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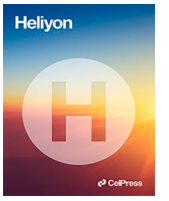

# Meta-analysis of the efficacy of budesonide and ambroxol hydrochloride inhalation in children with pneumonia and their effects on inflammatory response

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A R T I C L E I N F O

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A B S T R A C T

Childhood pneumonia, often caused by acute upper respiratory tract infections or bronchitis, is one of the leading causes of mortality in children. Nebulized inhalation, as a low-risk treatment method, has garnered significant attention. However, its effectiveness and safety remain controversial. In this study, a systematic review of relevant literature on the use of budesonide (BUD) and ambroxol hydrochloride (AMB) inhalation in the treatment of childhood pneumonia was conducted, and a total of 10 articles were included. The meta-analysis revealed an odds ratio (OR) of 1.61 and an $I^2$ value of 0.00 % for the effectiveness of combined BUD and AMB inhalation therapy in children with pneumonia, indicating no heterogeneity among the studies in terms of effectiveness. The OR values for BUD or AMB inhalation in alleviating cough, lung auscultation abnormalities, respiratory distress, body temperature, and cyanosis of the lips in children with pneumonia all favored the combined BUD therapy, showing significant relief of the aforementioned symptoms. However, due to variations in drug dosage and administration methods, high heterogeneity was observed. This study suggested that combined BUD and AMB inhalation therapy has better efficacy in treating childhood pneumonia, and BUD combined with AMB inhalation is more effective in alleviating symptoms such as cough, lung auscultation abnormalities, respiratory distress, normalizing body temperature, and reducing cyanosis of the lips. Nevertheless, further validation is required due to the limited sample size and substantial heterogeneity in the included studies. To sum up, this study provides the first analysis of the efficacy and inflammatory response of BUD and AMB inhalation in children with pneumonia. Future research should aim to verify and clarify these findings, considering the limitations of the existing studies in terms of sample size and heterogeneity.

## 1. Introduction

### 1.1. Background

Pneumonia is a common and serious infection that affects the lungs and can be caused by various pathogens, such as bacteria, viruses, fungi, or parasites. Pneumonia can occur at any age, but it is particularly prevalent and severe in children under 5 years old.

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According to the World Health Organization (WHO), pneumonia is the leading cause of death among children worldwide, accounting for 15 % of all under-five deaths. In 2019, an estimated 672,000 children died of pneumonia, most of them in low- and middle-income countries 1.

Mycoplasma pneumoniae (M. pneumoniae) is one of the most common causes of community-acquired pneumonia (CAP) in children, especially in school-aged children. M. pneumoniae pneumonia (MPP) accounts for 10–40 % of CAP cases in children and can cause mild to severe respiratory symptoms, such as cough, fever, wheezing, and dyspnea. MPP can also lead to complications and extrapulmonary manifestations, such as bronchial hyperreactivity, asthma exacerbation, otitis media, meningitis, encephalitis, and myocarditis [1–3].

### 1.2. Diagnosis and treatment

The diagnosis of pneumonia in children is based on clinical signs and symptoms, such as cough, tachypnea, chest indrawing, and hypoxemia. The diagnosis of MPP is more challenging because of the lack of specific clinical features and the difficulty in obtaining reliable laboratory tests. The diagnosis of MPP usually requires the detection of M. pneumoniae-specific antibodies or nucleic acids in serum or respiratory specimens, but these methods have limitations in terms of availability, sensitivity, specificity, timeliness, and cost-effectiveness [4].

The treatment of pneumonia in children depends on the etiology, severity, and age of the child. The treatment usually involves empirical antibiotic therapy based on local epidemiology and resistance patterns, followed by targeted therapy based on microbiological results [5]. However, antibiotic therapy has drawbacks such as adverse effects, toxicity, drug interactions, and emergence of resistance [6]. Therefore, alternative or adjunctive therapies are needed to improve the outcomes of pneumonia in children.

### 1.3. Aerosol inhalation therapy

One of the potential alternative or adjunctive therapies for pneumonia in children is aerosol inhalation therapy. Aerosol inhalation therapy is a method of delivering drugs directly to the respiratory tract through inhalation devices such as nebulizers or inhalers. Aerosol inhalation therapy has several advantages over systemic administration, such as higher local drug concentration, lower systemic absorption and toxicity, faster onset of action, and fewer side effects [7].

One of the commonly used drugs for aerosol inhalation therapy is budesonide (BUD), which is an inhaled corticosteroid (ICS) that has anti-inflammatory and immunomodulatory effects on the airway mucosa. BUD can reduce airway hyperresponsiveness, inflammation, edema, mucus secretion, and bronchospasm, thereby improving pulmonary function and reducing respiratory distress [8]. BUD has been shown to be effective and safe for the treatment of various respiratory diseases in children and adults, such as asthma, bronchiolitis, chronic obstructive pulmonary disease (COPD), and acute respiratory distress syndrome (ARDS) [9].

Another commonly used drug for aerosol inhalation therapy is ambroxol hydrochloride (AMB), which is a mucolytic agent that can enhance mucus clearance by reducing mucus viscosity and increasing ciliary activity. AMB can also exert anti-inflammatory, antioxidant, antibacterial, antiviral, and immunomodulatory effects on the respiratory tract [10]. AMB has been shown to be effective and safe for the treatment of various respiratory diseases in children and adults, such as bronchitis, cystic fibrosis (CF), pneumonia, and tuberculosis (TB).

### 1.4. Rationale and objective

Although BUD and AMB have been widely used for aerosol inhalation therapy in clinical practice for different respiratory diseases, their efficacy and safety for the treatment of pneumonia in children are still controversial. Some studies have reported positive results with BUD and AMB for pneumonia in children, while others have reported negative or inconclusive results [11–13]. Moreover, the quality of evidence from these studies is low or moderate due to small sample sizes, heterogeneous populations, inconsistent interventions, and variable outcomes [14].

Therefore, there is a need for a systematic review and meta-analysis to synthesize the available evidence on the efficacy and safety of BUD and AMB for aerosol inhalation therapy for pneumonia in children. The objective of this study is to evaluate the effects of BUD combined with AMB for aerosol inhalation therapy on clinical outcomes, such as mortality, morbidity, length of hospital stay, and adverse events, in children with pneumonia. This study is innovative in that it is the first systematic review and meta-analysis to compare the effects of BUD combined with AMB versus other treatments for aerosol inhalation therapy for pneumonia in children. This comparison will help to determine the optimal treatment regimen and to identify the potential benefits and risks of BUD and AMB for pneumonia in children. This study will provide a comprehensive and reliable evidence base for clinical decision making and future research on aerosol inhalation therapy for pneumonia in children.

## 2. Materials and methods

### 2.1. Article retrieval

Computer was employed to retrieve articles published from the establishment of databases to April 1st, 2022 from PubMed, Embase, MEDLINE, Science Direct, The Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang database, Database of Chinese sci-tech periodicals, and China Biology Medicine disc (CBM). The retrieved articles were random controlled trials

(RCTs) or cohort studies on the treatment of children with pneumonia with BUD and the aerosol inhalation of AMB. The retrieval strategies were as follows. Key English search terms included "Budesonide", "Hydrochloric acid", "ambroxol hydrochloride", "ambroxol", "aerosol inhalation", and "pneumonia". After several pre-retriveals, the retrieval strategies were determined. Professional periodicals were manually searched to avoid omission. In addition, all subjects in the retrieved articles were humans. During the retrieval, subject terms were combined with free terms for several retrievals to obtain includable articles. After that, the search engine was utilized to trace all articles. Finally, RevMan5.3 provided by Cochrane collaboration network was employed to assess the quality of included articles.

### *2.2. Inclusion and exclusion criteria*

The inclusion criteria were as follows.

A. The study included children under 5 years of age diagnosed with pneumonia.
B. All patients underwent treatment with BUD or AMB inhalation.
C. All patients provided informed consent, and their clinical data were complete.
D. The study reported at least one clinical outcome relevant to the objectives of this paper, such as mortality rate, fever duration, cough duration, length of hospital stay, absorption of lung abnormalities on imaging, and adverse reactions.

The exclusion criteria were as follows.

A. Studies with duplicate publications or duplicated data.
B. Studies involving subjects who did not meet the age or diagnostic criteria.
C. Non-randomized controlled trials, such as observational studies, retrospective studies, and case reports.
D. Incomplete articles with no access to full text even after contacting the authors.
E. Studies that did not report any clinical outcomes relevant to the objectives of this work.
F. Studies with low quality or incomplete data.

### *2.3. Data extraction*

Two professionals independently conducted literature screening and data extraction using Microsoft Excel (Microsoft, the United States) according to the predefined inclusion and exclusion criteria. They cross-checked the final results of inclusion and resolved any disagreements through discussion or consultation with a third-party expert. The extracted data included basic data (title, the first author, publication year, country, publication journal, and article source), basic characteristics of the subjects (gender ratio, age, and the sample size of experimental group and control group), treatment course (single drug therapy or combined therapy and efficacy), the key elements of bias risk evaluation (random methods and whether blind method and allocation concealment were implemented), and outcome indicators and measured data (OR, CR, PR, and safety outcome AEs). To ensure the accuracy and reliability of the data analysis, a statistical expert was invited to review and provide guidance on our data analysis methods and results.

## 3. Article evaluation criteria

The bias risk evaluation criteria of Cochrane collaboration network was adopted for RCTs.

A. Whether correct random allocation methods were utilized. If random number table method, computer-generated random sequence, coin tossing, dicing, or draw was performed, correct random allocation methods were adopted. Otherwise, the answer was "No". If the specific random method was unidentifiable due to the lack of information, the answer was "Unclear".
B. Whether complete allocation concealment was employed. If central concealment (telephone, network, or pharmacy monitoring), drug utensil with similar appearance, or airtight and opaque envelope was adopted, the answer was "Yes". Otherwise, the answer was "No". If whether allocation concealment was implemented couldn't be determined due to the inadequacy of information, the answer was "Unclear".
C. If all patients, doctors, outcome measurers, and statisticians were performed with blind method or not, but no bias was caused to the measurement of outcome indicators, blind method was correct. If there was bias in the measurement of outcome indicators even though no blind method was adopted or blind method could hardly be successfully carried out, the answer was "No". If it was difficult to determine whether correct blind method was adopted, the answer was "Unclear".
D. If no data loss or the cause of data loss had no impacts on the measurement of outcome indicators, outcome data were complete. Otherwise, the answer was "No". If it was difficult to determine whether outcome data were complete due to the deficiency of information, the answer was "Unclear".
E. If all pre-designed measurement indicators were reported, there was selective reporting. Otherwise, the answer was "No". If it was hard to determine whether selective reporting existed due to the deficiency of information, the answer was "Unclear".
F. If no other bias sources were detected, the answer was "Yes". Otherwise, the answer was "No". If it was hard to determine whether there were other bias sources, the answer was "Unclear".

According to the included articles, each item was rated low risk, high risk, or unclear risk. The research evidence was rated levels A, B, and C in the order of high quality to low quality.

### 3.1. Statistical methods

RevMan5.3 software (Cochrane, the United States) and Stata (Stata Corp, the United States) were utilized. Odds ratio (OR) was set as the effect indicator for binary variable and mean difference (MD) was set as the effect indicator for continuous variable. Besides, point estimate values of both effect indicators and corresponding 95 % confidence interval (CI) were calculated. The heterogeneity

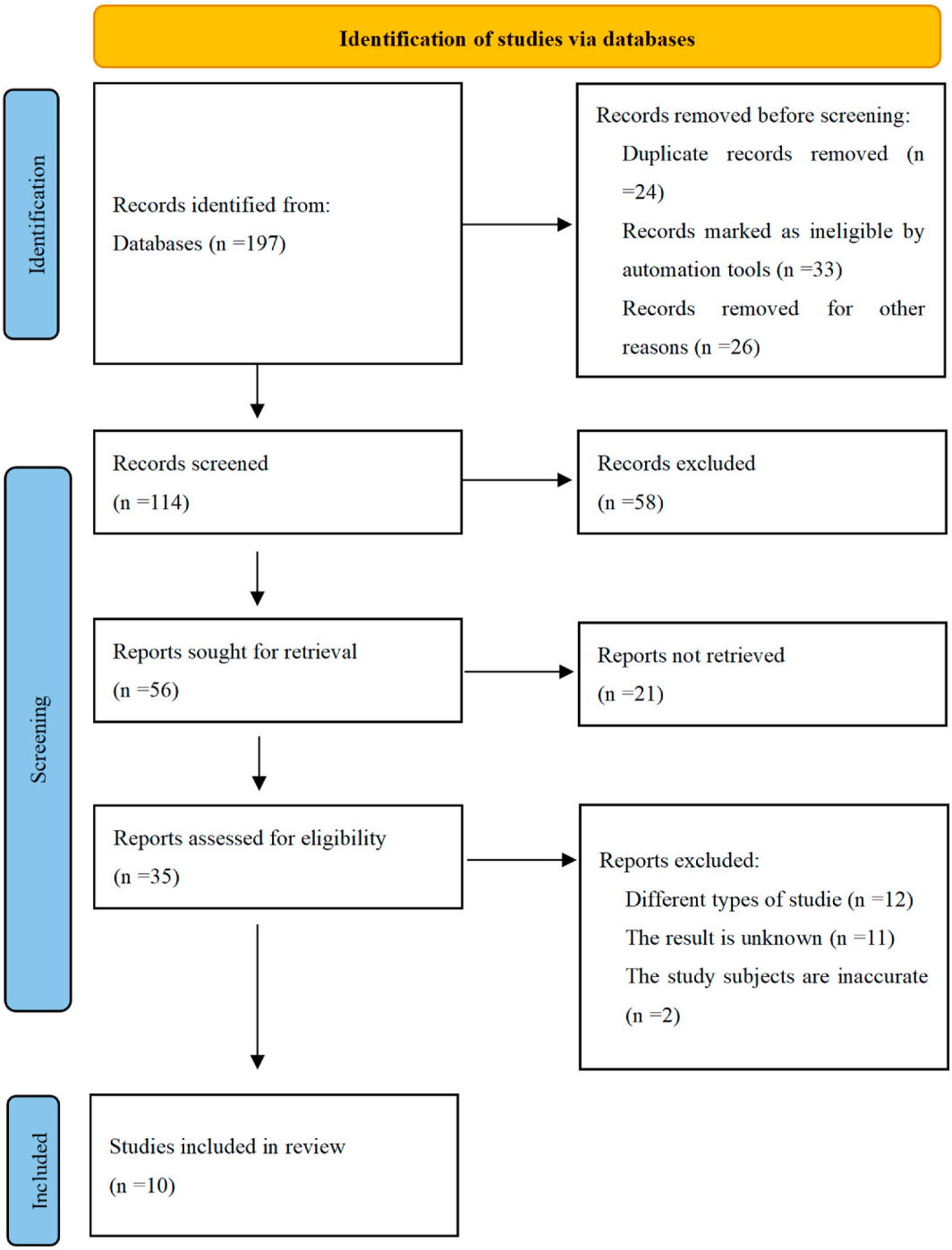


**Fig. 1.** The process for article retrieval.

between the included articles was analyzed using $X^2$ test (test level was $\alpha = 0.1$). What's more, the size of the heterogeneity was quantitatively determined based on $I^2$. Fixed effect model was utilized for the meta-analysis if no statistical differences were detected in the heterogeneity among included articles. Otherwise, random effect model was employed and subgroup analysis was carried out for the investigation into possible sources of the heterogeneity. The test level of the meta-analysis was set as $\alpha = 0.05$. After that, forest plots, summary receiver operating characteristic (SROC) curves, and funnel plot asymmetric linear regression were drawn. The funnel plots with different treatment indicators were utilized to detect and analyze potential publication bias.

## 4. Results

### 4.1. Retrieval results and basic data on the articles

197 articles were obtained through database retrieval. Firstly, 24 articles published repeatedly and 33 ineligible articles were removed. In addition, 26 articles were eliminated for other reasons. The remaining 114 articles were preliminarily selected. After that, 58 articles were excluded by reading abstracts and titles and then 56 articles were left. Besides, 21 research reports and 21 reviews were removed and 35 were left. Next, all the remaining articles were read one by one and 12 articles with incorrect research types were excluded. What's more, 11 articles with incomplete or inaccessible treatment results and 2 whose subjects were not humans were removed. Finally, 10 articles were included in the meta-analysis [15–24]. The process for article retrieval was displayed in Fig. 1.

The basic data on the included articles were extracted by reading the contents of the articles. Among 10 included articles, A total of 524 pediatric pneumonia patients were treated with AMB aerosol inhalation, while 522 pediatric pneumonia patients were treated with BUD and AMB aerosol inhalation. In addition, the sample size ranged from 51 to 184. Among the 10 articles included in this analysis, detailed descriptions were provided regarding the process of treating pediatric pneumonia with BUD and AMB aerosol inhalation, documenting the changes observed in patients before and after treatment. The basic characteristics of the included articles were presented in Table 1.

The quality of 10 included articles was evaluated. It was demonstrated that 6 articles were rated grade A (60 %), 2 were rated B (20 %), and 2 were rated C (20 %). The evaluation and summary of risk bias of the included articles drawn by RevMan5.3 were illustrated in Figs. 2 and 3.

### 4.2. Evaluation of heterogeneity

The heterogeneity of therapeutic effectiveness of the included articles was evaluated. The heterogeneity results for the effectiveness of BUD and AMB aerosol inhalation in treating pediatric pneumonia showed no heterogeneity among the studies ($I^2 = 0.00$ %). However, regarding the outcomes of cough disappearance, lung auscultation improvement, alleviation of respiratory distress, achievement of normal body temperature, and resolution of cyanosis in pediatric pneumonia patients treated with BUD or AMB aerosol inhalation, there was high heterogeneity observed among the studies ($I^2 = 92.1$ %, $I^2 = 76.92$ %, $I^2 = 84.19$ %, $I^2 = 94.82$ %, and $I^2 = 67.06$ %). To further verify whether there was heterogeneity between the data on the above 2 therapies and compare the differences in various treatment indicators, random effect model should be adopted for the summary of heterogeneity test and the fitting of funnel plots.

### 4.3. Meta-analysis of therapeutic effectiveness

OR was set as clinical outcome indicator. As illustrated in Fig. 4, the pooled OR for the effectiveness of BUD and AMB aerosol inhalation in treating pediatric pneumonia, based on seven studies, was 1.61 with a 95 % CI of (1.05, 2.18), $I^2 = 0.00$ %. This indicates that the likelihood of successfully treating pneumonia in the treatment group was 1.61 times higher than in the control group, and there was no heterogeneity observed in the effectiveness of BUD and AMB aerosol inhalation among the study groups. The lowest OR and 95%CI amounted to 1.21 and (−0.15,2.57), respectively, while the highest OR and 95%CI amounted to 2.30 and (0.17,4.44), respectively. However, there were substantial differences in the number of effectively treated patients between the treatment and

**Table 1**
Basic data on the included articles.

| Author | Year | Concentrations | | Case | Age (Years/Days) | Indicators |
|---|---|---|---|---|---|---|
| | | AMB | BUD | | | |
| Chen [15] | 2017 | 15mg × 2/d | 0.25 mg, 15min | 60/60 | 3.3/3.2(Y) | ①②③④⑤ |
| Chen [16] | 2019 | 7.5 mg, 6L/min | 1 mL, 6L/min | 37/37 | 16.24/16.04(D) | ③④⑥ |
| Gao [17] | 2019 | 0.2 mL, 6–8 L/min | 1 mL, 6–8 L/min | 62/46 | 15.5/15.7(D) | ①②③④⑤ |
| Li [18] | 2018 | 15mg × 2/d | 0.5–1 mg | 92/92 | 4.51/4.42(Y) | ①②③⑤⑥ |
| Liu [19] | 2015 | 15mg × 2/d | 1mg × 2/d | 36/36 | 4.02/3.51(Y) | ①②③⑤ |
| Luo [20] | 2012 | 7.5 mg, 6–8L/min | 1 mL, 6–8 L/min | 20/31 | / | ①③④⑥ |
| Shi [21] | 2020 | 0.25 mg/kg | 30 mg/(kg·d) | 45/45 | / | ①②③④⑤ |
| Ye [22] | 2013 | 15mg × 2/d | 0.5mg × 2/d | 78/78 | 2.52/2.46(Y) | ②③④⑤ |
| Yu [23] | 2021 | 15mg × 2/d | 2mg × 2/d | 55/58 | 3.62/3.57(Y) | ②③⑤ |
| Zhang [24] | 2019 | 15mg × 2/d | 0.5mg × 2/d | 39/39 | 3.69/3.75(Y) | ①②③⑤ |

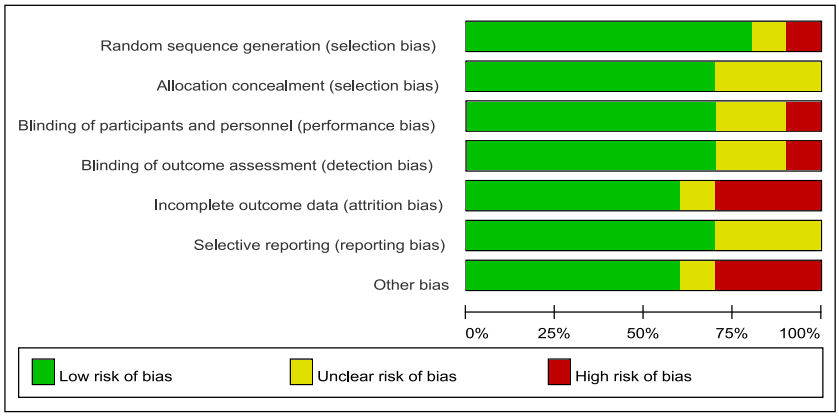


**Fig. 2.** Evaluation of risk bias of the included articles drawn by RevMan5.3.

control groups in the studies conducted by Luo et al. (2012) and Shi et al. (2020). This variability may be attributed to factors such as patient characteristics, experimental conditions, and treatment protocols.

As displayed in Fig. 5, heterogeneity test was conducted on the effectiveness of the treatment of children with pneumonia with BUD and the aerosol inhalation of AMB. According to the assessment of the heterogeneity among different articles and potential abnormal values, the heterogeneity among them was insignificant with high accuracy. The funnel plot of the effectiveness of the treatment of children with pneumonia with the above therapy was illustrated in Fig. 6. It was found that the bias risks of all articles were low. The above research findings demonstrated that the combined therapy of BUD and the aerosol inhalation of AMB was more effective.

#### *4.3.1. Meta-analysis of cough disappearance time*

MD was set as clinical outcome indicator. As presented in Fig. 7, MD, 95%CI, and $I^2$ of cough disappearance time of the treatment of children with pneumonia with BUD and the aerosol inhalation of AMB in 8 articles amounted to −1.68, (−1.84,-1.53), and 92.10 %, respectively. This indicates that BUD and AMB aerosol inhalation therapy can lead to a faster relief of cough symptoms. However, the high heterogeneity observed with an $I^2$ value of 92.10 % suggests significant statistical differences among these studies, which may be attributed to variations in study design, study quality, study population, treatment dosage, and other factors. The lowest OR and 95%CI amounted to −2.99 and (−3.41,-2.57), respectively, while the highest OR and 95%CI amounted to −0.44 and (−0.81,-0.07), respectively. The studies conducted by Chen (2017), Gao et al. (2019), and Li et al. (2018) all reported shorter cough disappearance time in the treatment group compared to the control group. However, certain studies such as Yu et al. (2021) did not find significant differences between the two groups, possibly due to variations in sample size, experimental conditions, disease severity, and other factors.

As displayed in Fig. 8, heterogeneity test was conducted on postoperative cough disappearance time. According to the assessment of the heterogeneity among different articles and potential abnormal values, the heterogeneity among them was insignificant with high accuracy. The funnel plot of postoperative cough disappearance time was illustrated in Fig. 9. It was found that the bias risks of all articles were low and bias occurred only in 2 articles.

#### *4.3.2. Meta-analysis of lung rales disappearance time*

MD was set as clinical outcome indicator. As presented in Fig. 10, MD, 95%CI, and $I^2$ of lung rales disappearance time of the treatment of children with pneumonia with BUD and the aerosol inhalation of AMB in 10 articles amounted to −1.61, (−1.91,-1.31), and 76.92 %, respectively. This also shows that BUD and AMB aerosol inhalation therapy can relieve lung rales more quickly. However, $I^2$ = 76.92 % indicates that there was great heterogeneity among these studies. The lowest OR and 95%CI amounted to −2.37 and (−2.78,-1.96), respectively, while the highest OR and 95%CI amounted to −0.61 and (−1.19,-0.04), respectively. Among them, Chen (2017), Gao et al. (2019), and Li et al. (2018) showed that the disappearance time of lung rales in the treatment group was significantly shorter than that in the control group.

As displayed in Fig. 11, heterogeneity test was conducted on postoperative lung rales disappearance time. According to the assessment of the heterogeneity among different articles and potential abnormal values, the heterogeneity among them was insignificant with high accuracy. The funnel plot of postoperative lung rales disappearance time was illustrated in Fig. 12. It was found that the bias risks of all articles were low and bias occurred in 4 articles.

#### *4.3.3. Meta-analysis of dyspnea disappearance time*

MD was set as clinical outcome indicator. As presented in Fig. 13, MD, 95%CI, and $I^2$ of dyspnea disappearance time of the treatment of children with pneumonia with BUD and the aerosol inhalation of AMB in 6 articles amounted to −1.99, (−2.18,-1.79), and 84.19 %, respectively. This further proves the effect of BUD and AMB aerosol inhalation therapy. The lowest OR and 95%CI amounted to −3.00 and (−3.55,-2.45), respectively, while the highest OR and 95%CI amounted to −1.10 and (−1.69,-0.51), respectively. Chen (2017), Gao et al. (2019) and Ye (2013) showed that the disappearance time of dyspnea in the treatment group was

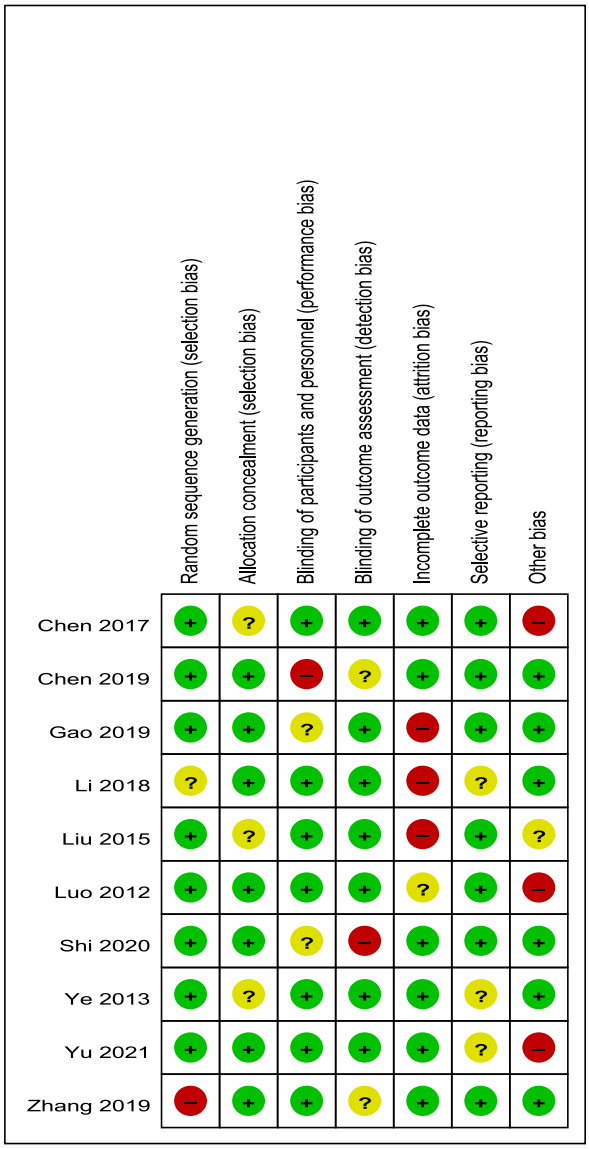


**Fig. 3.** Summary of risk bias of the included articles drawn by RevMan5.3. Note: "+", "-", and "?" represented low risk, high risk, and unclear, respectively.

significantly shortened, which indicated that BUD and AMB aerosol inhalation therapy had a good effect. However, studies such as Luo et al. (2012) and Shi et al. (2020) showed that the difference between the two groups was not significant.

As displayed in Fig. 14, heterogeneity test was conducted on postoperative dyspnea disappearance time. According to the assessment of the heterogeneity among different articles and potential abnormal values, the heterogeneity among them was insignificant with high accuracy. The funnel plot of postoperative dyspnea disappearance time was illustrated in Fig. 15. It was found that the bias risks of all articles were low and bias occurred in 3 articles.

#### *4.3.4. Meta-analysis of fever removal time*

MD was set as clinical outcome indicator. As presented in Fig. 16, MD, 95%CI, and $I^2$ of fever removal time of the treatment of children with pneumonia with BUD and the aerosol inhalation of AMB in 8 articles amounted to −1.33, (−1.72,-0.94), and 94.82 %, respectively. The treatment group decreased by 1.33 days compared with the control group, which indicated that BUD and AMB aerosol inhalation therapy could lower the body temperature faster. The lowest OR and 95%CI amounted to −1.99 and (−2.21,-1.77), respectively, while the highest OR and 95%CI amounted to −0.33 and (−0.52,-0.14), respectively. Among them, in the studies of Chen (2017), Gao et al. (2019), Liu (2015), and Zhang (2019), the temperature of the treatment group returned to normal significantly faster than that of the control group. This further proves that BUD and AMB aerosol inhalation therapy can effectively shorten the course of disease. However, some studies such as Ye (2013) and Yu et al. (2021) showed that the time difference between the two groups was not

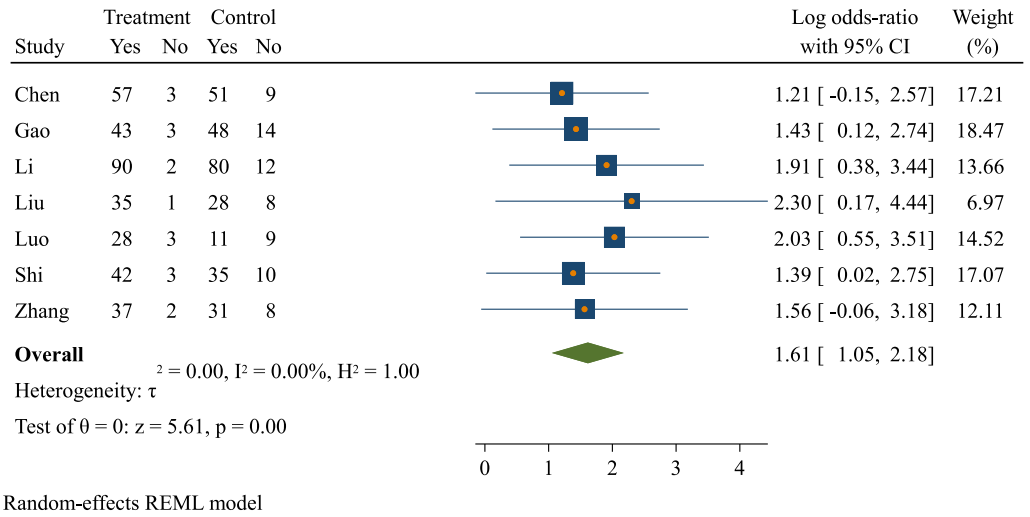


**Fig. 4.** Forest plot of the effectiveness of BUD and the aerosol inhalation of AMB
CI: confidence interval; df: degree of freedom.

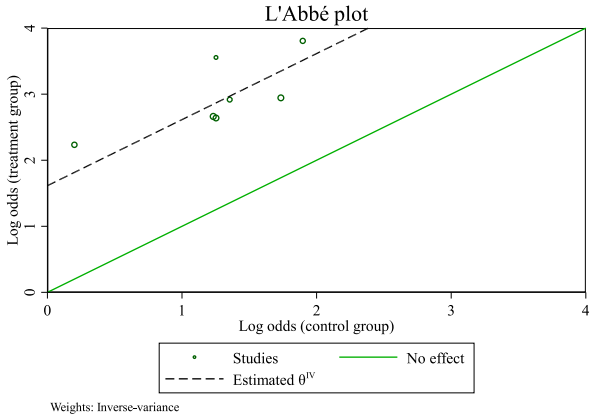


**Fig. 5.** Labbe heterogeneity test on the effectiveness of BUD and the aerosol inhalation of AMB.

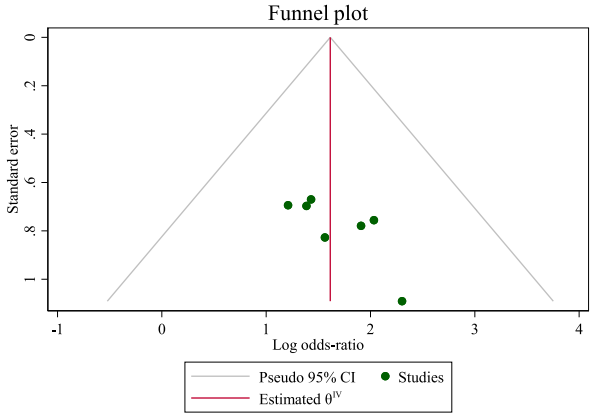


**Fig. 6.** Funnel plot of the effectiveness of BUD and the aerosol inhalation of AMB.

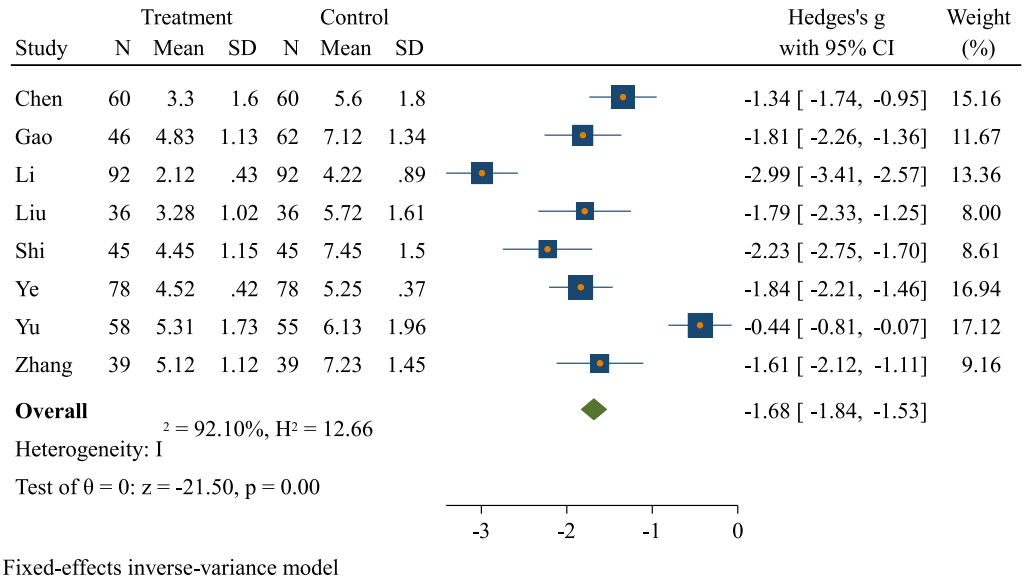


**Fig. 7.** Forest plot of cough disappearance time after the treatment with BUD and the aerosol inhalation of AMB.
CI: confidence interval; df: degree of freedom.

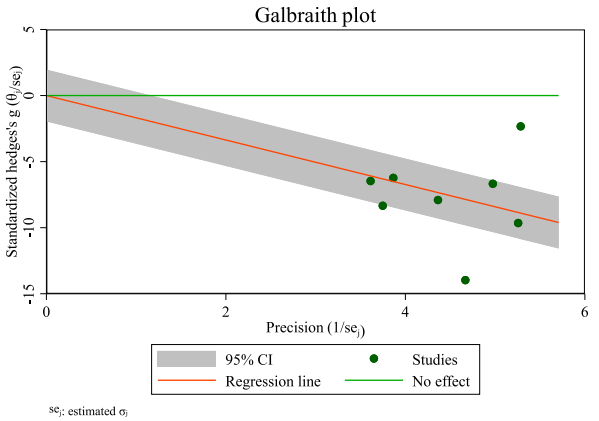


**Fig. 8.** Galbraith heterogeneity test on postoperative cough disappearance time.

significant.

As displayed in Fig. 17, heterogeneity test was conducted on postoperative fever removal time. According to the assessment of the heterogeneity among different articles and potential abnormal values, the heterogeneity among them was insignificant with high accuracy. The funnel plot of postoperative fever removal time was illustrated in Fig. 18. It was found that the bias risks of all articles were low and bias occurred in 3 articles.

### *4.3.5. Meta-analysis of lip cyanosis disappearance time*

MD was set as clinical outcome indicator. As presented in Fig. 19, MD, 95%CI, and $I^2$ of lip cyanosis disappearance time of the treatment of children with pneumonia with BUD and the aerosol inhalation of AMB in 3 articles amounted to −1.20, (−1.67,-0.73), and 67.06 %, respectively. The treatment group decreased by 1.20 days compared with the control group, which showed the effect of BUD and AMB aerosol inhalation therapy on improving cyanosis of lips. However, $I^2$ = 67.06 % indicates that there was some heterogeneity among these studies. The lowest OR and 95%CI amounted to −1.56 and (−2.19,-0.93), respectively, while the highest OR and 95%CI amounted to −0.82 and (−1.12,-0.52), respectively. Only three studies (Chen et al. (2019), Li et al. (2018) and Luo et al. (2012)) reported the disappearance time of oral cyanosis, which may have some influence on the results. However, in these three studies, it was observed that BUD and AMB aerosol inhalation therapy had an advantage over the control group in the disappearance time of cyanosis.

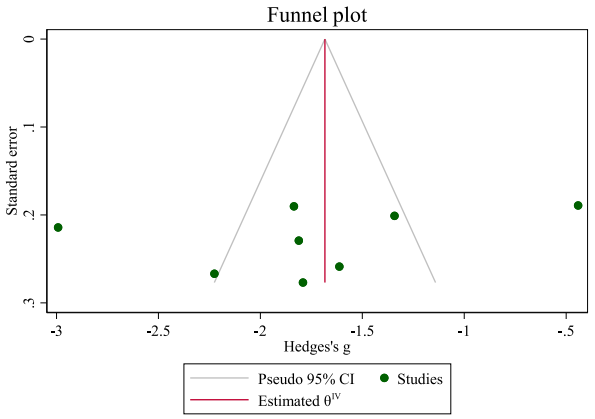


**Fig. 9.** Funnel plot of postoperative cough disappearance time.

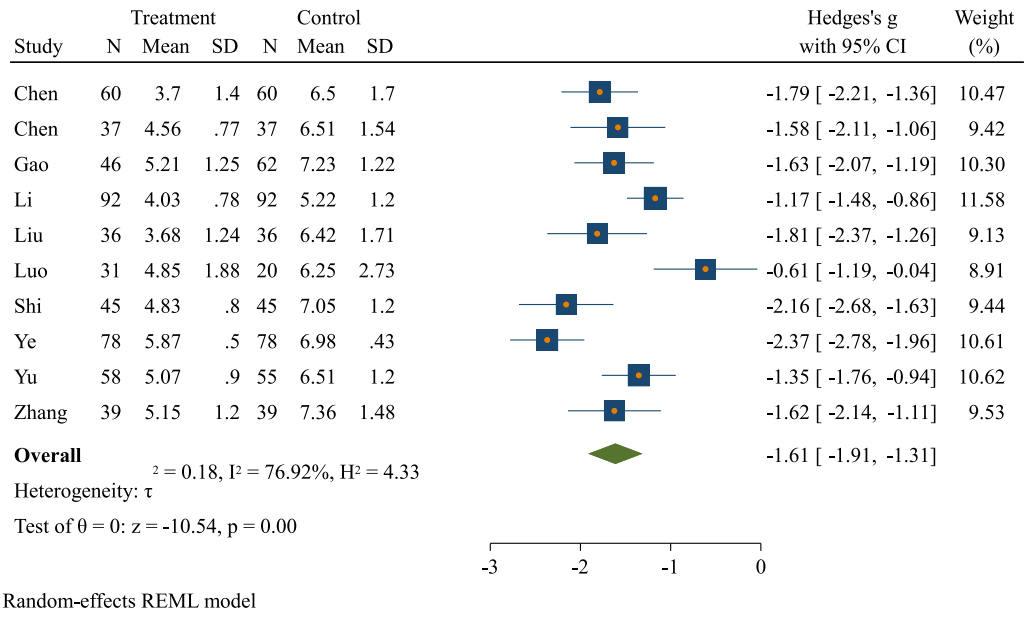


**Fig. 10.** Forest plot of lung rales disappearance time after the treatment with BUD and the aerosol inhalation of AMB.
CI: confidence interval; df: degree of freedom.

As displayed in Fig. 20, heterogeneity test was conducted on postoperative lip cyanosis disappearance time. According to the assessment of the heterogeneity among different articles and potential abnormal values, the heterogeneity among them was insignificant with high accuracy. The funnel plot of postoperative lip cyanosis disappearance time was illustrated in Fig. 21. It was found that the bias risks of all articles were low.

### *4.3.6. Reliability analysis*

The analysis models were changed to perform sensitivity analysis. According to the meta-analysis, the summarized results showed no apparent changes after different analysis models were applied, which demonstrated that the included articles were stable. Funnel asymmetric linear regression analysis model showed good consistency.

## 5. Discussion

Glucocorticoid is a lipophilic sex hormone, which exerts physiological and pharmacological effects through glucocorticoid receptors with high affinity in cytoplasm [25]. Inhaled glucocorticoid aerosol can reach the target organ directly, and has the characteristics of low concentration, quick onset, and few side effects, and the curative effect is remarkable [26]. BUD is the only aerosol

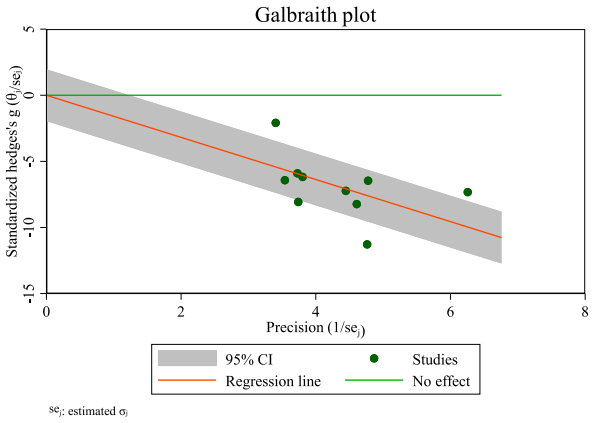


**Fig. 11.** Galbraith heterogeneity test on lung rales disappearance time after the treatment with BUD and the aerosol inhalation of AMB.

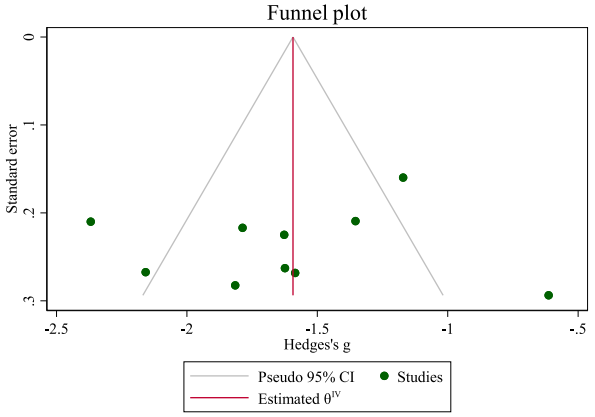


**Fig. 12.** Funnel plot of lung rales disappearance time after the treatment with BUD and the aerosol inhalation of AMB.

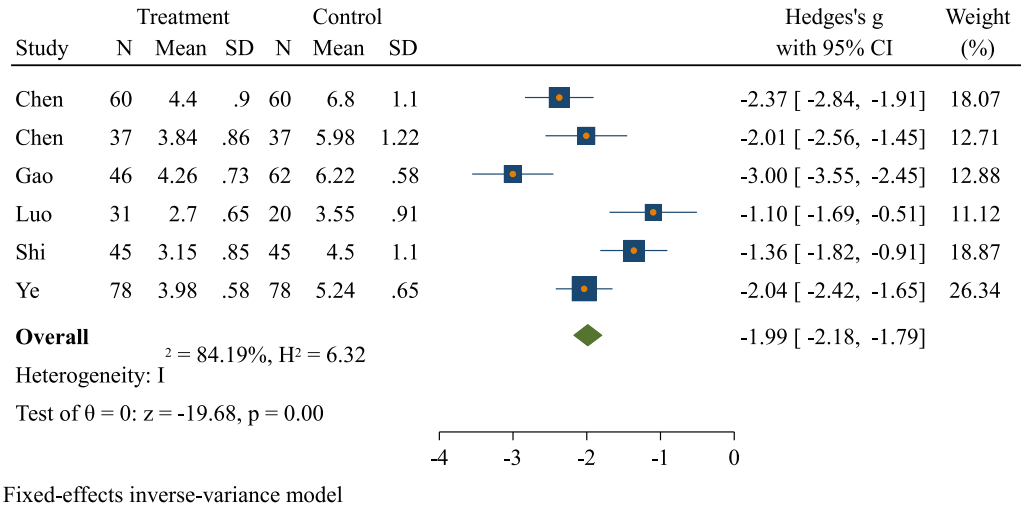


**Fig. 13.** Forest plot of dyspnea disappearance time after the treatment with BUD and the aerosol inhalation of AMB.
CI: confidence interval; df: degree of freedom.

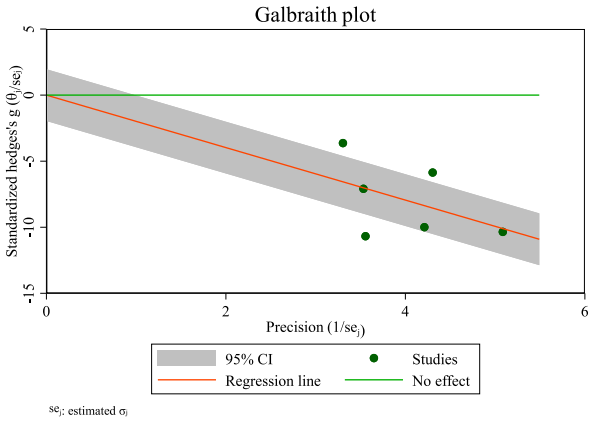


**Fig. 14.** Galbraith heterogeneity test on dyspnea disappearance time after the treatment with BUD and the aerosol inhalation of AMB.

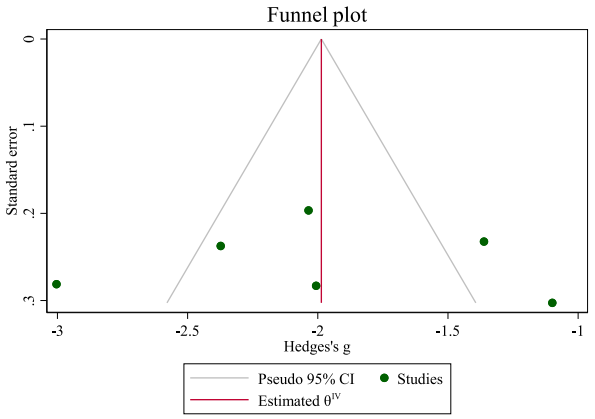


**Fig. 15.** Funnel plot of dyspnea disappearance time after the treatment with BUD and the aerosol inhalation of AMB.

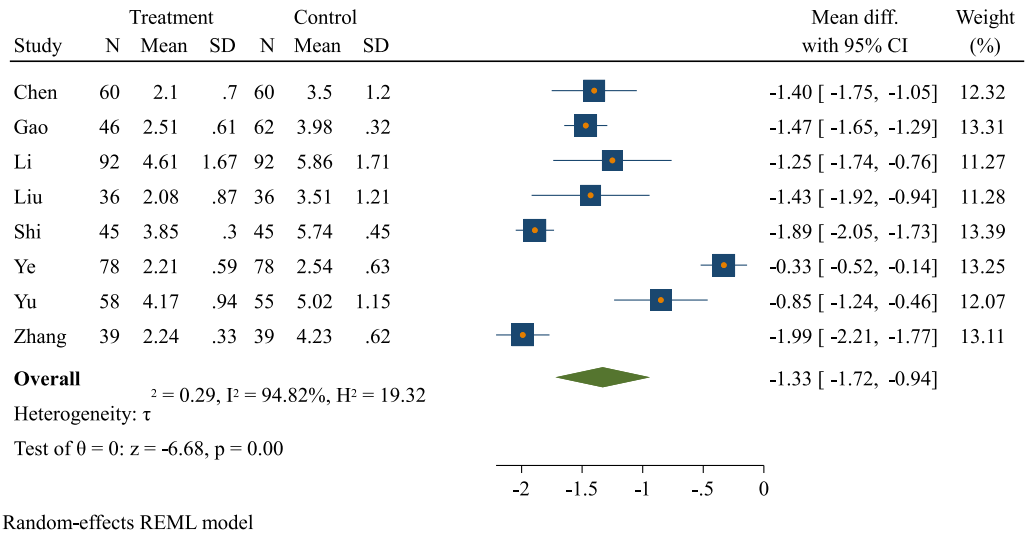


**Fig. 16.** Forest plot of fever removal time after the treatment with BUD and the aerosol inhalation of AMB.
CI: confidence interval; df: degree of freedom.

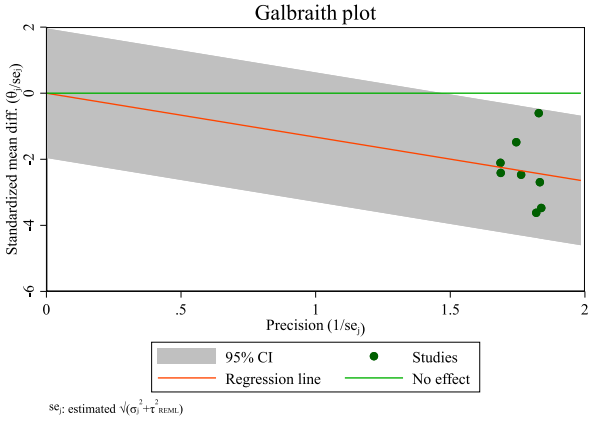


**Fig. 17.** Galbraith heterogeneity test on fever removal time after the treatment with BUD and the aerosol inhalation of AMB.

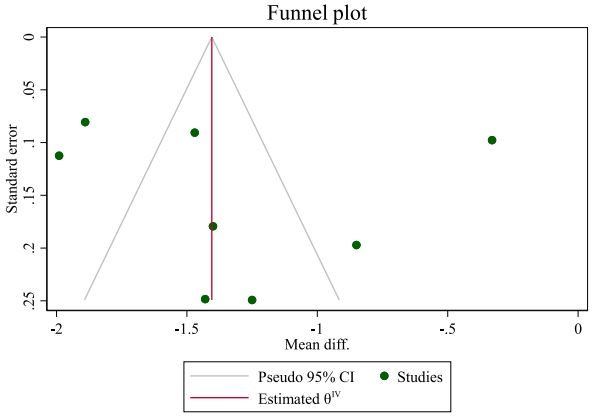


**Fig. 18.** Funnel plot of fever removal time after the treatment with BUD and the aerosol inhalation of AMB.

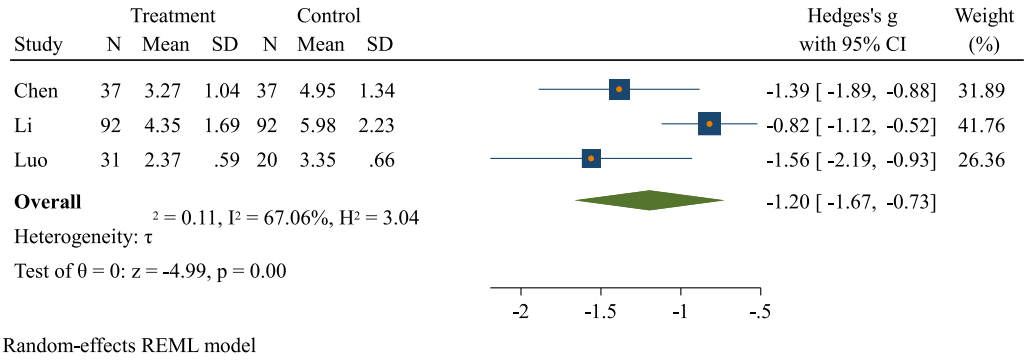


**Fig. 19.** Forest plot of lip cyanosis disappearance time after the treatment with BUD and the aerosol inhalation of AMB.
CI: confidence interval; df: degree of freedom.

glucocorticoid approved by FDA and SFDA in all ICS. AMB is a mucolytic agent, which can enhance mucus clearance and exert anti-inflammatory, antioxidant, antibacterial, antiviral, and immunomodulatory effects on respiratory tract [27].

Recently, two studies reported the positive results of BUD and AMB in the treatment of pneumonia in children. One study, a randomized controlled trial, compared the effects of inhaled BUD and placebo on recent newborns with respiratory distress syndrome (RDS) [28]. Bronchopulmonary dysplasia (BPD) was compared with placebo. The study also reported that there was no serious adverse event associated with BUD. The other study is a retrospective cohort study, comparing the efficacy of atomized inhalation of AMB

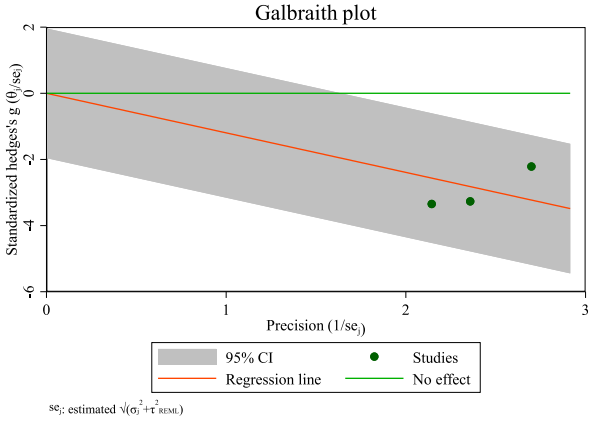


**Fig. 20.** Galbraith heterogeneity test on lip cyanosis disappearance time after the treatment with BUD and the aerosol inhalation of AMB.

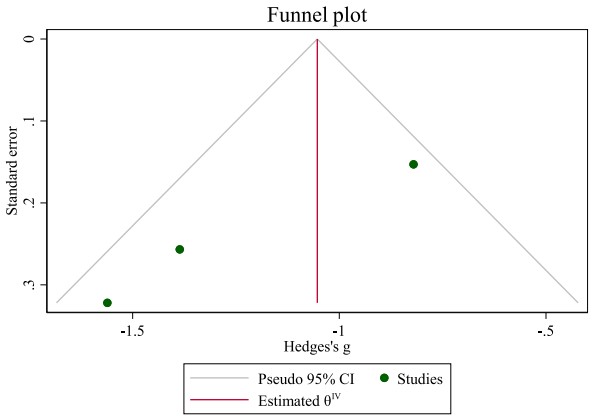


**Fig. 21.** Funnel plot of lip cyanosis disappearance time after the treatment with BUD and the aerosol inhalation of AMB.

combined with terbutaline with terbutaline alone in the treatment of severe pneumonia in children [29,30]. It was found that AMB combined with terbutaline significantly shortened the time of fever reduction, cough disappearance, lung rales, disappearance time, chest shadow absorption time, and hospitalization time compared with terbutaline alone. The study also reported that AMB combined with terbutaline can significantly improve the immune function of children with severe pneumonia and reduce the level of inflammation. There were no adverse reactions related to AMB or terbutaline in this study. In this research, the meta-analysis was implemented to systematically evaluate the therapeutic effects of BUD and the aerosol inhalation of AMB on neonatal pneumonia. The combined therapy was more effective (OR = 1.61, $I^2$ = 0.00 %). No heterogeneity was detected among different articles. According to the results of the heterogeneity cough disappearance, lung rales disappearance, dyspnea disappearance, normal body temperature, and lip cyanosis disappearance among neonates with pneumonia undergoing the combined therapy, remarkable heterogeneity was detected among different articles ($I^2$ = 92.1 %, $I^2$ = 76.92 %, $I^2$ = 84.19 %, $I^2$ = 94.82 %, and $I^2$ = 67.06 %).

There are some limitations in this study, because there are few related studies, so the number of studies included is small and the quality of evidence is medium. Secondly, the intervention dose, mode, and duration of BUD and AMB are not standardized in different studies, which may affect the treatment effect and adverse events. Therefore, more high-quality randomized controlled trials are needed to compare the efficacy of BUD combined with AMB and other drugs in the treatment of pneumonia in children. Future research should also use reliable laboratory tests to diagnose pneumonia and its etiology, standardize the intervention dose and duration of BUD and AMB, and use objective outcome indicators such as lung function test and inflammatory markers to evaluate the treatment effect and adverse events. The innovation of this study is that it is the first systematic evaluation and meta-analysis to compare the therapeutic effect of BUD combined with AMB with other treatments on children pneumonia. This comparison will help to determine the best treatment plan and determine the potential benefits and risks of BUD and AMB for pneumonia in children. This study will provide a comprehensive and reliable evidence base for clinical decision-making and future research of aerosol inhalation therapy for children's pneumonia.

## 6. Conclusion

Based on meta-analysis, BUD combined with AMB aerosol inhalation is more effective in treating children pneumonia compared with AMB aerosol inhalation. Neonatal pneumonia has played a certain role in relieving cough, lung rales, dyspnea, body temperature, and cyanosis of mouth and lips. Nevertheless, there are some limitations in this study. For example, due to the different dosage and administration methods of drugs in different studies, there is a certain heterogeneity between studies. In the follow-up study, further analysis should be carried out with the enrichment of new clinical trials.

## Author Contribution Statement

Huanan Shen, Xingni Zhao, Liangyin Xu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

## Data availability statement

Data included in article/supp. material/referenced in article.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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