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Comparison of therapeutic effect of azithromycin against doxycycline in scrub typhus: systematic review and meta-analysis

S.C. Sharda, M.S. Bhatia

Department of Internal Medicine, Division of Acute Care and Emergency Medicine, Postgraduate Institute of Medical Education and Research (P.G.I.M.E.R.), Chandigarh, India

ABSTRACT:

— ***Objective:*** The clinical impact of antibiotic resistance on treating scrub typhus remains unclear. This systematic review and meta-analysis aims to assess the effectiveness of azithromycin compared to doxycycline in treating scrub typhus.

— ***Materials and Methods:*** We searched Pubmed, Embase, and Directory of Open Access Journals from database inception to 31st March 2022. Articles were eligible for inclusion if they compared azithromycin vs. doxycycline in scrub typhus patients of all age groups with respect to defervescence within 48 hours and treatment failure after 5 days in the two groups. The dichotomous outcomes were analyzed using Mantel-Haenszel random-effects meta-analysis for odds ratio (OR) with their 95% confidence intervals (CI).

— ***Results:*** From the 156 records identified, 7 full-text articles were eligible for inclusion, all having a low to moderate risk of bias. The meta-analysis of five studies, including 1,051 patients, showed that the rate of defervescence within 48 hours was lower with azithromycin (n=512) compared to doxycycline (n=539) (OR: 0.46, 95% CI: 0.28 to 0.76, p=0.002, I^2: 35%). Pooled analysis of seven studies, including 1,346 patients, did not show a significant difference between the rates of treatment failure at 5 days in the two groups receiving azithromycin (n=641) *vs.* doxycycline (n=705) (OR: 1.51, 95% CI: 0.51 to 4.45, p=0.45, I^2: 45%).

— ***Conclusions:*** The findings of this meta-analysis suggest that while scrub typhus patients treated with azithromycin or doxycycline have similarly low rates of treatment failure, the use of doxycycline results in more rapid resolution of fever compared to azithromycin.

— ***Keywords:*** *Scrub Typhus, Azithromycin, Doxycycline, Orientia tsutsugamushi, Treatment, Antibiotics.*

INTRODUCTION

Scrub typhus is an under-recognized cause of acute febrile illness in tropical countries[1,2]. The causative organism is *Orientia tsutsugamushi*, a Gram-negative bacteria transmitted by the bite of larval stages of trombiculid mites (chiggers), which may lead to eschar formation at the site of the bite. It is an intracellular pathogen and can lead to extensive endothelial damage and venulitis. It affects all age groups and, if untreated, can lead to hepatic dysfunction, acute kidney injury, coagulopathy, meningoencephalitis, acute respiratory distress syndrome, and death in the second week of illness[3]. Doxycycline is used for treatment, and defervescence in response to doxycycline has been used as confirmation of the diagnosis of scrub typhus in resource-limited settings, but there have been reports of resistance and treatment fail-

Corresponding Author: Mandip Singh Bhatia, MD; e-mail: bhatiamandip@gmail.com

ure[4,5]. Azithromycin is the suggested alternative with the theoretical advantages of increased intracellular half-life and post-antibiotic effect. However, there is a lack of high-quality evidence directly comparing its efficacy to that of doxycycline[6,7]. The purpose of this systematic review and meta-analysis was to evaluate the current evidence regarding the efficacy of azithromycin *vs*. doxycycline for the treatment of scrub typhus with respect to defervescence in 48 hours after administration of the first antibiotic dose in serologically confirmed cases of scrub typhus and rates of treatment failure in the two groups.

MATERIALS AND METHODS

Objectives

The primary objective of this systematic review and meta-analysis was to compare the efficacy of azithromycin *vs*. doxycycline in treating patients with scrub typhus. Specifically, we aimed to assess the proportion of patients achieving defervescence within 48 hours of the first antibiotic dose. The secondary objectives included evaluating the mean time to defervescence and comparing the rates of treatment failure between the two groups. Treatment failure was defined as the persistence of fever or the development of new organ dysfunction or failure after 5 days of initiating antibiotic therapy, including conditions such as acute respiratory distress syndrome, acute kidney injury, encephalopathy, and shock.

Eligibility Criteria

Studies were deemed eligible for inclusion if they examined the effects of azithromycin and doxycycline in treating scrub typhus in patients with serologically confirmed diagnoses. Eligible studies had to report data on at least one of the predefined primary or secondary outcomes. The details of the inclusion and exclusion criteria are as follows:

Inclusion criteria

- Population: studies including patients of all age groups diagnosed with scrub typhus, confirmed by serologic testing using the Enzyme-Linked Immunosorbent Assay (ELISA) for scrub typhus IgM with Optical Density (OD) >0.5.
- Interventions: studies that compared the use of oral or parenteral azithromycin with oral or parenteral doxycycline as therapeutic agents for treating scrub typhus.
- Study design: randomized controlled trials, non-randomized comparative studies, and cohort studies comparing azithromycin and doxycycline were eligible.

Exclusion criteria

- Population: studies involving patients with co-infections or comorbid conditions where scrub typhus was not the primary diagnosis (e.g., concurrent leptospirosis or malaria) were excluded.
- Intervention: studies that included comparisons involving antibiotics other than azithromycin or doxycycline (e.g., chloramphenicol, rifampicin) for the treatment of scrub typhus were excluded.
- Study design: case reports, case series, review articles, opinion pieces, and studies without a control group (e.g., single-arm studies) were not considered.
- Language: studies published in languages other than English were excluded due to resource constraints in translation.
- Outcome reporting: studies that did not report data on any of the predefined primary or secondary outcomes, or where outcome data could not be extracted or calculated for meta-analysis, were excluded.

Outcomes

Primary outcome

The primary outcome was the proportion of patients achieving defervescence, defined as the resolution of fever to a temperature <37.5°C within 48 hours of the first dose of antibiotic.

Secondary outcomes

- Mean time to defervescence, measured in hours from the time of the first antibiotic dose until the temperature fell below 37.5°C.
- Treatment failure rate, defined as the persistence of fever or development of new organ failure after 5 days of antibiotic therapy. Specific criteria for organ failure included: acute respiratory distress syndrome (pO_2/FiO_2 <300); acute kidney injury (serum creatinine >1.5 mg/dL or an increase of >0.3 mg/dL from baseline); encephalopathy (Glasgow Coma Scale <15); shock (systolic blood pressure <90 mm Hg despite adequate fluid resuscitation).

Search Strategy

A comprehensive search of electronic databases – PubMed, Embase, and the Directory of Open Access Journals (DOAJ) – was conducted from database inception through March 31, 2022, by the principal investigator (SCS). Details of the search strategy for individual databases are as follows: (a) Pubmed- #1: (scrub typhus[MeSH Terms]) OR (Scrub typhus[Title/Abstract]), #2: (azithromy-

cin[MeSH Terms]) OR (azithromycin[Title/Abstract]), #3: (doxycycline[MeSH Terms]) OR (doxycycline[Title/Abstract]), #4: ((#1) AND (#2)) AND (#3); (b) Embase- #1: 'scrub typhus'/exp/mj OR 'scrub typhus':ti,ab,kw, #2: 'azithromycin'/exp/mj OR azithromycin:ti,ab,kw, #3: 'doxycycline'/exp/mj OR doxycycline:ti,ab,kw, #4: #1 AND #2 AND #3; (c) Directory of Open Access Journals- scrub typhus doxycycline azithromycin (All Fields).

Data Extraction

Two reviewers (SCS and MSB) screened the titles and abstracts of all identified records using predefined eligibility criteria. Full-text articles were obtained for studies that met the inclusion criteria based on the initial screening, and a second round of eligibility assessment of full-text articles was conducted (SCS and MSB). Data extraction was performed by the reviewers (SCS and MSB) using a standardized form. It included study characteristics (e.g., authors, study period, site, design, and sample size), participant demographics, method of allocation and details of interventions, and outcomes (defervescence rates at 48 hours, mean time to defervescence, and treatment failure rates after 5 days). Data were entered into Review Manager (RevMan) software, version 5.4 (The Cochrane Collaboration, 2020; Copenhagen, Denmark) by one investigator (SCS) and cross-verified by a second investigator (MSB) to ensure accuracy. The eligible studies were evaluated according to the Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence document, with Level 1 being high quality of evidence and Level 5 being low quality of evidence[8].

Risk of Bias Assessment

The risk of bias for each included study was assessed independently by two reviewers (SCS and MSB) using the Cochrane Risk of Bias tool. This assessment included evaluation of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data and selective reporting[9]. Discrepancies between reviewers were resolved through discussion.

Statistical Analysis

Quantitative synthesis was done using Mantel-Haenszel random-effects meta-analysis to account for the heterogeneity of the included studies. The dichotomous outcomes were analyzed for odds ratio (OR), and continuous outcomes were analyzed for mean difference (MD) with their 95% confidence intervals (CI). p-value <0.05 was considered significant. The heterogeneity among studies was assessed by visual inspection of Forest plots and by calculating tau-squared and I-squared statistics. I^2>50% was considered to represent significant heterogeneity. Pre-specified subgroup analysis was done for adult and pediatric age-group patients. We defined 14 years as the cut-off age for differentiating between pediatric and adult patients in this study. The age threshold was chosen based on the World Health Organization (WHO) criteria, which often uses the age of 14 years as the upper limit for classifying pediatric patients in clinical guidelines[10]. Sensitivity analyses were done by including only the recent studies published in the last 10 years (2012-onwards). Publication bias was assessed by constructing funnel plots and performing Egger's regression test.

RESULTS

A systematic database search flow diagram is shown in Figure 1. 156 records were identified through database searching. After the removal of duplicate records, the titles of 92 records were screened, and 22 records were selected for evaluation of abstracts. 14 records were excluded based on the abstract, and the full text of 8 records was retrieved. One full-text record was excluded for the irrelevant control group. Finally, seven studies were eligible for inclusion[12-18]. The characteristics of the included studies are given in Table 1. Figure 2 displays the risk of bias for eligible studies included in the meta-analysis based on the pre-specified domains. All the eligible studies were evaluated as having a low to moderate risk of bias. However, none of the studies had a high risk of bias.

Five studies[12,13,16-18], including 1,051 patients, compared the therapeutic effect of resolution of fever within 48 hours after administration of the first antibiotic dose in the group of scrub typhus patients receiving azithromycin (n=512) *vs.* the group of patients receiving doxycycline (n=539). Meta-analysis of these five studies showed that the rate of defervescence within 48 hours was lower in the group of patients receiving azithromycin compared to the doxycycline group (OR: 0.46, 95% CI: 0.28 to 0.76, p=0.002, I^2: 35%); without significant heterogeneity (Figure 3). Four studies[12,13,15,18], including 1,015 patients, reported the mean time to defervescence after the first antibiotic dose for treatment with azithromycin (n=491) *vs.* doxycycline (n=524). Pooled analysis of these four studies revealed a trend towards delayed defervescence in azithromycin group compared to the doxycycline group (MD: 5.09 hours, 95% CI: -0.28 to 10.46, p=0.06, I^2: 70%) (Figure 4). Seven studies, including 1,346 patients, compared the rates of treatment failure with azithromycin (n=641) *vs.* doxycycline (n=705) in scrub typhus patients defined by persistence of fever or development of organ failure after five days of start of antibiotic treatment[12-18]. Meta-analysis of these seven studies did not show a significant difference be-

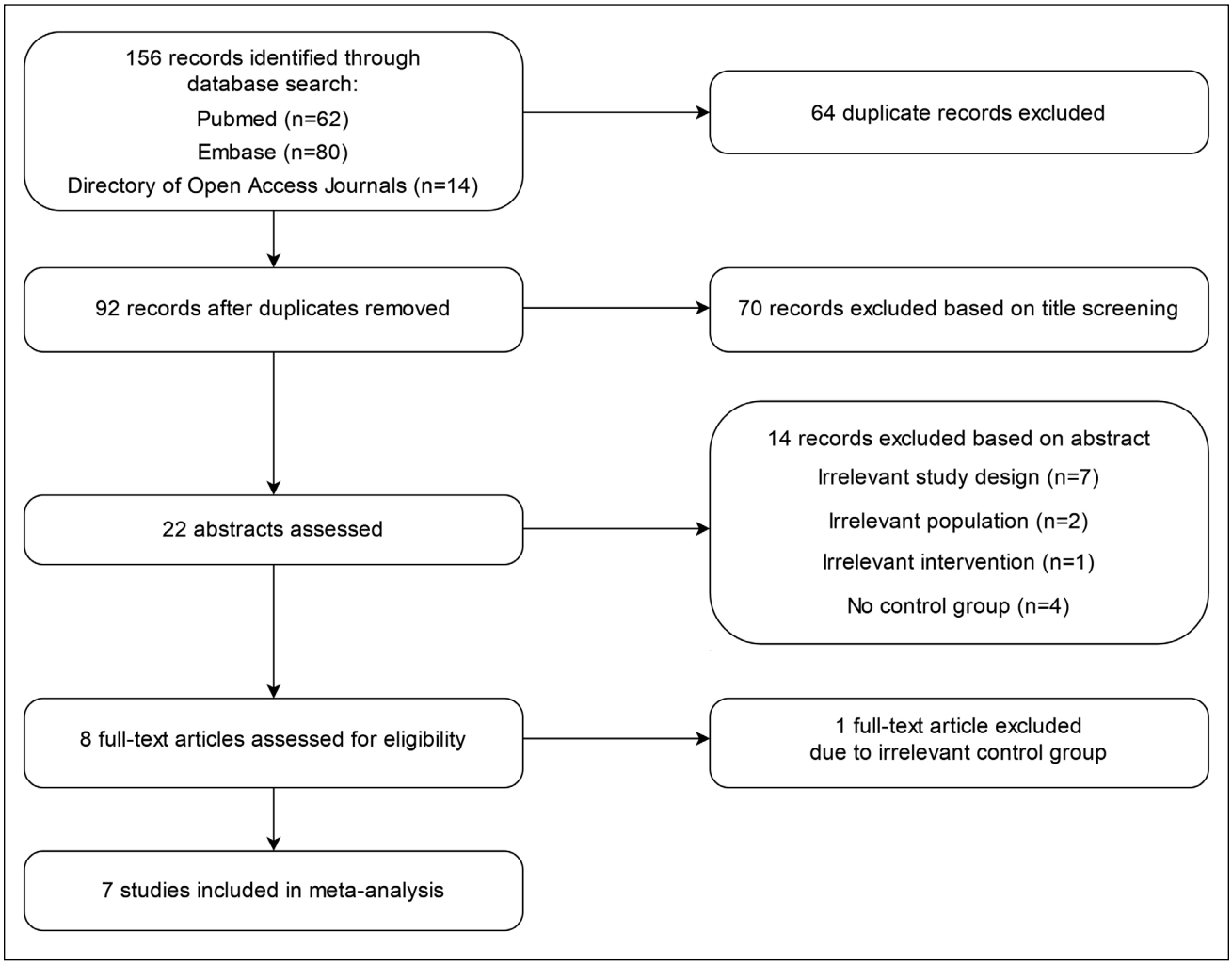

Figure 1. Systematic database search flow diagram.

Table 1 . Characteristics of included studies.

Author (year)	Study design	Country	Age of participants	Interventions and sample size		Outcomes			Level of evidence*
				Azithromycin	Doxycycline	Deferve-scence in 48 hours	Mean time to deferve-scence	Treat-ment failure	
Arun Babu et al[12] 2021	Prospective Comparative	India	<12 years	316	344	✓	✓	✓	3
Barnabas et al[13] 2021	Prospective Comparative	India	>15 years	57	46	✓	✓	✓	3
Jang et al[14] 2014	Retrospective Comparative	South Korea	>16 years	73	108	X	X	✓	3
Kabir et al[15] 2022	Randomized Controlled Trial	India	1-15 years	56	58	X	✓	✓	2
Kim et al[16] 2004	Randomized Controlled Trial	South Korea	>18 years	47	46	✓	X	✓	2
Phimda et al[17] 2007	Randomized Controlled Trial	Thailand	>14 years	30	27	✓	X	✓	2
Veerappan et al[18] 2021	Retrospective Comparative	India	<14 years	62	76	✓	✓	✓	3

*Based on the Oxford Centre for Evidence-Based Medicine Levels of Evidence, where Level 1 represents the highest quality of evidence and Level 5 represents the lowest quality[8].

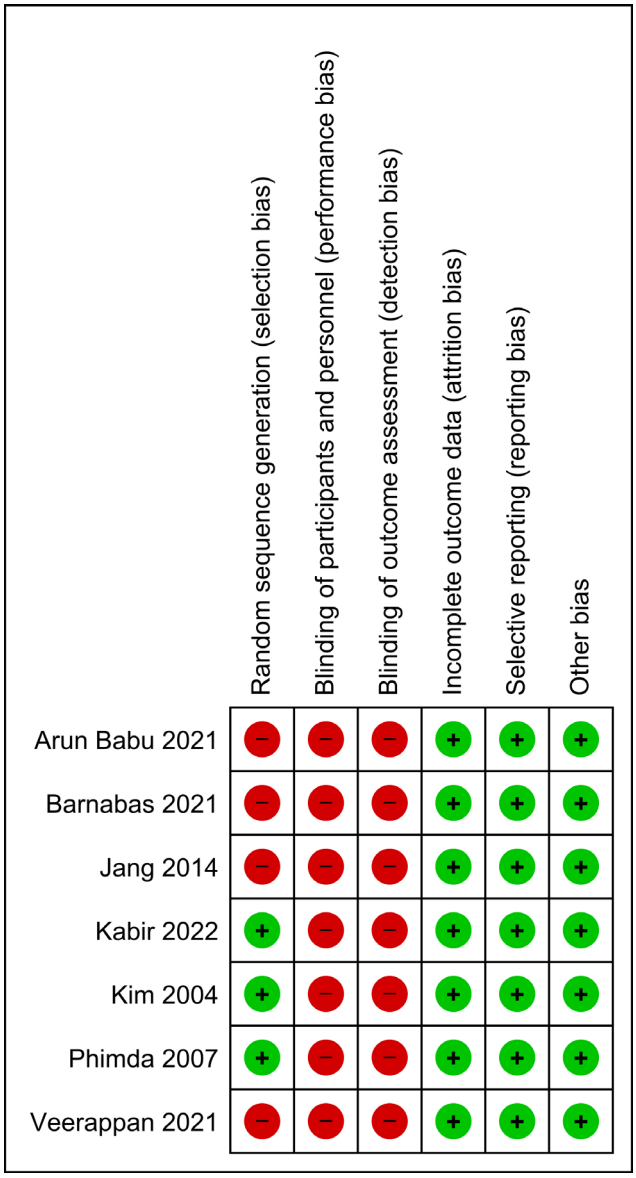

Figure 2. Risk of bias for included studies.

tween the rates of treatment failure at 5 days in the two groups receiving azithromycin *vs.* doxycycline (OR: 1.51, 95% CI: 0.51 to 4.45, p=0.45, I^2:45%); without significant heterogeneity (Figure 5).

Subgroup analysis was performed for studies including adult (age ≥14 years) patients *vs.* pediatric (age <14 years) patients for the outcomes of defervescence within 48 hours and treatment failure at 5 days. For adult patients treated with azithromycin (n=134), resolution of fever within 48 hours after the start of treatment was comparable to those receiving doxycycline (n=119) (OR: 0.60, 95% CI: 0.19 to 1.85, p=0.37), while for pediatric patients, azithromycin (n=378) led to lower rates of defervescence in 48 hours compared to doxycycline (n=420) (OR: 0.42, 95% CI: 0.21 to 0.82, p=0.01) (Figure 6). Subgroup analysis demonstrated that adult patients treated with azithromycin (n=207) had similar rates of treatment failure at 5 days as those treated with doxycycline (n=227) (OR: 0.95, 95%CI: 0.20 to 4.45, p=0.95). Treatment failure rates for pediatric patients treated with azithromycin (n=434) did not differ significantly from those receiving doxycycline (n=478) (OR: 2.70, 95% CI: 0.67 to 10.90, p=0.16) (Figure 7).

Sensitivity analyses were performed by only including studies published in the last 10 years (2012-onwards) for the outcomes of defervescence within 48 hours and treatment failure at 5 days (Supplementary File 1). The results of the sensitivity analysis were consistent with the primary meta-analysis. Three studies[12,13,18] published since 2012 were included in the sensitivity analysis for defervescence in 48 hours, which showed that patients who received azithromycin (n=435) had lower rates of resolution of fever in 48 hours compared to those who received doxycycline (n=466) (OR: 0.49, 95% CI: 0.34 to 0.69, p≤0.0001). Five studies[12-15,18] published in the last 10 years were included in the sensitivity analysis for treatment failure at 5 days, which demonstrated that the rates of treatment failure did not differ significantly in patients who received azithromycin (n=564) *vs.* doxycycline (n=632) (OR: 1.88, 95% CI: 0.57 to 6.25, p=0.30). A funnel plot was constructed, and Egger's regression test was performed to assess the publication bias for studies reporting the primary outcome of defervescence within 48 hours (p=0.29), which did not indicate any funnel plot asymmetry (Supplementary File 2).

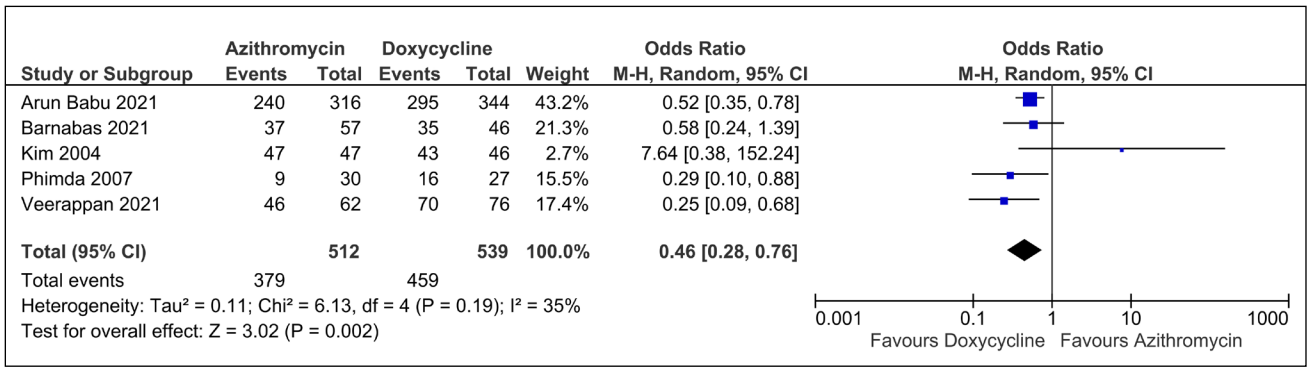

Figure 3. Forest plot comparing the therapeutic effect of azithromycin (n=512) and doxycycline (n=539) with respect to defervescence within 48 hours after the first antibiotic dose.

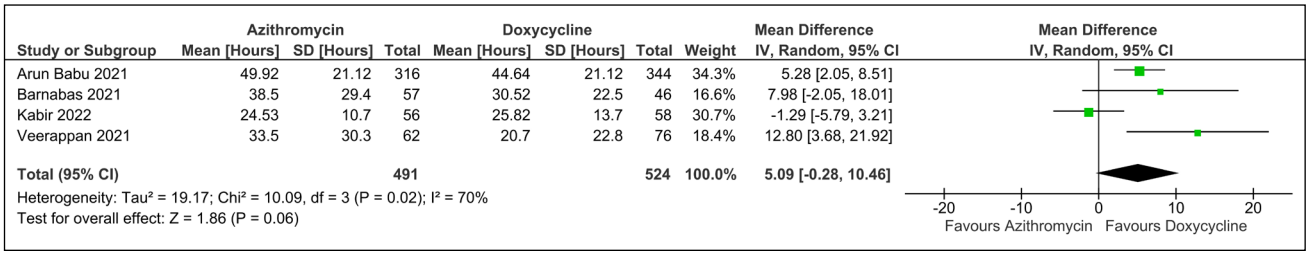

Figure 4. Forest plot for mean time to defervescence in scrub typhus patients treated with azithromycin (n=491) *vs.* doxycycline (n=524).

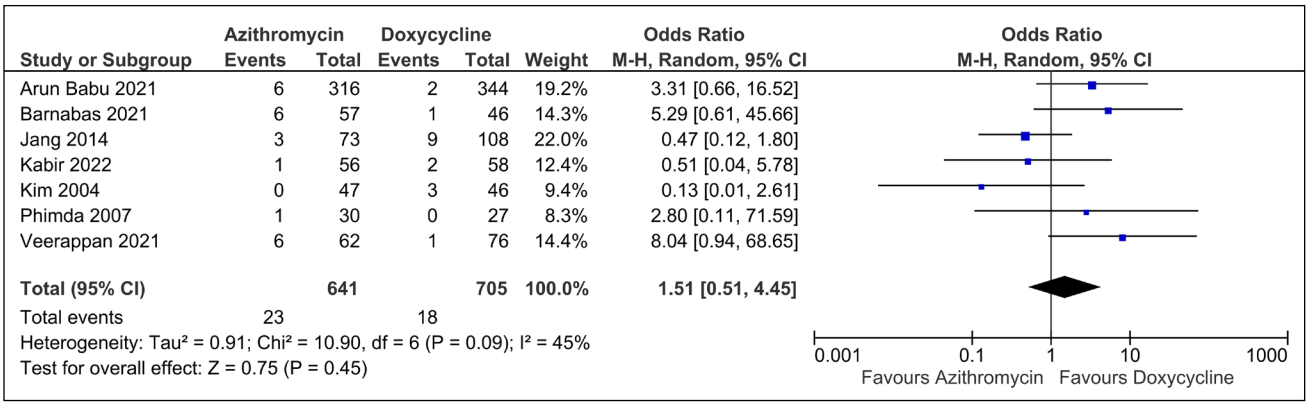

Figure 5. Forest plot for treatment failure at 5 days in scrub typhus patients treated with azithromycin (n=641) compared to doxycycline (n=705).

DISCUSSION

The results of this systematic review and meta-analysis provide insight into the comparative efficacy of azithromycin and doxycycline in treating scrub typhus, a disease of significant public health importance in tropical regions. Scrub typhus, caused by *Orientia tsutsugamushi*, presents with non-specific febrile illness, making timely and effective treatment crucial to prevent severe complications such as multiple organ dysfunction syndrome (MODS), acute respiratory distress syndrome (ARDS), and death. The clinical

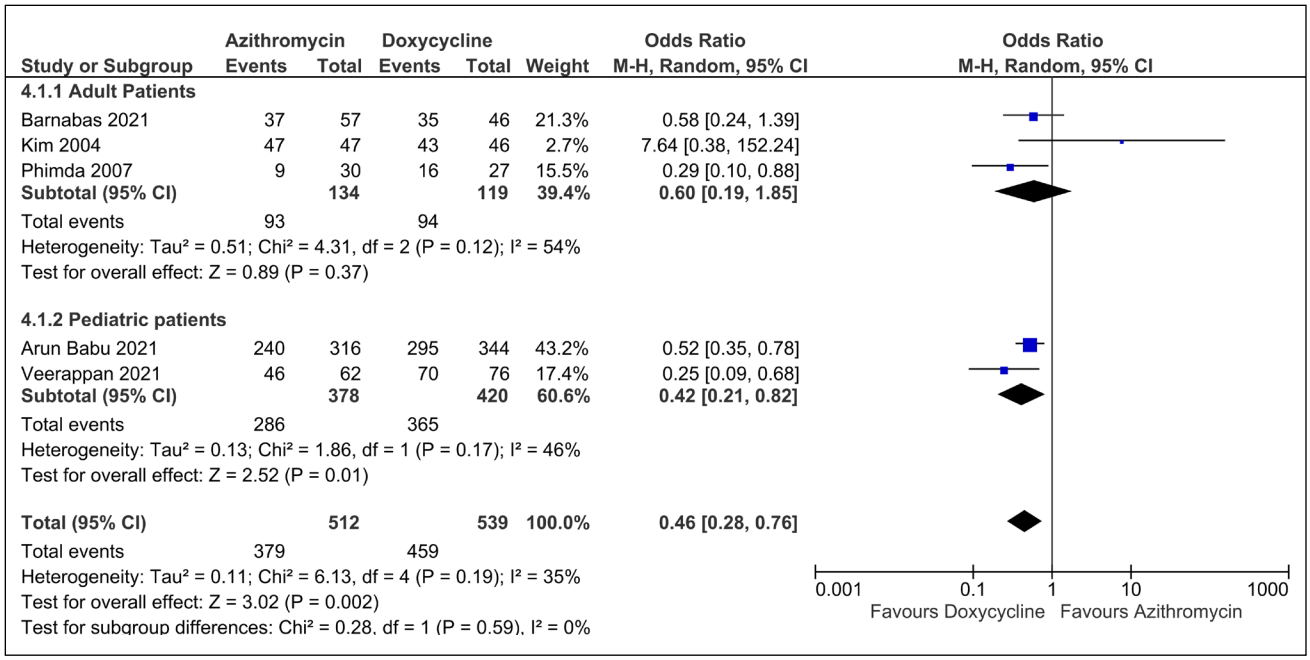

Figure 6. Subgroup analysis for adult patients and pediatric patients for defervescence within 48 hours after first dose of azithromycin *vs.* doxycycline.

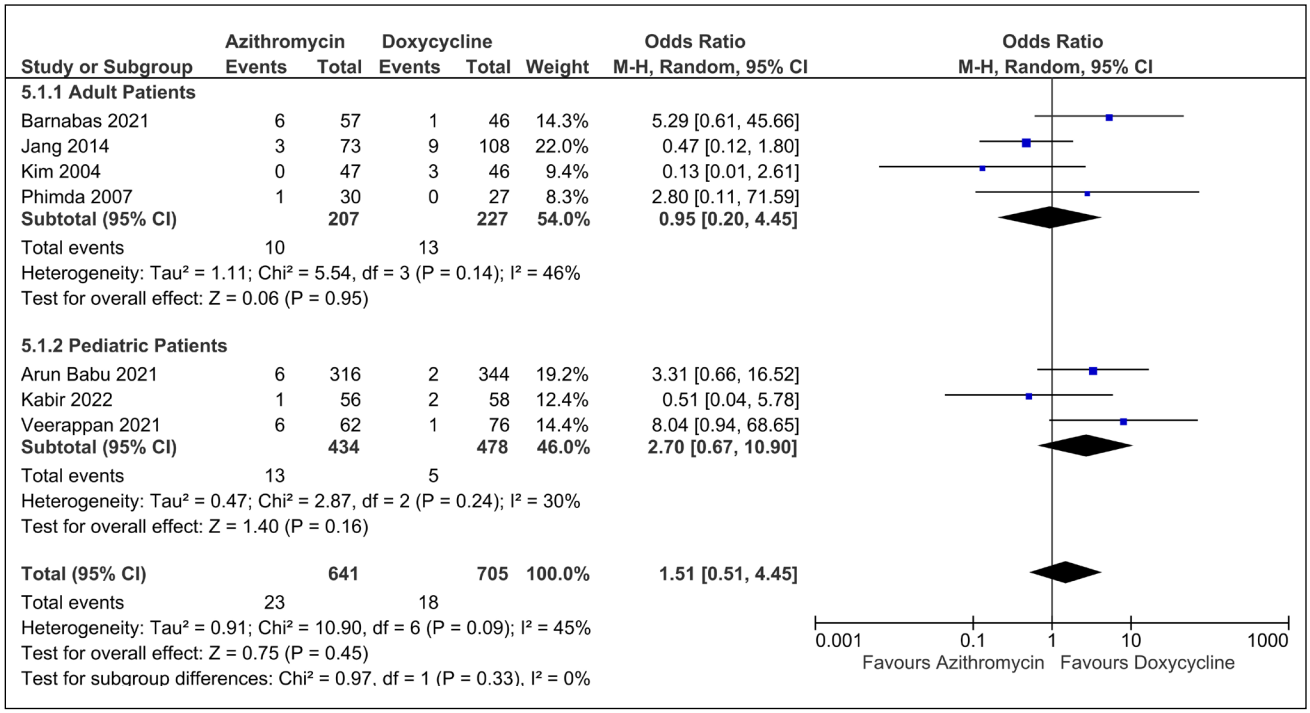

Figure 7. Subgroup analysis for adult patients and pediatric patients for treatment failure at 5 days with azithromycin *vs.* doxycycline.

significance of antibiotic resistance in scrub typhus patients is uncertain[4]. Watt et al[5] reported attenuated therapeutic response to treatment with doxycycline in scrub typhus patients in Thailand, raising the possibility of regional resistance patterns. *In vitro* antibiotic susceptibility testing by Strickman et al[6] demonstrated that doxycycline-resistant strains of scrub typhus retained sensitivity to azithromycin and supports the latter as a critical alternative in the face of resistance. Wangrangsimakul et al[19] have questioned the clinical relevance of doxycycline resistance, suggesting that therapeutic efficacy may not be significantly compromised in most cases.

A recent randomized controlled trial by Varghese et al[20] compared the efficacy of combination therapy with doxycycline and azithromycin against each agent used alone in treating severe scrub typhus. The study found that combination therapy led to a lower incidence of the primary outcome – a composite of 28-day mortality, persistent fever on day 5, and persistent complications on day 7. However, the 28-day mortality was 13% in the combination therapy group, compared to 11% in the doxycycline group (HR: 1.22, 95% CI: 0.74 to 1.99) and 12% in the azithromycin group (HR: 1.09, 95% CI: 0.67 to 1.76). The rate of defervescence in the combination therapy group was 96%, compared to 98% in the doxycycline group (HR: 0.90, 95% CI: 0.75 to 1.07) and 95% in the azithromycin group (HR: 1.00, 95% CI: 0.84 to 1.20). Therefore, the observed difference in the primary outcome was mainly attributed to the persistence of complications at 7 days. Chung et al[21] have questioned the relevance of combination therapy, arguing that the clinical significance of persistent complications at day 7 is already captured by the 28-day mortality rate. They re-analyzed the results of the Varghese et al[20] study and found that the inclusion of non-life-threatening renal and hepatic complications in the definition of persistent complications at day 7 made the statistical analysis significant but not clinically meaningful. Chung et al[21] concluded that while the combination of doxycycline and azithromycin showed statistical superiority, it lacked clinical significance over monotherapy. Sil et al[22] have recommended that monotherapy should remain the preferred approach for managing scrub typhus.

This systematic review and meta-analysis was undertaken to guide decision-making regarding the choice of first-line antibiotics for the treatment of scrub typhus. The certainty of results of the meta-analysis for each outcome is assessed as moderate due to the risk of bias in the included studies. This meta-analysis highlights two key clinical outcomes: defervescence within 48 hours of antibiotic initiation and treatment failure after five days. Rapid defervescence is a critical marker of effective treatment, particularly in regions where diagnostic resources are scarce, and clinical judgment plays a central role in managing febrile illnesses. The results showed that scrub typhus patients treated with doxycycline have higher chances of resolution of fever within the first 2 days of initiation of treatment compared to those treated with azithromycin. This provides important clinical evidence for continued susceptibility of scrub typhus to doxycycline and supports its use as a first-line agent for scrub typhus. Another important finding was the similarly low rate of treatment failure after 5 days with both azithromycin and doxycycline, suggesting that both medications are equally efficacious for the treatment of scrub typhus, and the choice

between them may depend on other factors such as adverse effects, availability, and cost. While azithromycin did not perform as well as doxycycline in terms of early fever resolution, the comparable rates of treatment failure after five days underscore its utility as a viable alternative, particularly in populations where doxycycline use may be contraindicated, such as in pregnant women and children under eight years of age. Azithromycin's safety profile and reduced risk of photosensitivity and gastrointestinal side effects make it a valuable option in such cases despite the slightly delayed time to defervescence. Additionally, its long intracellular half-life and activity against intracellular pathogens like *Orientia tsutsugamushi* remain theoretical advantages, although not fully reflected in clinical outcomes.

The subgroup analysis further delineates the effectiveness of these antibiotics in pediatric and adult populations. Pediatric patients showed a statistically significant lower rate of defervescence within 48 hours with azithromycin, while the adult subgroup showed no significant difference between the two antibiotics. This finding suggests that age-specific factors, such as differences in immune response or drug metabolism, may influence the clinical response to azithromycin. The sensitivity analysis, which restricted the included studies to those published within the last decade, reaffirmed the robustness of the primary findings, with doxycycline consistently showing faster fever resolution. At the same time, both drugs demonstrated comparable efficacy in preventing treatment failure. Our findings, which show more rapid defervescence with doxycycline but no difference in long-term treatment failure, suggest that resistance, although a potential concern, may not yet be a widespread clinical issue in the regions studied.

Several limitations warrant mention. Most notably, adverse effects were not analyzed in this review, which is an important consideration in antibiotic selection. Future studies could address this gap by comparing the side-effect profiles of these two agents, particularly in high-risk populations such as the elderly and those with co-morbid conditions. Additionally, the relatively small sample sizes and potential biases, such as selection bias and lack of blinding in many of the included studies, could impact the generalizability of the findings. Finally, there remains a need for ongoing surveillance to inform treatment guidelines and explore regional variations in treatment response.

CONCLUSIONS

In conclusion, this systematic review and meta-analysis demonstrated that doxycycline is more effective than azithromycin in achieving defervescence within 48 hours in patients with scrub typhus. Despite this, the rates of treatment failure after five days were similar between the two antibiotics. These findings support the continued use of doxycycline as the first-line treatment for scrub typhus, particularly when rapid fever resolution is a priority. Azithromycin remains a suitable alternative, especially in patients for whom doxycycline is contraindicated. The findings of this meta-analysis should guide clinicians in optimizing treatment strategies for scrub typhus, balancing rapid symptom resolution with patient safety and antibiotic stewardship. This is particularly crucial in resource-limited settings, where timely, effective therapy can significantly reduce morbidity and mortality from scrub typhus.

Authors' Contributions:
SCS conceived and designed the study. SCS and MSB searched and reviewed the articles for eligibility and extracted the data. SCS performed the statistical analysis and drafted the manuscript, and MSB contributed significantly to its revision. All authors agree to assume full responsibility for the entirety of the paper.

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Conflict of Interest:
The authors declare that there is no conflict of interest.

Data Availability:
All data generated or analyzed during this study are included in this article and its supplementary materials.

AI Disclosure:
In the preparation of this manuscript, artificial intelligence tools were utilized, including Grammarly for grammar correction and ChatGPT for language improvement to ensure clarity in the presentation of the study's findings. Additionally, Review Manager (RevMan 5.4, The Cochrane Collaboration, 2020) software was employed to conduct the meta-analysis, including data synthesis and statistical analysis, including figures.

Ethics Approval and Informed Consent:
Not applicable.

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