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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

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 reviewing 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.

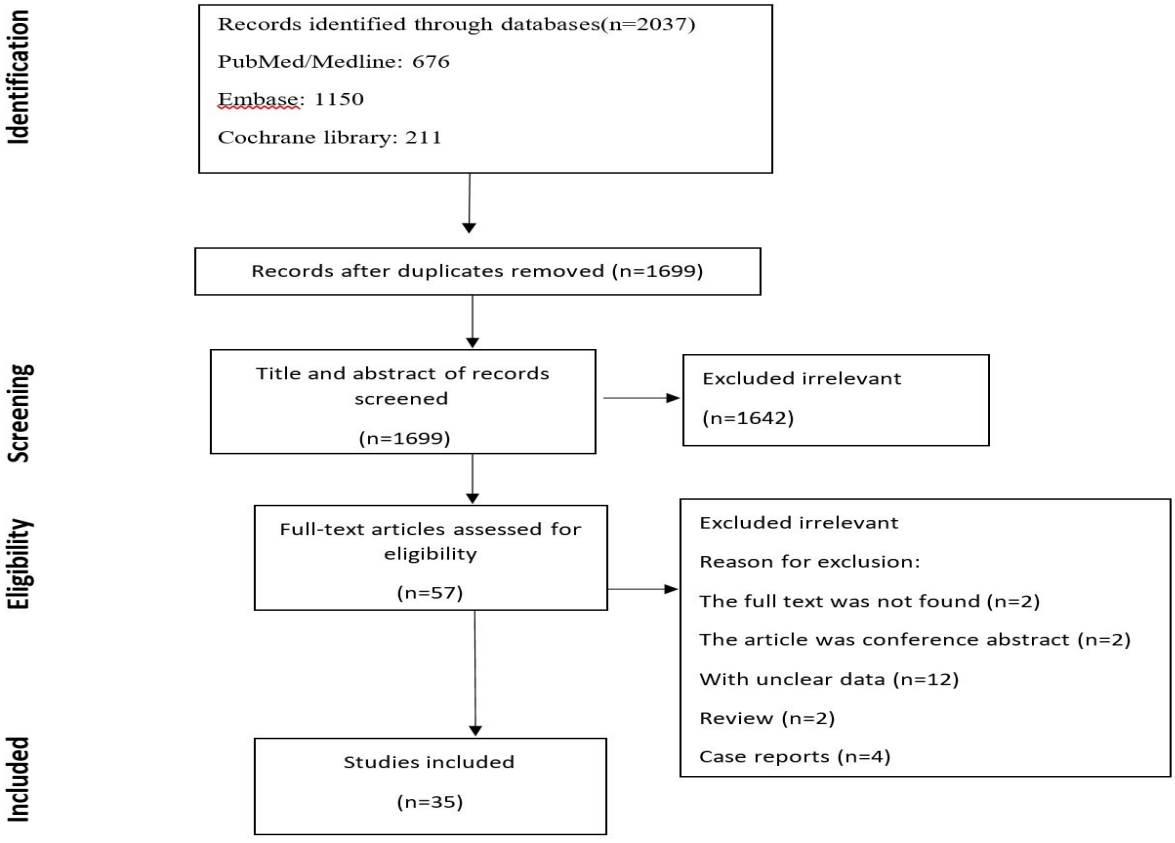

Fig. 1: Flow chart of study selection for inclusion in the systematic review and meta-analysis.

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).

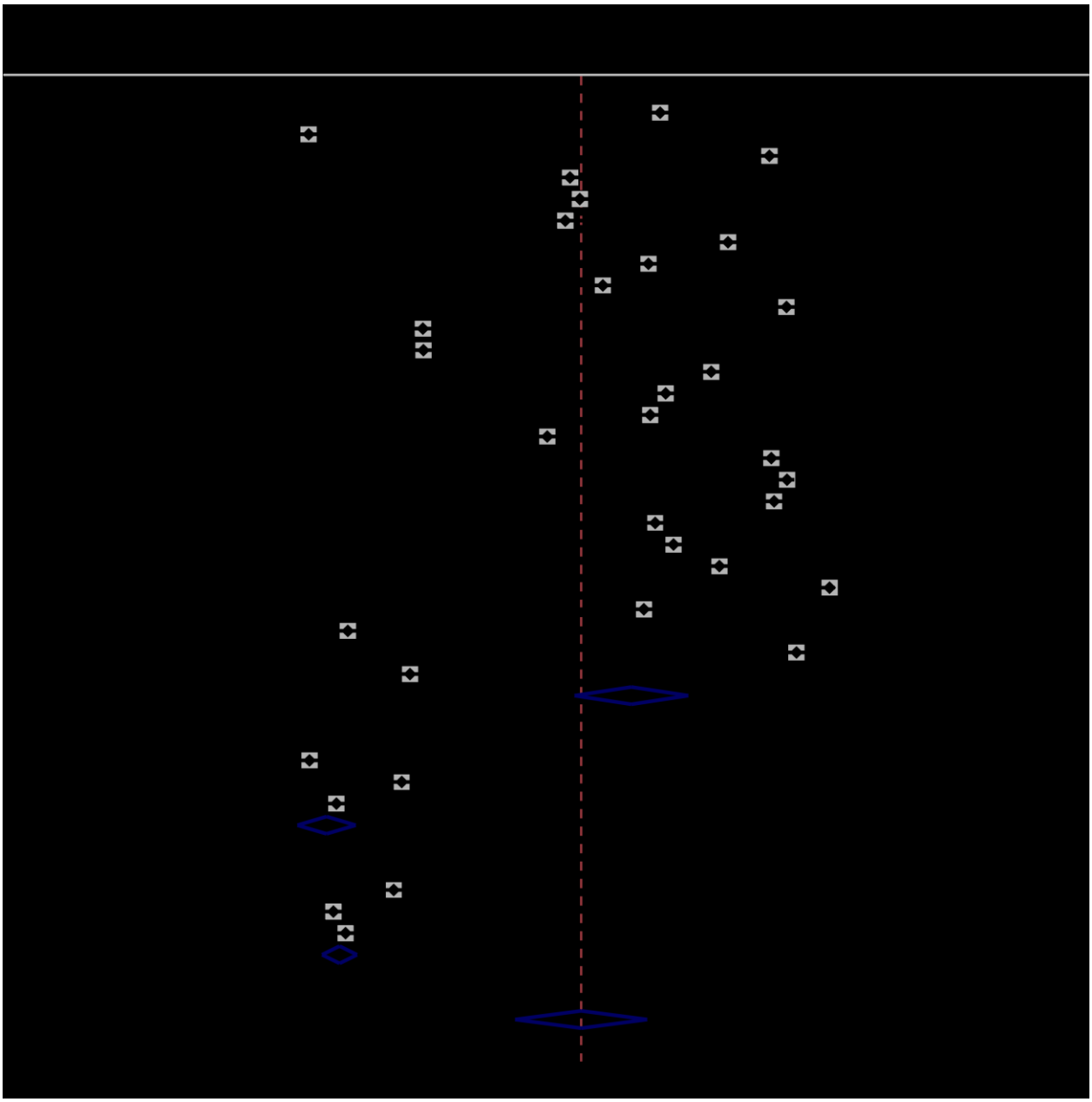

Fig. 2: Forest plot for pooled prevalence of macrolide resistance among regions of America, Asia and Europe

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).

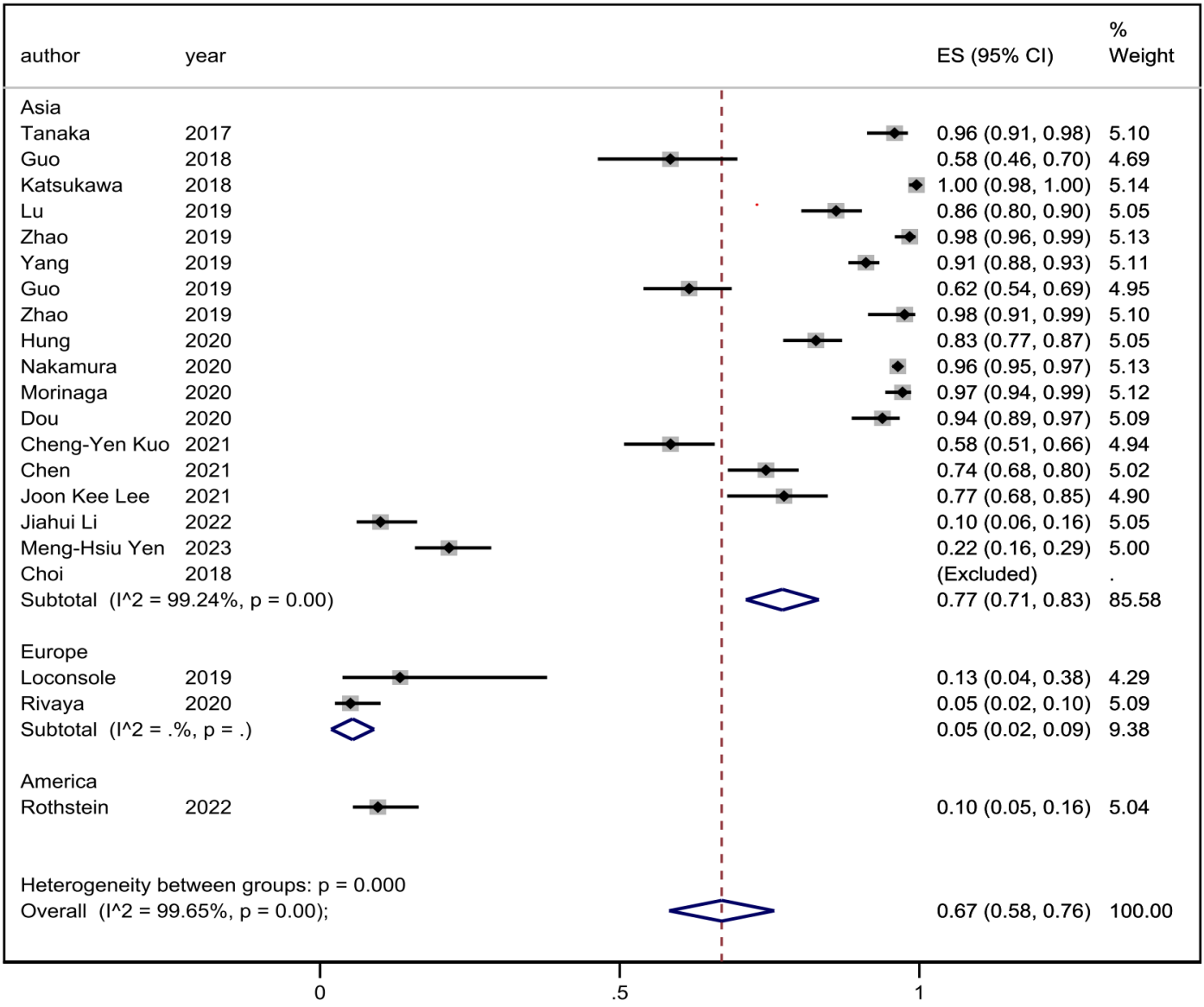

Fig. 3: Forest plot for pooled prevalence of A2063G among regions of America, Asia and Europe
Sixteen eligible studies for determining of A2064G were analyzed. Overall pooled prevalence was 3 % (2%-4%), I2=87.44%; *P* <0.001

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).

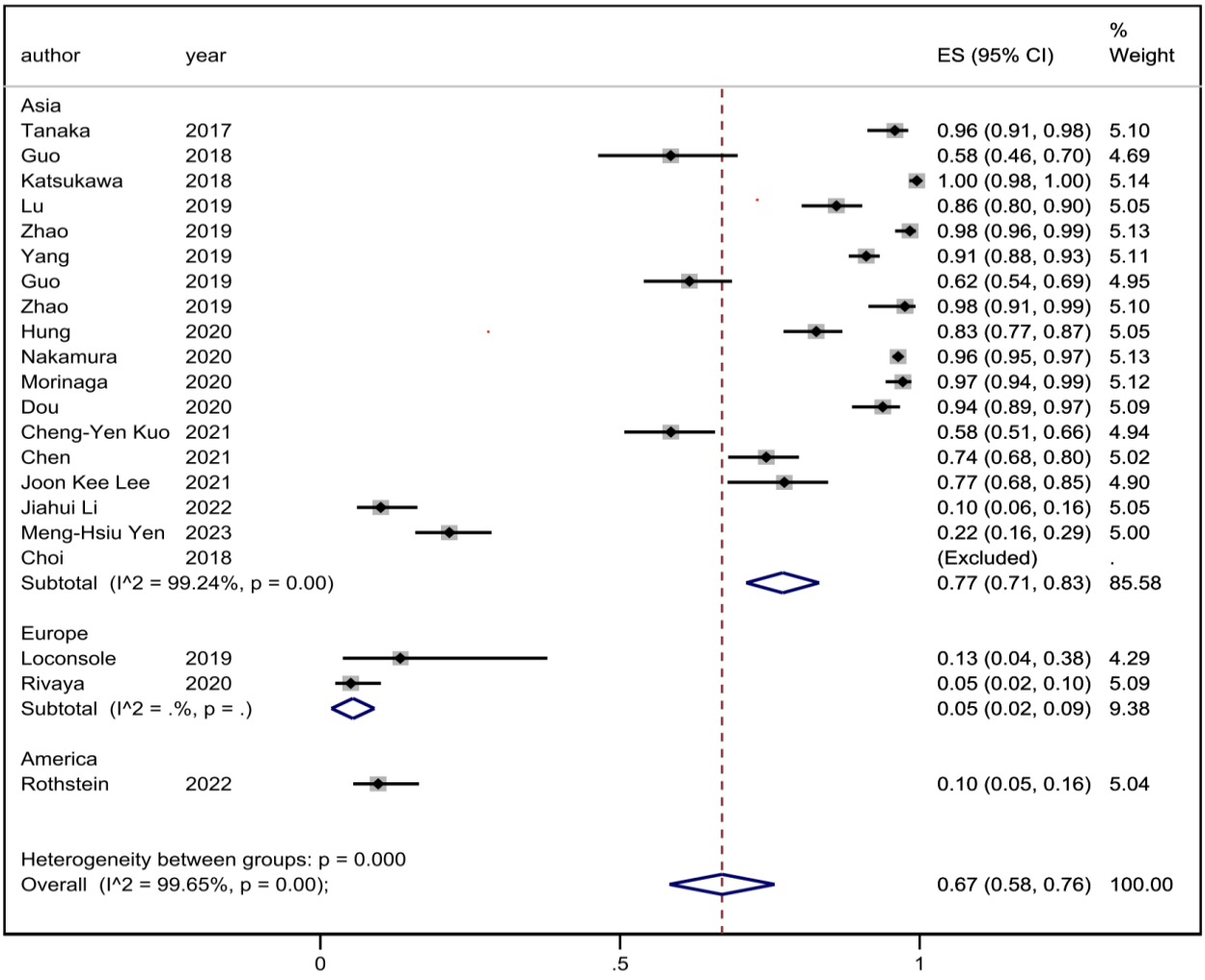

Fig. 4: Forest plot for pooled prevalence of A2064G among regions of America, Asia and Europe

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.

References

1. Carrie R, Chris S, Evan J, et al (2015). Community-acquired pneumonia requiring hospitalization among US children. *N Engl J Med*, 372 (9):835-45.
2. Shin EJ, Kim Y, Jeong JY, et al (2018). The changes of prevalence and etiology of pediatric pneumonia from National Emergency Department Information System in Korea, between 2007 and 2014. *Korean J Pediatr*, 61 (9):291-300.
3. Waites KB, Talkington DF (2004). Mycoplasma pneumoniae and its role as a human pathogen. *Clin Microbiol Rev,* 17 (4):697-728.
4. Narita M (2010). Pathogenesis of extrapulmonary manifestations of Mycoplasma pneumoniae infection with special reference to pneumonia. *J Infect Chemother,* 16 (3):162-9.
5. Principi N, Esposito S (2013). Macrolide-resistant Mycoplasma pneumoniae: its role in respiratory infection. *J Antimicrob Chemother,* 68 (3):506-11.
6. de Groot RCA, Meyer Sauteur PM, Unger WWJ, et al (2017). Things that could be Mycoplasma pneumoniae. *J Infect,* 74 Suppl 1:S95-S100.
7. Pereyre S, Goret J, Bébéar C (2016). Mycoplasma pneumoniae: Current Knowledge on Macrolide Resistance and Treatment. *Front Microbiol,* 7:974.
8. Dumke R, Catrein I, Herrmann R, Jacobs E (2004). Preference, adaptation and survival of Mycoplasma pneumoniae subtypes in an animal model. *Int J Med Microbiol,* 294 (2-3):149-55.
9. Atkinson TP, Balish MF, Waites KB (2008). Epidemiology, clinical manifestations, pathogenesis and laboratory detection of Mycoplasma pneumoniae infections. *FEMS Microbiol Rev,* 32 (6):956-73.
10. Rasmussen JN, Voldstedlund M, Andersen RL, et al (2010). Increased incidence of Mycoplasma pneumoniae infections detected by laboratory-based surveillance in Denmark in 2010. *Euro Surveill,* 15 (45): 19708.
11. Gullsby K, Olsen B, Bondeson K (2019). Molecular Typing of Mycoplasma pneumoniae Strains in Sweden from 1996 to 2017 and the Emergence of a New P1 Cytadhesin Gene, Variant 2e. *J Clin Microbiol,* 57 (6):e00049-19.
12. Morozumi M, Takahashi T, Ubukata K (2010). Macrolide-resistant Mycoplasma pneumoniae: characteristics of isolates and clinical aspects of community-acquired pneumonia. *J Infect Chemother,* 16 (2):78-86.
13. Chironna M, Sallustio A, Esposito S, et al (2011). Emergence of macrolide-resistant strains during an outbreak of Mycoplasma pneumoniae infections in children. *J Antimicrob Chemother,* 66 (4):734-737.
14. Okazaki N, Narita M, Yamada S, et al (2001). Characteristics of macrolide-resistant Mycoplasma pneumoniae strains isolated from patients and induced with erythromycin in vitro. *Microbiol Immunol,* 45 (8):617-20.
15. Hubert D, Dumke R, Weichert S, et al (2021). Emergence of Macrolide-Resistant Mycoplasma pneumoniae during an Outbreak in a Primary School: Clinical Characterization of Hospitalized Children. *Pathogens*, 10 (3):328.
16. Miyashita N, Akaike H, Teranishi H, et al (2013). Macrolide-Resistant Mycoplasma pneumoniae Pneumonia in Adolescents and Adults: Clinical Findings, Drug Susceptibility, and Therapeutic Efficacy. *Antimicrob Agents Chemother,* 57 (10):5181-5185.
17. Moher D, Liberati A, Tetzlaff J, et al (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med,* 151 (4):264-9, W64.
18. Wang Y, Xu B, Wu X, et al (2021). Increased Macrolide Resistance Rate of M3562 Mycoplasma pneumoniae Correlated With Macrolide Usage and Genotype Shifting. *Front Cell Infect Microbiol,* 11:675466.
19. Sun H, Xue G, Yan C, et al (2017). Changes in Molecular Characteristics of Mycoplasma pneumoniae in Clinical Specimens from Children in Beijing between 2003 and 2015. *PLoS One,* 12 (1):e0170253.

20. Yan C, Xue G, Zhao H, et al (2019). Molecular and clinical characteristics of severe Mycoplasma pneumoniae pneumonia in children. *Pediatr Pulmonol,* 54 (7):1012-1021.
21. Nakamura Y, Oishi T, Kaneko K, et al (2021). Recent acute reduction in macrolide-resistant Mycoplasma pneumoniae infections among Japanese children. *J Infect Chemother,* 27 (2):271-276.
22. Okada T, Morozumi M, Tajima T, et al (2012). Rapid effectiveness of minocycline or doxycycline against macrolide-resistant Mycoplasma pneumoniae infection in a 2011 outbreak among Japanese children. *Clin Infect Dis,* 55 (12):1642-9.
23. Morozumi M, Tajima T, Sakuma M, et al (2020). Sequence Type Changes Associated with Decreasing Macrolide-Resistant Mycoplasma pneumoniae, Japan. *Emerg Infect Dis,* 26 (9):2210-2213.
24. Xue G, Li M, Wang N, et al (2018). Comparison of the molecular characteristics of Mycoplasma pneumoniae from children across different regions of China. *PLoS One,* 13 (8):e0198557.
25. Zhao F, Li J, Liu J, et al (2019). Antimicrobial susceptibility and molecular characteristics of Mycoplasma pneumoniae isolates across different regions of China. *Antimicrob Resist Infect Control,* 8:143.
26. Lenglet A, Herrador Z, Magiorakos AP, et al (2012). Surveillance status and recent data for Mycoplasma pneumoniae infections in the European Union and European Economic Area, January 2012. *Euro Surveill,* 17 (5): 20075.
27. Adriaenssens N, Coenen S, Versporten A, et al (2011). European Surveillance of Antimicrobial Consumption (ESAC): outpatient macrolide, lincosamide and streptogramin (MLS) use in Europe (1997-2009). *J Antimicrob Chemother,* 66 Suppl 6:vi37-45.
28. Dumke R, Ziegler T (2019). Long-Term Low Rate of Macrolide-Resistant Mycoplasma pneumoniae Strains in Germany. *Antimicrob Agents Chemother,* 63 (5):e00455-19.
29. Ferguson GD, Gadsby NJ, Henderson SS, et al (2013). Clinical outcomes and macrolide resistance in Mycoplasma pneumoniae infection in Scotland, UK. *J Med Microbiol,* 62 (Pt 12):1876-1882.
30. Kurkela S, Puolakkainen M, Hokynar K, et al (2019). Mycoplasma pneumoniae outbreak, Southeastern Finland, 2017–2018: molecular epidemiology and laboratory diagnostic lessons. *Eur J Clin Microbiol Infect Dis,* 38 (10):1867-1871.71.
31. Pereyre S, Guyot C, Renaudin H, et al (2004). In vitro selection and characterization of resistance to macrolides and related antibiotics in Mycoplasma pneumoniae. *Antimicrob Agents Chemother,* 48 (2):460-5.
32. Waites KB, Balish MF, Atkinson TP (2008). New insights into the pathogenesis and detection of Mycoplasma pneumoniae infections. *Future Microbiol,* 3 (6):635-48.
33. Morozumi M, Hasegawa K, Kobayashi R, et al (2005). Emergence of macrolide-resistant Mycoplasma pneumoniae with a 23S rRNA gene mutation. *Antimicrob Agents Chemother,* 49 (6):2302-6.
34. Cao B, Zhao CJ, Yin YD, et al (2010). High prevalence of macrolide resistance in Mycoplasma pneumoniae isolates from adult and adolescent patients with respiratory tract infection in China. *Clin Infect Dis,* 51 (2):189-94.
35. Zhao F, Liu G, Wu J, et al (2013). Surveillance of Macrolide-Resistant Mycoplasma pneumoniae in Beijing, China, from 2008 to 2012. *Antimicrob Agents Chemother,* 57 (3):1521-1523.
36. Zhao F, Liu L, Tao X, et al (2015). Culture-Independent Detection and Genotyping of Mycoplasma pneumoniae in Clinical Specimens from Beijing, China. *PLoS One,* 10 (10):e0141702.
37. Zhao H, Li S, Cao L, et al (2014). Surveillance of Mycoplasma pneumoniae infection among children in Beijing from 2007 to 2012. *Chin Med J (Engl),* 127 (7):1244-8.
38. Zhou Y, Zhang Y, Sheng Y, et al (2014). More Complications Occur in Macrolide-Resistant than in Macrolide-Sensitive Mycoplasma pneumoniae Pneumonia. *Antimicrob Agents Chemother,* 58 (2):1034-1038.
39. Oishi T, Takahashi K, Wakabayashi S, et al (2019). Comparing Antimicrobial Susceptibilities among Mycoplasma pneumoniae Isolates from Pediatric Patients

in Japan between Two Recent Epidemic Periods. *Antimicrob Agents Chemother,* 63 (7):e02517-18.
40. Yu JL, Song QF, Xie ZW, et al (2017). iTRAQ-based Quantitative Proteomics Study in Patients with Refractory Mycoplasma pneumoniae Pneumonia. *Jpn J Infect Dis,* 70 (5):571-578.
41. Cardinale F, Chironna M, Chinellato I, et al (2013). Clinical Relevance of Mycoplasma pneumoniae Macrolide Resistance in Children. *J Clin Microbiol,* 51 (2):723-724.
42. Spuesens EB, Meyer Sauteur PM, Vink C, et al (2014). Mycoplasma pneumoniae infections--does treatment help? *J Infect,* 69 Suppl 1:S42-6.
43. Luo Z, Luo J, Liu E, et al (2014). Effects of prednisolone on refractory mycoplasma pneumoniae pneumonia in children. *Pediatr Pulmonol,* 49 (4):377-80.
44. Oliva A, Siccardi G, Migliarini A, et al (2020). Co-infection of SARS-CoV-2 with Chlamydia or Mycoplasma pneumoniae: a case series and review of the literature. *Infection,* 48 (6):871-877.
45. Rothstein TE, Cunningham SA, Rieke RA, et al (2022). Macrolide Resistance in Mycoplasma pneumoniae, Midwestern United States, 2014 to 2021. *Antimicrob Agents Chemother,* 66 (4):e0243221.
46. Guo Z, Liu L, Gong J, et al (2022). Molecular features and antimicrobial susceptibility of Mycoplasma pneumoniae isolates from paediatric inpatients in Weihai, China: Characteristics of M. pneumoniae In Weihai. *J Glob Antimicrob Resist,* 28:180-184.
47. Chen D, Zhang NL, Zhang T, et al (2021). [Detection of drug-resistance genes of Mycoplasma pneumoniae in bronchoalveolar lavage fluid of children with refractory Mycoplasma pneumoniae pneumonia]. *Zhongguo Dang Dai Er Ke Za Zhi,* 23(7):707-712.
48. Kakiuchi T, Miyata I, Kimura R, et al (2021). Clinical Evaluation of a Novel Point-of-Care Assay To Detect Mycoplasma pneumoniae and Associated Macrolide-Resistant Mutations. *J Clin Microbiol,* 59 (7):e0324520.
49. Kuo CY, Tsai WC, Lee HF, et al (2022). The epidemiology, clinical characteristics, and macrolide susceptibility of Mycoplasma pneumoniae pneumonia in children in Southern Taiwan, 2019-2020. *J Microbiol Immunol Infect*, 55(4):611-619.
50. Dou HW, Tian XJ, Xin L, et al (2020). Mycoplasma pneumoniae Macrolide Resistance and MLVA Typing in Children in Beijing, China, in 2016: Is It Relevant? *Biomed Environ Sci,* 33 (12):916-924.
51. Morinaga Y, Suzuki H, Notake S, et al (2020). Evaluation of GENECUBE Mycoplasma for the detection of macrolide-resistant Mycoplasma pneumoniae. *J Med Microbiol,* 69 (12):1346-1350.
52. Rivaya B, Jordana-Lluch E, Fernández-Rivas G, et al (2020). Macrolide resistance and molecular typing of Mycoplasma pneumoniae infections during a 4 year period in Spain. *J Antimicrob Chemother,* 75 (10):2752-2759.
53. Hung HM, Chuang CH, Chen YY, et al (2021). Clonal spread of macrolide-resistant Mycoplasma pneumoniae sequence type-3 and type-17 with recombination on non-P1 adhesin among children in Taiwan. *Clin Microbiol Infect,* 27 (8):1169.e1-1169.e6.
54. Noori Goodarzi N, Pourmand MR, Arfaatabar M, et al (2020). First Detection and Characterization of Macrolide-Resistant Mycoplasma pneumoniae from People with Community-Acquired Pneumonia in Iran. *Microb Drug Resist,* 26 (3):245-250.
55. Waites KB, Ratliff A, Crabb DM, et al (2019). Macrolide-Resistant Mycoplasma pneumoniae in the United States as Determined from a National Surveillance Program. *J Clin Microbiol,* 57 (11): e00968-19.
56. Guo D, Hu W, Xu B, et al (2019). Allele-specific real-time PCR testing for minor macrolide-resistant Mycoplasma Pneumoniae. *BMC Infect Dis,* 19 (1):616.
57. Yang TI, Chang TH, Lu CY, et al (2019). Mycoplasma pneumoniae in pediatric patients: Do macrolide-resistance and/or delayed treatment matter? *J Microbiol Immunol Infect,* 52 (2):329-335.
58. Lu CY, Yen TY, Chang LY, et al (2020). Multiple-locus variable-number tandem-repeat analysis (MLVA) of macrolide-susceptible and -resistant Mycoplasma pneumoniae in children in Taiwan. *J Formos Med Assoc,* 119 (10):1539-1545.
59. Rodriguez N, Mondeja B, Sardiñas R, et al (2019). First detection and characterization of

macrolide-resistant Mycoplasma pneumoniae strains in Cuba. *Int J Infect Dis,* 80:115-117.

60. Zhao F, Liu J, Shi W, et al (2019). Antimicrobial susceptibility and genotyping of Mycoplasma pneumoniae isolates in Beijing, China, from 2014 to 2016. *Antimicrob Resist Infect Control,* 8:18.
61. Loconsole D, De Robertis AL, Mallamaci R, et al (2019). First Description of Macrolide-Resistant Mycoplasma pneumoniae in Adults with Community-Acquired Pneumonia in Italy. *Biomed Res Int,* 2019:7168949.
62. Katsukawa C, Kenri T, Shibayama K, et al (2019). Genetic characterization of Mycoplasma pneumoniae isolated in Osaka between 2011 and 2017: Decreased detection rate of macrolide-resistance and increase of p1 gene type 2 lineage strains. *PLoS One,* 14 (1):e0209938.
63. Guo DX, Hu WJ, Wei R, et al (2019). Epidemiology and mechanism of drug resistance of Mycoplasma pneumoniae in Beijing, China: A multicenter study. *Bosn J Basic Med Sci,* 19 (3):288-296.
64. Choi JH, Seong GM, Ko Y, et al (2019). Prevalence and Clinical Features of Community-Acquired Pneumonia Caused by Macrolide-Resistant Mycoplasma pneumoniae Isolated from Adults in Jeju Island. *Microb Drug Resist,* 25 (4):577-581.
65. Shinto K, Kato K, Narita T, et al (2018). [Evaluation of novel nucleic acid detection kit for Mycoplasma pneumoniae]. *Rinsho Biseibutshu Jinsoku Shindan Kenkyukai Shi,* 28 (2):85-89.
66. Tashiro M, Fushimi K, Kawano K, et al (2017). Comparison of Efficacy of Antimicrobial Agents Among Hospitalized Patients With Mycoplasma pneumoniae Pneumonia in Japan During Large Epidemics of Macrolide-Resistant M. pneumoniae Infections: A Nationwide Observational Study. *Clin Infect Dis,* 65 (11):1837-1842.
67. Du D, Liao S, Wu Y, et al (2017). Serological Analysis and Drug Resistance of Chlamydia pneumoniae and Mycoplasma pneumoniae in 4500 Healthy Subjects in Shenzhen, China. *Biomed Res Int,* 2017:3120138.
68. Tanaka T, Oishi T, Miyata I, et al (2017). Macrolide-Resistant Mycoplasma pneumoniae Infection, Japan, 2008-2015. *Emerg Infect Dis,* 23 (10):1703-1706.
69. Lee JK, Choi YY, Sohn YJ, et al (2022). Persistent high macrolide resistance rate and increase of macrolide-resistant ST14 strains among Mycoplasma pneumoniae in South Korea, 2019–2020. *J Microbiol Immunol Infect,* 55 (5):910-916.
70. Jiang T, Sun L, Wang T, et al (2023). The clinical significance of macrolide resistance in pediatric Mycoplasma pneumoniae infection during COVID-19 pandemic. *Front Cell Infect Microbiol,* 13:1181402.
71. Yen MH, Yan DC, Wang CJ, et al (2023). The clinical significance of and the factors associated with macrolide resistance and poor macrolide response in pediatric Mycoplasma pneumoniae infection: A retrospective study. *J Microbiol Immunol Infect,* 56 (3):634-640.
72. Zhan XW, Deng LP, Wang ZY, et al (2022). Correlation between Mycoplasma pneumoniae drug resistance and clinical characteristics in bronchoalveolar lavage fluid of children with refractory Mycoplasma pneumoniae pneumonia. *Ital J Pediatr,* 48 (1):190.
73. Li J, Maiwald M, Loo LH, et al (2022). Clinical characteristics of macrolide-resistant Mycoplasma pneumoniae infections among hospitalised children in Singapore. *Ann Acad Med Singap,* 51 (10):653-656.