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ORIGINAL RESEARCH

The effects of macrolides in children with reactive airway disease: a systematic review and meta-analysis of randomized controlled trials

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Purpose: Childhood reactive airway diseases (RADs) are concerning problems in children's airways and may be preceded by bronchiolitis and may progress to childhood asthma. The severity of the disease is indicated by deterioration in pulmonary functions, increased usage of rescue medications, and recurrent wheezing episodes. Macrolides have both antimicrobial and anti-inflammatory functions and have been used as adjunctive therapy in childhood RADs.

Patients and methods: We conducted a meta-analysis to evaluate the effect of macrolides in children with RAD. Literature searches were systematically conducted using an electronic database from inception to August 2018. The Cochrane review risk of bias assessment tool was used to assess the quality of each randomized controlled trial.

Results: Sixteen randomized controlled trials comprising 1,415 participants were investigated in this meta-analysis. Children treated with macrolide therapy showed significantly better pulmonary functions in both forced expiratory volume in one second (% predicted) (difference in means=–9.77, 95% CI=–14.18 to –5.35, $P<0.001$; $I^2=0\%$) and forced expiratory flow 25–75 (% predicted) (difference in means=–14.14, 95% CI=–26.11 to –2.18, $P=0.02$; $I^2=29.56\%$). In addition, the short-acting β-agonist usage days and recurrent wheezing risk were significantly lowered in children with macrolide treatment (standardized difference in means=–0.34, 95% CI=–0.59 to –0.09, $P=0.007$, $I^2=27.05\%$ and standardized difference in means=–0.53, 95% CI=–0.81 to –0.26, $P<0.001$, $I^2=0\%$, respectively). Furthermore, the growth of *Moraxella catarrhalis* from nasal swabs was less in children treated with macrolides (odds ratio=0.19, 95% CI=0.11–0.35, $P<0.001$). Children who took macrolides had a lower risk of adverse events (risk ratio=0.83, 95% CI=0.70–0.98, $P=0.024$, $I^2=0\%$).

Conclusion: This current meta-analysis suggested that adjunctive therapy with macrolides is safe and effective for achieving better outcomes in childhood RAD.

Keywords: macrolides, childhood, asthma, recurrent wheezing, bronchiolitis, pulmonary function, efficacy, reactive airway disease

Introduction

Asthma remains a significant burden in both developing and developed countries and causes morbidity and mortality.[1] Acute exacerbation in both partially and poorly controlled asthma is the major factor contributing to morbidity and the cost of insurance, particularly in children.[2] Childhood asthma is often preceded by acute, severe, and recurrent episodes of severe lower respiratory tract infections in the initial years of life.[3] Nearly one-third of preschool children present with recurrent wheezing during the first 5–6 years of life.[4] Among children diagnosed with recurrent wheezing or asthma, ~20% of them visit emergency departments (EDs), and 7% of them are

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hospitalized each year, which are major stresses for both families and health care resources.[5–7] Infants hospitalized with bronchiolitis are at significantly increased risk for both recurrent wheezing and childhood asthma.[8] There are overlapping characteristics and similarities among childhood asthma, recurrent wheezing and bronchiolitis, and they may be considered to be one disease in different periods of time in some children. Therefore, the differentiation of specific reactive airway disease (RAD) entities in clinical practice is often not possible.

There has been little progress in the treatment of asthma exacerbations and long-term care over the past 20 years, as well as limited evidence for the management and prevention of preschool wheezing. High doses of inhaled steroids administered early have been proved to prevent severe asthma exacerbations in adolescents and adults while posing a risk of diminished linear growth in children with asthma.[9,10] Furthermore, only hydration, oxygen, and the use of inhaled short-acting β2 agonists (SABAs) have shown evidence of being successful for the treatment of preschool childhood wheezing.[11,12] Finally, there has been no effective treatment to change the long-term disease course in childhood asthma, recurrent wheezing, and bronchiolitis. Thus, identification of a better treatment to alleviate the severity of both asthma exacerbation and recurrent wheezing is of clinical importance.

There is emerging evidence that both viral and bacterial agents play important roles in the pathogenesis of both asthma exacerbations in children and recurrent wheezing in young infants.[13–15] Viral agents such as rhinovirus are significant factors in disease progression from bronchiolitis to asthma and in triggering asthma exacerbations.[16] Atypical infections are common in pediatric severe asthma and severe chronic bronchitis and likely are pathogenic across the broad spectrum of RAD syndromes.[17–20] Of the causative pathogens, both *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are strongly associated with new-onset asthma, recurrent wheezing, refractory bronchitis, acute bronchiolitis, and asthma exacerbations in children.[18,21–24] It has been reported that *C. pneumoniae* infection is common in school-age children and the immune response to chronic *C. pneumoniae* infection may intercommunicate with allergic inflammation to exacerbate asthma symptoms.[15] In patients with asthma with *M. pneumoniae* infection, the use of macrolides may alleviate the symptoms of asthma. In addition, treatment with clarithromycin in patients with asthma who are colonized with mycoplasma and chlamydia species led to a reduction in pro-inflammatory and T-helper 2 cytokines, such as tumor necrosis factor-alpha, IL-5, and IL-12 mRNA, in bronchoalveolar lavage (BAL) and airway tissue.[25,26] Recently, a toxin produced by *M. pneumoniae*, the community acquired respiratory distress syndrome (CARDS) toxin was identified.[27] Although without statistical significance, Wood et al declared a strong correlation between poor asthma control and testing positive for CARDS toxin and concluded that CARDS toxin could deteriorate asthma symptoms.[28] In addition, the upper airway colonization with capsular polysaccharide bacteria can predict subsequent recurrent wheezing and asthma diagnosis at the age of 5 years.[29] These studies provide a foundation for the use of macrolides in children with asthma and recurrent wheezing.

In addition to the well-established antimicrobial activity of macrolides, they have also been characterized to have an anti-inflammatory effect.[30,31] The immunomodulatory activity of macrolides has been hypothesized to have a role in the therapy of chronic inflammatory airway diseases, such as asthma and COPD.[32,33] Previous serial studies[34,35] in adult asthma patients have shown the benefits of 6–12 weeks of azithromycin treatment in the improvement of overall asthma symptoms. They discussed both the anti-inflammatory and antimicrobial mechanism of azithromycin, and finally proved that the anti-inflammatory effects wane after the treatment is completed, whereas the antimicrobial effects persist at 1 year of follow-up.[35] Johnston et al reported that the early use of telithromycin in an acute asthma episode significantly improved symptom scores and lung function compared with a control group irrespective of the bacteriological status, implicating a non-antimicrobial mechanism.[36] A recent report also showed that azithromycin treatment during respiratory syncytial virus (RSV) bronchiolitis not only reduced airway IL-8 levels and overall respiratory morbidity but also prolonged the time to a third wheezing episode.[37]

A previous meta-analysis published by the Cochrane library tried to elucidate the role of macrolides for chronic asthma and reported positive effects for both forced expiratory volume in one second (FEV_1) and asthma symptoms;[38] however, each results included almost adult studies with only one child study in each result and may be insufficient to represent the true condition in children. Another meta-analysis only included children under 2 years of age, and the limited number of studies provided insufficient data for final analysis due to the heterogeneous outcomes between the included studies.[39] In addition, the analysis[39] included antibiotics other than macrolides and also showed no benefits. Such results may be related to the variability of adult asthma and childhood asthma. Therefore, it may be the

reason why there is currently no clear evidence that the use of macrolides in the treatment of childhood wheezing is of significant clinical benefit.

Since the two meta-analyses conducted in 2014, several new reports have been published within the past 4 years.[37,40–43] To update the published data and focus this issue precisely on the specific age group and the extended effects of macrolides, we conducted this detailed meta-analysis of the effects of macrolides in children with RAD, such as bronchiolitis, recurrent wheezing, and asthma.

Methods

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines (Table S1).[44] We searched the following databases from inception to the end of August 2018: Embase, PubMed, and the Cochrane Library and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). We used the keywords "Asthma" or "Chronic cough" or "infantile asthma" or "wheezing" or "wheez*" and "Erythromycin" or "Azithromycin" or "Zithromax" or "Clarithromycin" or "macrolide(s)" in our search. Our strategy is shown in Table S2. To ensure a comprehensive search, we did not limit the language, year or type of publication. Two authors (W-TL and S-JL) conducted the search independently, and disagreements were resolved through discussion with the third author (T-LY).

Study selection and methodological quality assessment

After the initial search, two independent reviewers (W-TL and T-LY) scanned each abstract from the search publications to identify trials that met the inclusion criteria for systematic review and meta-analysis. Two review authors (W-TL and T-LY) independently reviewed the full-text articles of the retrieved trials that met the inclusion criteria. The randomized controlled trials (RCTs) included met all of the following eligibility criteria: 1) focused on human children aged <18 years; 2) included a control group, including concurrent use of inhaled corticosteroid (ICS), Montelukast, long-acting and short-acting bronchodilators, in the study design; 3) included the use of a macrolide such as troleandomycin, erythromycin, azithromycin, or clarithromycin by the intervention group; 4) investigated the efficacy of macrolide treatment in children with asthma/recurrent wheezing/chronic bronchitis/acute bronchiolitis; and 5) provided data for clinical disease control and serological biomarkers change. We excluded the following: 1) articles irrelevant to the topic, 2) duplicate publications and populations, 3) trials of a crossover study design, and 4) studies without sufficient data for extracting or calculating the pooled analysis. Quality assessment of all included studies was conducted independently by four researchers (M-CT, H-HC, Y-JC, and HHL) using the Cochrane review risk of bias assessment tool.[45] The adequacy of randomization, allocation concealment, blinding methods, implementation of the intention-to-treat analysis, dropout rate, complete outcome data, selective data reporting, and other biases was assessed. Each domain was categorized as low, high, or unclear.

Data extraction and analysis

Five authors (M-CT, H-HC, Y-JC, HHL, and CYL) independently extracted the data from all included studies, and the following data were collected: first author's name, year of publication, country of publication, number of patients, age of patients, sex ratio of patients, number of patients in the intervention and control groups, type of intervention (including the length of treatment), concomitant treatment and baseline medications, clinical outcome measures (including the timing of the outcome in relation to the treatment and the outcome persistent after treatment), and severe adverse effects.

Meta-analysis

Because of the significant heterogeneity expected among the participants of all the included studies, a random-effect model was used rather than the fixed-effect model.[46] Comprehensive Meta-Analysis software version 3 (Biostat, Englewood, NJ, USA) was used for all the analyses. Dichotomous data were calculated using an OR or risk ratio with 95% CI. Difference in means (MD) or standardized difference in means (SMD) with 95% CI was used for analysis of continuous outcomes. Heterogeneity was quantified with the Q test and I^2 statistics to evaluate the dispersion of the true effect of the included trials.[47] Publication bias was evaluated by visual inspection of the funnel plots and Egger's tests.[48] Subgroup analysis was performed to further analyze the effects of clinical variables as possible origins of heterogeneity, such as duration of macrolides, type of macrolides, and the different age group. Finally, meta-regression analyses were conducted only when data could be assessed throughout more than five trials.

Results

Description of studies and quality assessment

Initial database searching disclosed the following results: 568 studies in PubMed, 1,363 studies in Embase, 440 studies

in Cochrane, and 60 studies in CINAHL. Of these 2,431 articles, we excluded 939 articles because of the duplications of studies. Of the remaining 1,492 articles, we excluded another 1,437 studies on the basis of title and abstract alone and retained 55 studies. Among the 55 studies, 16 studies were non-RCTs, 8 studies were without sufficient data for pooled analysis, 7 studies included participants over 18 years of age, 1 study used antibiotics other than macrolides as intervention medications, and the baseline controller medications between the intervention and control group in one study were different. Therefore, a total of 22 RCTs were included in our systemic review. Figure 1 shows the searching process. Most of the included studies showed low bias using the Cochrane assessment tool.

Demographics

Among the 22 RCTs, a total of 2,091 participants with ages ranging from 0 to 18 years were enrolled. These studies were held worldwide, with eight studies in the USA;[32,37,42,49–51] three trials in Brazil;[52–54] two trials each in Australia/New Zealand[55,56] and Bangladesh;[57,58] and one trial each in the Philippines,[59] Taiwan,[40] Turkey,[60] Greece,[61] Italy,[62] Denmark,[43] and Canada.[41] Eight RCTs enrolled children with an underlying asthma diagnosis with or without hospitalization or an ED visit, mostly aged more than 5 years;[32,40,49–51,59,61,62] 11 studies enrolled toddlers hospitalized because of bronchiolitis aged less than 3 years[37,41,43,52–58,60,63,64] and 2 trials recruited children aged 12–71 months with recurrent wheezing with an ED visit.[41,42] Three studies shared identical patient groups with different outcome assessments.[37,56,63] Other characteristics of the included trials are listed in Table 1.

Intervention

Among the 22 eligible studies using macrolides as adjunctive therapy, azithromycin was the most commonly used macrolide in the included studies, comprising 13 trials.[37,41–43,51–56,62–64] Five studies used clarithromycin.[32,40,59–61] Two studies used troleandomycin.[49,50] Two studies used erythromycin.[57,58] The dose and duration of supplemented macrolides were in the following ranges: 5–12 mg/kg/day for 3–14 days and 30 mg/kg/week for 8 weeks, 5–15 mg/kg/day for 5 days to 4 weeks and 250 mg/day or 250 mg on alternate days for 2 weeks or 12 weeks with azithromycin, clarithromycin, and troleandomycin, respectively. Systemic steroids were prescribed concomitantly in school-aged children with underlying asthma in two trials[49,50] and in preschool children with hospitalizations/ED visits in two trials,[41,52] respectively. ICSs were used in most studies (6/7) in school-aged children with an asthma diagnosis and all trials (3/3) in preschool children with recurrent wheezing. For studies that enrolled toddlers (all <2 years of age) hospitalized for acute bronchiolitis, an ICS was not used in any of the studies

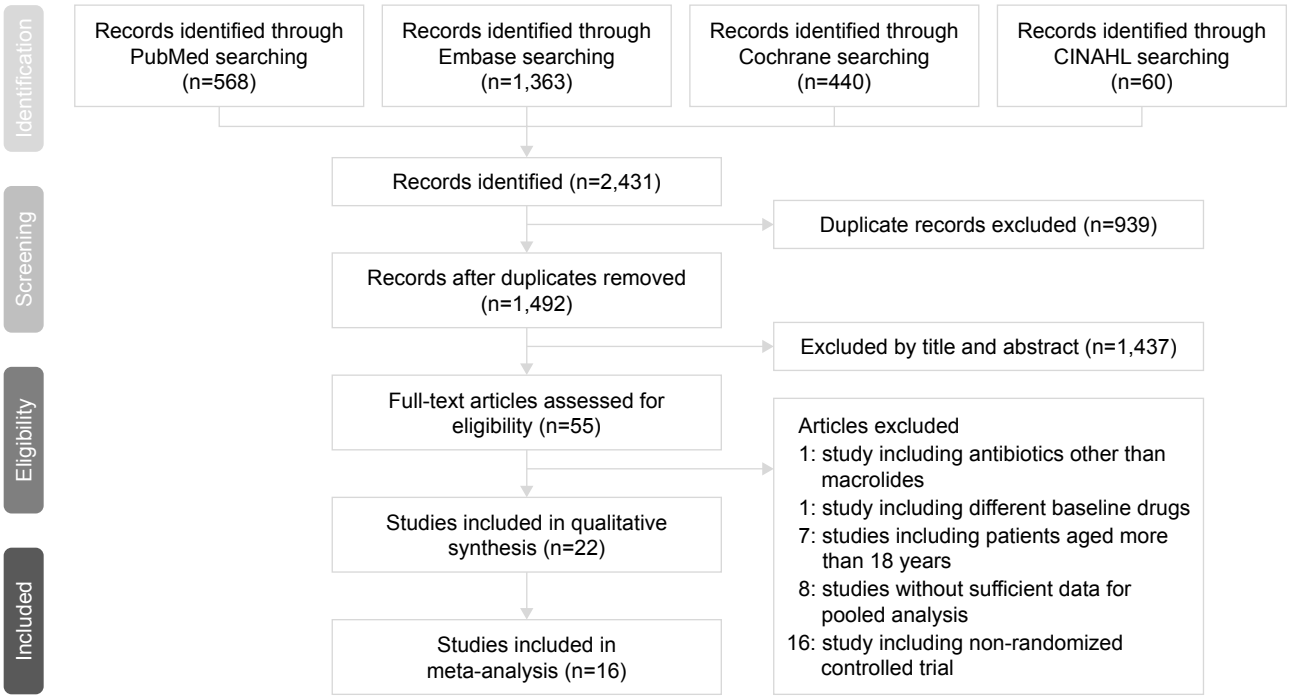


Figure 1 The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram.

(0/9), and concomitant non-macrolide antibiotics were used in the minority (3/9).

Outcome measurement

Meta-analysis investigating the long-term effects of macrolides and placebo among children with asthma, recurrent wheezing and bronchiolitis

Is macrolide treatment beneficial to the pulmonary function of children with asthma and recurrent wheezing?

A total of four studies[49,50,59,62] including 59 children and 3 studies[50,59,62] including 49 children were enrolled for meta-analysis to determine the FEV_1% and forced expiratory flow (FEF) 25%–75% after treatment. All the participants in the corresponding trials were children with asthma, and children in almost all (three of four) studies were aged more than 6 years. Two[49,50] of the four studies enrolled children with severe, steroid-dependent asthma. The post-treatment FEV_1% of children with asthma was significantly higher in the macrolide group than those in the placebo group (MD=–9.77, 95% CI=–14.18 to –5.35, $P<0.001$; $I^2=0\%$, $\tau=0.000$) (Figure 2A). Although there was publication bias (t value=12.31, $df=2$, $P=0.007$), the results of the meta-analysis did not change (MD=–10.33, 95% CI=–14.60 to –6.06) after the trim and fill test (with two potentially missing studies to the left of the mean). The significance of the results became nonsignificant after deleting the study by Chiong et al[59] who enrolled children with FEV_1% <80% before treatment and used clarithromycin 15 mg/kg/day for 3 weeks (MD=–5.03, 95% CI=–15.67–5.61, $P=0.354$). In general, macrolides were seldom used for more than 2 weeks for the purpose of antimicrobial effects. In addition, we found that participants in the included studies (listed in Table 1) could be approximately grouped into two categories according to the duration of treatment: less than 3 weeks (12 articles) and more than 3 weeks (8 articles). Therefore, we tried to do subgroup analysis according to the duration of macrolides, although the heterogeneity was not significant. The results of subgroup meta-analysis of trials showed a significantly better treatment effect on FEV_1% in children who took macrolides for more than 3 weeks (MD=–10.09, 95% CI=–14.75 to –5.43, $P<0.001$; $I^2=0\%$) (Figure 2B). Meanwhile, the post-treatment FEF 25%–75% of children with asthma in the macrolide group was also better than those in the placebo group (MD=–14.14, 95% CI=–26.11 to –2.18, $P=0.02$; $I^2=29.563\%$, $\tau=6.532$) (Figure 2C). There was no significant publication bias (t value=0.086, $df=1$, $P=0.945$). The result became nonsignificant by removing the studies by Piacentini et al (MD=–14.01, 95% CI=–29.36 to 1.34, $P=0.074$)[62] or Chiong et al (MD=–2.29, 95% CI=–21.12 to 16.55, $P=0.812$).[59]

Does macrolide therapy decrease the need for rescue SABA usage?

In the four RCTs[37,41,43,60] including 430 participants, macrolides were associated with significantly fewer SABA usage days throughout the follow-up periods (SMD=–0.34, 95% CI=–0.59 to –0.09, $P=0.007$) (Figure 3A). There was neither significant heterogeneity (Q value=4.112, $df=3$, $P=0.250$, $I^2=27.047\%$, $\tau=0.133$) nor publication bias (t value=1.526, $df=2$, $P=0.266$). However, after removing data from the study by Stokholm et al,[43] which used azithromycin 10 mg/kg/day for 3 days in children aged 1–3 years, the results showed no significant difference between the macrolides and placebo group (SMD=–0.30, 95% CI=–0.66 to 0.06, $P=0.098$). The included studies were composed of preschool children hospitalized for bronchiolitis or who presented to the ED with wheezing.

It was possible to perform subgroup analysis by dividing the four trials into two groups according to the type of macrolides. Azithromycin (n=356) was used in three RCTs. The results showed significantly less SABA usage days in children with bronchiolitis using macrolides (SMD=–0.32, 95% CI=–0.53 to –0.11, $P=0.003$, $I^2=0.000\%$) (Figure 3B). However, there were insufficient data for studies using non-azithromycin macrolides since only one study used clarithromycin.

Does macrolide treatment lower the risk of recurrent wheezing?

For the risk of recurrent wheezing, 115 participants in the macrolides group showed significantly less recurrent wheezing (SMD=–0.53, 95% CI=–0.81 to –0.26, $P<0.001$, $I^2=0\%$, $\tau=0.000$) (Figure 4) than the 99 patients in the placebo group among the selected three studies.[53,54,61] There was no significant publication bias (t value=6.522, $df=1$, $P=0.097$). The enrolled children in the three studies were composed of school-aged children with intermittent mild to persistent asthma[61] and toddlers less than 1-year-old hospitalized for acute bronchiolitis and the follow-up time were 3 months in two studies and 6 months in one study.[53,54]

Does macrolide therapy alter the upper airway bacteria?

In three studies[55,56,64] including 325 children less than 2 years of age hospitalized for bronchiolitis, patients in the macrolides group showed significantly less *Moraxella catarrhalis*

Table 1 Characteristics of randomized controlled trials using macrolides on children with asthma, recurrent wheezing and bronchiolitis

Reference	Country	Population (M%:F%)	Age (range/mean±SD)	Intervention:control
Ball et al 1990[49]	USA	15 children severe, steroid-requiring asthma	8–18 years (13.1±3.0) 13.8±3.0 vs 12.4±3.2	5:5:5
Kamada et al 1993[50]	USA	18 children severe, steroid-requiring asthma (36%:64%)	6–17 years 14.3±2.9 vs 11.3±2.7	6:7:5
Fonseca-Aten et al 2006[32]	USA	43 children history of recurrent wheezing/asthma with an AE to ED (74%:26%)	4–17 years 112.5 (62–187) vs 100 (50–181) months	22:21
Piacentini et al 2007[62]	Italy	16 children hospitalized for asthma (75%:25%)	13.9±2.4 vs 12.9±2.6	8:8
Tahan et al 2007[60]	Turkey	21 infants hospitalized for RSV bronchiolitis, first episode of wheezing (57%:43%)	≤7 months 2 (1–6) vs 2 (1–7)	12:9
Rasul et al 2008[57]	Bangladesh	60 children hospitalized for bronchiolitis (72%:28%)	0–2 years (80% below 6 months)	15:22:23
Strunk et al 2008[51]	USA	55 children moderate-to-severe persistent asthma (58%:42%)	6–18 years (11.2±2.6)	17:19:19
Kabir et al 2009[58]	Bangladesh	295 children hospitalized for breathing difficulty/chest indrawing (73%:27%)	<24 months	99:99:97 IV ampicillin: oral erythromycin: no antibiotics (P-Ab: O-Ab: N-Ab)
Koutsoubari et al 2012[61]	Greece	40 children intermittent/mild persistent asthma with an acute AE (45%:55%)	6–14 years 9.1±2.7 vs 8.4±2.5	18:22
Pinto et al 2012[52]	Brazil	184 infants hospitalized with AB (60%:40%)	≤2 months 3.1±2.2 vs 3.1±2.3	88:96
Mccallum et al 2013[55]	Australia/ New Zealand	96 children hospitalized, O_2-required bronchiolitis (68%:32%)	≤18 months 5.3 (3–9.4) vs 5 (3–8.5)	50:46
Chiong-Manaysay and Andaya 2014[59,a]	Philippines	23 children with FEV_1 <80% before treatment	Children	13:10

Intervention	Concomitant/baseline medication (I:C) %	Outcome measure	Severe adverse events (%)
Troleandomycin 250 mg QD × 2 days the QOD × 7 times, totally 2 weeks	Methyl-prednisolone 40 mg/1.73 m^2	Steroid dose reduction, symptoms scores, morning plasma cortisol concentration, FEV_1, FVC, TGV, methacholine PC_{20}, eosinophil count after 2 weeks, methylprednisolone clearance	Nil
Troleandomycin 250 mg QD or QOD depending on steroid protocol for 12 weeks	Prednisolone ≥20 mg QOD, bronchodilator ≥4 times/day, theophylline, ICS 500–1,000 μg BID	Steroid dose reduction, symptoms scores, need for extra prednisolone, PEFR, pre-bronchodilator FEV_1, FEF 25%–75%, methacholine PC_{20}, morning plasma cortisol concentration, urinary cortisol excretion, bone density, hip flexor strength after 12 weeks	Abnormal liver function (7.6%)
Clarithromycin 15 mg/kg/day, BID for 5 days, orally	SABA (39 of 43), LABA (3 of 43), and/or ICS (12 of 43)	serum/nasopharyngeal aspirates: TNF-α, IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, GM-CSF, RANTES, eotaxin, MIP-1α, MIP-1β, MCP-1; *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* detection in nasopharyngeal swabs/serologic test; dyspnea, wheeze, cough, asthma score	NR
Azithromycin 10 mg/kg QD for 3 consecutive days/week × 8 weeks	ICS (fluticasone, 100–200 μg/day; beclomethasone dipropionate, 200–400 μg/day), SABA as needed	FEV_1, FVC, FEF 25%–75%, bronchial hyper-responsiveness (expressed as the dose–response slope of FEV_1 fall after hypertonic saline inhalation, and induced sputum)	NR
Clarithromycin (15 mg/kg) QD × 3 weeks	β2-agonist (when SpO_2 <94%, RR >60 breaths/min, wheezing on auscultation, respiratory distress)	Primary outcome: LOS; duration of need for O_2, IVF and β2-agonist Secondary outcomes: changes in the IL-4, IL-8, eotaxin, IFN-γ levels, readmission rate 6 months after discharge	NR
Erythromycin orally	O_2 (for those with SpO_2 <95%) and nebulization	Progress of the symptoms after 72 hours, progress of the signs after 72 hours, outcomes of bronchiolitis (improved, deteriorated, hospital stay)	NR
Azithromycin 250 mg QD (for those 25–40 kg) or 500 mg QD (for those >40 kg)	Budesonide 400–800 μg BID; Serevent Diskus® 50 μg BID (run-in/post randomized)	Primary outcome: time to inadequate asthma control *M. pneumoniae*, *C. pneumoniae* detection in nasal washes: PCR assays	NR
P-Ab (50 mg/kg/dose 6 hourly IV) O-Ab (10 mg/kg/dose 6 hourly)	Nebulized salbutamol at 0.15 mg/kg/6–8 hours, O_2 inhalation (SpO_2 <90%), IVF maintenance	18 symptoms/signs which were graded on a two-point recovery scale of "rapid" and "gradual", indicating improvement within "four days" and "beyond four days", respectively	NR
Clarithromycin 15 mg/kg × 3 weeks	Prophylactic treatment according to asthma control level (GINA) ICS (61.1:59.1)	Primary outcome: days without symptoms within subsequent 12 weeks. Secondary outcome: symptom-free days after first AE, number/severity of periods with loss of control, time to first loss of control, PEFR variability, duration of the index episode, FEV_1, mean daily morning PEFR; RT-PCR in nasal wash samples	NR
Azithromycin 10 mg/kg/day × 7 days	Antibiotics (4.5:6.3); Steroid (4.5:7.3); bronchodilator (20.5:21.8)	Primary outcomes: LOS, duration of O_2 Other variables: antibiotic use, broncho-dilators use, admission to the PICU, immunofluorescence for adenovirus, parainfluenza, influenza, RSV	NR
Azithromycin (30 mg/kg), single large dose of oral liquid	Antibiotics (72.0:70.0); Supplemental IVF (38.0:41.0)	Primary endpoints: LOS, duration of O_2 Other outcomes: any respiratory-related readmissions in 6 months of discharge, identification of respiratory viruses and bacterial pathogens (RT-PCR/culture)	Nil
Clarithromycin 15 mg/kg/day bid × 3 weeks	NR	Asthma Control Test questionnaires and spirometry (FVC, FEV_1, FEV_1/FVC, FEF 25%–75% and PEFR) prior medication and after the study period	NR

(*Continued*)

Table 1 (*Continued*)

Reference	Country	Population (M%:F%)	Age (range/mean±SD)	Intervention:control
Bacharier et al 2015[42]	USA	443 children histories of recurrent, severe wheezing (62%:38%)	12–71 months (41.5±16.5) 42.5±16.4 vs 40.2±16.6	223:220 RTIs 473:464
Beigelman et al 2015[37]	USA	39 infants hospitalized with RSV bronchiolitis (59%:41%)	1–18 months (3.8±2.9) 3.7±3.7 vs 3.9±2.0	19:20
Beigelman et al 2015[63]	USA	39 children hospitalized with RSV infection (59%:41%)	1–18 months (3.8±2.9) 3.7±3.7 vs 3.9±2.0	19:20
Mccallum et al 2015[56]	Australia/ New Zealand	219 children hospitalized with bronchiolitis (62%:38%)	≤24 months 5.7 (3–10) vs 5.6 (3–9)	106:113 (LOS/6-month readmission) 59:74 (O_2 duration) 100:110 (day 21 clinical review)
Silveira D'Azevedo V et al 2016[53,a]	Brazil	91 infants hospitalized with AB	<12 months	51:40
Stokholm et al 2016[43]	Denmark	72 children recurrent asthma-like symptoms, troublesome lung symptoms ≥3 days (65%:35%)	1–3 years 2.0±0.6	74:74 episodes
Wan et al 2016[40]	Taiwan	56 children with mild persistent asthma (63%:37%)	5–16 years 10.1±3.1 vs 10.2±3.1	36:20
Zhou et al 2016[64]	USA	39 infants hospitalized with first RSV bronchiolitis (59%:41%)	1–18 months (3.8±2.9) 3.7±3.7 vs 3.9±2.0	19:20
Mandhane et al 2017[41]	Canada	222 children presenting to ED with wheezing (72%:28%)	12–60 months 34.8±13.6 vs 30.5±13.9	110:112 (primary analysis); 87:82 (secondary analysis)
Pinto et al 2017[54,a]	Brazil	83 infants hospitalized with AB	<12 months	46:37

Note: [a]Studies have been only reported as abstracts.

Abbreviations: AB, acute bronchiolitis; AE, acute exacerbation; AGE, acute gastroenteritis; BHR, bronchial hyper-responsiveness; BID, twice per day; C, control; DRS, dose response slope; ECP, eosinophil cation protein; ED, emergency department; F, female; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FeNO, fractional exhaled nitric oxide; FEF 25%–75%, forced expiratory flow between 25% and 75% of vital capacity; GINA, Global Initiative For Asthma; GM-CSF, granulocyte-macrophage colony stimulating factor; I, intervention; ICS, inhaled corticosteroid; IL, interleukin; ICU, intensive care unit; IFN, interferon; IV, intravenous; IVF, intravenous fluid; LABA, long-acting inhaled β-agonist; LOS, length of stay; LRTI, lower respiratory tract infection; LTRA, leukotriene receptor antagonist; M, male; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; methacholine PC20, concentration of methacholine required to induce a 20% decrease in FEV_1; NR, not reported; PEFR, peak expiratory flow rate; QD, every day; QOD, every other day; RR, respiratory rate; RSV, respiratory syncytial virus; RTI, respiratory tract infection; RT-PCR, real-time polymerase chain reaction; SpO_2, saturation of peripheral oxygen; SABA, short-acting β-agonist; TGV, thoracic gas volume.

by nasal swab (OR=0.19, 95% CI=0.11–0.35, $P<0.001$) (Figure 5). There was neither significant heterogeneity (Q value=0.731, I^2=0%, P=0.694, τ=0.000) nor publication bias (t value=4.660, df=1, P=0.134). The significance was not changed after removing any single study.

Adverse events

Compared with the placebo, participants in the macrolides group were associated with a lower risk to develop any adverse events (risk ratio=0.83, 95% CI=0.70–0.98, P=0.024, I^2=0%, τ=0.000, RCTs=7) (Figure 6A).

Intervention	Concomitant/baseline medication (I:C) %	Outcome measure	Severe adverse events (%)
Azithromycin 12 mg/kg/day × 5 days	Albuterol 4 times daily for the first 48 hours/whenever needed at any time during the RTI	Primary outcome: number of RTIs not progressing to a severe LRTI (prescription of oral corticosteroids) Secondary outcome: numbers of urgent care/ED visits, hospitalizations. Symptom scores, albuterol use, time to second RTI	Nil
Azithromycin 10 mg/kg/day × 7 days then 5 mg/kg/day × 7 days	Antibiotic treatment (0:2); hypertonic saline treatment (1:0)	Primary outcomes: serum and nasal lavage IL-8 levels, proportion of participants with ≥2 additional wheezing episodes after treatment Secondary outcomes: proportion of participants with ≥3 wheezing episodes, with diagnosed asthma, being-prescribed with ICS, the time to second and third episode, the number of, ED visits for respiratory symptoms, courses of OCS, days of rescue albuterol, days with respiratory symptoms	Nil
Azithromycin 10 mg/kg/day × 7 days then 5 mg/kg/day × 7 days	Antibiotic treatment (0:2); hypertonic saline treatment (1:0)	RSV load in nasal lavage samples obtained on randomization, day 8, and day 15	Nil
Azithromycin 30 mg/kg/dose weekly × 3 times	Nonmacrolide antibiotics prescribed prior to hospital (45.0:42.0); during hospital (61.0:60.0); IVF (23.0:20.0)	Primary endpoint: LOS, duration of O_2, day 21 clinical review, 6 months readmission; microbiology: Nasopharyngeal swabs for virus/bacteria (RT-PCR/culture)	Nil
Azithromycin × 7 days	NR	Wheezing and hospitalization in a follow-up 1, 3, and 6 months after the AB	NR
Azithromycin 10 mg/kg/day × 3 days	ICS (84%:80%); Montelukast (64.0:57.0)	Primary outcome: duration of episodes of troublesome lung symptoms after initiation of treatment Secondary outcomes: time from treatment to the next episode of troublesome lung symptoms, episodes that turned into severe AE (need for oral steroids/hospitalization), and the duration of β2 agonist use after treatment	1:1 Hospitalized for AGE: 4 days after randomized Hospitalized for pneumonia: 20 days after randomized
Clarithromycin 5 mg/kg/day × 4 weeks	Fluticasone propionate 50 μg/puff bid	Childhood asthma control test, FEV_1, FEF 25%–75%, FeNO, total IgE, absolute eosinophil count, ECP level	NR
Azithromycin 10 mg/kg/day × 7 days then 5 mg/kg/day × 7 days	Antibiotic treatment (0:2); hypertonic saline treatment (1:0)	Recurrent wheezing: assessed monthly over a year following the initial episode Microbiome sequencing ≥ changes in nasal lavage microbial communities following the study treatments	Nil
Azithromycin 10 mg/kg/day at day 1 then 5 mg/kg/day × 4 days (day 2–5)	Prior ED: ICS (62.7:58.9) SABA (35.5:36.6); At ED discharge: SABA (79.1:73.2) OCS (59.1:62.5) ICS (57.3:50.9)	Primary outcome: time (days) to respiratory symptoms resolution Secondary outcomes: the number of days children used a SABA during the 21 day follow-up, time to disease exacerbation during the following 6 months	Nil
Azithromycin × 7 days	NR	LOS, identification of respiratory viruses, recurrent wheezing/hospital readmission post-AB	NR

There was no significant publication bias (t value=1.525, df=5, P=0.188). After removing the study by Mandhane et al,[41] the results showed no significant difference between the macrolides and placebo groups (risk ratio=0.87, 95% CI=0.57–1.32, P=0.517). Most of the reported adverse events were related to gastrointestinal upset, such as nausea, vomiting, and abdominal pain. However, there were no enough data to do subgroup analysis according to the category of adverse events. It was possible to perform subgroup analysis according to the type of macrolides and

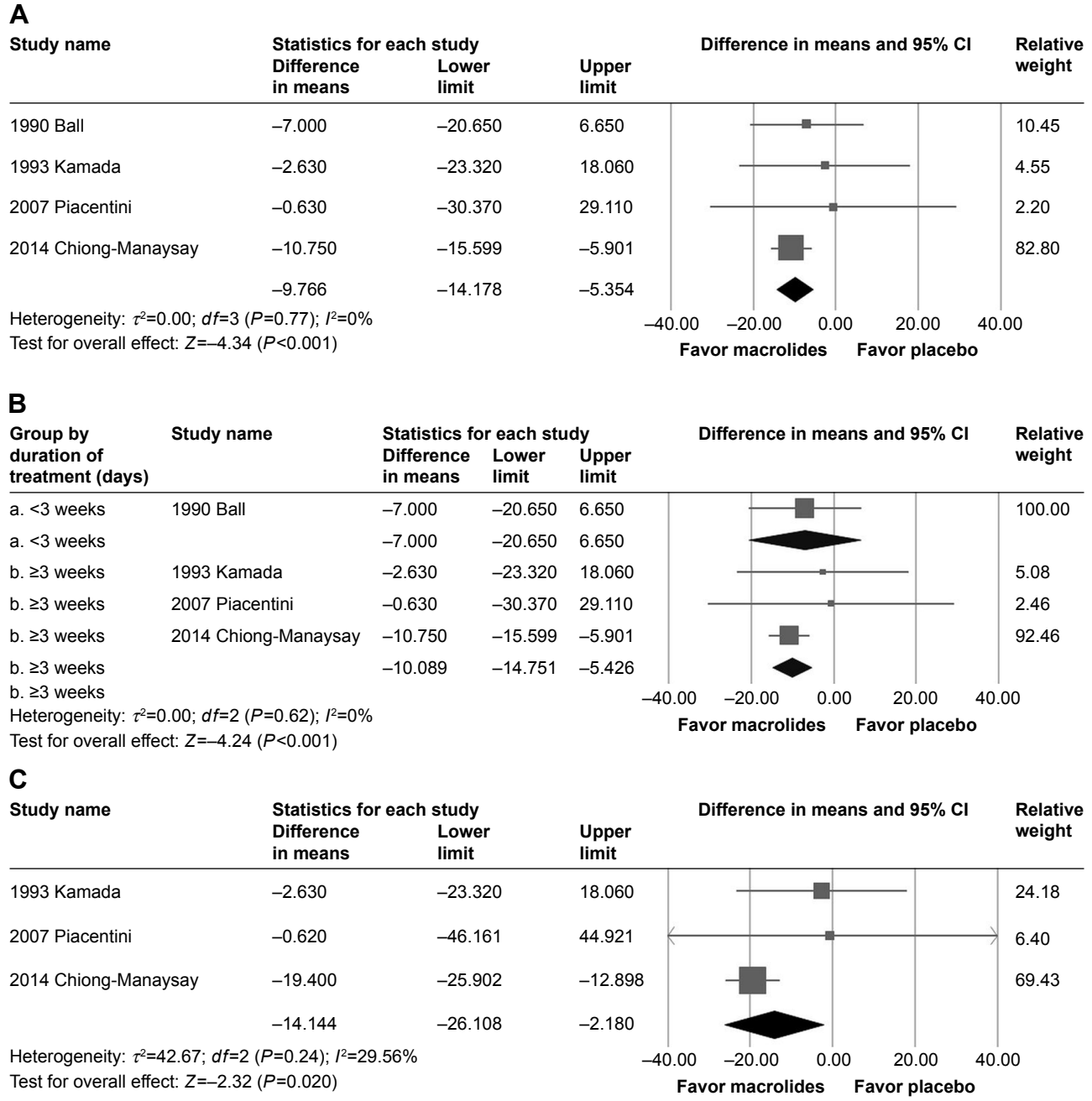


Figure 2 (**A**) Forest plot of the decreased forced expiratory volume percentage (FEV_1%) between the macrolides group and the placebo group. (**B**) Forest plot of subgroup analysis of FEV_1% by the duration of macrolides. (**C**) Forest plot of the decreased forced expiratory flow (FEF) 25%–75% between the macrolides group and the placebo group.

the age of participants. The results showed that participants taking azithromycin (risk ratio=0.83, 95% CI=0.70–0.98, *P*=0.024, RCTs=5) but not troleandomycin (risk ratio=1.00, 95% CI=0.12–8.61, *P*=1.000) had lower risk of adverse effects (Figure 6B). Preschool children also had a lower risk of developing any adverse events (risk ratio=0.82, 95% CI=0.70–0.97, *P*=0.021, RCTs=4) but school-aged children did not (risk ratio=1.458, 95% CI=0.252–8.428, *P*=0.674) (Figure 6C).

Meta-regression

To examine the heterogeneity of the present analysis, we performed a meta-regression analysis using the male sex ratio and the duration of macrolides as moderators in the single meta-regression. We found that the effect of macrolides on the adverse events was not significantly confounded by the male sex ratio (slope=–0.549, *P*=0.183) (Figure S1) and the duration of macrolides (slope=0.021, *P*=0.326) (Figure S2).

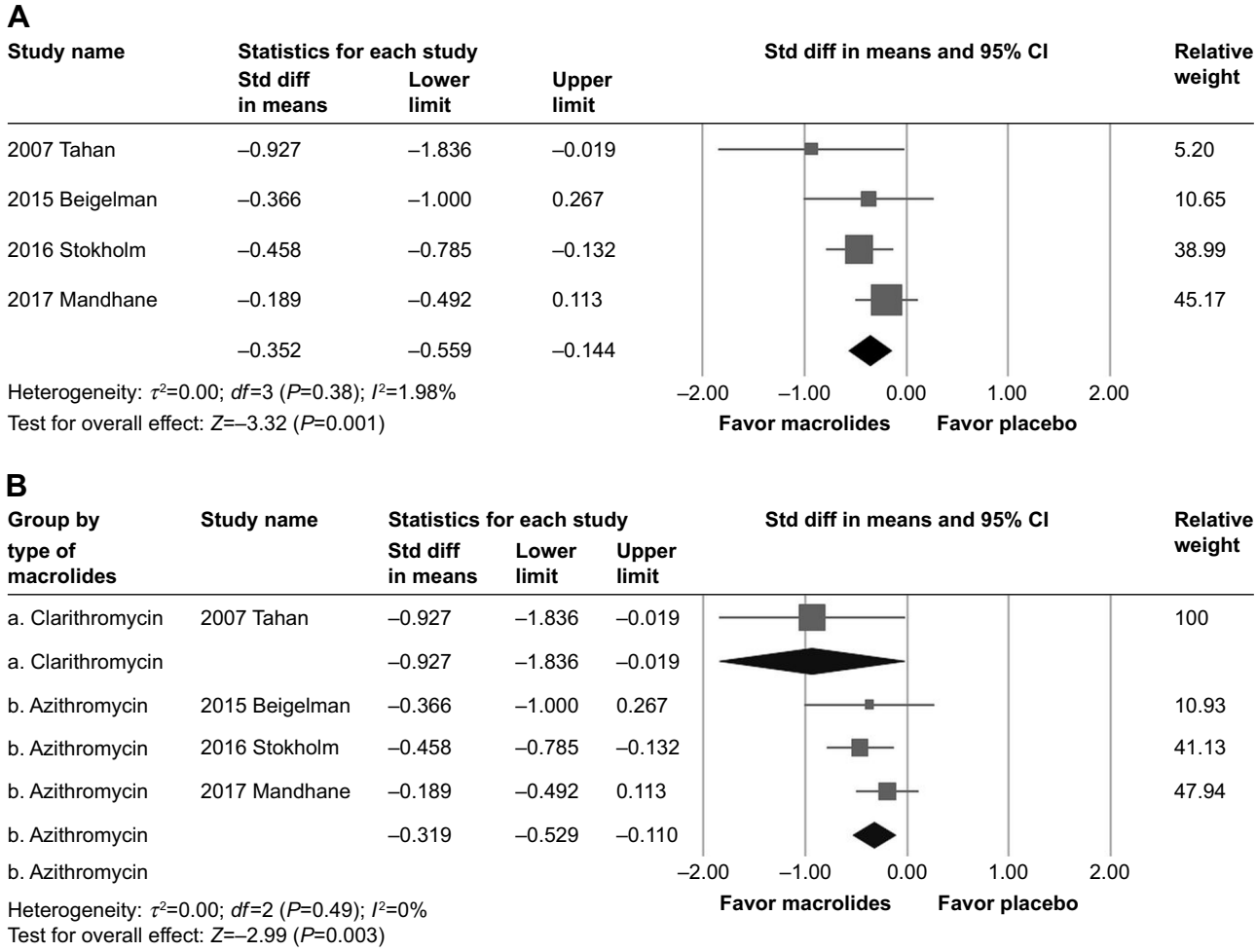


Figure 3 (**A**) Forest plot of the SABA usage days between the macrolides group and the placebo group. (**B**) Forest plot of subgroup analysis of SABA usage days by the type of macrolides.
Abbreviations: SABA, short-acting β2-agonist; std diff, standardized difference.

Discussion

The current meta-analysis summarizes the effects of macrolides in children; six RCTs suggested that the supplementation with macrolides improves both the FEV_1% and the FEF 25% with a mean difference of 10.43% and 19.41%, respectively. Moreover, pooled results from four trials showed that participants taking macrolides had fewer days of rescue SABA usage and three studies found that macrolides lowered the risks of recurrent wheezing. Furthermore, macrolides decreased the growth of *M. catarrhalis* in the upper

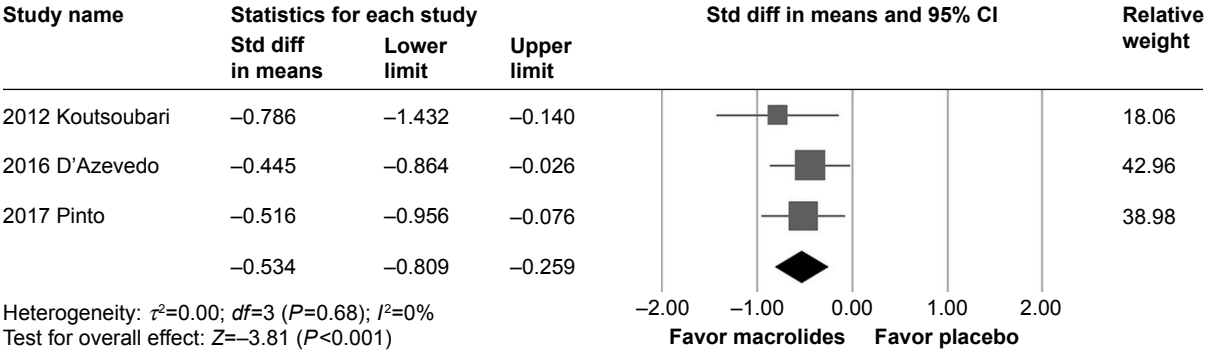


Figure 4 Forest plot of the recurrent wheezing risks between the macrolides group and the placebo group.
Abbreviation: Std diff, standardized difference.

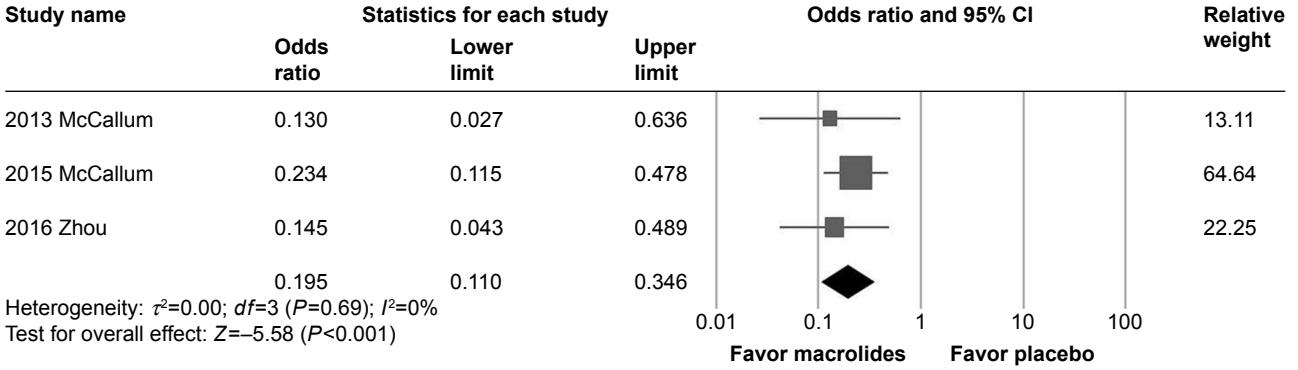


Figure 5 Forest plot of the nasal swab *Moraxella catarrhalis* between the macrolides group and the placebo group.

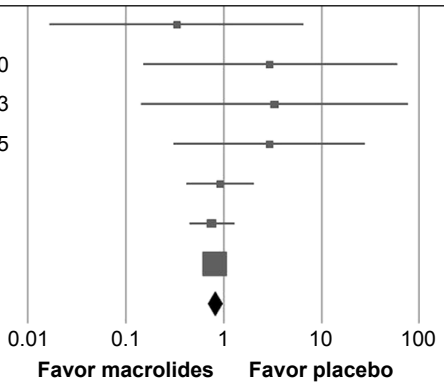
airway. Finally, compared with participants who were taking placebos, those who were taking macrolide therapy had fewer adverse events.

To the best of our knowledge, this is the first meta-analysis to comprehensively investigate the efficacy of macrolides on childhood RAD including asthmatic and asthma-like diseases, such as recurrent wheezing and acute bronchiolitis. Our analysis included both school-aged children with more definitive asthma diagnoses and preschool children with concerning respiratory problems mimicking or preceding asthma. Compared with the two recent meta-analyses[38,65] that enrolled studies on both adult and childhood asthma and focused on the effectiveness of macrolides on chronic asthma control and acute exacerbations, our study supplied more information on the analysis of treatment efficacy not only on the usefulness of pulmonary function tests, subsequent SABA usage, recurrent wheezing, but also the pathogenic bacteria status and the adverse drug reactions. The stricter inclusion criteria (only RCTs in the meta-analysis), the more recent search, and the concentrated age group (only children less than 18 years of age) ensured that the current meta-analysis is more up-to-date than the previous studies.

Our results are consistent with previous reports with regard to the effects of macrolides in the improvement of FEV_1% in patients with asthma.[38] Nevertheless, the analysis of FEV_1% in Kew et al only enrolled one study recruiting adolescents in the pooled nine trials. In the current analysis, we pooled four trials and further found that macrolides improve pulmonary functions in both the large and small airways in school-aged children. However, the optimal dose and duration of macrolide treatment needed to offer a potential positive effect have not yet been established.[37] Among the included studies in Kew et al, subgroup analysis according to the duration of macrolides was not done. In the current study, we found that those who use macrolides for more than 3 weeks had an increase in FEV_1% from such treatment (Figure 2B). Although the evidence is limited considering the scanty numbers of included studies in current analysis, it is worth noted that the positive effects of macrolides in lung function in Kew et al may related to the prolonged duration (ranged from 4 to 52 weeks), which were far more than the general treatment. The effectiveness of prolonged macrolides treatment may be contributed to the antimicrobial effects rather than anti-inflammatory effects, which was shown in adult asthma studies.[34,35] In addition, either incident *M. pneumoniae* or recurrent/chronic *C. pneumoniae* infection was thought to be related to newly-onset asthma and asthma exacerbation, even in non-atopic patients.[15,66] Moreover, azithromycin taken daily for 1 year also benefit adult with COPD[67] but had no benefits for adult with asthma who had only 3 days of treatment.[68] Therefore, it seems that an extended treatment of macrolides could indeed lower the carrier status of *C. pneumoniae/M. pneumoniae* and help to improve the pulmonary functions. Even though macrolides are characterized by their broad spectrum of activity against common community-acquired respiratory pathogens and are widely used as first-line therapy, drug resistance has emerged with some common respiratory pathogens, such as *Streptococcus pneumoniae*.[69] Moreover, previous studies[70] determined that preschool wheezing is associated with pulmonary bacterial infection such as *Haemophilus influenzae*, *S. pneumoniae*, and *M. catarrhalis*, and patients received significant benefits from various classes of antibiotic therapy, including amoxicillin, amoxicillin/clavulanic acid, cefuroxime, and trimethoprim–sulfamethoxazole. The duration of these antibiotics varied, ranging from 2 to 16 weeks. Therefore, macrolides alone may not be enough to eradicate other respiratory pathogenic bacteria, which may also interfere the respiratory disease outcome. For those who take azithromycin, further studies are needed to make precise recommendations regarding the optimal duration, most appropriate, and safe macrolides to improve pulmonary functions in children with asthma.

A

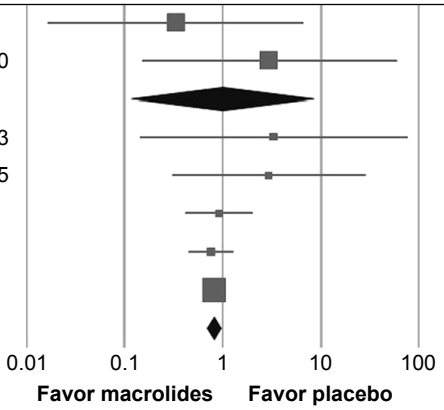
Study name	Risk ratio	Lower limit	Upper limit	Relative weight
1990 Ball	0.333	0.017	6.654	0.31
1993 Kamada	3.000	0.150	59.890	0.31
2008 Strunk	3.333	0.145	76.753	0.28
2015 Bacherier	2.960	0.310	28.235	0.54
2015 Beigelman	0.921	0.415	2.043	4.32
2016 Stokholm	0.760	0.449	1.284	9.95
2017 Mandhane	0.819	0.684	0.981	84.29
	0.827	0.701	0.976	



Heterogeneity: τ^2=0.00; *df*=6 (*P*=0.78); I^2=0%
Test for overall effect: *Z*=–2.25 (*P*=0.024)

B

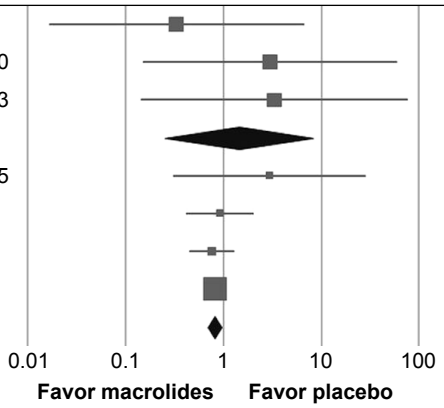
Group by type of macrolides	Study name	Risk ratio	Lower limit	Upper limit	Relative weight
a. Troleandomycin	1990 Ball	0.333	0.017	6.654	50.00
a. Troleandomycin	1993 Kamada	3.000	0.150	59.890	50.00
a. Troleandomycin		1.000	0.116	8.613	
b. Azithromycin	2008 Strunk	3.333	0.145	76.753	0.28
b. Azithromycin	2015 Bacherier	2.960	0.310	28.235	0.54
b. Azithromycin	2015 Beigelman	0.921	0.415	2.043	4.35
b. Azithromycin	2016 Stokholm	0.760	0.449	1.284	10.02
b. Azithromycin	2017 Mandhane	0.819	0.684	0.981	84.81
b. Azithromycin		0.826	0.699	0.975	
b. Azithromycin					



Heterogeneity: τ^2=0.00; *df*=2 (*P*=0.71); I^2=0%
Test for overall effect: *Z*=–2.26 (*P*=0.024)

C

Group by age group	Study name	Risk ratio	Lower limit	Upper limit	Relative weight
a. School age	1990 Ball	0.333	0.017	6.654	34.35
a. School age	1993 Kamada	3.000	0.150	59.890	34.35
a. School age	2008 Strunk	3.333	0.145	76.753	31.30
a. School age		1.458	0.252	8.428	
b. Preschool	2015 Bacherier	2.960	0.310	28.235	0.54
b. Preschool	2015 Beigelman	0.921	0.415	2.043	4.36
b. Preschool	2016 Stokholm	0.760	0.449	1.284	10.04
b. Preschool	2017 Mandhane	0.819	0.684	0.981	85.05
b. Preschool		0.823	0.697	0.972	
a. School age					



Heterogeneity: τ^2=0.00; *df*=2 (*P*=0.49); I^2=0%
Test for overall effect: *Z*=0.42 (*P*=0.674)
b. Azithromycin
Heterogeneity: τ^2=0.00; *df*=3 (*P*=0.70); I^2=0%
Test for overall effect: *Z*=–2.30 (*P*=0.021)

Figure 6 (**A**) Forest plot of the adverse events risks between the macrolides group and the placebo group. (**B**) Subgroup analysis of the adverse events risks by the type of macrolides. (**C**) Subgroup analysis of the adverse events risks by the age group.

As with the former meta-analysis[65] that pooled two studies from children and adults for each and concluded that macrolide users had longer symptom-free days, our study demonstrated less SABA usage in the macrolides group. The subgroup analyses showed that children hospitalized for bronchiolitis received more benefits from macrolide therapy, especially in those who took azithromycin. Both participants infected by RSV and non-RSV showed better responses than those taking placebos (data not shown). In contrast to the previous meta-analysis that failed to demonstrate the advantage of macrolides for an exacerbation, current analysis revealed a lower risk of recurrent wheezing among children. Animal models[71] had shown that azithromycin attenuated viral-dependent neutrophilic airway inflammation and was associated with decreased concentrations of BAL inflammatory mediators, such as IL-8 and granulocyte-macrophage colony-stimulating factor. In preschool children with recurrent wheezing, the cell profile from BAL also revealed neutrophil-mediated, but not eosinophil-mediated inflammation in the airway, which is often the situation in asthmatic adults.[70,72] Therefore, the anti-neutrophilic properties of macrolides may serve as the mechanistic rationale for the prevention of recurrent wheezing. Furthermore, IL-8 is the main and potent neutrophilic activator and is characteristically elevated, especially during viral bronchiolitis, such as RSV infection.[37] It may explain the better response to macrolides among those patients with bronchiolitis on the lower recurrent wheezing risk in our analysis. Moreover, Kloepfer et al[73] had shown that co-detection of viruses with upper airway polysaccharide bacteria in children was associated with an increased risk of asthma exacerbation. The decreased carriage status of *M. catarrhalis* after macrolide treatment in our analysis (Figure 5) further strengthened this theory. Finally, the concentration of azithromycin in alveolar macrophage and BAL is 100-fold more than that in serum, and, together with their intracellular aggregated feature, results in a long half-life.[74] The long-lasting effects may also be the reason for the improvement of long-term efficacy such as pulmonary function, less rescue medication usage, and lower risks of recurrent wheezing.

Nevertheless, there were insufficient data to be pooled to find the relationship between macrolides and residential bacteria other than *M. catarrhalis* in the airway. Further well-designed, placebo-controlled studies are required to clarify the influences of residential and pathogenic airway pathogens on the effect of macrolide therapy.

It is safe to take macrolides as the adjunctive therapy to treat childhood reactive disease in current analysis, especially for those who take azithromycin (Figure 6B). The safety of azithromycin had also been approved in adults who were treated with a longer duration for other disease ranged from 3 to 12 months in previous studies.[75,76]

Limitations

There are several limitations of this study. First, we could not perform the subgroup analysis because of the lack of studies, such as those regarding steroid dose reduction, time to respiratory symptoms relief, nasal IL-8, and concomitant medications, thereby limiting the strength of our analysis. Second, because of limited numbers of included trials, it was not possible to perform more meaningful meta-regressions to examine the impact of variables that may affect the heterogeneity of some constructed results in the current study. Third, some of the included trials had a small sample size and could not provide details on the randomization processes. Fourth, the following time in each study varied and may thus limit the usability in some results. Fifth, some reported results in current analysis were driven by one study[41,59,62] within the analysis and may need more validation studies to make a stronger conclusion. Finally, we could not discover the precise pathophysiology behind our findings because of the basic limitation of the meta-analysis.

Conclusion

The present meta-analysis adds new evidence to the current knowledge about macrolides treating childhood RAD such as asthma, recurrent wheezing, and bronchiolitis. First, using macrolides as adjunctive therapy can improve pulmonary functions in both large and small airways in school-aged children. In addition, azithromycin treatment can decrease the need for rescue SABA usage among preschool children with recurrent wheezing or bronchiolitis. Furthermore, the recurrent wheezing risks and upper airway *M. catarrhalis* growth could be lowered by macrolide supplementation in children with a history of wheezing. Finally, macrolide therapy exhibits fewer risks of adverse events, especially for preschool children and those who use azithromycin. Additional large RCTs focusing on the optimal dose, biochemical features behind the wheezing phenotype, the role of the colonization airway pathogens, and head-to-head comparison of different macrolides' efficacy and mechanism are required to validate these findings.

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Author contributions

All authors contributed equally to this study and have read and approved the final manuscript. S-JL and W-TL conducted the search. W-TL and T-LY designed and conducted the study and analyzed the data, performed the validation of the results. W-TL wrote the paper. M-CT, H-HC, Y-JC, HHL, CYL, T-LY, and W-TL extracted the data. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 PRISMA-P checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1 abstract
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2, 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3, Table S2
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3, 4
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3, 4
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	5–9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3, Table S3
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	3
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	3, Table S3
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3, 4, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	6–9, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see Item 12).	5, 8–10, Table S3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6–11, Fig 2–6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6–11, Fig 2–6

(*Continued*)

Table S1 (*Continued*)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6–11
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see Item 16]).	6–11, Fig 2, Fig 3, Fig 6
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	11–12
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	15

Abbreviation: PRISMA-P, Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.

Table S2 Searching strategy

PubMed
((((((((((Asthma OR asthma*))) OR infantile asthma) OR chronic cough) OR ((Bronchitis, Chronic OR chronic bronchitis))) OR ((Respiratory Sounds OR wheezing OR wheez*))) OR (Bronchiolitis OR Bronchiolitides OR acute bronchiolitis)) OR (Bronchiolitis, Viral OR Viral Bronchiolitides))) in All Fields
AND
((((((Erythromycin OR T-Stat OR Erycette OR Erymax OR Ilotycin))) OR ((Clarithromycin OR TE-031 OR A-56268 OR Biaxin))) OR macrolide) OR ((Azithromycin OR Azythromycin OR Sumamed OR Toraseptol OR Vinzam OR CP-62993 OR CP 62993 OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Ultreon OR Zitromax OR Goxal OR Zentavion))) in All Fields
Filters: Child: birth-18 years
Embase
('asthma' OR 'asthma'/exp OR asthma OR asthma*) OR ('chronic bronchitis'/exp) OR ('abnormal respiratory sound'/exp) OR (infantile NEAR/3 asthma) OR (chronic NEAR/3 cough) OR (chronic NEAR/3 bronchitis) OR ('wheezing'/exp OR wheezing OR wheez*) OR ('bronchiolitis'/exp) OR ('viral bronchiolitis'/exp) OR ((viral AND bronchiolitides OR bronchiolitis OR bronchiolitides OR acute) AND bronchiolitis) OR ((viral NEAR/3 bronchiolitides) OR bronchiolitis OR bronchiolitides OR (acute NEAR/3 bronchiolitis))
AND
('erythromycin'/exp OR erythromycin OR 't stat'/exp OR 't stat' OR 'erycette'/exp OR erycette OR 'erymax'/exp) OR (('azithromycin'/exp OR azithromycin OR 'azythromycin'/exp OR azythromycin OR 'sumamed'/exp OR sumamed OR toraseptol OR 'vinzam'/exp OR vinzam OR 'cp 62993'/exp OR 'cp 62993' OR cp) AND 62993 OR 'cp62993'/exp OR cp62993 OR 'zithromax'/exp OR zithromax OR 'azitrocin'/exp OR azitrocin OR 'azadose'/exp OR azadose OR 'ultreon'/exp OR ultreon OR 'zitromax'/exp OR zitromax OR goxal OR zentavion) OR ('clarithromycin'/exp OR clarithromycin OR 'te 031'/exp OR 'te 031' OR 'a 56268'/exp OR 'a 56268' OR 'biaxin'/exp OR biaxin) OR ('macrolides'/exp OR macrolides OR 'macrolide'/exp OR macrolide)
AND
([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim)
Cochrane
(MeSH descriptor: [Asthma] explode all trees) OR (MeSH descriptor: [Bronchitis, Chronic] explode all trees) OR (MeSH descriptor: [Respiratory Sounds] explode all trees) OR (MeSH descriptor: [Bronchiolitis] explode all trees) OR (MeSH descriptor: [Bronchiolitis, Viral] explode all trees) OR (Asthma or asthma* or infantile asthma or chronic cough or chronic bronchitis or Respiratory Sounds or wheezing or wheez*:ti,ab,kw (Word variations have been searched)) OR (Bronchiolitis or Bronchiolitides or acute bronchiolitis or Viral Bronchiolitides:ti,ab,kw (Word variations have been searched))

(*Continued*)

Table S2 (*Continued*)

AND
(MeSH descriptor: [Erythromycin] explode all trees) OR (MeSH descriptor: [Azithromycin] explode all trees) OR (MeSH descriptor: [Clarithromycin] explode all trees) OR (MeSH descriptor: [Macrolides] explode all trees) OR (Erythromycin or T-Stat or Erycette or Erymax or Ilotycin:ti,ab,kw (Word variations have been searched)) OR (Azithromycin or Azythromycin or Sumamed or Toraseptol or Vinzam or CP-62993 or CP 62993 or CP62993 or Zithromax or Azitrocin or Azadose or Ultreon or Zitromax or Goxal or Zentavion:ti,ab,kw (Word variations have been searched)) OR (Clarithromycin or TE-031 or A-56268 or Biaxin:ti,ab,kw (Word variations have been searched)) OR (macrolides or macrolide*:ti,ab,kw (Word variations have been searched))
CINAHL
(MH "Asthma+") OR ("chronic cough") OR (infantile asthma) OR (MH "Bronchitis, Chronic") OR (MH "Respiratory Sounds") OR (MH "Bronchiolitis") OR (asthma* OR infantile asthma OR chronic cough OR chronic bronchitis OR Respiratory Sounds OR wheezing OR wheez* OR Bronchiolitis OR Bronchiolitides OR acute bronchiolitis OR viral bronchiolitis OR Viral Bronchiolitides)
AND
((MH "Erythromycin") OR "Erythromycin") OR (T-Stat OR Erycette OR Erymax OR Ilotycin) OR ((MH "Clarithromycin") OR "Clarithromycin") OR (TE-031 OR A-56268 OR Biaxin) OR ((MH "Antibiotics, Macrolide") OR "macrolide") OR ((MH "Azithromycin") OR "Azithromycin") OR (Sumamed OR Toraseptol OR Vinzam OR CP-62993 OR CP 62993 OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Ultreon OR Zitromax OR Goxal OR Zentavion)
Narrow by Subject Age: all child

Abbreviation: CINAHL, Cumulative Index to Nursing and Allied Health.

Table S3 Risk of bias assessment of each included study[a]

Study validity domains	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Probiotics							
Ball et al,[1] 1990	Unclear	Unclear	Low	Low	Low	Unclear	Low
Kamada et al,[2] 1993	Low	Low	Low	Low	Low	Unclear	Unclear
Fonseca-Aten et al,[3] 2006	Unclear	Unclear	Unclear	Unclear	High	Low	Unclear
Piacentini et al,[4] 2007	Low	Unclear	Low	Low	Unclear	Low	Unclear
Tahan et al,[5] 2007	Low	Unclear	Low	Low	Low	Low	Unclear
Rasul et al,[6] 2008	Low	Low	Low	Low	High	Low	Unclear
Strunk et al,[7] 2008	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Kabir et al,[8] 2009	Low	Unclear	Unclear	Unclear	Low	Low	Unclear
Koutsoubari et al,[9] 2012	Low	High	High	High	Low	Low	Unclear
Pinto et al,[10] 2012	Low	Unclear	Unclear	Unclear	Low	Low	Unclear
Mccallum et al,[11] 2013	Low	Low	Low	Low	Low	Low	Unclear
Chiong-Manaysay and Andaya,[12] 2014	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Bacharier et al,[13] 2015	Low	Low	Low	Low	Low	Low	Unclear
Beigelman et al, [14] 2015 (letter)	Low	Low	Low	Low	Low	Low	Unclear
Beigelman et al,[15] 2015	Low	Low	Low	Low	Low	Low	Low
Mccallum et al,[16] 2015	Low	Low	Low	Low	Low	Low	Low
Silveira D'Azevedo et al,[17] 2016	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Stokholm et al,[18] 2016	Low	Low	Low	Unclear	Low	Low	Low
Wan et al,[19] 2016	Low	Low	Unclear	Unclear	Low	Low	Unclear
Zhou et al,[20] 2016	Unclear	Unclear	Low	Low	Low	Low	Low
Mandhane et al,[21] 2017	Low	Low	Low	Low	Unclear	Low	Low
Pinto et al,[22] 2017	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Notes: [a]Each domain has been evaluated as being "High", "Low", or "Unclear" regarding the risk of bias following the guidelines of Cochrane. Collaboration's tool for assessing risk of bias, the thorough and original evaluation form is attached in the following pages. "Low" in all Domains would place a study at "Low Risk of Bias"; "High" in any of the Domains would place a study at "High Risk of Bias"; "Unclear" in any of the domains would place the study at "Unclear Risk of Bias".

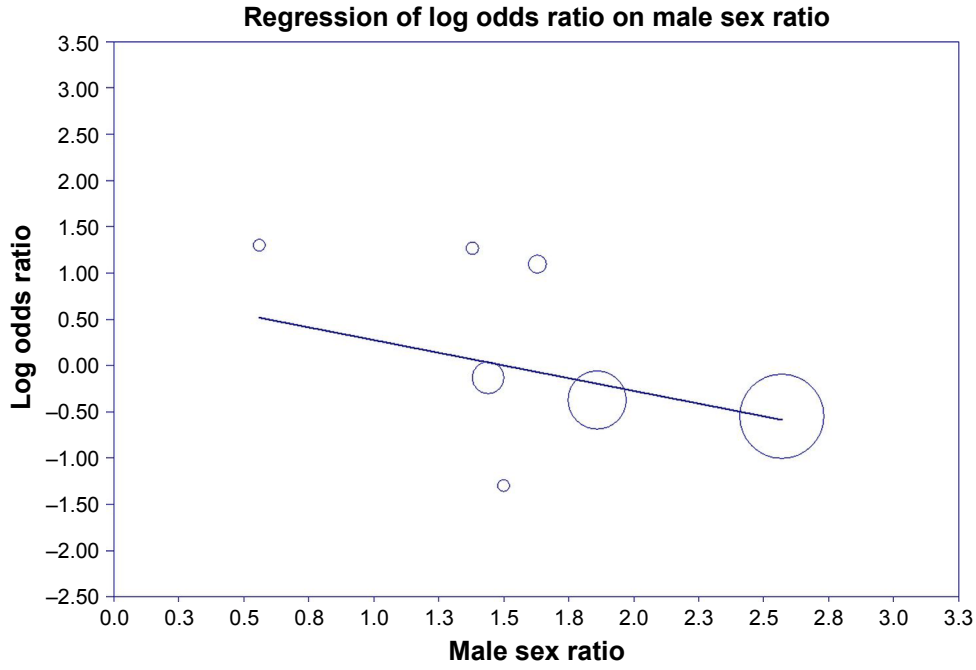

Figure S1 Meta-regression scatter plot showing there was no correlation between adverse events risk and male sex ratio.

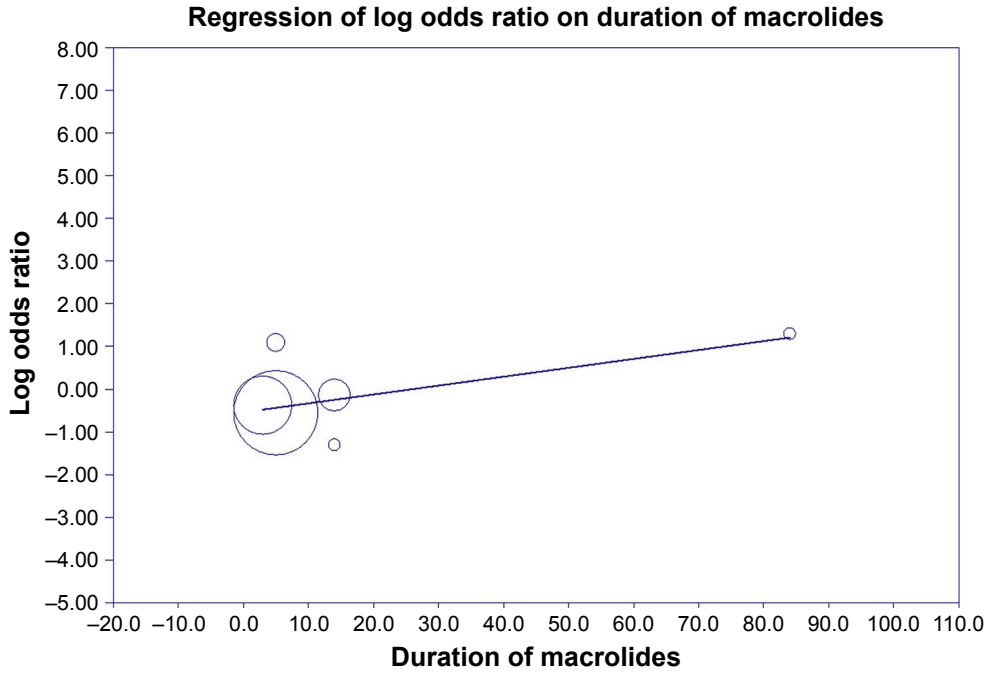

Figure S2 Meta-regression scatter plot showing there was no correlation between adverse events risk and the duration of macrolides.

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