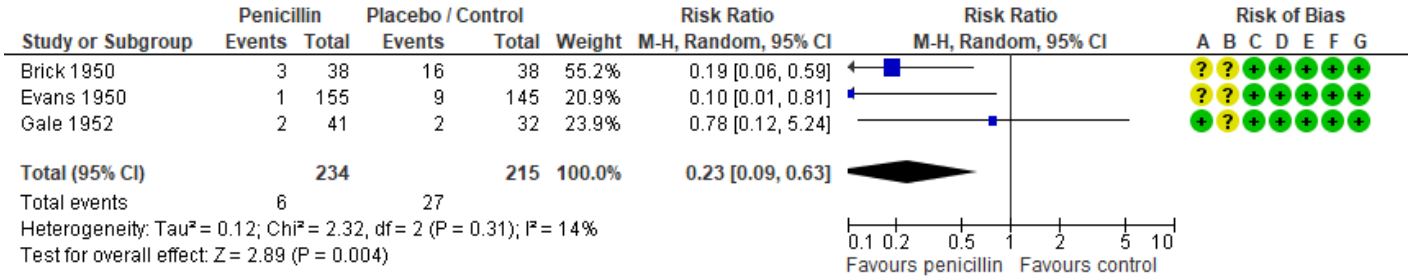
Study or Subgroup	Penicillin Events	Penicillin Total	Placebo / Control Events	Placebo / Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brick 1950	3	38	6	38	23.2%	0.50 [0.13, 1.85]
Evans 1950	0	155	4	145	18.0%	0.10 [0.01, 1.91]
Feinstein 1966	1	82	2	79	7.9%	0.48 [0.04, 5.21]
Gale 1952	0	41	2	32	10.8%	0.16 [0.01, 3.16]
Kohn 1953	1	40	19	106	40.2%	0.14 [0.02, 1.01]
Total (95% CI)		**356**		**400**	**100.0%**	**0.25 [0.10, 0.60]**
Total events	5		33			

Heterogeneity: Chi² = 2.17, df = 4 (P = 0.70); I² = 0%
Test for overall effect: Z = 3.08 (P = 0.002)

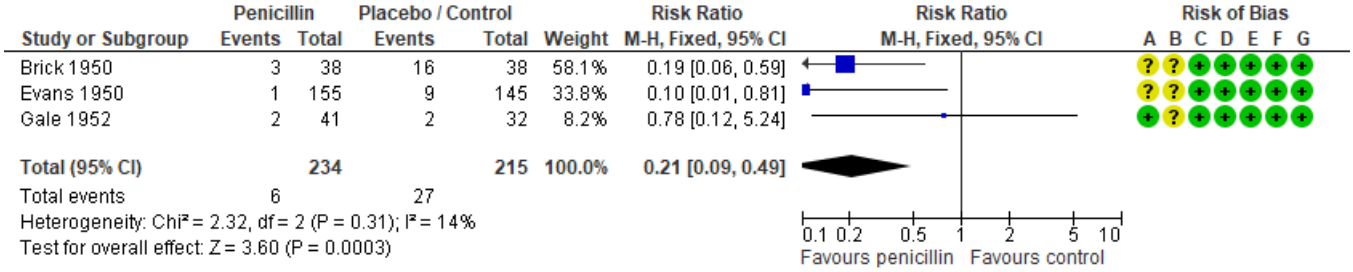


Morbidity: Streptococcal throat infection (clinical symptoms + strep A positive test)

Random effect model

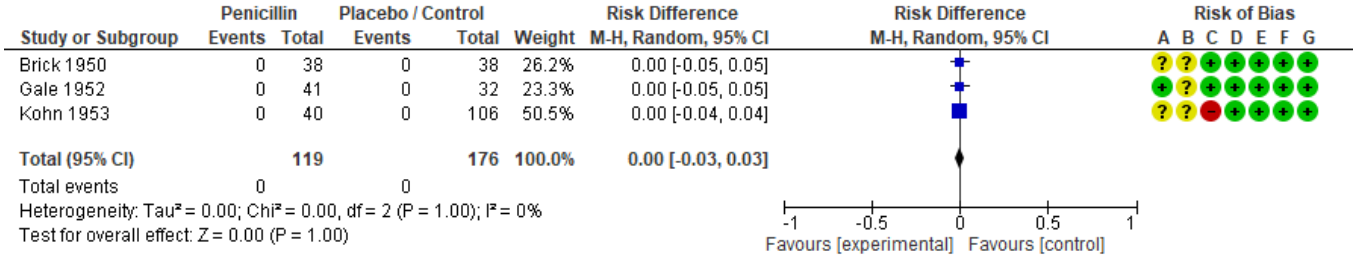


Fixed effect model



Adverse events

Random effect model



Summary of findings table (GRADE)

Prophylactic penicillin compared to no prophylactic penicillin for children and adolescents with rheumatic fever or rheumatic heart disease

Patient or population: Children and adolescents with rheumatic fever or rheumatic heart disease
Setting: Hospital, clinic, home (Canada, India, UK and USA)
Intervention: Prophylactic penicillin
Comparison: No prophylactic penicillin (placebo/control/no penicillin)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with prophylactic penicillin				
Mortality – all cause follow up: range 1 years to 5 years	52 per 1 000	**81 per 1 000** (24 to 266)	**RR 1.55** (0.47 to 5.11)	1140 (2 RCTs) (Kohn 1953; Padmavati 1973)	⨁◯◯◯ VERY LOW [a,b]	The evidence is very uncertain about the effect of prophylactic penicillin on all-cause mortality among children and adolescents with rheumatic fever or rheumatic heart disease
Mortality - due to heart failure or carditis follow up: range 1 years to 5 years	23 per 1 000	**37 per 1 000** (19 to 71)	**RR 1.64** (0.85 to 3.16)	1140 (2 RCTs) (Kohn 1953; Padmavati 1973)	⨁◯◯◯ VERY LOW [a,b]	The evidence is very uncertain about the effect of prophylactic penicillin on mortality due to heart failure or carditis among children and adolescents with rheumatic fever or rheumatic heart disease
Rheumatic heart disease progression						Outcome not reported in the included studies
Rheumatic fever recurrences follow up: range 6 months to 5 years	83 per 1 000	**25 per 1 000** (10 to 60)	**RR 0.30** (0.12 to 0.73)	756 (5 RCTs) (Brick 1950; Evans 1950; Feinstein 1966; Gale 1952; Kohn 1953)	⨁⨁⨁◯ MODERATE [a]	Prophylactic penicillin probably reduces rheumatic fever recurrences among children and adolescents with rheumatic fever or rheumatic heart disease
Streptococcal throat infections follow up: range 6 months to 2 years	126 per 1 000	**29 per 1 000** (11 to 79)	**RR 0.23** (0.09 to 0.63)	449 (3 RCTs) (Brick 1950; Evans 1950; Gale 1952)	⨁⨁⨁◯ MODERATE [a]	Prophylactic penicillin probably reduces streptococcal throat infections among children and adolescents with rheumatic fever or rheumatic heart disease
Adverse events follow up: range 6 months to 5 years	0 per 1 000	**0 per 1 000** (0 to 0)	RR not estimable	295 (3 RCTs) (Brick 1950; Gale 1952; Kohn 1953)	⨁◯◯◯ VERY LOW [a,c]	The evidence is very uncertain about the effect of prophylactic penicillin on adverse events among children and adolescents with rheumatic fever or rheumatic heart disease
Disability/ Quality of life						Outcome not reported in the included studies

***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
a. Mostly old studies where it is unclear whether it is a true RCT resulting in high risk of bias (downgraded 1 point for risk of bias)
b. Broad 95% CI that crosses the "the line of no effect" (downgraded 2 points for imprecision)
c. Number of events are very low and unable us to detect group differences (downgraded 2 points for imprecision)

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

References to included studies

Brick 1950
Brick M, McKinley H, Gourley M, Roy TE, Keith JD. Oral penicillin prophylaxis in rheumatic fever patients. Canadian medical association journal 1950;63(3):255-8.

Evans 1950
Evans PJA. Oral penicillin in the prophylaxis of streptococcal infection and rheumatic relapse. Proceedings of the royal society of medicine 1950;43(3):12.

Feinstein 1966
Feinstein AR, Spagnuolo M, Levitt M, Jonas S, Tursky E. Discontinuation of antistreptococcal prophylaxis. A double-blind study in rheumatic patients free of heart disease. JAMA 1966;197(12):949-52.

Gale 1952
Gale AH, Gillespie WA, Perry CB. Oral penicillin in the prophylaxis of streptococcal infection in rheumatic children. Lancet 1952;2(2):61-3.

Kohn 1953
Kohn KH, Milzer A. Prophylaxis of recurrences of rheumatic fever with penicillin given orally. JAMA 1953.

Padmavati 1973
Padmavati S, Sharma KB, Jayaram O. Epidemiology and prophylaxis of rheumatic fever in Delhi--a five year follow-up. Singapore medical journal 1973;14(3):457-61

Reference to the ongoing study

Beaton 2019
Beaton A, Okello E, Engelman D, Grobler A, Scheel A, DeWyer A, Sarnacki R, Omara IO, Rwebembera J, Sable C, Steer A. Determining the impact of Benzathine penicillin G prophylaxis in children with latent rheumatic heart disease (GOAL trial): Study protocol for a randomized controlled trial. Am Heart J. 2019 Sep;215:95-105. doi: 10.1016/j.ahj.2019.06.001. Epub 2019 Jun 8. PMID: 31301533.

Reference to the review we used as protocol

Manyemba 2002
Manyemba J, Mayosi BM. Penicillin for secondary prevention of rheumatic fever. Cochrane Database of Systematic Reviews 2002, Issue 3. Art. No.: CD002227. DOI: 10.1002/14651858.CD002227.

Suggested citation

Fønhus MS, Dalsbø TK. Secondary prophylaxis with penicillin for rheumatic fever or established rheumatic heart disease - a rapid review. 2020. Norwegian Institute of Public Health (NIPH).

NIPH
Norwegian Institute of Public Health

The work behind this rapid review was carried out by researchers at NIPH September-December 2020 and was approved by Department Director, Ingvil Von Mehren Sæterdal December 2020. Last revision: January 2021