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Review

Assessing the evidence for antibiotic management of laboratory-confirmed *Streptococcus A* skin infections to prevent acute rheumatic fever and rheumatic heart disease: a systematic review

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ABSTRACT

Objectives: Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) are potential sequelae of untreated group A streptococcal (*Strep A*) infections. Guidelines focus on treating *Strep A* pharyngitis but seldom on skin infections. This systematic review explored whether directed antibiotic therapy for superficial *Strep A* skin infections prevents ARF/RHD.

Methods: We searched PubMed, Scopus, Cochrane Library, and clinical trial registries for published and ongoing trials measuring the eradication of *Strep A* and clinical resolution of polymicrobial infections with antibiotics through December 13, 2024. We calculated risk ratios and absolute risk differences, using the grading of recommendations, assessment, development, and evaluation (GRADE) to assess the certainty of evidence.

Results: No trials were reported on ARF/RHD outcomes. However, we identified 12 trials and pooled data comparing penicillin, cotrimoxazole, macrolides, and cephalosporins. There was probably no difference between interventions for eradicating *Strep A* (very low certainty evidence). For clinical resolution, cotrimoxazole was comparable to intramuscular benzathine benzylpenicillin and macrolides to penicillin (moderate certainty evidence). First- and second-generation cephalosporins showed no difference (low certainty evidence), whereas third-generation cephalosporins demonstrated improved clinical response (moderate certainty evidence). Benzathine benzylpenicillin-associated injection-site pain and oral antibiotic-associated gastrointestinal disorders were commonly reported.

Conclusions: The available evidence for directed treatment of *Strep A* skin infections to prevent ARF/RHD is uncertain, requiring further research, with consideration of antimicrobial resistance and the limited antibiotic pipeline.

Introduction

Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) pose a high burden of disease for disadvantaged communities in low- and middle-income countries (LMICs) and among older adults in high-income countries (HIC) [1]. In 2019, the estimated mortality associated with untreated RHD in LMICs was more than 288,000, representing 2% of cardiovascular deaths [1]. ARF is an autoimmune response to infections caused by group A β-hemolytic streptococci (GABHS), also known as *Streptococcus pyogenes (Strep A)* [2]. Typical presentations include pharyngitis with emerging evidence of ARF-associated *Strep A* skin infections [3–5]. Recently, a New Zealand retrospective analysis of administrative data, specifically among Māori and Pacific Peoples showed that confirmed GABHS-positive skin infection was strongly associated with subsequent ARF compared with GABHS-negative skin swabs, with a risk ratio (RR) of 5.1 and a 95% confidence interval (CI) of 1.8-15.0. In addition, dispensing antibiotics did not reduce the risk of ARF following the diagnosis of GABHS skin infection [5]. Recurrent ARF commonly manifests as carditis or arthritis [4]. Approximately 60% of ARF progresses to RHD, a chronic valvular disease [2]. Antibiotic treatment of *Strep A* pharyngitis likely reduces ARF by 70-80% [6], and secondary antibiotic prophylaxis may reduce the risk of disease progression [1]. Primordial

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prevention (e.g., hand washing) [7] and antibiotic management of superficial *Strep A* skin infections may prevent invasive infections and post-streptococcal sequelae [6] and are potentially cost-effective strategies for containing RHD [8]. Acute bacterial skin and skin structure infections are polymicrobial, commonly caused by both *Staphylococcus aureus* and *Strep A*, with emerging reports of community-acquired methicillin-resistant *S aureus* (MRSA) [9]. These infections represent a broad spectrum of disease severity, categorized as purulent (e.g., bullous impetigo, carbuncles, abscesses), predominantly caused by *S aureus* [10], whereas *Strep A* infections are mostly non-purulent (e.g., non-bullous impetigo, erysipelas, cellulitis, necrotizing fasciitis) [4]. Impetigo, the most common superficial skin infection, affects approximately 162 million children [3] and is highly contagious and prevalent among indigenous LMIC populations [3].

Non-bullous impetigo erythematous macules progress to pustules that spread on scratching. Lesions frequent the lower extremities or face and may be painful, with local lymph node swelling [10]. Superficial infections are self-limiting, resolving within 2-3 weeks, but empiric antibiotic therapy may prompt resolution and prevent transmission within communities.

For localized impetigo, topical mupirocin and fusidic acid are superior to oral antibiotics [11]. For extensive impetigo, among oral antibiotics, penicillin was not as effective as erythromycin and cloxacillin, reinforcing the changing microbiology of impetigo to *S. aureus* (including MRSA) [12]; however, in endemic tropical settings, oral cotrimoxazole was non-inferior to intramuscular (IM) benzathine benzylpenicillin [13] reported in a systematic review [13] that also suggested a potential benefit of mass drug administration (MDA) therapies for impetigo in these settings. In non-endemic settings, limited evidence suggests topical preparations may be beneficial (e.g., ozenoxacin 1%, retapamulin) [13]. Resistance to topical antibiotics has been reported [9,14], underscoring the importance of judicious antibiotic use.

Notably, no evidence has been published to inform the choice of antibiotic treatment for *Strep A* skin infections to prevent ARF/RHD. This systematic review, commissioned by the World Health Organization to inform a clinical guideline for ARF/RHD prevention and management, evaluates the efficacy and safety of antibiotic treatment of laboratory-confirmed superficial *Strep A* skin infections and whether antibiotic treatment reduced the subsequent risk of ARF/RHD.

Methods

We conducted a systematic review aligned with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 reporting guidelines [15] (PROSPERO registration: CRD42023386889). The PRISMA checklist is provided in Supplementary Table S1. This is one of two complementary reviews commissioned by the World Health Organization (WHO) for guidelines informing antibiotic choice for treating laboratory-confirmed or clinically suspected *Strep A* skin infections to prevent ARF/RHD.

Criteria for inclusion of studies

Participants with laboratory-confirmed *Strep A* skin infections from any ethnicity, socioeconomic, educational background, and geographical region were considered. Our original protocol did not define the health care setting, but in discussion with the WHO Guideline Steering Group, we restricted trials to primary care or outpatient settings, relevant to the clinical presentation of superficial skin infection. Additional pre-determined inclusion criteria included randomized controlled trials (RCTs) of antibiotics compared with other or no antibiotic treatments (focusing on penicillin vs placebo or other antibiotics; cephalosporins vs other antibiotics, including an intraclass comparison of cephalosporins). Outcomes sought were duration and severity of *Strep A* skin infection, rates of ARF or RHD (incidence and/or prevalence), treatment adherence, any adverse events (AEs), antibiotic resistance, and acceptability to the provider and patient/caregivers.

Search strategy

We searched PubMed, Scopus, and the Cochrane Library until December 1, 2022 (subsequently updating the search to December 13, 2024) without date or language restrictions. We used medical subject heading terms, keywords, and word variants for streptococcal infection, skin infection, and antibiotics (including β-lactam, macrolides, fluoroquinolone, tetracycline, sulfonamide, aminoglycoside). We adapted the PubMed search for other databases (Supplementary File S1). Searches were performed for both WHO-commissioned reviews, manually checking for either laboratory or clinically diagnosed trials. We sought conference proceedings and manually screened citations of relevant articles to identify additional trials. WHO-ICTRP and Clinicaltrials.gov were searched for planned, ongoing, or completed trials.

Data collection and analysis

Following the automated removal of duplicates, reviewers independently (TDL, DM, NB, EO, TK, AH, LR) and in duplicate screened titles and abstracts of retrieved records using Covidence software [16]. Full texts of potentially relevant articles were screened, and articles were identified for evidence synthesis. Disagreements between reviewers were resolved by discussion or consultation with another reviewer.

Reviewers independently extracted data into a pilot-tested standardized Microsoft Excel database (Supplementary File S2), with conflicts resolved by discussion. We extracted data on characteristics of trials and participants, interventions, comparators, pre-specified outcomes, regions, settings, type of skin infections, bacterial characteristics, and study follow-up periods (categorized as $<$ or $\geq$4 weeks). We reported effect sizes of dichotomous data as RRs or risk differences (RDs), with 95% CIs. We did not identify eligible trials using cross-over or cluster-RCT designs. An intent-to-treat analysis was used.

Each study was appraised for potential risk of bias independently by reviewers (TDL, DM, AH, MEE) (Supplementary File S4) using Cochrane's Risk of Bias 2.0 (RoB 2) tool [17]. We focused on primary outcomes (clinical resolution) and assessed the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result, rating trials as "low-," "some concerns-," or "high risk-" of bias.

Statistical analysis

Where the data were sufficiently homogenous, a meta-analysis was conducted. Heterogeneity was assessed through visual inspection of the forest plots and the I^2 statistic [18]. A random-effects model (Mantel-Haenszel method) was used to estimate effects using RevMan software (version 5.0) [19]. Where a meta-analysis was not possible, we reported individual trial results. We had planned to conduct subgroup and sensitivity analyses to assess the robustness of findings and explore the effect of bias, but the data were insufficient.

Certainty of evidence

We used the grading of recommendations, assessment, development, and evaluation (GRADE) approach [20] to assess the certainty of evidence for each outcome. We used GRADEpro GDT, rating evidence as "high," "moderate," "low," or "very low" certainty, with considerations of internal validity (risk of bias, inconsistency, imprecision) and external validity (directness of results) [20]. The GRADE evidence profiles with summarized findings are reported in Supplementary File S5.

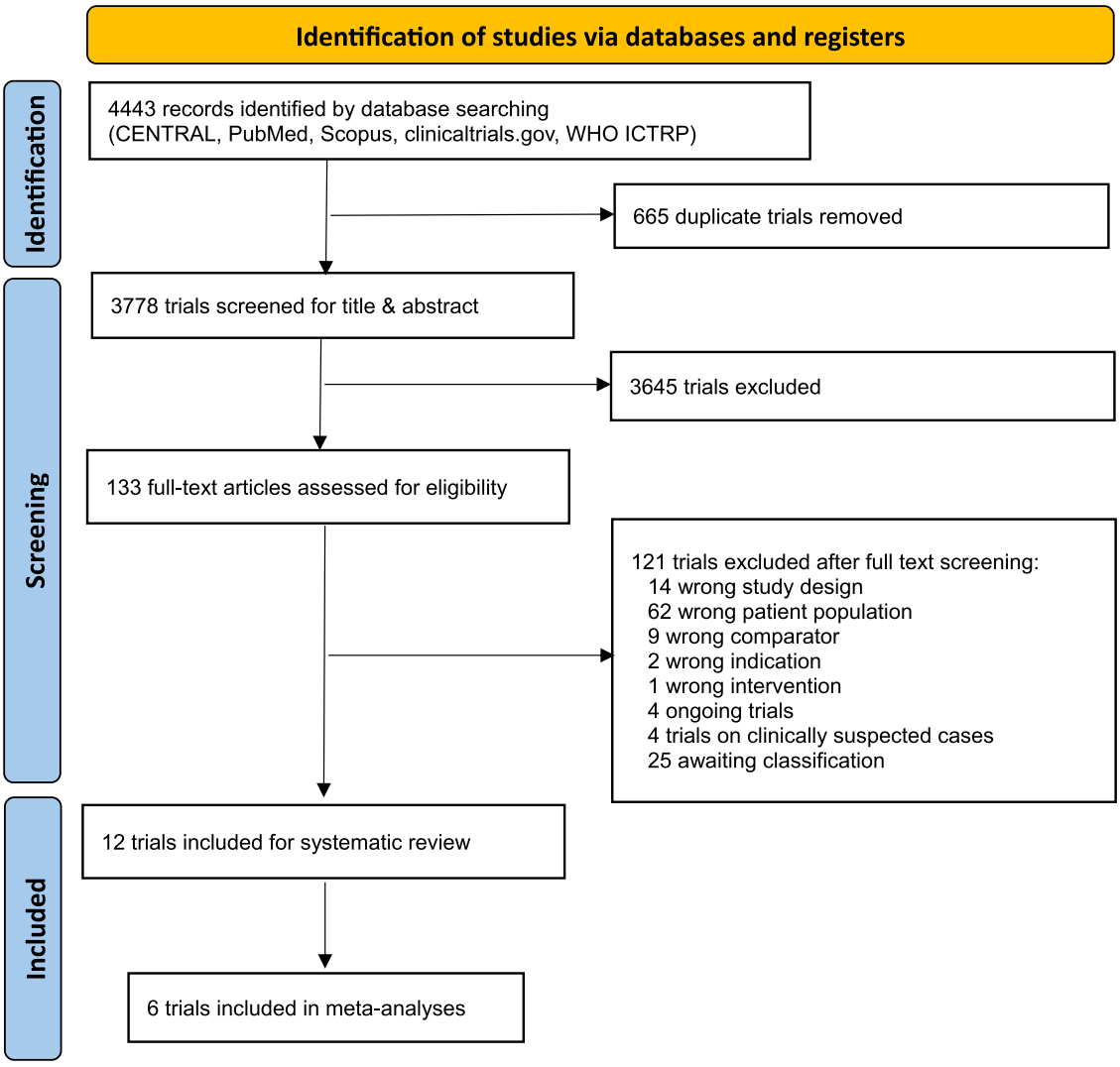

Figure 1. PRISMA flow diagram of the screening and selection process according to PRISMA 2020 guidelines.
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; WHO, World Health Organization.

Role of the funding sources

The WHO commissioned this review to inform their clinical guideline on the prevention and management of ARF and RHD (meeting convened on April 17, 2023). The funder reviewed the study protocol but had no role in data collection, analysis, interpretation, or writing of the report. The WHO Guideline Steering Group and methodologist guided the refining of eligibility criteria.

Results

Our searches yielded 4443 records (Figure 1). We removed duplicates and screened abstracts, followed by a full-text eligibility assessment of 133 records. Twelve trials conducted in primary care or outpatient settings, comparing penicillin vs placebo, penicillin vs other antibiotics, cephalosporins vs other antibiotics, and a cephalosporin intraclass comparison, were included in the systematic review, of which six were included in the meta-analysis. These trials were limited and sparse, precluding the need to assess heterogeneity. Excluded trials are listed in Supplementary Table 2.

Included trials compared penicillin [21–26] and cephalosporins to other antibiotics (Table 1) [27–32]. No placebo-controlled trials investigating penicillin were identified. Six trials were conducted in HIC [23,26–31], whereas four were conducted in LMICs or regions with marginalized population groups [21,22,24,25]. One multicenter trial was conducted in LMIC and HIC settings [32]. Trial settings were primary care [22,25–28] or hospital outpatient settings [23,29,32], with no information reported for four trials [21,24,30,31]. Most studies were conducted in the 1990s.

Seven trials were conducted among 1443 children [22–25,27,30,32] (2 months to 17.9 years) and two trials among 436 adults [21,31]. Three trials had no age restrictions, ranging from 1 to 78 years (n = 2215) [27,29,30]. Superficial skin infections were impetigo (including purulent crusted and purulent non-bullous impetigo) [22,25,27], perianal dermatitis [23] and a range of uncomplicated infections [21,24,26,28–31]. At baseline, there were lower proportions of *Strep A* than *S. aureus* [21,24–32], except in one trial where comparable rates were reported (89.6% vs 81.1%) among isolates cultured from crusted nonbullous impetigo sores (both pathogens in 74.2% children) [22]. In another trial, all perianal streptococcal dermatitis swabs cultured *Strep* A [23].

No trial was reported on the duration and severity of *Strep A* skin infections, rates of ARF/RHD, or acceptability of treatment for providers and patients. We considered *Strep A* eradication and clinical response rates surrogate measures for resolving confirmed *Strep A* skin infections, noting that most are polymicrobial. There was wide variation

Table 1
Characteristics of included studies.

Citation	Country, setting (Funding)	Population (n); range of age	Study design *(Timing of outcome assessment)*	Type of skin infections (severity) and causative pathogen(s)	Study drugs	Outcomes reported
PENICILLIN COMPARISONS						
Amaya-Tapia et al. [21]	Mexico, NR (Funding: NR)	Adults (n = 62); 17.5-62.1 years	Blinded randomized study *(NR)*	Uncomplicated SSSIs (mild, moderate, severe) *S. aureus:* 55.7%; *Strep species (including S. pyogenes*): 4.9%	Azithromycin, oral, 500 mg daily for 3 days *vs* Dicloxacillin, oral, 250 mg four times a day for 7 days	Clinical efficacy: 29/31 vs 30/31; RD -0.03 (95% CI -0.14 to 0.07) Bacterial efficacy: NR Adverse events: 1/30 (3.3%) vs 0/30 (0%); RD 0.03 (95% CI -0.05 to 0.12)
Bowen et al. [22]	Northern Territory of Australia (Aboriginal communities), primary care (Funding: Australian National Health and Medical Research Council)	Children (n = 508); 4.6-8.8 years	Open-label, multicenter, outcome-assessment-blinded, non-inferiority, randomized (1:1:1) controlled trial *(Efficacy: 7 days* *Adverse events: 30 days)*	Purulent or crusted non-bullous impetigo due to scabies, tinea corporis, pediculosis (mild, moderate, severe) *Strep A:* 89.6%; *S. aureus:* 81.1%; Both: 74.2%	Cotrimoxazole, oral, 4/20 mg twice daily for 3 days (CTX3) *or* Cotrimoxazole, oral, 8/40 mg daily for 5 days (CTX5) vs Benzathine Pen G, IM once daily for 5 days or twice daily for 3 days	Treatment/ clinical success at day 7 (primary): 283/334 vs 135/156; RD -0.02 (95% CI -0.08 to 0.05) Detection of *S pyogenes* on days 7: NR Antibiotic resistance (*S pyogenes*): 7/455 vs 0/455; RD 15 (95% CI 0.86-261.86) Adverse events: 5/343 vs 49/165; RD 0.05 (95% CI 0.02-0.12) Treatment adherence: 327/343 vs 161/165; RD -0.02 (95% CI -0.05 to 0.01)
Meury et al. [23]	Switzerland, outpatients (Funding: NR)	Children (n = 35); 1.1-11.6 years	Prospective, open, randomized (1:1) controlled trial *(7-10 days)*	Perianal dermatitis *Strep A:* 100%	Cefuroxime, oral[b] 20 mg/kg daily in 2 divided doses for 7 days *vs* Penicillin, oral, 50,000-100,000 U/kg daily in 3 divided doses for 10 days	Clinical response (primary): 13/14 vs 7/15; RD 0.46 (95% CI 0.18-0.75)
Rodriguez-Solares et al. [24]	Central & South America (Costa Rica, Guatemala, Panama, Venezuela), NR (Funding: NR)	Children (n = 118); 1-12 years	Open, randomized, multicenter trial *(7 -10 days)*	Uncomplicated SSSIs *Strep A:* 10.5% *S. aureus:* 80.2%	Azithromycin, oral, 10 mg/kg (500 mg/day maximum dose), daily for 3 days *vs* Cloxacillin ester: • Dicloxacillin, oral, 12.5-25 mg/kg daily, depending on infection severity (administered in four doses for 7 days *or* • Flucloxacillin, oral (administered in four doses) for 7 days: *2-10 years:* 500-1000 mg daily*>10 years.*: 1-2 g daily	Clinical cure: 57/58 vs 57/59; RD 0.02 (95% CI -0.04 to 0.07) Bacteriologic response: 5/5 (100%) vs 4/4 (100%); RD 0 (95% CI -0.34 to 0.34) Safety (adverse events): 2/58 vs 2/59; RD 0 (95% CI -0.07 to 0.07)
Tong et al. [25]	Australia (Northern Territory), remote Aboriginal community setting (Funding: Australian National Health and Medical Research Council, Australian National Heart Foundation, Ian Potter Foundation, and the Rio Tinto Aboriginal Foundation)	Children (n = 13); 2 months to 16 years	Pilot randomized controlled trial *(7 days)*	Purulent or crusted impetigo (mild, moderate) *Strep A:* 30.8%; *S. aureus:* 100%	Cotrimoxazole, oral, 4/20 mg/kg (up to 160/800 mg) twice daily for 5 days *vs* Benzathine Pen G, IM 45 mg/kg (up to 900 mg) as a single dose	Clinically assessed successful treatment on day 7 (primary): 5/6 vs 7/7; RD -0.17 (95% CI -0.51 to 0.18) Bacterial resolution on day 7: 3/3 vs 1/1; RD 0(95% CI -0.68 to 0.68)

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Table 1 (*continued*)

Citation	Country, setting (Funding)	Population (n); range of age	Study design *(Timing of outcome assessment)*	Type of skin infections (severity) and causative pathogen(s)	Study drugs	Outcomes reported
Villiger et al. [26]	New Zealand, primary care (Funding: Beecham Research Laboratories)	Adults/ children (n = 200); 1-78 years	Multicenter, randomized controlled trial (9-10 days)	Uncomplicated SSSIs (mild/moderate/severe) *Strep A:* 2.1%; *S. aureus:* 57.8%	Mupirocin, topical applied three times a day - *short-term:* 4-6 days - *intermediate duration*: 7-8 days - *long-term*: 9-10 days *vs* Flucloxacillin/erythromycin, oral, two-four times a day *(general practitioners dosed antibiotics as per standard practice)* - *short-term:* 4-6 days - *intermediate duration*: 7-8 days - *long-term*: 9-10 days	Clinical response rating: 100/101 vs 79/80; RD 0 (95% CI -0.03 to 0.03) Bacteriologic assessment: NR
CEPHALOSPORIN COMPARISONS						
Bass et al. [27] *(Methodology described in initial study, Demidovich 1990)*	Hawaii (Honolulu). pediatric clinic (Funding: NR)	Children (n =32); 3.25-4.35 years	Prospective double-blind placebo-controlled trial *(3-10 days)*	Impetigo (NR) *Strep A*: 0%; *S. aureus:* 100%; Both: 13.6%	• Mupirocin 2%, topical applied three times a day for 10 days *or* • Bacitracin 500 units/g, topical, applied three times a day for 10 days *vs* Cephalexin, oral,[a] 50 mg/kg/day administered in three divided doses (maximum dose: 500 mg/dose) for 10 days	Clinical response: • Mupirocin, topical vs cephalexin, oral: 7/7 vs 10/10; RD 0.00 (95% CI -0.21 to 0.21) • Bacitracin, topical vs cephalexin, oral: 3/9 vs 10/10; RD -0.67 (95% CI -0.99 to -0.35) Bacteriologic response: NR Treatment adherence: NR
Bucko et al [28] *(2 parallel-group trials; 1) cefditoren vs cefuroxime; 2) cefditoren vs cefadroxil)*	United States (69 sites in the cefadroxil, 63 sites in the cefuroxime study), primary care (Funding: TAP Pharmaceutical Products Inc)	Adults/ children (n = 1,685); 12-95 years	Two randomized (1:1:1) double-blind, multicenter, parallel group trials *(14 days)*	Uncomplicated SSSIs *Strep A*: 4·2%; *S. aureus:* 46·7%	Cefditoren, oral[c] 200 mg twice daily for 10 days ***or*** 400 mg, twice daily for 10 days *vs* Cefuroxime,[b] oral, 250 mg twice daily for 10 days ***or*** Cefadroxil,[a] oral, 500 mg twice daily for 10 days *(cefuroxime 250 mg in Study l and cefadroxil 500 mg in Study 2)*	Clinical response: 591/707 vs 277/556; RD 0.34 (95% CI 0.29-0.39) Microbiologic response: 33/36 vs 8/8; RD -0.08 (95% CI -0.26 to 0.09) Adverse events: 429/1129 vs 63/556; RD 0.27 (95% CI 0.23 to 0.31) Treatment adherence: NR
Gooch et al. [29]	United States (10 centers, outpatient (Funding: In part by Glaxo Inc)	Adults/ children (n = 330); 4-90 years	Randomized, investigator-blinded, parallel-group, multicenter trial *(20- 24 days)*	Uncomplicated SSSIs (mild to moderate) *Strep A*: 5.1%; *S. aureus:* 41.4%	Cefuroxime, oral[b] 250 mg twice daily for 10 days *vs* Cephalexin,[a] oral 500 mg twice daily for 10 days *or* Cefadroxil, oral[a] 500 mg twice daily for 10 days	Clinical response: 89/107 vs 162/223; RD 0.11 (95% CI 0.01-0.20) Bacteriologic response: 4/5 vs 5/6; RD -0·03 (95% CI -0.49 to 0.43) Adverse events: 15/107 vs 32/223; RD 0.00 (95% CI -0.08-0.08)
Jacobs et al. [30]	United States, primary care (Funding: Glaxo Inc)	Children (n = 238); 60.8-72.9 months	Multicenter, randomized (2:1), single-blinded trial *(30 days)*	Uncomplicated SSSIs *Strep A*: 33·8%; *S. aureus:* 66·2% Both: 15·6%	Cefuroxime, oral[b] 30 mg/kg daily, in two doses, 12 hourly (maximum daily dose: 1 g) for 10 days *vs* Cefadroxil, oral[a] 30 mg/kg daily in two doses 12 hourly (maximum daily dose: 1g) for 10 days	Clinical response: 135/156 vs 65/92; RD 0.16 (95% CI 0.05-0.27) Bacteriologic response: NR Safety (adverse events): 15/189 vs 6/98; RD 0.02 (95% CI -0.04 to 0.08)

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Table 1 (*continued*)

Citation	Country, setting (Funding)	Population (n); range of age	Study design *(Timing of outcome assessment)*	Type of skin infections (severity) and causative pathogen(s)	Study drugs	Outcomes reported
Neldner et al. [31]	United States (17 sites), NR (Funding: Abbott Laboratories)	Adults (n = 374); 17-82 years	Randomized, double-blind, multicenter trial *(12 to 19 days)*	Uncomplicated SSSIs (mild to moderate) *Strep A*: 4.0%; *S. aureus:* 41.0%	Temafloxacin, oral 600 mg twice daily for 7 to 10 days *vs* Cefadroxil, oral[a] 500 mg twice daily for 7 to 10 days	Clinical response: 91/95 vs 102/106; RD 0 (-0.06 to 0.05) Bacteriologic response: 3/3 vs 5/6; RD 0.17 (95% CI -0.28 to 0.61) Adverse events: 63/183 vs 47/191; RD 0·10 (95% CI 0.01; 0·19)
Wible et al. [32]	Multicenter (91 sites in the United States, Canada, Mexico, Argentina, Brazil, Chile, and Peru), NR (Funding: Pharmacia Corporation)	Children (n = 499); 4.9-17.9 years	Prospective, randomized, blinded, comparator controlled multicenter, trial *(10-21 days post-therapy)*	Uncomplicated SSSIs (mild, moderate) *Strep A*: 13.2%; *S. aureus:* 57.5%	Linezolid, oral 5-11 years: Linezolid suspension oral, 10 mg/kg (up to 600 mg) 12 hourly for 10-21 days 12-17 years: Linezolid tablet, oral, 600 mg 12 hourly for 10-21 days *(Actual duration: 12.3 ± 3.5 days)* *vs* Cefadroxil, oral[a] 5-11 years: Cefadroxil[a] suspension, oral, 15 mg/kg (up to 500 mg) 12 hourly for 10-21 days 12-17 years: Cefadroxil[a] capsule, oral 500 mg 12 hourly for 10-21 days *(Actual 12.3 ± 3.4 days)*	Resolution of clinical signs and symptoms of infection (primary): 201/221 vs 189/210; RD 0.01 (95% CI -0.05 to 0.06) Microbiologic efficacy (primary): 37/37 vs 26/27; RD 0·04 (95% CI -0.05; 0·13) Safety assessment: 111/248 vs 117/251; RD -0.02 (95% CI -0.11 to 0.07) Treatment adherence: 245/248 vs 248/251; RD 0 (95% CI -0.02 to 0.02)

Benzathine Pen G, Benzathine benzylpenicillin G; CI, confidence interval; IM, intramuscular; n, sample size; NR, not reported; RD, risk difference; *S aureus, Staphylococcus aureus; Strep* A, Streptococcus pyogenes; SSSIs, Skin and skin structure infections.

[a] First-generation cephalosporin = cephalexin, cefadroxil.

[b] Second-generation cephalosporin = cefuroxime.

[c] Third-generation cephalosporin = cefditoren.

in the time points assessing outcomes, including early follow-up (2-6 days from randomization) [27,29–31], end-of-therapy [23,26,27], test-of-cure (ranging from 5-14 days post−therapy) [22,24,25,28–32], and late follow-up [30,32]. *Strep A* eradication rates were assessed in seven trials, among microbiologically evaluable participants at various clinical assessment timepoints [22,24,25,28,29,31,32]. AEs were reported in most trials [21,22,24,28–31], antibiotic resistance was reported in one trial [22], and treatment adherence was reported in two trials [22,32].

Risk of bias

For the primary outcome (clinical efficacy, improvement, success, or cure) one trial was judged as low risk of bias [22]. However, most trials pre-dated 2010 and did not report sufficient information. Four studies were assessed as having a high risk of bias in the domains of randomization [26,27], deviations from the intended interventions [27], missing outcome data [27,28], and measurement of the outcome [21]. There were some concerns among the remaining trials [23–25,29–32] (Supplementary File S4). We aimed to explore publication bias, but there were insufficient studies with shared outcomes to create funnel plots.

Effectiveness and safety of the interventions

No trials were reported on the duration and severity of *Strep A* skin infections, rates of ARF/RHD, or provider and patient acceptability of therapy. Meta-analysis was only possible for three therapeutic comparisons for most outcomes: (i) cotrimoxazole, oral vs β-lactamase sensitive penicillin, benzathine benzylpenicillin, IM [22,25]; (ii) macrolide, oral vs β-lactamase resistant penicillin, oral [21,24]; and (iii) second-generation cephalosporins vs first-generation comparisons [29,30], an intraclass comparison.

The effect of cephalosporin (cefuroxime) compared with oral penicillin on *Strep A* eradication is uncertain (RD 46.2% more; 6.5 more to 115.7 more; 1 trial; n = 29, very low certainty evidence) [23].

Two trials reported on cotrimoxazole vs IM benzathine benzylpenicillin [22,25]. For *Strep A* eradication, the effect of cotrimoxazole compared with IM benzathine benzylpenicillin is uncertain (RD 0 fewer per 1000; 590 fewer to 1000 more; one trial; n = 4; very low certainty evidence) [25]. Cotrimoxazole (84.5%) may result in a similar clinical response compared with IM benzathine benzylpenicillin (RD 26 fewer per 1000; from 87 fewer to 44 more; two trials; n = 503; moderate certainty evidence) [22,25] (Figure 2a). Cotrimoxazole results in slightly lower treatment adherence compared with IM benzathine benzylpenicillin (95.6% vs 97.6%); RD 2% fewer, 5.9 fewer to 1.0 more; one trial; n = 508; high certainty evidence [22]. Cotrimoxazole results in a slight reduction in AEs compared with IM benzathine benzylpenicillin (1.5% vs 29.7%; RD 28.2% fewer; 29.1 fewer to 26.1 fewer; one trial; n = 508; high certainty evidence) [22]. Pain at the injection site at 48 hours associated with IM benzathine benzylpenicillin was the most reported AE (30%; 48/160), with 10% (5/48) of study participants requiring analgesia post-injection [22].

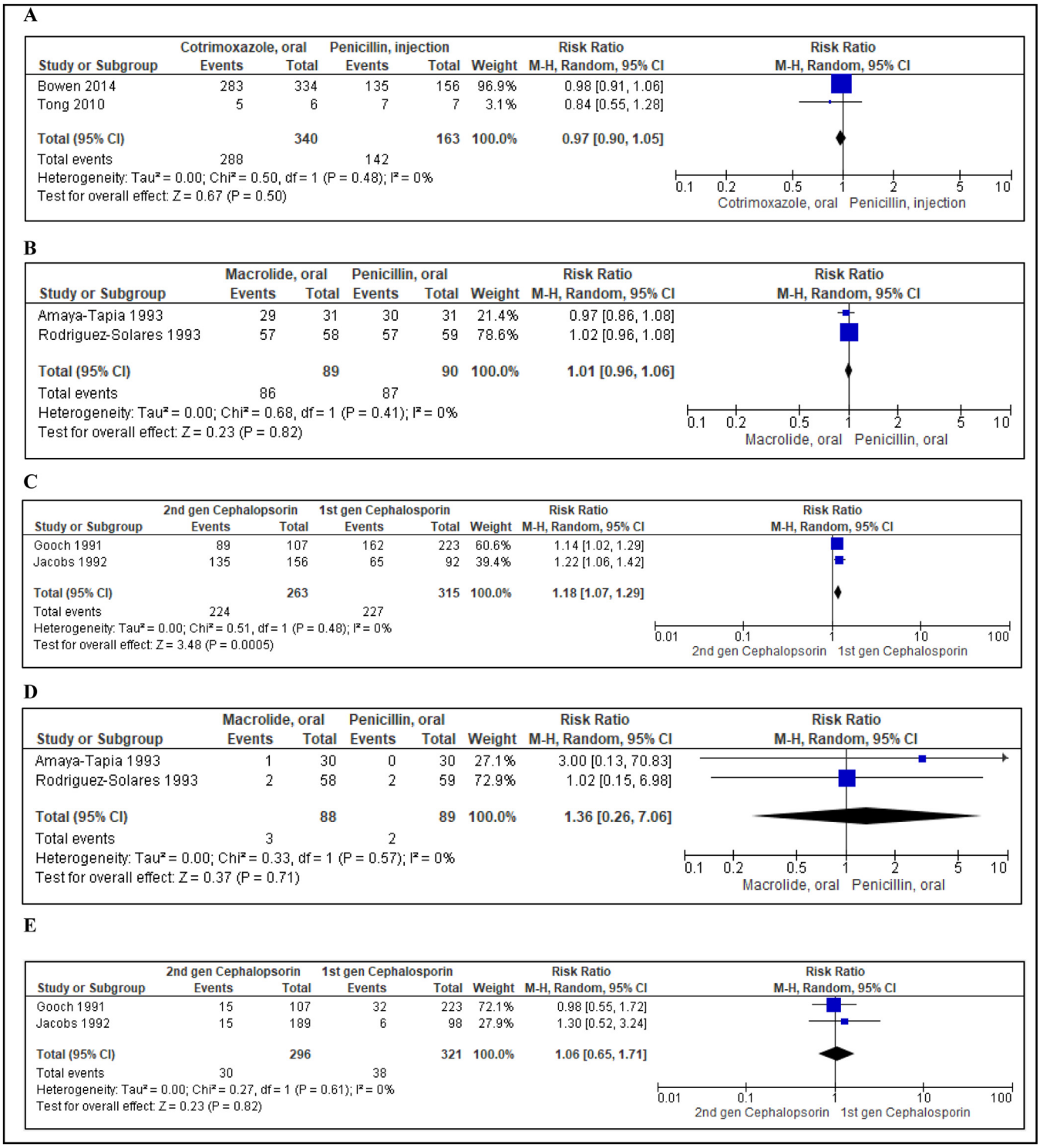

Figure 2. Forest plot of pooled risk ratios (RRs) for clinical response of (a) cotrimoxazole vs IM benzathine benzylpenicillin; (b) macrolides vs penicillin; (c) second- vs first-generation cephalosporins; and adverse events of (d) macrolides vs penicillin; and (e) second- vs first-generation cephalosporins (RRs are random-effects estimates calculated by Mantel-Haenszel method).
IM, intramuscular; RR, risk ratios.

There was one hospital admission for a benzathine benzylpenicillin-injection site *S aureus* buttock abscess. Another participant developed moderate injection-site swelling which resolved when benzathine benzylpenicillin was switched to cephalexin. There were no episodes of anaphylaxis reported [22]. Cotrimoxazole probably results in little to no difference in antibiotic resistance compared with IM benzathine benzylpenicillin (0% vs 1.54%; RD 0%; 0 fewer to 0 fewer; 1 trial; n = 910); moderate certainty evidence [22].

The effect of macrolides compared with oral penicillin is uncertain for *Strep A* eradication (RD 38 more per 1000; 100 fewer to 219 more; one trial; n = 9; very low certainty evidence) [24]. Macrolides compared with penicillin results in little to no difference in clinical response (RD

0.0%; 9.7 fewer to 4.8 more; two trials; n = 179; low certainty evidence) (Figure 2b) [21,24]. The effect of the macrolide, azithromycin (3.4%), on AEs compared with penicillin, dicloxacillin/flucloxacillin is uncertain (RD 3.4% vs 2.2%; 8 more per 1000; from 17 fewer to 136 more; two trials; n = 177; very low certainty evidence) (Figure 2d) [21,24]. Treatment-associated AEs reported were mild gastrointestinal adverse drug reactions.

For the comparison of mupirocin, topical vs oral penicillin, there was little to no difference for clinical resolution of skin infections (RD 0%; 3 fewer to 3 more; one trial; n = 181; very low certainty evidence) [26].

Evidence from a single trial regarding the effect of fluoroquinolone on *Strep A* eradication vs cephalosporin was assessed as very uncertain (RD of 9.2% more; 29.2 fewer to 75 more; one trial; n = 9; very low certainty evidence) [31]. Similarly, the evidence is very uncertain for the clinical resolution of *Strep A* skin infections (RD 0%; 5.8 fewer to 4.8 more; one trial; n = 201). Fluoroquinolones may increase AEs compared with cephalosporins (RD 9.8% more; 0.5 more to 22.6 more; one trial; n = 374; low certainty evidence). Commonly reported AEs were mild and manifested as diarrhea (6.6% vs 7.9%), nausea (8.7% vs 4.7%), somnolence (6% vs 6.3%), headache (8.7% vs 1%), and dizziness (4.4% vs 4.7%) [31].

One trial demonstrated that linezolid may have little to no effect on *Strep A* eradication vs cephalosporin (RD 3.9% more; 4.8 fewer to 14.4% more; one trial; n = 64; very low certainty evidence) [32]. Similarly, there was little to no difference in clinical response (RD 0.9% more; 4.5 fewer to 6.3 more; one trial; n = 431; very low certainty evidence) [32]. Linezolid probably does not increase/reduce treatment adherence compared with cephalosporin (cefadroxil) (RR 1.00, 95% CI 0.98-1.02; one trial, n = 499; moderate certainty), and little to no difference in AEs were reported (RD 1.9% fewer; 9.8 fewer to 75 more; one trial; n = 499; low certainty evidence). Commonly reported AEs included gastrointestinal symptoms (19% vs 23.1%); headache (6.5% vs 4.0%) and respiratory tract complications (6.0% vs 9.2%) [32].

The effect of bacitracin, topical on the clinical resolution of polymicrobial skin infections, compared with cephalosporin with treatment failures reported among bacitracin-treated patients was uncertain (RR 0.37, 95% CI 0.16-0.86; one trial; n = 19; very low certainty evidence) [27].

Topical mupirocin compared with oral cephalosporin for clinical response is uncertain (RR 1.00, 95% CI 0.80-1.25; one trial; n = 17; very low certainty evidence) [27].

Data from two trials were sourced for the comparison of second- vs first-generation cephalosporins [29,30]. The effect of second-generation cephalosporins compared with first-generation oral cephalosporins, on *Strep A* eradication is uncertain (RR 0.96, 95% CI 0.55-1.96; 1 trial; n = 11; very low certainty evidence) [29]. Low certainty evidence suggests that second-generation cephalosporins results in little to no difference in clinical response compared with first-generation cephalosporins (RR 1.18, 95% CI 1.07-1.29; one trials; n = 578) (Figure 2c) [29,30], whereas moderate certainty evidence suggests that second-generation cephalosporin probably may have little effect on AEs compared with first-generation cephalosporins (RR 1.06, 95% CI 0.65-1.71; two trials; n = 617) (Figure 2e) [29,30]. Commonly reported AEs were mild to moderate in severity and included gastrointestinal AEs (diarrhea, nausea, vomiting, abdominal pain).

Very low certainty evidence suggests that third-generation oral cephalosporin may have little to no effect on *Strep A* eradication compared with first/second-generation cephalosporins (RR 0.96, 95% CI 0.79-1.16, one trial; n = 44) [28]. However, third-generation cephalosporins likely result in a slight improvement in clinical response (RD 33.9% more; 26.4 more to 41.8 more; one trial, n = 1263; moderate certainty evidence). Third-generation cephalosporin results in more AEs compared with first/second-generation cephalosporins (RD 26.6% more; 18.5 more to 37.2 more; 1 trial; n = 1685; moderate certainty evidence). Commonly reported AEs were mild and included diarrhea (33% vs 15%), nausea (12% vs 11%), and headaches (8% vs 6%).

Discussion

Our systematic review included 12 trials conducted across geographic settings, reporting on 4094 participants, with ages ranging from 2 months to 95 years. We found a paucity of data on the efficacy and safety of antibiotics for treating laboratory-confirmed *Strep A* skin infections in primary care/outpatient settings to prevent ARF/RHD.

Follow-up periods were short, ranging from 1-4 weeks, which limits our understanding of whether the use of antibiotics impacts post-streptococcal sequelae, such as RHD. This is understandable, given the resource intensity of conducting trials and that Medicine Regulatory Authorities' guidance does not require assessment of long-term outcomes for regulatory approval of antibiotics for skin infections [33].

We quantitatively assessed three therapeutic comparisons: (i) cotrimoxazole, oral vs benzathine benzylpenicillin, IM; (ii) macrolide, oral vs β-lactamase resistant penicillins, oral; and (iii) second- vs first-generation cephalosporins. No trial explicitly reported on the duration and severity of *Strep A* skin infections or rates of ARF/RHD. Therefore, we used surrogate outcomes to determine the effectiveness of antibiotics.

The evidence is very uncertain about the effect of antibiotics on *Strep A* eradication rates. Skin infections often present as a plethora of pathogens, commonly *S. aureus* (with MRSA emerging) and *Strep A* (in smaller proportions), and empirical treatment is generally presumptive [4]. The risk and severity of skin infections are determined by the interplay between the host's cutaneous barrier function and commensal organisms' virulence [34], with *S aureus* predominant in temperate regions, and *S. pyogenes* in tropical regions [13]. Pyoderma is endemic in tropical regions where scabies infestation and overcrowding are prevalent, and untreated episode(s) lead to post-streptococcal sequelae, including ARF and RHD [22,35], though treating underlying scabies may be sufficient [13]. Guidelines categorize syndromic management of skin infections, guiding on drainage with cotrimoxazole or doxycycline for mild infections; and propose penicillin (including IM benzathine benzylpenicillin), cephalosporins, or clindamycin for moderate infections [4]. For the uncommon presentation of MRSA, oral cloxacillin (or equivalent), or cephalexin is preferred [4].

This systematic review provides an updated review of treatment strategies for *Strep A* skin infection. For the clinical resolution of polymicrobial skin infections, cotrimoxazole was comparable to IM benzathine benzylpenicillin to treat impetigo, and cefuroxime (cephalosporin) may be as efficacious as flucloxacillin to treat perianal dermatitis. Limited evidence suggests no difference between penicillin/cephalosporin and other oral antibiotics (azithromycin, temafloxacin, linezolid). Among topical preparations, bacitracin was associated with the most treatment failures compared with oral cephalexin, whereas mupirocin may be comparable to oral flucloxacillin and oral cephalexin, but the evidence is very uncertain. Similarly, there was no difference in clinical response between second- and first-generation cephalosporin therapies, whereas third-generation cephalosporin had an improved clinical response compared with older-generation cephalosporins, noting that selection pressure due to extensive use of antibiotics generally contributes to antibiotic resistance and treatment failure (older-generation cephalosporins having more widespread exposure) [36].

Treatment adherence was similar between cotrimoxazole, oral vs benzathine benzylpenicillin, IM, and linezolid, oral vs cephalosporin, oral (cefadroxil), and there was no significant difference in antibiotic resistance of *Strep A* isolates between cotrimoxazole and IM benzathine benzylpenicillin (with 1.54% cotrimoxazole-resistant *Strep A* isolates identified). Penicillin is considered the standard of care for uncomplicated *Strep A* skin infections as it is effective, safe, has a narrow spectrum, and low cost [4]. Cephalosporins may be considered an option but have broader spectrums than penicillin [4]. Irrational broad-spectrum usage may induce antibiotic resistance [4], as reported for macrolides (an alternative option in β-lactam allergy) [4] and topical preparations (mupirocin, bacitracin, and fusidic acid) [13,14]. GABHS resistance to

cotrimoxazole has also been reported in India [37] with emerging resistance in the Northern Territory of Australia [22]. This necessitates continuous antimicrobial surveillance. To minimize syndromic management, directed treatment of *Strep A* skin infections requires further research (adequately powered, with a sufficient population of microbiologically evaluable isolates) to determine the feasibility, acceptability, and affordability of point-of-care *Strep A* rapid diagnostic tests.

Commonly reported AEs were mild, including injection-site pain with IM benzathine benzylpenicillin and gastrointestinal disorders with oral antibiotics. Serious treatment-associated AEs included an injection-site buttock abscess with IM benzathine benzylpenicillin and elevated lipase level in a study participant with comorbid viral gastroenteritis associated with oral linezolid.

Similarly, the systematic review of published literature (August 2011 to February 2020) by Gahlawat et al. [13] reported that oral cotrimoxazole was comparable to benzathine benzylpenicillin G injection in treating severe impetigo in endemic settings. Our systematic review of published RCTs to December 2024 found very low certainty evidence suggesting comparable efficacy among treatment strategies (benzathine benzylpenicillin IM, cotrimoxazole, oral penicillin, macrolides, and cephalosporins) for eradicating laboratory-confirmed Strep A skin infections. All highlight the need for judicious antibiotic use and research to develop new antibiotics.

Strengths and limitations

This study represents the first comprehensive review to explore the evidence for antimicrobial eradication of *Strep A* skin infections to prevent ARF/RHD. However, the study has several limitations. Due to the lack of evidence, the potential impact of treating *Strep A* skin infections to prevent ARF/RHD remains uncertain. Thus, we were unable to answer the primary research question posed by the WHO guideline group. However, we provide a review of the evidence regarding the use of antimicrobials for treating *Strep A* skin infections. This review was restricted to primary care and outpatient settings, and penicillin and cephalosporin comparisons. We only included RCTs, but these were few, with small sample sizes and poor methodological quality likely due to the lack of new drugs in the pipeline. The scope of this review did not include community-based MDA strategies, but evidence in this field is emerging [38]. However, merely managing scabies infestation may be effective in preventing *Strep A* impetigo [13]. Azithromycin-associated resistance has also been reported in an MDA program for scabies-associated impetigo. This is a concern, as this impacts other established MDA strategies (e.g., for trachoma) [13]. Observational studies describe the potential role of scabies in the development of ARF but need investigation. More recently, *Strep A* has been implicated as the cause of exudative cutaneous ulcers in a yaw-endemic tropical region [39]. Further research is needed for the MDA of antibiotics in endemic settings. Furthermore, patient and provider acceptability of the intervention remains uncertain due to sparse data.

Implications for research and practice

Robust, high-quality studies are needed to determine the preferred choice of antibiotic for laboratory-confirmed *Strep A* skin infections in endemic settings to prevent ARF/RHD. Though, researching directed treatment of *Strep A* skin infections may be challenging, as skin infections are polymicrobial and pathogens other than GABHS (such as *S. aureus*), need consideration. Treating the underlying cause of impetigo, such as scabies or eczema may be feasible and acceptable in preventing skin infections, however, there may be a potential association of scabies, *Strep A* skin infection and ARF that requires further investigation. Of concern are the reports of antibiotic resistance, likely due to irrational antibiotic use (particularly broader spectrum therapies) and pressure selection.

Conclusion

The available evidence for laboratory-directed treatment of *Strep A* skin infections to prevent ARF/RHD is very uncertain. More robust, high-quality studies are needed to determine the preferred choice of antibiotic and the longer-term impact on ARF and RHD. Resistance patterns, availability, and cost are additional factors that would guide antibiotic choice, specifically in endemic settings, to determine the public health impact. Conducting research directed at *Strep A* skin infections may be challenging, as skin infections present as polymicrobial infections, and eradication of other microbes such as *S. aureus*, needs to be considered.

Declarations of competing interest

MEE is a member of the RHD Taskforce of the Pan African Society of Cardiology. MEE does not receive any commercial funding. TK is a member of the National Essential Medicines Committee informing national guidance across all levels of care, a member of the National Ministerial Advisory Committee for Vaccines for COVID-19, co-leads the South African GRADE Network, and co-directs Cochrane Africa. TDL, AH, FB, DM, JO, NB, and TK do not receive any commercial funding, although, the South African Medical Research Council, receives a variety of income from pharmaceutical and other commercial companies.

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Ethical approval

No ethics approval was required for this publication.

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Author contributions

NB, TDL, DM, AH, MEE, and TK conceived the scope of the review with the development of the protocol. JO did the literature search, and TDL searched clinical registries. Data curation and analysis were undertaken by TDL, DM, AM, FB, NB, MEE, and TK. Data synthesis and estimate generation were performed by TDL, AH, FB, DM, and TK. TDL, AH, and FB drafted the first iteration of the manuscript and TDL generated the tables and figures. TDL and TK verified the underlying data. TK reviewed the final version of the manuscript. All authors had access to raw data, made substantial contributions to the critical review, editing, and editing of the manuscript, and have read and approved the final version.

Data sharing

The authors declare that all supporting data are available within the article (and its online supplementary files) and upon request from the corresponding author. The study protocol is available on PROSPERO at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=386889

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2025.100642.

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