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Qingkailing Injection (清开灵注射液) for Treatment of Children Pneumonia Induced by Respiratory Syncytial Virus: A Meta-Analysis of Randomized Controlled Trials*

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ABSTRACT **Objective:** To evaluate the efficacy and safety of Qingkailing Injection (清开灵注射液, QKL) for treatment of children pneumonia caused by respiratory syncytial virus (RSV). **Methods:** Randomized clinical trials (RCTs) comparing QKL with ribavirin injection in the treatment of children pneumonia induced by RSV were searched in PubMed, Science Direct, Cochrane Library, Chinese VIP database, CNKI and Wanfang databases from their inception to March 2014. Meta-analyses were performed using RevMan 5.2 software. The methodological quality of the selected RCTs was evaluated by the Modified Jadad Score. The primary outcome measures were effective rate and the secondary outcomes were relief time of fever and cough. **Results:** Seven RCTs with 992 cases published from 2008 to 2013 were identified. The meta-analysis results indicated that QKL was more effective in cure rate [risk ratios (RR)=1.32, 95% CI (1.17, 1.50), $P<0.01$], total effective rate [RR=1.07, 95% CI (1.02, 1.13), $P=0.009$] and less fever clearance time [mean difference=–0.73, 95% CI (–1.22, –0.23), $P=0.004$], compared with ribavirin injection in the treatment of RSV-induced children pneumonia. No dead case was reported in all trials. There were 3 trials mentioned adverse events, 2 reported no obvious adverse event occurred while 1 reported adverse events described as skin hypersensitivity, elevation of ALT, a mild abnormal of hepatic and renal function in both QKL and ribavirin group. **Conclusions:** QKL was an effective and relatively safe option for the treatment of RSV-induced children pneumonia. These therapeutic effects were promising but need to be interpreted with caution due to variations in the treatment and methodological weakness in the studies.

KEYWORDS Qingkailing Injection, respiratory syncytial virus, ribavirin, pneumonia, children, respiratory tract infection, meta-analysis, randomized controlled trials, Chinese medicine

Respiratory syncytial virus (RSV) is a negative-strand RNA virus of the family *Paramyxoviridae* and is remarkable for its ability to cause recurrent infections in immunocompetent individuals throughout life. It is a major cause of respiratory tract infection in infants and young children worldwide.[1,2] However, current disease intervention strategies for RSV are limited and largely ineffective.[3,4] New disease intervention strategies are urgently required.

Currently, there is yet no routine effective, generally accepted, specific treatment for children respiratory tract infection induced by RSV. The treatment for RSV infection is primarily supportive. The nucleoside analog ribavirin is the only approved clinically treatment for RSV infection, but its use is controversial because of questions about its efficacy, concerns on adverse reaction, and its high cost.[5] The American Academy of Pediatrics does not recommend the routine use of ribavirin in children with bronchiolitis. Therefore, confirmation of the effectiveness of Chinese medicine (CM) is necessary.

Qingkailing Injection (清开灵注射液, QKL),[6] a well-known CM formula in China, has been widely used in clinical practice.[7,8] It is prepared from 8 medicinal materials or their extracts, including *Radix Isatidis*, *Flos Lonicerae*, *Fructus Gardenise*, *Cornu Bubali*, *Concha Margaritifera Usta*, *Baicalinum*, *Acidum Cholicum* and *Acidum Hyodesoxy-cholicum*.[9] Thirty-three

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components in QKL were identified in all.[10] Indications for its use include upper respiratory inflammation, viral encephalitis, hepatitis, stroke, cerebral thrombosis, tonsillitis, tracheitis and high fever. In 1992 QKL was specified as a "must-have" medicine for CM emergency clinics by the State Administration of Traditional Chinese Medicine of China (SATCM).[11] Literature showed that QKL could promote endothelial nitric oxide synthase expression, reduce calcium overload, regulate matrix metalloproteinase-9 expression, and inhibit inflammation in a murine model of cerebral ischemia/reperfusion.[12-15]

Recently, Yun, et al[16] reported that QKL could inhibit the expression of Toll-like receptor 4 (TLR4) and TLR4 signal transduction pathway to resist RSV infection. QKL possessed neuraminidase inhibitory activity and displayed significant *in vitro* anti-influenza viral activities in cytopathic effect (CPE) experiment.[17,18] QKL was also an effective immune regulatory agent which could regulate immune response *in vitro* and *in vivo*.[12,19,20]

Some clinical studies reported the effectiveness of QKL on children pneumonia induced by RSV ranging from case reports and randomized clinical trials (RCT),[21-27] but the evidence for its effect remains unclear. The aim of this study was to assess the quantity, quality and overall strength of the evidence on QKL in the treatment of children pneumonia induced by RSV.

METHODS

Database and Search Strategies

The electronic databases of PubMed, Science Direct and Cochrane Library, China Network Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP) and Wanfang databases were searched by using a combination of terms of "Qingkailing OR Qing Kai Ling OR QKL" and "respiratory syncytial viral OR RSV OR virus" OR "respiratory tract infection" OR "virus pneumonia" without language limitation. Reference lists from trials selected by electronic searching. All searches ended before March 2014.

Inclusion Criteria

The diagnosis of pneumonia caused by RSV infection was made according to the "Scheme for Children's Pneumonia Prevention and Treatment" and "Scheme for Prevention and Treatment of Children's Four Diseases",[28] the outcome was evaluated according to the standard formulated in reference to the relative items in the "Standard for Diagnosis and Efficacy Evaluation of TCM Diseases and Syndromes: Pediatric Diseases",[29] promulgated by SATCM as follows: (1) cured: patient's breathing recover to normal condition (times in 1 min restore to normal range); rales in the lungs disappear; X-ray examination showing disappearance of the inflammatory shadow in the lung (bilateral lung field clear); virological examination of respiratory tract convert to negative; (2) markedly improved: patient's breathing recover to normal (times in 1 min restored to normal range); rales in the lungs disappear; X-ray examination showing inflammatory shadow in the lung basically disappear (no small spots/pieces of blurry shadow found in bilateral lung fields); virological examination of respiratory tract convert to negative; (3) improved: patient's breathing recover to normal basically (times in 1 min not higher than 10 plus the upper limit for children of corresponding age); rales in the lung decrease; X-ray examination shows that part of the inflammatory shadows in the lung disappear; virological examination of respiratory tract convert to negative); (4) ineffective: the patients show no significant change or their symptoms and signs even aggravate. Total effective rate was evaluated by the combination of cure, markedly improve and improve. The subjects enrolled were inpatients matching the above-mentioned standards with ages between 3 months to 6 years. Etiological immunofluorescent examination shows positive RSV in nasopharyngeal secretion.

A study was included in the meta-analysis if it was a RCT; involved patients with RSV; compared QKL with other antivirus regimens. The test group treated through intravenous dripping of QKL alone or in combination of other CM was included, but the trials treated with other CM injections in QKL group were excluded. The primary outcome measures were effective rate and the secondary outcome were relief time of fever and cough. Non-randomized studies and unpublished data were excluded, as well as case reports.

Data Extraction

One researcher (He S) conducted the searches. The resultant titles and abstracts were screened independently by He S and Ye CL. Irrelevant citations

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were excluded. The full texts of potentially relevant articles were obtained. Two researchers (Luo YJ and Ye CL) independently extracted data from the trials that met the inclusion criteria. All disagreements were resolved through discussion, or if required by a third person (Zhang ZY) for verification.

Quality Assessment

Evaluation of the methodological quality of the RCTs included in the meta-analysis was independently performed by the same reviewers with the Modified Jadad Score,[30] The overall Modified Jadad Score ranged from 0 to 7 points (score ⩽3 is low quality; ⩾4 is high quality).

Assessment of Risk of Bias in Included Studies

In accordance with recommendations in the Cochrane Handbook, the methodological quality of trials was independently evaluated using the Cochrane risk of bias assessment tool. For each study the following domains were assessed: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessors; incomplete outcome data; and selective outcome reporting.

Data Analysis

Revman 5.2.1 software from the Cochrane Collaboration for data analyses was used. Dichotomous data were expressed as risk ratios (RR) with 95% confidence interval (CI). Continuous data were expressed as mean differences (MD) with 95% CI. Statistical heterogeneity was tested by the I^2. Meta-analysis was used if the trials had acceptable homogeneity (I^2<85%) of study design, participants, interventions, controls, and outcome measures. Sensitivity and subgroup analysis was used to explore heterogeneity. Meta-analyses were performed using fixed-effect models (I^2<25%) for homogeneous studies and random-effects methods prior to fixed-effect models when there was substantial heterogeneity (25% < I^2 < 85%).

RESULTS

Description of Included Trials

The initial search identified 673 publications. After duplicates had been removed, potentially relevant articles were further assessed. A total of 372 articles were excluded because they were non-clinical studies, or irrelevant to QKL treatment for Children RSV infection. Seventy-three full text were retrieved and 63 trials were excluded based on the inclusion criteria. Of the remaining 10 RCTs were included.[21-27,31-33] Three RCTs were included in Cochrane Library.[31-33] Two RCTs were English literature.[25,32] All studies were conducted in China. However, 4 studies were conducted in the same hospitals and at the same time period. So the largest sample size of the 4 studies was included.[25,31-33] In the end, 7 RCTs (992 participants) were analyzed.[21-27] The details of these trials are given in Figure 1.

The age of patients in the included studies ranged from 3 months to 4 years old and the total duration of treatment varied from 8 to 14 days. All included trials applied standard medicine diagnostic

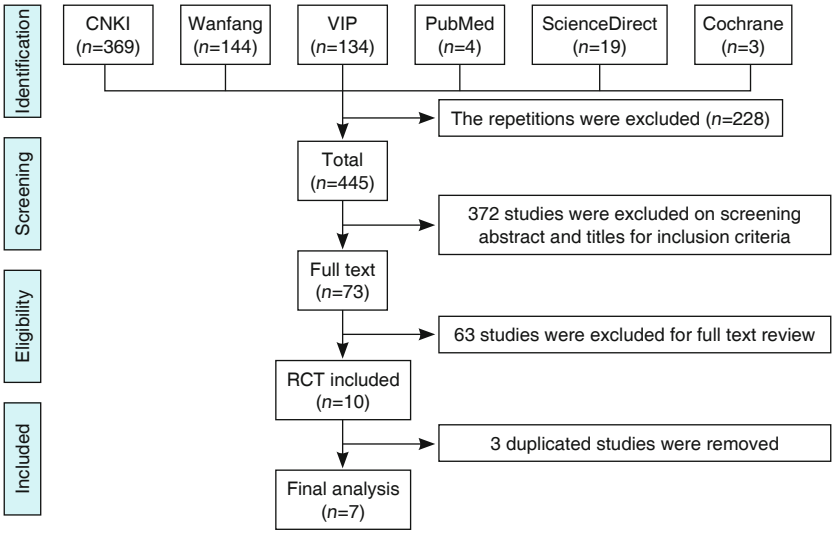

Figure 1. Flow Diagram of the Process for Selecting Articles for Meta-Analysis

Table 1. Main Characteristics of Included RCTs

Study	Case (T/C)	Treatment	Control	Course (d)	Adverse event
Xu F 2011[21]	43/43	Q, 10–15 mL, IV/qd E, 10 mL, P.O/tid X, 5–7.5 mL, P.O/tid	R, 10 mg/kg, IV/qd C, 2.5–5 mL, P.O/tid	10	No
Ji H 2013[22]	57/57	Q, 10 mL, IV/qd	R, 10 mg/kg, IV/qd	10	Unclear
Ju HX 2013[23]	94/94	Q, 10–15 mL, IV/qd E, 10 mL, P.O/tid	R, 10–15 mg/kg, IV/bid A, 7.5 mg, IV bid/tid	14	9/38
Ding JF 2009[24]	30/37	Q, 10–15 mL, IV/qd E, 10 mL, P.O/tid	R, 10 mg/kg, IV/qd A, 7.5–15 mg, IV/qd	1–8	Unclear
Wang SC 2008[25]	148/149	Q, 10–15 mL, IV/qd E, 10 mL, P.O/tid X, 5–7.5 mL, P.O/tid	R, 10 mg/kg, IV/qd C, 2.5–5 mL, P.O/tid	10	Unclear
Wang YQ 2012[26]	100/100	Q, 10–15 mL, IV/qd E, 10 mL, P.O/tid	R, 10 mg/kg, IV/qd C, 2.5–5 mL, P.O/tid	10	No
Yang YN 2013[27]	20/20	Q, 10–15 mL, IV/qd E, 10 mL, P.O/tid	R, 10 mg/kg, IV/qd A, 7.5–15 mg, IV/qd	10	Unclear

Notes: T/C: treatment/control; Q: Qingkailing Injection (清开灵注射液); E: Ertong Qingfei Solution (儿童清肺口服液); R: Ribavirin Injection; C: Compound Guaiacol Potassium Sulfonate Oral Solution (复方愈创木酚磺酸钾口服液); X: Xiaoer Kechuanning Liquid (小儿咳喘宁口服液); A: Ambroxol Hydrochloride Injection; P.O: oral administration; IV: intravenous injection; qd: once daily; bid: twice daily; tid: trice daily

criteria for pneumonia caused by RSV. The dose range of QKL was from 10 to 15 mL and dose route was intravenous injection in all included studies. Most of the included trials were designed to comparing QKL plus conventional treatment with ribavirin injection plus conventional treatment and only 1 trial[21] compared QKL with ribavirin injection alone (Table 1).

Quality Assessment of Included RCTs

Quality assessment of included RCTs are presented in Table 2. Two included RCTs[25,26] were assessed to be of good quality in terms of methodology with Modified Jadad score ⩾4. Other included RCTs were assessed to be of low quality with Modified Jadad score ⩽3.

Table 2. Quality Assessment Score of Included RCTs

Study	Randomization	Concealment of allocation	Blinding	Withdrawals and dropouts	Jadad score
Xu F 2011[21]	1	1	0	0	2
Ji H 2013[22]	1	1	0	0	2
Ju HX 2013[23]	1	1	0	0	2
Ding JF 2009[24]	2	1	0	0	3
Wang SC 2008[25]	2	2	0	0	4
Wang YQ 2012[26]	2	2	0	0	4
Yang YN 2013[27]	1	1	0	0	2

Risk of bias assessment details are provided in Figures 2–3. The selection bias and reporting bias were of low risk, while the performance bias and detection bias were of high risk.

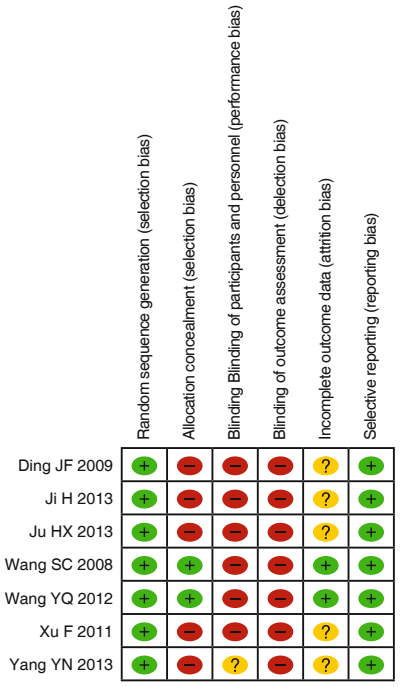

Figure 2. Assessment of Risk of Bias for Included Studies Based on Cochrane Handbook

Notes: +:low risk; ?:unclear risk; −:high risk

All the included trials reported the effective rate and no dead case, only 3 mentioned the adverse effect. Three trials[21,25,26] compared the relief time of fever and cough after treatment,

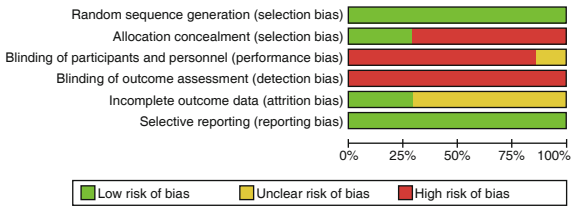

Figure 3. Percentages of Each Risk of Bias Item Across All Included Studies

respectively. Two trials[25,26] reported the clearance time of phlegm. Two trials[21,26] reported the clearing up time of pulmonary rale. One trial compared the hospital stays.[21]

Effect of Interventions

All 7 trials reported clinical effective rate to evaluate the outcome,[21-27] The data of cure rate was reported in 6 trials.[21,23-27]

Cure and Effective Rate

The meta-analysis showed significant differences between groups of QKL and ribavirin injection in cure rate [RR: 1.32, 95% CI (1.17, 1.50), *P*<0.01; Figure 4] and total effective rate [RR: 1.07, 95% CI (1.02, 1.13), *P*<0.01; Figure 5].

Relief Time of Fever and Cough

Three trials[21,25,26] provided data of relief time of fever and cough. The results of meta-analysis showed there was significant difference between QKL treatment and rivavirin treatment groups for fever relief time (MD: –0.73; 95% CI, –1.22 to 0.23, *P*<0.01; Figure 6), while no statistic significance for cough relief time (MD: –0.22; 95% CI, –0.98 to 0.55, *P*=0.58; Figure 7).

Death and Adverse Effect

All 7 trials reported no dead case. Three trials[21,23,26] reported adverse events, while the other 4 did not mention it. No adverse events occurred in 2 trials, and 1 trial[23] reported adverse events described as skin hypersensitivity, elevation of alanin-aminotransferase (ALT), a mild abnormal of hepatic and renal function; 8 cases appeared in the QKL group and 39 appeared in the ribavirin group.

Sensitivity Analysis

The results of sensitivity analysis showed that the meta-analysis results of cure rate with different effect size, analysis method and effect model were consistent that the meta-analysis results of cure rate were reliable. While the meta-analysis results of RR

	Treatment		Control			RR	RR
Study or subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% CI	M–H, Fixed, 95% CI
Ding JF 2009	17	30	16	37	7.3%	1.31 [0.81, 2.13]	
Ju HX 2013	52	94	39	94	19.8%	1.33 [0.99, 1.80]	
Wang SC 2008	80	148	68	149	34.4%	1.18 [0.94, 1.49]	
Wang YQ 2012	76	100	60	100	30.4%	1.27 [1.04, 1.54]	
Xu F 2011	24	43	12	43	6.1%	2.00 [1.15, 3.46]	
Yang YN 2013	10	20	4	20	2.0%	2.50 [0.94, 6.66]	
Total (95% CI)		435		443	100.0%	1.32 [1.17, 1.50]	
Total events	259		199				
Heterogeneity: Chi^2=4.89, df=5 (*P*=0.43); I^2=0%							
Test for overall effect *Z*=4.33 (*P*<0.0001)							

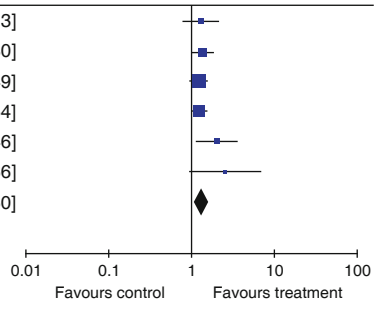

Figure 4. Forest Plot of Cure Rate Comparison between QKL and Ribavirin Groups

	Treatment		Control			RR	RR
Study or subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% CI	M–H, Fixed, 95% CI
Ding JF 2009	30	30	36	37	15.2%	1.02 [0.95, 1.11]	
Ji H 2013	57	57	56	57	19.7%	1.02 [0.97, 1.07]	
Ju HX 2013	94	94	77	94	12.8%	1.22 [1.11, 1.34]	
Wang SC 2008	148	148	148	149	23.2%	1.01 [0.99, 1.03]	
Wang YQ 2013	96	100	86	100	13.8%	1.12 [1.02, 1.22]	
Xu F 2011	42	43	38	43	10.4%	1.11 [0.98, 1.24]	
Yang YN 2013	20	20	17	20	4.9%	1.17 [0.96, 1.43]	
Total (95% CI)		492		500	100.0%	1.07 [1.02, 1.13]	
Total events	487		458				
Heterogeneity: Tau^2=0.00, Chi^2=22.59, df=6 (*P*=0.0009); I^2=73%							
Test for overall effect *Z*=2.61 (*P*=0.009)							

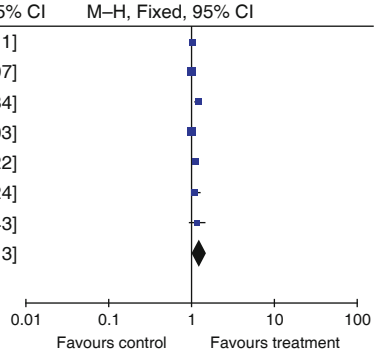

Figure 5. Forest Plot of Total Effective Rate Comparison between QKL and Ribavirin Groups

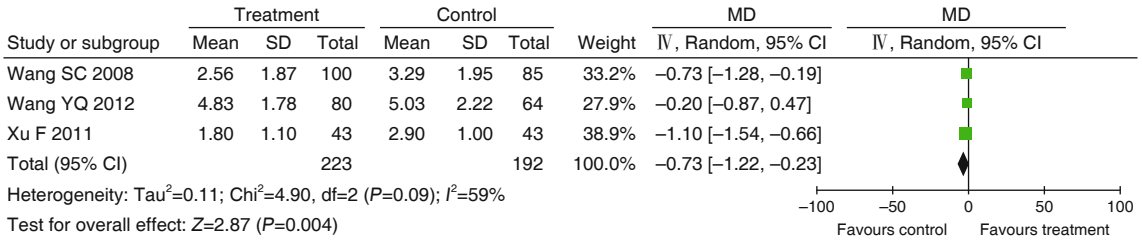

Figure 6. Forest Plot of Fever Clearance Time Comparison between QKL and Ribavirin Groups

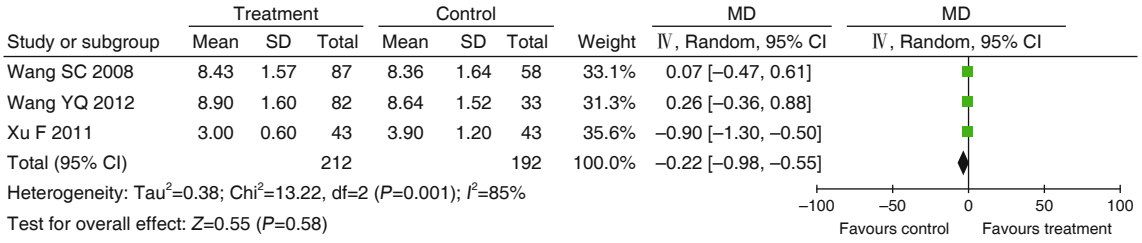

Figure 7. Forest Plot of Cough Relief Time Comparison between QKL and Ribavirin Groups

for total effect was significant different between fixed model [1.08 (1.05, 1.11), *P*<0.01] and random model [1.08 (0.99, 1.18), *P*=0.07] with analysis method M-H. The meta-analysis results of cough relief time was significant different between MD [–0.38 (–0.67, –0.10), *P*=0.009] and standard mean difference [–0.16 (–0.39, 0.06), *P*=0.15] with fixed model.

DISCUSSION

This review of randomized trials provided the current evidence that QKL had an effect on reducing the relief time of fever and cough for children RSV pneumonia. The results of meta-analysis demonstrated that QKL alone or plus other CM (Ertong Qingfei solution or Xiaoer Kechuanning liquid) maybe more effective than Ribavirin Injection alone or plus other medicine (Compound *Guaiacol Potassium* Sulfonate oral solution or Ambroxol Hydrochloride injection) for children RSV pneumonia. The cure rate of the QKL group was 32% more than the ribavirin group. While the effective rate of the QKL group was 7% more than the ribavirin group. In consistency with it, meta-analysis of the relief time of fever and cough in 3 trails showed QKL was more effective than ribavirin.

These promising observations should be interpreted with caution for several reasons. First, among 7 trials with 992 patients included in the meta-analysis, only 1 multicenter and cooperative study was found and most of the existing trials were small size. Second, inadequate reporting of allocation concealment, blinding, intention to treat analysis, and dropouts account in all the trials may have created potential performance biases and detection biases. So every trial had an unclear risk of bias or a high risk of bias. Third, only published studies were included in this meta-analysis and all trials were conducted in China. Therefore, publication bias may have occurred. Fourth, the sensitivity analysis results showed that the meta-analysis results of cure rate and fever clearance time were relatively reliable, while the meta-analysis results of total effect and cough relief time were of low reliability.

For the outcomes, only 3 trials reported the relief time of fever and cough after treatment. However, the relief time of fever and cough are important outcomes of QKL. One trial reported QKL could significantly shorten hospital stay compared with ribavirin group. It indicated hospital stays may be an important outcome to assess the effect of QKL. Therefore, we suggest future RCTs to assess QKL effect combining with the data of hospital stays.

Adverse effects were reported by Ju, et al[34] described as skin hypersensitivity, elevation of ALT, a mild abnormal of hepatic and renal function, while other trials did not report adverse effects. The reliable conclusion regarding safety cannot be determined from this paper due to the limited evidence provided by the eligible trials. Another paper about the safety of QKL concluded that, although some cases of adverse effects for QKL were reported, QKL carries a low risk

of adverse drug reactions and adverse events, and some adverse events that do occur may be ascribed to improper use of the drug.[34] However, ADRs reported for QKL from 1978 to 2007 were 258 cases in total, mainly included skin lesion (90 cases, 28.48%), anaphylactic shock (73 cases, 23.10%), respiratory system lesion (62 cases, 19.62%) and digestive system lesion (29 cases, 9.18%).[35] Therefore, large-scale clinical trials with long-term follow up are required to proper assess the safety of QKL and some strategies should be established to reduce the adverse events caused by QKL.

According to the low quality of studies, the variety of interventions and the variance of outcome measures, further high quality RCTs are needed to assess the effectiveness of QKL for treatment of children RSV-induced pneumonia. Randomization methods need to be more rigorous. By using appropriate placebo, blinding of patients, the other care providers or at least the outcome assessors will minimize performance and assessment biases.

In conclusion, although some limitations exist in this meta-analysis, based on the results of our meta-analysis, it is found that QKL is an effective and relatively safe option for the treatment of children RSV pneumonia. However, the solid results are needed more multicenter, large scale and cooperative RCTs to confirm. If the positive effects of QKL were confirmed by high quality RCTs, it would lead to a promising treatment for children RSV pneumonia and could benefit patients all over the world.

Conflict of Interest

The authors have no conflict of interest.

Author Contributions

ZHANG ZY designed the study, performed critical revision, and approval of article. HE S and LI WS conducted data collection, analysis and drafted article. LUO YJ and YE CL assessed original text.

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