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REVIEW

Global status of Azithromycin and Erythromycin Resistance Rates in *Neisseria gonorrhoeae*: A Systematic Review and Meta-analysis

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Background: The widespread development of antibiotic resistance or decreased susceptibility in *Neisseria gonorrhoeae* (NG) infection is a global and significant human public health issue. **Objectives**: Therefore, this meta-analysis aimed to estimate worldwide resistance rates of NG to the azithromycin and erythromycin according to years, regions, and antimicrobial susceptibility testing (AST). **Methods**: We systematically searched the published studies in PubMed, Scopus, and Embase from 1988 to 2021. All analyses were conducted using Stata software. **Results**: The 134 reports included in the meta-analysis were performed in 51 countries and examined 165,172 NG isolates. Most of the included studies were from Asia (50 studies) and Europe (46 studies). In the metadata, the global prevalence over the past 30 years were 6% for azithromycin and 48% for erythromycin. There was substantial change in the prevalence of macrolides NG resistance over time (P <0.01). In this metadata, among 58 countries reporting resistance data for azithromycin, 17 (29.3%) countries reported that >5% of specimens had azithromycin resistance. **Conclusions**: The implications of this study emphasize the rigorous or improved antimicrobial stewardship, early diagnosis, contact tracing, and enhanced intensive global surveillance system are crucial for control of further spreading of gonococcal emergence of antimicrobial resistance (AMR).

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Abbreviations: NG, *Neisseria gonorrhoeae*; AST, antimicrobial susceptibility testing; AMR, antimicrobial resistance; WPR, weighted pooled resistance rate; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing.

Keywords: Animicrobial Resistance, *Neisseria gonorrhoeae*, antibiotic resistance, azithromycin, erythromycin, systematic review and meta-analysis

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INTRODUCTION

Sexually transmitted infections (STIs) are a significant human health issue around the world [1,2]. Gonorrhea, as one of the most frequent bacterial STIs, continues to be a major threat to public health [3]. In 2020, the WHO estimated that there were 82.4 million (95% CI 47.7 million-130.4 million) new cases of gonorrhea among adolescents and adults. Antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* (NG) is a developing clinical and public health challenge [3]. Emerging azithromycin-resistance among the NG reported in most countries which would lead to an increase in serious problems, including infertility, ectopic pregnancy, and increased transmission of HIV [4]. Thus, an effective and inexpensive anti-infective agent is a necessity to control gonorrhea. The aim of this meta-analysis is: (1) to assess the weighted pooled resistance rate (WPR: proportion of strains resistant to specific antibiotic agent) rates of NG to azithromycin and erythromycin according to years, regions, and antimicrobial susceptibility testing (AST).

Methods

This review is reported accordant with the Preferred Reporting Items for Systematic Reviews and Meta Analyses guidelines (PRISMA) [5].

Search Strategy and Study Selection

We systematically searched for studies in four international databases including PubMed, Scopus, and Embase (until August 2021) by utilizing the related keywords: ("*Neisseria gonorrhoeae*" OR "gonorrhoea" OR "Gonococcus") AND ("antimicrobial resistance" OR "antibiotic resistance" OR "macrolides resistance" OR "azithromycin resistance" "erythromycin resistance") in the Title/Abstract/Keywords fields. The search strategy was designed and conducted by study investigators.

Reference lists of all studies were also reviewed for any other related publication. The records found through database searching were merged and the duplicates were removed using EndNote X8 (Thomson Reuters, New York, NY, USA). One of the team researchers randomly assessed the search results and confirmed that no relevant study had been ignored. All these steps were done by the three authors and any disagreements about article selection were resolved through discussion, and a fourth author acted as arbiter.

Inclusion and Exclusion Criteria

The included articles met the following criteria: (1) original study that investigated NG AMR in human clinical isolates; (2) peer-reviewed articles published in English between January 1980 and August 2021; (3) sample size of NG isolates; (4) the methods used for resistance testing (MIC-based methods, disk diffusion, mix methods (both methods)); (5) reported the AMR rate in NG isolates following the criteria by the Clinical and Laboratory Standards Institute (CLSI) standards [6], European Committee on Antimicrobial Susceptibility Testing (EUCAST) [7], and/or the WHO WPR Resistance Surveillance Programme guidelines [8]. The clinical azithromycin resistant breakpoints were interpreted using the EUCAST (>0.5 µg/mL) and CLSI (epidemiological cutoff value ≥2.0 µg/mL). In 2019, EUCAST and CLSI excluded their clinical breakpoints for azithromycin and an epidemiological cutoff value (MIC >1 mg/L) has been used for the identification of non-susceptible isolates with determinants of azithromycin resistance [9]. Studies were excluded if they contained duplicate data or were overlapping articles, (2) animal research, reviews, meta-analysis and/or systematic review, conference abstracts, and macrolides resistance were not evidently described.

Data Extraction and Assessment of Study Quality

Data extracted from each included study was; author, study period, publication year, regions, sample size of NG isolates, sample size of macrolides resistant NG isolates, and AST (disk diffusion, agar dilution, microbroth dilution, E-test). The Newcastle-Ottawa scale (NOS) was adapted for cross-sectional studies for quality assessment [10]. NOS is based on a star scoring system, which a maximum of 8 (for cross-sectional studies) can be awarded to each study. Quality assessment was checked independently by two authors, and any disagreements were solved by the third. Studies that received a score of 6 or above were considered to be high quality.

Statistical Analysis

Cross-sectional articles presenting eligible information on macrolides susceptibility in NG isolates were pooled and analyzed based on random-effects model with Stata/SE software, v.17.1 (StataCorp, College Station, TX, USA). Freeman-Tukey double arcsine transformation was performed to estimate the WPR. The inconsistency across studies was examined by the forest plot as well as the I^2 statistic. Values of I^2 (25%, 50%, and 75%) were interpreted as the presence of low, medium, or high heterogeneity, respectively. So, the DerSimonian and Laird random effects models were used [11]. Macrolides resistance rate was expressed as percentage and 95% confidence interval (CI) basis. Publication bias was calculated using Egger's test.

Study Outcomes

The primary outcome was the WPR rate of NG to azithromycin and erythromycin resistance. Subgroup

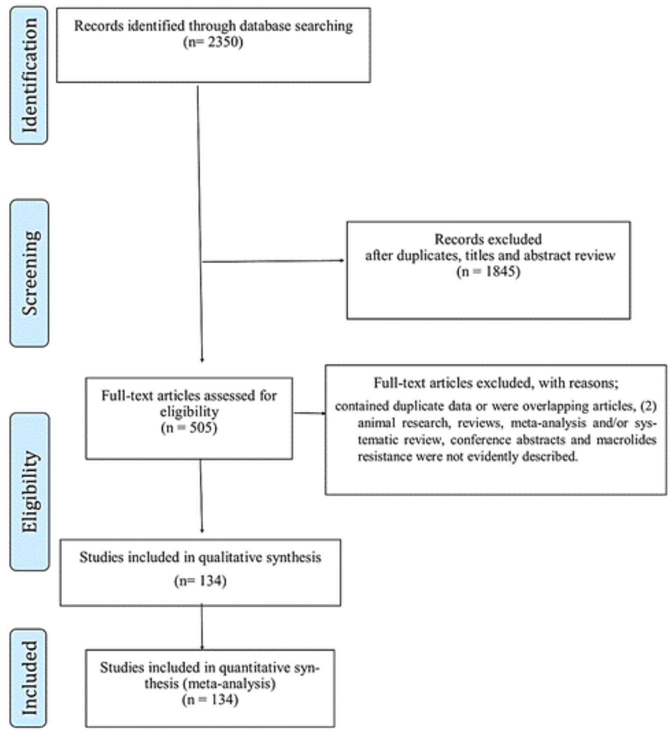

Figure 1. **Flow chart of study selection**.

analyses were then utilized by year publication (1988-2013, 2014-2018, and 2019-2021), (2) regions, (3) AST, and (4) interpretation of resistance (CLSI, EUCAST, and WHO).

RESULTS

Results of the Systematic Literature Search

Initially, a total of 2,350 studies were identified. The full texts of the remaining 505 articles were reviewed. Ultimately, 134 studies were included [12-145] based on their irrelevance/duplication and the inclusion and exclusion criteria (Figure 1). The 134 reports included in the analysis were conducted in 51 countries, examined 165,172 NG isolates, and were published between 1988 and 2021. The main group of included articles (50 studies) were conducted from Asia and Europe (46 studies) (Table 1). The macrolides WPR rates and the subgroup analyses by year, continents, AST, and interpretation of resistance are shown in Table 1.

Azithromycin Resistance

The susceptibility to azithromycin was determined in 133 studies included 165,172 NG isolates; the WPR was 6% (95% CI 5%-7%) with substantial heterogeneity (I^2=98.76%; *P*=0.01) was observed between included studies (Table 1). Also, significant publication bias was detected (Egger rank correlation test, *P* <0.01). To analyze the trends for changes in the prevalence of azithromycin resistance in more recent years, we performed a subgroup analysis for three periods (1988-2013; 2014-2018; and 2019-2021) (Table 1, Figure 2). The subgroup analysis that compared the data from 1988-2013 (WPR 2.31%; 95% CI 1.40%-3.40%), 2014-2018 (WPR 6.85%; 95% CI 4.62%-9.46%), and 2019-2021 (WPR 7.25%; 95% CI 5.62%-9.06%) indicated an increase in the resistance rate. However, there was significant variation in the proportion of azithromycin resistance isolates over time (*P* <0.01). Among 51 countries reporting resistance data for azithromycin, 22 (43.13%) countries (China, Bangladesh, Brazil, Guyana, Cuba, Israel, Korea, Germany, Vietnam, Italy, Belarus, Norway, Hungary, Slovenia, Estonia, Poland, Spain, Iran, Argentina, Ethiopia, Ireland, and Côte d'Ivoire) reported that >5% of specimens had azithromycin resistance (Figures 3 and 4). There was a statistically significant difference in the azithromycin resistance rates between different continents (*P* <0.01); and this rate was higher in South America than Asia (9.2% vs. 6.3%), Europe (9.2% vs. 5.8%), Africa (9.2% vs. 5.3%), North America (9.2% vs. 2.1%,), and Oceania (9.2% vs. 1.7%) (Figure 4). No significant difference was found in the method used for AST and the interpretation of resistance (*P*=0.36).

Table 1. Subgroup Analysis for Azithromycin and Erythromycin Resistance Rates

Variables	Number of Studies (n, N)	Prevalence (%) of Resistance (95% CI)	Heterogeneity (I^2) (%)	Egger test
Azithromycin	133 (6104, 165172)	6.00 (5.00-7.00)	98.76	<0.01
Publication date				
1988-2013	34 (409, 52191)	2.31 (1.40-3.40)	94.85	
2014-2018	46 (2018, 68318)	6.85 (4.62-9.46)	98.82	
2019-2021	53 (3677, 44013)	7.25 (5.62-9.06)	97.22	
Continent				
North America	15 (819, 96842)	2.13 (1.10-3.43)	98.71	
Asia	49 (1945, 17500)	6.36 (4.07-9.07)	97.48	
Africa	15 (307, 2995)	5.28 (0.35-14.15)	98.32	
Europe	45 (2887, 45035)	5.88 (4.63-7.26)	96.19	
South America	8 (139, 1752)	9.27 (4.89-14.79)	90.68	
Oceania	1 (7, 398)	1.76 (0.71-3.59)	0.00	
Interpretation of resistance				
CLSI	65 (1823, 112801)	4.00 (3.00-5.00)	98.20	
EUCAST	60 (3237, 44863)	7.00 (6.00-9.00)	96.64	
WHO	8 (1044, 6858)	8.00 (3.00-14.00)	98.23	
AST				
MIC-based methods	116 (5772, 160099)	5.64 (4.46-6.93)	98.86	
Disk diffusion	10 (185, 2005)	9.24 (1.79-20.78)	94.38	
Mix methods	7 (147, 2418)	2.76 (0.376.80)	97.65	
Erythromycin	16 (3010, 13161)	21 (13-29)	98.69	0.68
Publication date				
1988-2013	11 (1423, 8186)	17.16 (6.08-32.12)	98.37	
2014-2018	1 (18, 25)	72.00 (50.61-87.93)	0.00	
2019-2021	4 (1569, 4950)	21.50 (7.17-40.61)	97.74	
Continent				
North America	4 (2713, 12123)	13.61 (6.01-23.62)	99.26	
Asia	3 (58, 176)	36.31 (0.00-93.16)	-	
Africa	4 (62, 223)	23.74 (0.00-88.05)	99.00	
Europe	5 (177, 639)	17.52 (0.45-49.43)	98.68	
South America		-	-	
Interpretation of resistance				
CLSI	10 (2791, 12527)	17.00 (9-26)	98.97	
EUCAST	5 (219, 558)	37.00 (13-64)	97.42	
WHO	1 (0, 76)	0.00 (0.00-2)	-	
AST				
MIC-based methods	1 (2, 12974)	24.11 (15.46-33.95)	98.92	
Disk diffusion	3 (18, 156)	12.58 (0.00-64.08)	0	
Mix methods	12 (2990, 31)	6.45 (0.79-21.42)	0	

CI, confidence interval; n, number of events (drug resistance); N, total number of isolates from the included studies

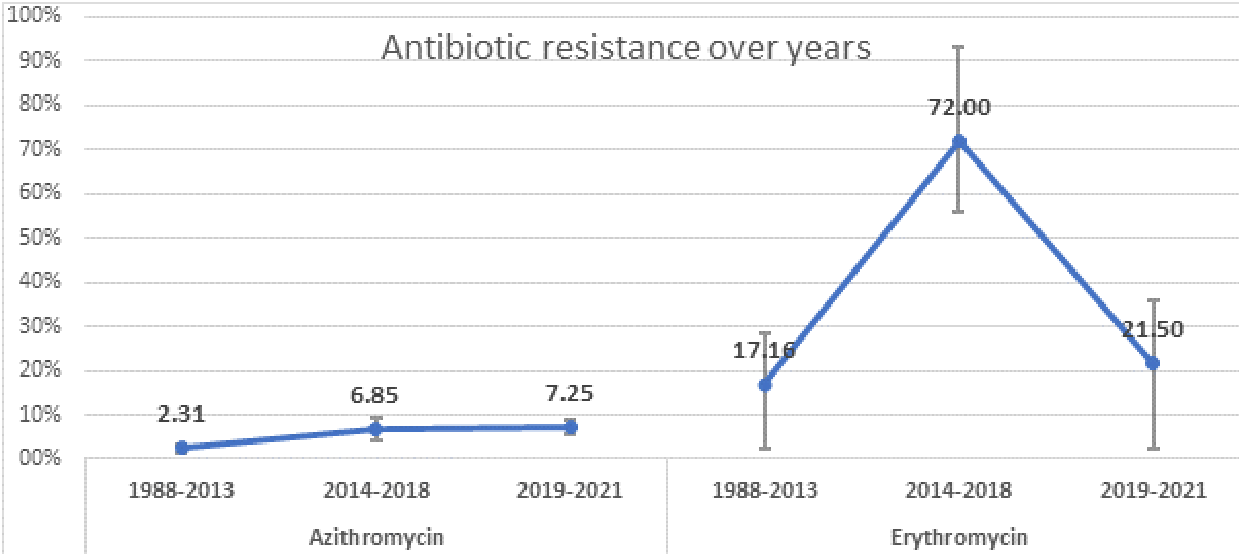

Figure 2. **The prevalence of antibiotics weighted pooled resistance over years**.

Erythromycin Resistance

The susceptibility to erythromycin was determined in 16 studies that included 13,161 NG isolates; the WPR was 21% (95% CI 13%-29%) with substantial heterogeneity (I^2=98.69%, *P* < 0.01) was observed between included studies (Table 1). Also, no significant publication bias was detected (Egger rank correlation test, *P*=0.68). As shown in the Table 1 and Figure 2, the prevalence of erythromycin resistance notably increased from 17.16% (95% CI 6.08-32.12) of 18 strains 1988-2013 reaching 72% (95% CI 50.61-87.93) of 1,569 strains in 2014-2018. Regarding erythromycin resistance, a huge increase was noted from the earlier time period of 1988-2013 to 2014-2018, but this was based on a single study [146] with very few isolates. The frequency of erythromycin resistance during the years 2019-2021 represents a gradual increase over the years 1988-2013. However, there was significant variation in the proportion of erythromycin resistance isolates over time (*P* <0.01). Among 11 countries reporting resistance data for erythromycin, 4 (~22%) countries (Bangladesh, Nigeria, Denmark, and Belarus) reported that >25% of specimens had resistance. There was a no statistically significant difference in the erythromycin resistance rates between different continents (*P*=0.83). No significant difference was found in the method used for AST (*P*=0.08). No significant difference was found in the interpretation of resistance based on CLSI, EUCAST, and WHO (*P*=0.79).

DISCUSSION

This metadata was conducted to study the prevalence of macrolides resistance in NG isolates around the world. It is proposed for the implication of continuous and robust monitoring of AMR of clinical NG isolates. NG AMR has become an important issue around the world in the past few decades [1,2]. In our metadata, the global WPRs over the past 30 years are higher than the 5% for azithromycin (6%) and erythromycin (21%). The WHO recommends that alternative agents should be used when NG AMR rate reaches a 5% threshold [147,148].

Ceftriaxone is the last choice for empirical first-line gonorrhea monotherapy in many countries [9]. However, emergence of decreased susceptibility or resistance to ceftriaxone have been stated globally. Currently most countries commonly suggest dual antimicrobial therapy (ceftriaxone 250-500mg plus azithromycin 1-2g) as empirical first-line gonorrhea treatment to prevent the emergence/accumulation of AMR [147]. However, as documented in the WHO's global gonococcal AMR surveillance 2017-18, there are major gaps in NG AMR surveillance [149]. The emergence of azithromycin and/or ceftriaxone resistance has been developing rapidly, which raises significant global challenges over the continued efficacy of current gonorrhea treatments [150-153]. During 2018, the WHO Gonococcal AMR Surveillance Programme (WHO-GASP) reported data on azithromycin resistance in NG among 61 countries in WHO regions; 44 (72%) countries reported that > 5% of specimens had resistance [1,2,9]. In this metadata, among 58 countries reporting resistance data for azithromycin, 17 (29.3%) countries (China, Bangladesh, Japan, Korea, Italy, Slovenia, Portugal, Slovenia, Iran, Denmark, Spain, and Ethiopia) reported that > 5% of specimens had azithromycin resistance. The area discrepancies in azithromycin-resistance rate of NG isolates may result from gonorrhea control policy, antibiotic stewardship, the lack of an

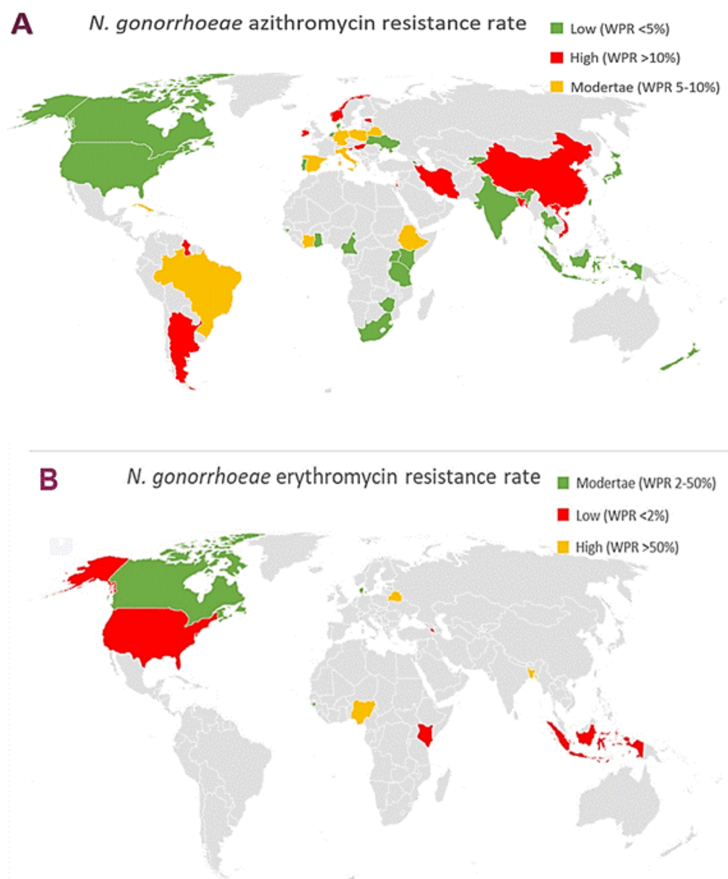

Figure 3. **Global map of reported weighted pooled resistance rates for (A) azithromycin and (B) erythromycin in the study**.

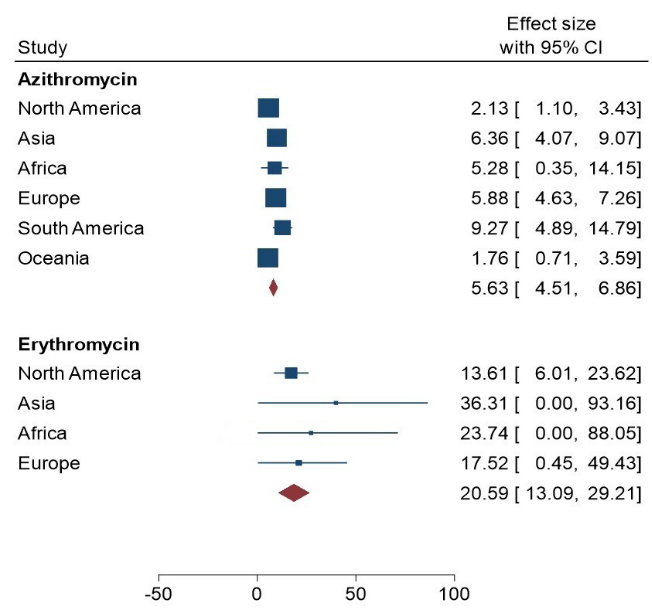

Figure 4. **Forest plot for the summary of azithromycin and erythromycin WPRs by regions**.

implementing response plans, antimicrobial misuse, and several AST methods. The selection and spread of azithromycin resistance are driven by unsuitable treatment of patients with suboptimal doses of azithromycin for gonococcal infection. Gonorrhea and AMR in NG are significant public health concerns globally, especially in Asian and European countries. In our metadata, the most reports were from Asia (50 reports) and Europe (46 studies) than on the other continents. Current evidence of AMR NG in Asian and European data supports rigorous monitoring of definite antibiotic policy, and active surveillance of infections. Furthermore, there is an alarm for the high prevalence (>10%) of azithromycin resistance in NG strains in China, Iran, Bangladesh, Myanmar, Vietnam, Norway, Ireland, Estonia, Hungary, and Slovenia. It is significant to appreciate the epidemiology of AMR in NG to inform treatment guidelines and prevention and control measures, in addition to wider gonorrhea prevention efforts.

This meta-analysis revealed a significant increase in the proportion of azithromycin resistance isolates over time, which is consistent with other reports [154,155]. Over the period, our findings showed that the trend of azithromycin resistance had increased from 1988-2013 to 2019-2021 (2.3% and 7.2%, respectively). Azithromycin resistance rate over times was increased as compared to erythromycin. The previous clinical and *in vitro* AMR data displayed early that erythromycin is not sufficiently effective for the treatment of gonorrhea [156,157]. So, due to the limited clinical effects of drugs (like; erythromycin) for the treatment of gonorrhea, currently most countries commonly suggest dual antimicrobial therapy (ceftriaxone 250-500mg plus azithromycin 1-2g) as empirical first-line gonorrhea treatment to prevent the emergence/accumulation of AMR [147]. The reason for the decrease in resistance to erythromycin in the past years is the lack of use of this drug in the treatment of gonorrhea.

The prevalence of azithromycin and erythromycin resistant NG isolates in South America (9.2%) and Asia (36.3%) is higher than in other continents. These results indicate that macrolides resistance patterns differed among geographic regions and in different periods.

Despite the significance of AST for clinical management of infection and AMR surveillance, the methodologies and breakpoints of the CLSI and EUCAST are used worldwide. Divergences in clinical breakpoints between CLSI and EUCAST considerably impact susceptibility interpretation of clinical isolates. This has implications not only for antibiograms at institutions switching between the two AST systems, but for broader AMR surveillance initiatives comparing data within and between countries using different systems or over the time period during which a shift in methodology is applied.

The creeping increase in the emergence of NG isolates with resistance to ceftriaxone plus azithromycin is a cause for a rising global challenge that necessitates further monitoring and investigation. The increase in emergence of reduced susceptibility or low- to high-level azithromycin resistance of NG strains has previously been reported to be related to mutational changes in the specific residues (the peptidyl-transferase loop) in domain V of the 23S rRNA, namely A2059G, C2611T, A2143G, A2058G, and multiple transferable resistance (Mtr) system as a tripartite efflux pump [158,159]. The main limitation of our review that is that we used collection date for data samples, rather than the publication date for analysis. The correct date of samples was not available or mentioned in all the included studies, so the authors performed the subgroup analysis by year published instead of the year of collection data of samples.

However, there were also several limitations of our meta-analysis to be addressed: (1) most of the included studies in this meta-analysis were conducted in European and Asian countries; (2); not including the strains identification code of NG in the included studies.

CONCLUSIONS

In this metadata, the global resistance prevalence was 6% for azithromycin and 48% for erythromycin. These are major insights into the epidemiological macrolides resistance pattern of NG over time and has highlighted the distribution of macrolides-resistant strains in continents/countries. The creeping increase in the emergence of NG isolates with resistance to ceftriaxone and/or azithromycin is a cause for a rising global challenge that necessitates robust monitoring and more investigation. The implications of this study emphasize the rigorous or improved antimicrobial stewardship, early diagnosis, contact tracing, and enhanced intensive global surveillance system are crucial for control of further spreading of gonococcal AMR.

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Data availability statement: All the data in this review are included in the manuscript.

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