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Review Article

Recent Macrolide Resistance Pattern of Mycoplasma Pneumonia in the World: A Systematic Review and Meta-Analysis

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Abstract

Background: We aimed to systematically review and analyze the prevalence and pattern of resistance in *Mycoplasma pneumoniae*.

Methods: We searched authentic scientific sources and databases, and reference lists of relevant articles from Jan 1, 2017, to Jun 1, 2023.

Results: Most of the included studies were conducted in Asia (11470 patients). The overall pooled prevalence was 53% (41%-65%), I2=99.69%; *P* <0.001. While subgroups analyses revealed that the pooled prevalence for America (3 studies), Asia (29 studies), and Europe (3 studies) was 9% (5%-12%), 62% (52%-73%), and 6% (1%-12%), respectively. Twenty-one eligible studies for determining of A2063G and 16 for A2064G were analyzed. Global pooled prevalence was 67% (58%-76%), I2=99.65%; *P*<0.001, and 3% (2%-4%), I2=87.44%; *P*<0.001 for A2063G and A2064G, respectively. Pooled prevalence of A2063G for America, Asia and Europe was 10% (5%-16%), 77% (71%-83%) and 5% (2%-9%), respectively.

Conclusion: While the prevalence of macrolide-resistant *M. pneumonia* is quite low in America, it is a great dilemma in East Asia and the low prevalence in most countries could be underestimated. This study revealed an increasing trend in macrolide resistance. Indiscriminate and improper use of macrolides may be a warning in this regard.

Keywords: Macrolide-resistant; Mycoplasma pneumoniae; Meta-analysis; Antimicrobial resistance; Drug resistance

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Introduction

Mycoplasma pneumonia has been recognized as one of the major causes of upper and lower respiratory tract disease in children and adults. After adding pneumococcal conjugate vaccine (PCV) 13 to national immunization programs in some countries, *M. pneumonia* has become leading cause of pediatric community-acquired pneumonia (CAP) (1, 2).

M. pneumonia infection cases chiefly represent mild or self-limited diseases. However, the *M. pneumonia* infection may occasionally lead to life-threatening and severe extra-respiratory manifestations such as skin lesions, hematologic disorders, cardiovascular and nervous disease (3-5).

The presence of extra-pulmonary manifestations of the *M. pneumonia* mainly depends on the host's immune response rather than on the pathogen itself (6). Infections caused by Macrolide-resistant *Mycoplasma pneumoniae* (MR-MP) can lead to an increased risk of complications, resulting in prolonged periods of fever, cough, hospitalization, and antibiotic treatment (7).

M. pneumonia infection is usually endemic in larger communities but also every 4-7-years outbreaks have been reported (8-10). The reason for these fluctuations may be due to antigenic shifts in strains and diminished herd immunity in populations (9, 11, 12).

M. pneumonia is a fastidious bacteria lacking a rigid cell wall; therefore, beta-lactam antimicrobial drugs are not a suitable choice for the *M. pneumonia* infection. Macrolides, tetracyclines, and fluoroquinolones are the first line of *M. pneumonia* infection treatment. Due to the side effects of tetracyclines and fluoroquinolones, only macrolides are recommended for children (7, 13).

Inappropriate use or overuse of macrolides has led to emerging of macrolide-resistant *M. pneumonia* strains. MR-MP was first reported in pediatric patients with CAP in 2001(14). The highest prevalence (13.6%-100%) of MR-MP was observed in Asia (7). However, the lowest resistance rate 0.2% has been revealed in Sweden (11).

Phenotypes of MR-MP are recognized by single nucleotide polymorphisms in the V domain of the single-copy *23S rRNA* gene (12, 15), and occurs more in children than in adults (16). The mutations that make a high level of macrolide resistance consist of the transition A2063G and the transversion A2064G, whereas the A2617G transition led to low-level resistance (12).

We conducted a systematic review and meta-analysis to evaluate spread of MR-MP in the world during recent years, to assess the emergence of resistant strains in the world, to characterize mechanisms of resistance, and analyze the correlation between genotype and macrolide resistance.

Materials and Methods

This study was based on the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) statement (17).

Search Strategy

We searched the PubMed/Medline, EMBASE, Cochrane Library, and reference lists of relevant articles from Jan 1, 2017 to Jun 1, 2023, using the keywords *Mycoplasma pneumoniae*, macrolide, antibiotic resistance, and drug resistance. The search was restricted to English articles.

Inclusion criteria

Two independent authors (I.A.D. and M.M.R). screened all titles and abstracts for eligibility. The study included articles with more than ten participants.

Review articles, editorial comments, case reports, and posters were excluded. However, correspondence or letters that fulfilled these criteria were also included.

Data Extraction and Quality Assessment

After full-text screening for eligibility and review, the three authors separately extracted data. We resolved disagreements by consensus or review-

ing by another reviewer. We extracted the following variables from each study, if available: author, journal, year of publication, study design, study country, period, detected point mutations, and anti-microbial resistance rate.

Data Analysis

Meta-analyses were performed on the extracted and evaluated epidemiological data for proportion outcome variables, which included factors associated with Macrolide resistance, A2063G and A2064G mutations. Forest plots were obtained to indicate the pooled estimates with 95% confidence intervals. We assessed heterogeneity using I2 measure within or between study designs. The null hypothesis was the absence of heterogeneity. If heterogeneity was rejected, a fixed model was used to calculate pooled estimates The meta-analysis was conducted using the STATA® version 17.0 (StataCorp, College Station, Lakeway, TX, USA). *P*-value <0.05 was considered a significant level.

Results

The studies included and excluded through the review process have been summarized in Fig. 1. The studies which have met the inclusion criteria and were chosen for the meta-analysis are listed in the Table 1.

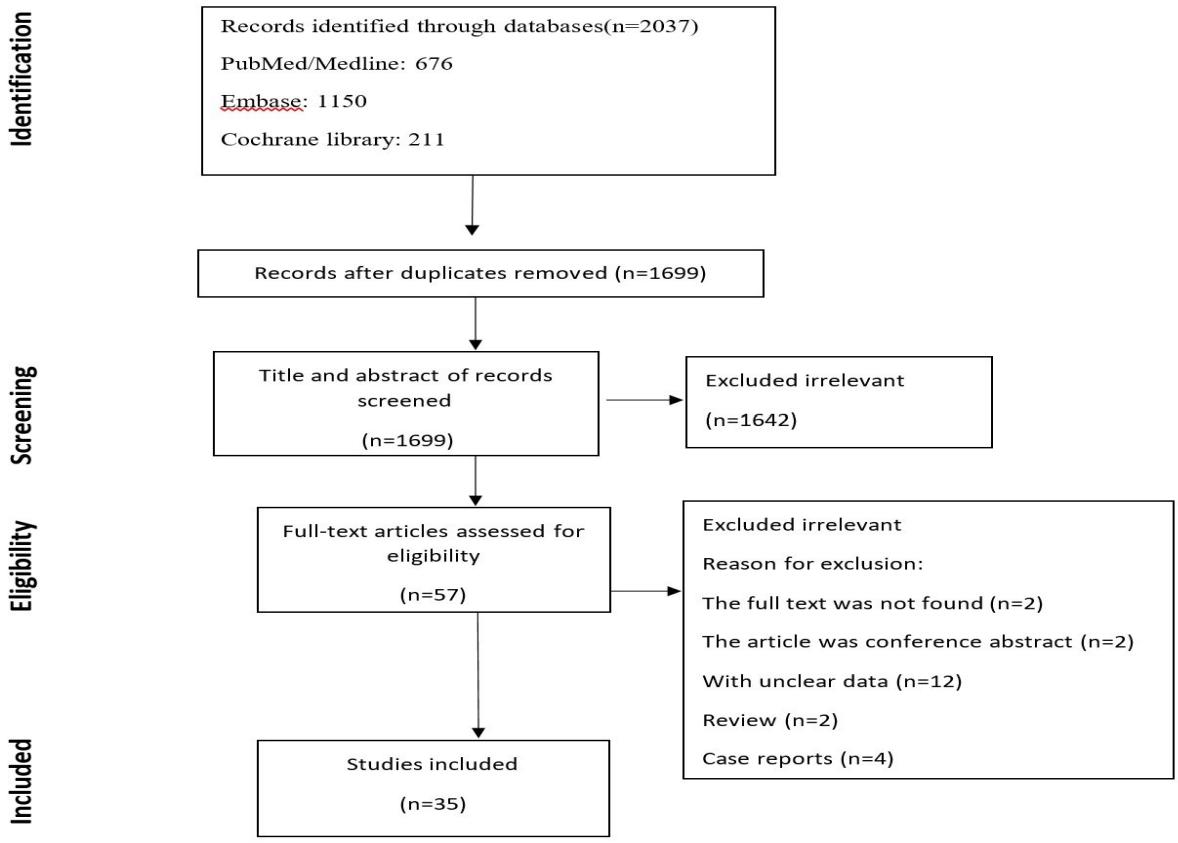

Fig. 1: Flow chart of study selection for inclusion in the systematic review and meta-analysis.

A total of 2037 records were found in the initial search, from which 1693 titles and abstracts were screened after removing duplicates. After the full-text review, 35 studies met the inclusion criteria and were chosen for the meta-analysis.

Table 1: Studies of the macrolide-resistant *Mycoplasma pneumoniae* (MR-MP) in world (2017–2022)

N	Authors	Year of study	Region	Population	Macrolide resistance rate
1	Rothstein et al. (45)	2022	America	114	10
2	Guo et al. (46)	2022	Asia	82	98.70
3	Chen et al. (47)	2021	Asia	207	70
4	Wang et al. (18)	2021	Asia	21	66.70
5	kakiuchi et al. (48)	2021	Asia	1524	90.94
6	Kuo et al. (49)	2021	Asia	105	88.10
7	Dou et al. (50)	2020	Asia	146	66
8	Morinaga et al. (51) *	2020	Asia	249	
9	Rivaya et al. (52)	2020	Europe	138	8
10	Nakamura et al. (21)	2020	Asia	1949	68.60
11	Hung et al. (53)	2020	Asia	226	77
12	Morozumi et al. (23)	2020	Asia	1092	46.80
13	Goodarzi et al. (54)	2019	Asia	270	56.90
14	Waites et al. (55)	2019	America	378	7.50
15	Zhao et al. (25)	2019	Asia	246	79.90
16	Guo et al. (56)	2019	Asia	164	90.85
17	Yang et al. (57)	2019	Asia	471	24
18	Lu et al. (58)	2019	Asia	180	24
19	Dumke et al. (28)	2019	Europe	166	3
20	Rodriguez et al. (59)	2019	America	27	18.50
21	Zhao et al. (60)	2019	Asia	81	65.40
22	Loconsole et al. (61)	2019	Europe	15	20
23	Katsukawa et al. (62)	2018	Asia	419	50.10
24	Guo et al. (63)	2018	Asia	65	87.69
25	Choi et al. (64)	2018	Asia	70	2.90
26	Shinto et al. (65)	2018	Asia	51	50.90
27	Tashiro et al. (66)	2018	Asia	1650	52.80
28	Du et al. (67)*	2017	Asia	102	
29	Tanaka et al. (68)	2017	Asia	145	67.60
30	Joon Kee Lee. (69)	2021	Asia	93	78.5
31	Ting-ting Jiang. (70)	2023	Asia	520	92.7
32	Meng-Hsiu Yen. (71)	2023	Asia	158	21.5
33	Xiao-Wen Zhan. (72)	2022	Asia	48	64.6
34	Jiahui Li. (73)	2022	Asia	139	10
35	Cheng-Yen Kuo. (49)	2021	Asia	159	88.1

* These studies have only the frequency of macrolide resistance genotypes.

Most of the included studies were conducted in Asia (29 studies). Studies sample size ranged from 15 to 1949, with 11470 patients.

Thirty-five eligible studies were included in order to evaluation of macrolide resistance. The overall pooled prevalence was 53% (41%-65%), I2=99.69%; P<0.001. While subgroups analyses revealed that the pooled prevalence for America (3 studies), Asia (29 studies) and Europe (3 studies) was 9% (5%-12%), 62% (52%-73%), and 6% (1%-12%), respectively. Moreover, the funnel diagram indicated that there was no publication bias in the studies (P<0.01) (Fig. 2).

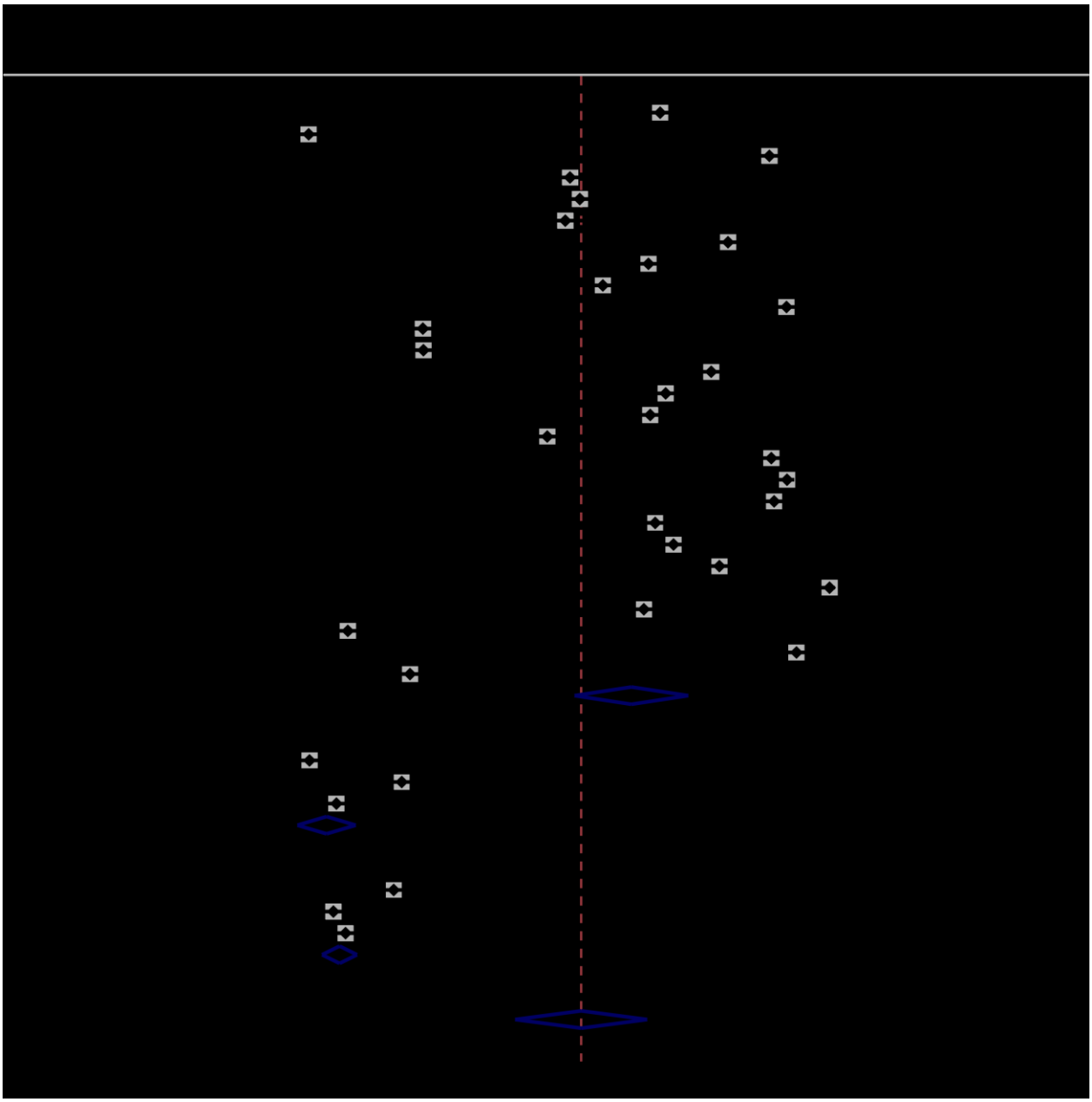

Fig. 2: Forest plot for pooled prevalence of macrolide resistance among regions of America, Asia and Europe

Twenty-one eligible studies for determining of A2063G were analyzed. Overall pooled prevalence was 67% (58%-76%), I2=99.65%; *P*<0.001. Pooled prevalence for America (1 study), Asia (18 studies) and Europe (2 studies) was 10% (5%-16%), 77% (71%-83%) and 5% (2%-9%), respectively. The funnel diagram, however, did not confirm the absence of publication bias in the present study (*P* <0.01) (Fig. 3).

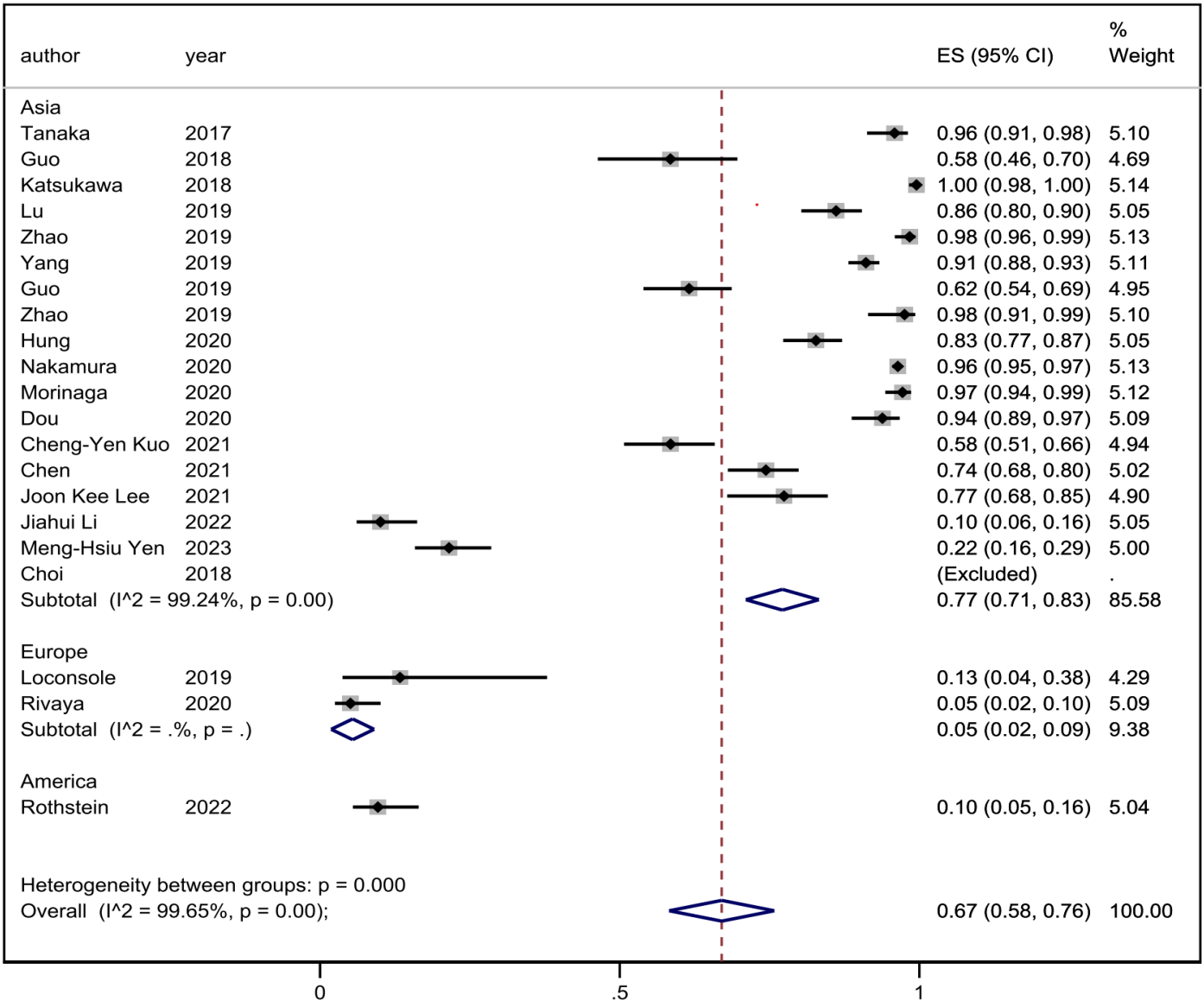

Fig. 3: Forest plot for pooled prevalence of A2063G among regions of America, Asia and Europe
Sixteen eligible studies for determining of A2064G were analyzed. Overall pooled prevalence was 3 % (2%-4%), I2=87.44%; *P* <0.001

Pooled prevalence for America (1 study), Asia (13 studies) and Europe (2 studies) was 9% (5%-15%), 3% (2%-4%) and 2% (0%-4%), respectively. The funnel diagram, however, did not confirm the absence of publication bias in the present study (*P* <0.01) (Fig. 4).

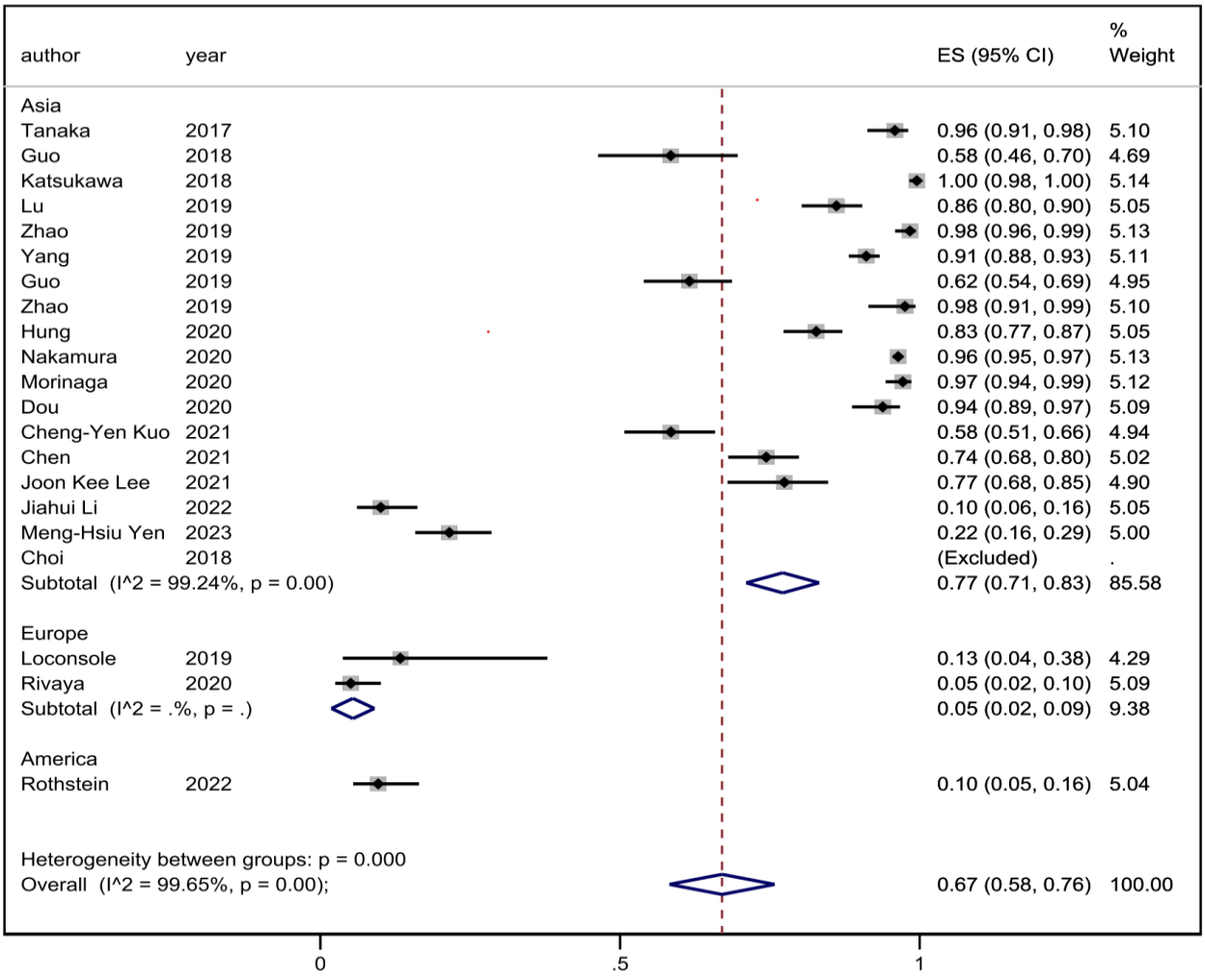

Fig. 4: Forest plot for pooled prevalence of A2064G among regions of America, Asia and Europe

Discussion

This systematic review and meta-analysis provide an overview of the spread of MR-MP infection in the world since 2017. The prevalence of MR-MP strains is a global and public health concern MR-MP strains emerged in 2000 and are spreading rapidly around the world(18). The highest resistance rates have been reported in Asia, mainly in China and Japan, at around 80–90%(18-20).

The incidence of MRMP in Japan has decreased in recent years (21). This decline has been recorded after the 2011-2012 outbreak (22). MR-MP rates decreased to 11.3% during the 2018–2019 period (23). High levels of MR-MP were reported in China between the 2013 and 2018 periods (24, 25). Regardless of Asia, the prevalence of MRMP in Europe is fairly low. The prevalence of MRMP is underestimated, as most European countries do not have national surveillance systems. This can be problematic because there is no rapid alert system to identify an increase in MRMP infection (26). The recorded rates of macrolide resistance in Europe suggest that MRMP strains lack a competitive advantage in a population that moderately used macrolides (27, 28). Italy and Scotland report the highest MRMP prevalence during the 2010-2011 outbreak (13, 29), while the Netherlands and Finland have not had MR-MP infections (18, 30). However, it is important to be cautious when comparing the prevalence rates mentioned in this report because the sample sizes in the studies vary significantly. The use of macro-

lides can directly lead to the development of drug-resistant strains of *M. pneumonia*, even after just a few days of treatment. This risk is especially high when patients are given inadequate drug concentrations, as has been seen with other antibiotics (31).

Macrolide resistance in *M. pneumonia* communicates with mutations in the *23S rRNA* gene (32). Various mutations in the *23S rRNA* gene were detected at positions 2063, 2064, and 2617 (5, 14, 33). "Notably, the A2063G mutation in domain V of the *23S rRNA* gene is the most prevalent in macrolide-resistant M. pneumonia isolates in China"(34-38).

M. pneumonia resistant rates may vary depending on the patient's background and the epidemiological situation of each country. For example, the decreased rate of MR-MP in recent years in Japan has been associated with the use of tosufloxacine, a fluoroquinolone, instead of macrolides for the treatment of *M. pneumonia* infections (39). Moreover, in Japan, the prevalence of the *M. pneumonia* p1 type could play a significant role in determining the restoration of sensitivity to macrolides (39).

The benefits of using antibiotics to treat *M. pneumonia* infections are not clear, as most infections are self-limiting (40). Macrolides seem to reduce the duration of symptoms; however, it cannot be attributed to their antibacterial or anti-inflammatory properties (41).

Evidence on whether patients benefit from the use of additional corticosteroids in the treatment of *M. pneumonia* infections is limited (42). The reason for using additional corticosteroid therapy with antibiotics in the management of *M. pneumonia* -infected patients with severe low respiratory tract infections is due to inflammation generated by an excessive immune response rather than by the pathogen itself (43).

Atypical pneumonia syndrome with fever, cough, and shortness of breath due to *M. pneumonia* can be challenging to distinguish from SARS-CoV-2 infection based on clinical presentations alone. Physicians treating patients with COVID19 should be aware that other respiratory pathogens can cause coinfection. Coinfections of *M. pneumonia* plus SARS-CoV-2 have been reported in the literature (44). Therefore, the SARSCoV2 diagnostic test should be performed in conjunction with testing for other respiratory pathogens to ensure better management of the patient.

Conclusion

To sum up, although the prevalence of macrolide-resistant *M. pneumonia* is relatively low in America, it is a great dilemma in Asia, particularly in the East. Moreover, there is not an active surveillance system for monitoring resistance patterns, thus, the low prevalence in most countries could be underestimated. This study revealed an increasing trend in macrolide resistance. During the outbreak of SARSCoV2, indiscriminate and incorrect consumption of several medications including macrolides based on hypothetical anti-inflammatory effects probably could be another warning and alarm regarding macrolide resistance. There is not enough data concerning fluoroquinolone resistance, however, this group of antibiotics could be an alternative for antimicrobial stewardship in the case of *M. pneumonia* macrolide resistance.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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