Systematic Review/Meta-analysis

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Adherence to penicillin treatment is essential for effective secondary prevention of rheumatic heart disease: a systematic review and meta-analysis

Ade M. Ambari, MD, PhD[a,b,*], Basuni Radi, MD, PhD[a,b], Bambang Dwiputra, MD[a,b], Dean Arityanti, MD[a], Thomas Rikl, MD[a,b], Maria P. Inggriani, MD[a], Faqrizal Ria Qhabibi, MD[a], Eliana Susilowati, MD[a], Indira Kalyana Makes, MD, MRes, MPH[a], Estu Rudiktyo, MD[a,b], Maarten J. Cramer, MD, PhD[c], Pieter Doevendans, MD, PhD, Prof[c,d], Budhi Setianto, MD, PhD, Prof[a,b], Anwar Santoso, MD, PhD[a,b]

Background: Penicillin is essential for secondary prevention of acute rheumatic fever (ARF) and rheumatic heart disease (RHD). However, the incidences of ARF recurrence and RHD progression remain high, particularly in endemic countries. This meta-analysis evaluated the effectiveness of penicillin adherence in secondary prevention of ARF recurrence and RHD progression.

Methods: The authors included original articles employing an observational study design in which the study population included patients with ARF or RHD and documented adherence to secondary prophylaxis with penicillin for secondary prevention. Systematic searches of the PubMed, Scopus, and Cochrane databases were performed. Moreover, the authors also conducted a snowballing literature search from Europe PMC to expand the included studies. The quality of each study was assessed using the National Institute of Health Quality Assessment Tool. The statistical analyses were conducted using Review Manager 5.4.1 software developed by Cochrane. In addition, the authors utilized pooled odds ratios (ORs) to compare the adherence techniques.

Results: A total of 310 studies were identified, of which 57 full-text articles were assessed for eligibility. The authors included six studies with 1364 patients for the qualitative synthesis and meta-analysis. Good adherence to penicillin for the secondary prophylaxis of ARF and RHD, significantly reduced the odds of ARF recurrence or RHD progression by up to 71% compared to that associated with poor adherence [pooled OR 0.29 (0.21 – 0.40); $I^2 = 0\%$ ($p = 0.56$); $Z = 7.64$ ($p < 0.00001$)].

Conclusion: Good adherence to penicillin for secondary prophylaxis in patients with ARF or RHD is essential for reducing the risk of ARF recurrence or RHD progression.

Keywords: acute rheumatic fever, adherence, penicillin, rheumatic heart disease, secondary prevention

Introduction

Rheumatic heart disease (RHD) is a major global health burden. In 2017, ~38–40.8 million cases of RHD were observed worldwide[1], with a significant discrepancy in the prevalence of RHD between endemic and non-endemic regions[2]. The prevalence of RHD is 3.4 cases per 100 000 people in non-endemic regions, whereas in endemic areas, it is greater than 1000 cases per 100 000 people[1]. RHD is responsible for premature deaths of 0.15 per 100 000 children and an annual case fatality rate of 1.5% of the global population[1,3]. According to the IMHE Global Burden of Disease report, the global prevalence of RHD exceeds 40 million cases, primarily concentrated in low-income and middle-income nations[4]. Furthermore, the prevalence of

HIGHLIGHTS

- Incidences of acute rheumatic fever and rheumatic heart disease remain high particularly in endemic countries.
- Penicillin adherence in acute rheumatic fever and rheumatic heart disease is believed to play a vital role in secondary prevention.
- Good adherence to penicillin for secondary prevention reduced the odds of acute rheumatic fever recurrence or rheumatic heart disease progression by up to 63%.
- Good adherence to penicillin is significantly essential for secondary prevention in acute rheumatic fever and rheumatic heart disease.

[a]Department of Cardiovascular Prevention and Rehabilitation, National Cardiovascular Center Harapan Kita, [b]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia, [c]Department of Cardiology, University Medical Centre Utrecht and [d]Central Military Hospital, Netherlands Heart Institute, Utrecht, The Netherlands

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*Corresponding author. Address: National Cardiovascular Center Harapan Kita Jl. Letjen S. Parman No. Kav. 87, RW 8, West Jakarta, DKI Jakarta, Indonesia 11420. Tel: +62 811 964 4123. E-mail: ade.ambari@inaprevent.org (A. M. Ambari).

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RHD increases with age, and the survival rate is determined by the availability of access and adherence to secondary prophylaxis to prevent ARF recurrence, the severity of the valve, and access to specialists and surgery[5,6]. Preventive measures have a vital role in efforts to reduce the global burden of RHD. RHD prevention and control is broadly divided into three parts, including primordial prevention, primary prevention, and secondary prevention[7,8].

Penicillin has been used for decades as a secondary preventive agent against group A streptococcus (GAS) infections that cause acute rheumatic fever (ARF) and RHD[9]. Intramuscular (IM) injection of benzathine penicillin G (BPG) is considered the first and most effective option for preventing ARF recurrence[10]. According to the scientific statement from the American Heart Association, prophylaxis with BPG as secondary prevention is crucial in preventing clinical deterioration and mortality in patients with RHD, in accordance with the newest guidelines[2]. Recent guidelines encourage the use of recommended antibiotic regimens as secondary prophylaxis in RHD and ARF, such as benzathine benzylpenicillin G at 600 000 units in children weighing less than 27 kg and 1 200 000 units in adults or children weighing more than 27 kg. The recommended dose is a single dose injected intramuscularly every 4 weeks[11]. The efficacy of antibiotics as a means of secondary prevention in reducing morbidity and mortality rates among patients with RHD has been substantiated by a rigorous randomized controlled trial conducted by Ralph *et al*.[12], which shows that secondary prevention is the cornerstone of international ARF and RHD control; however, the effectiveness is limited by suboptimal adherence. This study demonstrates that adherence has a crucial role in determining the efficacy of secondary prevention, a pivotal aspect in managing ARF and RHD.

Previous studies have suggested a correlation between poor adherence to penicillin and a high incidence of RHD[13]. A recent study reported that proper prophylaxis is important in patients with prior ARF[14]. In this evolving landscape, the purpose of this meta-analysis was to assess the effect of penicillin adherence on the secondary prevention of ARF recurrence and RHD progression. Moreover, up until now, there has been no meta-analysis undertaken regarding adherence to secondary prevention of ARF recurrence and RHD progression, which makes this novelty in this study. In addition, the results of this meta-analysis study are expected to enrich scientific evidence related to the correlation between secondary prevention adherence and outcomes such as ARF recurrence and RHD progression. Previously, this evidence has been limited to qualitative systematic reviews and separate research studies.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement was used to perform this meta-analysis[15], Supplemental Digital Content 1, http://links.lww.com/MS9/A388. This study was registered in PROSPERO. Furthermore, the work has been reported in line with AMSTAR (Assessing the Methodological Quality of Systematic Reviews), Supplemental Digital Content 2, http://links.lww.com/MS9/A389.

Eligibility criteria

We incorporated original research articles employing an observational study design, including cross-sectional and cohort studies (both prospective and retrospective). These studies focused on patients diagnosed with RHD according to the World Heart Federation or ARF by modified Jones criteria, in which penicillin was administered as secondary prevention. The diagnostic criteria were assessed based on a history of ARF or RHD in medical records or echocardiography confirmed RHD. Secondary prevention measures include IM, BPG, and oral penicillin antibiotics, considering the difficulty in accessing BPG injections in some countries. The outcomes of the included studies were ARF recurrence or RHD progression. Furthermore, accessible full-text articles as our source of secondary data are included in the inclusion criteria. Nevertheless, non-original articles such as systematic reviews, case reports, case series, and commentaries were excluded. All original articles were published in English between 2000 and 2022, and duplicate studies were removed.

Search strategy and study selection

Systematic searches of the PubMed, SCOPUS, and Cochrane databases were performed. We used the identifying terms in all fields with: ("acute rheumatic fever" OR "ARF" OR "rheumatic heart disease" OR "RHD") AND ("secondary prophylaxis" OR "secondary prevention") AND ("adherence" OR "compliance") AND ("penicillin" OR "benzathine penicillin G"). Moreover, we also conducted a snowballing literature search from Europe PMC to expand the included studies. The detailed search strategy is presented in Supplementary Table 3, Supplemental Digital Content 3, http://links.lww.com/MS9/A390. The limit for the study publishing years were from 2000 to 2022. Duplicate results were excluded from analysis. Six authors—A.M.A., E.S., D.A., T.R., M.P.I., and F.R.Q.—independently screened the titles and abstracts of each original article, thoroughly read the full text of the articles and discussed the selected articles together. The remaining investigators thoroughly read the full text of the selected articles and provided final suggestions. Finally, the studies that were discussed and approved by the authors were included in the qualitative and quantitative analyses. Disagreements were resolved by consensus.

Inclusion and exclusion criteria

We searched for articles published in the English language between the years 2000 and 2022. The included studies addressed patients with ARF or RHD who received secondary prophylaxis using oral or IM penicillin in retrospective or prospective settings (cohort, case-control, and cross-sectional). The exclusion criteria included non-accessible or restricted full paper access, non-original articles or case reports, and studies with no data on the rates of adherence to penicillin. The expected outcomes were ARF recurrence and/or RHD progression (in patients with ARF who developed RHD or worsening of RHD lesions) in patients with good or poor adherence. Studies that did not report ARF recurrence or RHD progression were excluded.

Quality assessment

The National Institutes of Health (NIH) Quality Assessment Tool for observational cohorts and cross-sectional studies was used to assess the quality of the included studies and analyze the risk of

bias and methodological quality of observational studies[16]. The NIH Quality Assessment Tool consists of 14 criteria for assessing study design, implementation, and results. Four authors (A.M.A., T.R., D.A., and M.P.I.) assessed all the included studies. The overall quality of the studies was classified as good, fair, or poor according to the investigators' agreement.

Statistical analysis

Dichotomous variables of ARF recurrence were used to calculate the pooled odds ratio (OR) using the Mantel–Haenszel formula. Heterogeneity was assessed using Q-statistics and I^2 tests to calculate the percentage of total variation across the studies. The Q-statistic results of less than 0.05 and I^2 of 40% indicated heterogeneity across the studies. The random effects model was used to incorporate the possible expected heterogeneity between studies. Statistical significance was set at p less than 0.05. Publication bias was analyzed using a DOI plot and the LFK index (MetaXL, http://www.epigear.com) to assess the asymmetry. Statistical analyses were performed using RevMan 5.4.1 (Review Manager, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Furthermore, a sensitivity analysis of our meta-analysis was carried out using the leave-one-out analysis to identify the aetiology of heterogeneity and assess the robustness of the results. The result of the sensitivity analysis was expressed as a leave-one-out forest plot, which was generated using Stata/MP 18 for Mac (StataCorp).

Results

Baseline characteristics and study selection

Our search between 20 January 2023 and 25 January 2023 retrieved a total of 292 studies from different databases. We identified 235, 46, and 11 studies from the Scopus, PubMed, and Cochrane databases, respectively. We screened the titles and abstracts of 235 studies after eliminating 57 duplicate studies and excluded 191 studies because they were neither original nor medical articles, did not discuss penicillin, RHD, or adherence in their abstracts. Forty-four full-text articles were assessed for eligibility, and 39 were excluded because of different outcome definitions. During 30 December 2023 until 3 January 2024 also conducted a snowballing literature search from Europe PMC to expand the included studies. The results of the snowballing literature search were obtained 18 studies that fit for eligibility assessment. A total of 17 studies or papers were excluded due to not evaluating desired outcomes ($n=6$), full-text paper unavailability ($n=5$), and not fitting our eligibility criteria including study design and year of publication ($n=6$). We included six studies for qualitative synthesis and meta-analysis (Fig. 1), with a total of 1364 patients. The baseline characteristics of the included studies are summarized in Table 1. These six studies were observational and BPG or oral antibiotics were administered to registered patients with a diagnosis of ARF or RHD for secondary prevention[17–20,22]. The age of the study population ranged from 0 to 41 years.

Adherence measurements

Various definitions of good adherence have been used in these studies. De Dassel *et al.*[19] and Belay *et al.*[18] defined good adherence as patients who received at least 80% of the penicillin injection dose, while Haran *et al.*[20] defined good adherence as patients who received at least 75% of the scheduled dose. Bassili *et al.*[17] defined it as at least 11 penicillin injections in the last 6 months or 22 injections during the last year of 2–4 weekly IM and daily oral penicillin, whereas Taddio *et al.*[22] defined it as greater than or equal to 12 penicillin injections per year. Furthermore, Pelajo *et al.*[21] defined a good adherence if patients did not skip or delay more than one dose of benzathine penicillin G during 6-month period.

Outcomes of the included studies

All the studies reported ARF recurrence or RHD progression[17–20,22]. Both Haran *et al.*[20] and Taddio *et al.*[22] reported the outcome as RHD progression in ARF patients. Bassili *et al.*[17], Pelajo *et al.*[21], and Belay *et al.*[18] reported ARF recurrence as the outcomes, while de Dassel *et al.*[19] reported both ARF recurrence and RHD progression as the study outcome[23].

Adherence to penicillin for secondary prevention and ARF recurrence

A total of 954 patients had good adherence, whereas 410 had poor adherence. The prevalence of good adherence to penicillin as secondary prophylaxis varied in each study, ranging from 12.9 to 83.8%[17–22]. Most of the included studies (two studies from Australia and one study from Ethiopia) defined adherence to penicillin treatment as taking a minimum of 75–80% of the doses[18–20] or more of not missing penicillin administration or receiving greater than 10 doses of penicillin shots per year[17,22]. Adherence to oral antibiotics was defined as receiving daily doses for the last 6 months or completing at least 80% of the prescribed doses each month. There is a significant association between good adherence to penicillin administration for secondary prevention of ARF recurrence and RHD progression in patients with ARF or RHD. Good adherence to penicillin administration significantly reduced the odds of ARF recurrence and RHD progression by up to 71% compared to the poor adherence [pooled OR 0.29 (0.21 – 0.40); $I^2=0\%$ ($p=0.56$) $Z=7.64$ ($p<0.00001$)] (Fig. 2). In the other words, when patients with ARF or RHD had poor adherence to penicillin secondary prophylaxis, the odds of ARF recurrence or RHD progression were approximately three times higher than in those with good adherence to penicillin.

Mode of administration

Penicillin for secondary prevention is administered or orally or by injection. All the studies[17–22] showed the beneficial effects of penicillin for the secondary prevention of ARF and RHD despite different injection intervals, ranging from 2 to 4 weeks. In two studies[17,18] penicillin was administered either by injection or orally penicillin. In patients who did not have access to IM penicillin owing to a lack of medication availability or a lack of skilled individuals to administer the injection in their location, Belay *et al.*[18] used amoxicillin instead of penicillin V as a secondary prophylaxis for RHD. Although amoxicillin is indicated for primary ARF prevention, there have been no trials on its use as secondary prophylaxis. When available, the suggested prophylactic medication is penicillin V, rather than amoxicillin. Amoxicillin was prescribed in Ethiopia owing to the unavailability of penicillin V[18].

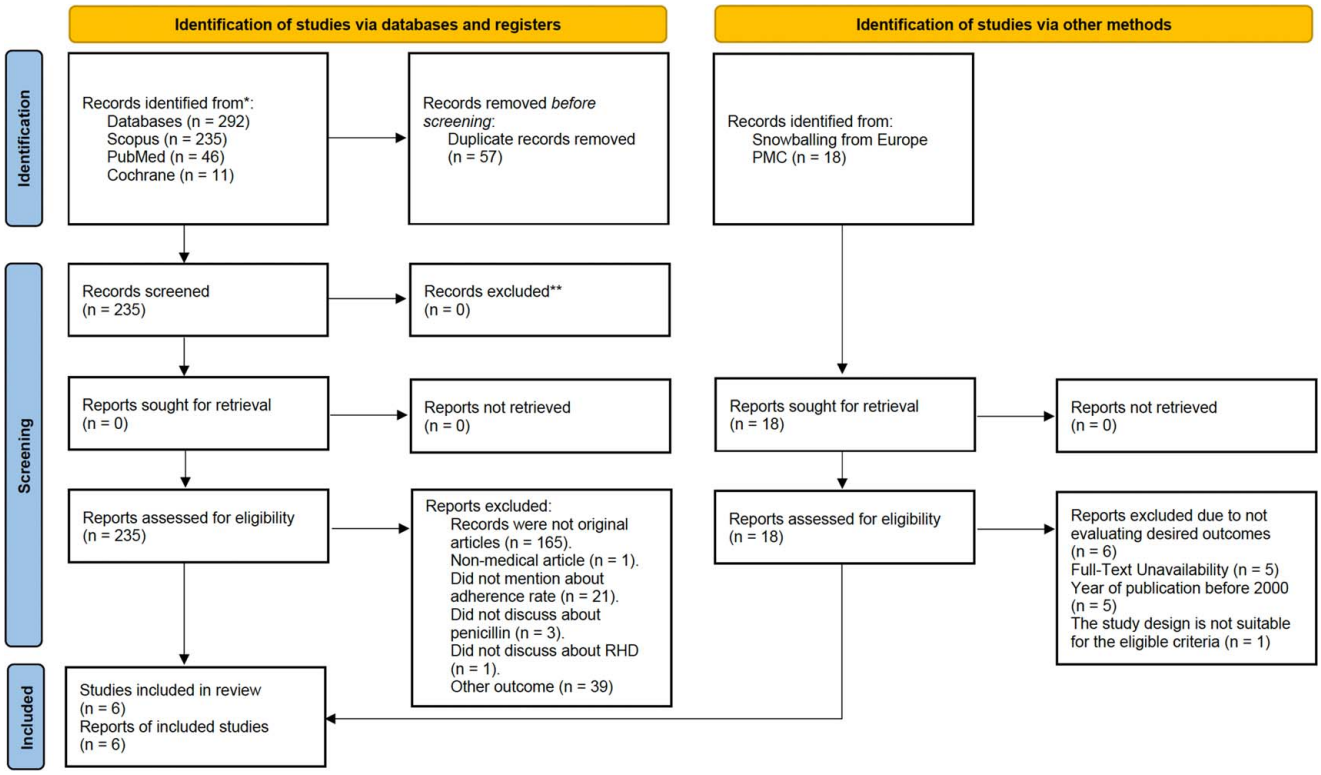

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Study Flow Diagram.

Quality assessment

Quality assessment of the included studies showed that most studies (five) had good overall quality (Supplementary Table 2, Supplemental Digital Content 4, http://links.lww.com/MS9/A391). The sample size of the included studies displayed a large variation, from the smallest sample size (23 subjects) to the largest sample size (536 subjects) (Table 1). Studies by Bassili *et al.*[17], de Dassel *et al.*[19], and Haran *et al.*[20] reported a loss to follow-up of less than 20%, whereas Taddio *et al.*[22], Pelajo *et al.*[21] reported a loss to follow-up of greater than 20%. Unfortunately, Belay *et al.*[18] did not report loss to follow-up after baseline (Supplementary Table 2, Supplemental Digital Content 4, http://links.lww.com/MS9/A391).

Publication bias

Our study showed an LFK index of 1.05 (Fig. 3), whereas the LFK index below ± 1 was considered no asymmetry, between ± 1 and ± 2 was considered minor asymmetry and exceeding ± 2 was considered major asymmetry in the DOI plot[24]. Despite the DOI plot and LFK index showing minor asymmetry, the number of included studies was limited. Therefore, publication bias could not be excluded from this meta-analysis.

Sensitivity analysis

The leave-one-out method conducts several meta-analyses by systematically omitting one study at a time during each analysis. In this study, the leave-one-out sensitivity analysis demonstrated that the pooled correlation coefficient remained robust and unaffected by any individual study. Figure 4 demonstrates that the omission of any individual study used in this meta-analysis does not alter the statistical significance of the findings (the p value remains below 0.05). The outcome of the sensitivity test conducted using the leave-one-out method demonstrates the robustness of the study findings.

Discussion

The main finding of this meta-analysis is that good adherence to penicillin is crucial for preventing further complications after ARF and RHD. Although the early course of ARF is mainly asymptomatic, 60% of individuals acquire carditis with persistent valve damage, known as RHD, if appropriate prophylaxis is not initiated[25]. Therefore, initiation and adherence to therapy is lifesaving; however, it is also difficult in the absence of notable symptoms in the early phases of the disease. The risk of ARF recurrence decreases by 17% for every 10% improvement in adherence[19]. A recent randomized controlled trial by Beaton *et al.*[14] reported that secondary prevention using penicillin injections every 4 weeks significantly lowered the risk of RHD progression in the current era, which shows that penicillin is still the appropriate therapy in this patient population, despite other reports of potential antibiotic resistance in these populations.

Our study suggests that in real-life data (which are not always comparable to trial data), greater than 60% of ARF recurrences and RHD progression can be halted by good adherence to penicillin as a secondary prevention of ARF and RHD. Therefore, we believe that this meta-analysis may be an additional consideration for health policymaking in patients with ARF and RHD. Most studies addressing adherence to the secondary prevention of ARF

TABLE 1

Baseline characteristics of the studies.

References	Country	Study design	Study population	Age	Samples (good adherence/poor adherence)	Secondary prophylaxis regimens	Definition of good adherence to penicillin as secondary prevention	Outcome	Median follow-up duration
Bassili *et al.*, [17]	Egypt	Cross-sectional	Children with RHD	0–15	127 (82/45)	2 weekly IM penicillin, 4 weekly IM penicillin, oral antibiotics	At least 11 penicillin injections in the last 6 months or 22 injections during the last year of 2–4 weekly IM and daily oral penicillin	ARF recurrence	4 months
Belay *et al.*, [18]	Ethiopia	Prospectivecohort	Children with RHD	5–17	272 (228/44)	4 weekly IM penicillin or oral Amoxicillin	≥ 80% IM penicillin (> 10 injections). For oral amoxicillin at least 80% doses per month (> 24 tablets per month in each of 12 months)	ARF recurrence, adherence to prophylaxis	12 months
de Dassel *et al.*, [19]	Australia	Case crossover	People living in the NT with a history of ARF or RHD	0– > 41	116 (15/101)	3 weekly IM penicillin, 4 weekly IM penicillin	≥ 80% IM penicillin at least 6 doses (based on a 4 weekly regimen)	ARF recurrence	6 years
Haran *et al.*, [20]	Australia	Prospective cohort	Patients diagnosed with ARF or RHD from 2010 to October 2013	5–16	23 (16/7)	4 weekly IM penicillin	≥ 75% IM penicillin scheduled doses	Echocardiographic RHD progression	27 months
Pelajo, *et al.*, [21]	Brazil	Retrospective cohort	Children and adolescents with a diagnosis of RF	1 month–13 years	536 (398/138)	4 weekly IM benzathine penicillin G	Patients did not skip or delay more than one dose of benzathine penicillin G during 6-month period.	Recurrent episodes of RF	6–18 months, more than 18 months the patients considered loss to follow-up.
Taddio *et al.*, [22]	Italy	Retrospective cohort	Patients with ARF from 2000 to 2015	Not Recorded	290 (215/75)	IM Penicillin (Intervals not stated)	IM penicillin injections > 12 injections per year	ARF recurrence, presence of RHD	4 years

ARF, acute rheumatic fever; IM, intramuscular; NT, northern territory; RF, rheumatic fever; RHD, rheumatic heart disease.

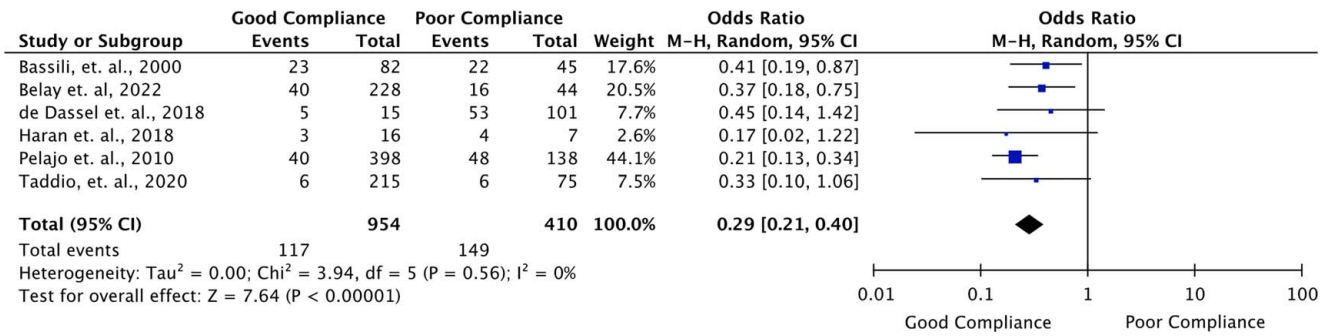

Figure 2. Forest plot on good adherence to penicillin as secondary prevention of acute rheumatic fever recurrence and rheumatic heart disease progression.

or RHD defined "good adherence" as taking greater than 80% of the scheduled doses of penicillin injections[18,19]. A study described taking greater than 75% scheduled doses as the cut-off for "good adherence"[20]. Others defined "good adherence" as the minimum number of injections taken over a period of time[17,22]. Poor medication adherence is a complex condition. Medication non-compliance may be intentional or unintentional. Intentional non-adherence is a deliberate procedure in which the patient chooses to depart from the treatment plan. This may be a logical decision-making process in which the individual assesses the risks and advantages of therapy against potential negative consequences. Unintentional non-adherence is a passive process in which the patient is negligent or forgetful about following a treatment schedule[26]. A systematic review of studies published between 1994 and 2014 by Kevat *et al.*[27] reported several factors associated with patient adherence to the secondary prevention of RHD. Non-adherence is more widespread among youngsters in semi-urban and rural locations[17]. Adherence may be reduced by a lack of faith in the therapy, a lack of a sense of "belonging" to the health provider, and a lack of familial support[27].

In rural areas, the availability of healthcare personnel is limited, and individuals have to make significant efforts to receive healthcare from alternative sites. The lack of a method for alerting individuals when their needles are being used is one factor contributing to low compliance[28]. The presence of healthcare professionals who have close, long-term interaction with the individuals, and an interest in preserving compliance may have a favourable influence on compliance[28]. Longenecker *et al.*[29] suggested that improving treatment retention, potentially

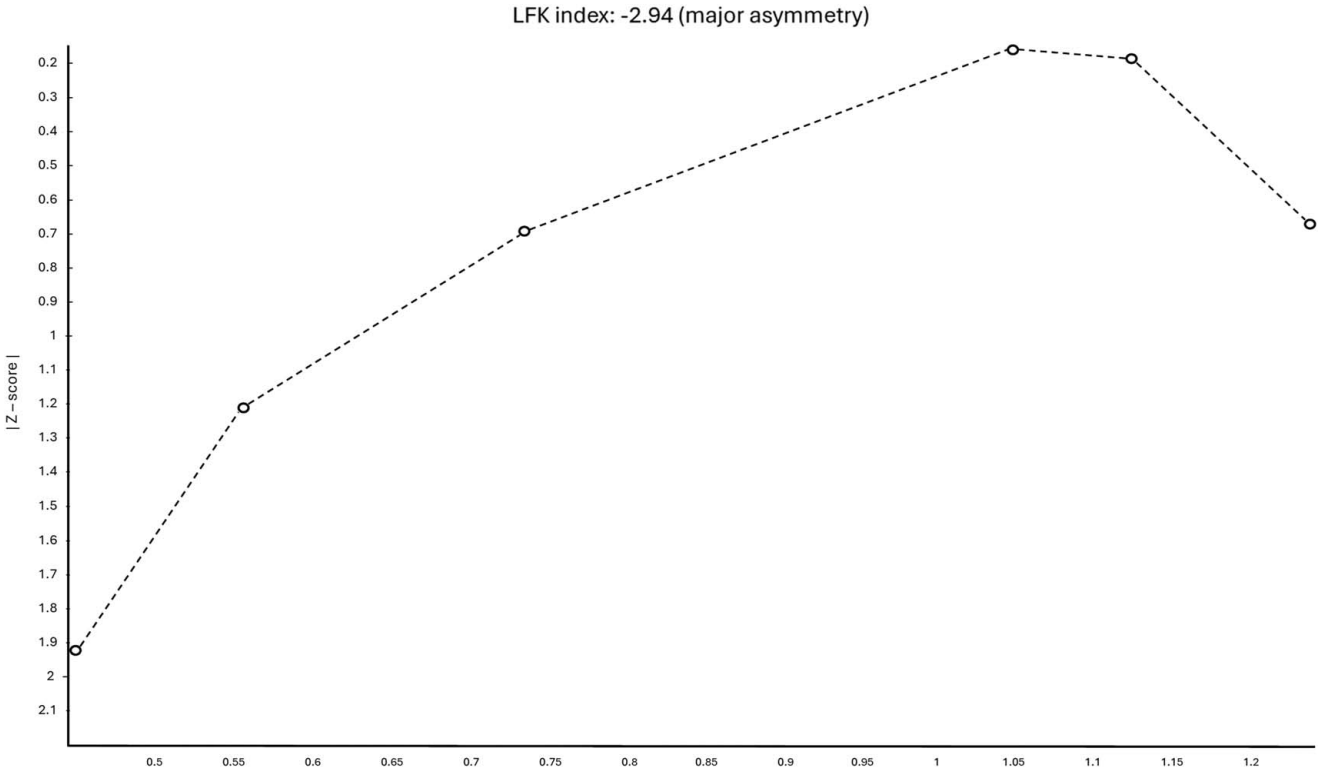

Figure 3. DOI plot analysis.

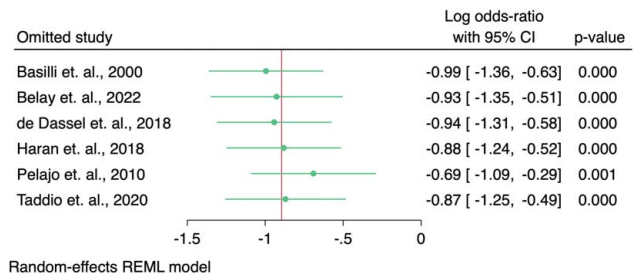

Figure 4. Forest plot of the leave-one-out method for sensitivity analysis.

through the decentralization of RHD services, would have the greatest influence on antibiotic prophylaxis use among RHD patients. All these factors should be considered to continuously improve adherence in these populations. Although oral penicillin is more practical for patients, the administration of penicillin by injection simplifier monitoring and guarantees compliance. The improved results linked to injections may be explained by the fact that patients are more likely to follow their recommended treatment schedules[30]. However, administering penicillin via injection may be costly and ineffective for patients in areas with difficult access to healthcare. To our knowledge, no study has compared the oral administration of penicillin versus injection for the outcome of ARF recurrence or RHD progression.

A multimodal strategy is necessary for the prevention and management of ARF and RHD, including early diagnosis, efficient treatment, and increased adherence to prophylaxis. Greater focus on enhancing the health system is necessary to improve adherence to secondary prophylaxis for ARF and RHD. This entails enhancing the accessibility and availability of antibiotics, educating healthcare professionals on effective counselling and communication techniques, and ensuring that treatment programs are adequately monitored and evaluated. To reduce the burden of ARF recurrence and RHD progression, promoting adherence to secondary prophylaxis is a crucial topic for future studies and interventions. Therefore, we underlined the significance of improving penicillin compliance as secondary prophylaxis in patients with ARF and RHD based on data over the last two decades.

Limitations

A constraint of this meta-analysis was the limited quantity of studies that examined adherence to secondary penicillin prophylaxis in relation to the recurrence of ARF. First, all included studies were published in the English language, and we did not incorporate other evidence published in different languages. Second, the included studies had different study setups and all observational studies had significant heterogeneity, particularly in the study population. Hence, the findings of this study should be modified to align with the specific medical practices and the clinical assessments made by healthcare providers. Moreover, the ages of subjects between groups were not separated in these studies.

Conclusion

Good adherence to secondary prophylaxis with penicillin, regardless of the method of administration, in patients with ARF or RHD is essential to prevent ARF recurrence or RHD progression. Thus, further regulations are required to mitigate the advancement of RHD and ARF, guarantee the availability of penicillin regimens, and address compliance issues.

Ethical approval

Not applicable.

Consent

Not applicable.

Sources of funding

Not applicable.

Author contribution

The conception or design of the study was initiated by A.M.A., B.S., A.S., B.R., B.D., E.R., P.D., and M.J.C. A systematic search was performed by A.M.A., E.S., D.A., T.R., and M.P.I. Data were extracted by A.M.A., E.S., D.A., M.P.I., and T.R. under the supervision of M.J.C. Quality assessment of the studies was performed by A.M.A., T.R., D.A., and E.S. under the supervision of M.J.C. The manuscript was drafted by A.M.A., E.S., D.A., T.R., F.R.Q., and M.P.I. and was critically revised by A.M.A., B.S., A.S., B.R., B.D., E.R., P.D., F.R.Q., I.K.M., and M.J.C. All authors provided their final approval and agreed to be accountable for all aspects of the work, ensuring its integrity and accuracy.

Conflicts of interest disclosure

There are no conflicts of interest.

Research registration unique identifying number (UIN)

1. PROSPERO.
2. Registration number: CRD42023421168.
3. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=421168.

Guarantor

Ade M. Ambari was responsible for the overall content of the study.

Data availability

The data underlying this article are available in the article and its supplementary materials.

Provenance and peer review

This research was not invited to be submitted.

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