Penicillin remains an effective agent against Group A *Streptococcus* in low- and middle-income countries: A systematic review and meta-analysis of antibiotic resistance and associated genes

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Background. Driven by the extensive use of antibiotics, antibiotic resistance has become an issue globally, in both hospital and community settings. Limited access to laboratory diagnostic testing often results in undetected resistance, which may only be detected once empiric treatment fails. There have been numerous reports on the increase of antibiotic resistance in group A *Streptococcus* (Strep A A), particularly macrolide resistance.
Objectives. To document the prevalence of antibiotic resistance in Strep A A in low- and middle-income countries (LMICs) to the most widely used antibiotics. Where possible, resistance data were correlated with *emm* typing data.
Methods. We employed an extensive search strategy to identify studies in LMICs reporting on Strep A A susceptibility to commonly prescribed antibiotics. Inclusion criteria required that isolates underwent *emm* typing. Two reviewers independently extracted data and assessed quality; statistical analyses, including meta-analysis using Stata software, evaluated the association between AMR and *emm* subtypes, and heterogeneity was assessed with Cochrane's Q and I^2 statistics.
Results. Fifty studies met the eligibility criteria and were included in this review. A range of phenotypic resistance testing methods was employed across the studies, the most common being disc diffusion. Three studies exclusively used molecular testing. For the Strep A A antimicrobial resistance (AMR) quantitative synthesis, 23 commonly used antibiotics were included in the meta-analysis. Increased resistance was observed among the macrolides (erythromycin, clindamycin, azithromycin), clarithromycin and tetracycline. Differences were observed in resistance patterns across *emm* types, with *emm*1, *emm*12 and *emm*60 showing higher resistance rates to tetracycline and erythromycin. The *erm*B (57.60%) and *tet*M (52.18%) genes were the most prevalent AMR genes among the studies. No resistance to penicillin, amoxicillin/clavulanic acid, cefotaxime, cefuroxime, linezolid, ofloxacin or teicoplanin was reported.
Conclusion. This review comprehensively characterises the latest evidence on the prevalence of antibiotic resistance in Strep A A in LMICs. Strep A A in LMICs continues to be highly susceptible to antibiotics *in vitro*, primarily to penicillins. Strep A A macrolide resistance patterns in LMICs are similar to those observed in high-income countries. The findings of this review may serve to inform effective treatment decisions and public health interventions.

Keywords: Strep A, *S. pyogenes*, antimicrobial resistance, AMR, LMIC, *emm* type

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Group A *Streptococcus* (Strep A) is a human bacterium responsible for a broad spectrum of infections, ranging from pharyngitis and scarlet fever to more severe infections such as necrotising fasciitis, acute rheumatic fever and the subsequent development of rheumatic heart disease (RHD). Strep A represents a significant global health burden, particularly in low- and middle-income countries (LMICs), contributing to substantial mortality and morbidity.[1] Strep A infections account for ~500 000 deaths annually worldwide, with the majority of RHD burden occurring in LMICs, where an estimated 80% of cases occur.[2,3] The incidence of invasive Strep A (iStrep A) is estimated at 6 cases per 100 000 people annually, resulting in ~163 000 deaths.[2,4] Despite the considerable burden, epidemiological data on antimicrobial resistance in Strep A, particularly in LMICs, are limited.

Antimicrobial resistance (AMR) in Strep A enables the pathogen to survive and proliferate in the presence of antimicrobial agents that are commonly used to treat Strep A infections. The emergence and spread of AMR is primarily attributed to the misuse and abuse of antibiotics, fostering an environment conducive to the growth and survival of resistant Strep A strains; this growing concern makes infections more challenging to treat, increasing the risk of complications and death.[5]

Although AMR has emerged as a significant public health challenge, Strep A remains susceptible to the penicillins and cephalosporins, with penicillin being the preferred treatment for Strep A infections for >50 years. For patients allergic to penicillin, macrolides such as erythromycin are recommended, with alternatives such as azithromycin or clarithromycin commonly used owing to

their ease of administration and tolerability.[6] In patients allergic to penicillin but not at risk for anaphylaxis, first- or second-generation cephalosporins may be prescribed as an alternative.

Between 2000 and 2015, global antibiotic usage increased by 65%, mainly owing to the rise in antibiotic resistance in LMICs.[7] Over the last few decades, there has been a notable increase in macrolide resistance, particularly in high-burden regions.[8] Resistance has also been reported to other classes of antibiotics, such as clindamycin and tetracycline.[9,10] Recognised by the World Health Organization as one of the top 10 public health threats, AMR is estimated to contribute to hundreds of thousands of deaths per year globally.[11,12]

Strep A exhibit two major mechanisms of resistance to macrolides: targeted-site modification through rRNA methylation, and efflux of the antibiotic.[13,14] Mutation-induced target site modification is rare in Strep A. Among Strep A isolates, cross-resistance to macrolides, lincosamides and streptogramin B (MLS_B) antibiotics is encoded by rRNA methylase genes (*erm*B and *erm*A).[15] Resistance to 14- and 15-membered macrolides (erythromycin and azithromycin) exclusively results from macrolide efflux, mediated by membrane proteins encoded by the *mef*A and *msrD* genes.[16,17]

Despite the documented rise in AMR, particularly in high-income countries, the extent of resistance among Strep A isolates in LMICs remains underexplored. These disparities may be influenced by factors such as local Strep A strains, site of infection and population characteristics.[18,19] The lack of consistent, high-quality data on AMR in LMICs contributes to the development of treatment guidelines that may not reflect local resistance patterns, posing challenges for effective management and control.[20,21] Moreover, low-quality data hamper efforts to track the spread of resistance, making it difficult to identify outbreaks and implement timely interventions. In addition to the burden of infectious diseases, LMICs often face challenges, including a shortage of adequately trained healthcare professionals, uncontrolled antibiotic use, widespread self-medication, restricted access to impartial information regarding antibiotics, insufficient availability of high-quality medications and limited access to newer therapeutic options.[22]

Despite the growing concern about AMR in Strep A, no comprehensive systematic review has been published on the status of AMR to antibiotics in Strep A isolates in LMICs. This review aims to assess the prevalence of antibiotic resistance in Strep A isolates from adults and children in LMICs, and correlate these findings with available *emm* typing and genomic AMR data. To achieve this, the available data on the presence of antibiotic resistance and *emm* typing in Strep A infections in LMICs were critically summarised.

Methods

This systematic review protocol was registered in the PROSPERO International Prospective Register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO; CRD42023460804) and was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) 2020 Statement.[23]

Research question

We structured our research question according to the *CoCoPop* mnemonic for systematic reviews:[24]

- Condition: AMR and *emm* type prevalence
- Context: LMICs
- Population: Strep A isolates from children or adults.

Thus, what is the prevalence of AMR and *emm* type profile among Strep A isolated from children or adults in LMICs? This systematic review seeks to document the distribution of AMR and *emm* types in Strep A infection in LMICs.

Search criteria

A broad search strategy was designed to enhance sensitivity. We searched various databases including Scopus, PubMed and Web of Science (accessed via IST Web of Knowledge), as well as Google Scholar, to retrieve relevant articles. Reference lists of relevant articles were checked for further titles for inclusion in the review. The main search included individual searches using medical subject heading (MeSH) terms 'antimicrobial susceptibility', 'antimicrobial resistance', '*S. pyogenes*', '*Streptococcus pyogenes*' and 'group A *Streptococcus*', and specific names of LMICs (appendix 1, Table S1: http://coding.samedical.org/file/2356). Two independent reviewers (KR and TS) critically appraised each study. Disagreements were discussed and resolved by a third reviewer (MEE). The search was not restricted by language nor any time-period cut-off. The search strategy was validated by checking if relevant publications already known were included in the search results list.

Eligibility criteria

Articles related to AMR and susceptibility patterns of Strep A isolated from participants of any age, ethnicity, and socioeconomic and educational background in LMICs were included in this review. Based on the abstract, articles of all types with any data on Strep A aetiology and antibiotic susceptibility patterns were included for further screening. Where duplicate publications used data more than once, the most recent and complete versions were considered. We included studies from LMICs focusing on Strep A *emm* typing with AMR data. Studies incorporating drug sensitivity testing done in a laboratory setting with defined cut-offs for drug susceptibility testing were also considered for inclusion. We considered published articles and all study designs, with no language restrictions. In addition, population-based studies clearly describing the denominator as total isolates were included.

Exclusion criteria

We excluded opinion pieces, letters, narrative reviews, case reports and other publications lacking primary data or with ambiguous method descriptions. Studies that reported AMR data without corresponding molecular diagnostic test (*emm* typing) were excluded. Studies that reported on outbreaks were also excluded. In addition, we excluded animal studies and studies with no information on the total number of Strep A isolates.

Selection procedure

Titles and abstracts of all articles identified by the search strategy were screened. The search strategy was conducted independently by two reviewers (KR and TS). In the event of uncertainty as to whether the article should be included, a third reviewer (MEE) was consulted.

Data extraction and management

Search results from all aforementioned databases and reference search results from published data were managed with the online Rayyan software platform.[25] Data extraction was conducted by KR and verified by a second reviewer (KE) and third reviewer (TS). Data extracted included article information (first author, year of publication, country, sample size, age group, number of specimens collected, clinical syndrome), pathogen identification and antimicrobial susceptibility testing (AST) methodology, *emm* types and AMR data. Antibiotics reported in ≥4 studies were subjected to a meta-analysis.

Assessment of study quality

We evaluated internal and external validity, and generalisability of the included studies for the risk of bias. The quality of the articles was assessed using a tool modified for the purpose of this review from Hoy *et al.*[26] (adapted by Salie *et al.*[27]); the revised version allows for a composite score to assist with a relative comparison between the studies, thereby reducing reviewers' subjectivity. Two independent reviewers (KR and KE) scored the quality of each study. Disagreements were discussed and resolved by a third reviewer (MEE). Briefly, a quantitative scoring system added to the risk of bias table allocates 4 points for external validly score and 3 points for internal validity. The scoring system tool categorises high-risk studies as those with an overall score of 0 - 3 points, moderate risk as 4 - 5, and low risk 6 - 7 points.

Statistical analysis

Two reviewers conducted statistical analyses using Stata version 15 (Stata Corp, USA). We used the *metaprop_one* routine to calculate the proportion of resistance, pool estimates and confidence intervals (CIs) for each Strep A antibiotic. To keep the effect of studies with extremely small or extremely large prevalence estimates on the overall estimate to a minimum, we stabilised the variance of the study-specific prevalence with the Freeman-Tukey single arcsine transformation before pooling the data with the random-effects meta-analysis model.[28,29] We calculated the pooled resistance estimates and their corresponding 95% CIs. Where a meta-analysis was not feasible, because data were either too heterogeneous or insufficient to allow for meaningful pooling, we compiled a narrative report of the results.

Heterogeneity between studies was assessed with Cochran's Q statistic and the I^2 statistic, which estimates the percentage of total variation across studies due to true between-study differences rather than by chance.[30] I^2s of 25%, 50% and 75% were indicative of low, medium and high heterogeneity, respectively. Nevertheless, we acknowledge that I^2 statistics may not be discriminative in meta-analyses of prevalence.[31] Additionally, we assessed the association between AMR and *emm* subtypes, and we conducted a separate meta-analysis for *emm* types with >30 isolates and AMR genes and *emm* subtypes present in >75 isolates. This is to ensure data homogeneity and reliability, specifically excluding those with small sample sizes or insufficient data.

Results

Literature search and study selection

The literature search retrieved 810 articles for consideration for inclusion from the respective electronic databases (Fig. 1). Following removal of duplicates and manual searching, 543 articles underwent screening based on title and abstract and, of these, 69 necessitated full-text review. Six additional articles were identified from Google Scholar and reference lists. Finally, 50 articles met the inclusion criteria and were included in the review. A comprehensive list of the excluded studies is reported in appendix 1, Table S2.

Study characteristics

Characteristics of the included studies are outlined in appendix 2, Table 1 (http://coding.samedical.org/file/2358). The 50 articles were from 17 countries, namely China (13 articles), India (8), Brazil (5), Lebanon (4), Serbia (4), Iran (2), Tunisia (2), Turkey (3), Egypt (1), Ethiopia (1), Laos (1), Malaysia (1), Mexico (1), Morocco (1), Gabon (1), Pakistan (1) and South Africa (1). Methods for detecting AMR included disk diffusion (*n*=28), agar dilution (*n*=7), broth dilution (*n*=7), whole genome sequencing (*n*=2), ETEST (*n*=2), polymerase chain reaction (*n*=1), broth dilution and agar dilution (*n*=1), Sensititre (*n*=1), and Vitek (*n*=1). Twenty studies provided information regarding invasive v. non-invasive infection; where invasive disease was not defined, we accepted the authors' classification of invasiveness.

Among the included articles, the majority (24%) were published between 2005 and 2014, followed by those published between 2015 and 2020 (15%), before 2005 (3%) and after 2021 (8%) (appendix 1, Table S3). This review included a diverse age range (i.e. children and adults) with either community (22%) or hospital-acquired (70%) infections, or both (8%). Among the different studies, five different interpretation guidelines were used: Clinical and Laboratory Standards Institute (CLSI) (68%), European Committee on Antimicrobial Susceptibility Testing (12%), National Committee for Clinical Laboratory Standards (6%), Antibiogram Committee of the French Society for Microbiology (4%) and American Clinical and Laboratory Standards Committee (2%) guidelines; 8% did not mention the guidelines used.

Assessment of risk of bias of the included studies

The risk of bias was assessed using the Hoy criteria as modified by Salie *et al.*[27] Risk of bias was classified as low and moderate in 17 and 33 studies, respectively. In the evaluation of the seven domains relevant to our review, most of the studies were determined to have a moderate to low risk of bias (appendix 1, Table S4). Most of the studies clearly define clinical phenotypes. The sampling frame for all studies accurately or closely represented the target population. The data obtained from all the included studies were directly from participants, not through a proxy, affirming the reliability of the sample collected. The participants and isolates of the included studies were distinctly outlined, along with a clear description of the AST method and mode of data collection.

Prevalence of antimicrobial resistant Strep A

Fifty articles (*n*=11 930 isolates) were amenable to meta-analysis. To be included in the meta-analysis, antibiotics had to have been reported in ≥4 studies. Antibiotics from 27 studies included 15 of the 20 antibiotics incorporated into the Sensititre STP6F system, which incorporates commonly used antibiotics. The highest pooled rate of detection of Strep A resistance was against tetracycline (50.89%; 95% CI 37.95 - 63.78), followed by clarithromycin (49.99%; 95% CI 12.82 - 87.17), azithromycin (36.84%; 95% CI 9.68 - 69.49), erythromycin (32.82%, 95% CI 18.57 - 48.82), and clindamycin (27.22%; 95% CI 12.73 - 44.56) (Table 1). The pooled estimate for macrolide resistance among Strep A isolates was 70.86% (95% CI 31.11 - 98.31). Among the studies analysed, the prevalence of Strep A resistance to gentamicin was 12.60% (95% CI 0.00 - 54.19), while for cefepime it was 7.54% (95% CI 0.00 - 49.88). The lowest pooled rate of detection of Strep A resistance was against amoxicillin, ampicillin, ceftriaxone, chloramphenicol, ciprofloxacin, levofloxacin, sulfamethoxazole-trimethoprim and vancomycin. No resistance was reported for penicillin or six other antibiotics, including amoxicillin/clavulanic acid, cefotaxime, cefuroxime, linezolid, ofloxacin and teicoplanin.

Molecular epidemiology of AMR

Prevalence of AMR genes in Strep A

Twelve studies provided data on the prevalence of erythromycin resistance genes among erythromycin-resistant isolates. Three genes are typically associated with macrolide resistance in Strep A, namely *erm*A, *erm*B and *mef*A. The highest pooled estimate of erythromycin-resistant Strep A isolates was associated with the *ermB*

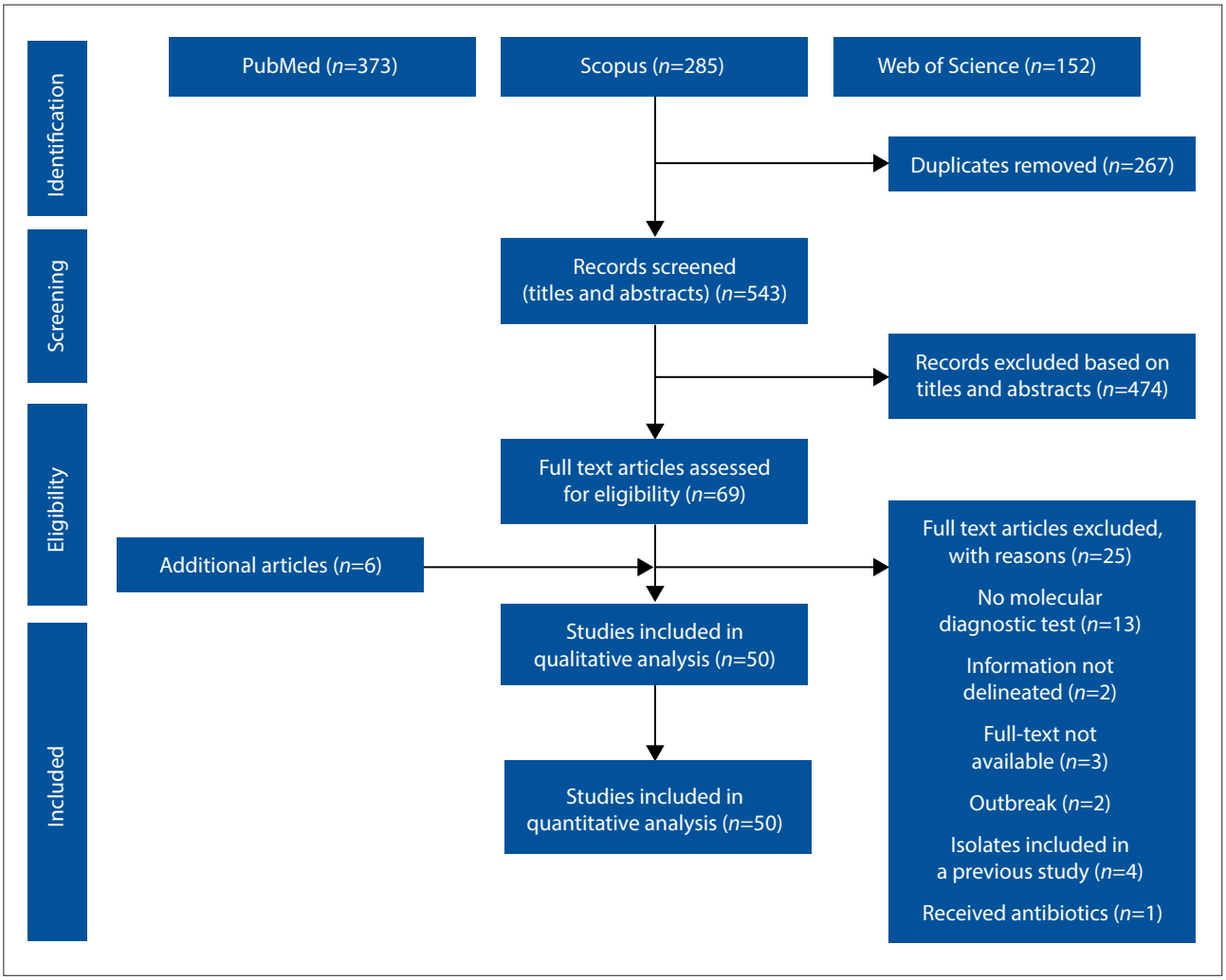

Fig. 1. PRISMA flow diagram of selection of articles for inclusion.

gene (57.60% (95% CI 28.40 - 82.32), followed by *mefA* (17.48% (95% CI 4.49 - 48.80) and *ermA* (16.74% (95% CI 6.17 - 38.09) (Table 2). Five studies reported on tetracycline (*tet*) resistance gene prevalence among tetracycline-resistant isolates. The most prevalent tetracycline resistant gene among the studies was *tet*M (52.18% (95% CI 10.69 - 90.87), and the least prevalent were *tet*K (2.16%; 95% CI 0.30 - 13.74), *tet*L (3.82%; 95% CI 0.18 - 46.04) and *tet*O (2.97%; 95% CI 0.34 - 21.42). The other *tet* genes (*tet*S, *tet*T) were not reported in these studies.

***Emm* type**

One hundred and eighty-nine *emm* types were reported in this review. The 10 most prevalent *emm* types are presented in appendix 1, Fig. S1. *Emm*12 (iStrep A, *n*=18; non-iStrep A, *n*=1 828) and *emm*1 (iStrep A, *n*=18; non-iStrep A, *n*=822) were the most prevalent *emm* types among the studies. Data on *emm* type association with antibiotic resistance were retrieved from 27 studies.

AMR and *emm* type

The meta-analysis evaluating the relationship between *emm* type and AMR among Strep A isolates (>30) in LMICs can be seen in Table 3. Tetracycline resistance was prevalent across multiple *emm* types, with *emm*60 (pooled estimate=100%; 95% CI 89.57 - 100) showing complete resistance and *emm*1 (97.30%; 95% CI 92.35 - 99.08) and *emm*12 (94.35%; 95% CI 92.15 - 96.24) exhibiting high levels of resistance. Conversely, *emm*75 (0%; 95% CI 0 - 5.83) demonstrated no resistance to tetracycline. Erythromycin resistance was widespread among *emm*1 (99.28; 95% CI 97.74 - 100) and *emm*12 (97.29%; 95% CI 95.90 - 98.42) isolates, with *emm*60 (100%; 95% CI 89.57 - 100) showing complete resistance. While clindamycin resistance was notably high in *emm*1 (87.39%; 95% CI 79.94 - 92.34) and *emm*12 strains (77.94%; 95% CI 74.07 - 81.37), it was absent in *emm*60 (0%; 95% CI 0 - 10.43) and *emm*75 strains (0%; 95% CI 0 - 5.83). Macrolide resistance was prevalent in *emm*1 (96.21%; 95% CI 91.44 - 98.37) and *emm*3 (99.49%; 95% CI 97.17 - 99.91), with *emm*12 (7.69%; 95% CI 2.65 - 20.32) exhibiting lower resistance and *emm*75 (100%; 95% CI 94.17 - 100) showing complete resistance.

AMR genes and *emm* type

The summary of studies investigating AMR genes (*erm*A, *erm*B, *mef*A) among different *emm* types of Strep A isolates (>75) is shown in Table 4. For the *erm*A gene, *emm*1 exhibited a pooled estimate of 0.66% (95% CI 0.00 - 2.31), while *emm*12 showed a slightly higher estimate of 1.57% (95% CI 0.23 - 3.78). Conversely, for the *erm*B gene, both *emm* types (*emm*1, *emm*12) demonstrated higher rates of detection, with estimates of 92.88% (95% CI 83.70 - 98.60) and 93.02% (95% CI 88.85 - 96.30), respectively. The *mef*A gene also exhibited low rates of detection, with *emm*1 at 1.64% (95% CI .00 - 7.08), and *emm*12 at 2.51% (95% CI 0.09 - 7.30). No differences were observed between *emm* types and AMR gene.

Table 1. Meta-analysis of the AMR of 23 antibiotics against Strep A isolates in LMICs

Antimicrobial drug	Studies, *n*	Isolates, *n*	Pooled estimate	95% CI	I^2
Amoxicillin	4	449	1.41	0.00 - 10.83	87.95
Amoxicillin/ clavulanic acid	4	324	0.00	0.00 - 0.58	0.00
Ampicillin	12	1 401	1.00	0.00 - 5.96	89.78
Azithromycin	13	2 120	36.84	9.68 - 69.49	99.54
Cefepime	6	819	7.54	0.00 - 49.88	98.40
Cefotaxime	9	1 248	0.00	0.00 - 0.11	0.00
Ceftriaxone	17	1 694	1.48	0.00 - 9.54	95.70
Cefuroxime	2	142	0.00	0.00 - 1.27	0.00
Chloramphenicol	24	4 982	0.90	0.50 - 2.40	87.40
Ciprofloxacin	4	419	7.20	1.53 - 16.13	83.64
Clarithromycin	8	1 882	49.99	12.82 - 87.17	99.63
Clindamycin	38	7 410	27.22	12.73 - 44.56	99.65
Erythromycin	43	11 215	32.82	18.57 - 48.82	99.69
Gentamicin	6	371	12.60	0.00 - 54.19	98.17
Levofloxacin	19	2 923	2.08	0.00 - 9.49	95.94
Linezolid	9	1 274	0.00	0.00 - 0.00	0.00
Macrolide	4	544	70.86	31.11 - 98.31	97.49
Ofloxacin	7	1 495	0.00	0.00 - 0.21	0.00
Penicillin	42	11 177	0.00	0.00 - 0.00	0.00
Sulfamethoxazole-trimethoprim	4	300	11.47	0.00 - 61.35	95.0
Teicoplanin	7	659	0.00	0.00 - 0.00	0.00
Tetracycline	43	9 135	50.89	37.95 - 63.78	99.36
Vancomycin	30	5 758	1.77	0.00 - 6.88	98.60

AMR = antimicrobial resistance; Strep A A = group A *Streptococcus;* LMICs = low- and middle-income countries; pooled estimate = prevalence of isolates resistant to the antimicrobial drug; CI = confidence interval; I^2 = heterogeneity index.

Table 2. Meta-analysis of AMR genes of total resistant Strep A isolates in LMICs

Antibiotic	AMR gene	Studies, *n*	Total resistant isolates, *n*	Prevalence, %	95% CI	I^2
Erythromycin	*ermA*	6	948	16.74	6.17 - 38.09	92.59
	ermB	13	1162	57.60	28.40 - 82.32	95.44
	mefA	10	894	17.48	4.49 - 48.80	94.54
	ermTR	5	194	16.51	1.32 - 74.46	89.26
	ermB + mefA	3	94	8.79	3.79 - 19.10	5.39
Tetracycline	*tetK*	3	174	2.16	0.30 - 13.74	56.46
	tetL	2	102	3.82	0.18 - 46.04	76.18
	tetM	5	240	52.18	10.69 - 90.87	95.26
	tetO	4	236	2.97	0.34 - 21.42	85.28
	tetS	1	72	0.68	0.04 - 10.02	-
	tetT	1	72	0.68	0.04 - 10.02	-

AMR = antimicrobial resistance; Strep A A = group A *Streptococcus*; LMICs = low- and middle-income countries; CI = confidence interval; I^2 = heterogeneity index.

Discussion

This systematic review provides evidence regarding the prevalence of antibiotic resistance in Strep A in LMICs, with a specific focus on commonly used antibiotics for Strep A treatment, AMR genes and *emm* types. Drawing from data compiled from 50 studies across 17 countries, this review reveals notable variations in Strep A resistance profiles to various antibiotics, with high resistance observed to tetracycline, clarithromycin and erythromycin, while resistance to others such as amoxicillin remained relatively low. Additionally, variability in the prevalence of AMR genes, such as *erm*B for erythromycin resistance and *tet*M for tetracycline, was noted among studies. Finally, this review provides evidence that certain *emm* types had higher resistance rates to specific antibiotics than others.

This review confirmed that Strep A isolates exhibit no resistance to penicillin, as reported in several studies conducted worldwide.[32,33] The remaining beta-lactam antibiotics showed little to no resistance among Strep A isolates, suggesting that these antibiotics remained effective in treating Strep A infections in LMICs. However, three studies from China[34] and India[35,36] demonstrated intermediate susceptibility to penicillin, albeit with a low overall proportion. There has been growing evidence for high macrolide resistance rates,[37] which is supported by our finding of a high proportion of macrolide resistance in Strep A isolates. We also observed, in these studies from LMICs, a high

Table 3. Meta-analysis of emm type and antimicrobial resistance of Strep A isolates (*n*=>30) in LMICs

Antimicrobial drug	*Emm* type	Studies, *n*	Isolates, *n*	Pooled estimate	95% CI
Tetracycline	*Emm1*	1	111	97.30	92.35 - 99.08
	Emm12	2	539	94.35	92.15 - 96.24
	Emm60	1	33	100	89.57 - 100
	Emm75	1	62	0.00	0.00 - 5.83
Erythromycin	*Emm1*	2	272	99.28	97.74 - 100
	Emm12	3	762	97.29	95.90 - 98.42
	Emm60	1	33	100	89.57 - 100
Clindamycin	*Emm1*	1	111	87.39	79.94 - 92.34
	Emm12	1	494	77.94	74.07 - 81.37
	Emm60	1	33	0.00	0.00 - 10.43
	Emm75	1	62	0.00	0.00 - 5.83
Macrolide	*Emm1*	1	132	96.21	91.44 - 98.37
	Emm3	1	39	99.49	97.17 - 99.91
	Emm12	1	196	7.69	2.65 - 20.32
	Emm75	1	62	100	94.17 - 100

Strep A A = group A *Streptococcus*; LMICs = low- and middle-income countries; pooled estimate = prevalence of isolates resistant to the antimicrobial drug; CI = confidence interval.
I^2 calculations were not provided by Stata software owing to an insufficient number of studies.

Table 4. Meta-analysis of macrolide-resistant genes and *emm* type in Strep A (*n*=>75) isolates in LMICs

AMR gene	*Emm* type	Studies, *n*	Isolates, *n*	Pooled estimate	95% CI	I^2
*erm*A	1	4	475	0.66	0.00 - 2.31	47.80
	12	5	843	1.57	0.23 - 3.78	72.55
*erm*B	1	4	475	92.88	83.70 - 98.60	89.81
	12	5	843	93.02	88.85 - 96.30	76.75
*mef*A	1	4	475	1.64	0.00 - 7.08	88.30
	12	5	843	2.51	0.09 - 7.30	90.28

Strep A A = group A *Streptococcus*; LMICs = low- and middle-income countries; AMR = antimicrobial resistance; pooled estimate = prevalence of isolates resistant to the antimicrobial drug; CI = confidence interval; I^2 = heterogeneity index.

prevalence of resistance among Strep A isolates to clarithromycin, azithromycin and erythromycin. While similar resistance trends have been reported in some European countries,[38,39] other countries in Europe report significantly lower resistance rates.[8,37] In the meta-analysis, the wide CIs for clarithromycin and azithromycin suggest significant variability across studies, likely due to differences in study settings, regional variations and the inclusion of both invasive and non-invasive isolates. Resistance to clindamycin was much higher in this current review than in the review conducted in Africa by Tadesse *et al*.[32] This difference may be influenced by the regional distribution of studies, with 5 studies from India and 13 studies from China, suggesting potential geographic variations in AMR.

Macrolide resistance has been attributed to genetic determinants.[37] This review identified *erm*B, commonly associated with the inducible macrolide-lincosamide-streptogramin B resistance phenotype, as the most prevalent macrolide resistance gene. The *mefA* gene, responsible for macrolide efflux, was the second most frequently detected resistance gene. These findings align with studies from European countries such as Italy, Belgium and France, where similar prevalence rates of macrolide resistance genes have been reported.[40-43] The *mef*A gene is one of the predominant mechanisms for macrolide resistance, alongside rRNA methylation.[44] The horizontal transmission of the *mef*A and *erm* genes, along with the increased use of macrolides, may contribute to the elevated prevalence rates of macrolide resistance.[39,42,45] The high levels of macrolide resistance suggest that special attention should be paid to the appearance of macrolide-resistant Strep A strains, as these antibiotics are typically used for Strep A treatment in the event of penicillin allergy.

Increased tetracycline resistance has been reported in several countries despite the fact that tetracycline is not employed in the treatment of Strep A. In this review, approximately half of the Strep A isolates included in the analysis were resistant to tetracycline. Tetracycline resistance poses a significant concern due to the fact that the *tet* genes are harboured on mobile genetic elements (MGEs), facilitating their horizontal transfer.[40] Tetracycline resistance in Strep A is primarily mediated by ribosomal protection genes such as *tet*M and *tet*O, and less commonly by efflux pumps encoded by *tet*K or *tet*L genes.[46] Our analysis indicates that the *tet*M gene showed the highest prevalence among tetracycline-resistant isolates. The increased resistance to tetracycline may be attributed to the selective pressure arising from the widespread use of tetracycline in the treatment of various human and veterinary infections, coupled with its increased use in animal foods, thereby promoting the transfer of genes from animals to humans via MGEs.[47]

Resistance to cefepime and vancomycin, respectively, has been observed in Ethiopia and Yemen,[48,49] though these are rare prevalences. Our analysis found Strep A resistance to cefepime, with a low pooled rate of resistance detected for vancomycin. However, Strep A remains largely susceptible to beta-lactam antibiotics, including cefepime, and no widely accepted mechanisms of vancomycin resistance exist. Reports of resistance to these antibiotics should be interpreted with caution, as they may stem from species misidentification or limitations in AST

testing. Confirmation by reference laboratories is essential to validate these findings.

Emm type distribution and AMR patterns serve as important components in understanding Strep A epidemiology and guiding therapeutic strategies. Among high-income countries, macrolide resistance predominantly occurs in *emm*1, *emm*4, *emm*12 and *emm*28 Strep A isolates.[43,50-52] In Europe, other *emm* types, including *emm*11, *emm*75 and *emm*77, have also been commonly linked to macrolide resistance.[8] This review documented differences in resistance patterns across various *emm* types, with certain *emm* types showing higher resistance rates to specific antibiotics than others. Notably, *emm*1 and *emm*12 isolates exhibited high erythromycin, clindamycin and tetracycline resistance. In addition, *erm*B was prevalent in *emm*1 and *emm*12 isolates, correlating with studies performed in high-income countries.[51] Of interest, an earlier systematic review indicated that these specific *emm* types are not prevalent in Africa.[27] Indeed, the prevalence of specific *emm* types in African studies was lower than in other regions. Trends in resistance from African countries showed generally lower macrolide resistance rates compared with regions such as Europe and Asia. The variation may be influenced by differences in antibiotic usage patterns, healthcare infrastructure and surveillance capacity. Furthermore, there is a paucity of studies on AMR in Strep A from Africa. Only three studies from the region were included in this review, limiting our ability to characterise resistance trends and highlighting the need for further research.

A notable strength of this review is the effective use of multiple databases and a comprehensive search strategy, to prevent missing eligible articles. We conducted a thorough and deliberate evaluation of all accessible data without imposing language limitations or constraints related to a specific clinical manifestation of disease, using the latest standard quality assessment tools for prevalence studies. However, an important limitation is the reduced number of studies included in the meta-analyses correlating *emm* types with resistance and resistance genes, which may have impacted the robustness of these specific findings. In addition, we were unable to compare data between invasive and non-invasive Strep A infections owing to the limited number of studies reporting on invasive infections, and the small sample size included in those studies. Furthermore, inconsistencies in measuring and reporting of susceptibility data pose challenges in comparing findings across different countries and laboratories, and at times, even within a single country. Nevertheless, since most of the studies in this review utilised the disk diffusion method and adhered to the CLSI guidelines, the validity of the final results is considered to be minimally affected by the variation in AMR methodology. Additionally, the resistance classifications were based on the interpretations provided by the respective studies. We acknowledge the potential variability in definitions, and have noted this as a limitation.

Conclusion

This review provides the most recent evidence on the prevalence of AMR Strep A across LMICs, which are characterised by poor access to healthcare and high incidence of infectious diseases. The results highlight notable resistance to tetracycline, clarithromycin and erythromycin. While resistance to macrolides and tetracyclines is a growing concern, beta-lactam antibiotics, including penicillin/ampicillin, remain highly effective, supporting the CLSI stance against routine susceptibility testing for these antibiotics. The review also identified gaps in the understanding of AMR trends, particularly from Africa, where studies are limited. Overall, these findings offer valuable insights into the epidemiology of Strep A resistance, and emphasise the need for continued surveillance and research to guide therapeutic strategies in LMICs.

Data availability. The data used for this study are available from the authors upon request.

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Author contributions. KR: conceptualisation, data curation, formal analysis, investigation, methodology, project administration, writing – original draft, writing – review and editing. TS: project administration, writing – review and editing. KE: project administration, writing – review and editing. CM: supervision, writing – original draft, writing – review and editing. MEE: conceptualisation, supervision, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, writing – original draft, writing – review and editing.

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