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Review

Pidotimod, an immunostimulant in pediatric recurrent respiratory tract infections: A meta-analysis of randomized controlled trials

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ABSTRACT

Objectives: Recurrent respiratory tract infections (RRTIs) remain a great challenge to pediatricians, because they can increase the risk of various complications and there is no confirmed effective treatment. In the present study, we aimed to assess the effectiveness and safety of pidotimod (PDT), an immunostimulant, in treatment of RRTIs in children aged 14 years and under.

Methods: PubMed, EMBASE, Web of Science, Cochrane Library, ClinicalTrials.gov, CBM and CNKI were searched from their inception up to February 2018. All randomized controlled trials (RCTs) using PDT with various treatment durations and enrolling participants < 14 years of age were included in the present review. The interventions were PDT plus conventional treatment (e.g. anti-bacterial and antiviral therapy) or PDT alone versus the conventional treatment plus placebo or conventional treatment alone.

Results: A total of 29 RCTs consisting of 4344 pediatric patients were included in this meta-analysis. Ten RCTs were published from Italy, Russia or Greece, and 19 RCTs were published by Chinese groups. However, appropriate randomization methods were only used in 15 trials. Only one study had explicit allocation concealment. Since only eight RCTs were double-blind and placebo controlled, the evidence was not assessed as high quality. The meta-analysis indicates that treatment with PDT resulted in a significant increase in the proportion of participants who had lower RTIs (RR 1.59; 95% CI 1.45–1.74, $p < 0.00001$) compared with the conventional treatment. PDT could significantly decrease the duration of cough and fever. The number of patients in using antibiotics was also remarkably decreased in the PDT treatment group. Moreover, PDT administration improved the levels of serum immunoglobulin (IgG, IgA, or IgM) and T-lymphocyte subtypes (CD3+, CD4+). Besides, PDT administration did not increase the risk of adverse events of any cause (RR = 1.05, 95% CI 0.72–1.54, $p = 0.80$).

Conclusions: PDT showed a good efficacy and safety in treatment of pediatric RRTIs. Further high-quality and large-scale RCTs are still required to provide confirmatory evidence.

Trial registration: The protocol of this study can be found at PROSPERO with the registration number of CRD42018093541.

1. Introduction

Respiratory tract infections (RTIs) are the most common illness in children, which might perhaps be attributed to their immature immune system [1]. Most of RTIs are the upper respiratory tract infections (URTIs), which is acute, self-limiting and caused by viral, bacterial or other pathogens. The main symptoms include variable degrees of sneezing, nasal congestion and discharge, sore throat, cough, fever and headache. Another part of RTIs is lower respiratory tract infections (LRTIs), including bronchitis, bronchiolitis and pneumonia. LRTIs are the leading cause of morbidity and mortality in young children. According to the data from WHO, about 0.935 million children die from LRTIs before age 5 [2]. At present, despite the introduction of new antibiotics and vaccines which help reduce the mortality and morbidity, recurrent respiratory tract infections (RRTIs) remain widespread and affect young people. From previous reports, the incidence of RRTIs is at least 6% in Italy [3], 10% in Finland [4], and nearly 18% in China [5,6]. Currently, there is no globally accepted definition of RRTIs. Different definitions of RRTIs from different countries and regions were listed in Table 1. All disease definitions concur that all underlying pathological conditions, such as primary or secondary immunodeficiency, cystic fibrosis, malformations of airways, or immotile-cilia syndrome, must be ruled out before a diagnosis of RRTIs can be made. However, the frequency of RRTIs, the lower limit of age and whether needs to

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Table 1
The criteria of RRTIs in different countries and areas.

	China [19]		Europe			
	Age	Frequency	Age	Frequency	Site	Frequency
Upper airways	0–2	≥7/Year	0–14	≥6/Year [3]	Pharyngo-tonsillitis	> 4/Y
	> 2–5	≥6/Year			otitis media	> 3 or 6 months
	> 5–14	≥5/Year			Rhinosinusitis	> 4/Year
Trachealis/bronchitis	0–2	≥3/Year	0–14	≥3/Year [20]		
	> 2–14	≥2/Year				
Pneumonia	0–14	≥2/Year				

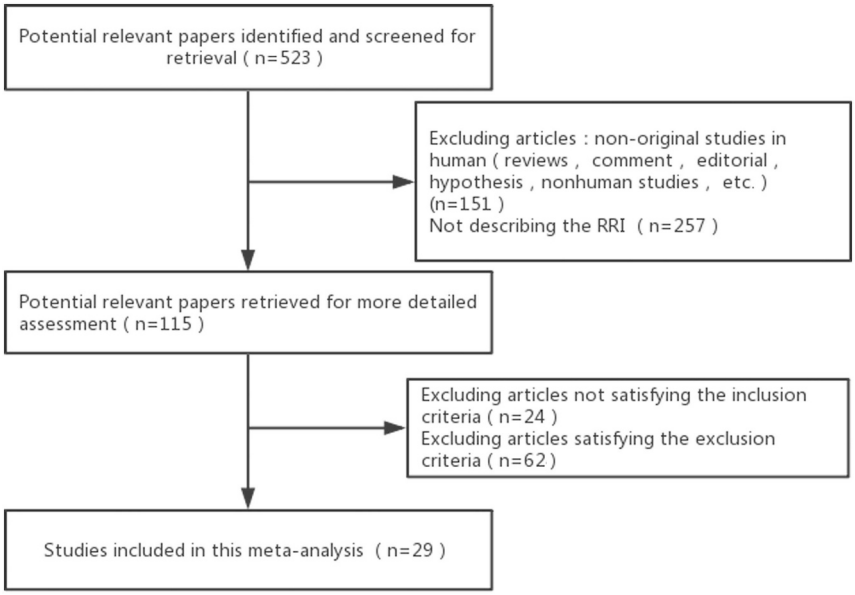

Fig. 1. Selection of studies for inclusion in the present meta-analysis.

distinguish the specific airway infection sites differ from each other.

The main risk factors of RRTIs in children are prematurity and atopy. Other risk factors include indoor or outdoor pollution, and exposure to secondhand smoke [7]. Children with RRTIs have no significant alterations in immunity, but mild and partial immune defects have frequently been described [8,9]. Nowadays, the socio-economic burden of RRTIs remains high in all countries, such as the cost of symptomatic drugs, antibiotics, hospitalization, as well as indirect costs, such as parental absences from work and loss of productivity [10]. As most RRTIs are caused by viral infections, antibiotics may be overused, leading to increased antibiotic resistance. There is growing interest in preventive treatment of RRTIs. Therefore, immunomodulatory agents are widely employed in the common practice to correct deviated immune functions [1].

Pidotimod (PDT, 3-L-pyroglutamyl-L-thiaziolidine-4-carboxylic acid) is a synthetic dipeptide molecule exerting effects on both innate and adaptive immunity. In 1993, PDT was first approved in Italy to be used as an immunomodulatory agent for respiratory and urinary tract infections, both in children (over 3 years of age) and adults with weak immune response. The treatment duration is not recommended, and the dosage is 400 mg twice a day in children. Besides respiratory and urinary tract infections, otolaryngology and gynecological infections were also recommended in 1997 Chinese dispensatory. It was approved to be used in children without defined minimum recommended age. For pediatric patients, the recommended dosage was used to be 400 mg twice a day at acute phase (2 weeks) and 400 mg once a day for at least 60 days for prevention. In March 2018, the CFDA revised and improved relevant provisions of PDT on following aspects [11]. The indication of PDT is reduced to a supplementary medicine to treat chronic or recurrent respiratory and urinary tract infections. Moreover, it can be only used in children older than 3 years at a dosage of 400 mg twice a day. The treatment duration is also shortened to < 60 days in the latest package insert. PDT is widely used in some European and Asian countries, including Italy, Russia, Mexico, Greece, Ukraine, China, South Korea and so on. Since 1990s, clinical studies have shown that PDT seems to have a beneficial effect on children with RRTIs in reducing the number of RTIs, shortening the duration of fever and decreasing the severity of the signs and symptoms. However, the sample sizes of these published RCTs are small and the results are not consistent. In the present review, we collected available randomized controlled trials (RCTs) of PDT to comprehensively evaluate its efficacy and safety in treatment of pediatric RRTIs.

2. Methods

2.1. Literature search strategy and selection criteria

A systematic search of the literature was performed a systematic search for published articles about PDT for children with RRTIs. Following electronic databases were searched from their inception up to February 2018, including PubMed, EMBASE, Web of Science, Cochrane Library, ClinicalTrials.gov, CBM and CNKI. The search was performed using the key terms: “pidotimod” OR “polimod” AND “children” OR “infants” OR “pediatric” without language restriction.

2.2. Study selection

In order to be included in this review, studies had to meet all of the

Table 2
Clinical data of included studies.

Studies	Nation	Sample (T/C)	Interventions		Treatment time (months)	Follow-up time (months)	Age (years)(T/C)	Endpoints
			Treated	Control				
Wang, H.L. 2017 [21]	China	60/59	Fixed dosage	CT	2	6	T: 5.34 ± 2.17 C: 5.28 ± 2.23	①⑤
Wu H. 2016 [22]	China	60/60	Loading dosage	CT	2.5	3	T:4–12C:3–12	①②③
Liu, C. J. 2016 [23]	China	40/40	Fixed dosage	CT	1	6	T:2.86 ± 0.53 C:2.92 ± 0.55	
Li, Y. J. 2016 [24]	China	44/44	Loading dosage	CT	2.5	12	T:3.5 ± 1.1 C:3.7 ± 1.2	①②③
Zhang, R. L. 2016 [25]	China	43/43	Loading dosage	CT	2.5	12	T:3.28 ± 1.05 C:3.34 ± 1.18	①⑤⑥
Jiang, D. H. 2016 [26]	China	97/97	Loading dosage	CT	3	12	T:3.8 ± 1.7 C:3.7 ± 1.8	①②③⑤⑥
Zheng, W. L. 2015 [27]	China	48/48	Fixed dosage	CT	3	12	T:6.57 ± 0.27 C:6.01 ± 0.32	①⑤
Shen, Y. Z. 2015 [28]	China	100/100	Loading dosage	CT	2	12	2–13	①⑥
Wu. L. X. 2015 [29]	China	46/46	Loading dosage	CT	2.5	12	T:5.95 ± 2.73 C:5.35 ± 2.28	②③⑤⑥
Namazova-Baranova, Ls2014 [30]	Russia	78/79	Fixed dosage	Antibiotics	1	6	3–6	①④
Licari, A. 2014 [31]	Italy	45/44	Fixed dosage	CT	2	2	4.9	④
Zhou, L. G. 2014 [32]	China	60/60	Loading dosage	CT	2	6	T: 3.1 ± 0.8 C: 3.4 ± 0.9	①⑤⑥
Zhou, H. 2013 [33]	China	72/68	Loading dosage	Antibiotics	2	12	7–12	①②③
Wang, Y. H. 2013 [34]	China	38/42	Fixed dosage	CT	3	6	T: 6.8 ± 1.7 C: 6.7 ± 1.5	①②③
Zhang, X. W. 2012 [35]	China	42/41	Loading dosage	CT	3.5	12	0.75–6	①②③⑤⑥
Liu, D. X. 2012 [36]	China	58/52	Loading dosage	CT	3	12	0.67–6	①
Ruan, D. Q. 2010 [37]	China	35/35	Loading dosage	CT	2	6	T:3.0 ± 0.7 C:3.1 ± 0.6	①
Zhang, L. 2010 [38]	China	105/90	Loading dosage	CT	2	12	0.5–12	①
Qu, J. P. 2009 [39]	China	23/22	Fixed dosage	CT	2	6	T:5.17 ± 2.37 C:5.37 ± 2.32	③⑦
Zhang, L. 2009 [40]	China	125/126	Loading dosage	CT + placebo	2.5	3	3–14	①
Peng, C. Y. 2009 [41]	China	140/120	Loading dosage	CT	1.5	12	T:3.74 ± 0.35 C:3.78 ± 0.36	①②③
Aivazis, V, 2002 [42]	Greece	32/18	Loading dosage	CT	1.25	9	T:5.2C:5.6	①
Burgio, Gr, 1994 [43]	Italy	50/40	Fixed dosage	CT + placebo	2	2	T:4.9 ± 2.57 C:4.5 ± 1.43	④⑦
Motta, G, 1994 [44]	Italy	117/118	Loading dosage	CT + placebo	2.5	3	6.7 ± 2.7	①②③⑦
Passali, D, 1994 [45]	Italy	205/211	Fixed dosage	CT + placebo	2	3	T:6.29 ± 2.78 C:6.51 ± 2.69	①③⑦
Careddu, P a, 1994 [46]	Italy	25/24	Fixed dosage	CT + placebo	0.67(20 days)	2	T:4.7C:4.9	①④⑦
Careddu, P, 1994 [47]	Italy	329/342	Fixed dosage	CT + placebo	2	3	T:5.63 ± 2.63 C:5.52 ± 2.42	①②③⑦
Caramia, G, 1994 [48]	Italy	60/60	Loading dosage	CT + placebo	2.5	0	2–8	③④⑦
Careddu, P, 1992 [49]	Italy	19/19	Fixed dosage	CT + placebo	0.67(20 days)	2	T:5.8 ± 3.22 C:7.3 ± 3.22	①④

Abbreviations: CT, conventional treatment.
Note: ①relapse;②cough;③fever;④antibiotics;⑤IgM, IgG or IgA;⑥CD3 + %, CD4 + % or CD8 + %;⑦Adverse events.

criteria as follows: 1) prospective RCTs; 2) patients aged from 0 to 14; 3) patients were diagnosed with RRTIs; 4) PDT was used along with conventional treatment in the experimental group (conventional treatment is defined as treatment for disease symptoms, such as anti-inflammatory, anti-bacterial and anti-viral therapies), while conventional treatment alone with or without placebo was used in the control group. The RCTs included “RRTIs” or “URTIs” or “LRTIs” or “acute respiratory infections,” or “recurrent tonsillitis.”

Trials were excluded if: 1) patients were diagnosed as primary or acquired immunodeficiency, such as Down syndrome (DS); 2) patients received medicines (immunomodulatory agents, macrolides, corticosteroids and so on) interfering with the curative effect; and 3) patients with the history of chronic diseases (including cystic fibrosis), cancer or the congenital malformation of airways.

2.3. Data extraction and quality assessment

Two independent investigators reviewed and crosschecked the data from all RCTs. All eligible trials were summarized and formatted as a table. The standard table included the first author, country or region, publication time, sample size, intervention protocol, end-points, adverse events (AEs), and risk of bias. The risk of bias was assessed by two independent investigators using the Cochrane Collaboration's tool for assessing risk of bias, followed by crosschecking. The following information was extracted: random sequence generation, allocation concealment, blinding of participants and researchers, incomplete outcome data, selective reporting, and other biases. Consensus adjudication was sought from a third investigator if discrepancy persisted.

2.4. Statistical analysis

Key variables defined as endpoints and the demographic data were extracted from the pertinent RCTs. These data were checked for consistency and adequacy. The completed data base was entered into RevMan (5.3 version) software of the Cochrane collaboration.

In the meta-analysis of RCTs, dichotomous data were expressed as a risk ratio (RR) with 95% confidence intervals (CI). Continuous data were expressed as a mean difference (MD) with 95% CI. Only the

Table 3
The dosing schedules used in the trials included in this meta-analysis.

	1st month				2nd month				3rd month				4th month			
Wang, H. L. 2017																
Zhang, R. L. 2016																
Wu, H. 2016																
Liu, C. J. 2016																
Jiang, D. H. 2016																
Wu, L. X. 2015																
Li, Y. J. 2016																
Zheng, W. L. 2015																
Shen, Y. Z. 2015																
Zhou, L. G. 2014																
Namazova. 2014																
Licari, A2014																
Zhou, H. 2013																
Wang, Y. H. 2013																
Zhang, X.W. 2012																
Liu, D. X. 2012																
Zhang, L. 2010																
Ruan, D. Q. 2010																
Zhang, L. 2009																
Qu, J. P. 2009																
Peng, C. Y. 2009																
Aivazis, V,2002																
Burgio, Gr,1994																
Motta, G,1994																
Passali, D,1994																
Careddu,P,1994																
Careddu,P,1994a																
Caramia,G,1994																
Careddu,P,1992																

Dosage regimen: Blue areas: twice a day. Pink areas: once a day.

available data were analyzed in the present meta-analysis, while the missing data were discarded. The heterogeneity was assessed 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 $p < 0.1$ was considered as statistically significant. 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. The level of statistical significance was set at $\alpha = 0.05$ for Z test in this meta-analysis.

3. Results

3.1. Description of included trials

Fig. 1 shows the details of study selection process. Through the computerized database search and exclusion of duplicates or overlapping, 523 potentially relevant papers were identified and screened for retrieval. After reviewing the title and abstract, 408 studies were excluded, including reviews, pre-clinical studies or those not investigating the RRTIs. Moreover, 87 studies were rejected from the remaining studies due to the following reasons: 21 studies were not prospective RCTs; three RCTs included patients who were not at the age from 0 to 14; three RCTs assessed the patients who were diagnosed with primary or acquired immunodeficiency, such as DS; 18 RCTs assessed the patients who received medicines (immunomodulatory agents, macrolides or corticosteroids and so on) interfering with the curative effect; 40 RCTs reported patients with the history of chronic diseases (including cystic fibrosis), cancer or the congenital malformation of airways. In addition, one RCT didn't provide pre-set efficacy outcome. Finally, 29 studies consisting of 4344 children (0–14 years old) using PDT for the prevention or treatment of RRTIs were included in this meta-analysis (Table 2).

3.2. Characteristics of studies and participants

The patients in the experimental group received oral treatment with PDT in granule or liquid or tablet dosage forms on an empty stomach. Participates were received a fixed dosage of 400 mg once or twice a day in continuous treatment. In the loading dosage, the participates were initially received PDT 400 mg twice a day at acute phase (2–4 weeks), followed by 400 mg once a day at next phase. Table 3 shows the dosing schedules used in the trials included in this meta-analysis. Treatment duration ranged from 20 days (0.67 month) to 3.5 months. Fig. 2 summarizes the study quality assessment of trials by the Cochrane Risk-of-Bias Tool. In the 29 included RCTs, appropriate randomization methods were used in 15 trials, such as a randomization list generated by computer or by a random number. Only one study adequately described allocation concealment, and the rest of RCTs were unclear. Only eight RCTs were double-blind and placebo controlled, while the others were unclear or without placebo. Moreover, the risk of attrition bias was low across all studies. There was low risk of bias for selective reporting and other potential sources across all of the included studies.

3.3. Increased proportion of participants who had lower RTIs

A total of 24 RCTs evaluated the episode number of RTIs as outcome measures. A total of 1912 pediatric patients were assigned to the PDT treatment groups, whereas 1848 patients were assigned to the conventional treatment group. Fig. 3 shows that the numbers of patients whose episodes of RTIs are under the preset value (relapse of RTIs ≤ 0, 1, 2) for different followed-up period. It indicates that treatment with PDT resulted in a significant increase in the proportion of participants who had lower RTIs (RR 1.59, 95% CI 1.45–1.74, $I^2 = 51\%$, $p < 0.00001$) compared with the conventional treatment in a random-effects model.

We conducted subgroup analyses. The results showed that treatment with PDT significantly increased the proportion of participants with 0 episode during a follow-up period of 1–3 months (eight RCTs, RR 1.72, 95%CI 1.47–2.02, $I^2 = 46\%$, $p < 0.00001$). The proportion of participants whose episodes were ≤1 during a follow-up period of 4–6 months was also significantly increased with PDT treatment (eight RCTs, RR 1.70, 95% CI 1.36–2.12, $I^2 = 52\%$, $p < 0.00001$). Moreover,

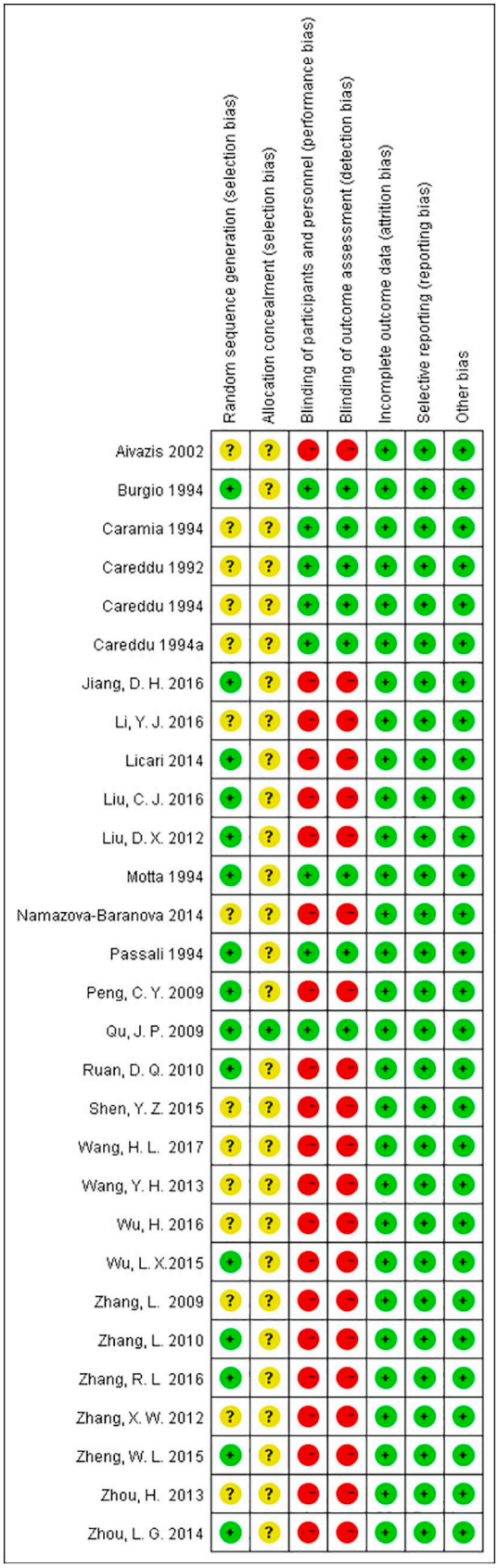

Fig. 2. Review authors' judgements about each risk of bias item for each included study.

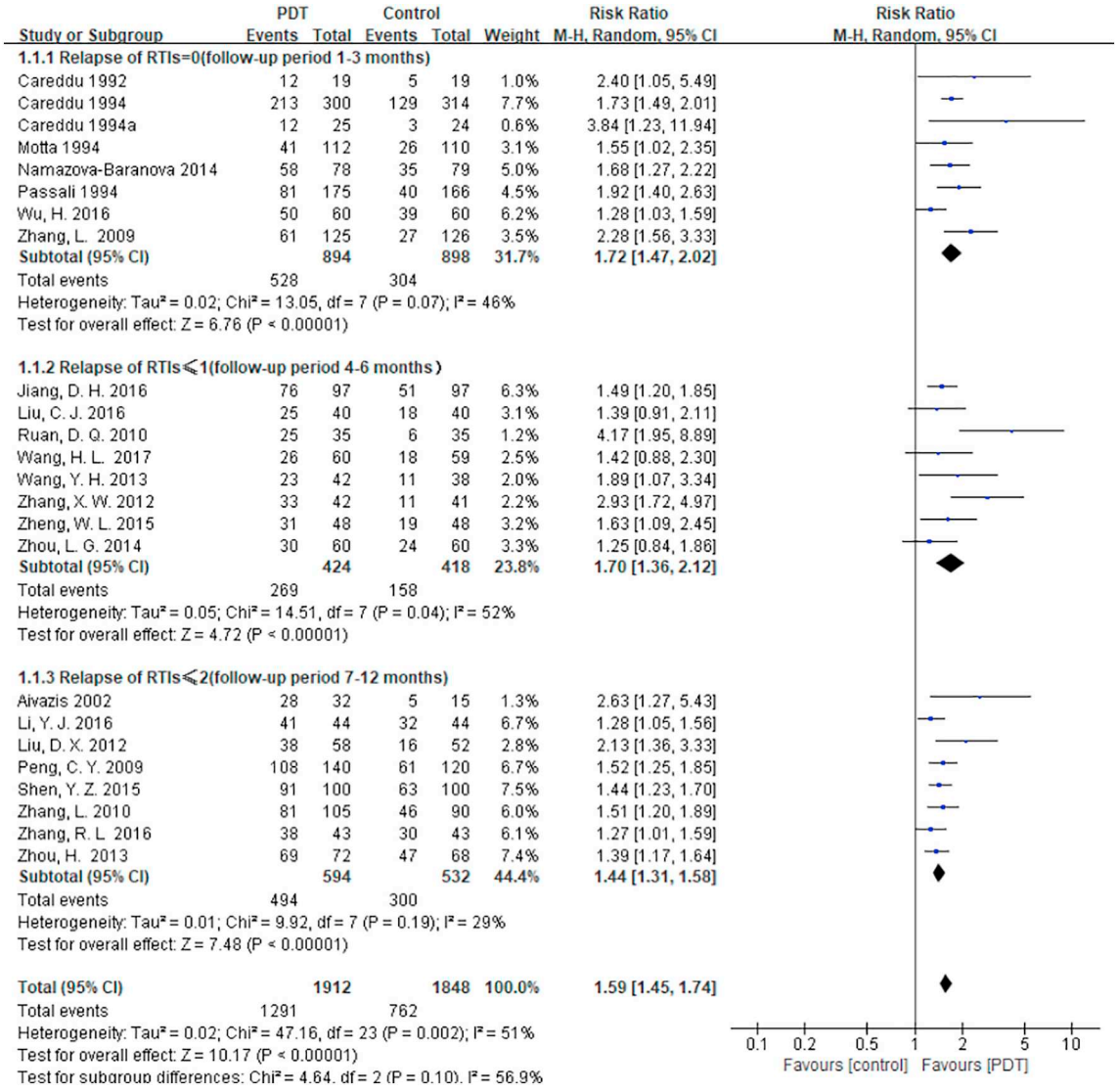

Fig. 3. Forest plots showing RR with 95% CI of the numbers of patients whose episodes of RTIs are under the preset value comparing with or without PDT in a random-effect model.

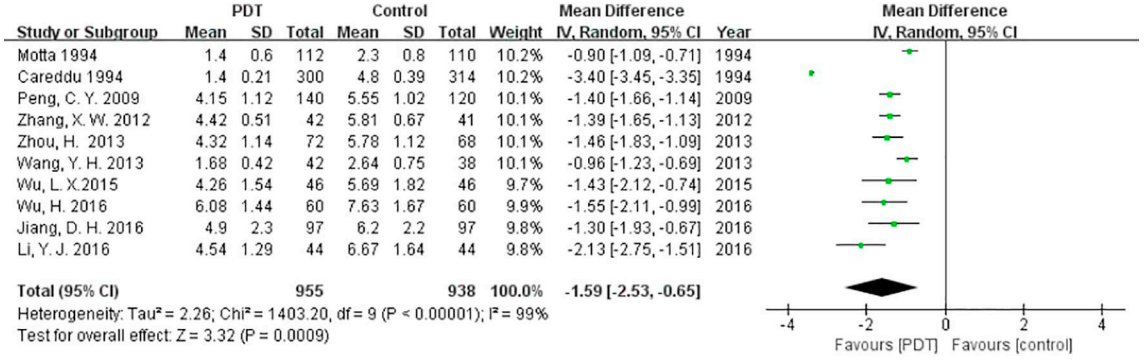

Fig. 4. Forest plots showing MD with 95% CI of the mean of day on cough compared with or without PDT in a random-effects model.

during a follow-up period of 7–12 months, the proportion of participants with ≤2 episodes was also higher than the control (eight RCTs, RR 1.44, 95%CI 1.31–1.58, I^2 = 29%, p < 0.00001).

3.4. Reduced cough and fever duration

Fig. 4 shows that the mean of days on cough was significantly decreased in the PDT treatment group (10 studies; 1893 participants; MD −1.59 days, 95% CI from −2.53 to −0.65, I^2 = 99%, p = 0.0009). This finding was similar to the fever duration in the PDT treatment group. Fig. 5 reveals that the mean of days on fever was significantly decreased (13 studies; 2399 participants; MD −1.68 days, 95% CI from −2.12 to −1.24, I^2 = 99%, p < 0.00001).

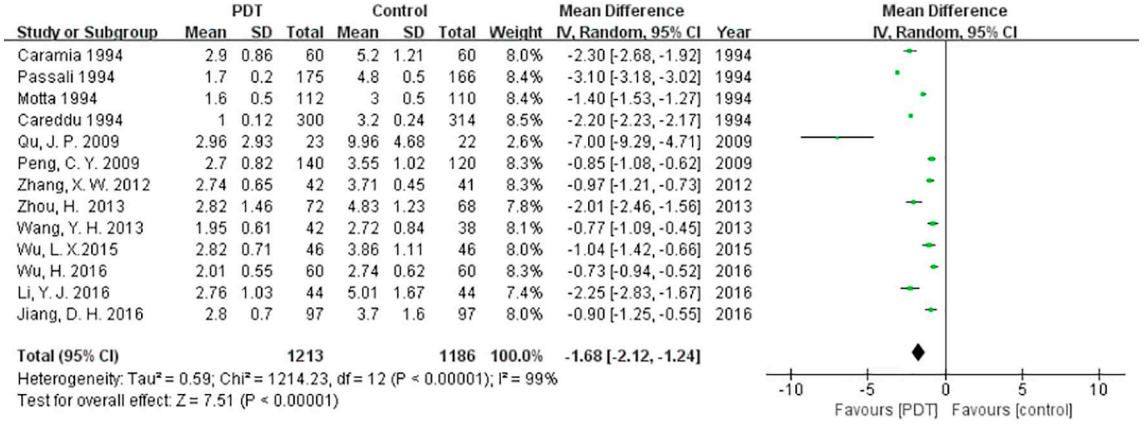

Fig. 5. Forest plots showing MD with 95% CI of the mean of day on fever compared with or without PDT in a random-effects model.

Fig. 6. Forest plots showing RR with 95% CI of the number of patients who were using antibiotics compared with or without PDT in a fixed-effects model.

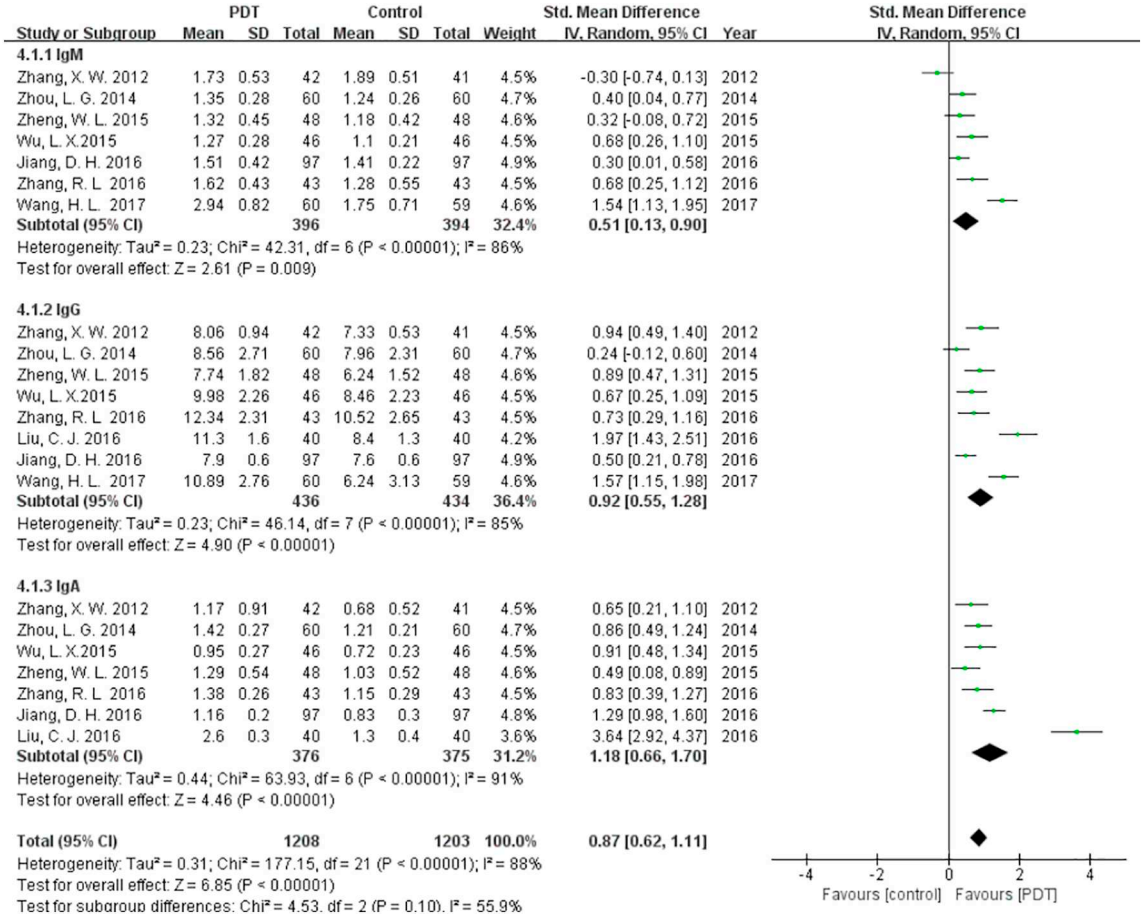

Fig. 7. Forest plots showing SMD with 95% CI for changes of serum levels of IgM, IgG and IgA compared with or without PDT in a random-effects model.

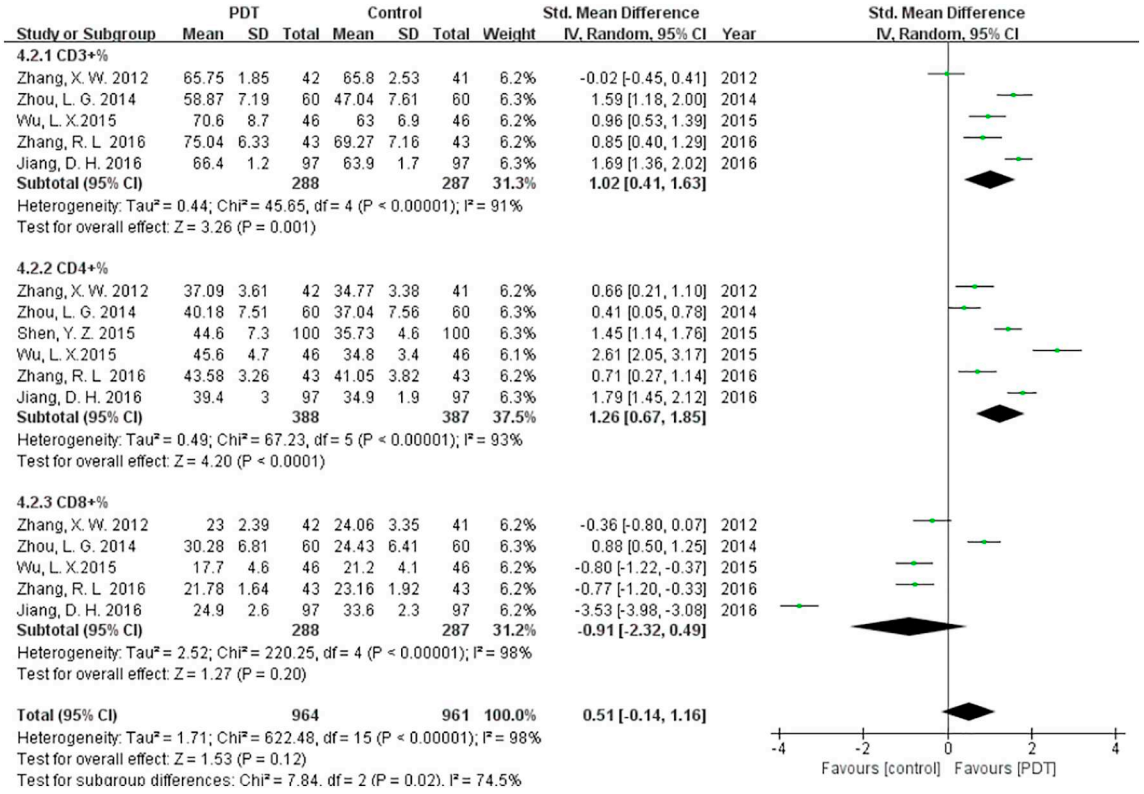

Fig. 8. Forest plots showing SMD with 95% CI for changes of T-lymphocytes CD3+, CD4+ and CD8+ levels compared with or without PDT in a random-effects model.

3.5. Decreased number of patients in using antibiotics

Six trials evaluated the number of patients in using antibiotics during the treatment and follow-up period as outcome measures. A total of 277 patients were assigned to the PDT treatment group, whereas 266 patients were assigned to the control group. Fig. 6 shows that PDT treatment significantly decreased the number of patients in using antibiotics (RR 0.41; 95% CI 0.32–0.51, $I^2 = 40\%$, $p < 0.00001$) compared with the conventional treatment in a fixed-effects model.

3.6. Increased level of serum immunoglobulin (IgM, IgG or IgA)

Some RCTs evaluated the changes of immunoglobulin levels. A total of 1208 patients were assigned to the PDT treatment group, whereas 1203 patients were assigned to the conventional treatment group. Fig. 7 shows that the PDT treatment significantly increased serum IgM (SMD 0.51, 95% CI 0.13–1.90; $I^2 = 86\%$, $p < 0.00001$), IgG (SMD 0.92, 95% CI 0.55–1.28; $I^2 = 85\%$, $p < 0.00001$) and IgA (SMD 1.18, 95% CI 0.66–1.70; $I^2 = 91\%$, $p < 0.00001$) levels compared with the conventional treatment.

3.7. Enhanced levels of T-lymphocyte subtypes (CD3+, CD4+)

Several RCTs provided data on CD3+, CD4+ or CD8+ counts. Fig. 8 shows that PDT treatment increased CD3+ counts (SMD 1.02%; 95% CI 0.41–1.63; $I^2 = 91\%$, $p = 0.001$) and CD4+ counts (SMD 1.26%; 95% CI 0.67–1.85; $I^2 = 93\%$, $p < 0.0001$) in a random-effects model. However, there were no significant differences in CD8+ T-lymphocyte levels (SMD -0.91%; 95% CI -2.32-0.49; $I^2 = 98\%$, $p = 0.20$) between the PDT and conventional treatment groups.

3.8. Safety

The results did not reveal any statistically significant increase in risk of AEs with PDT (RR = 1.05, 0.72–1.54; $I^2 = 0\%$, $p = 0.80$; 8294 participants). Instances of potential AEs to PDT were rare. Overall, 47 AEs occurred with PDT treatment in comparison to 45 with placebo. Most AEs affected the gastrointestinal tract and were mild and transient. Diarrhea was detected in 14/674 (2.1%), and vomiting was reported in 10/786(1.3%). In addition, skin rash, including urticarial and erythema, was diagnosed in 10/606 (1.7%), and both events were evenly represented between intervention and control arms (Fig. 9).

4. Discussion

As a synthetic dipeptide molecule with immunomodulatory properties, PDT is a highly purified molecule with high reproducibility among batches, and its pharmacokinetic study is more adequate compared with other immunomodulatory agents. PDT is rapidly absorbed by the gastrointestinal tract with a bioavailability of 45%, and it is eliminated unmodified via renal excretory mechanisms [12]. The result showed that the proportion of dendritic cells (DCs) expressing activation and costimulatory molecules was significantly higher in children receiving PDT plus antibiotics compared with the controls. A significant increase in tumor necrosis factor-alpha (TNF-α) and/or interleukin-12 (IL-12) secretion and expression of toll like receptor 2 was observed in PDT-treated children compared with the controls, followed by an increased release of pro-inflammatory cytokines by monocytes. In the PDT-treated group, the expressions of antimicrobial peptides and genes involved in the inflammatory response at the mRNA levels were also augmented compared with the controls. These findings all suggested that PDT can reduce the risk of early recurrences [13].

PDT administration has been associated with the upregulation of a number of genes involved in the activation of innate immune responses and antimicrobial activity [14]. Therefore, PDT may be effective on a specific category of people, such as children with RRTIs. In 2015, an Italian RCT enrolling 57 healthy children has shown that PDT doesn't prove to be statistically superior to placebo for the prevention of ARTI

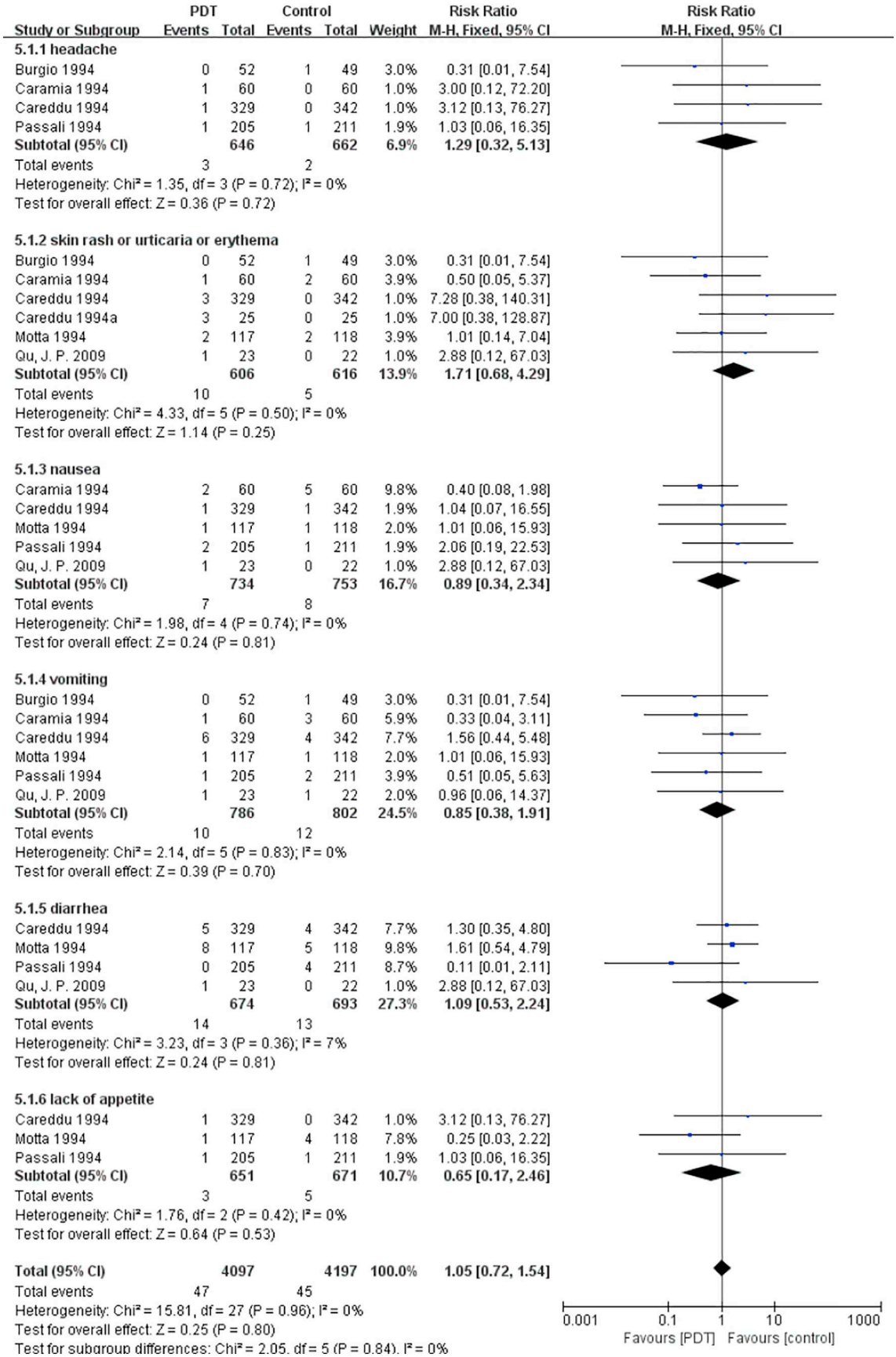

Fig. 9. Forest plots showing RR with 95% CI of the number of patients who had AEs compared with or without PDT in a fixed-effects model.

in a population of healthy children who just start kindergarten [10]. However, PDT administration together with standard antibiotics is associated with a favorable persistent immunomodulatory effect in children with CAP(Community-acquired pneumonia) [13]. Besides, DS is associated with several defects of both specific and non-specific immunities, and RRTIs are one of the major causes of morbidity in children with DS. The beneficial effects of PDT have also been confirmed by a study over a 90-day treatment period, showing a significant reduction in the number of days of fever, severity of the signs and symptoms of the acute episodes and consumption of antibiotics and antipyretic drugs [15].

When a child presents a higher susceptibility to RRTIs, first of all, pediatricians should suggest eliminate the possible pathogenic factors, such as environmental factors (indoor or outdoor pollution and passive smoking) or deficiency of vitamins, trace elements or calcium. Moreover, anti-bacterial or antiviral treatment can be conducted in the acute phase [3]. In addition, immunomodulatory agents, such as bacterial lysates and PDT, have been recommended as a useful option in management of RRTIs [16]. Modulation of the immune system can reduce the risk of recurrence and development of RRTIs. An important strategy for RRTI treatment is to increase the immune response or enhance the innate defense mechanism.

Our meta-analysis showed that PDT is beneficial in children with RRTIs. It can significantly reduce the relapses of RTIs and the use of antibiotics, and decrease the duration of fever and cough in children with RRTIs. In addition, PDT can improve the levels of serum immunoglobulin (IgG, IgA or IgM) and T-lymphocyte subtypes (CD3+, CD4+). These findings suggested that PDT administration might significantly increase the activity of the immune system, thus reducing the risk of recurrences in children with RRTIs. However, the levels of serum immunoglobulin and T-lymphocyte subtypes were only observed at the end of the treatment. Therefore, further studies should be carried out to evaluate how long this positive immune effect persists.

In our meta-analysis, PDT administration was safe, and the potential AEs were rare. Moreover, the risk of such AEs was the same between PDT-treated participants and controls, which was consistent with most studies reported. The post-marketing surveillance and literature showed that PDT has occasional damage to the digestive system, nervous system, skin and its appendages. No serious adverse events have been reported in human studies, except for one case of suspected enoch-Schönlein purpura [17]. However, no other AEs associated with autoimmune diseases have been reported so far.

Despite the encouraging result in our meta-analysis of PDT in RRTI treatment, several potential limitations should be pointed out. First, most the included trials had a poor methodological quality, such as lack of sufficient information on allocation concealment, lack of sufficient details on the randomization method and using non-blind method. Second, the heterogeneity was relatively high in some analysis. Different follow-up periods could only explain part of heterogeneity from the subgroup analysis in Fig. 3. The patients' characteristics at baseline, treatment duration and dosage of PDT and severity of RRTIs might also contribute to the high heterogeneity. Third, with regard to the potential for missing data, we made strenuous efforts to identify unspecified outcomes in measuring the data on the given figures and add the missing standard deviation that is estimated by other RCTs included in this meta-analysis [18].

In conclusion, based on published studies, our analysis showed that PDT was a safe and effective immunomodulatory agent for treatment of pediatric RRTIs. However, the results should be interpreted with caution because of the low evidence level. Further high-quality evidence and universally accepted standard from RCTs are necessarily required.

Contributorship statement

Hui Niu contributed in data collection, data-analysis and writing the paper; Rui Wang contributed in experiment design and protocol; Yuting Jia contributed in data collection and analysis; as a corresponding author, Yun Cai contributed in experiment design, protocol, data-analysis and writing.

Competing interests

None declared.

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Data sharing statement

The data was not contained unpublished data. The data sets used and/or analyzed during the study are available from the corresponding author on reasonable request.

Patient and public involvement

There are no patients or public involved. Not required.

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