Dermatology Practical & Conceptual

Meta-Research Study on the Quality of Randomized Controlled Trials Evaluating Drug Therapy for Impetigo

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ABSTRACT

Introduction: Impetigo is a common, highly contagious bacterial skin infection primarily affecting children. Treatment usually involves topical or oral antibiotics, and numerous clinical trials have been published to support these therapeutic approaches.

Objectives: To evaluate the methodological quality of randomized clinical trials (RCTs) on the pharmacological treatment of impetigo in children and adolescents.

Methods: This meta-research evaluated RCTs on systemic or topical pharmacological treatments for impetigo in children and adolescents. A comprehensive literature search was conducted in September 2024 across MEDLINE, Embase, CENTRAL, and LILACS databases. The methodological quality of the included RCTs was assessed using the Cochrane Risk of Bias tool. Data are presented as percentages.

Results: Twenty-one RCTs on pharmacological treatments for impetigo were identified and assessed. The findings identified some methodological concerns: i) 53% to 57% of RCTs had an unclear risk of selection bias due to insufficient information on randomization and allocation concealment; ii) 71% were at high risk of bias for blinding of participants and personnel, while 57% had a high risk for

blinding of outcome assessors; iii) 24% exhibited a high risk of attrition bias due to significant participant losses without justification; iv) 81% had an unclear risk of bias due to the lack of registered protocols available.

Conclusions: Based on the methodological quality of the assessed RCTs, this study highlights the need for more rigorous design and reporting standards in future research on pharmacological treatments for impetigo to enhance the reliability and validity of the evidence, thereby supporting more informed clinical decision-making.

Introduction

Randomized controlled trials (RCTs) are the gold standard for generating high-quality evidence on the effects of healthcare interventions. Their methodological rigor, particularly in minimizing bias, ensures more accurate and valid estimates of treatment effects. As a result, RCTs play a pivotal role in informing clinical practice and shaping healthcare policies, either directly or through their integration into systematic reviews and meta-analyses [1–3].

However, the reliability and applicability of RCT findings are highly dependent on their methodological quality. Across diverse medical fields, persistent deficiencies such as inadequate randomization, poor allocation concealment, insufficient blinding, high attrition without appropriate handling, and the absence of prospective protocol registration remain prevalent. These shortcomings introduce various sources of bias, leading to distorted effect estimates and ultimately compromising the credibility of the evidence base [1,4–6].

The evidence on pharmacological treatments is well established in the context of impetigo, a common and highly contagious superficial bacterial skin infection that predominantly affects children [7,8]. Numerous RCTs have evaluated the efficacy and safety of both topical and systemic antibiotics for this condition. However, despite the substantial body of research, no prior study has systematically examined the methodological quality of these trials. This represents a critical gap, as deficiencies in trial design and reporting can undermine not only the validity of individual studies but also the reliability of evidence syntheses and the clinical guidelines derived from them. Moreover, systematically identifying recurring methodological limitations can inform improvements in the design, conduct, and reporting of future trials, ultimately contributing to more transparent, rigorous, and trustworthy research that underpins evidence-based clinical practice [1,4].

Objective

This meta-research study aimed to evaluate the methodological quality of the RCTs on the pharmacological treatment of impetigo in children and adolescents.

Methods

This meta-research study adheres to the methodological guidance proposed by Murad et al. [9] and the relevant items of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10] to enhance the quality and transparency of the study report.

Criteria for Inclusion of Studies

Randomized clinical trials (RCTs) that evaluated the efficacy of systemic or topical pharmacological interventions, including antimicrobial and antiseptic agents, for treating impetigo in children and adolescents, regardless of dosage, treatment duration, or route of administration. Studies were eligible if the authors identified them as "randomized clinical trials." Studies employing quasi-randomized methods, such as allocation based on date of birth, medical record number, or alternation, were not considered due to the high risk of selection bias associated with these designs.

Search Strategy

A comprehensive literature search was conducted on 19 September 2024 to identify the RCTs using the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE), by PubMed; Excerpta Medica Database (Embase), by Elsevier; The Cochrane Central Register of Controlled Trials (CENTRAL) (by Wiley); Latin American Literature on Health Sciences and the Caribbean - LILACS (Biblioteca Virtual em Saúde - BVS) (Table S1).

Selection of Studies and Data Collection

Two independent reviewers screened the titles and abstracts using the Rayyan platform [11]. References that met the eligibility criteria were then selected for a more detailed analysis through full-text reading. A third author resolved disagreements between reviewers about the inclusion or exclusion of studies. Data extraction was conducted by two independent reviewers who collected the following information from the included RCTs: year, participants' characteristics, intervention, comparator groups, outcomes assessed, and funding sources.

Assessment of the Methodological Quality of the Included Studies

Two reviewers independently assessed the methodological quality (risk of bias) of each included RCT, using the Cochrane Risk of Bias (RoB) tool (version 1.0) following the recommendations of the Cochrane Handbook of Systematic Reviews of Interventions [12]. This tool is composed of seven domains that assess potential sources of bias that could affect the study's validity, as follows:

- Random sequence generation (selection bias): evaluate the method used to generate the random sequence for assigning participants to intervention or control groups. It assesses whether the process was genuinely random, helping to ensure that any systematic factors did not influence group allocation.
- Allocation concealment (selection bias): examines whether the allocation of participants to intervention or control groups was concealed from those assigning participants. Proper concealment prevents selection bias by ensuring the researchers cannot predict or influence the group assignment.
- Blinding of participants and personnel (performance bias): assesses whether participants and personnel were blinded to the administered intervention. Blinding helps prevent performance bias, where knowledge of the intervention may influence how participants or staff behave or interact, potentially skewing the study results.
- Blinding of outcome assessors (detection bias): evaluates whether those assessing outcomes were blinded to the intervention received by participants. Blinding of outcome assessors helps prevent detection bias, where knowledge of the intervention might influence outcome assessment.
- Incomplete outcome data (attrition bias): analyses how incomplete outcome data (e.g., losses and withdrawals) were handled. It covers the difference in the number of participants withdrawn from each group (intervention and control) and how the losses were considered in the data analyses.
- Selective reporting: assesses whether the study reported all intended outcomes. This domain identifies any selective reporting of results that could skew findings, as published studies are more likely to report analyses showing significant differences between groups rather than those with non-significant differences.
- Other sources of bias: examines any other potential sources of bias not covered by the previous domains. It includes factors such as baseline data imbalance and other factors affecting the study's validity.

Blinding and incomplete outcome data were evaluated separately for each outcome, as recommended. However, since all outcomes of interest in this meta-research study were subjective (cure response, bacteriological response, adverse events, and quality of life), the lack of blinding in these domains could have potentially influenced the results, which were assessed together. The judgment of risk of bias for each domain is categorized into three levels: (1) low risk of bias, when the method is adequately addressed in the study; (2) high risk of bias, when the method is inadequately addressed; (3) unclear risk of bias, when there is insufficient information to make a definitive assessment.

Data Synthesis

The risk of bias assessments were reported as absolute frequencies and proportions for each domain of the RoB tool. In addition, 95% confidence intervals (95% CI) for proportions were calculated using the Wilson score interval, in the binomial R® software package (version 4.5).

Results

Search Results

The database search yielded 907 references. After removing six duplicates and screening the titles and abstracts, 878 studies were excluded for not meeting the inclusion criteria. Twenty-nine studies were assessed in full text, and eight were excluded [7,13-17] because they were not randomized clinical trials (RCTs). Consequently, 21 studies were included in this meta-analysis [18-38] (Figure 1).

Characteristics of the Included Studies

The 21 randomized controlled trials (RCTs) published between 1986 and 2023 included 2,876 participants diagnosed with impetigo. The most common interventions were macrolide antibiotics, bacterial protein synthesis inhibitors, penicillins, cephalosporins, quinolones, sulfonamides, and antifungals. These interventions were compared regarding their effects via topical versus oral administration or against a placebo (Table 1).

Risk of Bias Assessment

The methodological quality of the included RCTs was assessed using the Cochrane Risk of Bias (RoB) tool following the assessment recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Figure 2 presents the overall assessment, while Table S2 provides detailed judgments for each study.

Only one RCT (5%, 95% CI: 0.85%–23%) was classified as having low risk of bias across all domains assessed [35], while three trials (14%, 95% CI: 0.5%–35%) demonstrated low risk in six out of the seven domains of the RoB tool [26,29,30].

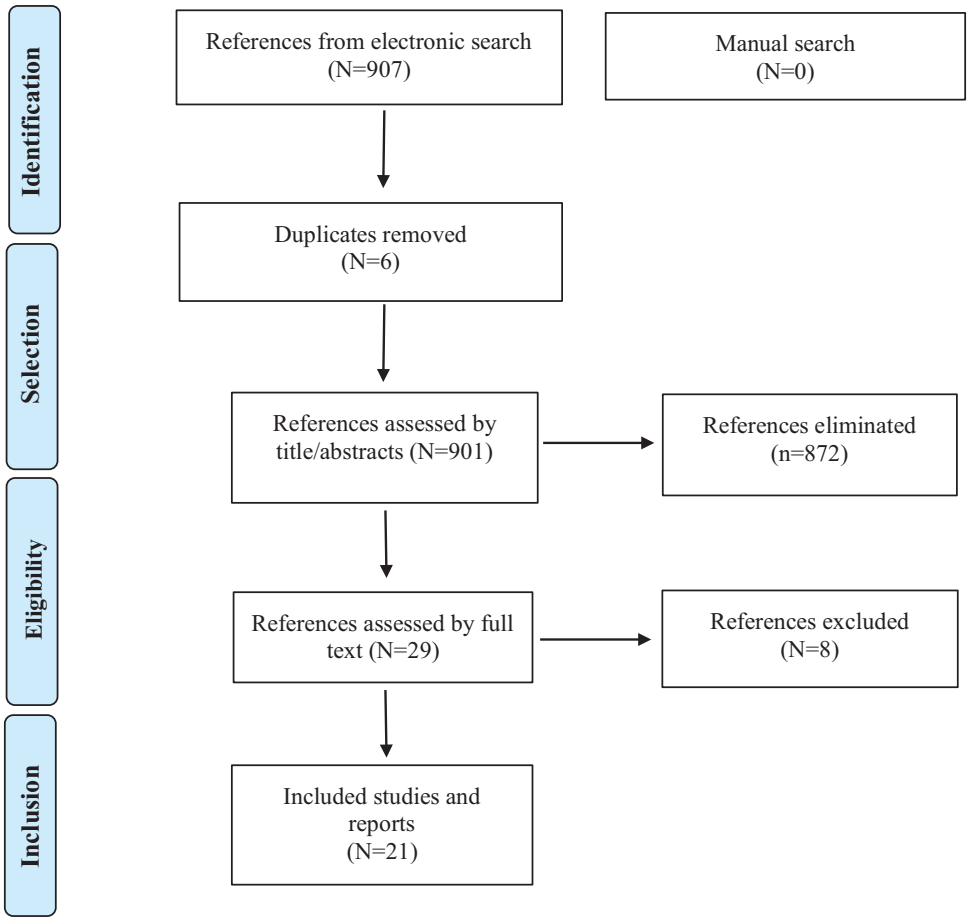

Figure 1. Flowchart of the study selection process.

Table 1. Characteristics of the Included Studies.

Study, year	Intervention / Number of participants (N)	Control / Number of participants (n)	Outcomes of interest	Funding sources
Anusharani 2019[18]	Topical 2% fusidic acid cream (N=50)	Topical 2% mupirocin ointment (n = 50)	• Clinical response • Adverse events	No sources
Barton 1988[19]	Oral erythromycin (40 mg /kg/day) (n = 29)	Oral dicloxacillin (25 mg/kg/day) (n = 30)	• Bacteriological response • Adverse events	Warner-Lambert Corporation
Ciftci 2002[20]	Mupirocin (Bactroban 2% ointment, 3 times/ day for 10 days) (n=25)	Terbinafine (Lamisil 1% cream topically, 3 times/day, for 10 days) (n=23)	• Clinical response • Bacteriological response • Adverse events	NR
Dagani 1992[21]	Oral erythromycin (50 mg/kg daily) + placebo ointment (n=51)	2% mupirocin ointment in polyethylene glycol + oral placebo suspension (n=51)	• Clinical response • Adverse events	Beecham Pharmaceuticals
Dash 2023[22]	Topical 1% ozenoxacin cream (n=16)	Topical 2% mupirocin cream (n=17)	• Clinical response • Bacteriological response	NR

Table 1. Characteristics of the Included Studies. *(continued)*

Study, year	Intervention / Number of participants (N)	Control / Number of participants (n)	Outcomes of interest	Funding sources
Demidovich 1990[23]	Oral penicillin V potassium (40 a 50mg/kg, daily for 10 days) (n=25)	Oral cephalexin monohydrate (40 a 50 mg/kg, daily for 10 days) (n=23) Oral erythromycin (30 a 40 mg/kg, daily for 10 days) (n=25)	• Clinical response • Adverse events	NR
Eells 1986[24]	15g of 2% mupirocin in polyethylene glycol (3 times/day for 12 days) (n=18)	15 g of the vehicle alone (3 times/day for 12 days) (n=20)	• Clinical response • Bacteriological response • Adverse events	NR
Goldfarb 1988[25]	2% mupirocin ointment (3 times/day, for 8 days) (n=30)	Oral erythromycin (40 mg/kg, daily, for 8 days) (n=32)	• Clinical response • Bacteriological response	Beecham Laboratories and Children's Research Foundation of Cleveland
Gropper 2014[26]	Topical ozenoxacin 1% cream (twice daily, for 5 days) (n=155)	Topical retapamulin 1% ointment (twice daily, for 5 days) (n=154) Placebo (twice daily, for 5 days) (n=156)	• Clinical response • Bacteriological response • Adverse events	Ferrer Internacional SA, Barcelona, Spain
Iovino 2011[27]	NVC-422 topical gel 0.1% (n=43)	NVC-422 topical gel 0.5% (n=45) NVC-422 topical gel 1,5% (n=41)	• Clinical response • Bacteriological response • Adverse events	NR
Jeffrey 1990[28]	Oral erythromycin (40 mg/kg/day, 4 times/day) + topically applied placebo (3 times/day) (n= 30)	Topical mupirocin 15g 2% (3 times/day) + orally administered placebo (4 times/day) (n= 24)	• Clinical response • Bacteriological response	United States Navy Bureau of Medicine and Surgery Clinical Investigation Program
Koning 2002[29]	Topical fusidic acid cream 2% (3 times/day, for 14 days) (n=78)	Placebo (3 times/day, for 14 days) (n=82)	• Clinical response • Bacteriological response	Fonds Alledaagse Ziekten of the Dutch College of General Practitioners
Koning 2008[30]	Topical retapamulin ointment 1% (twice daily for 5 days) (n=139)	Topical placebo (twice daily for 5 days) (n=71)	• Clinical response • Bacteriological response • Adverse events	GlaxoSmithKline
Kuniyuki 2005[31]	Topical 3% Oxytetracycline-hydrochloride (n=28)	Topical tetracycline and oral antibiotics (cefdinir, fosfomycin and minocycline) (n=21)	• Clinical response • Bacteriological response	NR

Table 1. Characteristics of the Included Studies. *(continued)*

Study, year	Intervention / Number of participants (N)	Control / Number of participants (n)	Outcomes of interest	Funding sources
Mclinn 1990[32]	Topical mupirocin ointment 2% (3 times/day) (n=29)	Oral erythromycin (30 to 40 mg/kg/day) (n=30)	• Clinical response • Bacteriological response • Adverse events	NR
Mertz 1989[33]	Topical 15g mupirocin ointment 2% (3 times/day, for 8 days) (n=28)	Oral erythromycin (30 to 50 mg/kg/day) (n=25)	• Clinical response • Bacteriological response	Beecham Laboratories, Bristol, Tenn
Nolting 1998[34]	Topical sulconazole nitrate 1% cream (twice daily, for 14 days) (n=32)	Topical miconazole nitrate 2% cream (twice daily, for 14 days) (n=34)	• Clinical response • Bacteriological response	NR
Oranje 2007[35]	Topical retapamulin ointment 1% (twice daily for 5 days) (n=345)	Topical sodium fusidate ointment 2% (3 times daily for 7 days) (n=172)	• Clinical response • Bacteriological response	GlaxoSmithKline
Rosen 2018[36]	Topical ozenoxacin cream 1% (twice daily for 5 days) (n=206)	Placebo (twice daily for 5 days) (n=206)	• Clinical response • Bacteriological response	Ferrer Internacional, SA.
Sudha 2017[37]	Oral azithromycin (10 mg/kg/day) (n=50)	Oral azithromycin (10 mg/kg/day) + Probiotic (n=50)	• Clinical response	No sources
Tong 2010[38]	Oral trimethoprim-sulfamethoxazole (4+20 mg/kg up to 160 + 800 mg) (n=7)	Intramuscular benzathine penicillin (45 mg/kg up to 900 mg) (n=6)	• Clinical response • Bacteriological response	Australian National Health and Medical Research Council, Australian National Heart Foundation, Cooperative Research Centre for Aboriginal Health, Ian Potter Foundation, and the Rio Tinto Aboriginal Foundation.

Abbreviations: N: number of participants, NR: not reported, NVC-422: N, N-dichloro-2, 2-dimethyltaurine.

Regarding the randomization process, which assesses the method by which participants were assigned to ensure comparable groups, 53% (11/21, 95% CI: 32%–72%) [18-23,25,27,31,32,37,38] of the RCTs presented an unclear risk of bias due to insufficient information provided for judgment. In contrast, 47% (10/21, 95% CI: 28%–68%) [21,24,26,28-30,33-36] clearly described the randomization process, which was typically carried out using a computer-generated randomization code, schedule, or list of random set numbers. No study was classified as having a high risk of bias in this domain. Similar proportions were observed regarding allocation concealment, where 57% (12/21, 95% CI: 37%–76%) [18-20,22-25,27,38,31,32,37] of the RCTs had an unclear risk of bias. In comparison, 43% (9/21, 95% CI: 24%–63%) [21,26,29,30,33-35,28] had a low risk of bias, with most studies describing methods such as the use of sequentially sealed opaque envelopes to ensure proper allocation concealment.

The assessment of the blinding domains evaluates whether participants and outcome assessors were aware of the intervention assigned to each group. This awareness can influence the results, especially when outcomes are measured subjectively or rely on patients' perceptions. Among the RCTs, 71% (15/21, 95% CI: 50%–86%) [18,20,22-25,27,31-28] were classified as high risk of bias for blinding of participants and personnel, and 57% (12/21, 95% CI: 37%–76%) [18-21,24,25,27,31,32,34,36,37] were at high risk of bias for blinding of outcome assessors. This indicates either knowledge of the intervention or insufficient information to assess blinding. The lack of blinding of participants and assessors

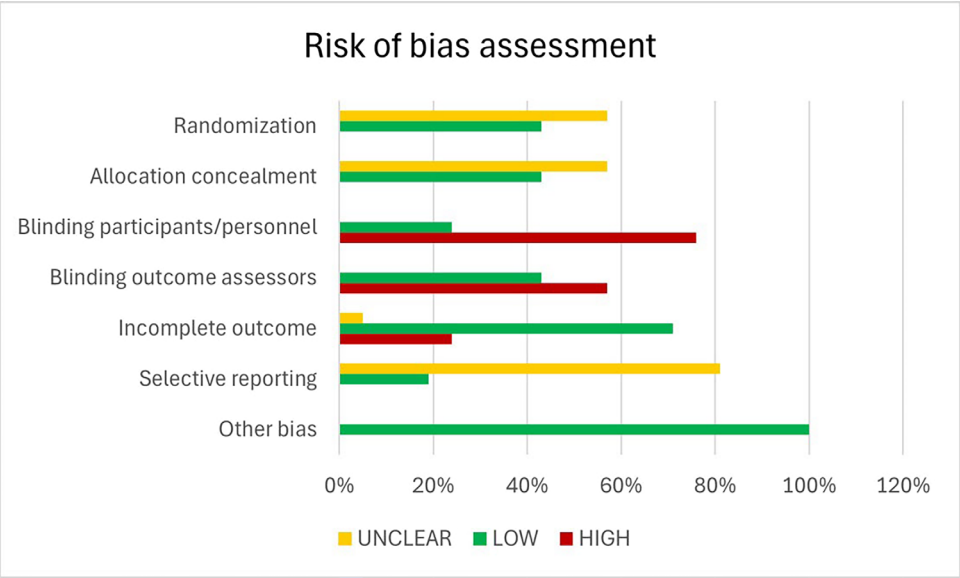

Figure 2. Risk of bias assessment.

can significantly impact the results since clinically relevant efficacy and safety outcomes were measured subjectively. With a low risk of bias, 29% (6/21, 95% CI: 14%–50%) [19,21,26,28-30] had adequate blinding of participants, and 43% (9/21, 95% CI: 24%–63%) [22,23,26,28-30,33,35,38] had adequate blinding of assessors. In these studies, the compared medications were identical in appearance and characteristics, or participants received a placebo that closely resembled the intervention, such as a placebo ointment for the oral administration group versus the topical treatment.

The incomplete outcome data domain assesses how results are reported, including participant losses or withdrawals during the study, and examines the impact of these losses on the final analysis. Among the included RCTs, 76% (16/21, 95% CI: 55%–89%) [18,19,21-23,25-27,29,31,32,34-38] were considered to have a low risk of bias, as they reported losses of less than 20% of participants and provided appropriate justifications. In contrast, 24% (5/21, 95% CI: 11%–45%) [20,24,28,30,33] had a high risk of bias due to losses exceeding 20% and lacking justification.

The selective reporting domain revealed that 81% (17/21, 95% CI: 60%–92%) [18-29,31-34,37] of the studies had an unclear risk of bias, as most did not provide a registered protocol, making it impossible to assess the differences between reported and unreported outcomes and results. No other source of bias was identified in the evaluated RCTs.

Discussion

This meta-research evaluated the methodological quality and risk of bias in randomized clinical trials (RCTs) concerning pharmacological treatments for impetigo in children and adolescents. Impetigo, a highly contagious skin infection, is a common condition requiring effective treatment options, yet evidence supporting various interventions remains uncertain. This study aimed to assess the reliability and applicability of current RCTs, mapping the methodological flaws to clinical practice and providing recommendations for future research. The results revealed that a significant proportion of the included RCTs exhibited unclear or high risks of bias, particularly in domains related to randomization, blinding, and handling of incomplete outcome data.

A significant proportion of the included studies presented an unclear or high risk of bias regarding the randomization process, with 53%–57% of studies lacking sufficient details. Randomization is critical to ensuring that participants are allocated to treatment groups without bias, guaranteeing comparability. Inadequate or poorly described randomization methods can lead to selection bias, potentially affecting the generalizability of the results and distorting the perceived treatment effect. Rigorous randomization procedures are essential to ensuring baseline comparability and to reducing the risk of bias [1,5,39].

Most studies had a high risk of bias concerning the blinding of participants and outcome assessors. This lack of blinding can introduce performance and detection biases. When participants or researchers know the treatment allocation, it may influence participant behavior and the interpretation of outcomes. For example, participants aware of receiving a placebo might report subjective outcomes differently from those receiving the active treatment. Similarly, unblinded assessors may unintentionally assess outcomes in a biased manner. Such biases can lead to overestimations or underestimations of treatment effects, affecting the reliability of study results [6].

Over 70% of the RCTs were classified as having a low risk of bias regarding participant losses or withdrawals during study follow-up. Incomplete outcome data can compromise the validity of the results and introduce bias if not adequately managed. It is crucial that future studies employ rigorous methods for dealing with missing data and that they provide transparent reporting to allow for accurate assessments of treatment efficacy [39].

Finally, regarding selective reporting bias, 81% of the evaluated RCTs were classified as having unclear risk of bias, mainly due to the lack of prospective protocol registration. The absence of a publicly available protocol compromises the ability to verify whether predefined outcomes were altered, selectively reported, or omitted, which may distort study conclusions by overestimating benefits or underestimating harms. This issue is particularly critical in impetigo clinical trials, in which outcomes are largely subjective and prone to bias. Mandatory prospective registration of clinical trials in international registries such as ClinicalTrials.gov and the WHO ICTRP should be strictly enforced to mitigate this bias. This practice is widely recognized as an essential safeguard for research integrity, as it increases transparency, reduces reporting bias, and ensures that all prespecified results are publicly accessible for verification [40-42].

The methodological weaknesses identified in the included RCTs are consistent with patterns observed in dermatology research. A meta-research study [42] assessed dermatological RCTs included in Cochrane reviews and reported a high prevalence of unclear risk of bias, particularly for allocation concealment (79%) and random sequence generation (64%), which closely reflects the findings of our study. Similarly, another recent meta-research study [43] evaluating systematic reviews of RCTs on vesiculobullous skin diseases found that over half (55.5%) of the reviews were rated as critically low quality according to the AMSTAR-2 tool assessment. This reinforces that the methodological limitations observed in impetigo trials are not isolated but are part of a widespread challenge.

This meta-research study has some limitations that should be acknowledged. First, although a comprehensive literature search was conducted, the possibility of missing relevant studies cannot be entirely excluded. Second, the risk of bias assessment depended on the quality and completeness of the reports provided by the original studies. Third, the wide confidence intervals observed in some risk of bias domains reflect the uncertainty associated with the relatively small number of included trials.

Another important consideration in our study was the choice of the Cochrane Risk of Bias tool version 1.0 rather than the updated version 2.0. Despite the methodological improvements introduced by RoB 2.0, particularly its outcome-level assessment framework, the choice to use RoB 1.0 was made because it includes a dedicated domain for selective reporting, a critical issue not explicitly assessed in RoB 2.0. Selective reporting bias is a significant concern in clinical research, occurring when pre-specified outcomes are omitted, reported incompletely, or presented selectively, leading to biased effect estimates with overestimation of benefits and underestimation of harms. The decision also reflects growing concerns in the literature regarding the complexity and operational challenges associated with RoB 2.0, which has demonstrated lower inter-rater reliability and considerable implementation challenges, even when applied by experienced systematic reviewers [44–46].

The methodological shortcomings identified in this meta-research have important implications for both clinical practice and future research. For clinicians, the variability and potential biases in the current evidence base emphasize the need for cautious interpretation of studies on impetigo treatments. Evidence derived from trials with a high risk of bias may not accurately represent the true efficacy and safety of pharmacological interventions, potentially leading to suboptimal treatment decisions. For researchers, these findings highlight the urgent need to strengthen methodological rigor in future RCTs. Key areas for improvement include robust randomization procedures, proper allocation concealment, adequate blinding, and appropriate handling of incomplete outcome data. Equally important is the commitment to transparency through prospective protocol registration and adherence to standardized reporting guidelines.

In this context, future RCTs should comply with the SPIRIT checklist for comprehensive and transparent protocol development [47,48] and the CONSORT statement to ensure complete and accurate reporting of trial findings [49], and they should incorporate the Cochrane Risk of Bias tool to guide risk of bias assessment and improve internal validity [12]. These practices are essential to enhancing the credibility, reproducibility, and utility of clinical research on impetigo. Ultimately, improving the methodological quality of trials will support more reliable evidence synthesis, inform guideline development, and guide decision-making about which treatments should be prioritized, recommended, or funded in clinical practice.

Conclusion

This meta-research study evaluated the methodological quality of 21 RCTs on pharmacological treatments for impetigo. The findings identified critical areas of concern: i) 53% to 57% of RCTs had an unclear risk of selection bias due to insufficient information on randomization and allocation concealment; ii) 71% were at high risk of bias for blinding of participants and personnel, while 57% had a high risk of blinding of outcome assessors; iii) 24% exhibited a high risk

of attrition bias due to significant participant losses without justification; iv) 81% had an unclear risk of bias due to the lack of registered protocols. These methodological weaknesses highlight the need for more rigorous design and reporting standards in future RCTs on impetigo treatments, adopting the SPIRIT checklist for protocol development, the CONSORT statement for reporting, and the Cochrane RoB 2.0 tool for bias assessment, to enhance the transparency, validity, and consistency of evidence to better support clinical decision-making.

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