Effectiveness and safety of tetracyclines and quinolones in people with *Mycoplasma pneumonia*: a systematic review and network meta-analysis

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Summary

Background The escalating resistance of *Mycoplasma pneumoniae* to macrolides has become a significant global health concern, particularly in low-income and middle-income countries (LMICs). Although tetracyclines and quinolones have been proposed as alternative therapeutic options, concerns regarding age-specific safety issues and the lack of consensus in recommendations across various national guidelines prevail. Thus, the primary objective of this study is to ascertain the most efficacious interventions for second-line treatment of *M. pneumoniae* infection while considering the age-specific safety issues associated with these interventions.

Methods In this systematic review and network meta-analysis we searched PubMed, Embase, CNKI, and WanFang Data, from inception up to November 11th, 2023. Studies of quinolones or tetracyclines for the treatment of people with *M. pneumoniae* infection were collected and screened by reading published reports, with any type of study included, and no individual patient-level data requested. A systematic review and direct meta-analysis compared the efficacy of tetracyclines and quinolones regarding time to defervescence (TTD) and the rates of fever disappearance within 24 h and 48 h of antibiotic administration, for managing *M. pneumoniae* infection. Bayesian network meta-analysis (NMA) was employed to indirectly assess the relative effectiveness of different interventions in people with *M. pneumoniae* infection and the safety profile of medication in paediatric patients. This study is registered with PROSPERO, CRD42023478383.

Findings The systematic review and direct meta-analysis included a total of 4 articles involving 246 patients, while the NMA encompassed 85 articles involving a substantial cohort of 7095 patients. The NMA measured the effectiveness across all ages and included 7043 patients, with a mean age of 37.80 ± 3.91 years. Of the 85 included studies, 14 (16.5%) were at low risk of bias, 71 (83.5%) were at moderate risk, and no studies were rated as having a high risk of bias. In the direct meta-analysis, no statistically significant differences were found between tetracyclines and quinolones concerning TTD (mean difference: −0.40, 95% CI: −1.43 to 0.63; I^2 = 0%), fever disappearance rate within 24 h of antibiotic administration (OR: 0.37, 95% CI: 0.08–1.79; I^2 = 58%), and fever disappearance rate within 48 h of antibiotic administration (OR: 1.10, 95% CI: 0.30–3.98; I^2 = 59%). However, the comprehensive NMA analysis of clinical response (in 70 studies; n = 6143 patients), shortening of TTD (in 52 studies; n = 4363 patients), shortening length of cough relief or disappearance (in 39 studies; n = 3235 patients), fever disappearance rate at 48 h (in four studies; n = 418 patients) revealed that minocycline exhibited the most favourable outcomes across these various parameters, and the analysis of fever disappearance rate at 24 h (in three studies; n = 145 patients) revealed that levofloxacin may be the most effective, as indicated by the rank probabilities and surface under the cumulative ranking area (SUCRA) value. Moxifloxacin ranked second in clinical response and in shortening the length of cough relief or disappearance, and third in shortening TTD. Notably, when evaluating the occurrence of adverse reactions in paediatric patients (in four studies; n = 239 children), levofloxacin was associated with the highest SUCRA value rankings for the rate of adverse events.

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Translation: For the Chinese translation of the abstract see Supplementary Materials section.

Interpretation Our findings suggest that tetracyclines and quinolones may be equally effective. Based on the age of participants in the included studies, minocycline may be the most effective intervention for children over eight years of age when all preventive measures are considered, whereas moxifloxacin may benefit people under eight years of age. However, these results should be interpreted with caution, given the limited number of studies and patients included, and the heterogeneity between included studies. Based on a limited number of studies in children, levofloxacin is likely to have one of the highest rates of adverse reactions. The majority of the studies included in the NMA were from the Asian region, and more randomised controlled trials comparing different therapeutic strategies in patients with *M. pneumoniae* are warranted. This comparative study provides clinical pharmacists and clinicians with important information to enable them to make informed decisions about treatment options, considering drug efficacy and safety.

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Keywords: *Mycoplasma pneumoniae*; Tetracyclines; Quinolones; Paediatric; Network meta-analysis

Research in context

Evidence before this study

Preliminary search of PubMed, Embase, CNKI, and Wanfang Data using the search terms "tetracyclines AND quinolones AND *Mycoplasma pneumoniae*", with a search period from database establishment to November 11th, 2023, we identified some studies between quinolones and tetracyclines in treating patients with *M. pneumoniae* infection. Additionally, we found a systematic review and meta-analysis associated with it. However, this study was limited to children, and did not evaluate safety and the results should be carefully interpreted as only a small number of studies were included.

Added value of this study

To our knowledge, our study represents the inaugural and most comprehensive meta-analysis to date, examining the efficacy of tetracyclines and quinolones treating *M. pneumoniae* infections in people and safety in children. Our results suggest that tetracyclines and quinolones may be equally effective in treating *M. pneumoniae* infection, but minocycline may be the most effective intervention for improving clinical response, reducing the duration of fever and cough, and increasing the rate of fever disappearance within 48 h in individuals over eight years old with *M. pneumoniae* infection. For patients under the age of eight, moxifloxacin may be most effective. Paediatric safety assessments revealed that adverse reactions to levofloxacin were particularly prominent.

Implications of all the available evidence

M. pneumoniae has exhibited a propensity to develop drug resistance, especially to macrolides, and some second-line therapies are being considered for the treatment of people with MRMP infection. How to use antibiotics safely and effectively to treat people with MRMP infection is a difficult problem to solve. Our study addresses some gaps in the literature and may provide reference evidence for clinical practice guidelines. However, the results of the direct meta-analysis should be interpreted with caution, given the limited number and high heterogeneity between included studies, and the limited number of direct studies comparing quinolones with tetracyclines in terms of efficacy in people and safety in children. Further high-quality randomized controlled trials will be needed in the future to generate additional scientific evidence.

Introduction

Mycoplasma pneumoniae has exhibited global dissemination, with an incidence rate of 8.61% worldwide from 2017 to 2020.[1,2] The withdrawal of non-pharmacological intervention (NPI) measures after the COVID-19 pandemic has led to the resurgence of *M. pneumoniae* infection.[1] Increasing evidence shows that the prevalence of *M. pneumoniae* infection is growing,[3,4] with a global trend towards a high prevalence of macrolide-resistant *Mycoplasma pneumoniae* (MRMP) strains in particular.[5] *M. pneumoniae* resistance rates are 80–90% in Asia,[6–8] and up to 26% have been reported in some parts of Europe and the United States.[9] The prevalence of MRMP strains is alarmingly high, often leading to serious extrapulmonary diseases that are life-threatening and difficult to treat[10–12] and are associated with heightened disease burden, diminished quality of life, and increased mortality.[13,14]

With the increasing rate of MRMP resistance, many guidelines recommend quinolones and tetracyclines as alternative treatments for MRMP infection. However, age-specific safety issues have caused uncertainty and hesitation about the optimal dosing regimen. For example, quinolones have cartilage erosion hazards,[15]

and tetracyclines may cause permanent staining of teeth and transient anostosis in children.[16] Some guidelines recommend inconsistent alternative treatment options. The Infectious Diseases Society of America (IDSA) supports doxycycline, levofloxacin, and moxifloxacin as second-line antibiotics for treating *M. pneumoniae* infections.[17] However, the Chinese guidelines recommend new tetracyclines and quinolones for the treatment of MRMP infection, and the recommendations for specific drugs are still unclear.[18] Beyond this, although certain data indicate that tetracyclines may be more effective than tosufloxacin in fever disappearance at 48 h in patients with MRMP infection, there is inadequate evidence to establish the superiority of either group.[19] This means that clinical pharmacists may lack sufficient high-quality evidence to assist clinicians in making comparisons and decisions.

Although *M. pneumoniae* pneumonia is often a self-limited disorder, clinicians should be aware that delaying the decision to use a second-line antibiotic may induce further complications and a healthcare-related burden if symptoms persist or show signs of clinical deterioration after failure of macrolide therapy.[20] Currently, there is no high-level evidence to confirm the superiority or inferiority of tetracyclines and quinolones in the treatment of patients suffering from *M. pneumoniae* infections, and there are substantial gaps in safety comparisons of alternative treatment options for use in MRMP-infected children. Therefore, this study aims to compare the effectiveness of quinolones and tetracyclines in the treatment of patients with *M. pneumoniae* infection and their safety in children for the first time and to determine the optimal treatment regimen and alleviate the expenditure of medical institutions for antibiotic-related drug resistance, which is essential to provide the most efficient treatment given the limited local resources and capabilities and provides evidence to guide future epidemic prevention and treatment in east Asia and even globally.

Methods

Search strategy and selection criteria

This systematic review and network meta-analysis (NMA) was conducted according to the Cochrane recommendations,[21] and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for network meta-analyses.[22] The study protocol was defined and registered prior to study initiation at the PROSPERO database (Registration Number CRD42023478383).

Two authors (FC and JL) independently searched PubMed, Embase, CNKI, and WanFang Data, which were used to collect relevant studies regarding data on the effectiveness of quinolones and tetracyclines in treating patients with *M. pneumoniae* infection, as well as data on the safety of *M. pneumoniae* in children. Considering the age-specific safety issues of quinolones and tetracyclines, safety-related studies were limited to children, and studies of efficacy were included in the general population regardless of age. The last search was updated to November 11th, 2023, to identify studies published since our initial search. There are no restrictions on the type of research. When the results of a study were reported in multiple publications, we included the study with the richest and most recent findings. We also searched the literature lists of relevant systematic reviews on quinolones or tetracyclines for the treatment of *M. pneumoniae* infections in patients and manually searched the references included in the reviews for additional access to relevant literature. The search terms were: "quinolones", "tetracyclines", "macrolides", "ciprofloxacin", "levofloxacin", "moxifloxacin", "tosufloxacin", "doxycycline", "minocycline", "chlortetracycline", "oxytetracycline", "*mycoplasma*", "*mycoplasma pneumoniae*", etc. In order to maximise the number of papers found, we searched using both MeSH and free-text terms without any language restrictions. The complete search strategies for all databases are provided in Supplementary Table S1.

By combining EndnoteX9 deduplication with manual deduplication, literatures were selected based on established inclusion criteria, and literature searches obtained from different databases are merged to establish a new information database and download the full text. Three authors (FC, JL and LW) independently reviewed and evaluated the titles, abstracts, and full text of the literature for studies considered relevant. Clinical studies of quinolones and tetracyclines for the treatment of patients with *M. pneumoniae* infection were included. Among them, clinical studies related to safety are targeted at children. Letters and conference abstracts, editorials, comments, expert opinions, and other literature that cannot obtain safety information for the case report series have been excluded. In addition, the following studies were excluded: patients were on multiple medications including quinolones or tetracyclines, and it was not possible to determine from the articles whether the clinical outcomes were caused by quinolones or tetracyclines; the studies included patients with pneumonia, but it was not possible to separately extract data on patients with *M. pneumoniae* infection; and the studies included data on the adverse effects of the medications after their use by the patients, but it was not possible to extract the data on children.

The common primary outcomes were direct or indirect comparisons of quinolones with tetracyclines, including overall clinical outcomes for patients with *M. pneumoniae* infection after treatment initiation and safety for children with *M. pneumoniae* infection. In this case, overall clinical effectiveness was assessed by clinical response, time to defervescence (TTD), length of cough relief or disappearance, and fever disappearance rate within 24 h and 48 h of antibiotic administration,

and safety was assessed by the probability of side effects after antibiotic use in children. Clinical response is defined as improvement in pneumonia signs, symptoms, and imaging after treatment without a cause of clinical failure. Safety was assessed by the incidence of adverse events (AEs) occurring. Progression of disease or signs and symptoms of disease were not reported as AEs unless they were more severe in intensity or more frequent than expected for the patient's condition.

We used the Cochrane Collaboration Risk of Bias tool (ROB 2.0)[23] to assess the risk of bias in randomised controlled trials (RCTs), the Risk of Bias in Non-randomised Studies of Interventions tool (ROBINS-I)[24] to assess non-RCTs, and the Newcastle–Ottawa Scale (NOS)[25] to assess the quality of cohort studies. Quality assessment was done by two independent reviewers (FC and JL), with a third researcher deciding in case of disagreement.

For RCTs, the overall risk of bias across the various domains was assessed following the Cochrane Handbook. When all domains were judged to be at low risk of bias, the overall risk of bias was considered low. The overall risk of bias assessment criteria for non-RCTs and cohort studies are shown in Supplementary Table S2.

Data analysis

Two researchers (FC and JL) jointly extracted and verified data, including: study characteristic (first author, year of publication), baseline characteristics and intervention measures of the patients, key elements of bias risk assessment, outcome indicators and outcome measurement data of concern. Data were extracted as intention-to-treat analyses assuming all dropouts to be treatment failures (i.e. no response to different drugs or placebos). Our research follows the extraction of raw data from each individual study, and for areas of disagreement, discussions and negotiations with third parties are used to resolve them. Information that was not identified but was important for this study was obtained from the authors of the original studies by e-mail and telephone contact, if needed.

The overall clinical efficacy of quinolones and tetracyclines in patients with *M. pneumoniae* infections and their therapeutic safety in children with *M. pneumoniae* infections were analysed separately. In addition, different varieties of the same drug class are studied separately because potential pharmacokinetic differences may affect efficacy or onset of action. A systematic review and direct meta-analysis were used to compare the differences between the two classes of drugs directly, and NMA was an indirect comparison of tetracyclines and quinolones with macrolides, respectively, and a direct comparison of tetracyclines and quinolones. Statistical analysis was performed using Review Manager 5.4 and R (V.4.0.2) with Odds Ratio (OR) as the analytical statistic; 95% confidence intervals (CI) and credible interval (CrI) were used to evaluate efficacy and safety. Heterogeneity between trials was assessed using I^2; if $I^2 < 25\%$ and $P > 0.05$, heterogeneity between the included literature was considered to be small; If $25 \leq I^2 \leq 50\%$, moderate heterogeneity is considered between the included literature and meta-analysis was performed using a fixed-effects model; conversely, If $I^2 > 50\%$, heterogeneity between the included literature was considered to be large and meta-analysis was performed using a random-effects model. NMA was performed on varieties of drugs, funnel plots were drawn to visually assess the presence of publication bias, and Egger's test was used to assess the asymmetry of the funnel plots.

The confidence in estimates of outcomes derived from the NMA were evaluated following the Confidence in Network Meta-Analysis (CINeMA) approach,[26] which is broadly based on Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[27] NMA was conducted within a Bayesian framework using Markov chain Monte Carlo methods and using R (V.4.0.2) software's ' BUGSnet 'and' GeMTC 'packages for calculations.[28,29] When there was a closed loop, direct and indirect evidence inconsistency was assessed using the node-split method. If the $P > 0.05$ between the two interventions' direct, indirect, and network comparisons, there was no statistical difference, and the agreement was good. Transitivity was assessed by a Bayesian random effects, network meta-regression, and the covariates included sample size, publication year, study design, mean age and country. The final model was used to calculate the probability of each treatment's cumulative ranking area on the lower surface of the curve, which represented the percentage of efficacy of the drug compared to the reference drug, with a higher surface under the cumulative ranking area (SUCRA) value indicating a higher ranking.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Literature search and selection

The bibliographic search yielded 14,454 citations, of which 8867 studies were identified as potential conditions based on abstract screening and retrieved for full-text evaluation. After manually reading the titles and abstracts of the remaining literature, 8758 articles were excluded that did not meet the inclusion criteria of this study in terms of patients and intervention measures. Further reading the entire article ruled out 24 articles including combination therapy, incomplete outcome data or inability to merge outcomes, in vitro experiments, and inability to obtain the entire article. Finally,

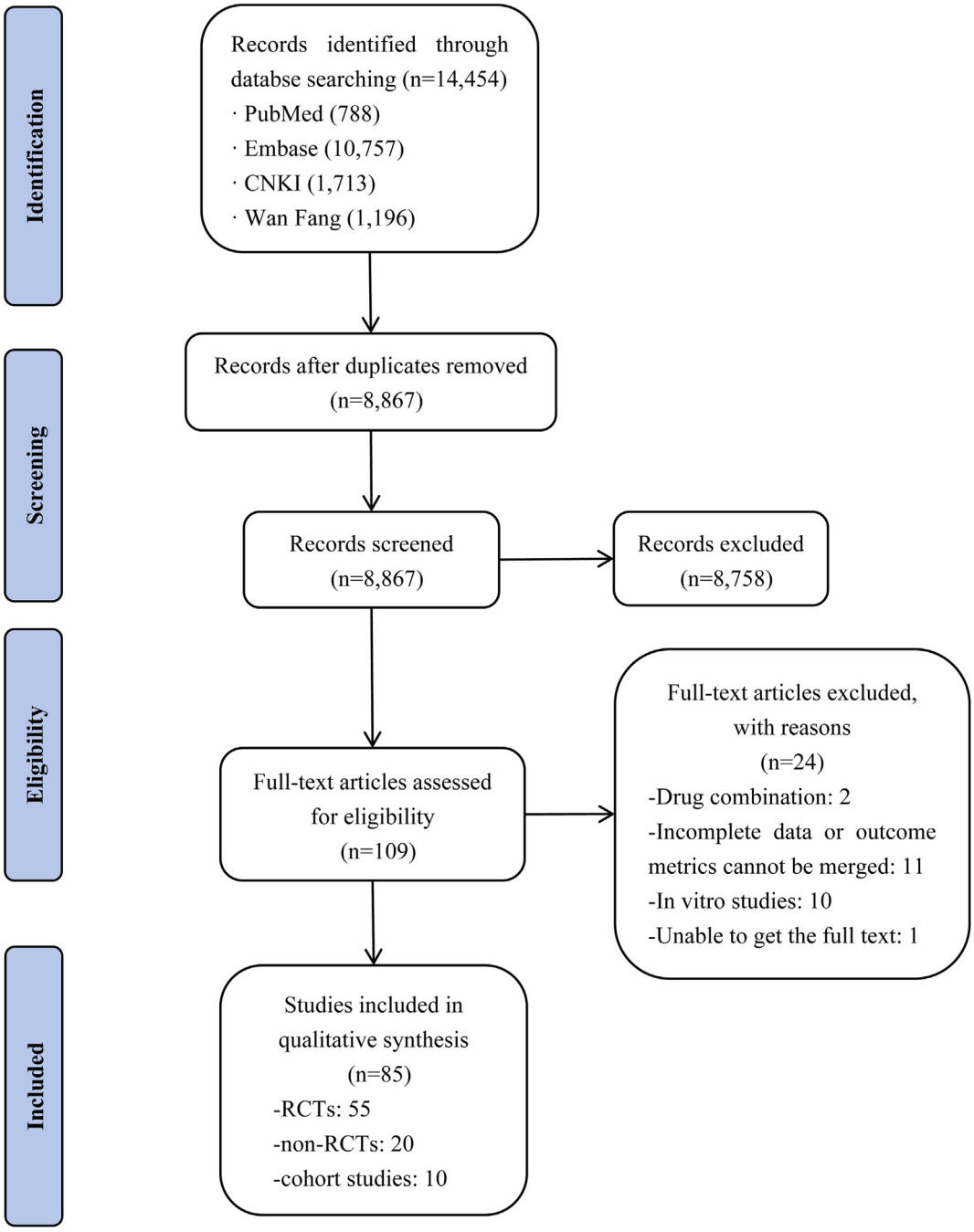

***Fig. 1:* Flow diagram of assessment of studies identified in the systematic review.** RCTs, randomised controlled trials.

85 articles were included. The literature screening process is shown (Fig. 1).

Basic characteristics of included literature

In order to evaluate the clinical efficacy of quinolones and tetracyclines in the treatment of *M. pneumoniae* infection in people and safety in children, a total of 85 studies were screened and included, specific information on the studies was shown in Table 1 and supplemented by Supplementary Table S3, including 55 RCTs,[30–54,55–84] 20 non-RCTs,[85–104] and 10 cohort studies.[105–114] A total of 7095 patients were infected with *M. pneumoniae*. The baseline situation of the treatment group treated with quinolones and tetracyclines was

First author, year	Country	Study design	Male (%)	Intervention	Control	Sample size (Intervention/Control)	Age,mean ± SD (Intervention/Control)	Duration of treatment (days)
Jiang-Rui Dai, 2016[30]	China	RCT	62.9	Azithromycin	Levofloxacin	70 (35/35)	52.1 ± 6.4/53.6 ± 6.8	21/15
Xiao-Lin Chen, 2015[31]	China	RCT	50.0	Moxifloxacin	Azithromycin	98 (49/49)	36.3 ± 9.3/36.5 ± 9.2	10
Jia-Yin Li, 2020[32]	China	RCT	58.8	Levofloxacin	Azithromycin	102 (51/51)	38.1 ± 6.4/37.9 ± 6.4	7
Hong-mei Gao, 2020[33]	China	RCT	NA	Levofloxacin	Azithromycin	80 (40/40)	NA	7
Li-Qing Jin, 2016[34]	China	RCT	69.3	Levofloxacin	Azithromycin	62 (31/31)	73.3 ± 7.4/74.6 ± 8.3	7
Zong-Liang Mai, 2021[35]	China	RCT	57.6	Levofloxacin	Azithromycin	66 (33/33)	51.09 ± 5.75/50.83 ± 5.68	7
Yi-Ping Liu, 2021[36]	China	RCT	42.7	Levofloxacin	Azithromycin	68 (34/34)	44.0 ± 7.7/43.5 ± 7.5	7
Sheng Tan, 2018[37]	China	RCT	55.8	Levofloxacin	Azithromycin	86 (43/43)	28.34 ± 3.59/27.26 ± 3.44	14
Xue-Yan Du, 2021[38]	China	RCT	55.0	Moxifloxacin	Azithromycin	60 (30/30)	46.11 ± 1.39/45.23 ± 1.77	14
Wei–wei Zhang, 2016[39]	China	RCT	54.7	Levofloxacin	Azithromycin	64 (32/32)	43 ± 2/45 ± 3	7
Hong-Wei Zhang, 2015[40]	China	RCT	59.3	Moxifloxacin	Azithromycin	108 (54/54)	45.3	14–21
Pei-Jun Chen, 2020[41]	China	RCT	53.1	Moxifloxacin	Azithromycin	96 (48/48)	29.30 ± 3.3/28.80 ± 3.5	5
Guo-Qiang Li, 1998[42]	China	RCT	44.4	Ciprofloxacin	Erythromycin	72 (40/32)	NA	NA
Ping Zhu, 2004[43]	China	RCT	66.7	Gatifloxacin	Erythromycin	42 (21/21)	42	14
Ping Xin, 2008[44]	China	RCT	58.3	Moxifloxacin	Azithromycin	36 (20/16)	NA	14
Cheng Tang, 2021[45]	China	RCT	NA	Moxifloxacin	Azithromycin	92 (46/46)	49.13 ± 1.42/49.54 ± 1.55	14
Hong-Jie Wang, 2022[46]	China	RCT	57.5	Moxifloxacin	Azithromycin	120 (60/60)	38.23 ± 2.81/38.15 ± 2.66	14
Ju Hu, 2014[47]	China	RCT	70.6	Moxifloxacin	Azithromycin	68 (34/34)	44[a]	14–21
Yun-Hu Pan, 2011[48]	China	RCT	59.3	Moxifloxacin	Azithromycin	98 (50/48)	45.3	14–21
Guo-Feng Bai, 2010[49]	China	RCT	59.8	Moxifloxacin	Erythromycin	92 (46/46)	24.3 ± 8.1	14
Li Xiao, 2019[50]	China	RCT	57.0	Moxifloxacin	Azithromycin	158 (79/79)	28.17 ± 7.93/28.39 ± 8.21	14
Hai-Xia Zhang, 2015[51]	China	RCT	64.6	Moxifloxacin	Azithromycin	48 (24/24)	34 ± 3.1	14–21
Wei Li, 2020[52]	China	RCT	50.6	Moxifloxacin	Azithromycin	156 (78/78)	40.1 ± 11.3/39.14 ± 10.1	5–7
Shao-Ming Liang, 2016[53]	China	RCT	60.5	Moxifloxacin	Azithromycin	220 (110/110)	38.9 ± 4.1/39.5 ± 4.5	14
Ting–Ting Lv, 2020[54]	China	RCT	54.2	Moxifloxacin	Azithromycin	48 (24/24)	42.17 ± 1.29	15
Yu-Qin Sun, 2014[55]	China	RCT	58.0	Moxifloxacin	Azithromycin	150 (75/75)	25.3 ± 9.6	15
Hong-Ying Xiao, 2017[56]	China	RCT	51.7	Moxifloxacin	Erythromycin	60 (30/30)	37 ± 4.5/40 ± 5.5	14
Xiang Zhu, 2016[57]	China	RCT	42	Moxifloxacin	Azithromycin	86 (43/43)	36.84 ± 2.16	14
Xiu-Qing Huang, 2016[58]	China	RCT	53.6	Moxifloxacin	Azithromycin	84 (42/42)	39.8 ± 3.4/39.6 ± 3.2	14
Rui Wang, 2018[59]	China	RCT	51.8	Moxifloxacin	Azithromycin	56 (28/28)	38.46 ± 2.28/39.22 ± 2.54	14
Wen-Xian Liu, 2015[60]	China	RCT	63.3	Moxifloxacin	Azithromycin	60 (30/30)	38.7 ± 4.8/38.5 ± 4.7	15
Xiao-Qiang Zhang, 2019[61]	China	RCT	52.9	Moxifloxacin	Azithromycin	104 (52/52)	45.75 ± 10.93/ 45.74 ± 10.91	14–27
Yan-Ge Jiao, 2018[62]	China	RCT	63.9	Moxifloxacin	Azithromycin	94 (47/47)	45.6 ± 3.1/45.2 ± 3.2	14
Yi-Lu Li, 2016[63]	China	RCT	56.3	Moxifloxacin	Azithromycin	80 (40/40)	56.1 ± 2.3/55.8 ± 2.5	7–14
Shi-Min Xue, 2016[64]	China	RCT	62.5	Moxifloxacin	Erythromycin	80 (40/40)	68.82 ± 1.27/69.27 ± 1.49	14
Xian Huang, 2015[65]	China	RCT	58.3	Moxifloxacin	Azithromycin	60 (30/30)	25.30 ± 2.50/25.20 ± 2.56	10–14

(Table 1 continues on next page)

First author, year	Country	Study design	Male (%)	Intervention	Control	Sample size (Intervention/Control)	Age,mean ± SD (Intervention/Control)	Duration of treatment (days)
(Continued from previous page)								
Bao-Qi Sun, 2017[66]	China	RCT	70.7	Moxifloxacin	Azithromycin	58 (29/29)	30.1 ± 8.6/30.9 ± 8.7	10–14
Li-Sheng Yang, 2013[67]	China	RCT	52.4	Moxifloxacin	Azithromycin	126 (65/61)	47/48	10–14
Zai-Qiang Jiang, 2011[68]	China	RCT	51.3	Moxifloxacin	Erythromycin	80 (40/40)	43.8 ± 11.5/41.8 ± 12.5	7–14
Ting Lu, 2018[69]	China	RCT	50	Moxifloxacin	Azithromycin	90 (45/45)	45.45 ± 11.13/45.71 ± 11.13	7
Xu-Ling Li, 2015[70]	China	RCT	53.9	Moxifloxacin	Erythromycin	102 (51/51)	25.2 ± 7.4/25.2 ± 7.5	7
Dong-Xia Hao, 2017[71]	China	RCT	42.2	Moxifloxacin	Azithromycin	128 (64/64)	46.3	14–21
Xin-Yan Shang, 2018[72]	China	RCT	56.7	Moxifloxacin	Azithromycin	120 (60/60)	44.5/43.5	10
Kang-Rong Ma, 2020[73]	China	RCT	61.1	Moxifloxacin	Azithromycin	18 (9/9)	52.42 ± 5.73/52.58 ± 5.69	20
Dan Yu, 2014[74]	China	RCT	55.0	Levofloxacin	Azithromycin	20 (10/10)	5.46 ± 1.54/5.36 ± 1.74	7–15
Qun Wang, 2014[75]	China	RCT	62.5	Levofloxacin	Azithromycin	80 (40/40)	35.25 ± 10.12	14
Jin Fan, 2008[76]	China	RCT	43.1	Levofloxacin	Azithromycin	58 (30/28)	NA	10–14
Dan-Hong Zhang, 2017[77]	China	RCT	64.0	Moxifloxacin	Erythromycin	50 (25/25)	57.3 ± 3.5/56.5 ± 2.9	14
Si-Jing Lu, 2010[78]	China	RCT	61.1	Levofloxacin	Azithromycin	108 (54/54)	73.5 ± 7.6	7
Ai-Zhi Dong, 2009[79]	China	RCT	61.7	Levofloxacin	Erythromycin	60 (30/30)	69.00/68.53	28
Hong-Fa Xie, 2012[80]	China	RCT	NA	Doxycycline	Azithromycin	113 (53/60)	NA	21
Hong-Zhou Ye, 2016[81]	China	RCT	41.7	Doxycycline/Azithromycin + methylprednisolone	Azithromycin	44 (21/23)	9.2 ± 1.6, 8.5 ± 1.8/ 9.3 ± 1.0	6
Xue Yang, 2013[82]	China	RCT	54.2	Minocycline	Azithromycin	59 (28/31)	9.78 ± 1.42/10.54 ± 1.96	5
Xiao-Dong Tao, 2010[83]	China	RCT	NA	Moxifloxacin	Levofloxacin	200 (120/80)	51.6	7–14
Min Zhao, 2001[84]	China	RCT	39.6	Sparfloxacin	Erythromycin	53 (28/25)	35.4 ± 6.02/32.6 ± 9.13	10–14
Yasuhiro Kawai, 2013[85]	Japan	non-RCT	NA	Clarithromycin/Tosufloxacin/ Minocycline	Azithromycin	150 (23,62,38/27)	8.4/8.0, 6.5, 9.8	14
H. Lode, 1995[86]	France, Germany, Italy, UK, Belgium, Greece, Israel, Netherlands, Spain	non-RCT	NA	Sparfloxacin/Amoxycillin-clavulanic acid	Erythromycin	20 (14/6)	55/56, 52	14
Mei Li, 2020[87]	China	non-RCT	69.0	Levofloxacin	Azithromycin	142 (71/71)	51.00 ± 3.75/51.25 ± 3.60	7
Ji-Hong Ma, 2001[88]	China	Non-RCT	55.0	Ciprofloxacin	Erythromycin	60 (30/30)	3–13	NA
Shu-Juan Cai, 2019[89]	China	non-RCT	0	Moxifloxacin	Azithromycin	45 (23/22)	64.5 ± 4.0/63.3 ± 4.2	14
Jun-Xi Wu, 2017[90]	China	non-RCT	43.3	Moxifloxacin	Azithromycin	60 (30/30)	49.27 ± 3.08	5–7
Jian-Hua Yu, 2017[91]	China	non-RCT	57.5	Moxifloxacin	Azithromycin	146 (73/73)	36.12 ± 5.14/37.12 ± 3.15	14
Xue-Lian Yan, 2020[92]	China	non-RCT	53.9	Moxifloxacin	Azithromycin	76 (38/38)	51.36 ± 5.34/52.24 ± 5.48	14
Xiu-Jun Wu, 2021[93]	China	non-RCT	56.3	Moxifloxacin	Azithromycin	80 (40/40)	48.17 ± 4.79/48.95 ± 4.31	14
Yan-Chun Liu, 2016[94]	China	non-RCT	66.3	Moxifloxacin	Azithromycin	86 (43/43)	41.5 ± 6.2/35.6 ± 5.3	14
Huan–Huan Ma, 2020[95]	China	non-RCT	62.7	Moxifloxacin	Azithromycin	53 (34/33)	37.8 ± 3.9/36.6 ± 4.4	14
Yu Ping, 2018[96]	China	non-RCT	53.4	Moxifloxacin	Azithromycin	88 (44/44)	30.85 ± 1.07/30.29 ± 1.94	14
Zhi-Jun Gong, 2018[97]	China	non-RCT	60.9	Moxifloxacin	Azithromycin	64 (32/32)	38.47 ± 2.99/39.23 ± 2.55	15
Kuan Wang, 2021[98]	China	non-RCT	56.7	Moxifloxacin	Azithromycin	90 (45/45)	32.03 ± 3.19/32.05 ± 3.16	14

(Table 1 continues on next page)

First author, year	Country	Study design	Male (%)	Intervention	Control	Sample size (Intervention/Control)	Age,mean ± SD (Intervention/Control)	Duration of treatment (days)
(Continued from previous page)								
Liang-Yu Zhang, 2022[99]	China	non-RCT	44.6	Moxifloxacin	Azithromycin	92 (46/46)	29.81 ± 4.20/31.81 ± 4.20	14
Zhi-Xin Chen, 2020[100]	China	non-RCT	57.0	Moxifloxacin	Azithromycin	100 (50/50)	42.15 ± 6.26/42.26 ± 6.31	5
Xia Liang, 2015[101]	China	non-RCT	55.0	Moxifloxacin	Azithromycin	202 (101/101)	44.2 ± 5.4/44.3 ± 5.3	14–21
Zhi-Ping Xu, 2016[102]	China	non-RCT	70.0	Moxifloxacin	Azithromycin	60 (30/30)	36.7 ± 4.1	3–7
Yu-Xian He, 2012[103]	China	non-RCT	47.6	Moxifloxacin	Erythromycin	126 (63/63)	23 ± 4.5/25 ± 3.4	14
Ya-Ping Wang, 2012[104]	China	non-RCT	NA	Levofloxacin	Azithromycin	42 (20/22)	NA	7–14
Seok Gyun Ha, 2018[105]	Korea	cohort	41.8	Doxycycline/Levofloxacin	prolonged macrolide	20 (6/14)	5.2/10.1, 9.7[a]	7–14
Takafumi Okada, 2012[106]	Japan	cohort	51.7	Minocycline/Doxycycline/ Tosufloxacin	Macrolides	94 (52,16,13/13)	8[a]	6
Yu-Shan He, 2022[107]	China	cohort	59.6	Moxifloxacin	Azithromycin	52 (31/21)	6.05 ± 3.49/6.96 ± 3.72	NA
Xing-Ru Tao, 2021[108]	China	cohort	62.2	Levofloxacin	Doxycycline	45 (29/26)	7.47 ± 1.68/8.89 ± 1.26	7–14
Wei-Hua Zhu, 2013[109]	China	cohort	54.9	Levofloxacin+ β-lactam/ Moxifloxacin	Azithromycin+ β-lactam	51 (23/28)	43.52 ± 18.13	7–14
Shan-Feng Li, 2016[110]	China	cohort	35.4	Moxifloxacin	Azithromycin	99 (63/36)	38.8 ± 15.5	3
Sheng-You Li, 2009[111]	China	cohort	NA	Gatifloxacin	Azithromycin	54 (28/26)	NA	14
Xian-Rong Zhou, 2007[112]	China	cohort	NA	Gatifloxacin	Azithromycin	54 (28/26)	NA	14
Yan-Zhe Li, 2009[113]	China	cohort	NA	Moxifloxacin	Azithromycin	68 (31/37)	NA	14
Ying Pang, 2021[114]	China	cohort	55.1	Doxycycline	Azithromycin	98 (46/52)	11.5 ± 2.1	5–7

[a]The median age of the children was used in the study; NA: Not Applicable; More details were listed in Supplementary Data (Supplementary Table S3.).

Table 1: **Summary characteristics of all included studies.**

comparable to that of the control group treated with other drugs. Because of the year in which the studies were included, the rate of resistance to macrolides in *M. pneumoniae* may vary. Therefore, we reported the rates of resistance to macrolides in *M. pneumoniae* in different years of the included studies (Supplementary Table S4).

Quality assessment of included studies

One RCT, seven non-RCTs, and six cohort studies were assessed as low overall risk of bias, 54 RCTs, 13 non-RCTs, and 4 cohort studies were assessed as moderate overall risk of bias, and there were no studies assessed as high overall risk of bias (Table 2). Detailed quality assessment results for each study are shown (Supplementary Tables S5–S7).

Systematic review and direct meta-analysis

Time to defervescence

Two retrospective cohort studies[105,108] directly compared quinolones and tetracyclines regarding TTD. Ha SG et al.[105] treated patients with levofloxacin and doxycycline for secondary treatment respectively, and the results showed that TTD was 5.1 ± 1.3 days for levofloxacin and 5.9 ± 2.2 days for doxycycline. Tao et al.[108] treated children with levofloxacin and doxycycline, and TTD was 3.79 ± 1.74 days in the levofloxacin group and 3.88 ± 2.47 days in the doxycycline group.

There was no statistically significant difference in TTD in the quinolones compared with the tetracyclines (mean difference [MD] = –0.40, 95% CI: –1.43 to 0.63, P = 0.44). And there was no significant heterogeneity between studies (I^2 < 50%) (Fig. 2).

Study type	Overall risk of bias			Total
	Low	Moderate	High	
RCTs	1	54	0	55
Non-RCTs	7	13	0	20
Cohort studies	6	4	0	10
Total	14	71	0	85

RCTs: randomised controlled trials.

Table 2: **Overall risk of bias results.**

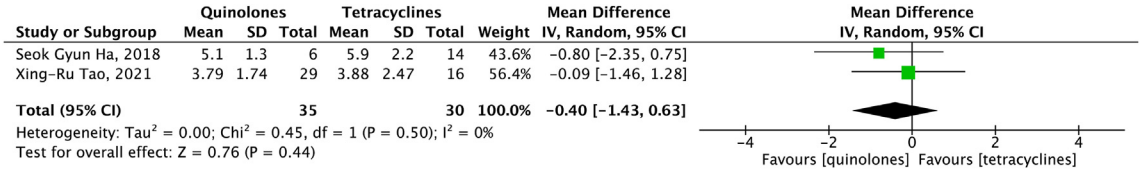

***Fig. 2:* Forest plot of pairwise comparison in terms of the time to defervescence with quinolones and tetracyclines.** Each horizontal line on the forest plot represents the pooled mean difference of quinolones compared with tetracyclines, with the mean difference plotted as a green rectangle and the 95% confidence interval plotted as the line. For each estimate, the black shaded area is the weight of the estimate in proportion to the overall effect. CI, confidence interval represents the mean treatment effect.

Fever disappearance rate within 24 h and 48 h of antibiotic administration

In two studies,[105,106] which compared the rate of fever disappearance within 24 h of antibiotic administration, Ha SG et al.[105] showed that the 24 h fever disappearance rate was 83.3% (5/6) in the levofloxacin group and 64.3% (9/14) in the doxycycline group. Okada T et al.[106] treated MRMP patients with minocycline, doxycycline, and tosufloxacin for secondary treatment, respectively, showed that the 24 h fever disappearance rate was 57.7% (30/52) in the minocycline group, 81.3% (13/16) in the doxycycline group, and 30.8% (4/13) in the tosufloxacin group.

There was no significant difference between the quinolones and the tetracyclines in terms of the fever disappearance rate in patients with 24 h of antibiotic administration (OR: 0.37, 95%CI: 0.08–1.79, $P = 0.22$). And there was heterogeneity between studies ($I^2 = 58\%$) (Fig. 3).

In a non-RCT and two cohort studies[85,105,106] comparing the rate of fever disappearance after 48 h with quinolones and tetracyclines, Ha SG et al.[105] showed that the 48 h fever disappearance rate was 83.3% (5/6) in the levofloxacin group and 85.7% (12/14) in the doxycycline group. Okada T et al.[106] showed the rate of 32.7% (17/52) in the minocycline group, 6.3% (1/16) in the doxycycline group, and 38.5% (5/13) in the tosufloxacin group. Kawai Y et al.[85] compared minocycline and tosufloxacin and showed a 48 h fever disappearance rate of 69% (43/62) and 87% (33/38) respectively.

There was no significant difference between the quinolones and the tetracyclines in terms of the fever disappearance rate in patients with 48 h of antibiotic administration (OR: 1.10, 95%CI: 0.30–3.98, $P = 0.88$). There was heterogeneity between studies ($I^2 = 59\%$) (Fig. 4).

Network meta-analysis

Clinical response

70 studies[30–34,36,38–41,43–50,52–72,74–78,80,82–84,86,87,89,91–104,108,110–113] reported clinical response, the definition of outcome measurement for each study were shown in Supplementary Table S8 and the evidence network relationship diagram is shown (Fig. 5(a)), involving 8 antimicrobials and a total of 6143 patients. Direct and indirect comparisons were formed for each intervention drug, partially forming a closed loop. The comparison-correction funnel plot is shown (Supplementary Fig. S1(a)), which has a poor left-right symmetrical distribution and tends to publish studies with positive results and small sample sizes, suggesting that there may be significant publication bias and small sample effects. The indirect comparison results are shown (Supplementary Fig. S2), and the analysis showed significant differences between levofloxacin and gatifloxacin and sparfloxacin ($P < 0.05$), and between moxifloxacin and gatifloxacin ($P < 0.05$). No statistically significant evidence of inconsistency was reported in the node splitting test of the prophylactic intervention NMA ($P > 0.05$) (Supplementary Fig. S3). The results of the pairwise meta-analysis are shown (Supplementary

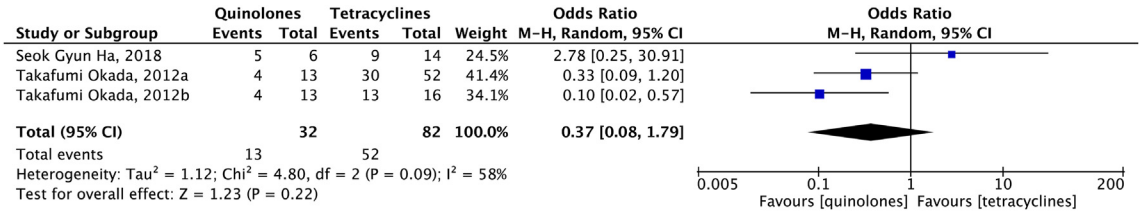

***Fig. 3:* Forest plot of pairwise comparison in terms of fever disappearance rate in patients with 24 h of quinolones and tetracyclines.** Each horizontal line on the forest plot represents the pooled odds ratio of quinolones compared with tetracyclines, with the odds ratio plotted as a blue rectangle and the 95% confidence interval plotted as the line. For each estimate, the black shaded area is the weight of the estimate in proportion to the overall effect. CI, confidence interval.

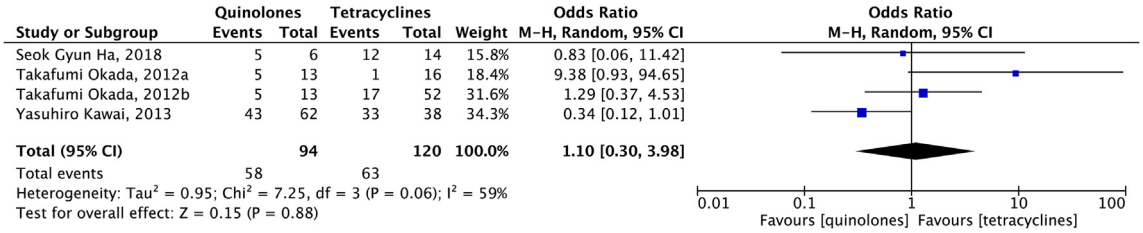

Fig. 4: **Forest plot of pairwise comparison in terms of fever disappearance rate in patients with 48 h of quinolones and tetracyclines.** Each horizontal line on the forest plot represents the pooled odds ratio of quinolones compared with tetracyclines, with the odds ratio plotted as a blue rectangle and the 95% credible interval plotted as the line. For each estimate, the black shaded area is the weight of the estimate in proportion to the overall effect. CI, confidence interval.

Table S9). The assessment of transitivity for this analysis is in Supplementary Table S10. The best probability ranking showed that minocycline (SUCRA 0.6994) ranked first in clinical response, moxifloxacin (SUCRA 0.3733) ranked second, levofloxacin (SUCRA 0.4013) ranked third, and the rest were doxycycline (SUCRA 0.3137), azithromycin (SUCRA 0.4578), gatifloxacin (SUCRA 0.2264), erythromycin (SUCRA 0.4534) and sparfloxacin (SUCRA 0.6810) (Supplementary Table S11). Probability ranking showed that for tetracyclines, minocycline was more clinically effective than doxycycline, and for quinolones, moxifloxacin was more effective than levofloxacin, gatifloxacin, and sparfloxacin (Fig. 6).

Time to defervescence and length of cough relief or disappearance

52 studies[31,32,34–37,39,41,42,45–52,56,59,61–71,73,74,79,82,87–91,95–103,105,108,109,114] reported on the TTD, with the network of evidence mapped in Fig. 5(b), involving 7 antimicrobials and a total of 4363 patients. 39 studies[31,32,34–37,39,41,42,46,49,50,52,56,59,63,65,66,68–70,74,82,87–90,95,96,98–103,108,109,114] reported on the length of cough relief or disappearance, and the network of evidence is shown in the evidence relationship diagram

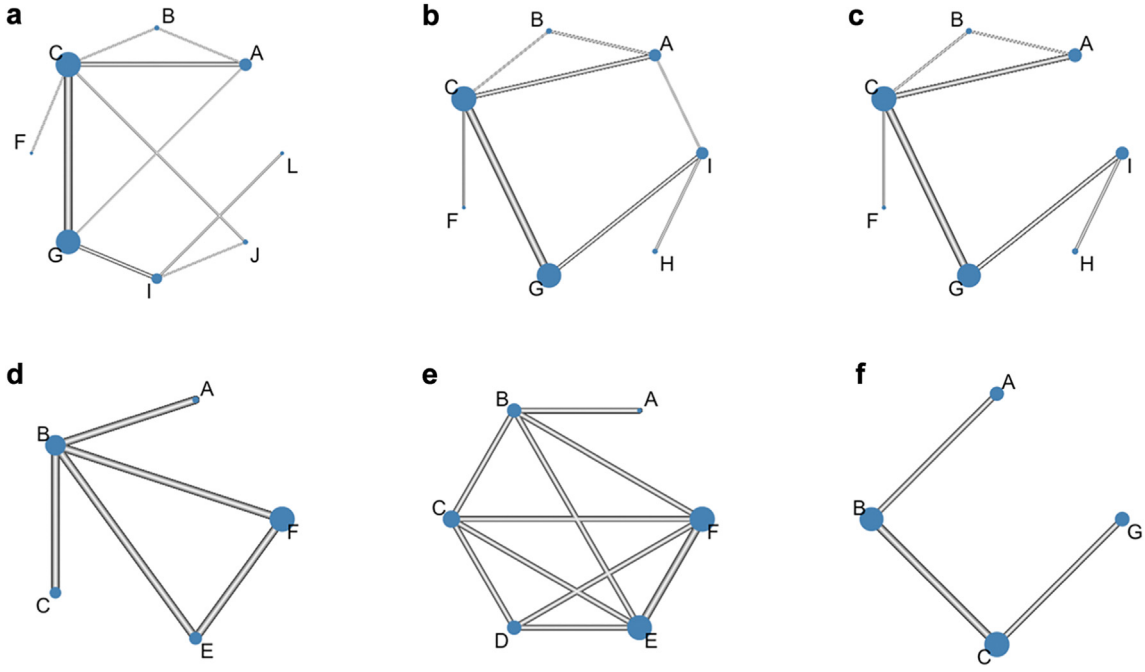

Fig. 5: **Network graphs comparing different outcomes across interventions.** Network plots of eligible direct comparisons. The width of the lines is proportional to the number of studies comparing each pair of treatments. The size of the nodes is proportional to the number of patients. (a) Clinical response; (b) Time to defervescence; (c) Length of cough relief or disappearance; (d) The fever disappearance rate of patients 24 h after antibiotic administration; (e) The fever disappearance rate of patients 48 h after antibiotic administration; (f) Clinical safety in children. A: Levofloxacin; B: Doxycycline; C: Azithromycin; D: Clarithromycin; E: Tosufloxacin; F: Minocycline; G: Moxifloxacin; H: Ciprofloxacin; I: Erythromycin; J: Gatifloxacin.

(Fig. 5(c)) for 7 antimicrobials involving a total of 3235 patients. The intervening drugs formed direct and indirect comparisons, partially closing the loop. The comparison-correction funnel plot is shown (Supplementary Fig. S1(b) and (c)), respectively, and the left-right symmetry distribution is poor. Studies with positive results and small sample sizes tend to be published, suggesting that there may be significant publication bias and small sample effects. The results of the indirect comparison are shown (Supplementary Figs. S4 and S5), which show that there was no statistically significant difference between two-by-two comparisons of tetracyclines and quinolones ($P > 0.05$). No statistically significant evidence of inconsistency was reported in the node splitting test ($P > 0.05$) (Supplementary Figs. S6 and S7). The results of a pairwise meta-analysis of these two outcomes are shown (Supplementary Table S9). The best probabilities showed that erythromycin (SUCRA 0.7695) ranked first in TTD, azithromycin (SUCRA 0.6645) ranked second, ciprofloxacin (SUCRA 0.2382) ranked third, and followed by levofloxacin (SUCRA 0.4016), moxifloxacin (SUCRA 0.4267), doxycycline (SUCRA 0.3253) and minocycline (SUCRA 0.7953). In terms of length of cough relief or disappearance, azithromycin ranked first (SUCRA 0.5730), erythromycin ranked second (SUCRA 0.4430), ciprofloxacin ranked third (SUCRA 0.2625), and followed by doxycycline (SUCRA 0.25744), levofloxacin (SUCRA 0.3993), moxifloxacin (SUCRA 0.5167) and minocycline (SUCRA 0.9156) (Supplementary Table S11). Probability ranking showed that for tetracyclines, minocycline was shorter than doxycycline for both TTD and length of cough relief or disappearance, whereas for quinolones, ciprofloxacin was longer than levofloxacin and moxifloxacin for TTD, and ciprofloxacin was longer than levofloxacin and moxifloxacin for length of cough relief or disappearance (Supplementary Figs. S8 and S9).

Fever disappearance rate within 24 h and 48 h of antibiotic administration

3 studies[81,105,106] reported fever disappearance rate in patients with 24 h medication, and the evidence network relationships are plotted (Fig. 5(d)), involving 5 antimicrobial drugs and a total of 145 patients. 4 studies[81,85,105,106] reported the febrile disappearance rate in patients with 48 h medication, and the evidence network relationship diagram is shown (Fig. 5(e)), involving 6 antimicrobials and a total of 418 patients. Direct and indirect comparisons were formed for each intervention drug, partially forming a closed loop. Comparison-correction funnel plots are shown (Supplementary Fig. S1(d) and (e)), with good left-right symmetrical distributability. The results of the indirect comparison showed that there was a statistically significant difference in the comparison between doxycycline and toxofloxacin (OR: 0.18, 95% CrI: 0.01–0.79, $P < 0.05$) (Supplementary Figs. S10 and S11). Except for the 48 h azithromycin versus doxycycline group ($P = 0.0029$), there was no statistically significant evidence of inconsistency in the node splitting test of the prophylactic intervention NMA ($P > 0.05$) (Supplementary Figs. S12 and S13). The results of a pairwise meta-analysis of these two outcomes are shown (Supplementary Table S9). Besides the fever disappearance rate within 48 h in the azithromycin versus doxycycline, no statistically significant evidence of inconsistency was reported in the node splitting test (Supplementary Figs. S12 and S13). The best probabilities showed that levofloxacin (SUCRA 0.7847) ranked first in the fever disappearance rate within 24 h, doxycycline (SUCRA 0.7297), minocycline (SUCRA 0.6306), followed by tosufloxacin (SUCRA 0.5058) and azithromycin (SUCRA 0.5562). Minocycline (SUCRA 0.4879) ranked first in the fever disappearance rate within 48 h and tosufloxacin (SUCRA 0.3501) ranked second, doxycycline (SUCRA 0.3141) ranked third, followed by levofloxacin (SUCRA 0.1512), clarithromycin (SUCRA 0.4228), azithromycin (SUCRA 0.6011) (Supplementary Table S11). Probability ranking showed that for tetracyclines, doxycycline was superior to minocycline in terms of 24 h fever disappearance rate and to doxycycline in terms of 48 h fever disappearance rate, whereas for quinolones, levofloxacin was superior to tosufloxacin in terms of 24 h fever disappearance rate, and tosufloxacin in terms of 48 h fever disappearance rate (Supplementary Figs. S14 and 15).

Clinical safety in children

4 studies[81,107,108,114] reported clinical safety in children, AEs measured in the included studies are shown (Supplementary Table S12). The evidence network relationship mapped in Fig. 5(f), involving 4 antimicrobials and a total of 239 patients. The intervening drugs formed an indirect comparison and did not form a closed loop. Comparison-correction funnel plots are shown (Supplementary Fig. S1(f)), with good left-right symmetrical distributability, mostly near the bottom of the funnel, suggesting a small sample effect. The results of a pairwise meta-analysis of these two outcomes are shown (Supplementary Table S9). Indirect comparison results are shown (Supplementary Fig. S16), and the analysis showed that there was no statistical difference between the four drugs ($P > 0.05$). The best probabilities ranked levofloxacin (SUCRA 0.3864), azithromycin (SUCRA 0.4522), followed by moxifloxacin (SUCRA 0.2127) and doxycycline (SUCRA 0.4130) (Supplementary Table S11). Probability ranking showed that for the paediatric medications, the incidence of adverse reactions were levofloxacin, moxifloxacin, and doxycycline in descending order (Supplementary Fig. S17).

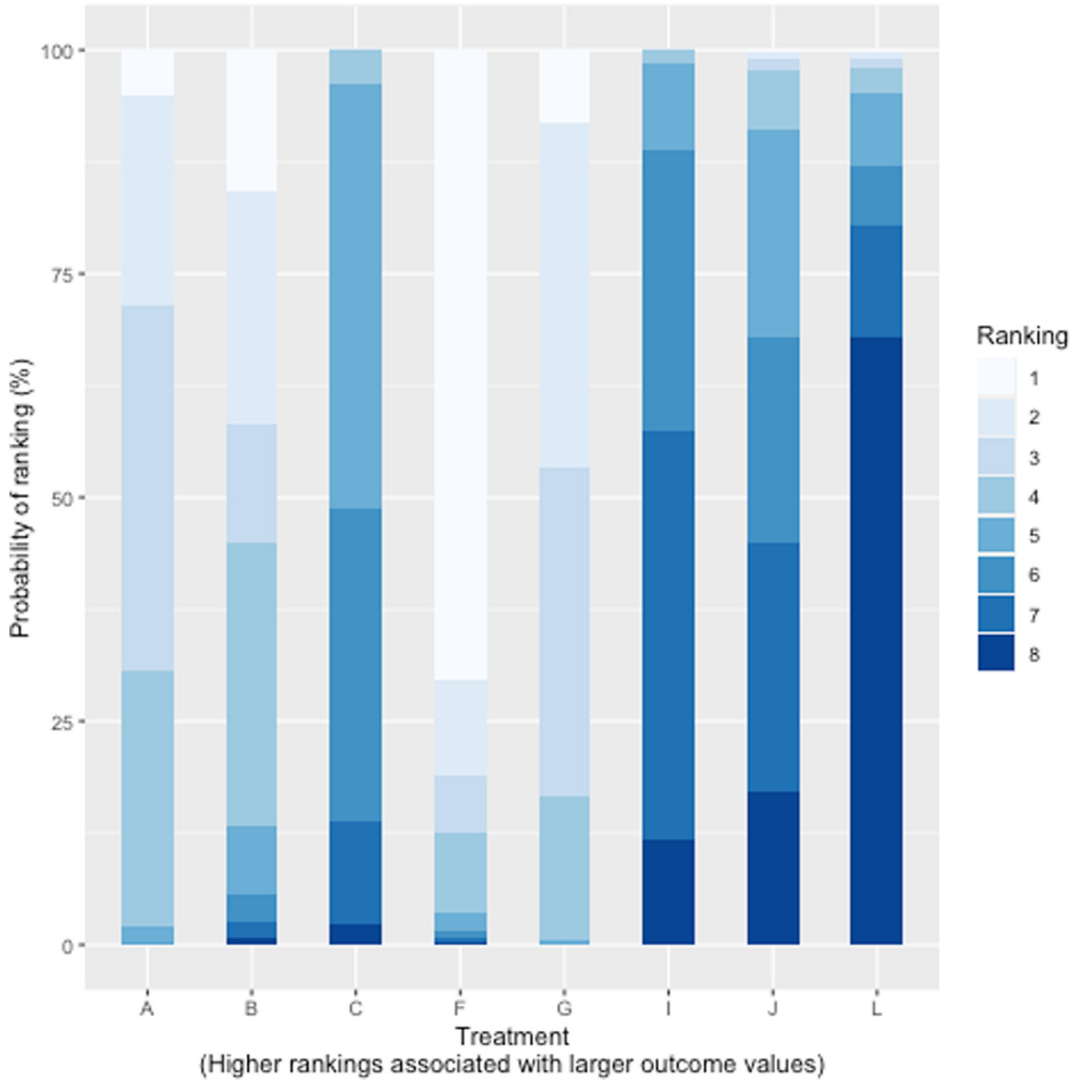

Fig. 6: **Probability ranking of treatment measures for *Mycoplasma pneumoniae* infection in terms of clinical response.** The Y-axis indicates the probability of being the first the second and so on most likely effective intervention. A: Levofloxacin; B: Doxycycline; C: Azithromycin; F: Minocycline; G: Moxifloxacin; H: Ciprofloxacin; I: Erythromycin; J: Gatifloxacin; L: sparfloxacin.

Discussion

This study represents the inaugural and most comprehensive meta-analysis to date, examining the efficacy of tetracyclines and quinolones treating *M. pneumoniae* infections in people and their safety in children. By integrating data from multiple countries, it delivers the latest evidence supporting the utilisation of these antibiotics. The utilization of tetracyclines and quinolones in paediatric patients is restricted due to age-specific safety issues. We broadened the efficacy evaluation to encompass the entire population without imposing age restrictions. However, due to concerns regarding child safety, we specifically focus on conducting drug safety evaluations for children.

In terms of age, quinolones use in children is associated with high AEs signalling in gastrointestinal reactions, hematologic and lymphatic disorders, cardiac, neurological, and musculoskeletal disorders.[115] In particular, patients aged 12–18 years reported the most in studies of fluoroquinolone (FQ)-induced tendinopathy, with tendon rupture occurring one week after administration and tendinopathy within the first month.[116] Quinolones have also been associated with seizures in children, with increased seizures (0.63%) in children without central nervous system disease (0.02%).[117] In previous data, the incidence of tooth discolouration caused by different tetracyclines varied between 23% and 92% in children.[118] Doxycycline and

minocycline are at significantly increased risk of dermatological adverse effects, and may cause hypersensitivity syndrome, serum sickness-like reactions, and drug-induced lupus.[119]

Since fever is the most important presenting feature of *M. pneumoniae* infection, clinicians keep adding additional antibiotics until defervesce in routine clinical practice. Also, increased TTD and decreased fever disappearance rate are associated with more extended hospital stays, increasing the duration of ongoing treatment, thereby increasing the hospital burden and the risk of acquisition of nosocomial infections. We chose to analyse TTD as a continuous outcome (mean difference) rather than time-to-event analysis, as almost all study participants who contributed some period of time to the event (defervescence). Some patients still have persistent cough and sputum symptoms after pneumonia. We also include the length of cough relief or disappearance as one of the outcomes of the systematic review in order to observe the symptoms of patients during the recovery period of pneumonia.

Due to the limited number of studies, we encompassed only four studies that systematically reviewed and directly compared quinolones and tetracyclines in populations infected with *M. pneumoniae*. The results indicated that there was no significant statistical difference between the two groups in terms of the TTD and the rate of fever disappearance within 24 h and 48 h of antibiotic administration. We focused on comparing NMA interventions using the Bayesian framework. Unfortunately, in terms of clinical treatment effectiveness, only levofloxacin, gatifloxacin, and sparfloxacin showed statistically significant differences ($P < 0.05$). There was a significant statistical difference between moxifloxacin and gatifloxacin ($P < 0.05$). In terms of antipyretic rate, there was only a significant statistical difference between doxycycline and tosufloxacin (OR: 0.18, 95%CrI: 0.01–0.79, $P < 0.05$). Nevertheless, we found that minocycline performed well in reducing fever, relieving or eliminating cough, demonstrating clinical response, and reducing fever within 48 h compared to other interventions. Minocycline has been found to have excellent bactericidal activity against macrolide-unresponsive *M. pneumoniae* and macrolide-sensitive *M. pneumoniae*.[120,121] It is also considered beneficial for diseases with inflammatory origins.[122] A study reported that there is no evidence to suggest that newer tetracyclines such as doxycycline and minocycline are associated with negative dental outcomes.[123] In Japan, the therapeutic efficacy of minocycline has been demonstrated in several studies.[85,106,124] Unfortunately, because there is a lack of clinical studies on the safety of minocycline in children, we are unable to fully evaluate its safety in this population.

Furthermore, the latest recommendations from the American Academy of Paediatrics now endorse the utilisation of doxycycline in children of all ages, with a maximum dosage of 21 days. This recommendation is based on the fact that doxycycline exhibits a lower affinity for calcium compared to other tetracycline drugs, thus reducing the risk of dental staining associated with short-term use.[125] While observational studies associated with Rocky Mountain spotted fever[118] support the safety of doxycycline in children younger than eight years of age, our efficacy studies involving newer tetracyclines only involved children over eight years of age, lacking a safety comparison between different tetracycline groups, and given that the next-generation tetracyclines have already been approved for use in patients aged eight years and older in many countries, they may be the preferred option for treating MRMP infection in ≥8-year-olds.

Among all the quinolones investigated, our NMA results demonstrate that moxifloxacin has a significant advantage in fever reduction, cough relief and clinical efficacy, and that moxifloxacin is safer in children than levofloxacin. Similar to previous studies, moxifloxacin was generally safe and well-tolerated, with few AEs that resulted in treatment interruption.[126] Compared to ciprofloxacin and moxifloxacin, levofloxacin may be associated with a higher risk of musculoskeletal injury.[127] A more plausible explanation is that moxifloxacin not only possesses antimicrobial activity but also exhibits a potent anti-inflammatory effect. He's study showed that moxifloxacin is a safe and effective alternative to severe refractory *M. pneumoniae* pneumonia (SRMPP) in children, including children <8 years old.[108] Torsufloxacin is more effective than levofloxacin in reducing fever at 48 h in patients. Torsufloxacin is a recently approved FQ antimicrobial agent, and there is limited data on its safety in children. In the future, we may require additional clinical data to substantiate the utilisation of torsufloxacin in patients infected with *M. pneumoniae*, particularly in paediatric cases.

Challengingly, our systematic review and meta-analysis identified several knowledge gaps. The Paediatric Infectious Diseases Society[17] and the National Health Commission of China[18] have reached a consensus on azithromycin as a first-line antibiotic for treating children with *M. pneumoniae* infections. However, there is inconsistency regarding the use of alternative treatment options for the treatment of children with MRMP infection. Guideline consensus in various countries worldwide has different recommendations on the treatment options for children with MRMP infection. Moreover, the existing guidelines do not clearly explain specific second-line treatment options' drug types and dosage courses. Jong Gyun Ahn[19] showed that compared with macrolides, tetracyclines may shorten fever duration and hospital length in patients with MRMP infection, and FQs may achieve defervescence within 48 h in patients with MRMP infection. However, these results should be interpreted carefully as only a small number of studies were included, no direct or

indirect comparison of the effectiveness and safety of tetracyclines and quinolones in children with MRMP infections exists, and they were heterogeneous.

This systematic review and meta-analysis addresses some gaps in the literature and provide information on the clinical efficacy of quinolones and tetracyclines in people and safety in children with MRMP infection. In particular, minocycline as the most effective possible intervention in people over eight years of age, moxifloxacin has great advantages in efficacy and safety compared with other quinolones in the treatment of *M. pneumoniae* population, including children under eight years of age, and levofloxacin's prominent AEs in alternative treatment regimens fill the gap in the efficacy and safety evaluation of related treatment regimens for MRMP infection in adults and children and provide reference evidence for clinical practice guidelines.

The study has some limitations. The limited number of studies and sample sizes have constrained the opportunity to obtain conclusive results. To increase the sample size, we did not impose any restrictions on the types of studies included in the analysis during the screening process, even if there are significant methodological differences that could lead to increased heterogeneity in the results. In the inclusion analyses, there were studies with small sample sizes, which may have contributed to publication bias. In this NMA, there are fewer studies that include direct comparisons between quinolones and tetracyclines. The majority of available studies are indirect, which may potentially skew the results. Another limitation to consider is the need to adjust for potential confounding factors, such as the heterogeneity of the study's burden of disease, sociodemographic factors, and economic factors in the country. These factors may have an impact on the stability of the results. In addition, likely due to the high MRMP resistance rate in Asia, the included studies were largely from Asia, with a large proportion from China, which may limit the generalisability of the findings. The results of this study may provide a reference for other countries or regions as the MRMP resistance rate rises globally. The difficulty is that there are differences in the definition of clinical response rate among different studies, and it is difficult to avoid heterogeneity in evaluating the efficacy of clinical response to drugs.

Current evidence suggests that tetracyclines have no significant advantages or disadvantages compared to quinolones in treating paediatric patients with *M. pneumoniae* infection. However, new tetracyclines, such as minocycline and doxycycline, may be the optimal choice for treating MRMP infections in people over eight years old, and the good efficacy and tolerability of moxifloxacin may benefit children under eight years of age with MRMP. Caution should be exercised when prescribing levofloxacin due to potential adverse reactions. Further high-quality RCTs will be needed in the future to generate additional scientific evidence.

Contributors

All authors contributed to the conception and design of the study and reviewed all documents and materials. FC and JL collected data, performed data analysis, interpreted results, and wrote the first draft of the manuscript. FC, JL and LW reviewed the protocol, screened articles, extracted data, and reviewed the results and manuscript. FC, JL and WL contributed to the systematic review protocol and critically reviewed the results and manuscript. FC, JL, WL, JR and LW contributed to the protocol development and reviewed the manuscript. All authors read and approved the final manuscript. LW and JR is the guarantor for this work. FC, JL and LW have access to and verify the underlying study data.

Data sharing statement

Data are presented in the current manuscript, its Supplementary Materials, or within the manuscripts or appendices of the included studies.

Declaration of interests

All authors declare no competing interests.

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Appendix A. Supplementary data

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