International Immunopharmacology 54 (2018) 198–209

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

Broncho-Vaxom in pediatric recurrent respiratory tract infections: A systematic review and meta-analysis

Ju Yin[a], Baoping Xu[a], Xiantao Zeng[b,c,d], Kunling Shen[a,*]

[a] Department of Respiratory, Beijing Children's Hospital, Capital Medical University, China National Clinical Research Center for Respiratory Diseases, 100045 Beijing, China
[b] Center for Evidence-Based and Translational Medicine, Zhongnan Hospital of Wuhan University, Wuhan 430071, China
[c] Center for Evidence-Based and Translational Medicine, Wuhan University, Wuhan 430071, China
[d] Department of Evidence-Based Medicine and Clinical Epidemiology, The Second Clinical College, Wuhan University, Wuhan 430071, China

ARTICLE INFO

Keywords:
Broncho-Vaxom
Pediatric recurrent respiratory infections
Meta-analysis
Efficacy
Safety

ABSTRACT

Objectives: Assess the efficacy and safety of Broncho-Vaxom in pediatric recurrent respiratory tract infections (RRTIs).

Methods: Published randomized controlled trials (RCTs) of Broncho-Vaxom for pediatric RRTI were searched using PubMed, Embase, Cochrane Library, CBM, CNKI, WanFang Data, and VIP databases up to January 2017. Risk of bias was evaluated in accordance to the guidelines of the Cochrane collaboration and the level of evidence was graded according to the GRADE.

Results: 53 RCTs involving 4851 pediatric patients were included in this meta-analysis. It showed that Broncho-Vaxom was positively correlated with a reduction in the frequency of respiratory infection [MD = −2.33, 95% CI (−2.75, −1.90), P < 0.00001] compared to the control group. The Broncho-Vaxom group was more effective than control groups in relation to the duration of antibiotics course, infections, fever, cough, and wheezing, increasing serum immunoglobulin levels (IgG, IgA or IgM), and T-lymphocytes subtype (CD3+, CD4+, or CD8+). However, Broncho-Vaxom had higher adverse event rates [RR = 1.39, 95% CI (1.02, 1.88), P = 0.04]; these were not serious and did not influence the treatment course.

Conclusion: Broncho-Vaxom shows a good efficacy for pediatric RRTIs on the basis of routine therapy (e.g. anti-infection and antiviral therapy). However, the level of evidence was low and more international multicenter clinical trials are needed to explore the efficacy and safety of Broncho-Vaxom.

1. Introduction

Recurrent respiratory tract infections (RRTIs) are one of the common diseases that are seen in children. It is defined as any upper or lower respiratory tract infections (RTIs) that occurs frequently per year, however, the concept of recurrence remains unclear since there is no generally agreed definition globally. China defines RRTIs through not only considering numbers but also ages (≥7 upper RTIs per year, ≥3 tracheobronchitis per year or ≥2 pneumonias per year if age is 0–2 years, ≥6 upper RTIs per year, ≥2 tracheobronchitis per year or ≥2 pneumonias per year if age is 2–5 years, ≥5 upper RTIs per year, and ≥2 tracheobronchitis per year or ≥2 pneumonias per year if age is 5–14 years) [1]. According to the guidelines of the Dutch College of General Practitioners referral for recurrent RTI is indicated if acute otitis media occurs > 4 times per year, sore throat occurs > 5 times per year, or if otitis media with effusion persists for > 6 months [2]. The duration of RRTIs is longer and it may affect children's growth as well as increase the chances of them suffering from other respiratory diseases as they enter adulthood.

The pathogenesis of RRTIs is complicated by the variety of antimicrobial causes as well as immunological and respiratory diseases [3]. There are no specific guidelines for the treatment of RRTIs at the moment. However, from an epidemiologic point of view, it has been shown that the prevalence of IgA and/or IgG subclass deficiency was 25% in patients with recurrent upper respiratory tract infections, 22% in patients with recurrent pulmonary infections, and 12.3% in patients with recurrent bronchiolitis [4]. IgG subclass deficiency is quite prominent in young children but rare in older children, suggesting a transient immaturity of the immune system as one of the possible pathogenic factors. Defects in the immune system such as common variable immunodeficiency and selective IgA deficiency are known to be linked with frequent respiratory infections by bacteria and viruses [5].

* Corresponding author at: No.56 Nanlishi Road, Xicheng District, 100045 Beijing, China.
E-mail address: kunlingshen1717@163.com (K. Shen).

https://doi.org/10.1016/j.intimp.2017.10.032
Received 16 June 2017; Received in revised form 10 October 2017; Accepted 30 October 2017

Table 1
Clinical data of included studies.

Studies	Sample (T/C)	Interventions		Endpoints	Age (years)[a]	Follow-up time (months)
		T	C			
Maestroni [62]	11/9	1 course	Placebo	①②	1–16	6
Ahrens [61]	83/72	1 course	Placebo	①③	2–16	6
Schaad [60]	45/49	1 course	Placebo	①③	0.67–12	6
Zagar [59]	29/22	1 course	Placebo	①③	4–12	6
Paupe [58]	61/55	1 course	Placebo	③	T6.6 ± 5.3 C7.6 ± 5.3	6
Gomez-Barreto [57]	26/30	1 course	Placebo	①③	T4.7 ± 1.7 C4.0 ± 1.8	6
Jara-Perez [56]	99/100	1 course	Placebo	①③	6–13	6
Tingxi Zhang [55]	15/15	1 course	Routine therapies	①②③⑤⑥	T4.1 ± 1.6 C13.8 ± 1.6	5
Gutierrez-Tarango [54]	26/28	2 courses	Placebo	①③	1–12	12
Schaad [53]	120/100	1 course	Placebo	①	3–8	6
Del-Rio-Navarro [52]	20/20	1 course	Placebo	①③	T4.0 ± 0.9 C4.1 ± 0.9	6
Jie Gao [51]	19/19	1 course	Routine therapies	②	T3–10 C3–10	3
Lihua Huang [48]	38/34	1 course	Routine therapies	②⑥	T3–10 C3–10	6
Junhui Yuan [49]	15/15	1 course	Routine therapies	①②③⑥⑦⑧⑨⑩	T4.0 ± 1.2 C7.1 ± 1.5	6
Huiyu Zhang [50]	36/37	1 course	Routine therapies	①②③⑥⑧⑨⑩	0.5–2.9	6
Jinsong Li [45]	39/38	1 course	Routine therapies	①②⑤⑧	0–8	6
Yu Tan [46]	45/44	1 course	Routine therapies	①③⑥⑧⑨⑩	1–10	6
Yongli Wu [47]	45/45	1 course	Routine therapies	①③⑤⑥	T6.5 ± 1.3 C6.2 ± 1.4	12
Ying Liao [41]	50/49	1 course	Routine therapies	①②③⑤⑥	T1–5 C1–6	12
Haiying Mo [42]	52/52	1 course	Routine therapies	①②③⑤⑦⑧⑨	T4.5 ± 1.5 C5.0 ± 1.5	6
Aiqi Zhang [43]	30/30	1 course	Routine therapies	①②	Not reported	3
Xin Zhao [44]	100/100	1 course	Routine therapies	②	T4.5 ± 1.1 C4.3 ± 1.2	6
Razi [40]	40/35	1 course	Placebo	①③	1–6	12
Hua Fu [36]	50/49	1 course	Routine therapies	①③⑤⑦⑧⑨	T2.3 ± 0.5 C1.9 ± 0.7	3
Yuan Gao [37]	76/83	1 course	Routine therapies	①③⑤⑦⑧	2–5	12
Min Song [38]	32/32	1 course	Routine therapies	②	T4.6 ± 1.9 C4.4 ± 2.0	6
Guoying Ye [39]	50/45	1 course	Routine therapies	③	T4.3 ± 0.7 C4.9 ± 0.9	6
Mingxia Chao [32]	31/30	1 course	Routine therapies	①②③	1–7	12
Beiling Hu [33]	47/46	1 course	Routine therapies	①③⑤⑦⑧	5–12	3
Aiping Liang [34]	36/37	1 course	Routine therapies	①④⑤	1–5	12
Yujing Zhang [35]	46/20	1 course	Routine therapies	①②③⑨	0.75–5	12
Xiongxiong Huang [25]	65/65	1 course	Routine therapies	①②③④⑤	0.58–3	6
Huiqun Ji [26]	35/31	1 course	Routine therapies	①	T3.7 ± 1.5 C3.3 ± 1.7	6
Juhong Li [27]	30/30	1 course	Routine therapies	②③	1.5–3	3
Zhihong Lou [28]	33/33	2 courses	Routine therapies	①④	T3.7 ± 1.9 C3.6 ± 2.0	12
Yuping Zhao [30]	50/50	1 course	Routine therapies	①②④⑤	1–7	12
Diqian Zhuang [31]	60/60	1 course	Routine therapies	②③	5.6 ± 2.8	6
Manfeng Zuo [29]	35/33	1 course	Routine therapies	①②③⑤⑦⑧	1–6	6
Guolin Chen [24]	75/75	1 course	Routine therapies	①②③⑦⑧⑨	T4.3 ± 1.8 C4.5 ± 1.5	6
Guie Li [22]	66/66	2 courses	Routine therapies	①②⑤⑦⑧	4.2 ± 1.6	6
Lancui Lu [23]	55/54	1 course	Routine therapies	①②④⑤	T1–10 C2–9	6
Jiayi Liao [19]	31/31	2 courses	Placebo	①②③	1–12	12
Ya Shen [20]	48/48	1 course	Routine therapies	①②⑤⑦⑧⑨	T3.5 ± 1.6 C3.8 ± 1.8	12
Ling Su [21]	84/84	1 course	Routine therapies	①②④⑤⑥	0–14	12
Shenfeng Gu [14]	40/40	1 course	Placebo	①③⑤⑦⑧	1–12	12
Fei Liu [15]	73/67	1 course	Routine therapies	①②⑦	T5.91 ± 0.38 C5.84 ± 0.34	6
Wei Zhang [16]	17/16	1 course	Routine therapies	①	1–12	12
Hongwen Zhu [17]	30/30	1 course	Routine therapies	①②③④⑤	T1–5 C1–6	6
Shaoxiong Zhuang [18]	30/30	1 course	Placebo	①②④⑤⑥⑦	0.5–4	6
Shiyan Luo [11]	45/45	1 course	Routine therapies	①②③④⑤	T1–14 C1–15	6

(*continued on next page*)

Table 1 (*continued*)

Studies	Sample (T/C)	Interventions		Endpoints	Age (years)[a]	Follow-up time (months)
		T	C			
Yincun Ye [12]	44/43	1 course	Routine therapies	②③	1–6	3
Liming Yin [13]	39/39	1 course	Routine therapies	①②③	T2–8 C2–9	12
Jingyang Li [10]	94/50	1 course	Routine therapies	①③	T3.17 ± 0.77 C3.20 ± 0.78	12

T: Broncho-Vaxom group; C: control group; endpoints: ① frequency of RTIs; ② serum immunoglobulin level; ③ adverse event rates; ④duration of infection; ⑤ the therapeutic time of antibiotics; ⑥ level of T cell subgroup; ⑦ febrile time; ⑧ cough length; ⑨ wheezing onset time.

[a] The age of the child enrolled was expressed as mean ± SD or range.

Table 2
Assessment of risk of bias.

	Random method	Allocation concealment	Blinding	Integrity of the results	Results reported selectively	Other bias
4 RCTs [52–54,56]	Random number table	Yes	Double blind	Yes	No	None
6 RCTs [10–13,20,32]	Random number table	Unclear	Unclear	Yes	No	None
2 RCTs [14,19,40]	Computer random	Yes	Double blind	Yes	No	None
1 RCT [14]	Computer random	Yes	Single blind	Yes	No	None
1 RCT [44]	Minimization	Unclear	Unclear	Yes	No	None
2 RCTs [26,33]	Semi-random	Unclear	Unclear	Yes	No	None
3 RCTs [48,50,51]	Not mentioned	Unclear	Unclear	Yes	No	None
6 RCTs [57–62]	Unclear	Unclear	Double blind	Yes	No	None
28 RCTs [15–18,21–25,27–31,34–39,41–43,45–47,49,55]	Unclear	Unclear	Unclear	Yes	No	None

Broncho-Vaxom is an orally administered immunomodulator containing the lyophilized bacterial lysate of eight pathogenic bacteria of the respiratory tract. Broncho-Vaxom stimulates immune defenses and the production of salivary and bronchoalveolar IgA as well as serum IgA and IgG [6]; it has been administered since the 1980s to adults and children in order to prevent recurrences of respiratory tract infections.

In addition to increasing IgA and IgG, Broncho-Vaxom has shown other immunomodulating effects, such as inducing the terminal maturation of human dendritic cells with an enhanced T cell-stimulatory capacity [7], up-regulating the Th1-specific cytokine IFN-γ, and the down-regulating the Th2-specific cytokine IL-4 [8]. All these effects could activate different systems in the chain of immunologic defense reactions.

Since the results of studies on Broncho-Vaxom are not consistent and the sample sizes of most studies are small, this paper explored randomized controlled trials (RCT) of Broncho-Vaxom used in pediatric RRTIs to evaluate the efficacy and safety of this procedure and to provide evidence for clinical use of Broncho-Vaxom in pediatric RRTIs.

2. Methods

2.1. Data sources

We performed a systematic review of published articles about Broncho-Vaxom for RRTIs in children. The data sources for the identification of randomized controlled trials included electronic databases such as: PubMed, Embase, Cochrane Library, CBM, CNKI, and WanFang Data and VIP databases while reference lists from included articles were hand-searched. The search was performed using the key terms: “Broncho-Vaxom”, “Broncho-Munal”, “Ommunal”, “OM-85”, “OM-85 BV”, “Lyophilised bacterial lysates”, and “Respiratory Tract infection” (up to January 2017) without language restriction.

2.2. Study selection

In order to be included in this review, studies had to meet all of the following criteria: 1) study design: RCTs without language restriction; 2) participants: children with diagnosis of RRTIs; 3) interventions and comparisons: the efficacy and safety of routine treatment for RTIs (routine treatment is defined as treatment for disease symptoms such as anti-infection and antiviral therapy) with or without placebo were compared with the routine treatment involving Broncho-Vaxom; 4) patients were treated by at least one course of Broncho-Vaxom (3 months per course); 5) outcome measures: the primary outcomes were the number of participants experiencing respiratory tract infections. The secondary outcomes included duration of antibiotics course, infections, fever, cough, and wheezing. Serum immunoglobulin levels (IgG, IgA or IgM) or T-lymphocytes subtype (CD3 +, CD4 + or CD8 +) were included as secondary outcomes. Trials were excluded if: 1) there were repeat published studies; 2) trials that used Broncho-Vaxom along with other treatments, such as acupoint application or interferon; 3) Broncho-Vaxom comparison with control groups use unconventional treatment, such as transfer factors or other immunomodulators; and 4) no data available.

2.3. Data extraction and quality assessment

Two independent authors reviewed and crosschecked the data from all trials. They recorded the first author, publication time, sample size, interventions protocol, outcomes, and risk of bias item. Disagreements among authors were resolved through negotiations.

We assessed the risk of bias using the Cochrane Collaboration's tool for assessing risk of bias [9]. The assessment was also conducted by two independent authors, followed by crosschecking. In case of disagreement, a consensus was sought and resolved with the third author. The following information were extracted: random sequence generation,

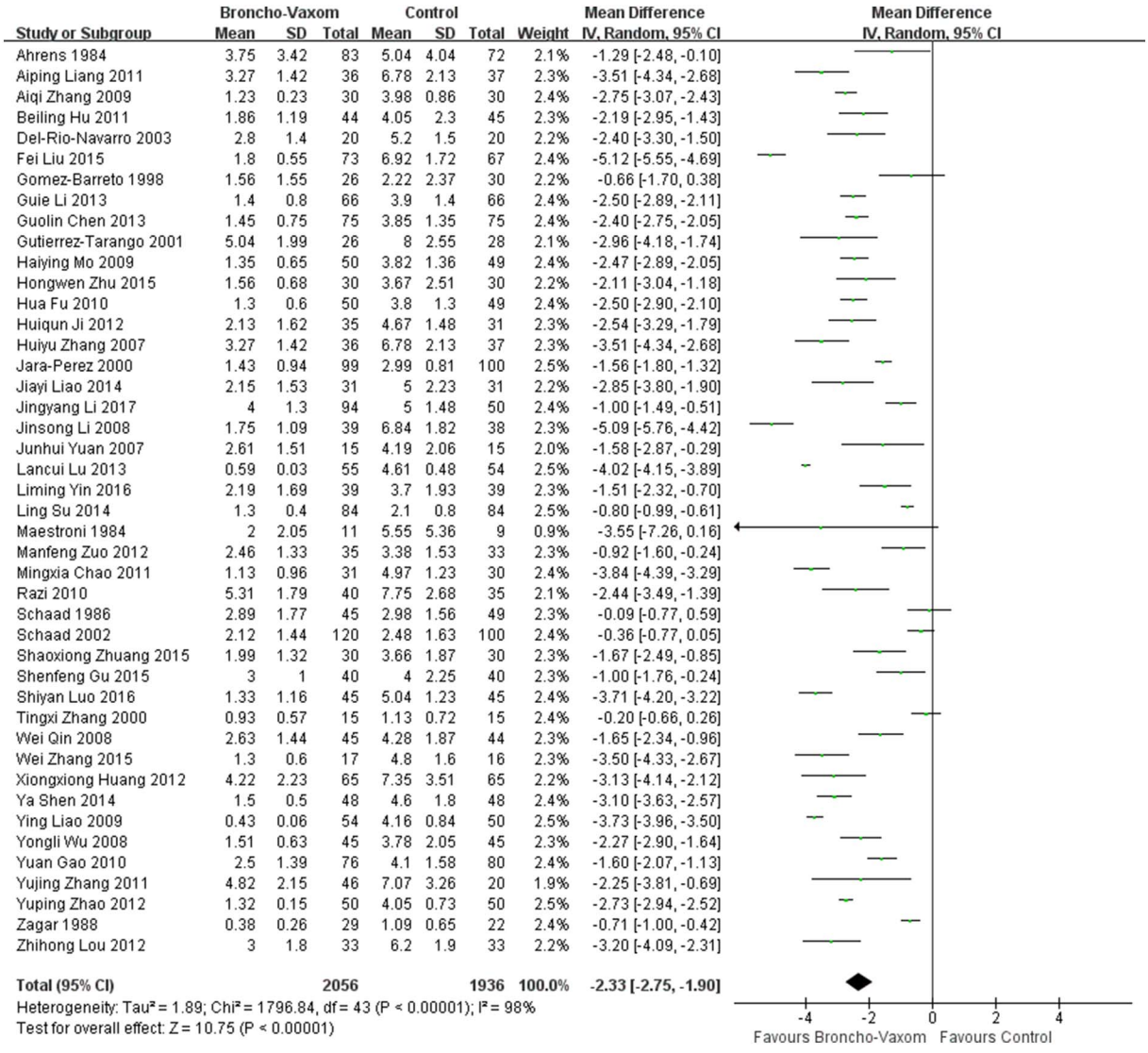

Fig. 1. Frequency of RTIs in Broncho-Vaxom and control group.

allocation concealment, blinding of participants and researchers, incomplete outcome data, selective reporting, and other bias.

2.4. Statistical analysis and quality of the evidence

In the meta-analysis of RCTs, dichotomous data was expressed as a risk ratio (RR) with 95% confidence intervals (CI). Continuous data was expressed as a mean difference (MD) with 95% confidence intervals (CI). The study only analyzed the available data and discarded the missing data. We assessed heterogeneity by using two statistics of heterogeneity (Cochrane Q test and I^2 statistic). Qualitative heterogeneity of effect differences between trials was estimated using a chi square test and was considered significant if $P < 0.1$. I^2 statistic was used to quantitatively assess the heterogeneity. Either a fixed-effects (in the presence of heterogeneity, $P < 0.1$ or $I^2 > 50\%$) or random-effects model (in the presence of heterogeneity, $P > 0.1$ or $I^2 < 50\%$) was used to calculate the combined effect size. Data was combined for the fixed-effects model using the Peto-modified Mantel-Haenszel method and the random-effects model using Dersimonian-Laird method. The level of statistical significance was set at $\alpha = 0.05$ for this meta-analysis. All analyses were performed using RevMan 5.3 version. The quality of the evidence was assessed by GRADEpro GTD software.

3. Results

823 relevant references were identified initially and 53 [10–62] were subsequently retained after step-by-step screening, including 11 studies published in English [40,52–54,56–62] and 42 in Chinese [10–39,41–51,55]. 4851 pediatric patients were included totally, of which 2491 were in Broncho-Vaxom group and 2360 in control group. Out of these 53 articles, 13 RCTs [14,18,19,40,52,53,56–62] were placebo-controlled on the basis of routine antibacterial and antiviral therapies while the others used routine treatment only; 4 RCTs [19,22,28,57] used two courses of Broncho-Vaxom (3 months per course), and the remaining articles used one course of Broncho-Vaxom. The features of these included studies are shown in Table 1.

The sizes of these studies are small. Only three studies' samples were slightly larger, about 100 in each intervention group [44,53,56]. The total participants of most studies were < 100. The age of the participants ranged from 0 to 16 years old.

3.1. Assessing the risk of bias in included studies

Only 14 (26.4%) RCTs [10–14,19,20,32,40,44,52–54,56] reported the correct random method, 7 (13.2%) [14,19,40,46,52–54,56] reported the right allocation method, 12 (22.6%) [19,40,52–54,56–62] adopted

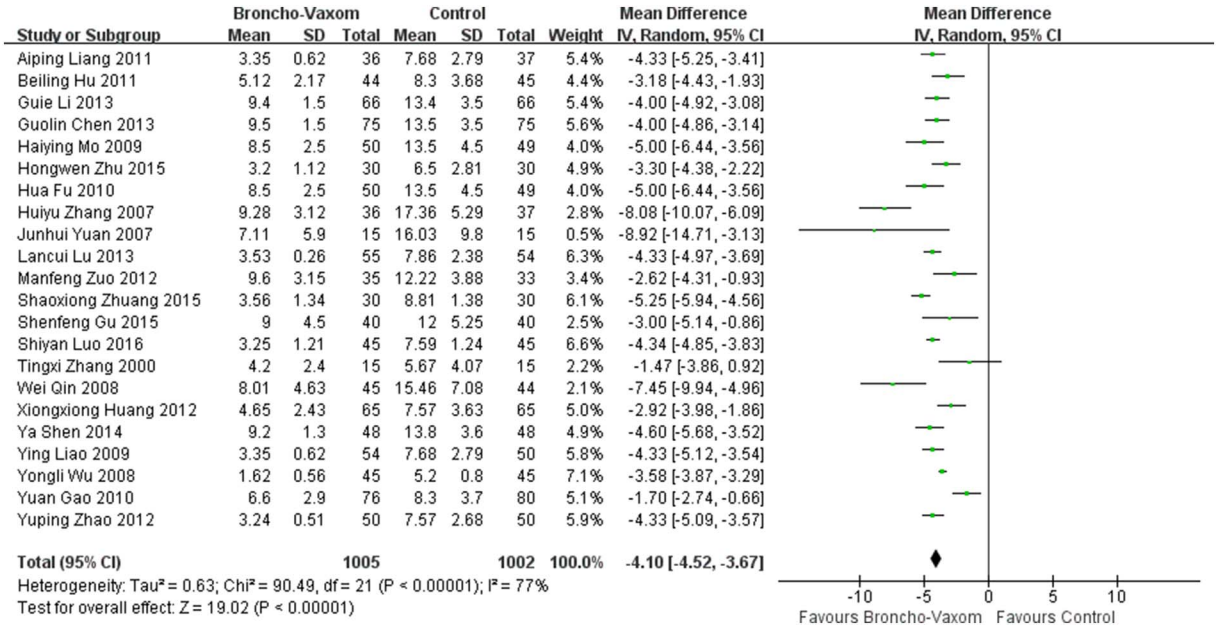

Fig. 2. Therapeutic time of antibiotics in Broncho-Vaxom and control group.

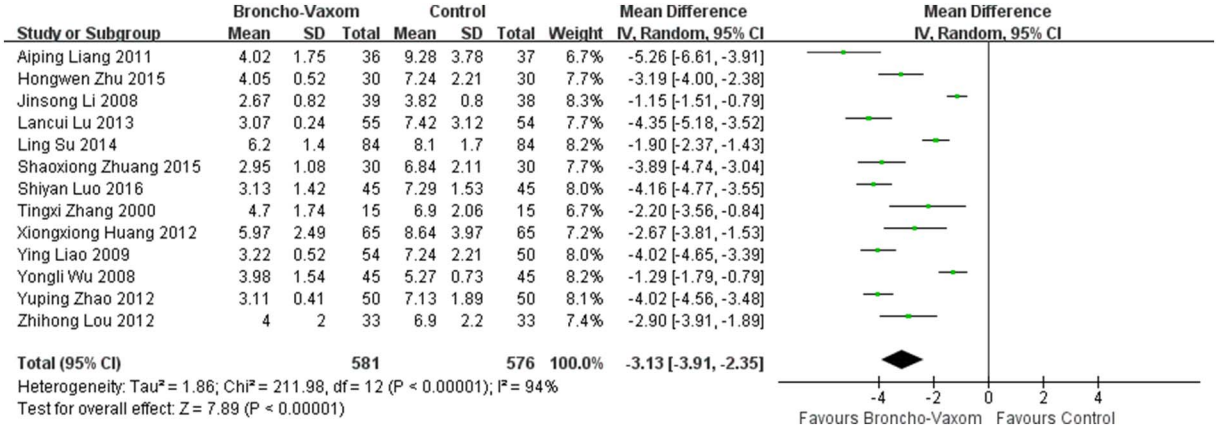

Fig. 3. The duration of infection in Broncho-Vaxom and control group.

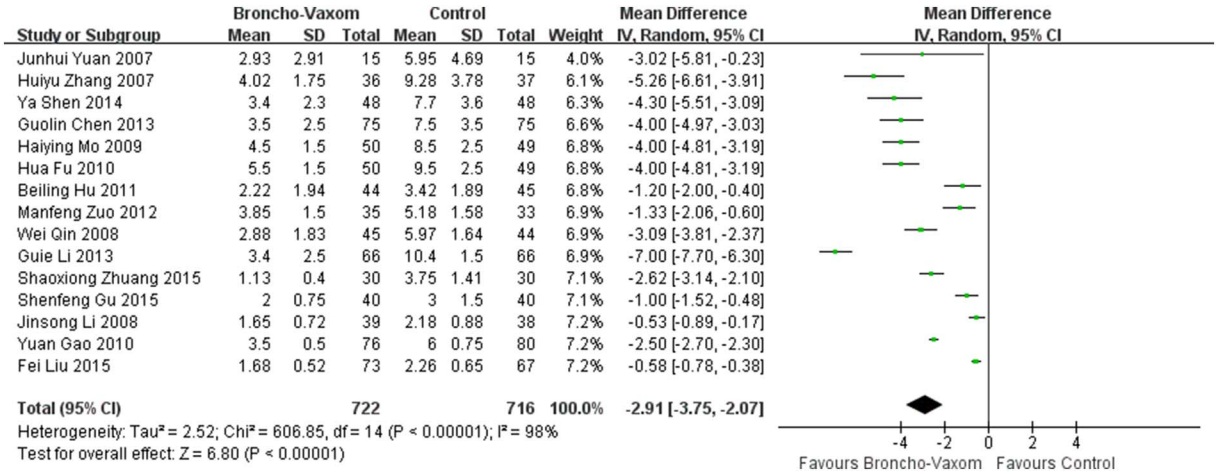

Fig. 4. The febrile time in Broncho-Vaxom and control group.

the double-blind method, and one (1.9%) [14] adopted the single course of treatment. 6 (11.3%) RCTs [57–62] did not report random and hidden methods, but the doctors and patients were double-blind, which can be treated as random and allocation concealment. The detailed assessment of risk of bias on included studies are shown in Table 2. In general, the description of the methodology was not clear in most of the studies.

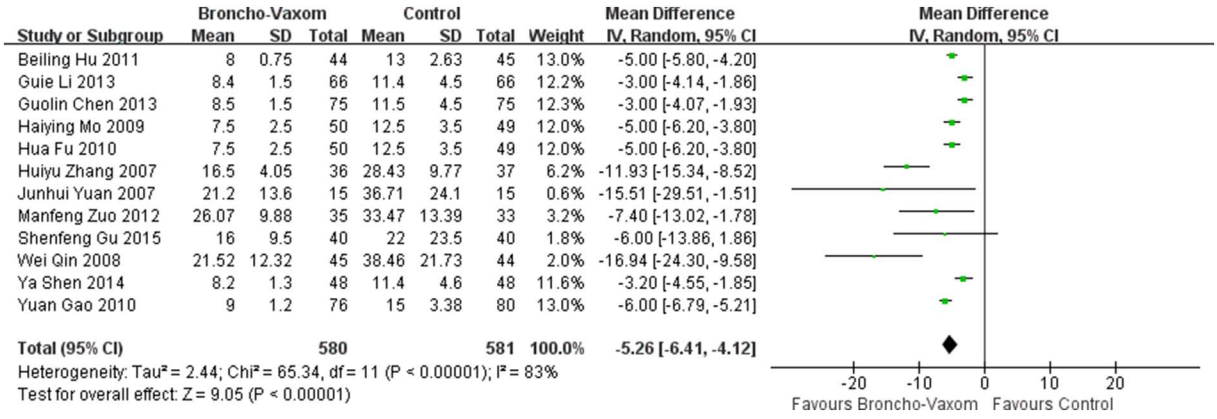

Fig. 5. The cough length in Broncho-Vaxom and control group.

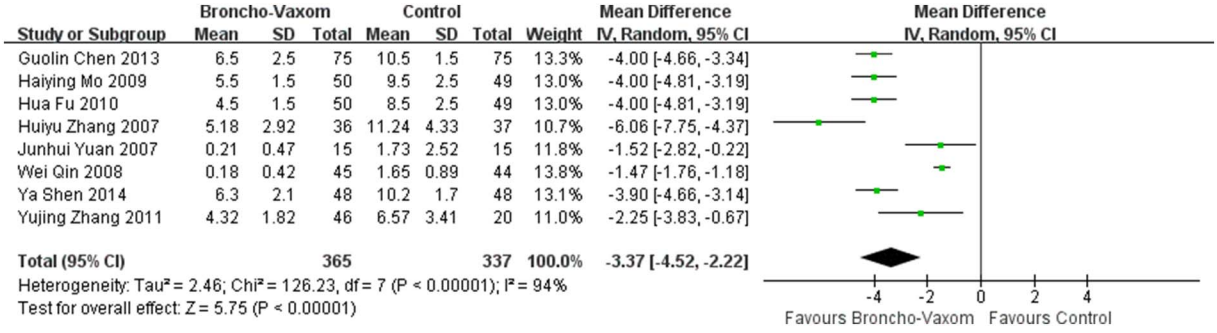

Fig. 6. Duration of wheezing in Broncho-Vaxom and control group.

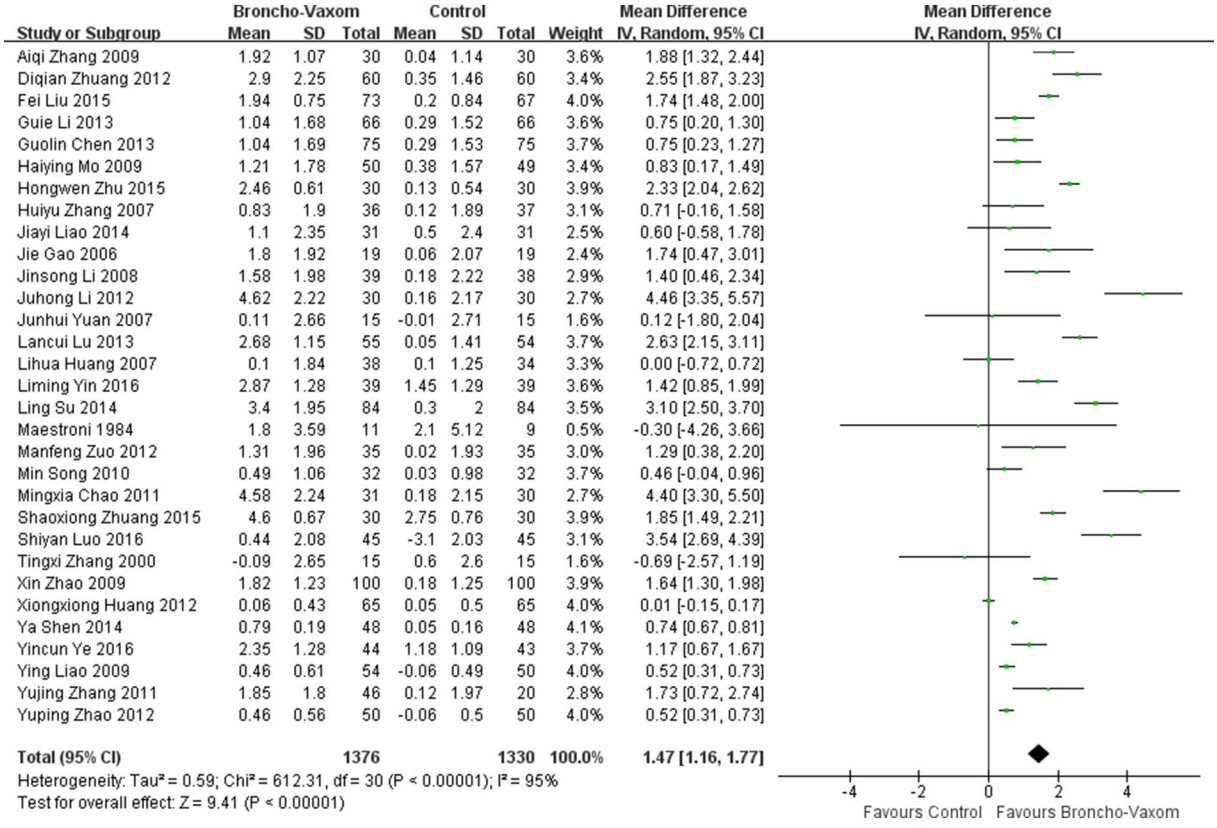

Fig. 7. The change of IgG in Broncho-Vaxom and control group.

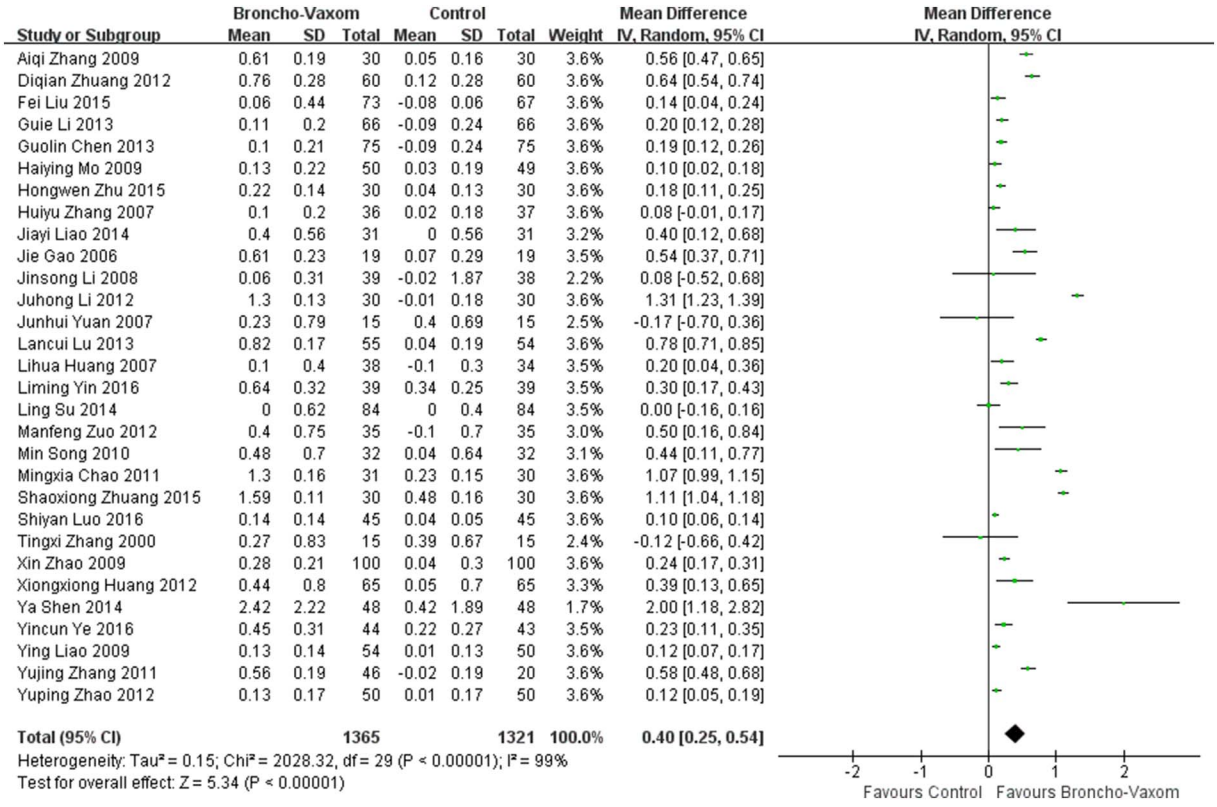

Fig. 8. The change of IgA in Broncho-Vaxom and control group.

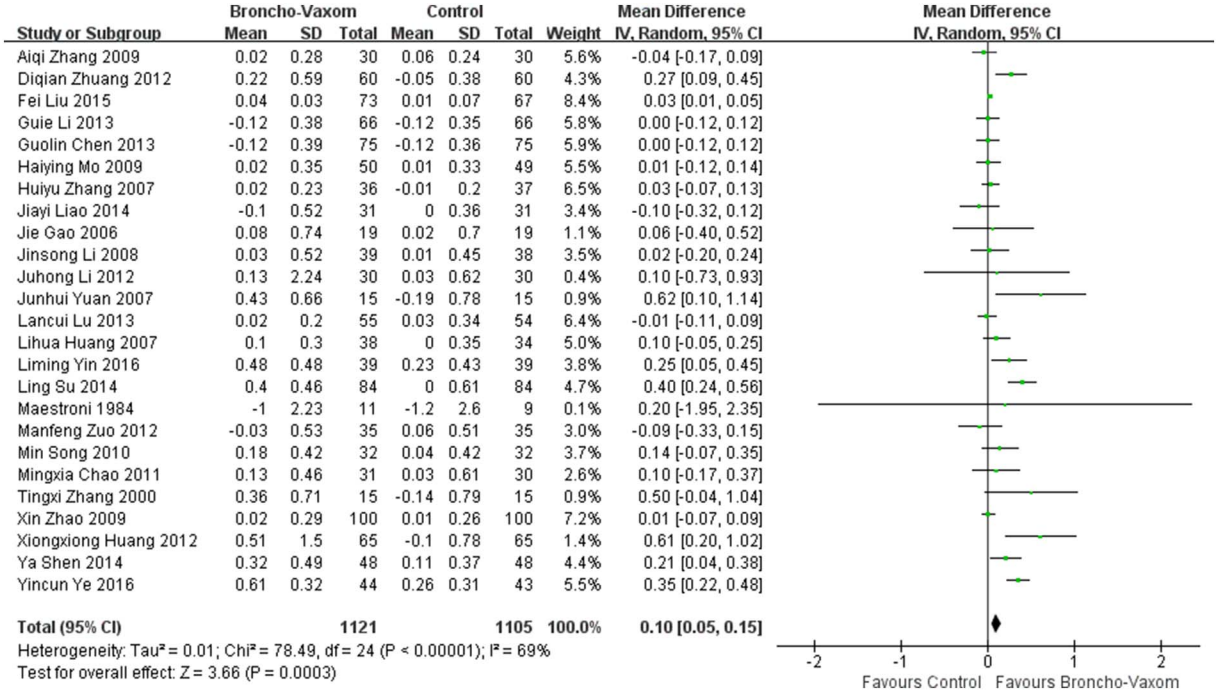

Fig. 9. The change of IgM in Broncho-Vaxom and control group.

3.2. Frequency of RTIs

A total of 44 RCTs reported the frequency of RTIs after receiving proper treatments where 2056 children were treated in the Broncho-Vaxom group and 1936 were treated in the control group. A random effect model was adopted to analyze the frequency because of the high heterogeneity among these included studies (I^2 = 98%, P < 0.00001). As shown in Fig. 1, the Broncho-Vaxom group was significantly associated with reduction in the frequency of RTIs [MD = −2.33, 95% CI (−2.75, −1.90), P < 0.00001].

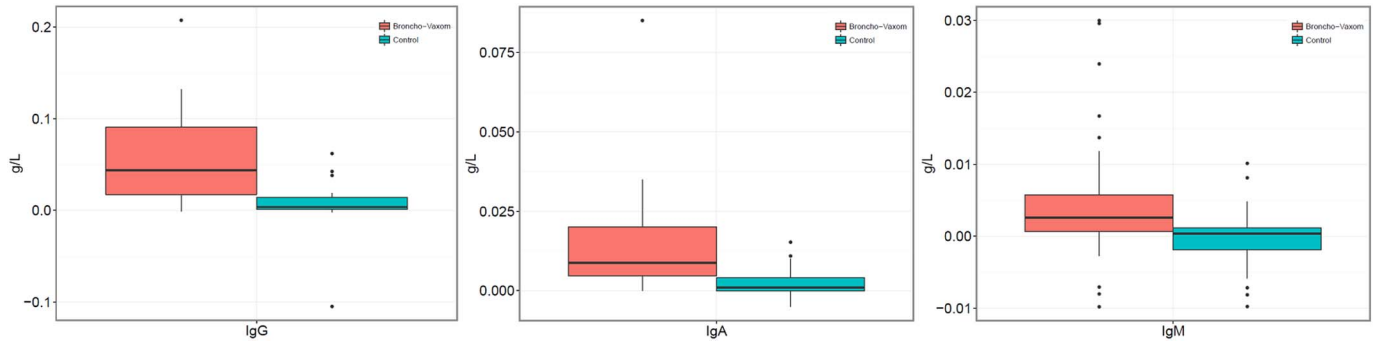

Fig. 10. Box-plots for the changes of serum immunoglobulin in Broncho-Vaxom and control group.

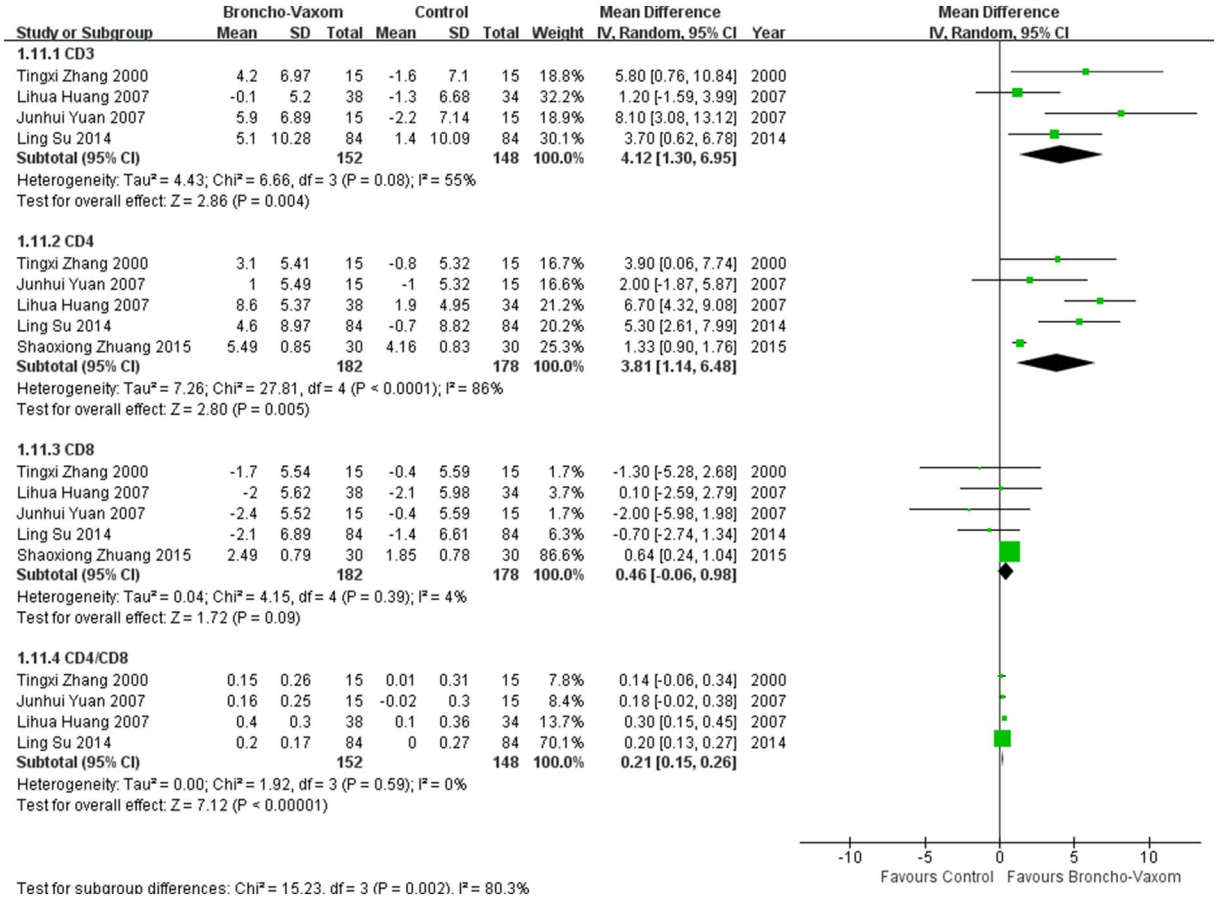

Fig. 11. The Level of T cell subgroup in Broncho-Vaxom and control group.

3.3. Therapeutic time of antibiotics

A total of 22 RCTs reported the therapeutic time of antibiotics with 1005 children in the Broncho-Vaxom group and 1002 in the control group. Due to the moderate heterogeneity of included studies (I^2 = 77%, P < 0.00001), a random effect model was adopted in the meta-analysis. It showed that the therapeutic time of antibiotics in the Broncho-Vaxom group was significantly shorter than that in the control group [MD = − 4.10 days, 95% CI (− 4.52, − 3.67), P < 0.00001] (Fig. 2).

3.4. Duration of infection

A total of 13 RCTs reported the duration of infection with 581 children in the Broncho-Vaxom group and 576 in the control group. The heterogeneity among these included studies was significant (I^2 = 94%, P < 0.00001) and a random effect model was adopted. The results showed that the duration of infection in the Broncho-Vaxom group was significantly lower than that in the control group [MD = − 3.13 days, 95% CI (− 3.91, − 2.35), P < 0.00001] (Fig. 3).

3.5. Febrile time

A total of 15 RCTs reported the febrile time with 722 children in the Broncho-Vaxom group and 716 in the control group. One study (Guie Li et al. [22]) used two courses of Broncho-Vaxom while the rest of the RCTs used Broncho-Vaxom 1 course. The heterogeneity among these included studies was significant (I^2 = 98%, P < 0.00001) and a

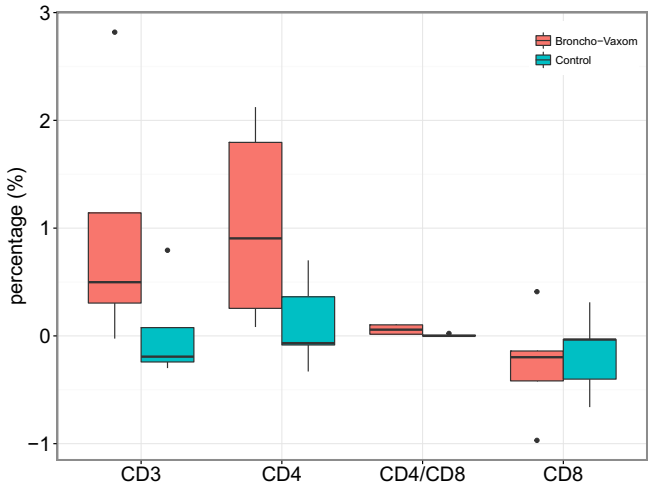

Fig. 12. Box-plot for the changes of T cell subgroup in Broncho-Vaxom and control group.

random effect model was adopted. According to the results, the febrile time of Broncho-Vaxom was significantly lower than the control group [MD = − 2.91 days, 95% CI (− 3.75, − 2.07), P < 0.00001] (Fig. 4).

3.6. Cough length

A total of 12 RCTs reported the cough time with 580 children in the Broncho-Vaxom group and 581 in the control group. One study (Guie Li et al. [22]) used two courses of Broncho-Vaxom while the rest of RCTs used Broncho-Vaxom 1 course. The heterogeneity among these included studies was significant (I^2 = 83%, P < 0.00001) and a random effect model was adopted. The cough length of Broncho-Vaxom group was significantly lower than the control group [MD = − 5.26 days, 95% CI (− 6.41, − 4.12), P < 0.00001] (Fig. 5).

3.7. Duration of wheezing

A total of 8 RCTs reported the wheezing onset time with 365 children in the Broncho-Vaxom group and 337 in the control group. All RCTs used the Broncho-Vaxom 1 course. The heterogeneity among these included studies was significant (I^2 = 94%, P < 0.00001) and a random effect model was adopted. It showed that the wheezing onset time in Broncho-Vaxom group was significantly lower than the control group [MD = − 3.37 days, 95% CI (− 4.52, − 2.22), P < 0.00001] (Fig. 6).

3.8. Level of serum immunoglobulin

31 RCTs reported the changes of serum IgG, 30 RCTs reported the changes of serum IgA, and 25 RCTs reported the changes of serum IgM, respectively. All these studies showed moderate to high heterogeneity (IgG: I^2 = 95%, P < 0.00001; IgA: I^2 = 99%, P < 0.00001; IgM: I^2 = 69%, P < 0.00001) and the random effect model was used to analyze the results. Broncho-Vaxom can significantly improve the level of IgG [MD = 1.47 g/L, 95% CI (1.16, 1.77), P < 0.00001; Fig. 7], IgA [MD = 0.40 g/L, 95% CI (0.25, 0.54), P < 0.00001; Fig. 8] and IgM [MD = 0.10 g/L, 95% CI (0.05, 0.15), P = 0.0003; Fig. 9]. Box-plots

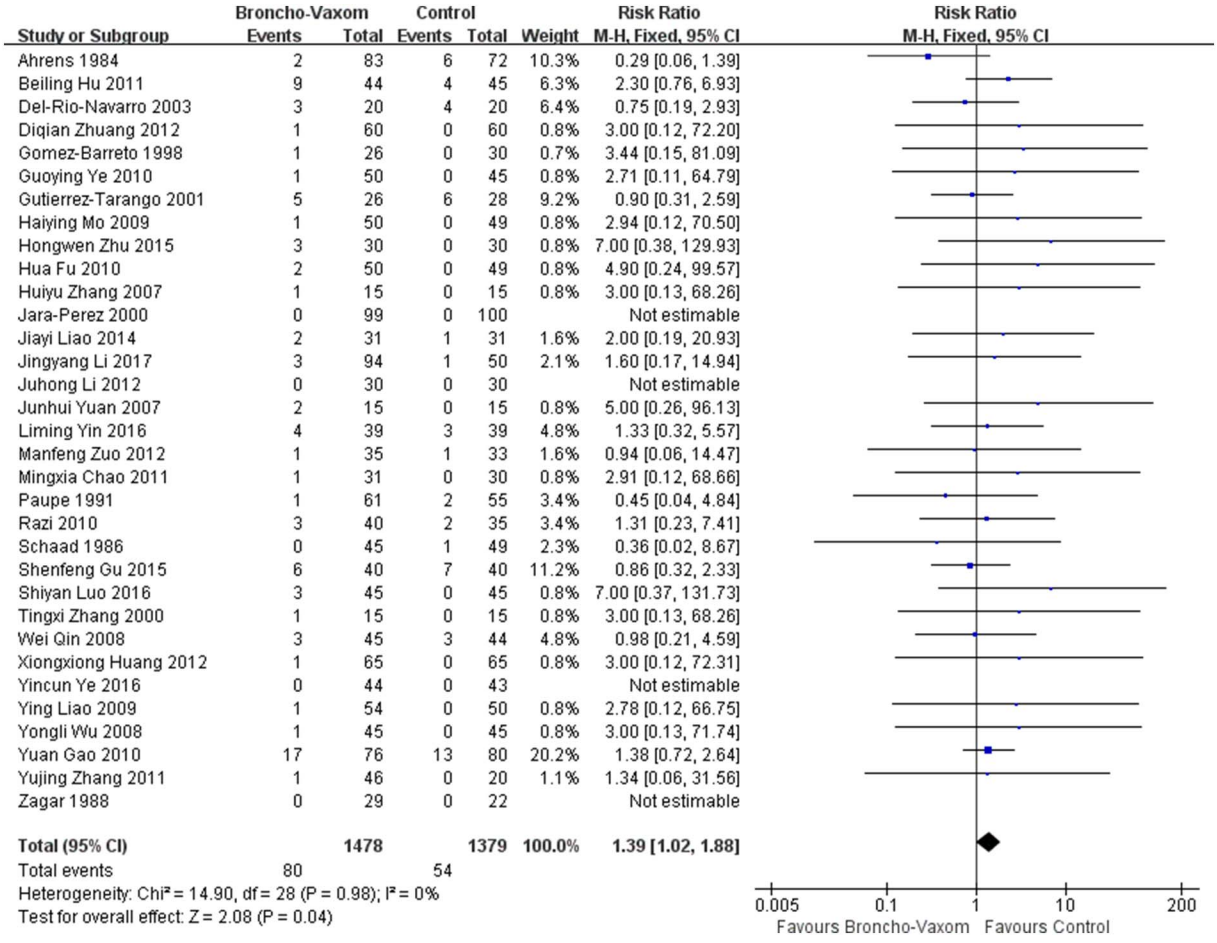

Fig. 13. The adverse event rate in Broncho-Vaxom and control group.

Table 3
Level of the included evidence for endpoints.

Endpoints	Sample	Number	RR (95% CI)	MD (95% CI)	Level of evidence
Frequency of RTIs	3992	44	–	− 2.33 (− 2.75, − 1.90)	Very low
Therapeutic time of antibiotics	2007	22	–	− 4.10 (− 4.52, − 3.67)	Very low
Duration of infection	1157	13	–	− 3.13 (− 3.91, − 2.35)	Very low
Febrile time	1438	15	–	− 2.91 (− 3.75, − 2.07)	Very low
Cough length	1161	12	–	− 3.37 (− 4.52, − 2.22)	Very low
Duration of wheezing	702	8	–	− 3.37 (− 4.52, − 2.22)	Very low
Serum IgG	2706	31	–	1.47 (1.16, 1.77)	Very low
Serum IgA	2686	30	–	0.40 (0.25, 0.54)	Very low
Serum IgM	2226	25	–	0.10 (0.05, 0.15)	Very low
CD3 +	300	4	–	4.12 (1.30, 6.95)	Very low
CD4 +	360	5	–	3.81 (1.14, 6.48)	Very low
CD8 +	360	5	–	0.46 (− 0.06, 0.98)	Very low
CD4 +/CD8 +	300	4	–	0.21 (0.15, 0.26)	Very low
Adverse events	2857	33	1.39 (1.02, 1.88)	–	Low

were drawn for the changes of each serum immunoglobulin for visual comparison in Broncho-Vaxom and control group (Fig. 10).

3.9. Level of T cell subgroup

4 RCTs reported the changes on CD3 + level, 5 RCTs reported the changes on CD4 + level, 5 RCTs reported the changes on CD8 + level, and 4 RCTs reported the ratio of CD4 +/CD8 + level. The results showed that Broncho-Vaxom can significantly improve the level of CD3 + [MD = 4.12%, 95% CI (1.30, 6.95), P = 0.004], CD4 + [MD = 3.81%, 95% CI (1.14, 6.48), P = 0.005] and CD4 +/CD8 + [MD = 0.21%, 95% CI (0.15, 0.26), P < 0.00001] (Fig. 11), but there were no differences between the two groups in terms of CD8 + [MD = 0.46%, 95% CI (− 0.06, 0.98), P = 0.09]. Box-plot was drawn for the changes of T cell subgroup for visual comparison in Broncho-Vaxom and control group (Fig. 12).

3.10. Adverse event

33 RCTs reported the incidence of adverse events, which were mostly rashes and mild gastrointestinal reactions; these adverse events had no influence on the treatment. The results showed that the adverse event rate was higher in the Broncho-Vaxom group compared with the control [RR = 1.39, 95% CI (1.02, 1.88), P = 0.04] (Fig. 13).

3.11. Level of evidence

The level of evidence for the adverse event rate was low and very low for the other endpoints (Table 3). This indicates that evidence should be interpreted with caution, since there is low evidence quality due to the limitations of the original studies. Further high-quality and adequately powered trials are needed.

4. Discussion

Our systematic review showed a significant reduction in RTIs, a decrease in the duration of the course of antibiotics, infections, fever, cough, and wheezing in children with RRTIs who were treated with Broncho-Vaxom in comparison to the control. In addition, Broncho-Vaxom significantly improved the level of serum immunoglobulin levels (IgG, IgA, or IgM) and T-lymphocytes subtype (CD3 +, CD4 +, or CD4 +/CD8 +). Adverse events of Broncho-Vaxom had no influence on the treatment. As described in the Results section, heterogeneity existed in each endpoint: different age spans included in these studies may be the cause of heterogeneity.

RTIs are important causes of morbidity, mortality, and disability in children [63] and therefore are one of the major costs for the health-care system [64]. The pathogenesis of RRTIs is complicated and has many factors including: anatomical and physiological characteristics of the respiratory system, deficiency of vitamins, trace elements or calcium, genetic and environmental factors, impaired immunity, and so on [65]. In order to treat RRTIs in children, possible pathogenic factors such as environmental and other controllable factors should be removed to enhance nutrition and physical exercise and add trace elements and vitamins; anti-bacterial or antiviral treatment can be conducted in the acute phase. In addition, immunomodulator agents, such as bacterial lysates, have been recommended as a useful option in RRTIs management.

The vast majority of recurrent RTIs are triggered by viruses, but these are frequently followed by bacterial super-infections [66]. Regardless of whether they are viral or bacterial, the presence of pathogens in the respiratory tract triggers the involvement of the innate and adaptive immune systems. A key event among the actions of the adaptive immune system is the production of IgA molecules. As a result, patients with impaired immunity and chronic inflammation are at greater risk of RTIs [67].

Broncho-Vaxom is an immunomodulator that is comprised of lyophilized bacterial lysates from 21 different bacterial strains, derived from the eight-major species and sub-species that are most often associated with RTIs. There are trials and meta-analyses that indicate Broncho-Vaxom reduced the number of RRTIs and enhanced immune function, (i.e. increasing in secretory IgA, serum IgA, serum IgG, serum IgM, and T cells). The percentages of different lymphoid subsets such as CD3 +, CD4 +, and CD8 + T cells as well as immunoglobins provide some of the main immunological parameters that reflect the immune reactive states. T lymphocyte-mediated immune function plays an important role in immune response and immune regulatory function of the body. The generation of antigen-specific memory CD4 + T cells could up-regulate T helper type 1 (Th1) immune responses, enhancing more efficient anti-microbial defenses in the long-term. In addition, the level of CD3 +, CD4 +, and CD4 +/CD8 + have a negative correlation with the risk of RTI [68,69]. Although extensive body trials and meta-analyses have shown the benefit of Broncho-Vaxom to RTI, the sizes of most studies are small.

In a systematic quantitative review of 13 clinical trials (2721 patients) testing Broncho-Vaxom, Steurer-Stey et al. found evidence in favor of Broncho-Vaxom for the prevention of ARTI in children, leading to fewer infections [70]. The number of studies included in the meta-analysis for each endpoint was small, with only two or three trials for each one. In 2010 Schaad performed a systematic review to assess the efficacy of Broncho-Vaxom for preventing the occurrence of pediatric RTIs [71]. Eight RCTs were included in the study (851 patients) and the author reported a 26.2% decrease of RRTIs in patients with Broncho-Vaxom (32% vs. 58.2%, P < 0.001). In a recent meta-analysis, 19 studies were assembled and appraised (959 patients) [72]. The results showed that during 12 months, compared with routine treatment alone,

patients with the addition of Broncho-Vaxom experienced an average of 2.963 times reduction of acute respiratory tract infection. Compared with these studies, more trials (53 trials) and samples (4851 patients) were included in our systematic review. More comprehensive endpoints were estimated, which included of the duration of antibiotics course, infections, fever, cough and wheezing, serum immunoglobulin levels, T-lymphocytes subtype, and adverse events. Finally, we used the GRADE system to grade the quality of evidence.

However, it should be mentioned that there are some limitations of the present systematic review. First, in addition to several high-quality trials, the overall studies that were included showed a low methodological quality. Second, due to the variation in study characteristics, it was not surprising that there was substantial statistical heterogeneity among individual studies. Finally, the patient sample size was relatively insufficient. As a result, all the factors that were mentioned above led to the low evidence level.

5. Conclusion

Our analysis indicated a significant efficacy of routine treatment regarding using Broncho-Vaxom on RRTIs in children as well as a good safety range. However, the results should be interpreted with caution because of the low evidence level. Further confirmatory evidence from high-quality and large-scale RCT trials is required.

Conflict of interests

The authors declare no conflict of interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

References

[1] Chinese Pediatric Society of Chinese Medical Association, The clinical concept and treatment principle of recurrent respiratory tract infections, Chin. J. Pediatr. 2 (46) (2008) 108–110, http://dx.doi.org/10.3321/j.issn:0578-1310.2008.02.008.
[2] R.A. Damoiseaux, et al., NHG-Standaard Otitis media acuta bij kinderen (NHG standard Otitis Media in children), Huisarts Wet 12 (49) (2006) 615–621.
[3] U.B. Schaad, S. Esposito, C. Razi, Diagnosis and management of recurrent respiratory tract infections in children: a practical guide, Arch. Pediatr. Infect. Dis. 4 (1) (2016) e31039, , http://dx.doi.org/10.5812/pedinfect.31039.
[4] H. Ozkan, et al., IgA and/or IgG subclass deficiency in children with recurrent respiratory infections and its relationship with chronic pulmonary damage, J Investig Allergol Clin Immunol 15 (1) (2005) 69–74.
[5] J.R. David, F.S. Rosen, Deficiencies in Immunoglobulins and Cell-mediated Immunity [CD-ROM], Scientific American Medicine, New York, 2000.
[6] A.M. Koatz, et al., Clinical and immunological benefits of OM-85 bacterial lysate in patients with allergic rhinitis, asthma, and COPD and recurrent respiratory infections, Lung 194 (4) (2016) 687–697, http://dx.doi.org/10.1007/s00408-016-9880-5.
[7] C. Zelle-Rieser, et al., A clinically approved oral vaccine against pneumotropic bacteria induces the terminal maturation of CD83 + immunostimulatory dendritic cells, Immunol. Lett. 76 (1) (2001) 63–67, http://dx.doi.org/10.1016/S0165-2478(00)00326-6.
[8] M. Huber, H. Mossmann, W.G. Bessler, Th1-orientated immunological properties of the bacterial extract OM-85-BV, Eur. J. Med. Res. 10 (5) (2005) 209–217.
[9] X. Zeng, et al., The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review, J. Evid. Based Med. 8 (1) (2015) 2–10, http://dx.doi.org/10.1111/jebm.12141.
[10] J. Li, J. Bao, Y. Bao, Bacterial lysates OM-85BV in children with asthma and nasal allergy symptoms, J. Pediatr. Pharm. 23 (1) (2017) 7–10, http://dx.doi.org/10.13407/j.cnki.jpp.1672-108X.2017.01.003.
[11] S. Luo, C. Ma, Efficacy of bacterial lysate on recurrent respiratory tract infections in children, Chin. Foreign Med. Res. 14 (26) (2016) 42–44, http://dx.doi.org/10.14033/j.cnki.cfmr.2016.26.022.
[12] Y. Ye, P. Jiang, Effect of Broncho-Vaxom on immune mechanism and inflammatory mechanism of recurrent respiratory tract infections in children and its efficacy, Clin. Educ. Gen. Pract. 14 (4) (2016) 424–426, http://dx.doi.org/10.13558/j.cnki.issn1672-3686.2016.04.018.
[13] L. Yin, H. Chen, X. Feng, Clinical study on bacterial lysates combined with budesonide in treatment of recurrent respiratory tract infection in children, Drugs Clin. 31 (8) (2016) 1273–1277.
[14] S. Gu, C. Wu, G. Xie, Efficacy of bacterial lysates in the adjuvant therapy for children with recurrent respiratory tract infections, Chin. J. Pract. Pediatr. 30 (3) (2015) 207–210.
[15] F. Liu, et al., Clinical effect analysis of Bronchovaxom in the treatment of children with recurrent respiratory tract infections, Chin. J. Nosocomiol. 25 (4) (2015) 942–944.
[16] W. Zhang, Efficacy of Broncho-vaxom in the adjuvant therapy for children with recurrent respiratory tract infections, Guide China Med. 13 (13) (2015) 70–71, http://dx.doi.org/10.15912/j.cnki.gocm.2015.13.050.
[17] H. Zhu, H. Zhang, W. Hu, Clinical observation on 60 cases of recurrent respiratory tract infections in children treated by Bronchovaxom combined with routine treatment, China Prac. Med. 10 (7) (2015) 140–141, http://dx.doi.org/10.14163/j.cnki.11-5547/r.2015.07.098.
[18] S. Zhuang, et al., Compliance of Bronchovaxom in treatment of recurrent respiratory tract infections, IMHGN 21 (14) (2015) 1948–1950, http://dx.doi.org/10.3760/cma.j.issn.1007-1245.2015.14.003.
[19] J. Liao, T. Zhang, Influence of OM-85 BV on hBD-1 and immunoglobulin in children with asthma and recurrent respiratory tract infection, Chin. J. Contemp. Pediatr. 16 (5) (2014) 508–512, http://dx.doi.org/10.7499/j.issn.1008-8830.2014.05.013.
[20] Y. Shen, Effect and mechanism of Broncho-Vaxom in the treatment of recurrent respiratory tract infections in children, J. Pediatr. Pharm. 20 (1) (2014) 32–34, http://dx.doi.org/10.13407/j.cnki.jpp.1672-108x.2014.01.015.
[21] L. Su, Y. Liu, Clinical analysis of treatment for children with recurrent respiratory tract infections, Chin. J. Nosocomiol. 24 (18) (2014) 4625–4626, http://dx.doi.org/10.11816/cn.ni.2014-134498.
[22] G. Li, Efficacy of Bronchovaxom in the treatment of children with recurrent respiratory tract infections, China Health Care Nutr. 7 (7) (2013) 629.
[23] L. Lu, Efficacy of Broncho-Vaxom in preventing or treating recurrent respiratory tract infections in children, China Health Care Nutr. 33 (5) (2013) 2627–2628, http://dx.doi.org/10.3969/j.issn.1004-7484(x).2013.05.482.
[24] G. Chen, X. Lan, H. Ye, Efficacy of Bronchovaxom in the treatment of children with recurrent respiratory tract infections, China Prac. Med. 8 (1) (2013) 163–164, http://dx.doi.org/10.3969/j.issn.1673-7555.2013.01.128.
[25] X. Huang, Diagnosis and treatment of infant respiratory tract infection in community outpatient department, Chin. Rural Health Serv. Adm. 32 (3) (2012) 316–317.
[26] H. Ji, Efficacy of Bronchovaxom in the treatment of children with recurrent respiratory tract infections, World Health Dig. Med. Period 9 (33) (2012) 108–109, http://dx.doi.org/10.3969/j.issn.1672-5085.2012.33.096.
[27] J. Li, Y. Hao, Clinical analysis of 30 cases of children with recurrent respiratory tract infections treated by bacterial lysate, China Mod. Med. 19 (3) (2012) 54–55, http://dx.doi.org/10.3969/j.issn.1674-4721.2012.03.027.
[28] Z. Lou, Efficacy of Bronchovaxom in the treatment of children with recurrent respiratory tract infections, Hebei Med. 34 (5) (2012) 726–727, http://dx.doi.org/10.3969/j.issn.1002-7386.2012.05.047.
[29] M. Zuo, et al., Effect observation of bacterial lysates in the treatment of iron deficiency anemia and recurrent respiratory infections in children, J. Pediatr. Pharm. 18 (2) (2012) 16–19, http://dx.doi.org/10.3969/j.issn.1672-108X.2012.02.007.
[30] Y. Zhao, Efficacy of Broncho-Vaxom (8 kinds of bacterial lysates) in the treatment of children with recurrent respiratory tract infections, Chin. Foreign Med. Res. 10 (35) (2012) 121–122, http://dx.doi.org/10.14033/j.cnki.cfmr.2012.35.114.
[31] D. Zhuang, F. Zhao, Y. Li, Effect of Broncho-vaxom on the mucosal immune function in children with recurrent respiratory tract infection, China Med. Her. 9 (32) (2012) 100–101, http://dx.doi.org/10.3969/j.issn.1673-7210.2012.32.040.
[32] M. Chao, et al., Efficacy of bacterial lysates in the adjuvant therapy for children with recurrent respiratory tract infections, Nanchang Da Xue Xue Bao (Med. Sci.) 51 (4) (2011) 74–75, http://dx.doi.org/10.3969/j.issn.1000-2294.2011.04.023.
[33] B. Hu, et al., Clinical efficacy of fluticasone plus combined with bacterial lysates in treatment of children with asthma, China Mod. Doct. 49 (16) (2011) 83–85, http://dx.doi.org/10.3969/j.issn.1673-9701.2011.16.039.
[34] A. Liang, Y. Zhang, F. Wang, Clinical observation on 73 cases of repeated respiratory tract infections treated by Broncho-Vaxom, J. Clin. Pulm. Med. 16 (2) (2011) 284–285, http://dx.doi.org/10.3969/j.issn.1009-6663.2011.02.070.
[35] Y. Zhang, Y. Sun, X. Zhao, Clinical research on bacterial lysates in prevention of wheezing onset induced by viral infection among preschool children, Matern. Child Health Care China 26 (25) (2011) 3904–3906.
[36] H. Fu, Z. Lin, Efficacy of Broncho-Vaxom in the treatment of children with recurrent respiratory respiratory tract infections, World Health Dig. Med. Period 7 (8) (2010) 58–59, http://dx.doi.org/10.3969/j.issn.1672-5085.2010.08.049.
[37] Y. Gao, et al., Therapeutic efficacy of bacterial lysates and montelukast treatment in children with intermittent asthma, Chin. J. Clin. Pharmacol. Ther. 15 (5) (2010) 547–550.
[38] M. Song, Efficacy of bacterial lysates in the treatment of children with recurrent respiratory tract infections, Jilin Yi Xue 31 (24) (2010) 4055, http://dx.doi.org/10.3969/j.issn.1004-0412.2010.24.029.
[39] G. Ye, Clinical observation on 50 cases of repeated respiratory tract infections in children treated by Broncho-Vaxom, Strait Pharm. J. 22 (3) (2010) 115–116, http://dx.doi.org/10.3969/j.issn.1006-3765.2010.03.053.
[40] C.H. Razi, et al., The immunostimulant OM-85 BV prevents wheezing attacks in preschool children, J. Allergy Clin. Immunol. 126 (4) (2010) 763–769, http://dx.doi.org/10.1016/j.jaci.2010.07.038.
[41] Y. Liao, Efficacy of Broncho-Vaxom in children with recurrent respiratory tract infections, China Mod. Doct. 47 (7) (2009) 81–82, http://dx.doi.org/10.3969/j.issn.1673-9701.2009.07.041.
[42] H. Mo, A. Xu, Effectiveness of Broncho-Vaxom in treating repeated respiratory tract infection in children, J. Mod. Med. Health 25 (18) (2009) 2758–2760.

[43] A. Zhang, L. Zhang, S. Fu, Effect of Broncho-vaxom on repeatedly respiratory infection in children, Prog. Mod. Biomed. 9 (19) (2009) 3690–3691, http://dx.doi.org/10.13241/j.cnki.pmb.2009.19.038.
[44] X. Zhao, et al., Effect of bacterial lysates on humoral immunity and clinical therapy in children with recurrent respiratory tract infection, Zhong Nan Yao Xue 7 (12) (2009) 946–948.
[45] J. Li, et al., Observation on the therapeutic effect of Broncho-Vaxom in treating repeated respiratory tract infections, Acta Acad. Med. CPAF 17 (3) (2008) 212–213.
[46] Y. Tan, Efficacy of oral bacterial lysates in children with bronchial asthma complicated with recurrent respiratory tract infections, China Mod. Doct. 46 (18) (2008) 186–187, http://dx.doi.org/10.3969/j.issn.1673-9701.2008.18.103.
[47] Y. Wu, et al., Efficacy of Broncho-Vaxom in children with recurrent respiratory tract infections, Clin. Focus 23 (9) (2008) 659–660, http://dx.doi.org/10.3969/j.issn.1004-583X.2008.09.022.
[48] L. Huang, et al., Efficacy of Broncho-Vaxom and the changes of immune function and normal respiratory flora in children with recurrent respiratory tract infection, Hebei Med. J. 29 (10) (2007) 1088–1090, http://dx.doi.org/10.3969/j.issn.1002-7386.2007.10.027.
[49] J. Yuan, X. Chen, Effect of Broncho-Vaxom on bronchial asthma with recurrent respiratory tract infections, Zhejiang Clin. Med. J. 9 (5) (2007) 627, http://dx.doi.org/10.3969/j.issn.1008-7664.2007.05.033.
[50] H. Zhang, et al., Efficacy and safety of Broncho-Vaxom in preventing recurrent respiratory tract infection in infants with asthma, J. Pract. Med. 23 (21) (2007) 3427–3428, http://dx.doi.org/10.3969/j.issn.1006-5725.2007.21.060.
[51] J. Gao, C. Yu, Efficacy of Broncho-Vaxom in children with recurrent respiratory tract infections, Hebei Med. J. 28 (4) (2006) 285, http://dx.doi.org/10.3969/j.issn.1002-7386.2006.04.028.
[52] B.E. Del-Rio-Navarro, et al., Use of OM-85 BV in children suffering from recurrent respiratory tract infections and subnormal IgG subclass levels, Allergol Immunopathol (Madr) 31 (1) (2003) 7–13, http://dx.doi.org/10.1016/S0301-0546(03)79158-7.
[53] U.B. Schaad, R. Mutterlein, H. Goffin, Immunostimulation with OM-85 in children with recurrent infections of the upper respiratory tract: a double-blind, placebo-controlled multicenter study, Chest 122 (6) (2002) 2042–2049, http://dx.doi.org/10.1378/chest.122.6.2042.
[54] M.D. Gutierrez-Tarango, A. Berber, Safety and efficacy of two courses of OM-85 BV in the prevention of respiratory tract infections in children during 12 months, Chest 119 (6) (2001) 1742–1748, http://dx.doi.org/10.1378/chest.119.6.1742.
[55] T. Zhang, H. Liang, Y. Fan, Efficacy of Broncho-Vaxom in children with recurrent respiratory respiratory tract infections, J. Pract. Med. 16 (9) (2000) 778–779, http://dx.doi.org/10.3969/j.issn.1006-5725.2000.09.039.
[56] J.V. Jara-Perez, A. Berber, Primary prevention of acute respiratory tract infections in children using a bacterial immunostimulant: a double-masked, placebo-controlled clinical trial, Clin. Ther. 22 (6) (2000) 748–759, http://dx.doi.org/10.1016/S0149-2918(00)90008-0.
[57] B.D. Gomez, et al., Safety and efficacy of OM-85-BV plus amoxicillin/clavulanate in the treatment of subacute sinusitis and the prevention of recurrent infections in children, Allergol Immunopathol (Madr) 26 (1) (1998) 17–22.
[58] J. Paupe, Immunotherapy with an oral bacterial extract (OM-85 BV) for upper respiratory infections, Respiration 58 (3–4) (1991) 150–154, http://dx.doi.org/10.1159/000195916.
[59] S. Zagar, D. Lofler-Badzek, Broncho-Vaxom in children with rhinosinusitis: a double-blind clinical trial, ORL J. Otorhinolaryngol. Relat. Spec. 50 (6) (1988) 397–404, http://dx.doi.org/10.1159/000276020.
[60] U.B. Schaad, J.C. Farine, T. Fux, Prospective placebo-controlled double-blind study using a bacterial lysate in infections of the respiratory tract and ENT region in children, Helv. Paediatr. Acta 41 (1–2) (1986) 7–17.
[61] J. Ahrens, Multicentre double-blind clinical trial with broncho-vaxom in children, Therapiewoche 34 (22) (1984) 3469–3475.
[62] G.J. Maestroni, G.A. Losa, Clinical and immunobiological effects of an orally administered bacterial extract, Int. J. Immunopharmacol. 6 (2) (1984) 111–117, http://dx.doi.org/10.1016/0192-0561(84)90005-5.
[63] World Health Organization, Acute respiratory infections: the forgotten pandemic, Bull. World Health Organ. 76 (1) (1998) 101–103 (105-7).
[64] G.A. Gates, Cost-effectiveness considerations in otitis media treatment, Otolaryngol. Head Neck Surg. 114 (4) (1996) 525–530, http://dx.doi.org/10.1016/S0194-59989670243-7.
[65] H. Yang, S. Sun, Etiology and treatment of recurrent respiratory tract infection in children, Hebei Bei Fang Xue Yuan Xue Bao (Yi Xue Ban) 26 (01) (2009) 66–68, http://dx.doi.org/10.3969/j.issn.2095-1396.2009.01.028.
[66] I. Yui, et al., Novel clinical features of recurrent human respiratory syncytial virus infections, J. Med. Virol. 86 (9) (2014) 1629–1638, http://dx.doi.org/10.1002/jmv.23809.
[67] A. Rantala, J.J. Jaakkola, M.S. Jaakkola, Respiratory infections in adults with atopic disease and IgE antibodies to common aeroallergens, PLoS One 8 (7) (2013) e68582, , http://dx.doi.org/10.1371/journal.pone.0068582.
[68] F. Pu, et al., Yogurt supplemented with probiotics can protect the healthy elderly from respiratory infections: a randomized controlled open-label trial, Clin. Interv. Aging 12 (2017) 1223–1231, http://dx.doi.org/10.2147/CIA.S141518.
[69] X.B. Feng, X.Q. Yang, J. Shen, Influence of iron deficiency on serum IgG subclass and pneumococcal polysaccharides specific IgG subclass antibodies, Chin. Med. J. 107 (11) (1994) 813–816.
[70] C. Steurer-Stey, et al., Oral purified bacterial extracts in acute respiratory tract infections in childhood: a systematic quantitative review, Eur. J. Pediatr. 166 (4) (2007) 365–376, http://dx.doi.org/10.1007/s00431-006-0248-3.
[71] U.B. Schaad, OM-85 BV, an immunostimulant in pediatric recurrent respiratory tract infections: a systematic review, World J. Pediatr. 6 (1) (2010) 5–12, http://dx.doi.org/10.1007/s12519-010-0001-x.
[72] J. Ma, et al., Effects of bacterial lysates in patients with recurrent respiratory tract infections: a meta-analysis, Chin. J. Drug Eval. 31 (05) (2014) 284–288, http://dx.doi.org/10.3969/j.issn.2095-3593.2014.05.010.