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Global prevalence of macrolide-resistant *Staphylococcus* spp.: a comprehensive systematic review and meta-analysis

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Background: *Staphylococcus* is a genus of bacteria responsible for various infections ranging from mild skin to severe systemic diseases. Methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci (CoNS) are significant challenges owing to their resistance to multiple antibiotics, including macrolides, such as erythromycin, clarithromycin, and azithromycin.

Objective: This study aimed to systematically review and synthesize data on the prevalence of macrolide resistance in *Staphylococcus* spp., identify trends and changes in resistance patterns over time, and assess how testing methods and guidelines affect reported resistance rates.

Methods: The study conducted a systematic search of the Scopus, PubMed, Web of Science, and EMBASE databases. Studies have reported the proportion of macrolide-resistant *Staphylococcus* spp. Two authors independently extracted and analyzed the data using a random-effects model. Heterogeneity was assessed, and subgroup analyses were performed based on country, continent, species, AST guidelines, methods, and period.

Results: In total, 223 studies from 76 countries were included. The pooled prevalence of resistance to erythromycin, clarithromycin, and azithromycin were 57.3, 52.6, and 57.9%, respectively. Significant heterogeneity was observed across studies ($I^2 > 95\%$, $p < 0.001$). Oceania (72%) had the highest erythromycin resistance, whereas Europe had the lowest (40.7%). Subgroup analyses revealed variations in resistance based on the species, with higher resistance in MRSA than in MSSA and CoNS than in other species. Over time, a slight decrease in erythromycin resistance has been observed (59.6% from 2015–2019 to 55% from 2020–2023).

Conclusion: This study emphasizes the high prevalence of macrolide resistance in *Staphylococcus* spp. and its notable regional variation. These findings highlight the necessity for standardized methodologies and global surveillance to manage macrolide resistance effectively. Controlling antibiotic resistance should prioritize enhancing public health measures and updating treatment guidelines.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=557756, CRD42024557756.

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KEYWORDS

Staphylococcus, macrolide, meta-analysis, methicillin-resistant *Staphylococcus aureus*, coagulase-negative staphylococci

1 Introduction

Staphylococcus is a genus of bacteria that can cause many infections, from mild skin infections to serious systemic diseases. These infections can affect the skin, lungs, bloodstream, and medical devices and have become a significant treatment challenge, particularly for methicillin-resistant *Staphylococcus aureus* (MRSA) (Tong et al., 2015; Cheung et al., 2021). It is estimated that approximately 30% of people carry *S. aureus* on their bodies without any symptoms. In 2019, *S. aureus* was associated with more than 1 million deaths, with an estimated range of 816,000 to 1,470,000 deaths (Ikuta et al., 2022). In the United States, the rate of invasive MRSA infections in the black population (66.5 cases per 100,000 person-years) is more than twice that of the white population (27.7 cases per 100,000 person-years). In Australia, the incidence of *Staphylococcus aureus* bacteremia (SAB) is 5.8 to 20 times higher among Indigenous Australians than among non-Indigenous Australians. Similarly, in New Zealand, Māori and Pacific Island communities have significantly higher rates of SAB than those of European descent (Tong et al., 2015). In recent years, there has been a significant increase in the rate of MRSA colonization in healthy individuals, potentially contributing to the spread of MRSA in both community and hospital settings (Barcudi et al., 2020). In addition, MRSA is a pathogen resistant to multiple antibiotics, complicating infection management and leading to increased healthcare costs and adverse outcomes (Abebe and Birhanu, 2023; Lan et al., 2024; Saleem et al., 2025). Globally, the pathogen-drug combination with the most significant increase in attributable burden was MRSA. Its attributable deaths have doubled from 57,200 (range 34,100-80,300) in 1990 to 130,000 (range 113,000-146,000) in 2021(Naghavi et al., 2024).

Antibiotic resistance is a global health crisis that threatens the effectiveness of treatments for bacterial infections. Misuse and overuse of antibiotics have accelerated the development of resistance, rendering many therapies ineffective (Yadav and Kapley, 2021; Estany-Gestal et al., 2024). Macrolides, such as erythromycin, clarithromycin, and azithromycin, are widely used to treat various staphylococcal infections. However, the increasing emergence of macrolide resistance in *Staphylococcus* spp. has become a critical challenge in treating infections caused by these bacteria. Resistance to macrolides has been attributed to the methylation of specific targets in the 23S rRNA by methylases encoded by *erm* genes, particularly *erm*(C) and *erm*(A), which can be constitutive or inducible. In addition, efflux pumps, such as ABC-F proteins encoded by *msr* genes and major facilitator superfamily transporters encoded by *mef* genes, drug inactivation by phosphotransferases encoded by *mph* genes, and esterase encoded by *ere* genes, confer macrolide resistance (Leclercq, 2002; Miklasinska-Majdanik, 2021; El Mammery et al., 2023; Mahfouz et al., 2023). These mechanisms show regional variation, reflecting differences in the prevalence of resistance genes and differences in antibiotic use practices (Miklasinska-Majdanik, 2021).

Overall, antibiotic resistance reduces the effectiveness of these antibiotics and complicates the treatment of common staphylococcal infections such as skin infections, pneumonia, and bacteremia.

The global burden of macrolide-resistant staphylococci affects both public health and healthcare systems. Data indicate increasing infection rates and resistance patterns, particularly in healthcare-associated infections where *S. aureus* is a leading cause of morbidity and mortality (An et al., 2024). The economic impact is also profound, with resistant infections leading to longer hospital stays, more complex treatment regimens, and increased healthcare costs (Lodise and McKinnon, 2007). However, the limited number of effective treatment options for resistant infections increases the risk of adverse outcomes. This underscores the importance of developing novel therapeutic approaches and implementing stringent infection control measures (Guo et al., 2020).

Previous research on macrolide resistance in *staphylococci* has been limited by study design and reporting inconsistencies, making it difficult to draw robust conclusions and identify consistent trends. In addition, many studies require extensive regional analyses, limiting the generalizability of findings and their impact on global health. Furthermore, gaps in understanding the temporal trends and dynamics of resistance highlight the need for longitudinal studies and broader surveillance efforts (Leclercq, 2002; Khader et al., 2019). Hence, standardized methodologies and collaborative efforts across regions are essential to improving our understanding and managing macrolide resistance in *staphylococci*.

The primary objective of this study was to systematically review and analyze the available data on the prevalence of macrolide resistance in *Staphylococcus* spp.

The secondary objectives were to identify trends and changes in resistance patterns over time, explore heterogeneity in resistance rates across regions and populations, and assess the impact of testing methods and guidelines on reported resistance rates. By addressing these objectives, this study aimed to fill the existing knowledge gaps and provide comprehensive insights into the dynamics of macrolide resistance in *Staphylococcus* spp. to guide future research and clinical practice.

2 Methods

This study was conducted according to PRISMA guidelines and included a meta-analysis to increase the robustness of the results. The study was registered in the PROSPERO registry under the code CRD42024557756.

2.1 Eligibility criteria

The inclusion criteria for this meta-analysis stipulated that studies must investigate *Staphylococcus* spp. macrolide resistance, report resistance rates, specify sample size determination and have complete English-language articles available. Only cross-sectional studies providing antimicrobial resistance (AMR) data, mainly those reporting baseline resistance levels before any interventions, were included. Such studies offer a population-based overview of resistance rates at a specific time and are, therefore, suitable for estimating the prevalence of macrolide resistance. Studies were excluded if published in languages other than English and were review articles, case reports, and case series studies.

2.2 Information sources

A comprehensive search was conducted in several major online databases, including Scopus, PubMed, Web of Science, and EMBASE, focusing on studies published through December 2023. These databases were selected for their extensive coverage of biomedical literature, ensuring a broad scope for the systematic review.

2.3 Search strategy

The search syntax was tailored to each database according to their respective guidelines ("*Staphylococcus**" OR "*S. aureus*" OR "*S. epidermidis*" OR "*S. saprophyticus*" OR "*S. lugdunensis*" OR "*S. hominis*" OR "*S. capitis*" OR "*S. haemolyticus*" OR "CoNS" OR "MRCoNS" OR "MRSA" OR "MSCoNS" OR "VISA" OR "VSSA") AND (macrolide* OR azithromycin OR clarithromycin OR erythromycin OR roxithromycin OR telithromycin OR spiramycin OR fidaxomicin) AND (resistant* OR susceptible*). This rigorous methodological approach ensured comprehensive coverage of relevant research topics.

2.4 Selection process

The systematic online database search results were imported into EndNote (version 20), removing duplicate entries. Two authors (NG and EP) independently screened and analyzed the relevant publications to minimize bias. Disagreements were resolved by a third author (TN).

2.5 Data collection process

Data extracted included first author(s), publication year, country, diagnostic method, sample source, number of positive tests, and total sample size. To ensure accuracy, two authors (MM and MB) extracted the data independently, and any disagreements were resolved by consensus.

2.6 Study risk of bias assessment

The quality of the included studies was assessed using the JBI tool. Two authors (MB and TN) independently evaluated the quality, and a third author (MSH) resolved disagreements.

2.7 Synthesis methods

This comprehensive systematic review and meta-analysis aimed to determine the global prevalence of macrolide-resistant *Staphylococcus* species. The analysis used proportions as the primary outcome measure. The main objective was to assess the prevalence of macrolide-resistant *Staphylococcus* strains, while the secondary objective sought to identify sources of heterogeneity between studies. Subgroup analyses investigated potential variability in resistance rates across different demographic and methodological factors. Additionally, trends in macrolide resistance over time were examined.

A random effects model was employed to analyze the data, allowing for considering variability within and between studies. The degree of heterogeneity was estimated using the DerSimonian-Laird method for τ^2. Along with τ^2, the Q-test for heterogeneity and the I^2 statistic (Higgins and Thompson, 2002) were also calculated. Heterogeneity was considered present if $\tau^2 > 0$, regardless of the Q-test results.

Subgroup analyses were performed across various factors to explore sources of heterogeneity, including countries, continents, antibiotic susceptibility testing (AST) guidelines, AST methods, *Staphylococcus* species, coagulase status, and year groups. This stratification helped identify macrolide resistance patterns and potential drivers across regions and testing protocols.

A Logit Transformation was applied to the proportions of macrolide-resistant *Staphylococcus* species to account for variations in the proportion data and stabilize the variance. The logit transformation—also known as the log-odds transformation—was used to ensure that the outcome variable remained within the 0 to 1 range, mainly when dealing with extreme proportions of resistance. This transformation also normalized the distribution of proportions, facilitating more accurate meta-regression modeling.

Meta-regression analysis was conducted to explore temporal trends in macrolide resistance over time. Moderator variables included country, continent, AST guidelines, and year group. This analysis aimed to identify how macrolide resistance in *Staphylococcus* species has evolved across different geographical regions and under varying testing conditions.

Outliers and influential studies were identified using studentized residuals and Cook's distances. Studies with studentized residuals exceeding the $100 \times (1–0.05 / (2 \times k))$ th percentile of a standard normal distribution were flagged as potential outliers (after applying a Bonferroni correction for $\alpha = 0.05$ and for k studies in the meta-analysis). Studies with Cook's distances greater than the median plus six times the interquartile range of Cook's distances were considered influential and examined for their impact on the overall estimates.

Funnel plot asymmetry was assessed using rank correlation and regression tests, with the standard error of the observed results serving as the predictor. This approach was used to evaluate potential publication bias. All statistical analyses were performed using R (version 4.2.1) and the metafor package (version 3.8.1) (Cochran, 1954; Begg and Mazumdar, 1994; Higgins and Thompson, 2002; Sterne and Egger, 2005; Viechtbauer, 2010; Viechtbauer and Cheung, 2010; Kuhn et al., 2015).

3 Results

3.1 Descriptive statistics

A total of 21,273 records as results of the systematic search were collected in reference manager software (EndNote version 20), and 14,285 duplicated articles were removed. Thousand eighty-eight articles were assessed in the title abstract for this section; 990 full-text articles were evaluated and excluded. Eventually, this systematic review and meta-analysis included 207 eligible studies. The reports came from 76 countries and six continents. The reports cover the years 2015 to 2023. The screening and selection of presages are summarized in the PRISMA flowchart (Figure 1). Characteristics and references of included studies are presented in Table 1.

3.2 Comprehensive overview of antibiotic resistance prevalence

Among 360 reports, the proportion of erythromycin-resistant isolates was 0.573 (95% CI: 0.556–0.590), based on 144,746 resistant isolates out of 293,411 isolates tested. The heterogeneity among reports was significant ($I^2 = 96.09\%$, $p = 0.001$). Similarly, the proportion of clarithromycin resistance, as assessed by 30 reports involving 4,015 resistant isolates out of 8,045 tested isolates, was 0.526 (95% CI: 0.380–0.668), with significant heterogeneity between reports ($I^2 = 98.76\%$, $p = 0.001$). In addition, the proportion of azithromycin-resistant isolates, derived from 83 reports containing 5,227 resistant isolates out of 10,553 isolates tested, was 0.579 (95% CI: 0.514–0.641), again with significant heterogeneity between reports ($I^2 = 96.50\%$, $p = 0.001$).

3.2.1 Prevalence of erythromycin resistance

A total of 293,411 isolates from 721 studies were included in the erythromycin resistance analysis. The estimated mean proportion based on the random effects model was 0.573 (95% CI: 0.556–0.590). This result indicates that the mean proportion differed significantly from zero ($z = 8.400$, $p < 0.001$). The heterogeneity between studies was significant, as noted in the Q-test ($Q(720) = 42{,}007.095$, $I^2 = 98.29\%$, $p < 0.001$) (Table 2). A forest plot illustrating the observed results and the random effects model estimate is shown in Figure 2.

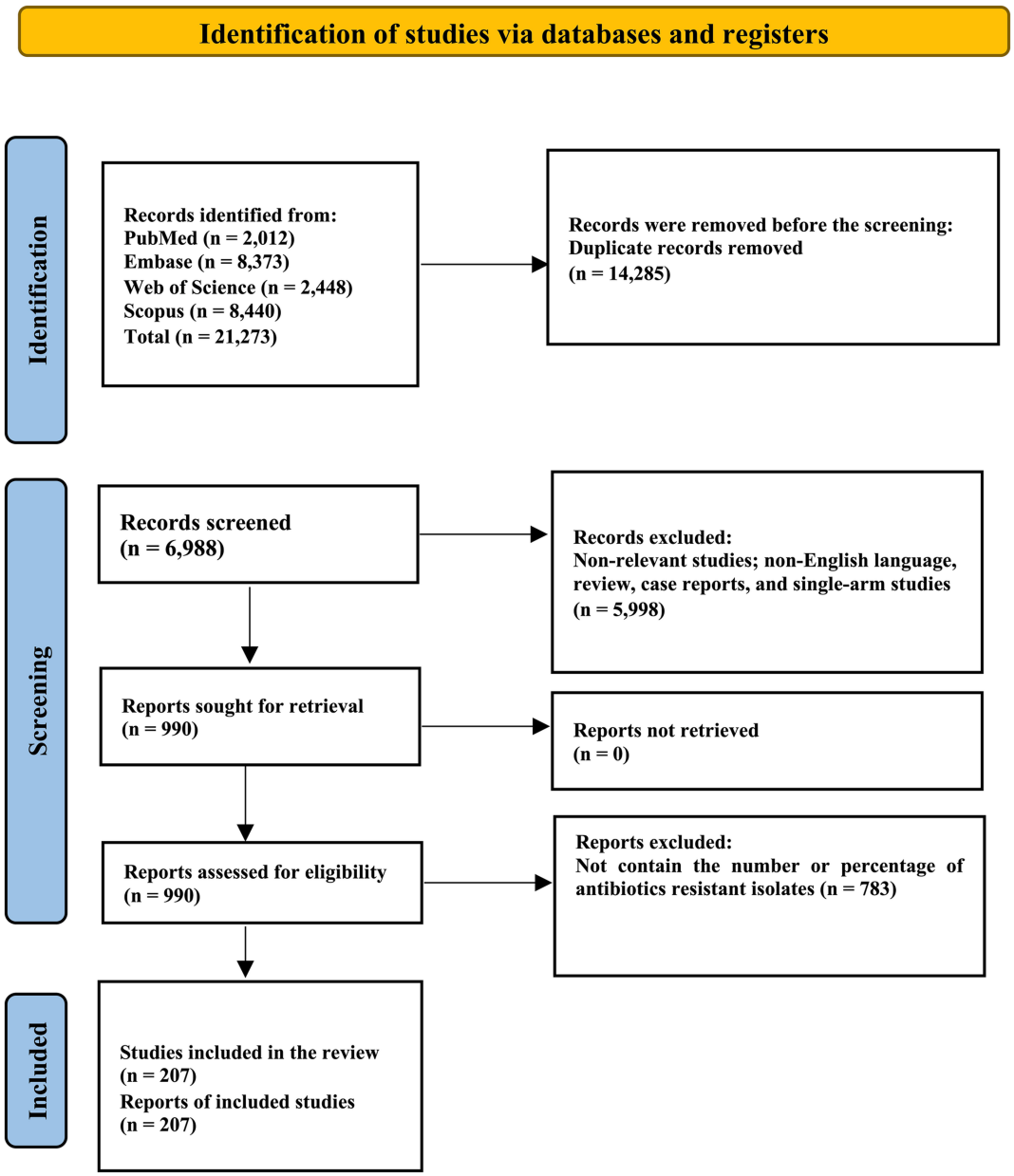

FIGURE 1
PRISMA flow diagram of study selection: this diagram illustrates the process of study identification, screening, eligibility assessment, and inclusion for the review. From a total of 21,273 records identified through databases, 207 studies were included in the final review after exclusion based on criteria such as duplication, irrelevance, and lack of data on antibiotic-resistant isolates.

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TABLE 1 A summary of the included studies in the meta-analysis is provided below, highlighting the characteristics employed.

Author	Countries	AST method	AST guideline	Quality group	Species	Erythromycin	Clarithromycin	Azithromycin
Asbell et al. (2015)	United States	MM	C	L	MRSA	ND	ND	283
Abbasi et al. (2017)	Iran	DD	C	L	MRSA	30	ND	ND
Changchien et al. (2016)	China	DD	C	L	MRSA	159	ND	ND
Qin et al. (2017)	China	MIC	C	L	MRSA	109	ND	ND
Baek et al. (2016)	South Korea	AM	C	L	MRSA	338	ND	ND
Noordin et al. (2016)	Malaysia	DD	C	L	MRSA	297	ND	ND
Gitau et al. (2018)	Kenya	DD	C	L	MRSA	129	ND	ND
Coombs et al. (2020)	Australia	AM	C	L	MRSA	174	ND	ND
Shashindran et al. (2016)	ND	DD	C	L	MRSA	84	ND	ND
Horvath et al. (2020)	Hungary	MM	E	L	MRSA	122	ND	ND
Numanovic et al. (2021)	ND	DD	E	L	MRSA	9	ND	ND
Nichol et al. (2019)	Canada	MM	C	L	MRSA	ND	305	ND
Chaleshtori and Kachoie (2016)	ND	DD	C	L	MRSA	ND	ND	10
Chen Y. L. et al. (2021)	Taiwan	DD	C	L	MRSA	16	ND	ND
Khemiri et al. (2017)	Libya	DD	E	L	MRSA	30	ND	ND
Li et al. (2016)	China	MIC	C	L	MRSA	553	ND	ND
Napp et al. (2016)	United States	ND	ND	L	MRSA	ND	ND	37
Akbariyeh et al. (2017)	ND	DD	C	S	MRSA	2	ND	ND
Elzorkany et al. (2019)	India	DD	C	L	MRSA	159	ND	ND
Dormanesh et al. (2015)	Iran	DD	C	L	MRSA	32	ND	ND
Larsen et al. (2015)	Denmark	DD	E	L	MRSA	56	ND	ND
Valle et al. (2016)	Philippines	AM	C	L	MRSA	3	ND	ND
Guo et al. (2021)	China	DD	C	L	MRSA	65	ND	ND
Tekeli et al. (2016)	Turkey	AM	C	L	MRSA	131	ND	ND
Xie et al. (2016)	China	DD	C	L	MRSA	58	ND	ND
Nasirian et al. (2018)	Iran	DD	C	L	MRSA	88	ND	ND
Chauhan et al. (2021)	India	DD	C	H	MRSA	15	ND	ND

(Continued)

TABLE 1 (Continued)

Author	Countries	AST method	AST guideline	Quality group	Species	Erythromycin	Clarithromycin	Azithromycin
Livermore et al. (2015)	ND	MM	E	L	MRSA	123	ND	ND
Modukuru et al. (2021)	India	DD	C	H	MRSA	174	ND	ND
Ukpai et al. (2021)	Nigeria	DD	MG	L	MRSA	122	ND	ND
Pushkar et al. (2022)	India	DD	C	L	MRSA	31	ND	ND
Islam and Shamsuzzaman (2015)	Bangladesh	DD	C	L	MRSA	ND	ND	11
Preeja et al. (2021)	India	DD	C	L	MRSA	54	ND	ND
Yao et al. (2023)	China	AM	C	L	MRSA	173	ND	ND
Conceicao et al. (2021)	Portugal	DD	E	L	MRSA	92	ND	ND
Raut et al. (2017)	Nepal	DD	C	L	MRSA	40	ND	ND
Pradhan et al. (2021)	Nepal	DD	C	L	MRSA	964	ND	ND
El-Baghdady et al. (2020)	Egypt	DD	C	L	MRSA	94	ND	ND
Liang et al. (2018)	China	AM	C	L	MRSA	51	ND	ND
Fateh Amirkhiz et al. (2015)	Iran	DD	C	L	MRSA	ND	ND	30
Chen P. Y. et al. (2021)	Taiwan	MM	C	L	MRSA	233	ND	ND
Taherirad et al. (2016)	Iran	DD	C	L	MRSA	36	ND	ND
Bhattacharya et al. (2016)	India	DD	C	L	MRSA	ND	180	ND
Ukpai et al. (2021)	Nigeria	DD	C	L	MRSA	122	ND	ND
Leibler et al. (2017)	United States	AM	C	L	MRSA	13	ND	ND
Lee et al. (2020)	Taiwan	MIC	C	L	MRSA	889	ND	ND
Kong et al. (2018)	China	DD	C	L	MRSA	5	ND	ND
Petrović et al. (2016)	Serbia	DD	C	L	MRSA	27	ND	ND
de Benito et al. (2018)	Spain	DD	C	L	MRSA	45	ND	ND
Goudarzi et al. (2018)	Iran	DD	C	L	MRSA	50	ND	ND
Ouidri (2018)	Algeria	DD	C	L	MRSA	9	ND	ND
Esmaeili Benvidi et al. (2017)	Iran	DD	C	L	MRSA	59	ND	ND
Yitayeh et al. (2021)	Ethiopia	DD	C	L	*S. Saprophiticus*	12	ND	ND

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10.3389/fmicb.2025.1524452

TABLE 1 (Continued)

Author	Countries	AST method	AST guideline	Quality group	Species	Erythromycin	Clarithromycin	Azithromycin
Asbell et al. (2015)	United States	MM	C	L	MRCONS	ND	ND	120
Sheeba et al. (2021)	India	ND	C	L	CONS	182	ND	ND
Almasri et al. (2016)	Palestinian Territories	MIC	C	L	*Staphylococcus Spp*	131	ND	ND
Maleki et al. (2019)	Iran	DD	C	L	*S. aureus*	18	ND	ND
Peng et al. (2021)	China	AM	C	L	*S. haemolyticus*	35	ND	ND
Al-Naqshbandi et al. (2019)	Iraq	AM	ND	L	*S. haemolyticus*	30	ND	ND
Pfaller et al. (2020)	ND	MM	E	L	*S. haemolyticus*	159	ND	ND
Bensaci and Sahm (2017)	United States	MM	E	L	*S. haemolyticus*	406	ND	ND
Khan et al. (2017)	Qatar	AM	C	L	*S. haemolyticus*	19	ND	ND
Khan et al. (2017)	India	DD	C	L	*S. haemolyticus*	4	ND	ND
Murugesan et al. (2015)	India	DD	C	L	*S. haemolyticus*	9	ND	ND
Bolatchiev (2020)	Russia	DD	E	L	*S. haemolyticus*	19	ND	ND
Belbase et al. (2017)	Nepal	DD	C	L	*S. haemolyticus*	34	ND	ND
Junaidi et al. (2023)	Malaysia	DD	C	L	*S. haemolyticus*	53	ND	61
Zamanian et al. (2021)	Iran	DD	C	L	*S. haemolyticus*	1,010	ND	ND
Ackers-Johnson et al. (2021)	Uganda	DD	E	L	*S. haemolyticus*	14	ND	ND
Kang and Kim (2019)	South Korea	ND	ND	L	*S. haemolyticus*	10	ND	ND
Al-Habsi et al. (2020)	Oman	AM	C	L	*S. haemolyticus*	2	ND	ND
Skender et al. (2022)	India	MIC	C	L	*S. haemolyticus*	1	ND	ND
Solomon and Salaudeen (2021)	Nigeria	DD	C	L	*S. haemolyticus*	7	ND	ND
Saxena et al. (2019)	India	DD	C	L	*S. haemolyticus*	3	ND	ND
Xu et al. (2019)	China	DD	C	L	*S. haemolyticus*	2	ND	ND
Talapan et al. (2023)	Romania	MM	C	L	*S. haemolyticus*	835	ND	ND
Cavanagh et al. (2016)	Norway	MIC	E	L	*S. haemolyticus*	29	ND	ND
Guo et al. (2019)	China	DD	C	L	*S. haemolyticus*	184	ND	ND
Shittu et al. (2015)	Nigeria	DD	C	L	*S. haemolyticus*	10	ND	ND
Bishr et al. (2021)	Egypt	MM	C	L	*S. haemolyticus*	19	ND	18

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10.3389/fmicb.2025.1524452

TABLE 1 (Continued)

Author	Countries	AST method	AST guideline	Quality group	Species	Erythromycin	Clarithromycin	Azithromycin
Getaneh et al. (2021)	Ethiopia	DD	C	L	*S. haemolyticus*	30	ND	ND
Mutonga et al. (2019)	Kenya	AM	ND	L	*S. haemolyticus*	3	ND	ND
Kumar et al. (2018)	India	ND	C	L	*S. haemolyticus*	29	ND	ND
Belete (2020)	Ethiopia	DD	C	L	*S. haemolyticus*	7	ND	ND
Bhavana et al. (2019)	India	DD	C	L	*S. haemolyticus*	6	ND	ND
Peterside et al. (2015)	Nigeria	DD	C	L	*S. haemolyticus*	27	ND	ND
Al-Taweel (2020)	Iraq	DD	C	L	*S. haemolyticus*	9	ND	ND
Hasanvand et al. (2019)	Iran	DD	C	L	*S. haemolyticus*	32	ND	ND
Wangai et al. (2019)	Kenya	DD	C	L	*S. haemolyticus*	29	ND	ND
Lee et al. (2019)	ND	MM	C	L	*S. haemolyticus*	31	ND	ND
Sutter et al. (2016)	United States	DD	C	L	*S. haemolyticus*	24,213	ND	ND
Luo et al. (2020)	China	AM	C	L	*S. haemolyticus*	67	ND	25
Tang et al. (2020)	ND	MIC	C	L	*S. haemolyticus*	21	ND	ND
Suneel Kumar et al. (2021)	India	DD	C	L	*S. haemolyticus*	9	ND	ND
Rahimi (2016)	Iran	DD	C	L	*S. haemolyticus*	87	ND	ND
Mehreen et al. (2018)	Pakistan	DD	C	L	*S. haemolyticus*	49	ND	ND
McHardy et al. (2017)	United States	MM	C	L	*S. haemolyticus*	193	ND	ND
Asaad et al. (2016)	ND	AM	C	L	*S. haemolyticus*	23	ND	ND
Javidnia et al. (2015)	Iran	DD	C	L	*S. haemolyticus*	16	ND	ND
Rampelotto et al. (2022)	Brazil	MM	C	L	*S. haemolyticus*	167	ND	ND
Choi et al. (2019)	South Korea	AM	C	L	*S. haemolyticus*	5	ND	ND
Li et al. (2018)	China	MIC	C	L	*S. haemolyticus*	216	ND	ND
Bai et al. (2019)	China	AM	C	L	*S. haemolyticus*	134	ND	ND
Aguinagalde et al. (2015)	India	MIC	E	L	*S. haemolyticus*	ND	190	199
Diriba et al. (2020)	Ethiopia	DD	C	L	*S. haemolyticus*	30	9	ND
Shidiki et al. (2018)	Egypt	DD	ND	H	*S. haemolyticus*	100	ND	ND
Selim et al. (2022)	Saudi Arabia	DD	ND	L	*S. haemolyticus*	100	ND	ND
Sultan et al. (2015)	India	DD	C	L	*S. haemolyticus*	32	ND	ND
Manandhar et al. (2021)	Nepal	DD	C	L	*S. haemolyticus*	127	ND	ND

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10.3389/fmicb.2025.1524452

TABLE 1 (Continued)

Author	Countries	AST method	AST guideline	Quality group	Species	Erythromycin	Clarithromycin	Azithromycin
Mahfouz et al. (2023)	Egypt	DD	C	L	*S. haemolyticus*	52	51	52
Yang et al. (2017)	China	AM	ND	S	*S. haemolyticus*	12	12	12
Soroush et al. (2016)	Iran	DD	C	S	*S. haemolyticus*	68	ND	ND
Hailegiyorgis et al. (2018)	Ethiopia	DD	C	L	*S. haemolyticus*	4	ND	ND
Mesbah Elkammoshi et al. (2016)	Malaysia	DD	C	L	*S. haemolyticus*	179	ND	ND
Agarwal et al. (2016)	India	DD	C	L	*S. haemolyticus*	10	ND	ND
Mama et al. (2019)	Ethiopia	DD	C	L	*S. haemolyticus*	22	ND	ND
Gungor et al. (2021)	Turkey	MIC	E	L	*S. haemolyticus*	36	ND	ND
Ramakrishna et al. (2021)	India	DD	C	L	*S. haemolyticus*	171	ND	ND
Wang et al. (2017)	China	AM	C	L	*S. haemolyticus*	4	ND	ND
Salarvand et al. (2023)	Iran	DD	ND	L	*S. haemolyticus*	88	ND	ND
Firoozeh et al. (2020)	Iran	DD	C	L	*S. haemolyticus*	17	ND	ND
Liu et al. (2015)	China	MIC	C	L	*S. haemolyticus*	116	ND	ND
Fu et al. (2020)	China	AM	C	L	*S. haemolyticus*	189	ND	ND
Akpaka et al. (2017)	Germany	DD	C	L	*S. haemolyticus*	124	ND	ND
Svent-Kucina et al. (2016)	Slovenia	DD	C	L	*S. haemolyticus*	8	ND	ND
Goudarzi et al. (2020)	Iran	DD	C	L	*S. haemolyticus*	86	ND	ND
Fasihi et al. (2016)	Iran	DD	C	L	*S. haemolyticus*	94	ND	ND
Okuda et al. (2016)	Gabon	MIC	E	L	*S. haemolyticus*	8	ND	ND
Ahangarzadeh Rezaee et al. (2016)	Iran	ND	ND	L	*S. haemolyticus*	104	ND	ND
Biset et al. (2020)	Ethiopia	DD	C	L	*S. haemolyticus*	2	ND	ND
Olufunmiso et al. (2017)	Nigeria	DD	C	L	*S. haemolyticus*	122	ND	ND
Tahbaz et al. (2019)	Iran	DD	C	L	*S. haemolyticus*	19	ND	ND
Rukan et al. (2021)	Pakistan	DD	C	L	*S. haemolyticus*	68	ND	ND
Eibach et al. (2017)	Ghana	DD	E	S	*S. haemolyticus*	14	ND	ND
Dayie et al. (2021)	Ghana	DD	C	L	*S. haemolyticus*	5	ND	ND

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10.3389/fmicb.2025.1524452

TABLE 1 (Continued)

Author	Countries	AST method	AST guideline	Quality group	Species	Erythromycin	Clarithromycin	Azithromycin
Salah et al. (2021)	Yemen	AM	ND	L	*S. haemolyticus*	4	ND	ND
Weldu et al. (2020)	Ethiopia	DD	ND	L	*S. haemolyticus*	7	ND	ND
Wan et al. (2016)	Taiwan	MIC	C	L	*S. haemolyticus*	274	ND	ND
John et al. (2023)	Nigeria	DD	C	L	*S. haemolyticus*	6	6	ND
Duncan et al. (2016)	United States	ND	E	L	*S. haemolyticus*	548	ND	ND
Saini et al. (2021)	India	DD	C	L	*S. haemolyticus*	14	ND	ND
Sanchez et al. (2020)	Spain	ND	C	L	*S. haemolyticus*	81	ND	ND
Chen P. F. et al. (2021)	China	MIC	C	L	*S. haemolyticus*	27	ND	ND
Almohammady et al. (2020)	Egypt	DD	C	L	*S. haemolyticus*	15	ND	ND
Iliya et al. (2020)	Kenya	DD	C	L	*S. haemolyticus*	26	ND	ND
Abouelnour et al. (2019)	Egypt	DD	C	S	*S. haemolyticus*	107	ND	ND
Boncompain et al. (2023)	Argentina	DD	C	L	*S. haemolyticus*	7	ND	ND
Al-Tamimi et al. (2021)	Jordan	DD	C	L	*S. haemolyticus*	57	ND	ND
Ullah et al. (2022)	Pakistan	DD	C	S	*S. haemolyticus*	5	ND	ND
Khan et al. (2015)	Nepal	DD	C	L	*S. haemolyticus*	4	ND	ND
Shivappa et al. (2018)	Turkey	DD	C	L	*S. haemolyticus*	7	ND	ND
Muhammad et al. (2020)	Pakistan	DD	C	L	*S. haemolyticus*	ND	ND	14
Kahsay et al. (2018)	Ethiopia	DD	C	L	*S. haemolyticus*	6	ND	ND
Liang et al. (2018)	China	AM	C	L	*S. haemolyticus*	26	ND	ND
Zhang et al. (2015)	China	DD	C	L	*S. haemolyticus*	58	ND	ND
El-Kersh et al. (2016)	Saudi Arabia	AM	C	L	*S. haemolyticus*	5	ND	ND
Fateh Dizji et al. (2023)	Iran	DD	C	L	*S. haemolyticus*	45	ND	ND
Baz et al. (2021)	Egypt	DD	ND	L	*S. haemolyticus*	39	38	ND
Vijay and Dalela (2016)	India	DD	C	L	*S. haemolyticus*	14	ND	ND
AL-Salihi et al. (2023)	Iraq	DD	C	L	*S. haemolyticus*	6	ND	ND
Joachim et al. (2017)	Tanzania	DD	C	L	*S. haemolyticus*	11	ND	ND
Goes et al. (2021)	Brazil	DD	C	L	*S. haemolyticus*	29	ND	ND

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10.3389/fmicb.2025.1524452

TABLE 1 (Continued)

Author	Countries	AST method	AST guideline	Quality group	Species	Erythromycin	Clarithromycin	Azithromycin
Sapkota et al. (2019)	Nepal	DD	C	L	*S. haemolyticus*	16	ND	ND
Abdulmanea et al. (2023)	Saudi Arabia	AM	C	L	*S. haemolyticus*	30	ND	9
Adhikari et al. (2023)	Nepal	DD	C	L	*S. haemolyticus*	226	ND	ND
Zhou et al. (2020)	China	AM	C	L	*S. haemolyticus*	17	ND	ND
Kim et al. (2020)	South Korea	DD	C	L	*S. haemolyticus*	ND	ND	14
El-Amir et al. (2019)	Egypt	DD	C	L	*S. haemolyticus*	ND	ND	2
Arabestani et al. (2018)	Iran	DD	C	L	*S. haemolyticus*	160	ND	ND
Roden et al. (2019)	ND	ND	ND	L	*S. haemolyticus*	5	ND	ND
Al-Humaidan et al. (2015)	Saudi Arabia	DD	C	L	*S. haemolyticus*	5	ND	ND
Mansson et al. (2015)	Sweden	DD	E	L	*S. haemolyticus*	6	ND	ND
Garza-Gonzalez et al. (2019)	Mexico	DD	C	L	*S. haemolyticus*	871	ND	ND
Bhatt et al. (2016)	China	DD	C	L	*S. haemolyticus*	81	ND	ND
Maina et al. (2016)	Kenya	AM	C	L	*S. haemolyticus*	36	ND	ND
Wurster et al. (2018)	United States	ND	C	L	*S. haemolyticus*	107	ND	ND
Cavalcante et al. (2020)	Brazil	ND	ND	H	*S. haemolyticus*	9	ND	ND
Taha et al. (2019)	Sweden	DD	E	L	*S. haemolyticus*	506	ND	ND
Kurup and Ansari (2019)	Guyana	DD	C	L	*S. haemolyticus*	14	ND	ND
Kulshrestha et al. (2021)	India	DD	C	S	*S. haemolyticus*	25	ND	ND
Mottola et al. (2016)	Portugal	MIC	C	L	*S. haemolyticus*	8	ND	ND
Lenart-Boron et al. (2016)	Poland	DD	E	L	*S. haemolyticus*	23	ND	ND
Uyar Güleç et al. (2020)	Turkey	MIC	C	L	*S. haemolyticus*	45	ND	ND
Al-Qaisi and Al-Salmani (2020)	Iraq	DD	C	S	*S. haemolyticus*	50	ND	ND
Kpeli et al. (2016)	Ghana	ND	C	L	*S. haemolyticus*	15	ND	ND
Demir et al. (2020)	Turkey	DD	E	L	*S. haemolyticus*	30	ND	ND
Singh and Hota (2019)	India	AM	C	L	*S. haemolyticus*	8	ND	ND

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10.3389/fmicb.2025.1524452

TABLE 1 (Continued)

Author	Countries	AST method	AST guideline	Quality group	Species	Erythromycin	Clarithromycin	Azithromycin
Dilnessa and Bitew (2016)	Ethiopia	DD	C	L	*S. haemolyticus*	3	ND	ND
Rajkumar et al. (2017)	India	DD	C	L	*S. haemolyticus*	3,058	ND	ND
Hoffmann et al. (2015)	Austria	MM	E	L	*S. haemolyticus*	73	ND	74
Kumar and Shetty (2021)	India	DD	C	L	*S. haemolyticus*	43	ND	ND
Ahmad et al. (2020)	India	DD	C	L	*S. haemolyticus*	ND	ND	3
Juda et al. (2016)	Poland	DD	E	L	*S. haemolyticus*	75	ND	ND
Ibadin et al. (2017)	ND	DD	C	L	*S. haemolyticus*	48	ND	ND
Tsige et al. (2020)	Ethiopia	DD	ND	L	*S. haemolyticus*	25	ND	ND
Banawas et al. (2023)	Saudi Arabia	MM	ND	L	*S. haemolyticus*	27	ND	ND
Mascaro et al. (2019)	Italy	DD	E	L	*S. aureus*	16	ND	ND
Lennartz et al. (2019)	Germany	DD	E	L	*S. aureus*	42	ND	ND
Al Zebary et al. (2017)	Iraq	DD	NCCLS	L	*S. aureus*	10	ND	ND
Sakabe and Del Fiol Fde (2016)	Brazil	ND	ND	L	*S. aureus*	5	ND	ND
Lin et al. (2018)	China	DD	C	L	*S. aureus*	28	ND	ND
Doss et al. (2017)	Egypt	DD	C	L	*S. aureus*	13	7	10
Liang et al. (2023)	China	AM	C	L	MSSA	127	ND	ND
Oydanich et al. (2017)	United States	AM	C	L	*S. aureus*	62	ND	ND
Gajdacs et al. (2021)	Hungary	ND	E	S	*Staphylococcus Spp*	ND	ND	67
Mostafa et al. (2015)	Iran	DD	C	L	*S. aureus*	95	ND	69
Soumya et al. (2017)	India	DD	ND	S	*S. epidermidis*	152	ND	ND
Parastan et al. (2020)	Iran	DD	C	L	*S. aureus*	93	ND	ND
Farah et al. (2019)	Saudi Arabia	MIC	C	L	*S. aureus*	507	ND	ND
Sotoudeh Anvari et al. (2015)	Iran	DD	C	L	*S. epidermidis*	13	ND	ND

AST method (Multiple Method, MM), Disk Diffusion (DD), Minimum Inhibitory Concentration (MIC) method, and Automated Method (AM). Publication Bias: Risk (S), Low Risk (L), High Risk (H). AST guideline: CLSI: C, EUCAST: E.

10.3389/fmicb.2025.1524452

TABLE 2 Meta-analysis statistics of worldwide antibiotic resistance in *Staphylococcus* spp.

Antibiotic	K (n, N)	Proportion 95%CI (LCI, HCI)	I^2	P1	P2
Erythromycin	721 (144,746, 293,411)	0.573 (0.556, 0.590)	98.29%	$p < 0.001$	$p < 0.001$
Clarithromycin	30 (4,015, 8,045)	0.526 (0.380, 0.668)	98.76%	$p = 0.727$	$p < 0.001$
Azithromycin	83 (5,227, 10,553)	0.579 (0.514, 0.641)	96.50%	$p = 0.017$	$p < 0.001$

K: Number of reports, n: Number of resistant isolates, N: Number of total isolates, LCI: 95% Lower Limit Confidence Interval, HCI: 95% Higher Limit Confidence Interval, P1: *p*-value of difference from zero resistance rate, P2: *p*-value of heterogeneity between reports.

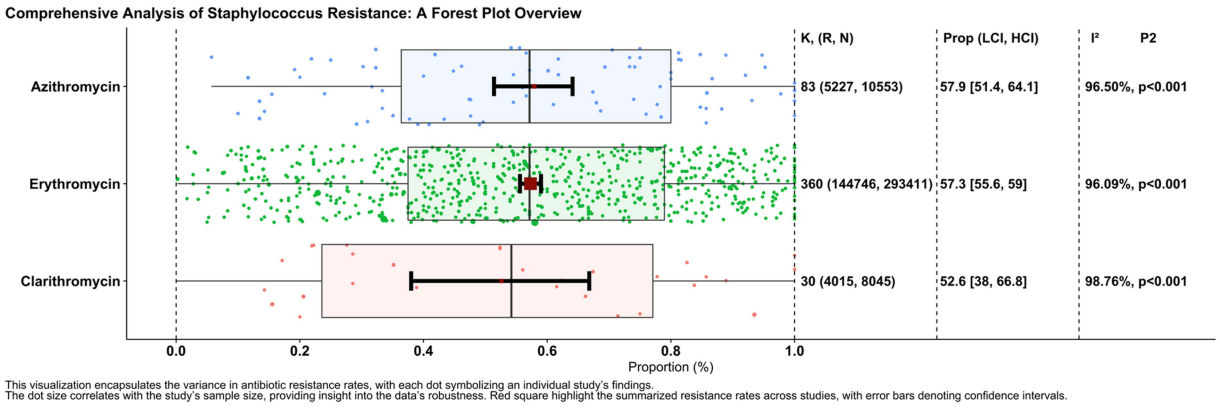

FIGURE 2
Forest plot of resistance rates for macrolide antibiotics against *Staphylococcus*: the forest plot summarizes the resistance rates of *Staphylococcus* species to Azithromycin, Erythromycin, and Clarithromycin across various studies. Each dot represents an individual study's data point, with red squares indicating pooled resistance estimates and black bars showing confidence intervals.

TABLE 3 Evaluation of publication bias in meta-analysis.

Antibiotic	Egger test	Begg test	Fail and safe	Trim and Fill
Erythromycin	$p < 0.001$	$p = 0.837$	104,799	0.501 (0.483, 0.518)
Clarithromycin	$p = 0.890$	$p = 0.432$	0	0.526 (0.380, 0.668)
Azithromycin	$p < 0.001$	$p = 0.264$	473	0.519 (0.455, 0.582)

This table provides a comprehensive assessment of potential publication bias in the meta-analysis using a range of statistical techniques. Included are statistics generated from Egger's Method, Begg's Method, the Fail-Safe N (NFS), and the Trim-and-Fill Method. These methods are applied to investigate the presence of bias and its impact on the meta-analysis results, ensuring the robustness and reliability of the findings.

Using the trim-and-fill method, the adjusted proportion was 0.501 (95% CI: 0.483–0.518). Analysis of the studentized residuals identified several studies with values greater than 3.979, suggesting potential outliers within the model. After excluding these potential outliers, the proportion was 0.501 (95% CI: 0.483–0.518). Cook's distance analysis also indicated that several studies were overly influential. After removing these influential studies, the proportion remained unchanged at 0.501 (95% CI: 0.483–0.518). Both the rank correlation test and the regression test suggested a potential funnel plot asymmetry ($p < 0.001$ and $p = 0.018$, respectively) (Table 3).

3.2.2 Prevalence of clarithromycin resistance

The clarithromycin resistance analysis included Eight forty-five isolates from 30 studies. The estimated average proportion based on the random-effects model was 0.526 (95%CI, 0.380, 0.668). Therefore, the average outcome was not significantly different from zero ($z = 0.349$, $p = 0.727$). According to the Q test, the outcomes were heterogeneous ($Q(29) = 2347.241$, $I^2 = 98.76\%$, $p < 0.001$). A forest plot showing the observed outcomes and the estimate based on the random effects model is shown in Figure 2. With the fill and trim method implementation, the proportion changed to 0.526 (95%CI, 0.380, 0.668). Examination of the studentized residuals revealed that none of the studies had values greater than 3.144. Hence, there was no indication of outliers in the context of this model. According to Cook's distance, none of the studies could be considered overly influential. Neither the rank correlation nor the regression test indicated funnel plot asymmetry ($p = 0.432$ and $p = 0.890$, respectively) (Figure 3).

3.2.3 Prevalence of azithromycin resistance

The analysis of azithromycin resistance included data from 83 studies with 10,553 isolates. Using a random effects model, the estimated mean proportion was 0.579 (95% CI: 0.514, 0.641), indicating that the mean outcome differed significantly from zero ($z = 2.385$, $p = 0.017$). The heterogeneity of the outcomes was confirmed by the Q-test ($Q(82) = 2342.061$, $I^2 = 96.50\%$, $p < 0.001$). After using the fill-and-trim method, the proportion was adjusted to

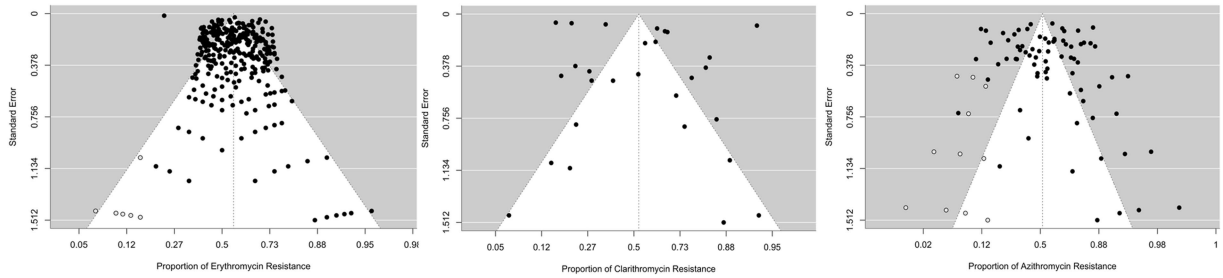

FIGURE 3
Funnel plots for publication bias analysis: funnel plots assessing the presence of publication bias in resistance studies for Erythromycin (left), Clarithromycin (middle), and Azithromycin (right). Symmetrical distributions indicate minimal bias, whereas asymmetries may suggest potential bias.

0.519 (95% CI: 0.455, 0.582). Analysis of the studentized residuals showed no study exceeded a value of 3.431, indicating no outliers in the model. Furthermore, Cook's distance analysis indicated that no single study had an undue influence on the results. While the regression test revealed funnel plot asymmetry ($p < 0.001$), the rank correlation test did not reveal significant asymmetry ($p = 0.264$).

3.3 Subgroup analysis

This section provides a detailed summary of the subgroup analyses performed on antimicrobial resistance. The full dataset is available in Table 4. The analyses examined variations in resistance rates across geographic regions, antimicrobial susceptibility testing (AST) methods, time trends, and study quality.

3.3.1 Subgroup analysis based on countries

Subgroup analysis revealed statistically significant differences in antimicrobial resistance prevalence between countries for azithromycin, clarithromycin, and erythromycin. Austria had the lowest resistance rate for azithromycin, with a prevalence of 13.5%, while Australia had the highest resistance rate at 92.1%. Pakistan had the lowest resistance rate (14.3%) for clarithromycin, while China had the highest (72.9%). The Philippines had the lowest resistance rate of 2.8% for erythromycin, while Canada had the highest resistance rate of 97.4% (Figure 4).

3.3.2 Subgroup analysis based on continents

Subgroup analysis revealed statistically significant differences in antimicrobial resistance prevalence between continents, particularly for azithromycin and erythromycin. Europe had the lowest resistance rate for azithromycin, with a prevalence of 31.1%, while Oceania had the highest resistance rate of 92.1%. Similarly, Europe had the lowest resistance rate for erythromycin, with a prevalence of 40.7%, while Oceania had the highest resistance rate at 72% (Figure 5A).

3.3.3 Subgroup analysis based on AST guideline

The subgroup analysis identified statistically significant differences in antibiotic resistance prevalence, including erythromycin, between different antimicrobial susceptibility testing (AST) guidelines. For erythromycin, the NCCLS guideline showed the lowest resistance rate with a prevalence of 35.3%, while the BSAC guideline showed the highest resistance rate at 82.3% (Figure 5B).

3.3.4 Subgroup analysis based on the AST method

Subgroup analysis revealed a statistically significant disparity in the prevalence of antibiotic resistance, including erythromycin, among the various AST methods. For erythromycin, the AST method with the lowest resistance rate was Disk Diffusion, with a prevalence of 55.7%. Conversely, the AST method, with the highest resistance rate, was automated, with a prevalence rate of 66% (Figure 5C).

3.3.5 Subgroup analysis based on species

Subgroup analysis revealed statistically significant differences in antibiotic resistance prevalence among different species, including erythromycin. For erythromycin, MSCoNS had the lowest resistance rate with a prevalence of 14.5%, while VISA had the highest resistance rate with a prevalence of 95.8% (Figure 5D).

3.3.6 Subgroup analysis based on coagulase

Subgroup analysis revealed statistically significant differences in the prevalence of antibiotic resistance, including erythromycin, among different coagulase types. For erythromycin, the coagulase type with the lowest resistance rate was ND, with a prevalence of 52.2%. In contrast, the highest resistance rate was observed for CoNS, with a prevalence of 63.2% (Figure 5E).

3.3.7 Subgroup analysis based on year-group

The subgroup analysis identified statistically significant differences in antibiotic resistance prevalence among different groups, including clarithromycin and erythromycin. For clarithromycin, the period with the lowest resistance rate was 2020–2023, with a prevalence of 40.5%, while the highest resistance rate was observed in 2015–2019, with a prevalence of 67.4%. Similarly, for erythromycin, the lowest resistance rate occurred during 2020–2023, with a prevalence of 55%, while the highest resistance rate was observed during 2015–2019, with a prevalence of 59.6% (Figure 5F).

3.4 Meta-regression

Meta-regression analysis was performed to examine the relationship between antimicrobial resistance rates and year of reporting. No statistically significant correlation was observed for erythromycin (r = −0.041, p-value = 0.007, 95% CI [−0.071, −0.011])

TABLE 4 Meta-analysis statistics of worldwide antibiotic resistance in staphylococcus spp. and subgroup analysis results.

Category	Subgroup	K (n, N)	Proportion 95%CI (LCI, HCI)	I^2	P1	P2	P3
Erythromycin							
Overall	ND	360 (144,746, 293,411)	0.573 (0.556, 0.590)	96.09%	$p < 0.001$	$p < 0.001$	NA
Countries	China	105 (11,791, 18,008)	0.731 (0.692, 0.766)	96.02%	$p < 0.001$	$p < 0.001$	p < 0.001
	Nepal	24 (3,996, 6,515)	0.620 (0.568, 0.669)	92.18%	$p < 0.001$	$p < 0.001$	
	Rwanda	1 (25, 138)	0.181 (0.125, 0.254)	0.00%	$p < 0.001$	$p > 0.999$	
	Iran	85 (5,568, 9,107)	0.627 (0.579, 0.671)	93.57%	$p < 0.001$	$p < 0.001$	
	Kuwait	4 (4,805, 11,978)	0.421 (0.370, 0.474)	94.75%	$p = 0.004$	$p < 0.001$	
	Ethiopia	35 (582, 1,493)	0.431 (0.345, 0.522)	86.72%	$p = 0.137$	$p < 0.001$	
	India	79 (7,667, 14,709)	0.557 (0.514, 0.599)	94.19%	$p = 0.010$	$p < 0.001$	
	Cameroon	1 (111, 201)	0.552 (0.483, 0.620)	0.00%	$p = 0.139$	$p > 0.999$	
	South Korea	11 (1,155, 1786)	0.576 (0.333, 0.787)	97.89%	$p = 0.550$	$p < 0.001$	
	Poland	8 (333, 873)	0.350 (0.235, 0.486)	91.39%	$p = 0.031$	$p < 0.001$	
	Spain	13 (12,781, 39,342)	0.425 (0.304, 0.556)	98.27%	$p = 0.262$	$p < 0.001$	
	Malaysia	8 (1,587, 2070)	0.704 (0.421, 0.886)	98.64%	$p = 0.151$	$p < 0.001$	
	Kenya	8 (475, 766)	0.517 (0.323, 0.705)	94.92%	$p = 0.872$	$p < 0.001$	
	United States	28 (48,494, 84,187)	0.558 (0.495, 0.618)	99.50%	$p = 0.070$	$p < 0.001$	
	Australia	2 (199, 477)	0.720 (0.121, 0.979)	93.84%	$p = 0.527$	$p < 0.001$	
	Hungary	1 (122, 153)	0.797 (0.726, 0.854)	0.00%	$p < 0.001$	$p > 0.999$	
	Nigeria	23 (857, 1,353)	0.626 (0.523, 0.718)	89.63%	$p = 0.017$	$p < 0.001$	
	Taiwan	7 (2,849, 5,223)	0.724 (0.331, 0.933)	99.71%	$p = 0.257$	$p < 0.001$	
	Colombia	2 (144, 353)	0.260 (0.055, 0.681)	94.04%	$p = 0.255$	$p < 0.001$	
	Libya	1 (30, 32)	0.938 (0.782, 0.984)	0.00%	$p < 0.001$	$p > 0.999$	
	Switzerland	4 (127, 243)	0.536 (0.457, 0.613)	21.30%	$p = 0.377$	$p = 0.283$	
	Pakistan	9 (470, 762)	0.703 (0.482, 0.857)	95.53%	$p = 0.070$	$p < 0.001$	
	Eritrea	2 (14, 102)	0.159 (0.067, 0.331)	60.43%	$p < 0.001$	$p = 0.112$	
	Oman	2 (12, 60)	0.194 (0.089, 0.371)	32.07%	$p = 0.002$	$p = 0.225$	
	Croatia	1 (523, 542)	0.965 (0.946, 0.978)	0.00%	$p < 0.001$	$p > 0.999$	
	Brazil	17 (1,013, 1740)	0.546 (0.436, 0.651)	93.59%	$p = 0.412$	$p < 0.001$	
	Ghana	11 (133, 833)	0.165 (0.117, 0.226)	74.51%	$p < 0.001$	$p < 0.001$	

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10.3389/fmicb.2025.1524452

TABLE 4 (Continued)

Category	Subgroup	K (n, N)	Proportion 95%CI (LCI, HCI)	I^2	P1	P2	P3
	Denmark	2 (185, 1856)	0.182 (0.030, 0.614)	99.08%	$p = 0.134$	$p < 0.001$	
	Japan	2 (216, 223)	0.966 (0.931, 0.983)	0.00%	$p < 0.001$	$p = 0.431$	
	Philippines	1 (3, 108)	0.028 (0.009, 0.083)	0.00%	$p < 0.001$	$p > 0.999$	
	Thailand	2 (39, 43)	0.900 (0.761, 0.962)	0.00%	$p < 0.001$	$p = 0.431$	
	Palestinian Territories	5 (539, 870)	0.569 (0.452, 0.680)	90.18%	$p = 0.248$	$p < 0.001$	
	Turkey	10 (1,371, 2,736)	0.626 (0.464, 0.765)	94.97%	$p = 0.127$	$p < 0.001$	
	Canada	1 (521, 535)	0.974 (0.956, 0.984)	0.00%	$p < 0.001$	$p > 0.999$	
	Israel	2 (274, 451)	0.358 (0.031, 0.906)	98.19%	$p = 0.687$	$p < 0.001$	
	Jordan	5 (124, 170)	0.787 (0.450, 0.943)	89.75%	$p = 0.089$	$p < 0.001$	
	Egypt	16 (987, 1,409)	0.788 (0.689, 0.863)	92.58%	$p < 0.001$	$p < 0.001$	
	Iraq	23 (749, 1,445)	0.565 (0.470, 0.656)	88.97%	$p = 0.177$	$p < 0.001$	
	Saudi Arabia	19 (1,141, 4,320)	0.610 (0.410, 0.778)	97.77%	$p = 0.279$	$p < 0.001$	
	Portugal	7 (295, 590)	0.535 (0.398, 0.666)	87.32%	$p = 0.622$	$p < 0.001$	
	Serbia	1 (27, 50)	0.540 (0.402, 0.672)	0.00%	$p = 0.572$	$p > 0.999$	
	Algeria	2 (18, 72)	0.250 (0.164, 0.362)	0.00%	$p < 0.001$	$p > 0.999$	
	South Africa	5 (208, 400)	0.530 (0.317, 0.733)	90.36%	$p = 0.788$	$p < 0.001$	
	Argentina	5 (86, 181)	0.479 (0.355, 0.605)	59.85%	$p = 0.742$	$p = 0.041$	
	Guyana	2 (52, 72)	0.737 (0.213, 0.967)	92.79%	$p = 0.388$	$p < 0.001$	
	Mexico	7 (1,448, 4,153)	0.522 (0.408, 0.634)	95.37%	$p = 0.702$	$p < 0.001$	
	France	2 (106, 227)	0.270 (0.037, 0.780)	79.93%	$p = 0.389$	$p = 0.026$	
	Qatar	1 (19, 20)	0.950 (0.718, 0.993)	0.00%	$p = 0.004$	$p > 0.999$	
	Russia	1 (19, 27)	0.704 (0.510, 0.844)	0.00%	$p = 0.040$	$p > 0.999$	
	Vietnam	5 (313, 408)	0.763 (0.619, 0.864)	85.59%	$p < 0.001$	$p < 0.001$	
	Afghanistan	1 (11, 98)	0.112 (0.063, 0.191)	0.00%	$p < 0.001$	$p > 0.999$	
	Uganda	4 (182, 303)	0.621 (0.355, 0.830)	88.22%	$p = 0.375$	$p < 0.001$	
	United Arab Emirates	1 (1, 3)	0.333 (0.043, 0.846)	0.00%	$p = 0.571$	$p > 0.999$	
	Italy	7 (664, 1,434)	0.408 (0.301, 0.525)	93.28%	$p = 0.124$	$p < 0.001$	
	Burkina Faso	1 (21, 149)	0.141 (0.094, 0.207)	0.00%	$p < 0.001$	$p > 0.999$	
	Mozambique	1 (84, 236)	0.356 (0.297, 0.419)	0.00%	$p < 0.001$	$p > 0.999$	
	Romania	1 (835, 1,672)	0.499 (0.475, 0.523)	0.00%	$p = 0.961$	$p > 0.999$	

(Continued)

10.3389/fmicb.2025.1524452

TABLE 4 (Continued)

Category	Subgroup	K (n, N)	Proportion 95%CI (LCI, HCI)	I^2	P1	P2	P3
	Norway	2 (58, 375)	0.173 (0.068, 0.373)	92.52%	$p = 0.003$	$p < 0.001$	
	Indonesia	2 (139, 211)	0.645 (0.541, 0.738)	27.49%	$p = 0.007$	$p = 0.240$	
	Kazakhstan	1 (1, 5)	0.200 (0.027, 0.691)	0.00%	$p = 0.215$	$p > 0.999$	
	Tanzania	3 (70, 249)	0.280 (0.133, 0.495)	87.51%	$p = 0.045$	$p < 0.001$	
	United Kingdom	2 (203, 631)	0.392 (0.219, 0.596)	77.49%	$p = 0.298$	$p = 0.035$	
	Tunisia	2 (21, 99)	0.215 (0.028, 0.722)	93.70%	$p = 0.258$	$p < 0.001$	
	Uruguay	1 (5, 100)	0.050 (0.021, 0.115)	0.00%	$p < 0.001$	$p > 0.999$	
	Germany	5 (394, 1,695)	0.283 (0.181, 0.413)	94.22%	$p = 0.002$	$p < 0.001$	
	Slovenia	1 (8, 274)	0.029 (0.015, 0.057)	0.00%	$p < 0.001$	$p > 0.999$	
	Gabon	1 (8, 103)	0.078 (0.039, 0.148)	0.00%	$p < 0.001$	$p > 0.999$	
	Greece	2 (343, 715)	0.398 (0.217, 0.612)	88.85%	$p = 0.350$	$p = 0.003$	
	Yemen	1 (4, 11)	0.364 (0.143, 0.661)	0.00%	$p = 0.372$	$p > 0.999$	
	Austria	2 (146, 1,098)	0.133 (0.114, 0.154)	0.00%	$p < 0.001$	$p > 0.999$	
	Gambia	1 (26, 293)	0.089 (0.061, 0.127)	0.00%	$p < 0.001$	$p > 0.999$	
	Bangladesh	1 (19, 29)	0.655 (0.469, 0.803)	0.00%	$p = 0.100$	$p > 0.999$	
	Niger	1 (4, 10)	0.400 (0.158, 0.703)	0.00%	$p = 0.530$	$p > 0.999$	
	Bulgaria	2 (296, 870)	0.340 (0.309, 0.372)	0.00%	$p < 0.001$	$p > 0.999$	
	Sweden	2 (512, 572)	0.654 (0.031, 0.991)	98.64%	$p = 0.759$	$p < 0.001$	
	Myanmar (Burma)	1 (86, 153)	0.562 (0.483, 0.639)	0.00%	$p = 0.126$	$p > 0.999$	
Continents	Asia	417 (44,949, 81,522)	0.638 (0.616, 0.660)	96.87%	$p < 0.001$	$p < 0.001$	p < 0.001
	Africa	119 (3,856, 8,241)	0.476 (0.423, 0.529)	93.22%	$p = 0.373$	$p < 0.001$	
	ND	54 (26,002, 58,611)	0.535 (0.453, 0.616)	99.54%	$p = 0.399$	$p < 0.001$	
	Europe	66 (17,977, 53,239)	0.407 (0.359, 0.456)	97.82%	$p < 0.001$	$p < 0.001$	
	Americas	63 (51,763, 91,321)	0.544 (0.499, 0.588)	99.08%	$p = 0.057$	$p < 0.001$	
	Oceania	2 (199, 477)	0.720 (0.121, 0.979)	93.84%	$p = 0.527$	$p < 0.001$	
AST Guideline	CLSI	563 (114,948, 218,991)	0.584 (0.565, 0.604)	98.25%	$p < 0.001$	$p < 0.001$	p < 0.001
	EUCAST	67 (24,762, 66,311)	0.430 (0.382, 0.480)	98.71%	$p = 0.006$	$p < 0.001$	
	Multiple Guideline	8 (778, 1,415)	0.507 (0.314, 0.697)	97.26%	$p = 0.946$	$p < 0.001$	
	NCCLS	6 (398, 871)	0.353 (0.200, 0.543)	90.72%	$p = 0.128$	$p < 0.001$	
	ND	74 (3,686, 5,519)	0.660 (0.601, 0.715)	92.23%	$p < 0.001$	$p < 0.001$	

(Continued)

10.3389/fmicb.2025.1524452

TABLE 4 (Continued)

Category	Subgroup	K (n, N)	Proportion 95%CI (LCI, HCI)	I^2	P1	P2	P3
	BSAC	1 (65, 79)	0.823 (0.723, 0.892)	0.00%	$p < 0.001$	$p > 0.999$	
	FMS	1 (4, 10)	0.400 (0.158, 0.703)	0.00%	$p = 0.530$	$p > 0.999$	
	CASFM	1 (105, 215)	0.488 (0.422, 0.555)	0.00%	$p = 0.733$	$p > 0.999$	
AST method	Automate	98 (9,062, 14,658)	0.660 (0.612, 0.705)	95.75%	$p < 0.001$	$p < 0.001$	p = 0.001
	Disk Diffusion	452 (72,252, 128,319)	0.557 (0.537, 0.576)	96.69%	$p < 0.001$	$p < 0.001$	
	MIX	73 (34,775, 77,633)	0.566 (0.507, 0.624)	99.44%	$p = 0.028$	$p < 0.001$	
	MIC	59 (25,047, 65,498)	0.568 (0.510, 0.624)	98.98%	$p = 0.023$	$p < 0.001$	
Species	MRSA	212 (41,180, 58,142)	0.710 (0.679, 0.740)	97.67%	$p < 0.001$	$p < 0.001$	p < 0.001
	S. saprophyticus	2 (91, 181)	0.593 (0.320, 0.819)	74.47%	$p = 0.514$	$p = 0.048$	
	Staphylococcus spp	19 (955, 1997)	0.522 (0.423, 0.619)	92.87%	$p = 0.662$	$p < 0.001$	
	S. hominis	5 (125, 166)	0.751 (0.678, 0.812)	0.00%	$p < 0.001$	$p = 0.448$	
	CoNS	42 (4,066, 7,352)	0.568 (0.505, 0.629)	95.30%	$p = 0.034$	$p < 0.001$	
	S. lugdunensis	4 (236, 1,142)	0.313 (0.144, 0.552)	91.74%	$p = 0.121$	$p < 0.001$	
	S. aureus	342 (92,286, 210,496)	0.496 (0.475, 0.516)	98.33%	$p = 0.680$	$p < 0.001$	
	S. haemolyticus	8 (500, 692)	0.787 (0.544, 0.919)	94.55%	$p = 0.023$	$p < 0.001$	
	S. epidermidis	41 (1953, 2,818)	0.676 (0.601, 0.744)	90.89%	$p < 0.001$	$p < 0.001$	
	MSSA	37 (2,868, 9,758)	0.305 (0.221, 0.404)	98.29%	$p < 0.001$	$p < 0.001$	
	MRCoNS	5 (381, 488)	0.777 (0.526, 0.916)	94.78%	$p = 0.032$	$p < 0.001$	
	MSCoNS	1 (10, 69)	0.145 (0.080, 0.249)	0.00%	$p < 0.001$	$p > 0.999$	
	VSSA	1 (57, 61)	0.934 (0.838, 0.975)	0.00%	$p < 0.001$	$p > 0.999$	
	VISA	1 (11, 11)	0.958 (0.575, 0.997)	0.00%	$p = 0.030$	$p > 0.999$	
	S. capitis	1 (27, 38)	0.711 (0.549, 0.832)	0.00%	$p = 0.012$	$p > 0.999$	
Coagulase	CPS	593 (136,402, 278,468)	0.565 (0.546, 0.584)	98.49%	$p < 0.001$	$p < 0.001$	$p = 0.021$
	CoNS	109 (7,389, 12,946)	0.632 (0.584, 0.677)	95.26%	$p < 0.001$	$p < 0.001$	
	ND	19 (955, 1997)	0.522 (0.423, 0.619)	92.87%	$p = 0.662$	$p < 0.001$	
year group	2020_2023	379 (62,408, 148,526)	0.550 (0.525, 0.575)	98.32%	$p < 0.001$	$p < 0.001$	p = 0.002
	2015_2019	342 (82,338, 144,885)	0.596 (0.575, 0.616)	97.62%	$p < 0.001$	$p < 0.001$	
Clarithromycin							
Overall	ND	30 (4,015, 8,045)	0.526 (0.380, 0.668)	98.76%	$p = 0.727$	$p < 0.001$	NA
Countries	Canada	2 (590, 3,348)	0.179 (0.135, 0.234)	92.92%	$p < 0.001$	$p < 0.001$	p < 0.001

(Continued)

10.3389/fmicb.2025.1524452

TABLE 4 (Continued)

Category	Subgroup	K (n, N)	Proportion 95%CI (LCI, HCI)	I^2	P1	P2	P3
	Japan	4 (2,261, 2,455)	0.660 (0.249, 0.920)	97.28%	$p = 0.462$	$p < 0.001$	
	Egypt	5 (105, 171)	0.590 (0.358, 0.788)	79.21%	$p = 0.452$	$p < 0.001$	
	Iran	3 (28, 77)	0.388 (0.177, 0.651)	78.75%	$p = 0.407$	$p = 0.009$	
	India	5 (896, 1735)	0.612 (0.438, 0.761)	97.37%	$p = 0.205$	$p < 0.001$	
	Kazakhstan	1 (1, 5)	0.200 (0.027, 0.691)	0.00%	$p = 0.215$	$p > 0.999$	
	Nigeria	4 (37, 56)	0.666 (0.407, 0.852)	55.45%	$p = 0.205$	$p = 0.081$	
	Ethiopia	2 (17, 70)	0.244 (0.157, 0.358)	0.00%	$p < 0.001$	$p = 0.589$	
	China	3 (79, 121)	0.729 (0.490, 0.883)	44.92%	$p = 0.060$	$p = 0.163$	
	Pakistan	1 (1, 7)	0.143 (0.020, 0.581)	0.00%	$p = 0.097$	$p > 0.999$	
Continents	Americas	2 (590, 3,348)	0.179 (0.135, 0.234)	92.92%	$p < 0.001$	$p < 0.001$	$p = 0.095$
	Asia	17 (3,266, 4,400)	0.580 (0.404, 0.738)	98.29%	$p = 0.372$	$p < 0.001$	
	Africa	11 (159, 297)	0.529 (0.358, 0.693)	81.76%	$p = 0.747$	$p < 0.001$	
AST Guideline	CLSI	24 (3,467, 7,231)	0.453 (0.291, 0.626)	98.92%	$p = 0.599$	$p < 0.001$	$p = 0.115$
	ND	4 (115, 137)	0.837 (0.765, 0.889)	0.00%	$p < 0.001$	$p = 0.989$	
	EUCAST	2 (433, 677)	0.640 (0.601, 0.677)	8.00%	$p < 0.001$	$p = 0.297$	
AST method	MIX	3 (597, 3,355)	0.192 (0.136, 0.263)	91.13%	$p < 0.001$	$p < 0.001$	p = 0.060
	Disk Diffusion	19 (707, 1,511)	0.503 (0.385, 0.620)	90.51%	$p = 0.964$	$p < 0.001$	
	MIC	6 (2,696, 3,162)	0.614 (0.352, 0.824)	98.76%	$p = 0.396$	$p < 0.001$	
	Automate	2 (15, 17)	0.861 (0.619, 0.959)	0.00%	$p = 0.007$	$p = 0.927$	
Species	MRSA	6 (576, 2,353)	0.607 (0.269, 0.867)	98.70%	$p = 0.552$	$p < 0.001$	$p = 0.582$
	S. aureus	12 (2,630, 3,066)	0.632 (0.422, 0.802)	97.35%	$p = 0.216$	$p < 0.001$	
	MSSA	2 (560, 2,167)	0.273 (0.154, 0.436)	98.16%	$p = 0.008$	$p < 0.001$	
	S. epidermidis	3 (15, 46)	0.560 (0.113, 0.927)	82.89%	$p = 0.837$	$p = 0.003$	
	CoNS	3 (199, 335)	0.320 (0.074, 0.735)	93.00%	$p = 0.404$	$p < 0.001$	
	Staphylococcus spp	3 (29, 57)	0.439 (0.132, 0.802)	85.03%	$p = 0.772$	$p = 0.001$	
	S. lugdunensis	1 (6, 21)	0.286 (0.134, 0.508)	0.00%	$p = 0.058$	$p > 0.999$	
Coagulase	CPS	20 (3,766, 7,586)	0.581 (0.398, 0.745)	99.15%	$p = 0.385$	$p < 0.001$	$p = 0.570$
	CoNS	7 (220, 402)	0.392 (0.180, 0.655)	89.36%	$p = 0.426$	$p < 0.001$	
	ND	3 (29, 57)	0.439 (0.132, 0.802)	85.03%	$p = 0.772$	$p = 0.001$	
Year Group	2020_2023	17 (946, 3,990)	0.405 (0.281, 0.543)	96.40%	$p = 0.177$	$p < 0.001$	p = 0.032

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10.3389/fmicb.2025.1524452

TABLE 4 (Continued)

Category	Subgroup	K (n, N)	Proportion 95%CI (LCI, HCI)	I^2	P1	P2	P3
	2015_2019	13 (3,069, 4,055)	0.674 (0.467, 0.830)	98.65%	$p = 0.098$	$p < 0.001$	
Azithromycin							
Overall	ND	83 (5,227, 10,553)	0.579 (0.514, 0.641)	96.50%	$p = 0.017$	$p < 0.001$	NA
Countries	United States	6 (630, 1,511)	0.452 (0.296, 0.618)	96.64%	$p = 0.577$	$p < 0.001$	p = 0.009
	Nepal	2 (94, 162)	0.554 (0.402, 0.696)	65.84%	$p = 0.487$	$p = 0.087$	
	Spain	2 (170, 883)	0.348 (0.033, 0.894)	99.34%	$p = 0.656$	$p < 0.001$	
	India	17 (1910, 3,360)	0.575 (0.458, 0.685)	96.84%	$p = 0.207$	$p < 0.001$	
	China	8 (916, 1,137)	0.768 (0.569, 0.893)	94.57%	$p = 0.011$	$p < 0.001$	
	Brazil	2 (65, 108)	0.808 (0.050, 0.997)	94.54%	$p = 0.520$	$p < 0.001$	
	Egypt	6 (92, 149)	0.609 (0.417, 0.773)	57.17%	$p = 0.262$	$p = 0.040$	
	Pakistan	5 (64, 75)	0.831 (0.722, 0.903)	0.00%	$p < 0.001$	$p = 0.746$	
	Bangladesh	6 (88, 182)	0.500 (0.398, 0.601)	41.23%	$p = 0.993$	$p = 0.130$	
	Iran	11 (469, 805)	0.563 (0.475, 0.648)	80.97%	$p = 0.160$	$p < 0.001$	
	Iraq	3 (108, 150)	0.770 (0.306, 0.962)	92.89%	$p = 0.243$	$p < 0.001$	
	Saudi Arabia	2 (45, 93)	0.481 (0.060, 0.930)	96.42%	$p = 0.954$	$p < 0.001$	
	Malaysia	1 (61, 209)	0.292 (0.234, 0.357)	0.00%	$p < 0.001$	$p > 0.999$	
	Kazakhstan	1 (1, 5)	0.200 (0.027, 0.691)	0.00%	$p = 0.215$	$p > 0.999$	
	Indonesia	1 (12, 22)	0.545 (0.341, 0.735)	0.00%	$p = 0.670$	$p > 0.999$	
	South Africa	1 (66, 89)	0.742 (0.641, 0.822)	0.00%	$p < 0.001$	$p > 0.999$	
	Austria	2 (148, 1,098)	0.135 (0.116, 0.156)	0.00%	$p < 0.001$	$p > 0.999$	
	South Korea	1 (14, 25)	0.560 (0.366, 0.737)	0.00%	$p = 0.549$	$p > 0.999$	
	Australia	1 (58, 63)	0.921 (0.823, 0.967)	0.00%	$p < 0.001$	$p > 0.999$	
	Hungary	2 (94, 172)	0.533 (0.209, 0.830)	95.14%	$p = 0.861$	$p < 0.001$	
Continents	Americas	8 (695, 1,619)	0.493 (0.345, 0.643)	95.81%	$p = 0.929$	$p < 0.001$	$p = 0.013$
	Asia	58 (3,782, 6,225)	0.604 (0.540, 0.666)	94.36%	$p = 0.002$	$p < 0.001$	
	Europe	6 (412, 2,153)	0.311 (0.149, 0.537)	98.29%	$p = 0.098$	$p < 0.001$	
	ND	3 (122, 255)	0.466 (0.053, 0.932)	97.70%	$p = 0.923$	$p < 0.001$	
	Africa	7 (158, 238)	0.641 (0.485, 0.772)	66.45%	$p = 0.076$	$p = 0.007$	
	Oceania	1 (58, 63)	0.921 (0.823, 0.967)	0.00%	$p < 0.001$	$p > 0.999$	

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10.3389/fmicb.2025.1524452

TABLE 4 (Continued)

Category	Subgroup	K (n, N)	Proportion 95%CI (LCI, HCI)	I^2	P1	P2	P3
AST Guideline	CLSI	67 (4,179, 7,351)	0.590 (0.528, 0.649)	94.82%	$p = 0.005$	$p < 0.001$	$p = 0.111$
	ND	8 (227, 430)	0.705 (0.388, 0.900)	94.99%	$p = 0.198$	$p < 0.001$	
	Multiple Guideline	1 (26, 60)	0.433 (0.315, 0.560)	0.00%	$p = 0.303$	$p > 0.999$	
	EUCAST	7 (795, 2,712)	0.363 (0.163, 0.625)	99.12%	$p = 0.304$	$p < 0.001$	
AST Method	MIX	9 (736, 1857)	0.668 (0.479, 0.815)	97.25%	$p = 0.080$	$p < 0.001$	p = 0.121
	Disk Diffusion	53 (2,265, 4,274)	0.553 (0.481, 0.622)	93.39%	$p = 0.151$	$p < 0.001$	
	MIC	6 (1,022, 1,601)	0.663 (0.564, 0.750)	89.68%	$p = 0.002$	$p < 0.001$	
	Automate	8 (875, 1,098)	0.748 (0.483, 0.904)	95.80%	$p = 0.065$	$p < 0.001$	
Species	MRSA	23 (1,353, 2,733)	0.637 (0.528, 0.733)	95.45%	$p = 0.014$	$p < 0.001$	$p = 0.074$
	mrCoNS	1 (120, 147)	0.816 (0.745, 0.871)	0.00%	$p < 0.001$	$p > 0.999$	
	S. lugdunensis	1 (21, 28)	0.750 (0.561, 0.876)	0.00%	$p = 0.012$	$p > 0.999$	
	S. aureus	40 (2,907, 6,072)	0.546 (0.442, 0.645)	97.45%	$p = 0.387$	$p < 0.001$	
	MSSA	3 (157, 533)	0.185 (0.067, 0.417)	94.30%	$p = 0.011$	$p < 0.001$	
	S. epidermidis	5 (157, 283)	0.509 (0.338, 0.678)	81.37%	$p = 0.917$	$p < 0.001$	
	CoNS	6 (407, 567)	0.767 (0.571, 0.891)	91.58%	$p = 0.010$	$p < 0.001$	
	Staphylococcus spp	4 (105, 190)	0.562 (0.296, 0.797)	88.15%	$p = 0.660$	$p < 0.001$	
Coagulase	CPS	66 (4,417, 9,338)	0.558 (0.485, 0.629)	96.90%	$p = 0.121$	$p < 0.001$	$p = 0.312$
	CoNS	13 (705, 1,025)	0.679 (0.563, 0.777)	88.70%	$p = 0.003$	$p < 0.001$	
	ND	4 (105, 190)	0.562 (0.296, 0.797)	88.15%	$p = 0.660$	$p < 0.001$	
Year Group	2015_2019	44 (3,537, 7,509)	0.584 (0.492, 0.671)	97.55%	$p = 0.073$	$p < 0.001$	$p = 0.901$
	2020_2023	39 (1,690, 3,044)	0.569 (0.483, 0.651)	93.20%	$p = 0.117$	$p < 0.001$	

K: Number of reports, n: Number of resistant isolates, N: Number of total isolates, LCI: 95% Lower Limit Confidence Interval, HCI: 95% Higher Limit Confidence Interval, P1: *p*-value of difference from zero resistance rate, P2: *p*-value of heterogeneity between reports, P3: *p*-value of difference between groups.

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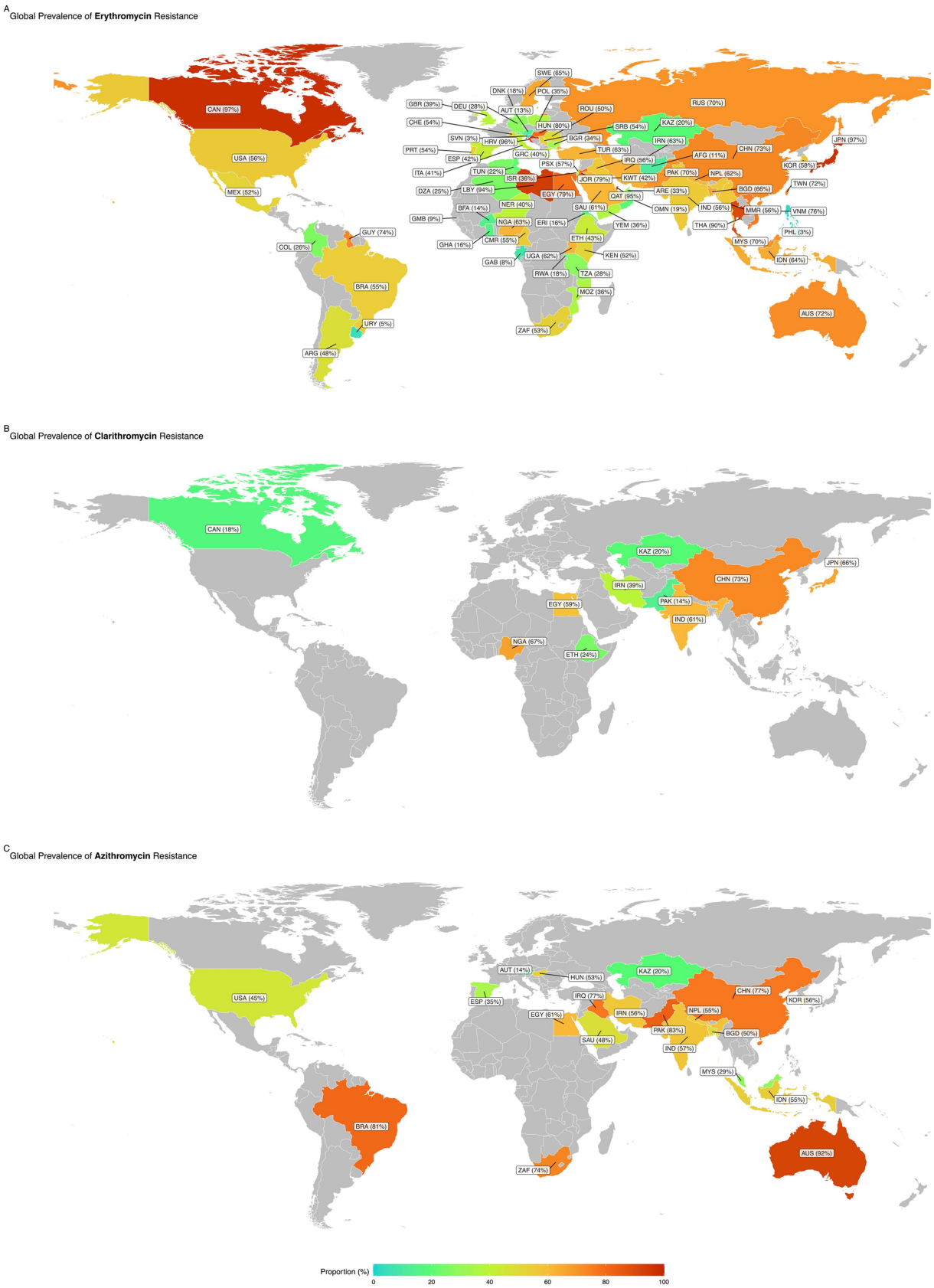

FIGURE 4
Global prevalence of antibiotic resistance in *Staphylococcus*: maps showing the worldwide prevalence of resistance to Erythromycin **(A)**, Clarithromycin **(B)**, and Azithromycin **(C)**. Regions with higher resistance proportions are highlighted in warmer colors (e.g., red), while areas with lower resistance rates are shown in cooler tones (e.g., green).

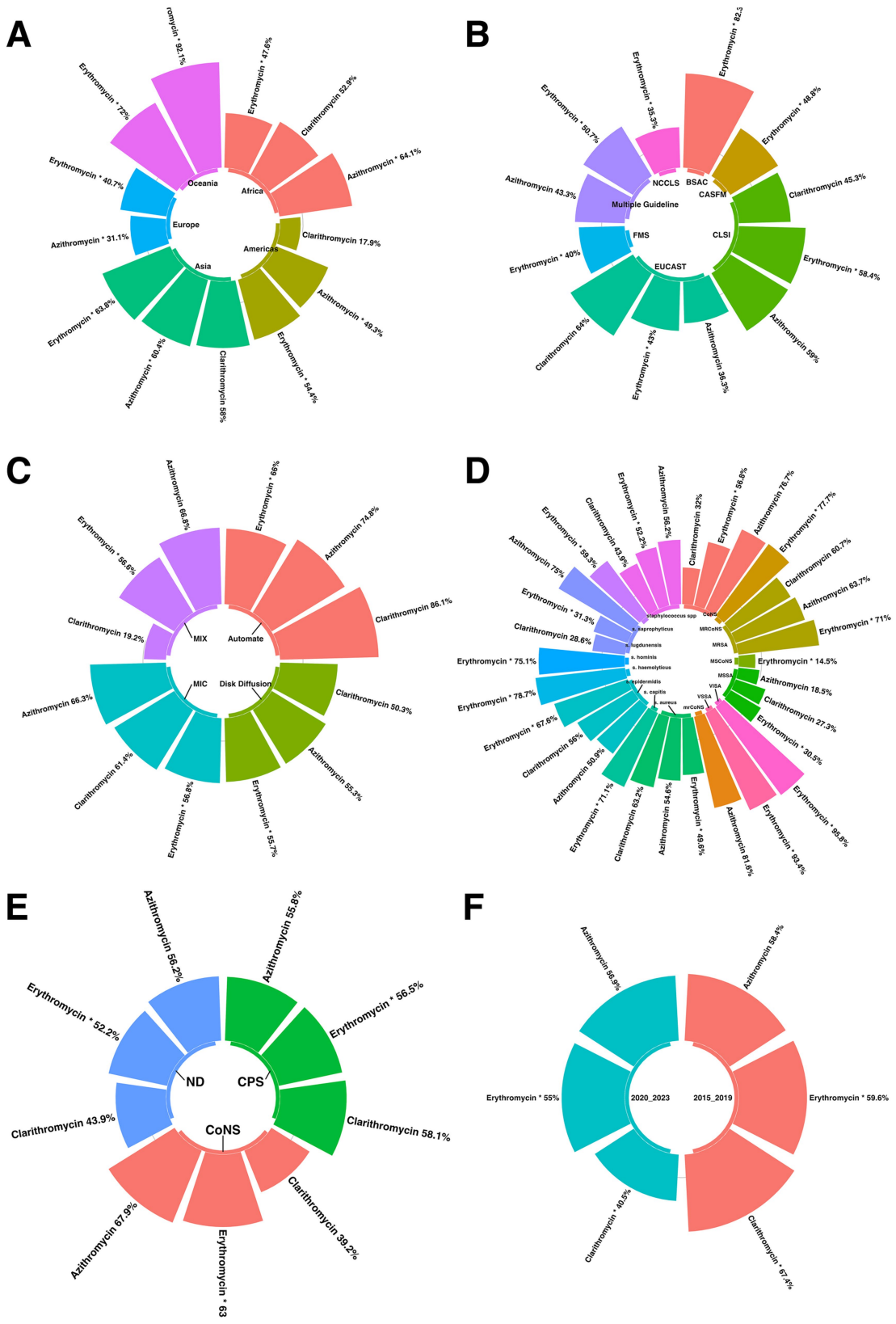

FIGURE 5
subgroup analysis results were illustrated in figures **(A)** compression of the prevalence of antibiotic-resistant *staphylococcus* isolates between continents; **(B)** Compression of the prevalence of antibiotic-resistant *staphylococcus* isolates between AST guideline; **(C)** Compression of the prevalence of *staphylococcus* isolates AST method; **(D)** Compression of the prevalence of antibiotic-resistant *staphylococcus* isolates based on species **(E)** Compression of the prevalence of antibiotic-resistant *staphylococcus* isolates based on coagulase; **(F)** Compression of the prevalence of *staphylococcus* isolates before and after 2020.

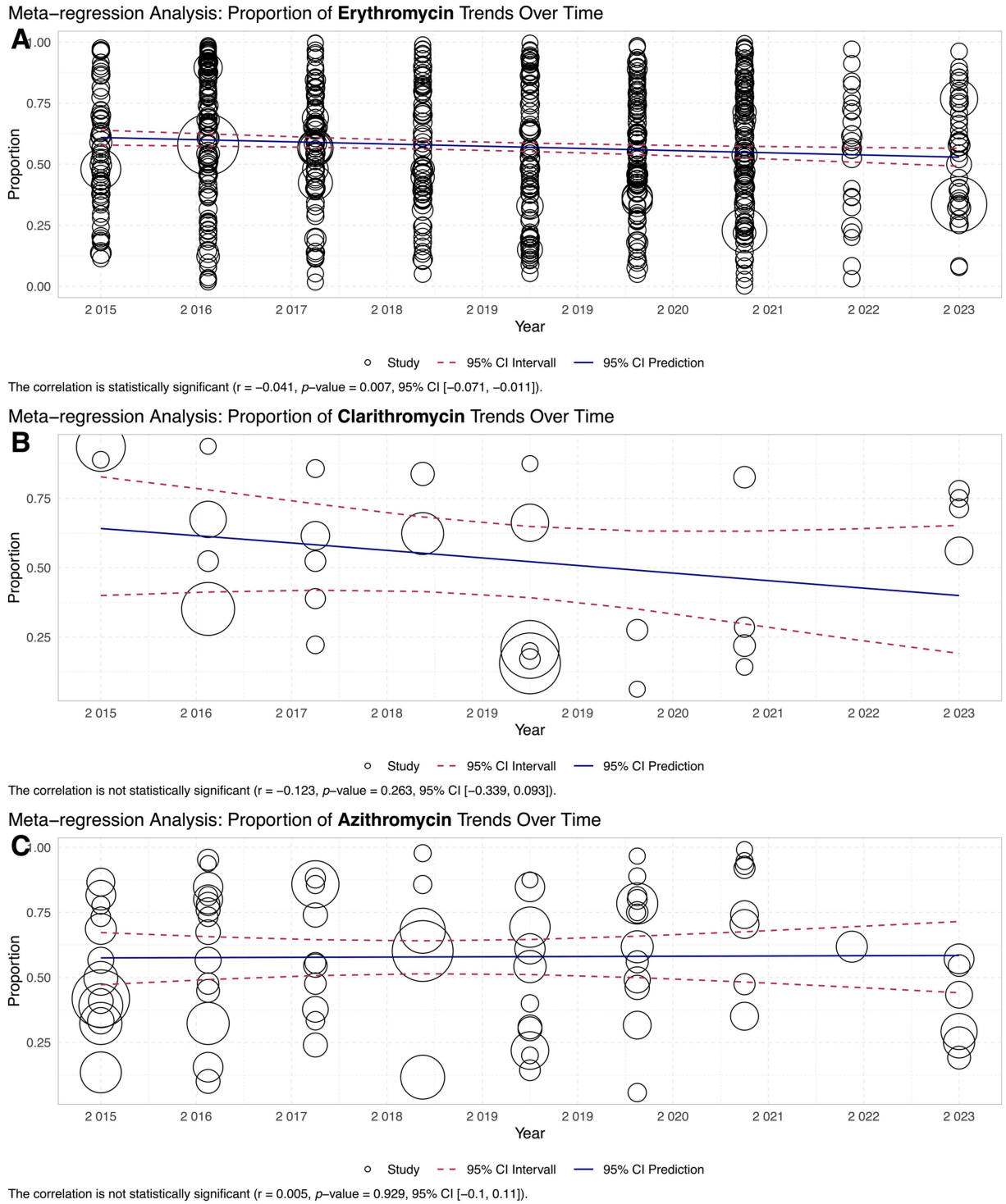

FIGURE 6
Trends in antibiotic resistance over time (2015–2023): meta-regression analysis plots the trends of resistance proportions for: **(A)** Erythromycin, showing a slight but statistically significant decline. **(B)** Clarithromycin, demonstrating a non-significant downward trend. **(C)** Azithromycin, with no significant trend observed. Data points represent study-specific resistance proportions over time, with bubble sizes reflecting sample size.

(Figure 6A). Similarly, the correlation was not statistically significant for clarithromycin (r = −0.123, *p*-value = 0.263, 95% CI [−0.339, 0.093]) (Figure 6B). These results suggest that resistance rates for azithromycin and clarithromycin remained relatively stable over the study period. In contrast, a statistically significant positive correlation was observed for azithromycin (r = 0.005, *p*-value = 0.929, 95% CI [−0.1, 0.11]) (Figure 6C), indicating an upward trend in erythromycin resistance rates over time.

4 Discussion

This systematic review and meta-analysis thoroughly evaluated the prevalence and trends of macrolide resistance in *Staphylococcus* species, explicitly focusing on resistance to erythromycin, clarithromycin, and azithromycin. By analyzing data from 207 studies conducted in 76 countries between 2015 and 2023, our findings provide valuable insights into global patterns of macrolide resistance in *Staphylococcus* species. Erythromycin, the first macrolide antibiotic discovered, remains effective in treating minor skin infections caused by penicillin-resistant *S. aureus* strains (Washington and Wilson, 1985). This meta-analysis revealed that erythromycin was the most commonly tested macrolide in antibiotic susceptibility studies, with data from 207 studies in 76 countries. The pooled prevalence of resistance was 57.3%, with significant heterogeneity between studies ($I^2 = 96.09\%$, $p < 0.001$). Evidence of publication bias was also detected using Egger's test ($p < 0.001$), resulting in an adjusted pooled prevalence of 50.1% after Fill and Trim analysis. These variations may be due to differences in study populations, periods, sampling methods, or clinical specimen types.

Subgroup analyses revealed significant regional differences in erythromycin resistance rates. Oceania had the highest resistance rate (72%, based on two reports), while Asia contributed the most studies (417 reports) with a pooled prevalence of 63.8%. In particular, China, Iran, and India reported resistance rates of 73.1, 62.7, and 55.7%, respectively, based on 105, 85, and 79 reports. In contrast, Europe had the lowest pooled prevalence of erythromycin-resistant isolates (40.7%, 44 reports), with Spain (13 reports) and Poland (8 reports) reporting prevalence rates of 42.5 and 35%, respectively. The lower resistance rates in Europe reflect increased public awareness and effective public health interventions to curb antimicrobial resistance.

On the other hand, prevalence rates of over 90% for erythromycin-resistant isolates in countries such as Qatar, Canada, Libya, Japan, and Croatia raise significant concerns. However, because these findings are based on AST performed at a single clinical center in each country, the results cannot be generalized to the entire population in these regions. This underscores the need for comprehensive national surveillance systems to monitor antimicrobial resistance in these areas.

Subgroup analysis by species revealed a pooled prevalence of erythromycin resistance in 49.6% of *S. aureus* isolates (342 reports). In addition, some studies included in this meta-analysis reported erythromycin resistance rates for *S. aureus* in two subgroups: MSSA (methicillin-susceptible *S. aureus*) and MRSA. The prevalence of resistance was significantly higher in MRSA than in MSSA (71% vs. 30.5%). However, more studies have focused on MRSA than MSSA (212 vs. 37). These findings are consistent with other meta-analyses that have reported pooled prevalence rates of erythromycin-resistant *S. aureus* isolates (Eshetie et al., 2016; Khanal et al., 2021; Chelkeba et al., 2022; Chelkeba and Melaku, 2022; Ezeh et al., 2023; Xu et al., 2024). However, most of these studies were based on data from one African country and had fewer studies than ours. Moreover, Chelkeba et al. (2022) and Chelkeba and Melaku (2022), during two separate meta-analyses conducted in Ethiopia, reported 50 and 45% prevalence rates for erythromycin-resistant *S. aureus* isolates in women with bacteriuria and patients with wound infections, respectively. In a meta-analysis review, Ezeh et al. (2023) reported a prevalence rate of 47% for erythromycin-resistant *S. aureus* isolates in Nigeria (66 reports) up to 2022. However, data from our meta-analysis highlighted a higher prevalence of erythromycin resistance in Nigeria (23 reports) than in Ezeh et al. (2023) (62.6% vs. 47%). The observed discrepancy in prevalence rates may be due to differences in the periods and number of studies included in these two meta-analyses. Subgroup analysis by species revealed a high pooled prevalence of erythromycin resistance among CoNS isolates at 56.8% (based on 42 reports). In addition, some studies independently reported the frequency of specific CoNS species, allowing pooled prevalence rates to be calculated for each species. Among these, *S. epidermidis* was the most commonly studied CoNS species (41 reports), with a pooled erythromycin resistance prevalence of 67.7%. Similar to our findings, Deyno et al. (2018) also reviewed the prevalence of antimicrobial resistance among clinical isolates of CoNS in Ethiopia through 2016, reporting a 30% prevalence of erythromycin-resistant CoNS. The discrepancy between our findings and Deyno et al. (2018) may be due to differences in the periods and geographic regions covered by these two meta-analyses. Specifically, our meta-analysis included data collected between 2015 and 2023, whereas Deyno et al. (2018) focused on data up to 2016. Furthermore, our study provided a global overview of antimicrobial resistance prevalence, whereas Deyno et al. (2018) limited their analysis to Ethiopia.

In addition, five studies reported a resistance prevalence of 77.7% among [methicillin-resistant Coagulase-Negative *Staphylococci* (MRCoNS)], which was significantly higher than the 14.5% reported in a single survey of MSCoNS. However, due to the unequal number of studies, this comparison lacks balance, and further research is needed to make a comprehensive and accurate comparison.

Overall, the prevalence of MRCoNS was significantly lower than that of MRSA. This difference may be attributed to the lower frequency of CoNS infections than *S. aureus* infections, reducing antimicrobial exposure. However, CoNS have transitioned from being non-pathogenic to emerging as pathogenic strains, potentially acquiring resistance genes from *S. aureus* (Yu et al., 2017).

In contrast, the prevalence of erythromycin resistance decreased slightly over time, from 59.6% in 2015–2019 to 55% in 2020–2023. This decline may reflect increased national efforts to combat antimicrobial resistance and the implementation of updated treatment guidelines and surveillance systems in developed countries. Similarly, a meta-analysis by Xu et al. (2024), found no significant change in erythromycin-resistant *S. aureus* isolates from Cystic fibrosis patients when comparing the periods 2008–2015 and 2015–2021.

Based on AST guidelines, the subgroup analysis showed higher resistance levels in the CLSI group compared to the EUCAST group (58.4% vs. 43%). However, this finding may be influenced by more studies using CLSI guidelines (563) compared to EUCAST guidelines (67 studies). Both guidelines are widely used but differ in their breakpoints for determining resistance. For example, EUCAST defines resistance as MIC >1, whereas CLSI uses MIC ≥8. Similarly, EUCAST considers a zone diameter of <21 mm resistant, while CLSI uses a zone diameter of ≤13 mm. These differences and variations in the number of studies likely contributed to the observed differences in erythromycin resistance prevalence.

This meta-analysis found fewer studies evaluated susceptibility testing for azithromycin and clarithromycin than erythromycin. It may be due to the limited clinical use of azithromycin and clarithromycin for treating staphylococcal infections compared to erythromycin. The pooled prevalence of azithromycin resistance was similar to that of erythromycin (57.3% vs. 57.9%). However, significant

heterogeneity between studies was observed ($I^2 = 96.5\%$, $p < 0.001$), and Egger's test indicated potential publication bias ($p < 0.001$). After applying fill and trim analysis, the pooled prevalence of azithromycin resistance was adjusted to 51.9%.

The highest resistance rates were reported in Oceania (92.1%, based on one report), while most studies (58 reports) were conducted in Asia, with a pooled prevalence of 60.4%. Specifically, India and Iran contributed 17 and 11 reports, respectively, with 57.5 and 56.3% resistance prevalence rates. Like erythromycin, Europe had the lowest prevalence of azithromycin resistance (31.1%, based on six studies). This low prevalence may be due to the limited number of European studies and the infrequent use of azithromycin to treat staphylococcal infections in this region. Alarmingly, high levels of azithromycin-resistant isolates were identified in Pakistan, Brazil, and China.

Subgroup analysis by species showed that *S. aureus* was the most commonly studied species, with a pooled resistance prevalence of 54.6% (40 reports). In addition, 23 studies reported a high prevalence of azithromycin resistance among MRSA isolates (63.7%), compared with only three studies evaluating MSSA isolates, which showed a much lower resistance prevalence of 18.5%. However, this comparison was biased due to the unequal number of studies. Subgroup analysis by the AST method showed that disc diffusion was the most commonly used method for antibiotic susceptibility testing, probably because of its accessibility and widespread acceptance. However, the highest prevalence of azithromycin resistance was associated with the automated method (74.8%, based on eight reports). Like erythromycin, the prevalence of azithromycin resistance decreased slightly over time, from 58.4% in 2015–2019 to 56.9% in 2020–2023.

Clarithromycin was the third macrolide antibiotic studied in this meta-analysis, with a pooled resistance prevalence of 52.6%; however, there was considerable heterogeneity between studies ($I^2 = 98.76\%$, $p < 0.001$). Most of the reports (17) were from Asia, with a pooled prevalence of 58%. *S. aureus* was the dominant species, with a resistance prevalence of 63.2%; six studies showed a prevalence rate of 60.7% among MRSA isolates and 27.3% among MSSA isolates (two reports). In contrast to erythromycin and azithromycin, the prevalence of resistance to clarithromycin decreased significantly over different periods (67.4% from 2015 to 2019 and 40.5% from 2020 to 2023).

Clarithromycin, the third macrolide antibiotic examined in this meta-analysis, had a pooled resistance prevalence of 52.6%, although significant heterogeneity between studies was observed ($I^2 = 98.76\%$, $p < 0.001$). Most reports (17 studies) were from Asia, with a pooled resistance prevalence of 58%. *S. aureus* was the predominant species, with a resistance prevalence of 63.2%. Among MRSA isolates, six studies reported a resistance prevalence of 60.7%, while MSSA isolates had a lower prevalence of 27.3% (based on two reports). In contrast to erythromycin and azithromycin, clarithromycin resistance decreased significantly over time, from 67.4% in 2015–2019 to 40.5% in 2020–2023.

This meta-analysis is the first to compare the prevalence of resistance to azithromycin and clarithromycin in *Staphylococcus* species. As a result, no previous meta-analyses have provided comparable global results.

A significant limitation of this study is the lack of differentiation between *Staphylococcus* species isolated from healthcare and community settings. This distinction is critical, as antibiotic resistance rates in healthcare settings are typically higher than in the community. Another limitation is the lack of data on resistance to newer macrolides, primarily due to the limited number of studies investigating them. This gap highlights the need for further research to provide accurate and comprehensive evidence.

5 Conclusion

This meta-analysis highlights a relatively high prevalence of macrolide resistance in *S. aureus* and CoNS isolates worldwide. These elevated resistance rates underscore the importance of regular epidemiologic surveillance of antimicrobial resistance and the implementation of stewardship programs. Most of the studies included in this analysis were conducted in Asia, while Europe had the lowest macrolide resistance rate. In addition, resistance to erythromycin and azithromycin remained relatively stable between 2015–2019 and 2020–2023. Nevertheless, antimicrobial susceptibility testing before treatment is recommended, and further research into the molecular and genetic mechanisms of macrolide resistance is strongly encouraged.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

TN: Data curation, Writing – original draft, Writing – review & editing. AZ: Supervision, Writing – original draft, Writing – review & editing. EP: Investigation, Project administration, Writing – original draft. MM: Investigation, Resources, Visualization, Writing – review & editing. NG: Project administration, Validation, Writing – original draft. MB: Investigation, Methodology, Project administration, Writing – original draft. MS: Formal analysis, Software, Supervision, Writing – original draft.

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Conflict of interest

AZ was employed by Quality Control Department of Temad Mfg, Co.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

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