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# Efficacy and safety of integrated traditional Chinese and Western medicine for the treatment of infant bronchiolitis

## A systematic review, meta-analysis and GRADE evaluation

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**Abstract**

**Background:** Infant bronchiolitis has a high death rate in severe cases. In China, traditional Chinese medicine (TCM) is commonly used to treat infant bronchiolitis. However, it has not received enough international attention.

**Objective:** We aimed to assess the efficacy and safety of integrated TCM and Western medicine for treating infant bronchiolitis.

**Methods:** We conducted a systematic review through 7 databases that included randomized controlled trials on integrated TCM and Western medicine for treating bronchiolitis, published in English or Chinese before February 4, 2021. To assess the risk of bias, the Cochrane Collaboration tool was employed to determine the quality of the included studies. We investigated clinical efficacy endpoints, hospitalization time, rates of recurrence, and adverse reactions and meta-analyzed the odds ratio (OR), mean difference (MD), and relative risk (RR), respectively. We assessed the overall certainty of the effect estimates using the GRADE approach. This study is registered with PROSPERO (CRD42021245294). Ethical approval is not required.

**Results:** Forty-six studies (6427 children) were available for inclusion. We used 41 (5490 participants), 11 (1350 participants), 5 (1083 participants), and 11 (1295 participants) studies to analyze clinical efficacy endpoints (OR: 3.31; 95% confidence interval [CI]: 2.93, 3.74; $P < .5$), hospitalization time (MD: –2.10; 95% CI: –2.87, –1.34; $P < .5$), recurrence rate (RR: 0·41; 95% CI: 0.30, 0.56; $P < .01$), and adverse reaction rate (RR: 0.87; 95% CI: 0.55, 1.39; $P = .57$), respectively.

**Conclusions:** Integrated TCM and Western medicine is superior to Western medicine alone for treating bronchiolitis in terms of clinical efficacy, hospitalization time, and recurrence rate, with no increase in the adverse reaction rate. TCM is useful as an alternative therapy for viral bronchiolitis. Although further studies are needed to establish specific protocols for the use of TCM in clinical practice, these results may strengthen guideline recommendations regarding the use of TCM.

**Abbreviations:** CI = confidence interval, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, MD = mean difference, OR = odds ratio, RR = relative risk, TCM = traditional Chinese medicine.

**Key Words:** alternative therapy, bronchiolitis, clinical efficacy, Traditional Chinese medicine

## 1. Introduction

Acute bronchiolitis refers to airway inflammation and lower respiratory tract obstruction in young children. It is almost always caused by viral infection. Respiratory syncytial virus, an enveloped, nonsegmented, negative, single-stranded RNA virus belonging to the paramyxovirus family, is the most common viral pathogen that causes bronchiolitis. Other viruses that cause bronchiolitis include rhinovirus, parainfluenza virus, human metapneumovirus, influenza virus, adenovirus, coronavirus, and human bocavirus.[1] According to guidelines, the upper age limit for the diagnosis of bronchiolitis ranges from 6 or 12 months, with 12 months and 2 years being the limit in many European countries and the United States, respectively.[2]

Bronchiolitis has a prevalence of 18% to 32% in the first year and 9% to 17% in the second year of life.[3,4] It is clinically diagnosed, with diagnostic laboratory and radiographic tests playing a limited role in most cases.[5] It is characterized by acute inflammation, edema, necrosis of the epithelial cells lining the small airways, increased mucus production, and bronchospasm. The signs and symptoms at initial presentation typically include rhinitis and cough, which may progress to tachypnea, wheezing,

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*Because this meta-analysis was performed on data extracted from previously published research, all of the data and study materials are available in the databases referred to in this article. We encourage interested parties to contact the corresponding author for further discussions.*

*Supplemental Digital Content is available for this article.*

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rales, use of accessory muscles, and/or nasal flaring.[6] The most common complications are dehydration, apnea, and secondary bacterial infection. Most infants with bronchiolitis experience mild clinical manifestations that usually resolve in 1 to 2 weeks.

However, some infants with bronchiolitis may develop respiratory failure and require mechanical ventilation. Bronchiolitis presents a huge clinical burden. It is the most common acute lower respiratory tract infection in infants and the primary cause of hospitalization in this age group.[7] In the United Kingdom, 2% to 3% of all infants <12 months of age will be hospitalized with bronchiolitis.[8] Despite over 70 years of research, its management remains controversial and, currently, the treatment is only supportive,[7] with no substantial progress in research on this condition.

Meanwhile, various additional treatment options are available in China. At present, traditional Chinese medicine (TCM) is commonly used to treat bronchiolitis at Chinese medicine hospitals, and general hospitals also often combine proprietary Chinese medicine to treat it. A large amount of clinical and experimental research data have been accumulated on the treatment of bronchiolitis using TCM. However, due to the language barrier, it has not received enough international attention. Therefore, we conducted a systematic review and meta-analysis of randomized controlled trials to investigate the effect of integrated traditional Chinese and Western medicine for treating infant bronchiolitis in terms of clinical efficacy, hospitalization time, rates of recurrence, and adverse reactions. We also critically assessed the level of evidence of our study using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

## 2. Materials and Methods

### *2.1. Search strategy and selection criteria*

This systematic review and meta-analysis has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.[9] We used Medical Subject Headings terms and the corresponding free words to search 7 databases (PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure, WanFang, Chinese Science and Technology Periodical Database, and SinoMed/Chinese Biomedical Literature Database) for articles on integrated traditional Chinese and Western medicine for treating bronchiolitis published in English or Chinese before February 4,2021. The search terms were as follows: "medicine, Chinese traditional," "drugs, Chinese herbal," "integrative medicine,"

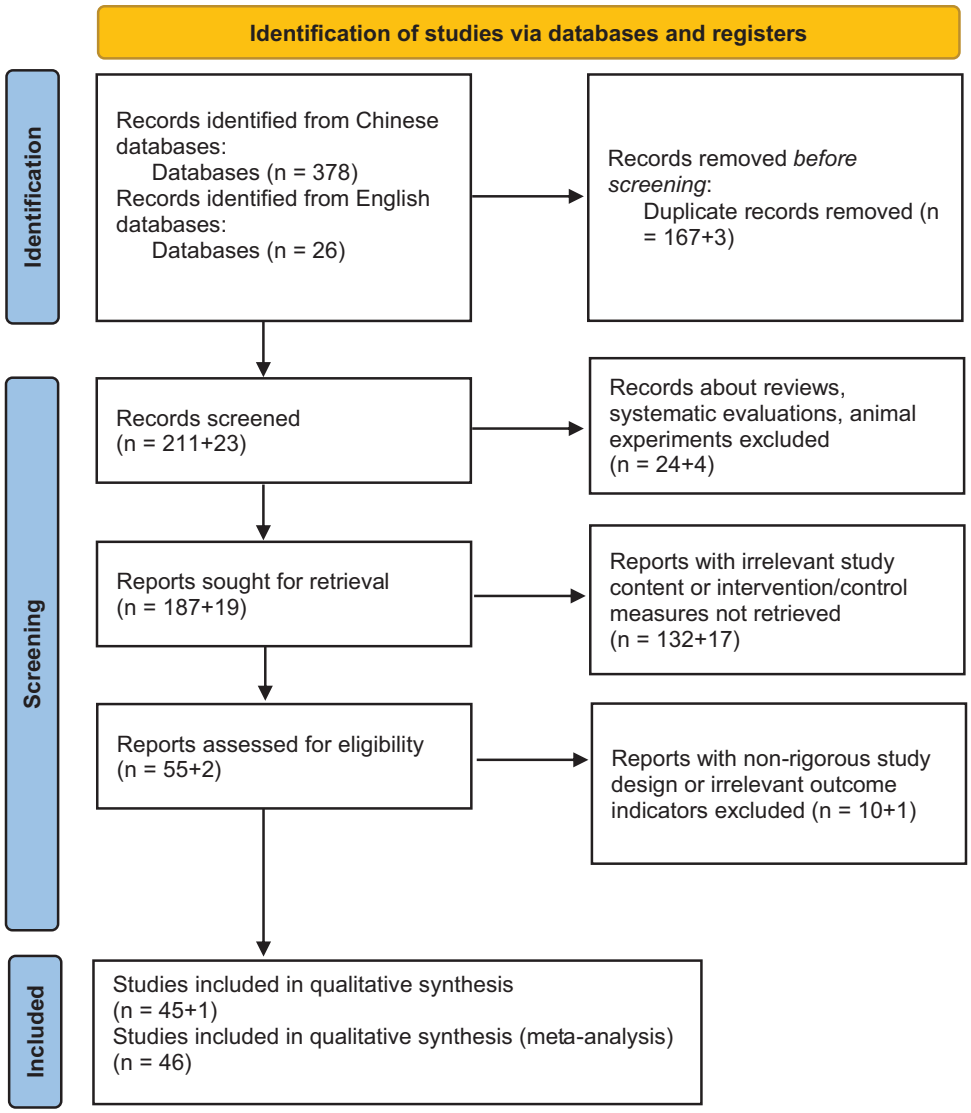


**Figure 1.** Study selection flowchart. CBM = Chinese Biomedical Literature Database, CNKI = China National Knowledge Infrastructure, VIP = Chinese Science and Technology Periodical Database.

**Table 1**

**Characteristics of the included studies.**

| Study | Year | Funding source | Distinguishing interventions | Duration of intervention (D) | N | Male, N (%) | Female, N (%) | Age ($\bar{x}$± s) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Experimental group | Control group |
| Jun J[10] | 2018 | Zhejiang province Excellent young talents project on TCM | Dialectical formula of TCM | 5 | 600 | 378 (63%) | 222 (37%) | 222.5 ± 12.2 D | 222.5 ± 12.2 D |
| Zongjun Y[11] | 2018 | NA | Dingchuan decoction | 7 | 96 | 56 (58%) | 40 (42%) | 2.34 ± 0.31 Y | 2.52 ± 0.45Y |
| Hui L[12] | 2018 | NA | Self-designed decoction | 7 | 88 | 48 (55%) | 40 (45%) | 12.68 ± 4.72 M | 14.02 ± 5.05 M |
| Huaxian L[13] | 2017 | NA | Self-designed decoction | 7 | 100 | 54 (54%) | 46 (46%) | 8.91 ± 1.27 M | 8.78 ± 1.23 M |
| Qiuzhen W[14] | 2017 | Major scientific and technological projects in Henan Province | Dingchuan decoction | 7 | 70 | 33 (47%) | 37 (53%) | 2.25 ± 0.27 Y | 2.17 ± 0.29 Y |
| Bin H[15] | 2017 | National TCM clinical research base project | Xiaoqinglong decoction | 7 | 123 | 79 (64%) | 44 (36%) | 7.06 ± 4.07 M | 6.92 ± 4.41 M |
| Ying H[16] | 2017 | NA | Shegan-Mahuang Decoction | 7 | 71 | 37 (52%) | 34 (48%) | 2.0 ± 0.7 Y | 2.0 ± 0.8 Y |
| Shang X[17] | 2017 | The Yunnan Provincial Bureau of Health, China and the Graduate School, Prince of Songkla University, Thailand | *Laggera pterodonta* mixture | 5 | 133 | 100 (75%) | 33 (25%) | Other forms | Other forms |
| Feng L[18] | 2017 | Natural Science Foundation of Hubei province | Xiaoqinglong decoction | 7 | 110 | 60 (55%) | 50 (45%) | 6.38 ± 1.24 M | 6.46 ± 1.32 M |
| Zhanjie W[19] | 2016 | NA | Self-designed decoction | 7 | 110 | 52 (47%) | 58 (53%) | 4·5 ± 1·3 M | 5·1 ± 1·2 M |
| Jing L[20] | 2015 | NA | Chinese patent medicine (Infantile Feire Kechuan oral solution) | 7 | 80 | 42 (53%) | 38 (48%) | 15.4 ± 2.7 M | 17.6 ± 2.3 M |
| Jvying L[21] | 2015 | NA | Self-designed decoction | 6 | 128 | 62 (48%) | 66 (52%) | 0.96 ± 0.18 Y | 0.99 ± 0.19 Y |
| Qing Q[22] | 2015 | NA | Chinese patent medicine (Infantile Magan granules) | 7 | 104 | 63 (61%) | 41 (39%) | 4.48 ± 0.31 M | 4.43 ± 0.32 M |
| Juanjuan Z[23] | 2014 | NA | Self-designed decoction | 10 | 80 | 45 (56%) | 35 (44%) | 4.61 ± 2.15 M | 4.72 ± 2.36 M |
| Hongxia L[24] | 2014 | NA | Self-designed decoction | NA | 200 | 129 (65%) | 71 (36%) | Other forms | Other forms |
| Teng H[25] | 2013 | Guangdong Provincial Bureau of TCM project | Chinese patent medicine (Infantile Kechuanling oral solution) | 7 | 68 | 50 (74%) | 18 (26%) | 10.17 ± 3.31 M | 10.20 ± 2.56 M |
| Guihua R[26] | 2013 | NA | Self-designed decoction | NA | 175 | 93 (53%) | 82 (47%) | 8.5 M | 8.8 M |
| Xiaohong L[27] | 2013 | NA | Self-designed decoction | 5–7 | 50 | 33 (66%) | 17 (34%) | 10.00 ± 8.05 M | 8.68 ± 7.72 M |
| Zhengguo H[28] | 2013 | NA | Dialectical formula of TCM | 7 | 80 | 45 (56%) | 35 (44%) | 11.2 ± 2.9 M | 12.5 ± 2.4 M |
| Sanxia S[29] | 2012 | NA | Self-designed decoction | 7 | 54 | 34 (63%) | 20 (37%) | 0.9 Y | 0.9 Y |
| Nairong G[30] | 2012 | NA | Self-designed decoction | 7 | 120 | 70 (58%) | 50 (42%) | 5.6 ± 1.2 M | 6.3 ± 1.7 M |
| Hao L[31] | 2010 | NA | Self-designed decoction | 7 | 87 | 49 (56%) | 38 (44%) | Other forms | Other forms |
| Sanbao M[32] | 2010 | NA | Xiaoqinglong decoction | 7 | 60 | 37 (62%) | 23 (38%) | Other forms | Other forms |
| Kedong W[33] | 2010 | NA | Self-designed decoction | 5–7 | 98 | 59 (60%) | 39 (40%) | 10.8 ± 6.5 M | 11.0 ± 6.3 M |
| Xiaohua H[34] | 2009 | NA | Shegan-Mahuang decoction | 7–10 | 304 | 157 (52%) | 147 (48%) | Other forms | Other forms |
| Min H[35] | 2009 | NA | Self-designed decoction | 5–10 | 86 | 53 (62%) | 33 (38%) | Other forms | Other forms |
| Jianbao L[36] | 2008 | NA | Self-designed decoction | 7–10 | 59 | 32 (54%) | 27 (46%) | Other forms | Other forms |
| Jinying Z[37] | 2008 | NA | Chinese patent medicine (Infantile Feire Kechuan Oral Solution) | 5–7 | 96 | 58 (60%) | 38 (40%) | 10.8 ± 5.7 M | 10.7 ± 5.8 M |
| Zhaohui G[38] | 2008 | NA | Xiaoqinglong decoction | 7 | 72 | 42 (58%) | 30 (42%) | Other forms | Other forms |
| Zhaoxia Z[39] | 2007 | NA | Self-designed decoction | 5–10 | 120 | 66 (55%) | 54 (45%) | Other forms | Other forms |
| Zuosheng Y[40] | 2007 | NA | Self-designed decoction | 5–7 | 133 | 69 (52%) | 64 (48%) | 11.8 ± 6.6 M | 11.7 ± 6.8 M |
| Hongmei P[41] | 2007 | NA | Self-designed decoction | 7 | 70 | 35 (50%) | 35 (50%) | Other forms | Other forms |
| Huimin X[42] | 2006 | NA | Self-designed decoction | 5 | 102 | 54 (53%) | 48 (47%) | 8.5 ± 1.6 M | 8.8 ± 1.3 M |
| Xiaoyu W[43] | 2006 | NA | Self-designed decoction | 6 | 90 | 49 (54%) | 41 (46%) | Other forms | Other forms |
| Dezhen L[44] | 2006 | NA | Self-designed decoction | 7 | 216 | 116 (54%) | 100 (46%) | 2.00 ± 0.36 Y | 2.00 ± 0.35 Y |
| Yonghua L[45] | 2005 | NA | Maxingshigan Decoction | 5 | 148 | NA | NA | Other forms | Other forms |
| Jinhua R[46] | 2004 | NA | self-designed decoction | 7 | 362 | 200 (55%) | 162 (45%) | Other forms | Other forms |
| Sujin X[47] | 2003 | NA | Dingchuan Decoction | 5–10 | 240 | 147 (61%) | 93 (39%) | 206.0 ± 10.0 D | 236.0 ± 10.2 D |
| Zhiying L[48] | 2002 | NA | Dialectical formula of TCM | 7 | 216 | 116 (54%) | 100 (46%) | 2.00 ± 0.36 Y | 2.00 ± 0.35 Y |
| Fangyun B[49] | 2001 | NA | Shegan-Mahuang Decoction | 7–10 | 120 | 58 (48%) | 62 (52%) | Other forms | Other forms |
| Pan Y[50] | 2001 | NA | self-designed decoction | 3 | 244 | 178 (73%) | 66 (27%) | Other forms | Other forms |
| Fuqu X[51] | 2001 | NA | self-designed decoction | 3–5 | 220 | NA | NA | Other forms | Other forms |
| Guangying G[52] | 2000 | NA | self-designed decoction | 5–6 | 204 | 161 (79%) | 43 (21%) | Other forms | Other forms |
| Xiao Q[53] | 2000 | NA | Maxingshigan decoction | 7–10 | 120 | 77 (64%) | 43 (36%) | Other forms | Other forms |
| Yirong Z[54] | 1995 | NA | Self-designed decoction | 7 | 88 | 56 (64%) | 32 (36%) | Other forms | Other forms |
| Guiying S[55] | 1993 | NA | Self-designed decoction | 5–7 | 232 | 159 (69%) | 73 (31%) | Other forms | Other forms |

D = days, M = months, NA = not clear, Other forms = counting by different age groups, TCM = traditional Chinese medicine, Y = years.

"complementary therapies," "medicine, traditional," "medicine, East Asian traditional," "bronchiolitis," "randomized controlled trial." We only selected literature from core journals in Chinese databases due to the large amount of data. Inclusion criteria for the selected studies were as follows: (1) Patients: infants with bronchiolitis diagnosed by a clinician or using recognized diagnostic criteria.[2] Intervention: infants in treatment groups who received combination therapy of orally administered TCM and the same conventional Western Medicine treatment as infants in the control group.[3] Comparison: infants in control groups received conventional Western medicine treatment according to the relevant guidelines for bronchiolitis.[4] Outcomes: clinical efficacy endpoint (invalid, effective, markedly effective, or cured), hospitalization time, and rates of recurrence and adverse reactions.[5] Study types: randomized controlled trials. On the other hand, studies were excluded based on (1) patients: infants with congenital heart disease, congenital airway dysplasia, chronic lung disease, malnutrition, or any other serious disease.[2] Intervention: infants who were administered TCM via injection or inhalation.[3] Comparison: infants who were administered Chinese patent medicine via the oral and injectable routes.[4] Outcomes: other outcome indicators that did not meet the requirements.[5] Study types: reviews, case reports, animal/cell experiments, repeated reports, and studies with incomplete data. Two reviewers independently screened the titles, abstracts, and full text of papers identified through our search and assessed them for risk of bias. Results were compared between reviewers; discrepancies were reconciled through discussion between the reviewers who extracted the data and, if these remained unresolved, the other authors were involved in resolving the discrepancy.

### 2.2. Data analysis

We developed a data extraction form to facilitate the electronic comparison of studies. The extracted data included study characteristics (study duration and funding), patient characteristics (age and sex), interventions (Chinese medicine formula), and outcomes (clinical efficacy endpoints, hospitalization time, and rates of recurrence and adverse reactions). The clinical efficacy endpoint data were analyzed using Stata version 14. Data regarding hospitalization time, recurrence rate, and adverse reactions were analyzed using Review Manager 5.3. The Cochrane Collaboration risk of bias assessment tool was used to assess the quality of the included studies.

The principal outcome of our analysis was the clinical efficacy endpoint. Forty-four studies evaluated the clinical efficacy, 11 evaluated the hospitalization time, 5 evaluated the recurrence rate, and 11 evaluated the rate of adverse reactions. We classified the studies according to the classical Chinese medicine formulae used and performed subgroup analysis of ten studies in which classical Chinese medicine formulae had been used. We calculated the effect size (odds ratio [OR]) and standard error of each trial based on the number of people with each clinical efficacy endpoint (invalid, effective, markedly effective, or cured) and calculated the pooled effect size (OR) to assess the clinical efficacy. We calculated the mean difference (MD) as the effect size for hospitalization time. We calculated the relative risk (RR) to assess the rates of recurrence and adverse reactions. The effect size and 95% confidence interval (CI) of each outcome were presented. Statistical significance was set at $P < .05$. We assessed heterogeneity using Cochran Q statistic and the $I^2$ statistic. The Egger test and funnel plots were used to detect potential publication bias. We performed subgroup analyses for trials using classical Chinese medicine formulae and compared the pooled effect sizes (OR) of the subgroups to determine the most effective classical Chinese medicine formulae.

Finally, we assessed the overall certainty of the effect estimates according to the GRADE system using the GRADEpro GDT online tool (https://gradepro.org/). Each outcome was evaluated separately, and limitations were categorized as follows: risk of bias, inconsistency, indirectness, imprecision, publication bias, large effect, plausible confounding, and dose-response gradient. The possible results for each category were "no serious limitations" (no downgrading), "serious limitations" (downgraded by 1 level), or "very serious limitations" (downgraded by 2 levels). The reasons for downgrading and the results and definition for each category have been reported in the footnote of the summary of findings (SoF) table (Material, Supplemental Digital Content, http://links.lww.com/MD/G893). The overall quality of the evidence was graded as high (++++), moderate (+++), low (++), or very low (+). The protocol for this study has been registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42021245294, https://www.crd.york.ac.uk/PROSPERO). Ethical approval is unnecessary because no people or animals are selected as subjects in this meta-analysis.

## 3. Results

A total of 1384 Chinese studies met our search criteria. After excluding Chinese studies that were not from core journals, we identified 404 studies, of which 378 were in Chinese and 26 were in English and reviewed the full text of 57 potentially eligible studies. A total of 46 studies met the criteria for inclusion in this analysis, of which 45 were in Chinese and 1 was in English (Fig. 1).

The included studies involved a total of 6427 children. All the studies were from China. Forty-six of them were published between 1993 and 2018, and 6 had received funding support,

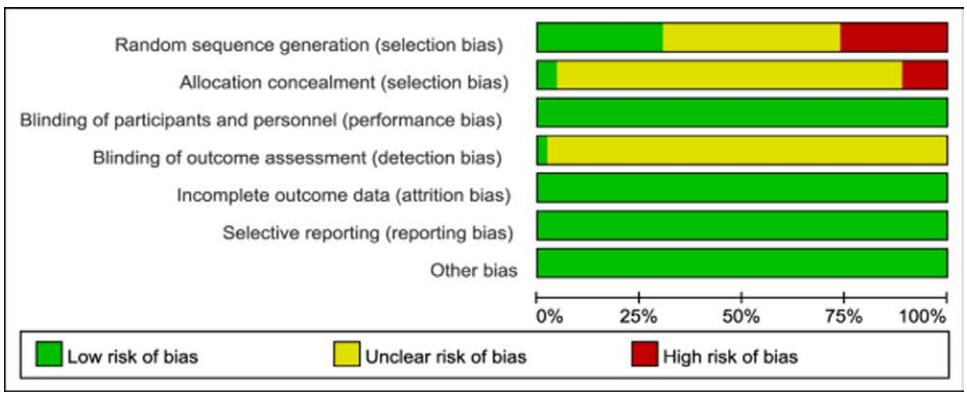


**Figure 2.** Risk of bias graph: Judgments about each risk of bias item presented as percentages across all included studies.

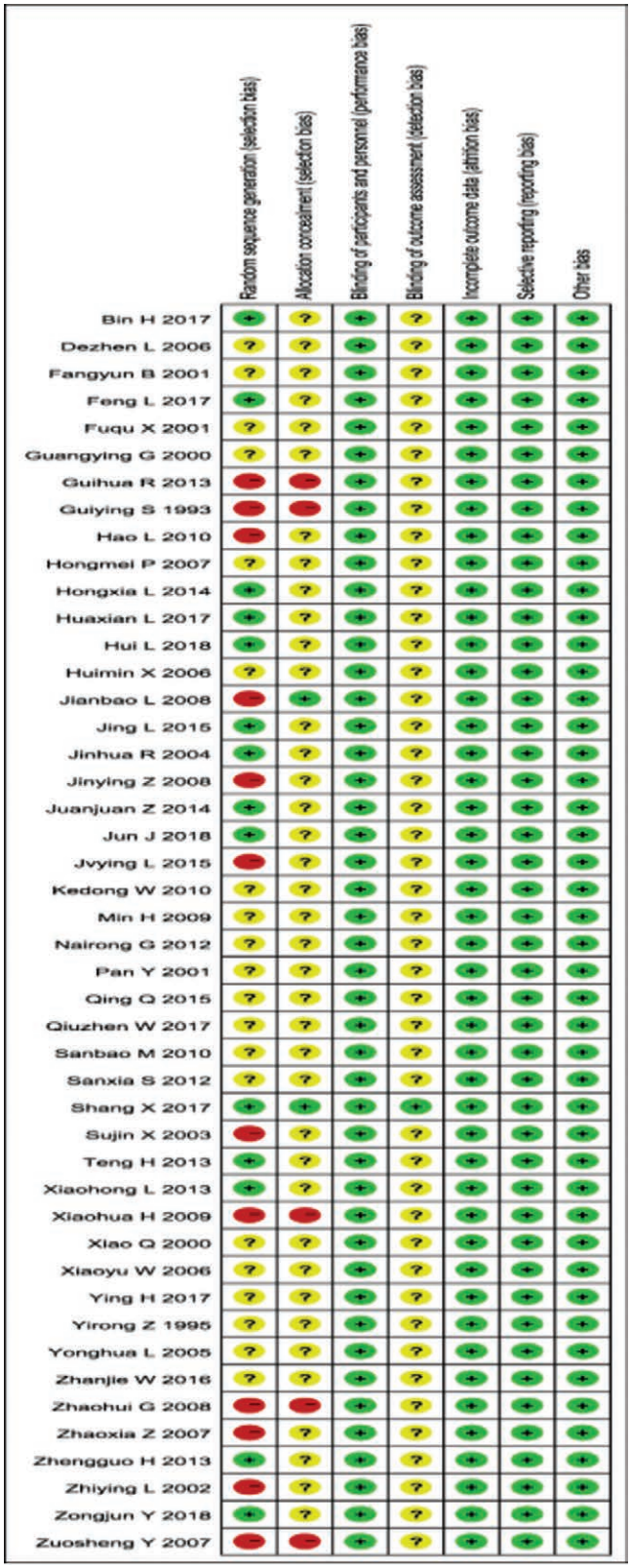


**Figure 3.** Risk of bias summary: Judgments about each risk of bias item for each included study.

including national (one study) and provincial (five studies) research funds. The duration of intervention in most of the studies ranged from 5 to 7 days, with a minimum of 3 days and a maximum of ten days. The follow-up time ranged from 2 weeks to 3 months. The details of these studies are shown in Table 1.

The results of the risk bias assessment are shown in Figures 2 and 3. Most studies had not clearly described the allocation concealment and blinding of outcome assessment, resulting in an uncertain risk of bias. Twelve studies had a high risk of bias regarding random sequence generation, and 5 studies had a high risk of bias regarding allocation concealment. All the studies showed a low risk of bias regarding the blinding of participants and personnel, incomplete outcome data, and selective reporting. The studies were of moderate quality, which is sufficient to conduct a meta-analysis. Forty-four studies were used to analyze clinical efficacy endpoints. We found a low degree of heterogeneity among these studies ($P < .05$ for the Q test; $I^2 = 49.0\%$, <50%). The values of H-statistics indicated that heterogeneity existed among these studies ($1.2 < H = 1.4 < 1.5$; 95% CI: 1.2, 1.7). Furthermore, the Galbraith diagram (Fig. 4) revealed 6 studies with a strong possibility of heterogeneity.

Therefore, we conducted a sensitivity analysis to determine the cause of heterogeneity. We found that the following studies had a significant impact on heterogeneity: Dezhen and Xiaoqin,[44] Pan and Xiuzhen,[50] and Xiaohua.[34] The pooled effect size of the meta-analysis increased after these 3 studies were removed from the analysis (Fig. 5). No heterogeneity was observed in the remaining 41 studies (5490 participants; $I^2 = 22.6\%$, <50%; $P = .102$, >.05) on retesting after removing these 3 studies. A fixed effect model was used for the meta-analysis. The pooled OR of the 41 studies was 3.31 (95% CI: 2.93, 3.74), which was statistically significant ($Z = 19.17$, $P < .05$), suggesting that the efficacy of integrated traditional Chinese and Western medicine for treating bronchiolitis was significantly greater than that of Western medicine alone. The details are presented as a forest plot in Figure 6.

The funnel plot created to determine whether publication bias existed in any of these studies (Fig. 7) was roughly symmetric, indicating no publication bias. Furthermore, the results of the Egger test did not indicate any publication bias ($P = .124$, >.05).

Eleven studies (1350 participants) were used to analyze hospitalization time. We found heterogeneity among these studies ($P < .05$ for the Q test; $I^2 = 98\%$, >50%). Therefore, a random-effect model was used for the meta-analysis. The pooled MD of the 11 studies was –2.10 (95% CI: –2.87, –1.34), which was statistically significant ($Z = 5.39$, $P \leq .05$), suggesting that integrated traditional Chinese and Western medicine for treating bronchiolitis was associated with a significantly shorter hospitalization time than Western medicine alone. The details are presented as a forest plot in Figure 8. The funnel plot created to determine whether publication bias existed in any of these studies (Fig. 9) was symmetric, indicating no publication bias.

Five studies (1083 participants) were used to analyze the recurrence rate. We found no heterogeneity among the 5 studies ($P = .47$, >.05 for the Q test; $I^2 = 0\%$, <50%). Therefore, a fixed effect model was used for the meta-analysis. The pooled RR of the 5 studies was 0.41 (95% CI: 0.30, 0.56), which was statistically significant ($Z = 5.57$, $P < .01$), suggesting that integrated traditional Chinese and Western medicine was associated with a significantly lower bronchiolitis recurrence rate than Western medicine alone. The details are presented as a forest plot in Figure 10.

Eleven studies (1295 participants) were used to analyze adverse reaction rates. We found no heterogeneity among the eleven studies ($P = .43$, <.05 for the Q test; $I^2 = 0\%$, <50%). Therefore, a fixed effect model was used for the meta-analysis. The pooled RR of the eleven studies was 0.87 (95% CI: 0.55, 1.39), which was not statistically significant ($Z = 0.57$; $P = .57$, >.05), suggesting that the adverse reaction rate did not significantly differ between integrated traditional Chinese and Western medicine and Western medicine alone. The details are presented as a forest plot in Figure 11.

Ten studies (1107 participants) in which the experimental group received classical Chinese medicine formulae were included for subgroup meta-analysis. The studies were classified into 4 groups based on the formula used, namely Xiaoqinglong

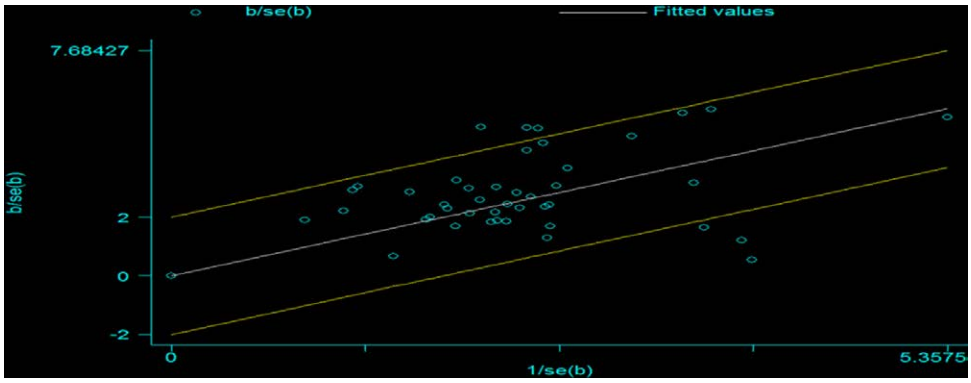


**Figure 4.** Galbraith diagram of the 44 studies that evaluated clinical efficacy endpoints.

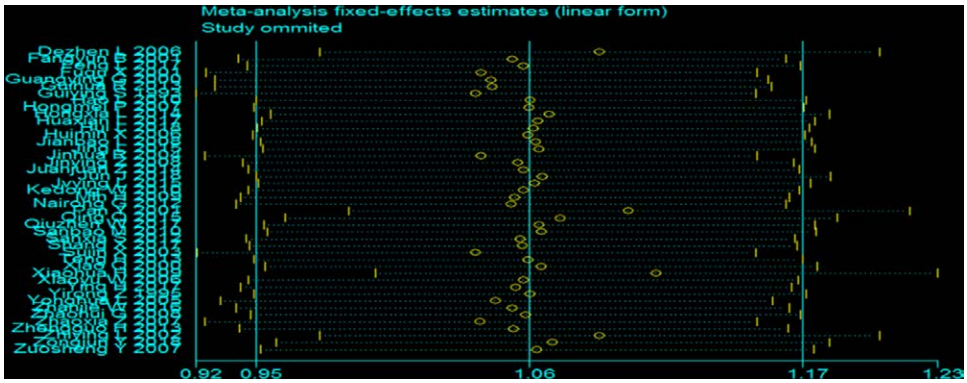


**Figure 5.** Meta-analysis of the 44 studies that evaluated clinical efficacy endpoints.

decoction, Shegan-Mahuang decoction, Maxingshigan decoction, and Dingchuan decoction. The results of these analyses are shown in Figure 12. We found no heterogeneity among the ten studies ($P$ = .276, >.1 for the Q test; $I^2$ = 18.2%, <25%). On comparing the pooled OR of the 4 groups, we found that the Shegan-Mahuang decoction group had the highest OR at 1.71, suggesting the clinical efficacy of Shegan-Mahuang decoction is higher than that of the other formulae.

We assessed the level of evidence of these outcomes using the GRADE criteria. For the treatment of bronchiolitis, integrated traditional Chinese and Western medicine was superior to Western medicine alone in terms of clinical efficacy (OR 3.31; 95% CI: 2.93, 3.74), hospitalization time (MD −2.10; 95% CI: −2.87, −1.34), and recurrence rate (RR 0.41; 95% CI: 0.30, 0.56), and the quality of this evidence was rated as high. Integrated traditional Chinese and Western medicine was not associated with a higher incidence of adverse reactions (RR 0.87; 95% CI: 0.55, 1.39) than Western medicine alone. The quality of this evidence was rated as moderate. The details are provided in the SoF table (Table 2).

## 4. Discussion

We found that, compared with Western medicine alone, integrated traditional Chinese and Western medicine for treating bronchiolitis results in a large increase in clinical efficacy, a large reduction in hospitalization time, and a large reduction in recurrence rate. Furthermore, it does not increase the incidence of adverse reactions and may even reduce the adverse reaction rate.

We assessed the overall certainty of the evidence using the GRADE approach. We found that TCM is safe and effective for the treatment of infant bronchiolitis and should be considered in the formulation of relevant guidelines.

Bronchiolitis is one of the most common respiratory diseases in infants, and it is the most common lower respiratory tract infection in children younger than 2 years of age.[56] Because the patients are young, the disease often progresses rapidly, and respiratory symptoms are most severe from the third to the seventh day after disease onset.[7] Severe bronchiolitis is often complicated by damage to multiple organs such as the heart, brain, liver, and gastrointestinal tract, resulting in respiratory failure, heart failure, myocarditis, and death. Although some scholars point out that bronchiolitis is a self-limiting disease,[1] its severity cannot be ignored. Long-term studies have shown that severe acute bronchiolitis in early childhood is associated with an increased risk of asthma that may persist into early adulthood.[57] Moreover, in these children with bronchiolitis, the overall risk of recurrent wheezing and asthma is 70% before school age and 50% in school age.[57,58] Rhinovirus-induced wheezing has been associated with an atopic predisposition and a high risk of subsequent asthma development in infants.[2]

Substantial knowledge gaps and controversies exist in the management of acute bronchiolitis.[2] Most guidelines primarily recommend supportive treatment, for example, oxygen therapy, nasal suctioning, mechanical ventilation, and hydration. Overall, the administration of corticosteroids, nebulized epinephrine, or antibiotics is not recommended.[3] Recent guidelines have suggested using palivizumab and motavizumab, which are monoclonal antibodies for the respiratory syncytial virus. However, studies found that the duration of hospitalization and severity of illness were not improved when these drugs were used to treat respiratory syncytial virus bronchiolitis.[59,60] Chinese guidelines mainly recommend Western medicine treatments, including bronchodilators, glucocorticoids, antibacterial drugs, ribavirin, and inhalation of 3% hypertonic saline aerosol.[61] However, antibiotics and glucocorticoids are often misused in clinical

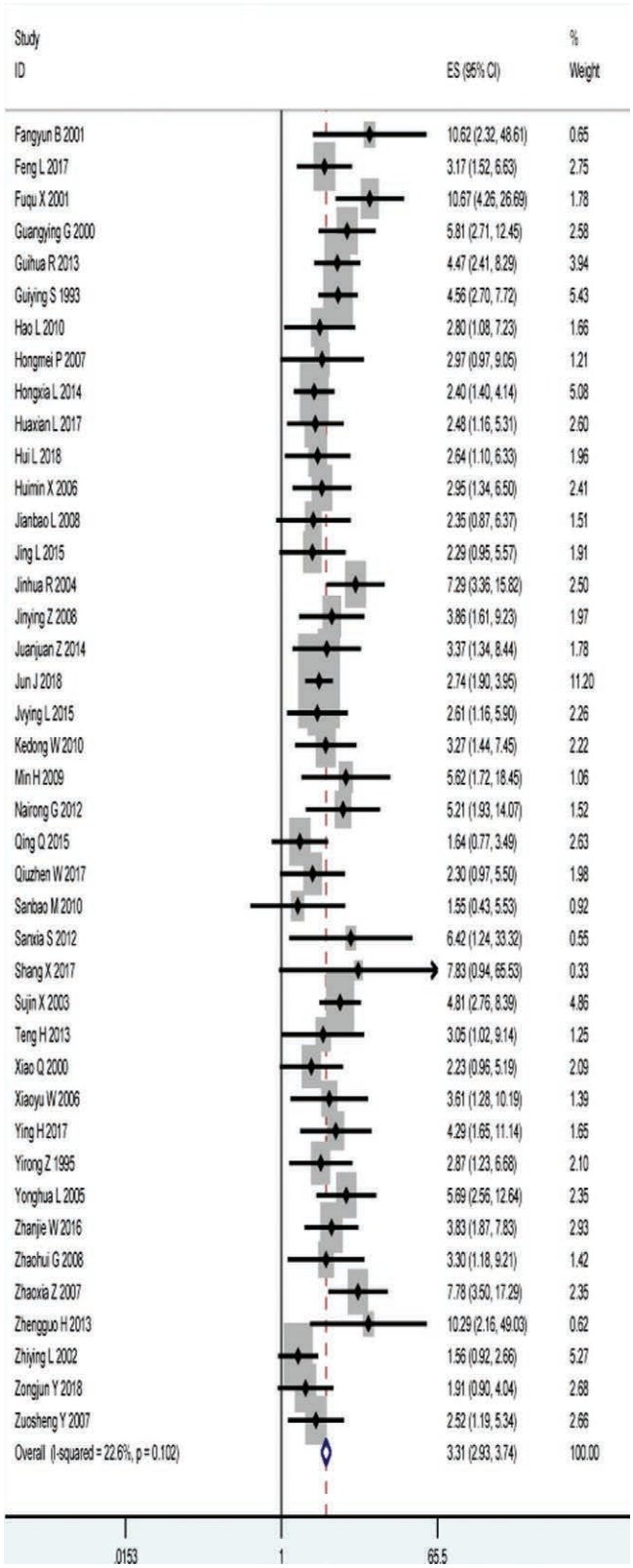


**Figure 6.** Forest plot of the 41 studies with no heterogeneity that were used to analyze clinical efficacy endpoints. CI = confidence interval, ES = effect size.

practice in China. Because of the drawbacks of the existing treatment modalities (high use of bronchodilators, antibiotics, and corticosteroids), we recommend using TCM to treat infant bronchiolitis.

Chinese practitioners have been using TCM for more than 2000 years, maintaining its continuity over generations. It is still commonly used in China. The term "bronchiolitis" was coined by practitioners of Western medicine. However, it is not a modern disease and has existed since ancient times. Although there is no name for this disease in Chinese medicine, TCM has played an important role in treating infant respiratory diseases since before the introduction of Western medicine. It is used to protect the life and health of children in China. The naming of this disease has improved understanding and research about it in Chinese medicine. Owing to the unique advantages offered by TCM in the treatment of bronchiolitis, a large number of studies have been conducted on this topic in recent decades. The results of our preliminary search showed that there were 1384 reports on the treatment of bronchiolitis with integrated TCM and Western medicine in Chinese databases, in addition to studies on TCM treatment alone and nonrandomized controlled studies. However, owing to the language barrier and lack of international awareness regarding TCM, few reports have been published internationally.

Bronchiolitis is almost exclusively caused by viral infection. While no specific drug has been developed, TCM plays an important role in treating viral pneumonia. Because Chinese herbal medicine is characterized by multiple components and it can treat diseases through multiple pathways and targets, TCM offers unique advantages in terms of relieving symptoms, shortening the treatment time, and reducing the likelihood of the development of severe pneumonia.[62] This is consistent with the results of our study. Many animal or cell studies have found that traditional Chinese herbal medicines and formulae have a variety of pharmacological effects related to the treatment of viral pneumonia, including viral inhibition/inactivation; regulation of immune and cellular inflammatory factors, the transcription factor nuclear factor-kappa B signaling pathway, the phosphatidylinositol 3-kinase/protein kinase B signaling pathway, and lymphocyte subsets; and host cell protection.[62] Studies have also shown that TCM exerts its antiviral activity by regulating the immune response to interfere with both viral infection and host reactions.[63] Furthermore, TCM has been shown to possess antiviral activity against various viral strains, including herpes simplex virus, influenza virus, human immunodeficiency virus, hepatitis B and C viruses, severe acute respiratory syndrome-coronavirus, and Middle East respiratory syndrome-coronavirus.[64]

Recently, a few reports have been published internationally about adverse reactions following TCM use. However, it is unknown whether the authors of these reports have investigated the reasons for the adverse reactions. There are many kinds of Chinese medicine, but only a few of them, such as Radix Aconiti Lateralis Preparata, Rhizoma Arisaematis, and Radix Euphorbiae Kansui, are toxic. Adverse reactions following TCM use are usually related to excessive dosage, prolonged medication use, and misuse of proprietary Chinese medicine by non-TCM practitioners. Currently, there are loopholes in the laws regarding the use of proprietary Chinese medicine. Physicians who do not understand the theory behind TCM can prescribe proprietary Chinese medicine without any restrictions. This often results in the occurrence of adverse reactions following the use of proprietary Chinese medicine. Here, we analyzed adverse reactions in 1295 children, and no obvious adverse severe reactions were noted. Accumulating evidence has demonstrated positive results regarding the therapeutic effects and safety profile of TCM against viral pneumonia.[62]

TCM formulae are more widely used than single herbs in the prevention and treatment of viral pneumonia. We performed subgroup analysis to compare the efficacy of 4 classical Chinese medicine formulae for the treatment

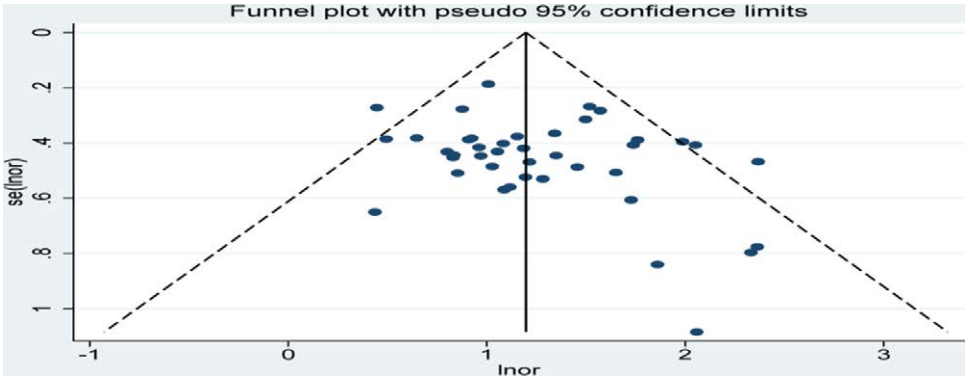


**Figure 7.** Funnel plot of the 41 studies with no heterogeneity that were used to analyze clinical efficacy endpoints.

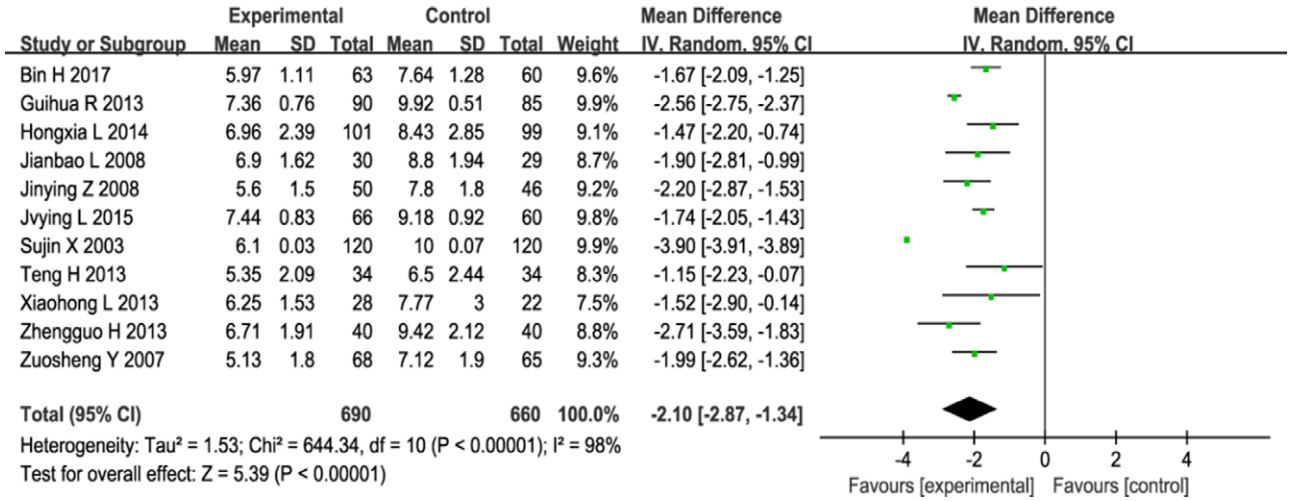


**Figure 8.** Forest plot of the 11 studies that were used to analyze hospitalization time. CI = confidence interval, IV = weighted mean difference, SD = standard deviation.

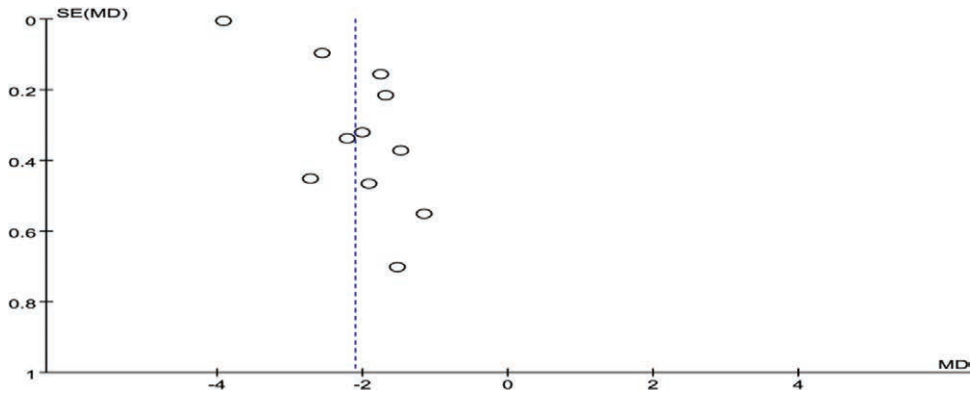


**Figure 9.** Funnel plot of the 11 studies that were used to analyze hospitalization time. MD = mean difference, SE = standard error.

of bronchiolitis and found that Shegan-Mahuang decoction showed the best efficacy. Shegan-Mahuang decoction has been mentioned in the famous ancient Chinese medical book "Cold Damage and Miscellaneous Diseases (Shanghan Zabing Lun)." Shegan-Mahuang decoction, also named Yakammaoto, is a classic TCM formula comprising 9 herbs, including Rhizoma Belamcandae, Herba Ephedrae, Rhizoma Zingiberis Recens, Herba Asari, Radix Asteris, Flos Farfarae, Fructus Schisandrae Chinensis, Fructus Jujubae, and Rhizoma Pinelliae. Shegan-Mahuang decoction has traditionally been used to relieve asthmatic symptoms.[65] It has been reported to improve cough variant asthma, postinfection cough, bronchitis, and other airway conditions.[66]

This study has some limitations. First, the confidence in the results might be limited by the quality of the included studies. Details regarding allocation concealment (selection bias) and blinding of outcome assessment (detection bias) were not mentioned in most included studies. Second, the experimental group received a self-designed TCM formula in many studies, while classical Chinese medicine formulae

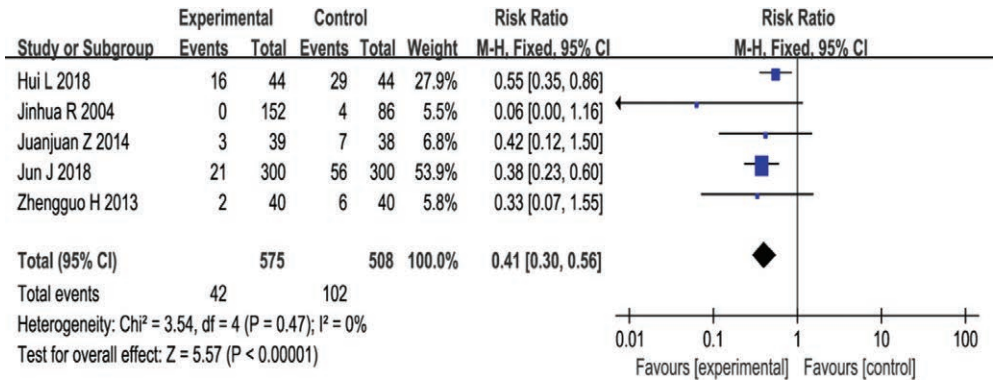


**Figure 10.** Forest plot of the 5 studies that were used to analyze recurrence rate. CI = confidence interval, M-H = Mantel-Haenszel test.

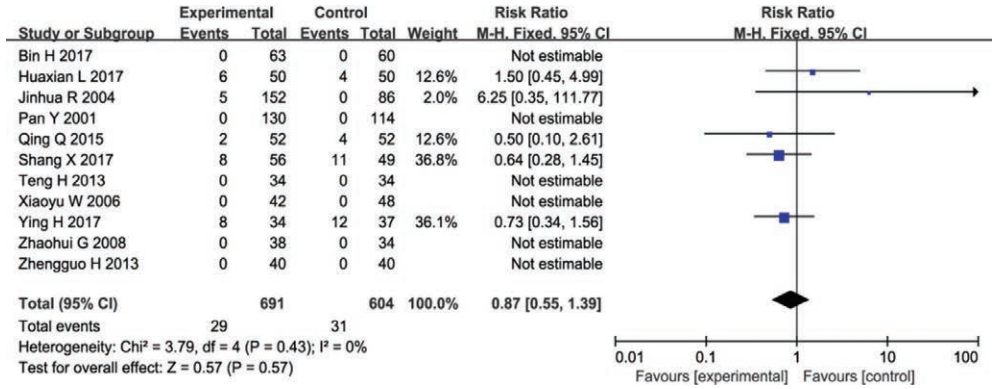


**Figure 11.** Forest plot of the 11 studies used to analyze adverse reaction rate CI = confidence interval, M-H = Mantel-Haenszel test.

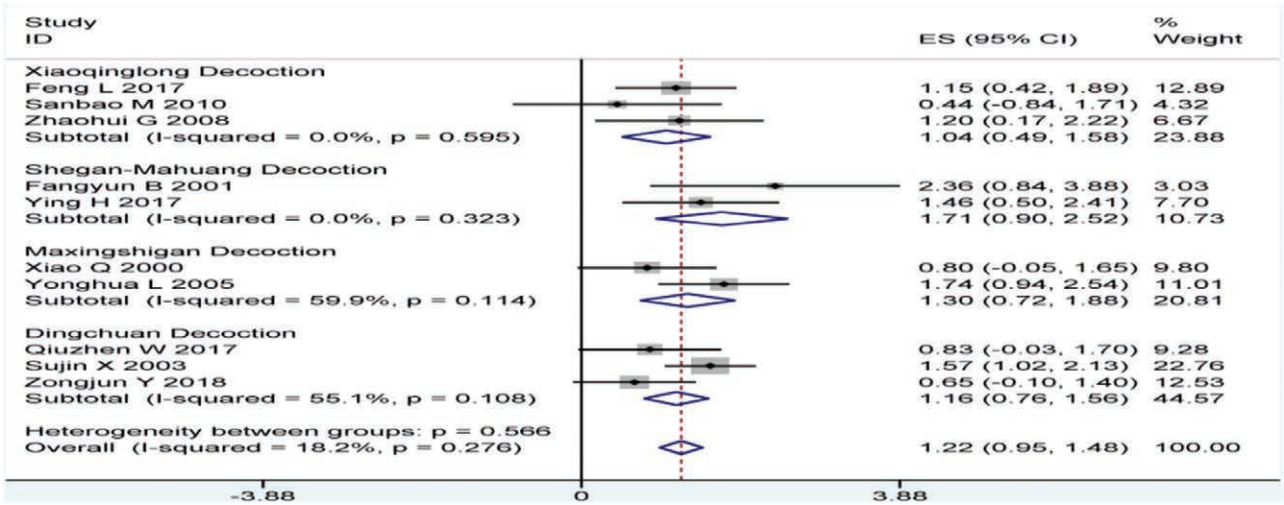


**Figure 12.** Forest plot of the results of the subgroup analysis. CI = confidence interval, ES = effect size.

were used in relatively few studies, leading to poor standardization and uniformity, and limiting clinical application. It is vital to establish standardized and unified TCM treatment protocols to promote the use of TCM to treat bronchiolitis. At the same time, to improve applicability to clinical practice, experimental research should be conducted to develop TCM formulae with antiviral effects. Third, few studies reported relevant laboratory test data, such as the levels of inflammatory markers, lymphocyte subsets, and lung function test results, and we could not analyze this data to provide strong evidence. Last, research data from outside China was lacking, and we look forward to more international research on this topic in the future.

## 5. Conclusion

Although further studies are needed to establish protocols for the use of TCM in clinical practice, our findings clearly lend support to the use of integrated traditional Chinese and Western medicine for the treatment of infant bronchiolitis. Until specific antiviral drugs and vaccines are developed and produced, TCM can be used as an alternative therapeutic option for treating viral bronchiolitis.

**Table 2**

**Summary of findings table.**

**Efficacy and safety of integrated traditional chinese and western medicine for the treatment of infant bronchiolitis**

**Patient or population**: Infants
**Setting**: Bronchiolitis
**Intervention**: Integrated Traditional Chinese and Western Medicine
**Comparison**: Western Medicine

| Outcomes | Anticipated absolute effects* (95% CI) Risk with western medicine | Risk with integrated traditional Chinese and western medicine | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| Recurrence rate analyzed using a fixed-effects model<br>Follow-up: 2 weeks to 3 months | 73 per 1000 | **30 per 1000** (22–41) | **RR 0.41** (0.30–0.56) | 1083 (5 RCTs) | ⨁⨁⨁⨁ HIGH | Integrated traditional Chinese and Western medicine results in a larger reduction in the recurrence rate of bronchiolitis than Western medicine alone. |
| Adverse reaction rate analyzed using a fixed-effects model<br>Follow-up: 3 days to 2 weeks | 51 per 1000 | **45 per 1000** (28–71) | **RR 0.87** (0.55–1.39) | 1295 (11 RCTs) | ⨁⨁⨁◯ MODERATE† | Integrated traditional Chinese and Western medicine may result in a reduction in the adverse reaction rate. Integrated traditional Chinese and Western medicine for treating bronchiolitis is not associated with a higher incidence of adverse reactions than Western medicine alone. |
| Hospitalization time analyzed using a random-effects model | | MD **2.1 days fewer** (2.87 fewer to 1.34 fewer) | – | 1350 (11 RCTs) | ⨁⨁⨁⨁ HIGH | Integrated traditional Chinese and Western medicine results in a larger reduction in hospitalization time than Western medicine alone. |
| Clinical efficacy endpoints (invalid, effective, markedly effective, and cured) analyzed using a fixed-effects model<br>Stata software was used<br>Follow-up: 3 to ten days | | OR **3.31 more** (2.93 more to 3.74 more) | – | 5490 (41 RCTs) | ⨁⨁⨁⨁ HIGH‡ | Integrated traditional Chinese and Western medicine results in a large increase in clinical efficacy than Western medicine alone. |

**High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty**: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
**Very low certainty**: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
GRADE Working Group grades of evidence
*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
†All included studies have described the occurrence of adverse reactions, but some of them did not specify the monitoring of liver and kidney function.
‡The judgment of the clinical efficacy endpoint is subjective to some extent.
CI = confidence interval, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, MD = mean difference, RR = risk ratio.

## Author contributions

HW and XL developed the rationale and objectives. HW wrote and registered the study protocol. XL and YW developed the inclusion criteria. HW performed the literature search. HW, CY, XC, and WW reviewed the literature search results, extracted data, and performed the bias assessment. CY and XC developed the statistical analysis methods and analyzed the data. HW and WW drafted the article. All authors contributed to the critical revision of the article. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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