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Review Article

Efficacy and Safety of Erythromycin in the Treatment of Mycoplasma Pneumonia in Children: A Systematic Review and Meta-Analysis

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ABSTRACT

Aim: The effectiveness and safety of erythromycin for treating mycoplasma pneumonia in pediatric patients is a subject of significant interest. This study aims to conduct a systematic review and meta-analysis to assess the efficacy and safety of erythromycin in the treatment of mycoplasma pneumonia in children, with the goal of providing evidence-based recommendations for pediatric care. **Methodology:** We systematically reviewed randomized controlled trials published prior to January 1, 2024, that evaluated the efficacy and safety of erythromycin in the treatment of mycoplasma pneumonia in children. Outcome measures of primary concern include clinical efficacy, complications or adverse events. We used the inverse variance method to perform a meta-analysis of random effects, representing the effects in terms of Standardized Mean Difference (SMD) or Mean Difference (MD) and giving a 95% Confidence Interval (CIs). In addition, we performed a risk assessment of bias using the Cochrane tool. A total of 68 relevant studies were searched and 4 literatures meeting the requirements were included, with a total of 599 children. **Results:** The results of meta-analysis showed that the efficacy of erythromycin in the treatment of mycoplasma pneumonia in children was not statistically significant compared with conventional treatment [RR=12.31, 95%CI (-1.23, 25.86)]. The safety of erythromycin in the treatment of mycoplasma pneumonia in children was significantly different from that of conventional treatment [RR=5.55, 95%CI (2.65, 11.65)]. Subgroup analysis showed that the meta-analysis results of the three literatures showed RR=1.95, 95%CI (1.01, 3.74), suggesting that there was no statistically significant difference between the two groups of children with diarrhea. The results of meta-analysis of the two literatures showed that RR=1.95, 95%CI (0.63, 6.04), indicating that there was no statistical significance in the difference between the two groups of children with abdomina. The results of meta-analysis of the two literatures showed that RR=3.95, 95%CI (1.62, 5.58), indicating that there was a statistically significant difference between the two groups of pain children. The results of trial sequence analysis showed that the results of clinical efficacy and safety were considered reliable and stable and the safety of the experimental group was better than that of the control group in the treatment of pediatric mycoplasma pneumonia. **Conclusion:** Erythromycin is effective and safe in the treatment of mycoplasma pneumonia in children. Due to individual differences and the severity of the disease, there are certain differences in clinical treatment effects and some adverse reactions and drug resistance problems also need to be paid attention to and solved.

Keywords: Erythromycin, Mycoplasma pneumonia in children, Clinical efficacy, Safety, Meta-analysis, Systematic evaluation.

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INTRODUCTION

Mycoplasma pneumonia is a common respiratory pathogen in children that can lead to pneumonia. It can cause various clinical symptoms and complications, posing a threat to children's safety.[1] Mycoplasma pneumonia can be caused by low immune function, congenital heart disease, vitamin D deficiency rickets, malnutrition, air pollution, and poor ventilation in infants and young children.[2] Mycoplasma pneumonia is caused by a unique type of infection and is a common pathogen in respiratory infections due to its small size and simple structure.[3] Mycoplasma is composed of only three simple cell membranes, with no outer cell wall, only the cell membrane and cytoplasm. The only visible organelle in its cells is the ribosome, but it is rich in proteins, so its antibacterial spectrum is different from the β-lactam antibiotics

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such as penicillin and cephalosporin that affect the synthesis of cell walls in the past.[4] Mycoplasma has strong seasonal transmission, which is more common in winter and spring, and mainly exists in respiratory tract infections, which are transmitted by droplets.[5] Infections of the respiratory tract and complications of the heart, brain, and kidneys are more common in children, so children's mycoplasma pneumonia infections have caused widespread concern.

The mechanism of action of macrolide antibiotics is mainly through inhibiting the synthesis of proteins, which plays an antibacterial role.[6] Macrolide antibiotics bind to the ribosome 50S subunit in bacteria, hinder the process of peptide transfer in bacteria, and selectively inhibit antibacterial action by blocking interference with mRNA synthesis of proteins.[7] The ribosome organelle serves as the exclusive site for protein synthesis in mycoplasma. Due to the absence of structural features like a cell wall, traditional antibiotics targeting cell wall synthesis are not effective in treating mycoplasma pneumoniae pneumonia. Therefore, antibiotics that disrupt ribosomal protein synthesis in mycoplasma, such as macrolides, tetracycline, and quinolones, are more suitable for treatment.[8] Numerous clinical studies have demonstrated that prolonged administration of tetracycline antibiotics can result in detrimental effects on the dental development and growth of children, while quinolones have been shown to impede normal bone development in pediatric patients. Therefore, due to the significant adverse reactions associated with these medications, they are not recommended for the treatment of Mycoplasma pneumoniae pneumonia in children.[9] Therefore, macrolide antibiotics are the main choice for the treatment of mycoplasma pneumoniae pneumonia and the commonly used macrolide antibiotics mainly include erythromycin. Erythromycin is mainly targeted at mycoplasma pneumoniae infection, making full use of the advantages of drug concentration in tissues and relatively small adverse drug reactions. However, with the widespread use of antibiotics, the resistance of bacteria has gradually increased, making treatment more difficult.[10] Therefore, it is important to study the efficacy and safety of erythromycin in the treatment of mycoplasma pneumonia in children.

Recent research on mycoplasma pneumonia has revealed that erythromycin may have a beneficial impact on treating children with this condition. However, the clinical efficacy and safety of erythromycin in pediatric mycoplasma pneumonia treatment remain a topic of debate. Variability in individual responses, disease severity, and the potential for complications or adverse reactions can influence treatment outcomes. Additionally, concerns regarding adverse reactions and drug resistance highlight the need for further investigation and resolution. To more comprehensively evaluate the efficacy and safety of erythromycin in the treatment of mycoplasma pneumonia in children, systematic review and meta-analysis have become an important research method. Through systematic review and meta-analysis, we can fully understand the efficacy and safety of erythromycin in the treatment of mycoplasma pneumonia in children. At the same time, it can explore the therapeutic effect and evaluate the incidence and severity of adverse reactions, to provide a more comprehensive reference for clinicians.

MATERIALS AND METHODS

Inclusion criteria

Study participants included children diagnosed with mycoplasma pneumonia. The experimental group received erythromycin treatment or a combination of other drugs with erythromycin, while the control group did not receive erythromycin treatment. Before treatment, there were no significant differences between the two groups. The study, a randomized controlled trial conducted in English, focused on the most relevant findings from the author's previous research. Outcome indicators: clinical efficacy, complications, or adverse reactions.

Exclusion Criteria

The literature reviewed encompassed studies involving pediatric patients with chronic illnesses affecting various bodily systems, including those lacking proper citations, *in vitro* investigations, duplicated publications, inadequately reported data, inconsistent statistical methodologies, unrevised content, review articles, non-English publications, and low-quality literature that was excluded from the analysis.

Literature Search

Our systematic review was performed by the Cochrane Manual for Systematic Review of Interventions[11] and reported by the Preferred Reporting Project (PRISMA) standards for Systematic Review and Meta-analysis.[12] Randomized controlled trials on the efficacy and safety of erythromycin in the treatment of mycoplasma pneumonia in children were searched in PubMed, Embase, Web of Science, and Cochrane databases by computer. References were strictly screened based on inclusion and exclusion criteria and references that ended on January 1, 2024, were strictly screened based on inclusion and exclusion criteria. To ensure the recall and accuracy of the references, a fuzzy search was carried out for the included references, and literature of randomized controlled trials and clinical controlled trials meeting the inclusion criteria were comprehensively collected. Search strategy: (Erythromycin) AND (Mycoplasma pneumonia) AND (Efficacy and Safety).

Data extraction and quality evaluation

Literature data were collected, including the first author, the year of publication, the number of study cases, the sex ratio of each group, the average age, and the mean and standard difference related to the study indicators. Two researchers were independently extracted and checked and the third researcher was asked to decide if the opinions were inconsistent. The

included literature was evaluated by the bias risk assessment criteria provided in Review Manager 5.4: (1) the generation of random methods; (2) Whether it is blind; (3) Assign hiding methods; (4) Outcome evaluation blind method or not; (5) Data integrity; (6) Reporting bias.

Statistical Analysis

The Rev Man 5.4 software was used for data merging and statistical analysis. The Odds Ratio (OR) and 95% Confidence Interval (CI) were used as the effect index for the bivariate analysis. The continuous variables were Weighted Mean Difference (WMD) and 95% Confidence Interval (CI) as the statistics of efficacy analysis. $p<0.05$ was considered statistically significant. Chi2 test and I2 were used to analyze heterogeneity. 95% CI and $I^2>75\%$ were considered to be too heterogeneous to merge. $I^2<25\%$ indicated small heterogeneity and $p<0.05$ indicated statistically significant differences. Publication bias was also evaluated using Rev Man 5.4 software to plot the Funnel plot. If the included papers are roughly symmetrical in the funnel plot, publication bias is considered to be less likely. If the distribution is asymmetrical in the funnel plot, it is considered that there is a large publication bias.

RESULTS

Literature screening results and basic characteristics

The research screening process is shown in Figure 1. 68 pieces of literature were searched according to the search strategy and then selected according to the title and abstract of the literature. Two reviewers were selected independently. After this step, 23 literatures that did not meet the inclusion criteria were excluded and 25 literatures with topics not relevant to this study were excluded. There were 6 journals with early warning or academic misconduct, 6 were republished, 4 did not meet the inclusion requirements and the remaining 4 met the inclusion criteria.[13-16] The basic characteristics are shown in Table 1.

Bias risk assessment

We used the Cochrane Collaboration's bias risk assessment tool, which evaluates items such as: Random sequence generation (selection bias), assignment hiding (selection bias), participant and person blindness (performance bias), outcome evaluation blindness (detection bias), incomplete outcome data (attrition bias), selective reporting bias (reporting bias) and other biases. Two trials had a high risk of bias due to non-implementation or patient blindness, or incorrect randomization methods. Only two randomized controlled trials had a low overall risk of bias. About 55% of the test results had incomplete data and about 20% of the test results had selective reporting. The results of Cochrane's bias risk assessment are shown in Figures 2 and 3.

Clinical Efficacy

All statistical analyses were performed using Review Manager version 5.4 (Cochrane Collaboration). In the final included literature, 4 literatures reported the efficacy and safety of erythromycin in the treatment of mycoplasma pneumonia in children according to the grade IV standard, including a total of 599 children, 306 children treated with erythromycin and 293 children treated with other treatments. The effective rate of

Table 1: Comparison of basic information of included literatures.

Study	Year	Age	Study design	Study population	Patients		Adverse reaction		Clinical effect		NOS score
					TP	TR	TP	TR	TP	TR	
Han R *et al.*[13]	2020	7.13	Randomized controlled study	Total 132 children with mycoplasma pneumonia.	66	66	Fever 2, cough 1, rale 4	Fever 7, cough 5, rale 4	98.04%	74.51%	9
Block S *et al.*[14]	1995	9.20	Randomized controlled study	Symptoms of pneumonia children ages 3 through 12 years.	130	130	Diarrhea 6 abdominal pain 9	Diarrhea 17 abdominal pain 21	98%	95%	8
Schönwald S *et al.*[15]	1990	9.3	Randomized controlled study	57 patients treated with azithromycin, Mycoplasma pneumoniae.	57	44	Diarrhea 1 abdominal pain 0	Diarrhea 3 abdominal pain 3	84%	82%	7
Zhang MY *et al.*[16]	2021	6.8	Randomized controlled study	106 children with a confirmed diagnosis.	53	53	Stomach ache 2, Diarrhea 1, Nausea 2	Stomach ache 8, Diarrhea 7, Nausea 10	96.23%	75.47%	8

Note: TR is erythromycin treatment or other drugs combined with erythromycin treatment measures; TP is not treated with erythromycin.

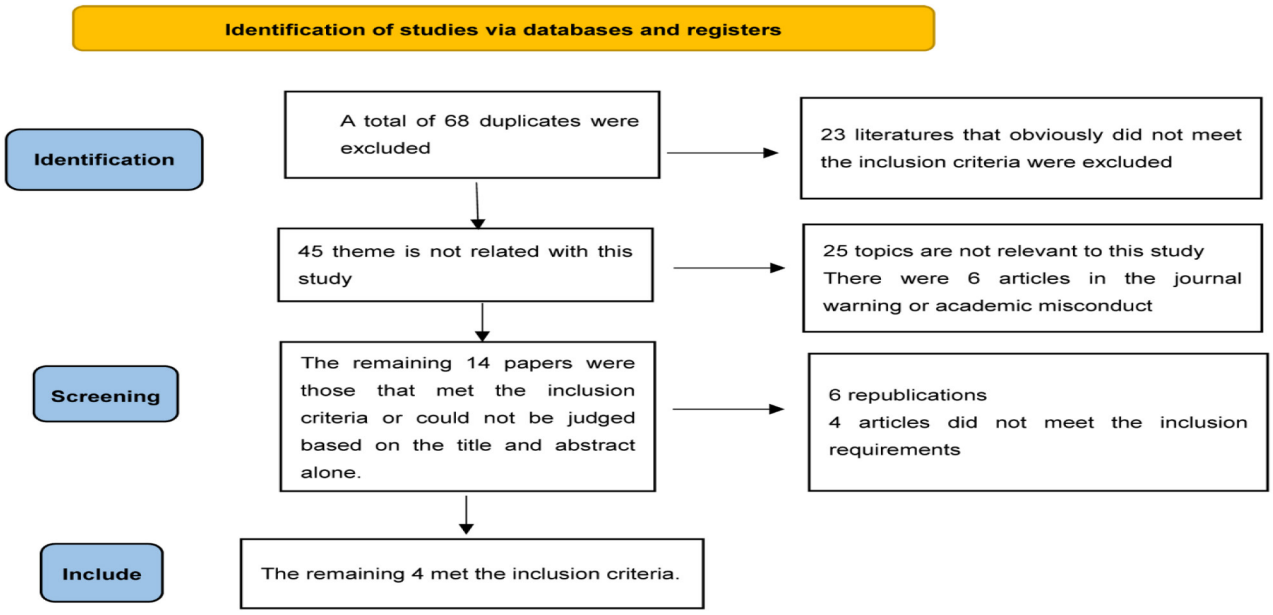

Figure 1: Literature screening process and results.

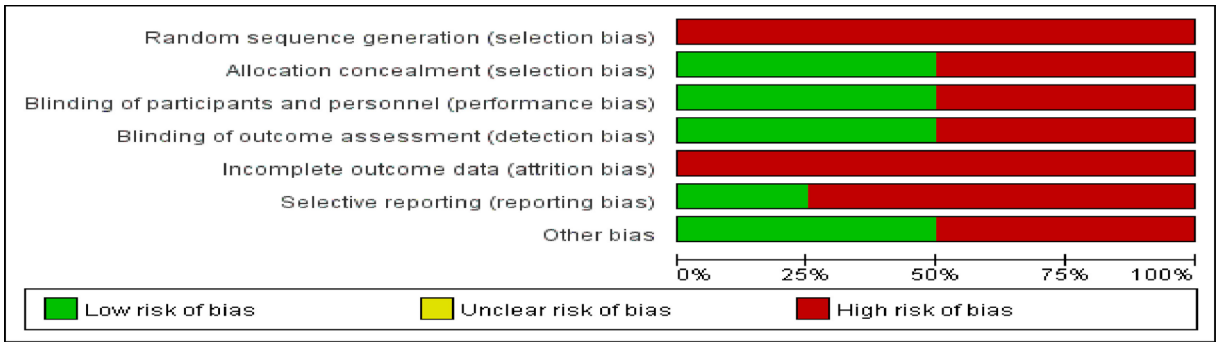

Figure 2: Analysis of the results of the basic characteristics of the included literature.

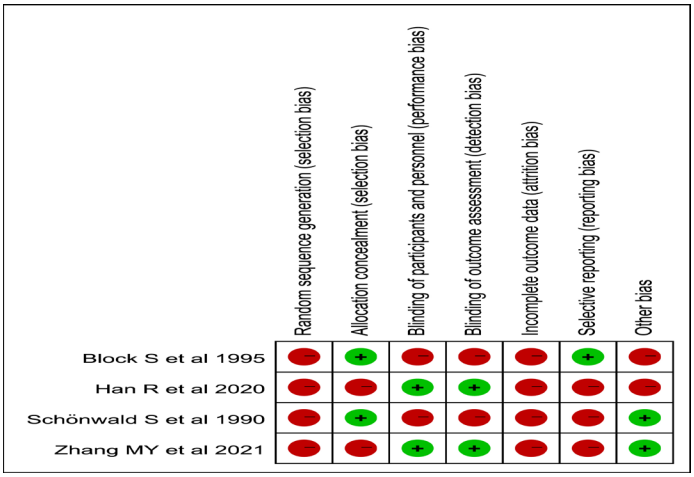

Figure 3: Included literature evaluation.

erythromycin in treating mycoplasma pneumonia in children was 98.04%. There was statistical heterogeneity among the studies (p<0.00001, 1^2=100%). The random effects model was used for analysis and the total effect size of the data was calculated for RR and 95% confidence interval. The results of the meta-analysis showed that RR=12.31, 95%CI (-1.23, 25.86), and p>0.05 corresponding to the Test for overall effect in the forest map, suggesting that the difference in the total effective rate of clinical efficacy was not statistically significant between the two groups (Figure 4).

Security Analysis

All statistical analyses were performed using Review Manager version 5.4 (Cochrane Collaboration). In the final included literature, 4 literatures reported the safety of erythromycin in the treatment of mycoplasma pneumonia in children according to the grade IV standard, including a total of 599 children, including

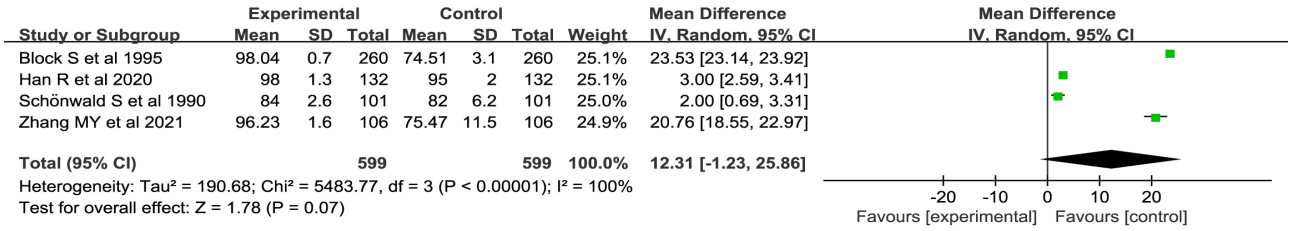

Figure 4: Clinical efficacy.

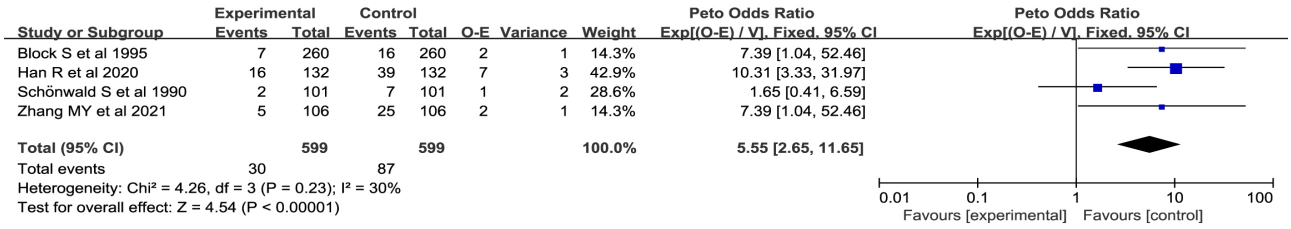

Figure 5: Security analysis.

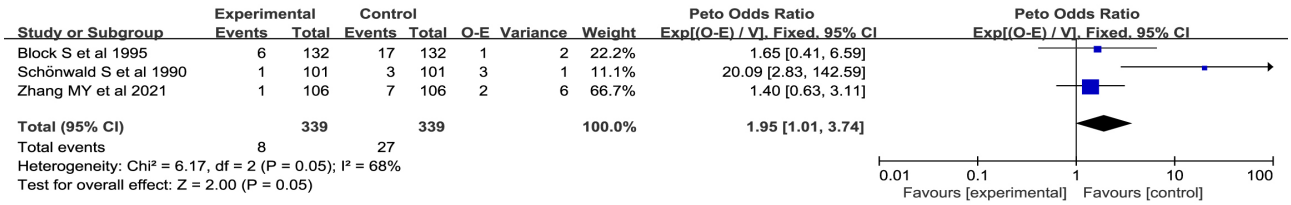

Figure 6: Forest map analysis of diarrhoea.

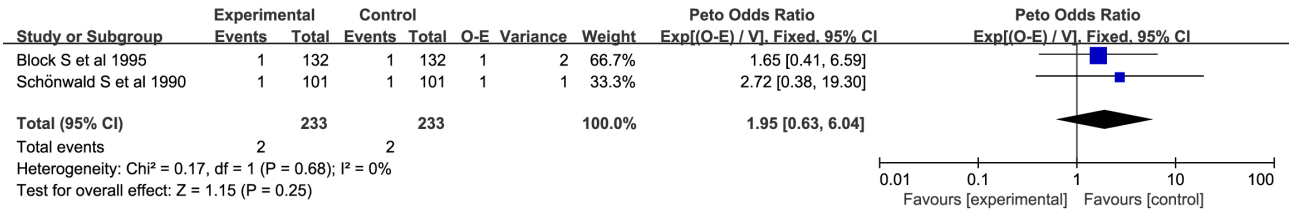

Figure 7: Forest map analysis by abdominal.

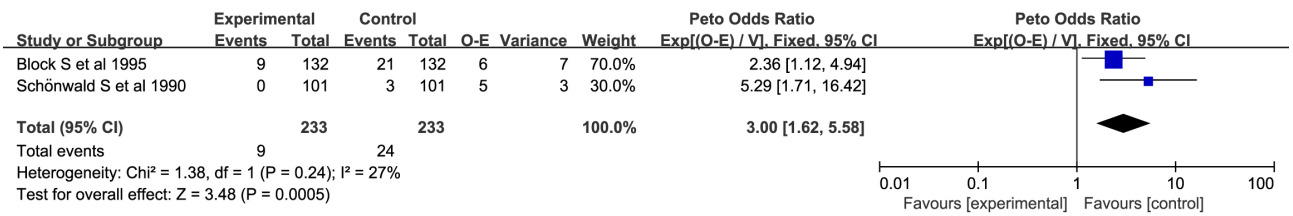

Figure 8: Forest map analysis of pain.

306 children treated with erythromycin and 293 children treated with other treatments. There was no statistical heterogeneity among the studies (p=0.23, I2=30%). The fixed-effect model was used for analysis and the number of children with adverse reactions was calculated for RR and 95% confidence interval. The results of the meta-analysis showed that RR=5.55, 95%CI (2.65, 11.65), and p value for Test for overall effect in the forest map was <0.05, suggesting statistically significant differences in the incidence of adverse reactions between the two groups (Figure 5).

Subgroup analysis

Three of the included papers described the number of effective cases of diarrhea. Meta-analysis was performed on children with diarrhea description and there was no statistical heterogeneity among studies (p=0.05, I2=68%). The random effects model was used for analysis. The results of meta-analysis showed that RR=1.95, 95%CI (1.01, 3.74), and the p value corresponding to the Test for overall effect in the forest map was=0.05, suggesting that there was no statistically significant difference between the three literature describing the diarrhea children treated between the two groups. Among the included literature, there were 2 literature describing the number of effective cases of the annotation. A meta-analysis was performed on children describing abdomina and there was no statistical heterogeneity among studies (p=0.24, I^2=68%). A fixed-effect model was used for analysis. The results of the meta-analysis showed that RR=1.95, 95%CI (0.63, 6.04) and p value >0.05 for the Test for overall effect in the forest map, suggesting that there was no statistically significant difference between the two groups of treated children described in the two kinds of literature. Among the included literature, there were 2 literature describing the number of effective cases of pain. Meta-analysis was performed on children describing pain and there was no statistical heterogeneity among studies (p=0.24, I2=27%). A fixed-effect model was used for analysis. The results of meta-analysis showed that RR=3.95, 95%CI (1.62, 5.58) and p value corresponding to the Test for overall effect in the forest map was <0.05, suggesting that there were statistically significant differences between the two groups described in the two literature (Figures 6-8).

Trial Sequential Analysis

Our study set a 5% risk of type I error and a 20% relative risk reduction (80% power) to assess the Required Information Size (RIS) and Trial Sequence Monitoring Boundary (TSMB). If the cumulative z value exceeds the TSMB and RIS thresholds, the sample size is sufficient. The results for clinical efficacy and safety are considered reliable and stable because Z-values cross trial sequence monitoring boundaries and information size is required. The results showed that the safety of the treatment group for mycoplasma pneumonia was better than that of the control group.

DISCUSSION

An extensive review of 68 pertinent studies was undertaken, resulting in the meticulous selection of four articles meeting stringent criteria, encompassing a cohort of 599 children. Utilizing systematic meta-analysis, it was determined that erythromycin did not exhibit a statistically significant superiority over conventional treatment for mycoplasma pneumonia in children, as evidenced by a Relative hazard Ratio (RR) of 12.31 and a 95% Confidence Interval (CI) of -1.23 to 25.86, suggesting comparable efficacy between the two treatments. However, in terms of safety, erythromycin shows a clear advantage. The safety of erythromycin in the treatment of mycoplasma pneumonia in children was statistically significant with an RR value of 5.55 and a 95% CI of 2.65 to 11.65 compared with conventional treatment. This suggests that although erythromycin and conventional treatments are comparable in efficacy, erythromycin may cause fewer adverse reactions during treatment and is safer and more reliable. Subsequent subgroup analysis revealed that, in the comparison of children with diarrhea, the meta-analysis findings from three articles indicated a relative risk of 1.95 with a 95% confidence interval ranging from 1.01 to 3.74. These results suggest that there was no statistically significant difference in the incidence of diarrhea between the two groups. In the comparison of children with abdomina (which may refer to abdominal discomfort or pain), the results of the meta-analysis of the two kinds of literature showed that RR=1.95 and 95% CI was 0.63 to 6.04, indicating that there was no significant difference in the incidence of abdominal discomfort or pain between the two groups. However, in the comparison of children with pain, the results of meta-analysis in two kinds of literature showed that RR=3.95 and 95% CI was 1.62 to 5.58, which suggested that there was a significant difference in the incidence of pain between the two groups and the incidence of pain was lower in the erythromycin treatment group.

The trial sequence analysis results provide additional support for the consistent and reliable clinical efficacy and safety of erythromycin in the treatment of mycoplasma pneumonia in pediatric patients. This finding holds significant implications for guiding clinical practice. While individual variations and disease severity may influence treatment outcomes, overall, erythromycin demonstrates favorable efficacy and safety in managing mycoplasma pneumonia in children. Relevant literature reports have found that erythromycin is effective in the treatment of mycoplasma pneumonia in children, further shortening the improvement time of clinical symptoms and signs, less adverse reactions, and high safety and clinical application value.[17-21] Mo *et al.* reported similar findings regarding the safety of combining traditional Chinese medicine with conventional treatments, highlighting reduced adverse effects in pediatric populations.[22] Additionally, Phimarn *et al.* emphasized the importance of considering cardiometabolic outcomes in treatment

strategies, which could be relevant for broader applications of erythromycin.[23] Wang F *et al.* believed that erythromycin sequential therapy combined with azithromycin in the treatment of mycoplasma pneumonia in children could effectively inhibit hyperinflammatory response, timely control the disease, improve lung function and reduce adverse reactions.[24] Sequential therapy of erythromycin combined with azithromycin for pediatric mycoplasma pneumonia has been proven to be an effective treatment regimen.[25] This strategy of combined drug use can not only reduce the inflammatory response of the body but also effectively relieve clinical symptoms and signs so that children can recover faster.[26] Meanwhile, the combined use of these two drugs can also reduce the incidence of adverse reactions and improve the safety of treatment.[27]

Our research is subject to certain constraints. The limited number of sources included in our study may heighten the potential for measurement bias. Furthermore, the assessment criteria used in the original literature are relatively simplistic, primarily relying on clinical outcomes categorized as either "effective" or "ineffective," lacking a comprehensive evaluation of specific clinical manifestations. This simplified evaluation method may not fully reflect the actual effect of erythromycin in the treatment of mycoplasma pneumonia in children. In future clinical studies, to ensure the accuracy and reliability of the results, we should apply randomized methods more rigorously and ensure adequate allocation of hidden and double-blind study designs. These measures serve to mitigate potential biases and confounding variables, thereby enhancing the robustness of research findings. Furthermore, efforts should be made to augment the study sample size to enhance the generalizability and representativeness of the results. In the selection of evaluation indicators, a comprehensive and detailed approach should be adopted, encompassing symptoms such as fever, cough, pulmonary rales, chest X-ray findings, and other clinical conditions post-medication, to provide a more thorough assessment of treatment efficacy and safety.

CONCLUSION

This systematic review and meta-analysis indicate that erythromycin is still effective and safe in the treatment of mycoplasma pneumonia in children. However, due to individual differences and the severity of the disease, there are certain differences in the effectiveness of treatment. In addition, some adverse reactions and drug resistance problems also need to be paid attention to and solved. Therefore, in clinical applications, it is necessary to pay attention to the rational use of antibiotics to avoid the abuse of antibiotics leading to resistance. To more fully evaluate the efficacy and safety of erythromycin in the treatment of mycoplasma pneumonia in children, more clinical trials and studies are still needed. At the same time, resistance monitoring and etiological diagnosis need to be strengthened to provide clinicians with a more reliable basis for developing more personalized, safe, and effective treatments.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

SMD: Standardized Mean Difference; **MD:** Mean Difference; **CI:** Confidence Interval; **RR:** Relative Risk; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **WMD:** Weighted Mean Difference; **OR:** Odds Ratio; **RIS:** Required Information Size; **TSMB:** Trial Sequence Monitoring Boundary.

SUMMARY

This systematic review and meta-analysis evaluate the efficacy and safety of erythromycin in treating mycoplasma pneumonia in children. Analyzing data from 4 studies with 599 children, the review found no significant difference in clinical efficacy between erythromycin and conventional treatments. However, erythromycin showed a significant advantage in safety, with fewer adverse reactions. The study suggests erythromycin is a safe and effective treatment option, though individual variations and disease severity can impact outcomes. Further research is needed to confirm these findings and address antibiotic resistance concerns.

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