PREVALENCE OF MACROLIDE RESISTANCE AMONG METHICILLIN-RESISTANT *Staphylococcus aureus* (MRSA): A META-ANALYTIC ASSESSMENT

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is a globally significant pathogen characterized by high virulence and exceptional adaptability. It shows resistance to multiple antibiotics, particularly β-lactams due to the *mecA* gene. This meta-analysis examined the widespread transmission of MRSA, which evades host defenses and thrives in various environments, focusing on the prevalence of macrolide resistance. Macrolides, such as azithromycin, clarithromycin, and erythromycin, are antibiotics that inhibit bacterial growth by disrupting protein synthesis. Drawing from 101 studies identified through a comprehensive search including PubMed, the analysis adhered to PRISMA guidelines and included only cross-sectional studies reporting baseline resistance data in MRSA strains. Using a random-effects model, the pooled prevalence of macrolide resistance was calculated at 88.51% (95% CI: 84.76–91.43), revealing a high burden of resistance with significant heterogeneity ($I^2 = 98.23\%$, $\tau^2 = 2.9087$, $Q = 6483.68$, $p < 0.0001$). Subgroup analyses showed 90.22% resistance for erythromycin, 79.96% for azithromycin, and 61.47% for clarithromycin. Each showed varying heterogeneity, reflecting study variability from geographic, methodological, and temporal differences. Evidence of publication bias was detected through Begg's rank correlation and Egger's regression tests, with statistically significant results ($p=0.0000$), suggesting potential overrepresentation of studies with positive findings. These findings underscore the clinical challenge posed by macrolide-resistant MRSA, limiting the efficacy of a widely used class of antibiotics. This emphasises the need for regional surveillance, antimicrobial stewardship, and tailored therapeutic strategies guided by local susceptibility profiles. The extreme heterogeneity underscores the need for customized interventions and ongoing research into resistance mechanisms and epidemiology. This study offers vital insights into the extent and diversity of macrolide resistance in MRSA, supporting public health efforts to combat antibiotic resistance in community and healthcare settings.

Keywords: heterogeneity, macrolide resistance, Methicillin-resistant, *Staphylococcus aureus*, MRSA, pooled prevalence, PRISMA

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INTRODUCTION

Staphylococcus aureus is a Gram-positive, facultatively anaerobic coccus that colonizes the skin and mucosal surfaces of humans. Microscopically, it appears in grape-like clusters and is catalase-positive, coagulase-positive, and capable of fermenting mannitol, features that aid in its laboratory identification [1]. Physiologically, *S. aureus* is highly adaptable, thriving across a broad range of temperatures and salt concentrations, which contributes to its environmental resilience and colonization potential [2]. Biochemically, it produces a wide array of virulence factors, including hemolysins, leukocidins, and protein A, which facilitate immune evasion, tissue invasion, and persistence within the host [3] [4]. While often a harmless commensal, *S. aureus* is also an opportunistic pathogen capable of causing a spectrum of infections, from superficial skin and soft tissue infections to severe diseases such as pneumonia, endocarditis, osteomyelitis, and sepsis [2] [5].

Methicillin, a β-lactam antibiotic introduced in the late 1950s, was developed to combat penicillin-resistant strains of *S. aureus*. Like other β-lactams, methicillin targets bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs). However, the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) has rendered this class of antibiotics ineffective against many strains. MRSA harbours the *mecA* gene, which encodes an altered PBP (PBP2a) with low affinity for β-lactams, conferring resistance to nearly all agents in this class [3]. MRSA is a major public health concern due to its high virulence, resistance to multiple antibiotics, and ability to cause outbreaks in both healthcare and community settings. It is associated with increased morbidity, mortality, and healthcare costs, making it a priority pathogen for surveillance and control [5].

Antimicrobial resistance (AMR) more broadly has become a global crisis, driven by factors such as antibiotic overuse, inadequate infection control, and the horizontal transfer of resistance genes among bacteria. Mechanisms like plasmid exchange, transposons, and integrons facilitate the rapid spread of resistance traits across species and environments [6]. This genetic plasticity accelerates the evolution of multidrug-resistant organisms, undermining the efficacy of existing treatments [7].

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Macrolides, including erythromycin, azithromycin, and clarithromycin, are commonly used antibiotics that inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit. They are often prescribed for respiratory tract infections, skin infections, and sexually transmitted diseases. However, resistance to macrolides, mediated by target site modification, efflux pumps, or enzymatic inactivation, has been increasingly reported in MRSA strains, limiting therapeutic options and complicating treatment strategies [8].

This meta-analytic assessment aims to quantify the prevalence of macrolide resistance among MRSA isolates and to provide insights into the evolving landscape of antimicrobial resistance in this clinically significant pathogen.

METHODOLOGY

The study was conducted according to the guidelines provided by PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) [9] [10].

Eligibility criteria, search criteria, and selection criteria

Inclusion criteria for meta-analysis required that studies focus on identifying methicillin-resistant *Staphylococcus aureus* (MRSA) and its resistance to macrolide antibiotics. Studies had to report resistance rates, be published in full in English, and adopt a cross-sectional design. Only those presenting antimicrobial resistance (AMR) data, particularly, baseline resistance levels before any intervention, were selected, as they provide prevalent estimates within a population at a specific point in time. Studies excluded were not published in English and were review articles, case reports, and case series.

A comprehensive literature search was conducted using keywords such as “MRSA Macrolide”, “MRSA Azithromycin/Clarithromycin/Erythromycin”, “Methicillin-resistant *Staphylococcus aureus* Macrolide”, and “Methicillin-resistant *Staphylococcus aureus* Azithromycin/Erythromycin/Clarithromycin”. The search was performed across multiple databases and search engines, including PubMed (n = 2,158), BioMed Central (n = 1,794), ScienceOpen (n = 8), and Google Scholar (n = 1,683), targeting studies published up to the present. Some sources were excluded due to limited accessibility or subscription-only access. Of the 5643 articles initially identified, 3964 duplicates were removed. An additional 1364 articles were excluded due to inaccessibility, such as language barriers or paywall restrictions. The remaining 315 articles were screened, and 214 were excluded for reasons including lack of relevance, absence of resistance isolate counts, or inconsistent units of measurement. Ultimately, 101 articles were deemed eligible and included in the meta-analysis.

Synthesis and analysis method

Extracted data encompassed the first author(s), year of publication, country of study, continent, AST diagnostic method, antibiotic type, sample source/origin, number of positive results (number of macrolide resistant isolates), and total

MRSA isolates. To maintain accuracy and consistency, three authors independently performed data extraction to reduce the risk of bias.

The analysis used proportions as the primary outcome measure. A random effect model was used to analyze the data [11], and the effect size was evaluated by using proportional analysis method [12]. The degree of heterogeneity (τ^2) was estimated using the DerSimonian-Laird method for τ^2 [13]. Along with τ^2, the Q-test for heterogeneity and the I^2 statistics [14] were also calculated. Heterogeneity was considered present if $\tau^2 > 0$, or $I^2 > 0$ regardless of the Q-test results [13] [14]. Subgroup analyses were conducted based on macrolide type to determine the prevalence of resistance associated with each type of macrolide. Publication bias was assessed using Begg's rank correlation and Egger's regression test [15] [16]. All statistical analyses were performed using Jamovi (version 2.6.44) and GraphPad Prism (version 10.1.1).

RESULTS AND DISCUSSION

Overall effect of macrolide resistance in MRSA

Table 01: overall effect of the prevalence of macrolide resistance in MRSA

Pooled proportion	Pooled proportion %	95% lower CI; confidence interval	95% upper CI	τ^2	Cochran's Q	Degree of freedom; df	I^2	p
0.8851	88.51	0.8476	0.9143	2.9087	6483.68	115	98.23%	0.0000

The findings from this meta-analysis reveal a concerningly high prevalence of macrolide resistance among methicillin-resistant *Staphylococcus aureus* (MRSA) isolates, with a pooled proportion of 88.51%. This suggests that nearly nine out of ten MRSA strains studied exhibit resistance to macrolide antibiotics, underscoring a significant clinical challenge in treating MRSA infections with this class of antibiotics. The 95% confidence interval (CI) ranging from 84.76% to 91.43% reflects a narrow margin around the pooled estimate, indicating a high degree of precision and reliability in the calculated prevalence. However, this precision is accompanied by extremely high heterogeneity, as evidenced by an I^2 value of 98.23% and a Cochran's Q statistic of 6483.68 with 115 degrees of freedom. Such a high I^2 implies that nearly all of the observed variability across the studies stems from true heterogeneity rather than chance. This could be attributed to differences in geographic regions, sample collection periods, diagnostic techniques, or local antimicrobial usage patterns. The tau-squared (τ^2) value of 2.9087 supports the existence of considerable between-study variance. The p-value of 0.0000 for the heterogeneity test strongly indicates that the heterogeneity observed is statistically significant. These findings highlight the importance of cautious interpretation and suggest the need for subgroup analyses to explore potential sources of variability.

Subgroup analysis stratified by specific macrolide types

Table 02: Subgroup analysis based on macrolide types

Macrolide	Pooled proportion	Pooled proportion %	95% lower CI	95% upper CI	τ^2	Cochran's Q	Degree of freedom; df	I²	p
Erythromycin	0.9022	90.22	0.8661	0.9294	2.9120	5789.62	97	98.32%	0.0000
Azithromycin	0.7996	79.96	0.5715	0.9227	4.4678	673.30	14	97.92%	0.0000
Clarithromycin	0.6147	61.47	0.3291	0.8385	0.8398	12.18	2	83.57%	0.0023

The subgroup analysis stratified by specific macrolide antibiotics highlights notable differences in resistance prevalence among MRSA isolates. Erythromycin exhibited the highest pooled resistance proportion at 90.22% (95% CI: 86.61–92.94), suggesting widespread resistance across the studies examined. The heterogeneity was substantial ($I^2 = 98.32\%$, $p < 0.0001$), pointing to considerable between-study variation likely influenced by regional and methodological differences.

Azithromycin showed a slightly lower but still significant resistance proportion of 79.96% (95% CI: 57.15–92.27). Despite its broader confidence interval, it was indicative of greater uncertainty in the estimate. It also exhibited high heterogeneity ($I^2 = 97.92\%$, $p < 0.0001$). The elevated tau-squared value of 4.4678 further suggests that true variation among studies was substantial.

Interestingly, Clarithromycin presented a comparatively lower resistance rate of 61.47% (95% CI: 32.91–83.85), with more moderate heterogeneity ($I^2 = 83.57\%$, $p = 0.0023$). This could imply regional variation in usage patterns or intrinsic differences in resistance development to this macrolide.

Assessment of publication bias

Table 03: Assessment of publication bias, using Begg's rank correlation test and Egger's regression. P<0.05 suggests that there is a publication bias in results

Begg's rank correlation test		Egger's regression test	
Kendall's Tau	p-value	Egger's intercept	p-value
0.3059	0.0000	5.3509	0.0000

Publication bias was evaluated through Begg's rank correlation test and Egger's regression test in the context of a meta-analysis examining the prevalence of macrolide resistance in *Staphylococcus aureus* (MRSA), specifically for erythromycin, azithromycin, and clarithromycin. Begg's test showed a Kendall's Tau of 0.3059 with a p-value of 0.0000, indicating a statistically significant association suggestive of publication bias. Similarly, Egger's regression test yielded an intercept of 5.3509 with a p-value of 0.0000, reflecting significant funnel plot asymmetry. Together, these results provide strong evidence of publication bias within the dataset, which should be considered when interpreting the pooled prevalence estimates of macrolide resistance.

This meta-analysis underscores a critically high prevalence of macrolide resistance among MRSA isolates, with an overall pooled proportion of 88.51%. The precision of the estimate is reinforced by a narrow confidence interval, yet its reliability is tempered by significant heterogeneity across studies. Metrics such as I^2 of 98.23%, Cochran's Q of 6483.68, and a tau-squared of 2.9087 reveal substantial between-study variability, likely influenced by regional, methodological, and clinical differences. Subgroup analyses further highlight variability in resistance patterns across specific macrolides. Erythromycin resistance was highest, followed by azithromycin and then clarithromycin. While these differences provide useful insight, the consistently elevated resistance across all three agents emphasizes a growing therapeutic limitation in using macrolides against MRSA.

CONCLUSION

This meta-analysis underscored the serious and growing threat posed by macrolide-resistant *Staphylococcus aureus* (MRSA), with consistently high resistance rates observed for erythromycin, azithromycin, and clarithromycin. The overall pooled prevalence highlighted a formidable challenge for clinical treatment, further complicated by substantial heterogeneity and confirmed publication bias across studies. These findings call for urgent, coordinated action to enhance antimicrobial stewardship, harmonize surveillance strategies, and expand research efforts, study designs, to better inform and address the evolving landscape of MRSA resistance globally.

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