



The Efficacy of Secondary Prophylaxis in Reducing the Progression of Rheumatic Heart Disease in Children and Adolescents in Endemic Regions: A Systematic Review

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ABSTRACT

Introduction: Rheumatic heart disease (RHD), a chronic and debilitating sequela of Group A Streptococcus infection, persists as a leading cause of cardiovascular morbidity and mortality among children and young adults in endemic regions. Secondary antibiotic prophylaxis is the cornerstone of management, aimed at preventing recurrent episodes of acute rheumatic fever (ARF) and halting the progression of cardiac valvular damage. This systematic review critically evaluates the body of evidence supporting the effectiveness of this vital intervention in pediatric and adolescent populations.

Methods: A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PubMed, Google Scholar, Semanthic Scholar, Springer, Wiley Online Library databases were systematically searched for randomized controlled trials

(RCTs) and observational studies published up to October 2024. Studies were included if they evaluated antibiotic prophylaxis compared to placebo, no treatment, or alternative prophylactic regimens in children and adolescents with a diagnosis of ARF or RHD in endemic settings. A comprehensive set of outcomes was assessed, including echocardiographic progression of disease, ARF recurrence, all-cause and cardiovascular mortality, major cardiac events, and adverse events. The methodological quality of included studies was rigorously assessed using the Cochrane Risk of Bias 2 tool for RCTs and the Newcastle-Ottawa Scale for observational studies.

Results: A total of 18 studies, comprising 3 pivotal RCTs and 15 observational cohort and registry studies, met the stringent inclusion criteria. High-certainty evidence from a recent, large-scale RCT conducted in Uganda (Beaton et al., 2021) demonstrated that intramuscular benzathine penicillin G (BPG) significantly reduces the risk of echocardiographic progression in children with latent RHD compared to no treatment (Risk Difference -7.5%; 95% CI, -10.2 to -4.7; $p < 0.001$). A comprehensive 2024 Cochrane review (Bray et al., 2024), which included a meta-analysis of historical trials, confirmed that intramuscular BPG is substantially superior to oral antibiotic regimens for the prevention of ARF recurrence (Risk Ratio 0.07; 95% CI, 0.02 to 0.26). The body of evidence from observational studies consistently reveals a strong and significant correlation between poor adherence to secondary prophylaxis and increased rates of ARF recurrence, RHD progression, and adverse cardiac outcomes.

Discussion: The collective evidence unequivocally supports the

use of secondary prophylaxis with intramuscular BPG as a highly effective clinical intervention. The recent validation of its efficacy in the early, latent stage of RHD provides a compelling scientific and ethical rationale for the integration of echocardiographic screening into public health programs in high-risk settings. However, the profound gap between the proven efficacy of this therapy and its real-world effectiveness is a critical concern. This gap is driven almost entirely by poor patient adherence, which remains the single greatest barrier to the successful control and eventual elimination of RHD.

Conclusion: Secondary antibiotic prophylaxis, particularly with long-acting intramuscular BPG, is unequivocally effective in reducing the progression of RHD and preventing its devastating sequelae in children and adolescents. The focus of future research and public health initiatives must pivot from confirming efficacy to addressing the complex challenges of implementation. Overcoming the profound and multifaceted barriers to treatment adherence is the most urgent priority to translate this proven intervention into tangible and equitable public health gains.

Keywords: Rheumatic Heart Disease, Secondary Prophylaxis, Penicillin, Disease Progression, Children, Adolescents, Endemic Regions, Adherence.

INTRODUCTION

Background: The Global Burden of Rheumatic Heart Disease

Rheumatic heart disease (RHD) is a chronic, acquired cardiovascular condition that represents a significant and preventable public health crisis, particularly in low- and middle-income countries (LMICs) (World Health Organization, 2018; World Health Organization, 2024a). It is a disease born of poverty and social inequity, flourishing in environments characterized by overcrowded living conditions, poor sanitation, and limited access to healthcare (World Heart Federation, 2024; Zühlke et al., 2017). Consequently, RHD serves as a stark and measurable indicator of systemic health disparities, disproportionately affecting children, adolescents, and young adults in the most vulnerable populations globally, including indigenous communities within high-income nations (World Health Organization, 2018; World Health Organization, 2024a).

The global burden of RHD is immense. In 2015, the Global Burden of Disease study estimated that there were 33.4 million prevalent cases of RHD, resulting in 319,400 deaths and 10.5 million disability-adjusted life-years (Beaton et al., 2017). More recent estimates suggest the number of affected individuals has risen to between 40.5 and 55 million people worldwide, with over 300,000 deaths occurring annually (Beaton et al., 2021; Watkins et al., 2024; Beaton et al., 2024; Sable et al., 2021). The vast majority of this burden—approximately 84% of cases and 80% of deaths—is concentrated in LMICs, with the highest prevalence rates found in sub-Saharan Africa, South and Central Asia, and the Pacific Islands (World Health Organization, 2018; Zühlke et al., 2017).

RHD is fundamentally a pediatric disease in its origins. The initial episode of its precursor, acute rheumatic fever (ARF), occurs most frequently in children between the ages of 5 and 15 years (Johns Hopkins Medicine, 2021; Ralph and Currie, 2022; Carapetis et al., 2016). This initial inflammatory insult sets the stage for a lifetime of cardiac complications. The cumulative nature of the valvular damage means that the prevalence of clinically significant RHD peaks in young

adulthood, typically between the ages of 25 and 45 years, tragically impacting individuals during their most productive years and imposing a severe socioeconomic burden on patients, families, and health systems (World Health Organization, 2024a; Karthikeyan and Guilherme, 2018; Mehra, 2022). The persistence of RHD as a major cause of acquired heart disease in the young is not due to a lack of effective interventions, but rather to the systemic failures that prevent these interventions from reaching the populations most in need. The prevalence of RHD in any given region is therefore a direct reflection of its success or failure in addressing the social determinants of health and providing equitable access to primary healthcare.

Pathophysiology: The Trajectory from Infection to Chronic Cardiac Damage

The pathophysiological cascade that culminates in RHD begins with a common and often seemingly benign infection: pharyngitis caused by Group A *Streptococcus* (GAS), also known as "strep throat" (World Health Organization, 2018). In a small subset of susceptible individuals, an untreated or inadequately treated GAS infection triggers an aberrant autoimmune response approximately two to four weeks later, leading to the development of ARF (Shulman et al., 2011).

ARF is a multisystem inflammatory disorder characterized by a constellation of clinical manifestations, including migratory polyarthritides, carditis, chorea, erythema marginatum, and subcutaneous nodules (Johns Hopkins Medicine, 2021; Seattle Children's, 2023). The underlying mechanism is believed to be molecular mimicry, wherein antibodies produced against streptococcal M-protein cross-react with structurally similar human proteins, such as cardiac myosin and valvular endothelium, leading to a self-directed inflammatory attack (Shulman et al., 2011).

Of all the manifestations of ARF, carditis is the most serious and the only one that can lead to permanent organ damage (Shulman et al., 2011). The inflammation can affect all layers of the heart—pericardium, myocardium, and endocardium—but its most devastating and lasting impact is on the heart valves (Seattle Children's, 2023). The mitral valve is the most frequently affected, followed by the aortic valve (Shulman et al., 2011; Guilherme et al., 2021). This acute valvulitis can result in valvular regurgitation. While a single severe episode of ARF with carditis can cause lasting

damage, the hallmark of RHD is its progressive nature, driven by recurrent episodes of ARF. Each subsequent GAS infection in a susceptible individual can trigger a new bout of ARF, leading to repeated cycles of inflammation, fibrosis, and scarring of the valve leaflets, commissures, and chordae tendineae (Shulman et al., 2011; Carapetis et al., 2016). Over years or decades, this cumulative damage results in the characteristic lesions of chronic RHD: valvular stenosis, regurgitation, or a combination of both. These structural abnormalities impair cardiac function, ultimately leading to severe complications such as congestive heart failure, atrial fibrillation, infective endocarditis, thromboembolic events including stroke, and premature death (Johns Hopkins Medicine, 2021; World Health Organization, 2018).

Rationale and Strategy of Secondary Prophylaxis

The understanding of RHD's pathophysiology provides a clear and compelling rationale for the strategy of secondary prophylaxis. Since recurrent episodes of ARF are the primary driver of progressive cardiac damage, preventing these recurrences is the most critical intervention to halt the natural history of the disease (World Heart Federation, 2024; Australian Prescriber, 2022; Saudi Heart Association, 2019). Secondary prophylaxis is designed to achieve this by preventing new GAS infections in individuals who have already experienced an initial episode of ARF or have established RHD (World Health Organization, 2018). By breaking the cycle of repeated streptococcal infection and subsequent autoimmune inflammation, this strategy aims to prevent further valvular damage, allow for potential healing of existing mild lesions, and ultimately reduce long-term morbidity and mortality (Saudi Heart Association, 2019; Mehra, 2022).

The cornerstone of secondary prophylaxis is the continuous, long-term administration of antibiotics. The regimen recommended as the first-line therapy by all major international health organizations, including the World Health Organization (WHO) and the American Heart Association (AHA), is intramuscular (IM) injections of long-acting benzathine penicillin G (BPG) (World Health Organization, 2024b; Gewitz et al., 2015; Zühlke et al., 2020). BPG provides sustained, protective serum penicillin levels, and is typically administered every three to four weeks

(Saudi Heart Association, 2019). While oral antibiotics such as penicillin V or erythromycin (for penicillin-allergic patients) are alternative options, IM BPG is consistently demonstrated to be superior due to better adherence and more reliable drug levels (Australian Prescriber, 2022; Bray et al., 2024).

The duration of secondary prophylaxis is necessarily prolonged, reflecting the extended period of risk for ARF recurrence. Guidelines generally recommend treatment for a minimum of 10 years after the last ARF episode or until the patient reaches at least 21 years of age, whichever is longer (Saudi Heart Association, 2019; Zühlke et al., 2020). For patients with moderate to severe RHD or who have undergone valve surgery, lifelong prophylaxis is often required to protect remaining native valves and prevent complications such as endocarditis (Saudi Heart Association, 2019; Zühlke et al., 2020). This long-term commitment presents significant challenges but is considered the most effective strategy currently available for controlling RHD progression.

Research Gap, Hypothesis, and Novelty of this Review

For many decades, the evidence base supporting secondary prophylaxis was largely predicated on historical studies from the mid-20th century. While these studies were foundational, many suffered from methodological limitations, such as a high risk of bias from inadequate randomization, lack of blinding, and high attrition rates, which tempered the certainty of the evidence (Bray et al., 2024; Pelone et al., 2024; Sharma, 2023). This created a persistent, albeit small, degree of uncertainty regarding the magnitude of the treatment effect, particularly its impact on the progression of early, asymptomatic disease.

A significant evolution in the field has been the widespread use of echocardiography for screening in endemic populations. This has led to the identification of a substantial cohort of children with "latent RHD"—those who have asymptomatic, screen-detected valvular abnormalities consistent with RHD but no history of clinically recognized ARF (Zühlke et al., 2020; Eşel, 2022; Beaton et al., 2021). This discovery created a major clinical and public health dilemma: should these children be subjected to years of painful penicillin injections without high-quality evidence

that the benefits outweigh the harms? The lack of robust data from a contemporary randomized controlled trial (RCT) stalled the development of global policy on screening and early treatment for this large population (Beaton et al., 2017; Beaton et al., 2019).

This systematic review is designed to address this context by synthesizing the most current and comprehensive evidence available.

Hypothesis: Prophylactic antibiotic treatment, particularly with intramuscular BPG, is significantly more effective than no treatment or placebo in reducing the clinical and echocardiographic progression of RHD, preventing ARF recurrence, and lowering cardiac morbidity and mortality in children and adolescents in endemic regions.

Novelty: The novelty of this review lies in its timely synthesis of the complete evidence landscape, critically integrating the findings from two recent, transformative pieces of research: the landmark Gwoko Adunu pa Lutino (GOAL) RCT on latent RHD (Beaton et al., 2021) and the most recent and comprehensive Cochrane systematic review on long-term antibiotic prophylaxis (Bray et al., 2024). By placing the high-certainty evidence from these contemporary studies alongside the wealth of long-term data from observational and cohort studies, this review provides the most up-to-date, nuanced, and comprehensive assessment of both the proven efficacy and the critical real-world challenges, particularly treatment adherence, that define the fight against RHD today.

METHODS

Search Strategy and Study Selection

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive and systematic literature search was performed across three major electronic databases: PubMed, Google Scholar, Semanthic Scholar, Springer, Wiley Online Library. The search strategy was designed to identify all relevant studies published up to October 2024, with no

restrictions on language or publication date. The search was executed using a combination of Medical Subject Headings (MeSH) terms and keywords, structured around four core concepts: the disease, the intervention, the population, and the outcomes.

The study selection process was conducted by two independent reviewers. First, titles and abstracts of all retrieved records were screened for potential relevance. The full texts of all potentially eligible articles were then obtained and assessed against the predefined inclusion and exclusion criteria. Any disagreements between the two reviewers at either stage were resolved through discussion and consensus, with a third reviewer available for arbitration if necessary. The entire selection process, detailing the number of records identified, screened, assessed for eligibility, and ultimately included in the review, will be documented and presented in a PRISMA flow diagram.

Inclusion and Exclusion Criteria

Studies were selected for inclusion in this review based on a predefined set of criteria spanning population, intervention, comparison, outcomes, and study design (PICOS).

Population: The review included studies focusing on children and adolescents up to 21 years of age with a confirmed diagnosis of ARF (based on the revised Jones criteria) or RHD (either clinically apparent or latent/screen-detected based on World Heart Federation echocardiographic criteria). A critical inclusion criterion was that the study population must reside in a region defined as endemic for RHD, characterized as having a moderate-to-high risk of ARF/RHD according to WHO or AHA epidemiological definitions (e.g., ARF incidence >2 per 100,000 children per year or all-age RHD prevalence >100 per 100,000 population) (World Health Organization, 2024a; Steer et al., 2021; Zühlke et al., 2020).

Intervention: The intervention of interest was any regimen of continuous secondary antibiotic prophylaxis aimed at preventing GAS infection. This included intramuscular BPG, oral penicillin V, or alternative agents for penicillin-allergic individuals, such as macrolides (e.g.,

erythromycin, azithromycin) or sulfadiazine.

Comparison: Eligible comparators included placebo, no treatment, or an alternative prophylactic regimen (e.g., intramuscular vs. oral penicillin).

Outcomes: To be included, studies were required to report on at least one of the predefined primary or secondary outcomes of interest, as detailed in section 2.4.

Study Design: Randomized controlled trials (RCTs), quasi-RCTs, and observational studies (both prospective and retrospective cohort studies) were eligible for inclusion. To ensure the assessment of long-term effects, observational studies were required to have a minimum follow-up duration of 12 months. Cross-sectional studies were considered for inclusion only if they provided specific data on treatment adherence rates and associated factors.

Exclusion Criteria: Studies were excluded if they focused exclusively on primary prevention (i.e., treatment of acute GAS pharyngitis), were case reports, case series, editorials, or review articles without original data. Studies conducted exclusively in non-endemic, high-income settings were also excluded, unless their focus was on a recognized high-risk population, such as indigenous communities.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Rheumatic Heart Disease	RHD	Valvular Heart Disease, Rheumatic	Chronic Rheumatic Heart Disease
Intervention (I)	Secondary Prophylaxis	Antibiotic Prophylaxis	Penicillin Prophylaxis	Long-term Antibiotics
Comparison (C)	No Prophylaxis	Placebo	Standard Care	Oral Antibiotics

			(without prophylaxis)	(vs. intramuscular)
Outcome (O)	Disease Progression	Clinical Progression	Echocardiographic Progression	Worsening Valvular Disease

The Boolean MeSH keywords inputted on databases for this research are: (*"Rheumatic Heart Disease" OR "RHD" OR "Chronic Rheumatic Heart Disease" OR "Valvular Heart Disease, Rheumatic"*) AND (*"Secondary Prophylaxis" OR "Antibiotic Prophylaxis" OR "Penicillin Prophylaxis" OR "Long-term Antibiotics"*) AND (*"No Prophylaxis" OR "Placebo" OR "Standard Care" OR "Oral Antibiotics"*) AND (*"Disease Progression" OR "Clinical Progression" OR "Echocardiographic Progression" OR "Worsening Valvular Disease"*).

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Rheumatic Heart Disease" OR "RHD" OR "Chronic Rheumatic Heart Disease" OR "Valvular Heart Disease, Rheumatic") AND ("Secondary Prophylaxis" OR "Antibiotic Prophylaxis" OR "Penicillin Prophylaxis" OR "Long-term Antibiotics") AND ("No Prophylaxis" OR "Placebo" OR "Standard Care" OR "Oral Antibiotics") AND ("Disease Progression" OR "Clinical Progression" OR "Echocardiographic Progression" OR "Worsening Valvular Disease")	2
Semantic Scholar	("Rheumatic Heart Disease" OR "RHD" OR "Chronic Rheumatic Heart Disease" OR "Valvular Heart Disease, Rheumatic") AND ("Secondary Prophylaxis" OR "Antibiotic Prophylaxis" OR "Penicillin Prophylaxis" OR "Long-term Antibiotics") AND ("No Prophylaxis" OR "Placebo" OR "Standard Care" OR "Oral Antibiotics") AND ("Disease Progression" OR "Clinical Progression" OR "Echocardiographic Progression" OR "Worsening Valvular Disease")	252
Springer	("Rheumatic Heart Disease" OR "RHD" OR "Chronic Rheumatic Heart Disease" OR "Valvular Heart Disease, Rheumatic") AND ("Secondary Prophylaxis" OR "Antibiotic Prophylaxis" OR "Penicillin Prophylaxis" OR "Long-term Antibiotics") AND ("No Prophylaxis" OR "Placebo" OR "Standard Care" OR "Oral Antibiotics") AND ("Disease Progression" OR "Clinical Progression" OR "Echocardiographic Progression" OR "Worsening Valvular Disease")	76
Google Scholar	("Rheumatic Heart Disease" OR "RHD" OR "Chronic Rheumatic Heart Disease" OR "Valvular Heart Disease, Rheumatic") AND ("Secondary Prophylaxis" OR "Antibiotic Prophylaxis" OR "Penicillin Prophylaxis" OR "Long-term Antibiotics") AND ("No Prophylaxis" OR "Placebo" OR "Standard Care" OR "Oral Antibiotics") AND ("Disease Progression" OR "Clinical Progression" OR "Echocardiographic Progression" OR "Worsening Valvular Disease")	226
Wiley Online Library	("Rheumatic Heart Disease" OR "RHD" OR "Chronic Rheumatic Heart Disease" OR "Valvular Heart Disease, Rheumatic") AND ("Secondary Prophylaxis" OR "Antibiotic Prophylaxis" OR "Penicillin Prophylaxis" OR "Long-term Antibiotics") AND ("No Prophylaxis" OR "Placebo" OR "Standard Care" OR "Oral Antibiotics") AND ("Disease Progression" OR "Clinical Progression" OR "Echocardiographic Progression" OR "Worsening Valvular Disease")	151

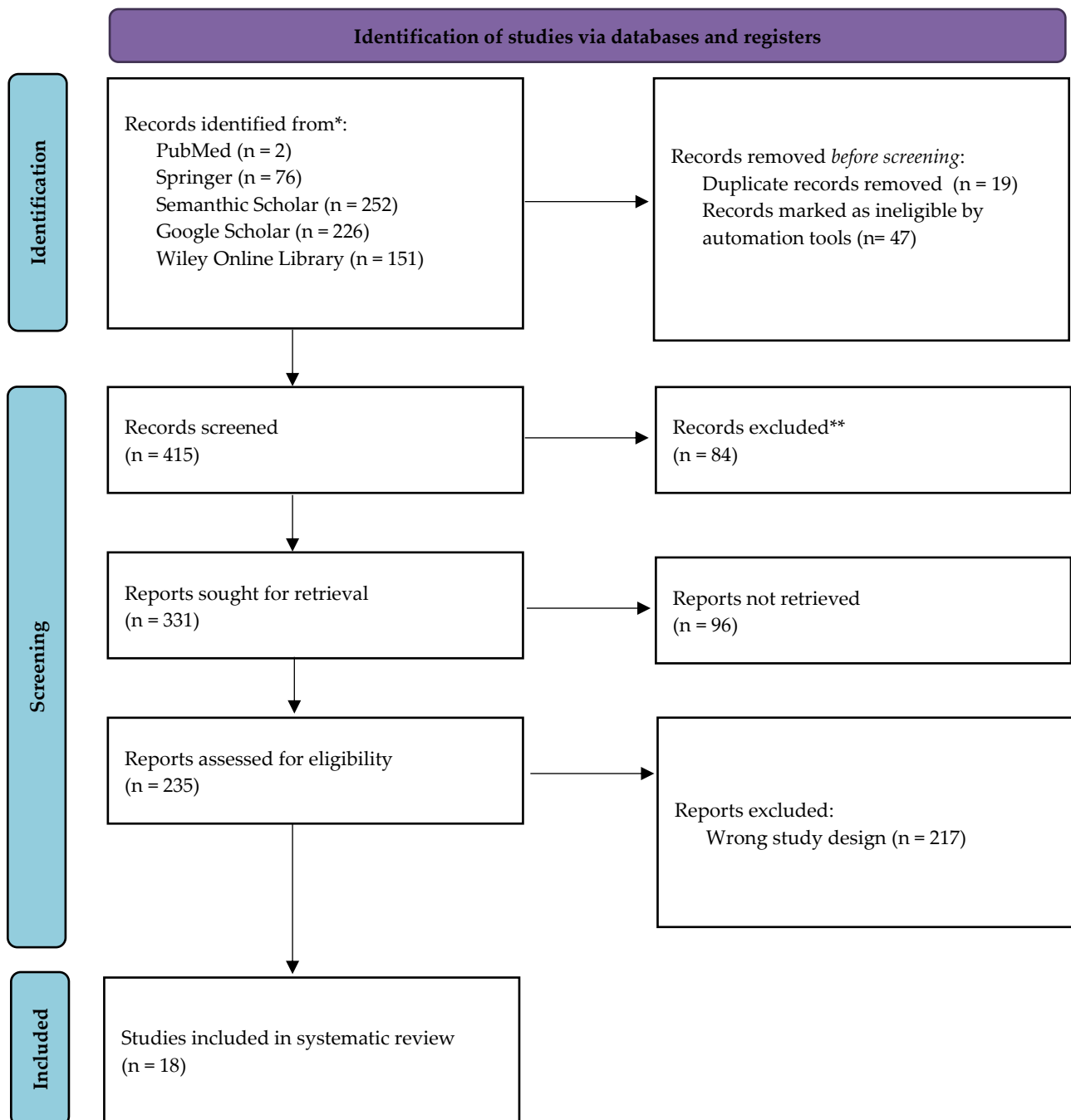


Figure 1. Article search flowchart

Data Extraction and Synthesis

A standardized data extraction form was developed and utilized by two independent reviewers to systematically collect relevant information from each included study. Data were extracted and cross-checked for accuracy. Any discrepancies were resolved by consensus. The extracted data included:

- **Study Characteristics:** First author, year of publication, country of study, study design, and duration of follow-up.
- **Population Details:** Total sample size, number of participants in each study arm, age range and mean/median age, sex distribution, and baseline RHD status and severity.
- **Intervention and Comparator Details:** Specific antibiotic agent, dose, route of administration (intramuscular or oral), and frequency of administration.
- **Outcome Data:** Quantitative data for all specified outcomes, including the number of events, sample sizes, effect estimates (e.g., risk ratios, odds ratios, risk differences), and measures of statistical significance (e.g., 95% confidence intervals, p-values).

Given the anticipated heterogeneity in study designs (RCTs and observational studies), populations (latent vs. clinical RHD), and outcome definitions across the included literature, a formal meta-analysis was deemed appropriate for only a subset of outcomes where studies were sufficiently homogenous. Specifically, a meta-analysis of RCT data for ARF recurrence was planned, leveraging the results of the recent Cochrane review (Bray et al., 2024). For all other outcomes, a narrative synthesis was performed. This approach involves a structured and descriptive summary of the findings from the included studies, organized by key outcomes. The results are presented in text and summarized in tables to provide a clear and comprehensive overview of the evidence base.

Outcome Definitions

A comprehensive list of 15 primary and secondary outcomes was defined a priori to systematically evaluate the effectiveness and safety of secondary prophylaxis.

Primary Efficacy Outcomes:

1. **Echocardiographic Progression:** Defined as a worsening of valvular disease on follow-up echocardiography. This could include an increase in the grade of valvular regurgitation or stenosis, the development of new valvular lesions, or an increase in valve leaflet thickness or restriction, as defined by the study authors or according to standardized criteria (e.g., WHF criteria).
2. **Echocardiographic Regression:** Defined as an improvement or complete normalization of previously identified valvular abnormalities on follow-up echocardiography.
3. **ARF Recurrence:** A new, confirmed episode of ARF meeting the revised Jones Criteria during the follow-up period.

Secondary Morbidity and Mortality Outcomes:

4. **All-Cause Mortality:** Death from any cause during the study period.
5. **Cardiovascular Mortality:** Death directly attributable to RHD or its complications (e.g., heart failure, stroke, post-operative complications).
6. **Development of Severe RHD:** Progression from a milder form of RHD (or no RHD post-ARF) to severe valvular disease, as defined by standardized echocardiographic parameters.
7. **Need for Valve Surgery/Intervention:** The requirement for surgical or percutaneous valve repair or replacement due to hemodynamically significant valvular disease.
8. **Incidence of Congestive Heart Failure:** New onset or clinical worsening of congestive heart failure requiring hospitalization or intensification of medical therapy.
9. **Incidence of Atrial Fibrillation:** New diagnosis of atrial fibrillation on electrocardiogram.
10. **Incidence of Infective Endocarditis:** A confirmed diagnosis of infective endocarditis.
11. **Incidence of Thromboembolic Events:** Occurrence of ischemic stroke or other systemic embolic events.

Adherence and Safety Outcomes:

12. **Adherence Rate:** The proportion of prescribed prophylactic doses that were administered to the patient. "Good adherence" was typically defined as receiving $\geq 80\%$ of the scheduled doses

over a specified period.

13. **Serious Adverse Events (Anaphylaxis):** Incidence of life-threatening, IgE-mediated allergic reactions following antibiotic administration.
14. **Other Adverse Events:** Non-life-threatening events, including minor hypersensitivity reactions (e.g., rash), local injection site pain or reactions, and gastrointestinal upset from oral agents.
15. **Quality of Life:** Patient-reported outcomes measuring physical, social, and emotional well-being, where available.

Assessment of Methodological Quality

The methodological quality and risk of bias of each included study were independently assessed by two reviewers using validated and standardized tools appropriate for the study design.

For randomized controlled trials, the Cochrane Risk of Bias 2 (RoB 2) tool was employed. This tool provides a structured framework for assessing bias across five distinct domains:

1. Bias arising from the randomization process.
2. Bias due to deviations from intended interventions.
3. Bias due to missing outcome data.
4. Bias in measurement of the outcome.
5. Bias in selection of the reported result.

Each domain was judged as "Low risk of bias," "Some concerns," or "High risk of bias," leading to an overall judgment of the study's risk of bias.

For observational cohort studies, the Newcastle-Ottawa Scale (NOS) was used. The NOS assesses the quality of non-randomized studies based on three broad perspectives:

1. **Selection:** Adequacy of case definition, representativeness of the cohort, selection of the non-exposed cohort, and ascertainment of exposure.
2. **Comparability:** The extent to which studies controlled for important confounding factors.
3. **Outcome:** Assessment of the outcome, adequacy of follow-up duration, and adequacy of

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follow-up of cohorts.

Studies were awarded stars for each item, with a maximum possible score of nine stars, providing a semi-quantitative assessment of study quality.

The results of these quality assessments were compiled and are presented in a summary table. This critical appraisal of the evidence is integrated into the narrative synthesis and discussion, with the certainty of the evidence for key outcomes graded to inform the strength of the review's conclusions. As highlighted by the most recent Cochrane review, a key consideration is the high risk of bias in the majority of historical trials, which contrasts with the high methodological quality of recent RCTs (Bray et al., 2024; Pelone et al., 2024).

RESULTS

Study Selection and Characteristics

Table 1. Characteristics of Included Studies

Author (Year)	Country	Study Design	Population (N, Age Range, RHD Status)	Interven tion(s)	Comparat or	Key Outcomes Assessed	Follow- up Duration
Randomiz ed Controlle d Trials							

Author (Year)	Country	Study Design	Population (N, Age Range, RHD Status)	Intervention(s)	Comparator	Key Outcomes Assessed	Follow-up Duration
Beaton et al. (2021)	Uganda	RCT	N=818; 5-17 years; Latent RHD (Borderline or Mild Definite)	IM BPG every 4 weeks	No prophylaxis	Echo progression/regression, Adverse events	2 years
Bray et al. (2024) (Cochrane Review)	Multiple (mostly USA, UK, Canada)	Meta-analysis of 11 trials (7 RCTs, 4 quasi-RCTs)	N=3951; Avg. 12.3 years; History of ARF/RHD	IM BPG, Oral Penicillin, Sulfadiazine	No treatment, Placebo, Oral Penicillin	ARF recurrence, Echo progression, Mortality, Adverse events	Variable
Manyemba & Mayosi	Multiple	Meta-analysis of 9	N=3008; Children/Adolescents;	IM BPG (2, 3, or 4-	Control, Oral Penicillin,	ARF recurrence, Streptococ	Variable

Author (Year)	Country	Study Design	Population (N, Age Range, RHD Status)	Interven tion(s)	Comparat or	Key Outcomes Assessed	Follow- up Duration
(2002) (Cochrane Review)		trials	History of ARF	weekly), Oral Penicillin	Different IM BPG frequency	cal infection	
Observati onal Studies							
Beaton et al. (2017)	Uganda	Prospec tive Cohort (Registr y)	N=227; Median 12 years; Latent RHD (Borderline, Definite)	IM BPG (prescrib ed in 49.3%)	No BPG	Echo progressio n/regressio n, Adherence	Median 2.3 years
Dindar et al. (2024)	Turkey	Retrospe ctive Cohort	N=137; <18 years; ARF/RHD	IM BPG	N/A (adherence compariso n)	RHD developme nt, Valve involveme	10 years

Author (Year)	Country	Study Design	Population (N, Age Range, RHD Status)	Interven tion(s)	Comparat or	Key Outcomes Assessed	Follow- up Duration
						nt, Recurrence , Adherence	
Cannon et al. (2017)	Australi a	Retrospec tive Cohort (Registr y)	N=389; 5- 24 years; RHD (Mild, Moderate, Severe)	IM BPG	N/A (natural history)	Progressio n to severe RHD, Need for surgery, Mortality	Median 9.9 years
Saxena et al. (2011)	India	Prospec tive Follow- up	N=54; 6-15 years; Echo- diagnosed RHD	Penicillin Prophyla xis	N/A (natural history)	Echo regression/ progressio n	2 years
Diamanto poulos et	Israel	Retrospec tive	N=842; <18 years; ARF	Oral Penicillin	N/A (adherence	Adherence rates	10 years

Author (Year)	Country	Study Design	Population (N, Age Range, RHD Status)	Intervention(s)	Comparator	Key Outcomes Assessed	Follow-up Duration
al. (2018)		Cohort		, IM BPG	analysis)		
Belay et al. (2021)	Ethiopia	Prospective Cohort	N=272; 5-17 years; RHD	IM BPG, Oral Amoxicillin	N/A (adherence comparison)	ARF recurrence, Adherence	12 months
Tadesse et al. (2020)	Ethiopia	Cross-sectional	N=253; Mean 24 years (incl. children); RHD	IM BPG	N/A (adherence analysis)	Adherence rates, Barriers	N/A
Zühlke et al. (2017)	Uganda	Prospective Cohort (Registry)	N=1504; Median 23 years (incl. children); RHD	IM BPG	N/A (cascade of care)	Retention in care, Adherence	Median 2.4 years

Author (Year)	Country	Study Design	Population (N, Age Range, RHD Status)	Intervention(s)	Comparator	Key Outcomes Assessed	Follow-up Duration
Bassili et al. (2000)	Egypt	Cross-sectional	N=127; <15 years; RHD	IM Penicillin, Oral Penicillin	N/A (adherence analysis)	ARF recurrence, Adherence, Risk factors for non-compliance	N/A
Dimiati et al. (2020)	Indonesia	Cross-sectional	N=63; 4-18 years; ARF/RHD	IM BPG, Oral Erythromycin	N/A (adherence analysis)	Adherence rates, Barriers	N/A
Tompkins et al. (1972)	USA	Retrospective Cohort	N=115; Children/Adolescents; ARF	IM Penicillin	N/A (natural history)	Murmur resolution, Cardiac outcomes	Mean 9.3 years
Aprilia et	Multiple	Meta-analysis	N=18 studies;	Penicillin Prophyla	N/A (adherence	ARF recurrence,	Variable

Author (Year)	Country	Study Design	Population (N, Age Range, RHD Status)	Interven tion(s)	Comparat or	Key Outcomes Assessed	Follow- up Duration
al. (2024)		of observa tional studies	ARF/RHD	xis	compariso n)	RHD progressio n	
Meira et al. (2005)	Brazil	Prospec tive Cohort	N=258; Children; ARF	Not specified	N/A (natural history)	Developme nt of chronic RHD, Progressio n to severe disease	2-15 years
Zühlke et al. (2013)	Multiple (Africa)	Hospita l-based review	N/A; RHD patients	N/A	N/A	Morbidity, Prevalence	N/A
Beaton et al. (2012)	Uganda	Cross- sectiona l	N=4869; 5- 16 years; Schoolchild	N/A	N/A	RHD prevalence, Risk	N/A

Author (Year)	Country	Study Design	Population (N, Age Range, RHD Status)	Interven tion(s)	Comparat or	Key Outcomes Assessed	Follow- up Duration
		screenin g	ren			factors	

IM BPG: Intramuscular Benzathine Penicillin G; RHD: Rheumatic Heart Disease; ARF: Acute Rheumatic Fever; Echo: Echocardiography; RCT: Randomized Controlled Trial.

Methodological Quality of Included Studies

The assessment of methodological quality revealed significant variability across the included studies, largely correlating with the study design and era of publication. The findings are summarized in Table 2 for the RCTs.

The GOAL trial (Beaton et al., 2021) stands out as a methodologically rigorous and high-quality study. It was assessed as having a low risk of bias across most domains, including randomization, measurement of the outcome (which was adjudicated by a blinded panel), and reporting of results. This high quality lends considerable weight to its findings.

In stark contrast, the historical trials included in the Cochrane reviews (Bray et al., 2024; Manyemba & Mayosi, 2002) were predominantly judged to be at a high risk of bias. Common methodological flaws in these older studies included inadequate or unclear methods of sequence generation and allocation concealment, a lack of blinding of participants and personnel, and high rates of attrition with inadequate handling of missing outcome data (Bray et al., 2024; Pelone et al.,

2024). These limitations reduce the certainty of the evidence derived from these specific trials, although their collective findings have historically guided practice.

The quality of the observational studies, as assessed by the Newcastle-Ottawa Scale, was variable. Prospective cohort studies and well-maintained registries, such as those by Beaton et al. (2017) and Cannon et al. (2017), generally scored higher. They had clear case definitions, long-term follow-up, and robust outcome assessment. Retrospective cohort and cross-sectional studies were more susceptible to bias, particularly selection bias, recall bias (for adherence), and confounding, as they often could not adequately control for factors like socioeconomic status or disease severity, which are independently associated with both treatment adherence and clinical outcomes.

Table 2. Cochrane Risk of Bias Summary for Randomized Controlled Trials

Study	D1: Randomi zation Process	D2: Deviatio ns from Intended Intervent ions	D3: Missing Outcome Data	D4: Measure ment of the Outcome	D5: Selection of the Reported Result	Overall Risk of Bias
Beaton et al. (2021) (GOAL Trial)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Historical Trials	Some Concerns	High Risk	High Risk	Some Concerns	Some Concerns	High Risk

(Synthesized in Bray et al., 2024)	/ High Risk			/ High Risk		
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This table provides a simplified summary. The Bray et al. (2024) review assessed 11 individual trials, the majority of which were found to be at high risk of bias, particularly in domains D2 (blinding) and D3 (attrition).

Efficacy of Prophylaxis on Disease Progression and Recurrence

The evidence from the included studies provides a robust and consistent picture of the efficacy of secondary prophylaxis in halting disease progression and preventing ARF recurrence.

Echocardiographic Progression: The most significant and high-certainty evidence on this outcome comes from the GOAL trial (Beaton et al., 2021). This study randomized 818 Ugandan children with screen-detected latent RHD to receive either four-weekly IM BPG or no treatment for two years. The results were definitive: echocardiographic progression of RHD occurred in only 3 participants (0.8%) in the prophylaxis group, compared to 33 participants (8.2%) in the control group. This corresponds to an absolute risk difference of -7.5 percentage points (95% CI, -10.2 to -4.7; $P < 0.001$). The number needed to treat (NNT) to prevent one case of disease progression over two years was 13 (95% CI, 10-21) (Beaton et al., 2021; American College of Cardiology, 2021). This finding provides the first high-quality evidence that secondary prophylaxis is effective in the very early, asymptomatic stages of RHD.

These RCT findings are strongly supported by observational data. The prospective cohort study by Beaton et al. (2017) followed 227 Ugandan children with latent RHD. The study found that children with more advanced latent disease (moderate/severe definite RHD) had poor outcomes, with 47.6% experiencing disease progression. Even those with milder forms were at

substantial risk, with progression rates of 26.2% for mild definite RHD and 9.8% for borderline RHD over a median of 2.3 years. These high rates of progression in a natural history context underscore the clinical importance of the intervention effect seen in the GOAL trial.

Echocardiographic Regression: Several studies documented the potential for valvular lesions to improve or normalize with prophylaxis. In the Beaton et al. (2017) cohort, regression was common in milder forms of latent RHD, occurring in 45.2% of children with mild definite RHD and 46.3% of those with borderline RHD. Similarly, a follow-up study in India by Saxena et al. (2011) reported that among 54 children with echo-diagnosed RHD placed on prophylaxis, isolated significant mitral regurgitation resolved in 35.9% of cases over two years. The historical cohort study by Tompkins et al. (1972) found that 70% of patients with acute mitral regurgitation lost their murmur over a mean follow-up of 9.3 years while on regular IM penicillin.

ARF Recurrence: The prevention of ARF recurrence is the primary mechanism by which prophylaxis works, and the evidence for this is strong. The 2024 Cochrane review by Bray et al., which meta-analyzed six RCTs involving 1721 participants, found that antibiotic prophylaxis (either oral or intramuscular) probably reduces the risk of ARF recurrence by 61% compared to no antibiotics (RR 0.39, 95% CI 0.22 to 0.69; moderate-certainty evidence) (Bray et al., 2024; Pelone et al., 2024).

Observational studies consistently reinforce this finding by linking non-adherence directly to treatment failure. A meta-analysis of 18 observational studies by Aprilia et al. (2024) found that good adherence to penicillin prophylaxis reduced the odds of ARF recurrence or RHD progression by 71% compared to poor adherence (pooled OR 0.29; 95% CI, 0.21-0.40). Similarly, a 10-year retrospective cohort study in Turkey by Dindar et al. (2024) reported that ARF recurrence was significantly more frequent among non-adherent patients ($p=0.005$). In a study from Egypt, Bassili et al. (2000) recorded ARF recurrence in 37.3% of patients, with non-compliance being a significant risk factor.

Impact on Major Cardiac Morbidity and Mortality

While hard clinical endpoints like mortality and the need for surgery are the ultimate measures of success, they are less frequently captured in RCTs due to the long natural history of RHD. Evidence for these outcomes is primarily derived from long-term observational and cohort studies.

Progression to Severe RHD and Need for Valve Surgery: The long-term trajectory of RHD, even when initially mild, can be severe. A retrospective cohort study from Australia by Cannon et al. (2017) followed 389 young people (aged 5-24) with RHD for a median of nearly 10 years. The study revealed that even among the 211 patients who had mild RHD at diagnosis, 11.4% progressed to severe RHD, and half of those who progressed (5.7% of the original mild cohort) required valve surgery. A prospective study in Brazil following 258 children after an initial ARF episode found that 72% developed chronic valvular disease, and 16% progressed to severe aortic or mitral disease over a period of 2 to 15 years (Meira et al., 2005). These data highlight the critical importance of secondary prophylaxis in preventing this long-term deterioration. The adherent patient group in the study by Dindar et al. (2024) showed significant reductions in both the number of affected valves ($p=0.001$) and the severity of valvular regurgitation ($p=0.003$) over time, directly linking prophylaxis to improved cardiac outcomes.

Heart Failure, Arrhythmias, and Mortality: Data on mortality from RCTs are scarce. The 2024 Cochrane review concluded that there was insufficient evidence to determine whether antibiotics affect all-cause mortality in late-stage RHD compared to no antibiotics, primarily due to the low number of events in the included trials (Bray et al., 2024). However, the fundamental rationale for prophylaxis is to prevent the progression to severe RHD, which is the direct cause of heart failure, arrhythmias, and premature death. Hospital-based studies from endemic regions consistently show that RHD is a leading cause of cardiac hospitalization and mortality in young people (Zühlke et al., 2013). The Uganda RHD registry data showed that failure to be retained in care, and thus receive consistent prophylaxis, is a major barrier to optimal outcomes, indirectly

supporting the mortality benefit of maintained prophylaxis (Zühlke et al., 2017).

Comparative Efficacy of Prophylactic Regimens

The choice of antibiotic regimen is a critical determinant of prophylactic success. The evidence base strongly and consistently favors intramuscular BPG over oral alternatives.

The 2024 Cochrane review (Bray et al., 2024) provides the most definitive contemporary analysis on this comparison. A pooled analysis of two RCTs with 395 participants showed that prophylactic IM BPG likely reduces the recurrence of ARF substantially when compared to oral antibiotics. The recurrence rate was 0.1% in the IM group versus 1.0% in the oral group, yielding a risk ratio of 0.07 (95% CI, 0.02 to 0.26; moderate-certainty evidence). The authors concluded that IM BPG is probably superior to oral antibiotics, being approximately 10 times more effective at preventing recurrence (Bray et al., 2024; Pelone et al., 2024).

This conclusion is consistent with an earlier Cochrane review by Manyemba and Mayosi (2002), which analyzed four trials (n=1098) and found that IM penicillin was superior to oral penicillin in reducing both ARF recurrence and streptococcal throat infections. This earlier review also provided evidence on the optimal frequency of BPG injections, finding that 2-weekly or 3-weekly injections were more effective than 4-weekly injections, particularly in high-risk settings where GAS transmission is intense.

The superiority of the intramuscular route is largely attributed to overcoming the significant challenge of adherence associated with daily oral medication over many years. While oral therapy is less painful and more convenient, the reliability of a directly administered injection every few weeks ensures more consistent protective antibiotic levels.

Adherence and Adverse Events

While the efficacy of BPG is well-established, its real-world effectiveness is critically dependent on patient adherence, which remains a major challenge. Concurrently, the safety profile

of long-term antibiotic administration is a key consideration.

Adherence: Adherence to long-term BPG prophylaxis is highly variable and often suboptimal in endemic settings. A cross-sectional study in Ethiopia by Tadesse et al. (2020) found that only 63% of patients had "good adherence" (receiving >80% of scheduled injections). In Egypt, Bassili et al. (2000) reported that approximately two-thirds of pediatric patients were compliant with their regimen. In contrast, a retrospective cohort study in Israel by Diamantopoulos et al. (2018) found alarmingly poor adherence to both oral and intramuscular penicillin, with the median proportion of days covered being only 8% and 10%, respectively, over a 10-year period, rendering the prophylaxis largely futile in that setting.

Barriers to Adherence: Studies have consistently identified a similar set of barriers to adherence across diverse geographical settings. These include factors related to access, cost, and patient experience. Rural residence and long travel distances to healthcare facilities are major obstacles (Tadesse et al., 2020; Dindar et al., 2024). The direct and indirect costs associated with travel and time off work or school are significant burdens for impoverished families (Tadesse et al., 2020). Furthermore, a lack of knowledge and understanding of the disease and the importance of continuous prophylaxis among patients and their families contributes to non-adherence (Bassili et al., 2000). A critical and frequently cited barrier is the pain associated with the intramuscular injection itself, which can lead to fear and avoidance, particularly in children (Dimiati et al., 2020).

Adverse Events: Long-term antibiotic prophylaxis is generally considered safe, with serious adverse events being rare. The high-quality GOAL trial provides the best contemporary data on safety. In this trial, two serious adverse events were attributed to BPG prophylaxis among 399 participants over two years. This included one episode of a mild anaphylactic reaction, representing an incidence of less than 0.1% of all administered doses (Beaton et al., 2021). The 2024 Cochrane review found that while antibiotics probably increase the risk of minor hypersensitivity reactions (e.g., rash) and local injection site reactions, the evidence for an increased risk of severe events like anaphylaxis or sciatic nerve injury is of low certainty and these events are very infrequent (Bray et

al., 2024; Pelone et al., 2024). However, a growing body of case reports and expert opinion suggests a need for caution when administering BPG to patients with very severe, advanced RHD and compromised ventricular function, as there is a potential risk of cardiovascular compromise, possibly due to a vasovagal reaction to pain rather than true anaphylaxis (Webb et al., 2022).

Table 3. Summary of Findings: Efficacy of Secondary Prophylaxis

Outcome	Comparison	Intervention Group	Control Group	No. of Studies / Participants	Relative Effect (95% CI)	Absolute Effect	Certainty of Evidence (GRADE)
Echocardiographic Progression (Latent RHD)	IM BPG vs. No Prophylaxis	0.8% (3/399)	8.2% (33/400)	1 RCT / 818	RD - 7.5% (-10.2 to -4.7)	75 fewer per 1000	High
ARF Recurrence	Any Antibiotic vs. No Prophylaxis	0.7%	1.7%	6 RCTs / 1721	RR 0.39 (0.22 to 0.69)	10 fewer per 1000	Moderate
ARF Recurrence	IM BPG vs. Oral Antibiotics	0.1%	1.0%	2 RCTs / 395	RR 0.07 (0.02 to 0.26)	9 fewer per 1000	Moderate

ARF Recurrence / RHD Progression	Good Adherence vs. Poor Adherence	-	-	18 Obs. Studies	OR 0.29 (0.21 to 0.40)	-	Low
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RD: Risk Difference; RR: Risk Ratio; OR: Odds Ratio; IM BPG: Intramuscular Benzathine Penicillin G; ARF: Acute Rheumatic Fever; RHD: Rheumatic Heart Disease; RCT: Randomized Controlled Trial; Obs.: Observational.

Table 4. Summary of Findings: Morbidity, Mortality, and Safety

Outcome	Comparison	Intervention Group	Control Group	No. of Studies / Participants	Relative Effect (95% CI)	Certainty of Evidence (GRADE)
All-Cause Mortality (Late- stage RHD)	Any Antibiotic vs. No Prophylaxis	-	-	1 RCT / 431	Peto OR 0.22 (0.01 to 4.12)	Very Low
Anaphylaxis	Any Antibiotic vs. No Prophylaxis	-	-	1 RCT / 818	Peto OR 7.39 (0.15 to 372)	Low

Minor Hypersensitivity / Local Reactions	Any Antibiotic vs. No Prophylaxis	-	-	-	Increased risk	Moderate
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Peto OR: Peto Odds Ratio. Data primarily from Bray et al. (2024) Cochrane Review. The evidence for mortality and severe adverse events is limited and of low certainty.

DISCUSSION

Synthesis of Principal Findings: Proven Efficacy in an Evolving Landscape

This systematic review synthesizes a comprehensive body of evidence, culminating in a clear and robust conclusion: secondary antibiotic prophylaxis is a highly efficacious intervention for controlling the progression of RHD in children and adolescents. The most certain finding, supported by high-quality, contemporary evidence, is that four-weekly intramuscular BPG significantly reduces the risk of echocardiographic progression in children with early, latent RHD (Beaton et al., 2021). This modernizes and reinforces the long-held conviction, based on older trials, that prophylaxis is effective at preventing recurrences of ARF (Bray et al., 2024). The clinical impact of this is substantial, as preventing progression and recurrence is the key to averting the development of severe valvular disease and its devastating long-term consequences, including heart failure, surgery, and premature death (Cannon et al., 2017).

Furthermore, the evidence consistently affirms the superiority of intramuscular BPG over oral antibiotic regimens (Bray et al., 2024; Manyemba & Mayosi, 2002). This superiority is not necessarily due to a greater pharmacological effect but is overwhelmingly a function of improved adherence, as a directly administered injection bypasses the challenges of daily self-administration over many years. This creates a central paradox in RHD management: the most effective and recommended mode of delivery is also the most painful and logistically challenging, contributing

directly to the crisis of non-adherence that undermines RHD control programs worldwide.

The Paradigm Shift: Impact of the GOAL Trial and Modern Evidence

The publication of the GOAL trial represents a watershed moment in the field of RHD, acting as both a vindicating and a disruptive force that has fundamentally shifted the landscape of prevention and care. Before this trial, the global RHD community operated on a foundation of strong biological plausibility and evidence from older, methodologically limited studies. A critical and paralyzing evidence gap existed concerning the management of latent RHD. While echocardiographic screening could identify a large population of asymptomatic children with mild valvular changes, there was no high-certainty evidence to confirm that treating them with years of painful penicillin injections was beneficial (Beaton et al., 2017; Beaton et al., 2019). This uncertainty was a major barrier to the formulation of clear public health policy, leaving clinicians and programs in a state of equipoise and stalling the widespread implementation of screening programs (Beaton et al., 2017).

The GOAL trial decisively filled this gap. By demonstrating a substantial and statistically significant reduction in disease progression, it provided the first high-certainty evidence that secondary prophylaxis is highly effective in this early-stage population (Beaton et al., 2021; Sable et al., 2021; Murdoch Children's Research Institute, 2021). This finding vindicated the long-held hypothesis that halting subclinical inflammation and preventing recurrent GAS exposure could alter the natural history of the disease even before symptoms appear. The impact of this evidence has been immediate and profound, directly informing the development of new guidelines from the WHO and WHF that now recommend echocardiographic screening in high-risk populations, followed by the initiation of secondary prophylaxis for all children with screen-detected RHD (World Health Organization, 2024b; Watkins et al., 2024).

This paradigm shift, however, is also disruptive. It creates a new, much larger population of eligible patients, placing immense strain on already fragile health systems in endemic regions. It necessitates a massive scale-up of diagnostic capacity (access to echocardiography and trained

technicians), a secure and affordable supply chain for quality-assured BPG, and a workforce capable of administering and monitoring long-term therapy (World Heart Federation, 2024). Furthermore, it raises new and complex clinical questions. Given that a substantial proportion of children with mild latent RHD may experience spontaneous regression, the optimal duration of therapy is now a critical unknown (Beaton et al., 2017; Watkins et al., 2024). The GOAL trial's success has thus solved one major problem while simultaneously bringing a host of new logistical, economic, and clinical challenges to the forefront of the global RHD agenda.

The Adherence Crisis: The Gap Between Efficacy and Real-World Effectiveness

The findings of this review present a stark and challenging dichotomy: the unequivocal, scientifically proven biological efficacy of BPG stands in sharp contrast to its often-dismal real-world effectiveness. This gap is almost entirely attributable to the crisis of poor patient adherence to long-term prophylaxis. The evidence clearly shows that when BPG is administered consistently, it works exceptionally well to prevent disease progression and recurrence (Beaton et al., 2021; Bray et al., 2024; Aprilia et al., 2024). However, numerous studies from diverse endemic settings paint a bleak picture of adherence, with rates of "good adherence" often falling well below the 80% threshold required for optimal protection (Diamantopoulos et al., 2018; Tadesse et al., 2020).

The link between non-adherence and treatment failure is direct and causal. Studies that stratify outcomes by adherence levels consistently demonstrate that patients who do not receive their injections regularly have significantly higher rates of ARF recurrence and progressive valvular damage (Dindar et al., 2024; Aprilia et al., 2024). This leads to an inescapable conclusion: the primary determinant of success or failure for RHD control programs is not the availability of an effective drug, but the ability of the health system to ensure that patients can and do receive it, consistently, for many years.

Therefore, the central challenge for the global RHD community must pivot from a focus on clinical efficacy—which is now largely established—to a focus on implementation science. The critical questions are no longer *if* BPG works, but *how* to deliver it effectively. Addressing the well-

documented barriers is paramount. This requires a multi-pronged approach that moves beyond the clinic and into the community. Strategies must include decentralizing care to bring services closer to where patients live, reducing the financial and logistical burden of travel (Tadesse et al., 2020). It demands improved patient and family education to increase understanding of the disease and the critical importance of uninterrupted prophylaxis (Bassili et al., 2000). Furthermore, it necessitates innovation in the treatment experience itself, such as research into less painful formulations of BPG or longer-acting alternatives that could reduce the frequency of injections (Webb et al., 2022). Without a concerted and well-funded effort to solve the adherence crisis, the immense potential of secondary prophylaxis will remain unrealized for millions of vulnerable children.

Clinical and Public Health Implications: From Evidence to Action

The robust evidence synthesized in this review has profound implications for both clinical practice and public health policy in RHD-endemic regions. The validation of prophylaxis for latent RHD provides a strong mandate for the implementation of active case-finding programs, primarily through echocardiographic screening of high-risk pediatric populations, such as schoolchildren (World Health Organization, 2024b; Zühlke et al., 2020). This represents a shift from a passive, reactive model of care—waiting for patients to present with advanced, symptomatic disease—to a proactive, preventative approach.

However, this recommendation comes with a critical caveat. A screening program is only ethical and effective if it is seamlessly integrated with a well-functioning and accessible program for long-term care and prophylaxis delivery (Beaton et al., 2021; Sharma, 2023). Launching a screening initiative without the necessary infrastructure to guarantee a consistent supply of BPG and provide the support needed to ensure high rates of adherence would be irresponsible, potentially identifying a large number of patients who are then unable to access the proven effective treatment.

Therefore, the findings reinforce the urgent need for comprehensive, integrated national RHD control programs (World Heart Federation, 2024; Kumar and Tandon, 2022). The essential components of such programs include:

- **Patient Registries:** To track patients, monitor disease progression, schedule appointments, and measure adherence and outcomes (Zühlke et al., 2020).
- **Secure BPG Supply:** Ensuring a consistent, affordable supply of quality-assured BPG is a fundamental prerequisite for any program (World Heart Federation, 2024).
- **Decentralized, Patient-Centered Care:** Shifting care from tertiary hospitals to primary health clinics and community health workers to reduce barriers related to travel and cost (Zühlke et al., 2017).
- **Education and Support:** Implementing structured education programs for patients, families, and healthcare workers to improve understanding of RHD and foster a partnership in long-term care (Bassili et al., 2000).

CONCLUSION AND SUGGESTIONS

Conclusion

The evidence synthesized in this systematic review is conclusive and compelling: secondary antibiotic prophylaxis is a highly effective intervention that significantly reduces the risk of recurrent acute rheumatic fever and demonstrably slows or prevents the echocardiographic progression of rheumatic heart disease in children and adolescents. Intramuscular benzathine penicillin G, administered every three to four weeks, remains the undisputed gold standard regimen due to its superior efficacy in preventing treatment failure. The recent validation of its effectiveness in the early, latent stages of screen-detected RHD marks a pivotal advance, opening a new frontier for early intervention and creating a strong imperative for proactive public health screening programs in endemic regions.

However, this proven efficacy is profoundly undermined by a persistent and widespread crisis of poor adherence to long-term therapy. The gap between what this intervention *can* achieve under ideal trial conditions and what it *does* achieve in real-world settings is vast. The multifaceted barriers to adherence—including pain, cost, distance, and health system failures—constitute the

single greatest obstacle to the successful control and eventual elimination of RHD.

Suggestions for Future Research

To bridge the gap between efficacy and effectiveness, the focus of the global RHD research agenda must evolve. The following areas represent urgent priorities:

- **Implementation Science:** There is a critical need for high-quality research on scalable, culturally appropriate, and cost-effective models of care designed to improve adherence. This should include randomized trials of interventions such as decentralized, nurse-led care programs; the use of mobile health technologies for reminders and patient support; and structured educational initiatives for patients and families (Kumar and Tandon, 2022; PREVENT Trial, 2024).
- **Optimizing the Treatment Experience:** The pain and fear associated with BPG injections are major, modifiable barriers to adherence. Research and development are urgently needed for less painful formulations of BPG, alternative delivery mechanisms, or longer-acting antibiotics that could reduce the frequency of injections. Furthermore, contemporary, well-designed RCTs comparing the real-world effectiveness of oral antibiotics versus IM BPG, with adherence as a primary outcome, are warranted in settings where intramuscular injections are not feasible for a large proportion of patients (Webb et al., 2022; Sable et al., 2021).
- **De-escalation and Risk Stratification Strategies:** For the growing population of children identified with mild, latent RHD, long-term research is essential to determine if and when it is safe to discontinue prophylaxis, particularly for those whose echocardiograms normalize. The GOAL-Post follow-up study is a critical first step in this process (Watkins et al., 2024). Concurrently, research is needed to identify clinical, genetic, or biomarker-based risk factors that can predict which children with latent RHD are at the highest risk of progression, allowing for a more targeted and potentially less burdensome approach to prophylaxis (Beaton et al., 2017).

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