Original Article

The burden of respiratory syncytial virus associated with acute lower respiratory tract infections in Chinese children: a meta-analysis

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Background: Respiratory syncytial virus (RSV), which is associated with acute lower respiratory tract infection (ALRTI), is highly common among children. The burden of RSV varies between countries. In China, the actual burden remains unclear. Thus, this meta-analysis aimed to quantify the positive rate of ALRTI-related RSV infections among Chinese children in recent years.

Methods: The PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), WanFang, and Chinese BioMedical (CBM) databases were searched to identify relevant cross-sectional studies published between January 1, 2015 and December 31, 2018. Subsequently, a meta-analysis was performed using R software.

Results: A total of 18 studies involving 66,799 ALRTI cases were finally included in the meta-analysis. Among those ALRTIs cases, the overall positive rate of RSV infection was 16.0% (95% CI: 12.9–19.6%). The rate was significantly higher in children <3 years (19.5%, 95% CI 13.3–27.6%) compared to those ≥3 years (5.6%, 95% CI: 2.3–13.2%; P<0.01). Moreover, stratified analysis revealed that RSV infection was most frequent in children <6 months (31.1%, 95% CI: 21.0–43.5%). The positive detection rate of RSV infection was significantly associated with season (P<0.01), with winter having the highest detection rate (29.0%, 95% CI: 21.3–38.2%), followed by autumn (20.9%, 95% CI: 10.5–37.3%), and summer having the lowest rate (6.4%, 95% CI: 2.3–16.9%). The rate of RSV infection was highest and lowest in November (49.4%, 95% CI: 29.0–70.0%) and June (1.3%, 95% CI: 0.6–2.8%), respectively. When stratified according to geographical region, RSV infections peaked in winter (South: 24.8%, 95% CI: 12.9–42.3%; North: 36.3%, 95% CI: 30.8–42.1%), followed by autumn (South: 13.9%, 95% CI: 6.5–27.4%; North: 32.7%, 95% CI: 20.2–48.3%).

Conclusions: In conclusion, our meta-analysis showed that among Chinese children with ALRTI, 16.0% had RSV infection. RSV infection frequently occurred in children under the age of 3 years, especially in those under 6 months. The rate of RSV infections was highest in winter, followed by autumn.

Keywords: Respiratory syncytial virus (RSV); acute lower respiratory tract infections (ALRTIs); children; meta-analysis; China

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Introduction

Acute lower respiratory tract infections (ALRTIs) present a persistent and pervasive problem in public health owing to the substantial burden they place on health-care services (1). ALRTI is one of the leading global causes of childhood morbidity and mortality, particularly in developing countries. Respiratory syncytial virus (RSV) is the most common viral pathogen identified in young children with ALRTI and primarily leads to pneumonia and bronchiolitis. In 2015, there were an estimated 33.1 million new cases of RSV-associated ALRTI diagnosed in young children around the world. Hospitalization was required in approximately 10% of these cases, which led to an estimated 59,600 in-hospital deaths (2). It is worth noting that, because of limited health care, more than 92% of all RSV-associated ALRI episodes and nearly 99% of related fatalities occur in developing countries; this places a great burden on patients, parents, and broader society (3). Thus, novel strategies focusing on children, who may have a naturally weak immune system compared to adults, should be developed to curb the burden imposed by RSV infection.

China is one of the biggest developing countries with the largest population in the world. China's climate varies substantially from region to region in terms of temperature and rainfall. A previous meta-analysis by Zhang *et al.* (4), which summarized relevant studies published between January, 2010 and March, 2015, evaluated the potential epidemiology of RSV infections among ALRTI patients in China. It found RSV infection to be a leading cause of viral ALRTIs in China, comprising 18.7% (95% CI: 17.1–20.5%) of all ALRTI cases, with a positive rate higher in children than in adult patients (4). Since then, a number of new studies have been published, yielding substantial new data (5-7). However, local variations in climate and the characteristics of study populations (e.g., rural *vs.* urban) have led to dramatic differences in the positive rates of RSV infection reported in individual studies. To date, the epidemiology of RSV infections among Chinese children has not been systematically summarized in English. It is therefore of great significance that a comprehensive meta-analysis to evaluate recent epidemiological data of RSV infections in Chinese patients is conducted, with a particular focus on children with ALRTIs.

In this meta-analysis, we aimed to estimate the burden of RSV-associated ALRTI in Chinese children by analyzing available studies published between January 1, 2015 and December 31, 2018. Specifically, this study was conducted to pool the positive rate of RSV infection among children with ALRTI in China, and to examine the rate in subgroup analyses incorporating different parameters such as age distribution, seasonality, and locations.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/tp-20-148).

Methods

Eligibility criteria

Studies meeting the following criteria were included in the meta-analysis: (I) all patients met diagnostic criteria for ALRTIs; (II) Chinese children younger than 18 years old; (III) containing outcome data of positive rate of RSV infection or providing sufficient information (the number of patients infected with HRSV and the number of patients screened) to calculate effect sizes; (IV) cross-sectional design; (V) obtained respiratory tract specimens for the detection of RSV; and (VI) RSV infections were confirmed through immunofluorescence assay or polymerase chain reaction. Articles meeting any of the following criteria were excluded: (I) systematic reviews, narrative reviews, or comments; (II) non-human studies; (III) Chinese journals not included in the Chinese core journals (2017 edition) evaluated by the Library of Peking University (8). In the event of overlapping data on the same patient population being reported in more than one publication, only the most comprehensive study was included.

Literature search

Searches were implemented of the PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang, and Chinese BioMedical (CBM) databases to identify studies published between January 1, 2015 and December 31, 2018. The following search terms were used: (Respiratorysyncytial virus OR RSV) and (Chinese OR China). The reference lists of enrolled papers and recent reviews were also manually searched.

Data collection process

The data were separately extracted from all eligible studies by two reviewers using a pre-defined form. The information recorded from each study included the first author's name, year of publication, patients' age and gender distribution, sample size, study period and settings, recruitment locations, diagnostic criteria of ALRTIs, type of sample collected for all patients [e.g., nasopharyngeal aspirate, nasopharyngeal swab, or bronchoalveolar lavage fluid (BALF)], methods for detecting RSV, the number of participants screened, and the number of patients with RSV infection. Any conflicts were resolved through discussion until a consensus was reached.

Case definition

ALRTI was defined according to the guidelines of the World Health Organization (WHO) as the presence of manifestations of acute respiratory tract infection including fever, coughing, rhinorrhea, and headache, and lower respiratory symptoms such as tachypnea, dyspnea, and rales upon auscultation (3).

Quality assessment

The methodological quality of the eligible cross-sectional studies was assessed using 11 items recommended by the Agency for Healthcare Research and Quality (AHRQ) (9). Each item was answered with "Yes", "No", or "Unclear". An answer of "Yes" scored 1 point; otherwise, the score was "0". The maximum score was 11, and studies with scores between 4 and 7 points were considered to be of moderate quality, while those with scores above 7 points were deemed to be of high quality.

Statistical analysis

The pooled positivity rate of RSV infections and the corresponding 95% confidence interval (CI) were calculated using R software (version 3.5.2, Auckland University, USA). Heterogeneity between included studies was determined by Chi-square-based Q-statistic test (statistical significance = $P<0.10$) and the I^2statistic. When the heterogeneity between studies was not good ($I^2<50\%$ and $P>0.1$), a fixed-effects model was adopted for the calculation of positivity rate; otherwise, a random-effects model was used. Moreover, subgroup analyses were conducted based on age distribution, study settings, publication language, method of detection for RSV infection, sample type, and seasonality. In the presence of significant heterogeneity, sensitivity analysis was carried out to test the stability of the overall results via eliminating individual studies in turn. Egger's test was also employed to quantify publication bias. All P values were two-sided, with $P<0.05$ suggesting statistical significance.

Results

Study selection and characteristics

After the literature search and subsequent eligibility screening, 18 articles (5-7,10-24) comprising 66,799 ALRTIs cases were finally included in the meta-analysis. *Figure 1* details the study selection process. The eligible articles were published between January 1, 2015 and December 31, 2018, with study periods ranging from January, 2006 to December, 2016. Of these studies, 6 were published in English (6,10,11,14,19,20) and the other 12 in Chinese. The ALRTIs cases were diagnosed as community-acquired pneumonia (CAP), lobar pneumonia, bronchitis, bronchiolitis, or other lower respiratory diseases. Respiratory specimens collected to test for RSV infection included nasopharyngeal aspirates (NPA), nasopharyngeal swabs (NPS), and BALF. RSV infections were assessed using immunofluorescence assays or polymerase chain reaction. All of the selected articles were of moderate quality according to the AHRQ recommended item checklist. *Table 1* presents the characteristics and quality scores of all of the included studies.

Overall analysis

The positive rate of RSV infection among Chinese children in the enrolled studies ranged from 1.2% to 49.2% (*Figure 2*). In a pooled sample of the 66,799 ALRTI patients involved, the overall positive rate of RSV infection was 16.0% (95% CI: 12.9–19.6%). Substantial heterogeneity presented for combined effect size ($P_h<0.01$, $I^2=99.0\%$) (*Table 2*). Consequently, subgroup analysis was performed to explore the potential source of this heterogeneity.

Subgroup analysis

The detection rates for RSV infection varied considerably

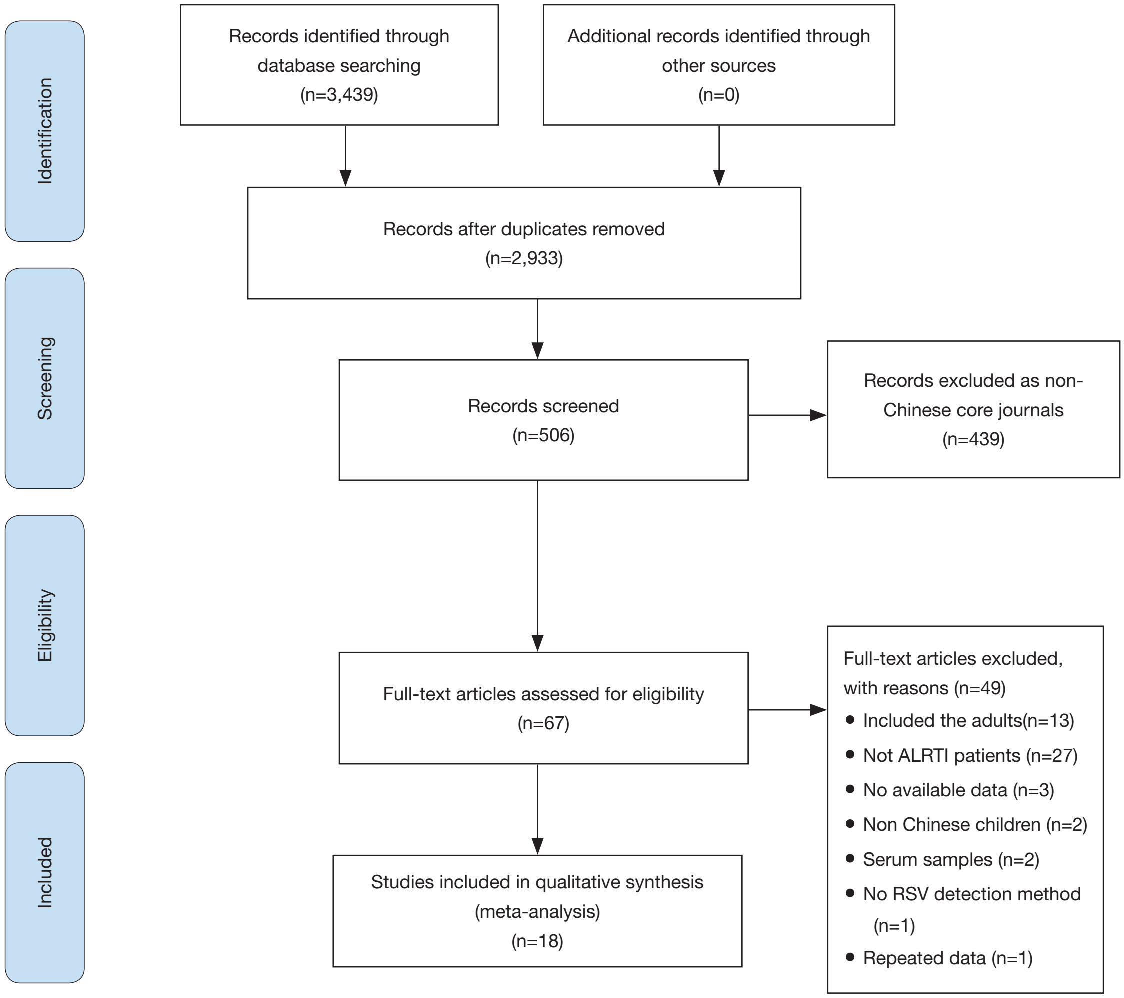

Figure 1 The flow diagram of the study selection process.

between groups of different age distributions, and decreased as the age rose (*Table 2*). Stratified analysis revealed that RSV infection was more frequently detected in children aged <3 years (19.5%, 95% CI: 13.3–27.6%) than in those aged ≥3 years (5.6%, 95% CI: 2.3–13.2%; P<0.01). Furthermore, the highest rate of RSV infection appeared among children <6 months (31.1%, 95% CI: 21.0–43.5%).

There were 6 studies that accounted for the seasonality of RSV infections (12,13,15,16,22,24). Our subgroup analysis showed that the positive rate of RSV infection was significantly associated with season. Winter had the highest rate (29.0%, 95% CI: 21.3–38.2%), followed by autumn (20.9%, 95% CI: 10.5–37.3%), while summer had the lowest rate (6.4%, 95% CI: 2.3–16.9%) (*Table 2*). When stratified according to location (southern and northern China), the seasonality characteristics of RSV infection still existed (*Figure 3*). Clear seasonal peaks occurred in winter (South: 24.8%, 95% CI: 12.9–42.3%; North: 36.3%, 95% CI: 30.8–42.1%) and autumn (South: 13.9%, 95% CI: 6.5–27.4%; North: 32.7%, 95% CI: 20.2–48.3%). Two studies (12,16) reported monthly isolation rates. There was an obvious increase in the positive detection rate for RSV infection from September, peaking in November (49.4%, 95% CI: 29.0–70.0%). Meanwhile, June had the lowest positive rate of RSV infection (1.3%, 95% CI: 0.6–2.8%) (*Figure 4*). No obvious differences were found by stratification according to study settings, publication language, detection methodology, and sample type. The

Table 1 Main characteristics of the included studies

Study ID	Region	Study period	Setting	Age (year), mean/range	Sample size			Disease subtype	Detection methods	Sample type	Positivity rate of RSV (%)	Quality score
					All	Male	Female					
Dong YW 2018 (5)	South	2009.7–2014.6	Inpatient	≤5	25,449	NR	NR	Pneumonia and bronchitis	IF	NPS	25.2%	4
Ge X 2018 (6)	South	2010.1–2016.12	In/outpatient	≤14	2,160	1,167	993	Bronchitis, pneumonia, asthmatic bronchitis, and other respiratory diseases	PCR	NPS	17.00%	5
Hao OM 2018 (7)	Multiple	2010.12–2013.6	Inpatient	≤5	429	239	190	Pneumonia	IF	NPS	49.20%	4
Liu P 2018 (10)	South	2013.1–2015.12	Inpatient	<18	10,123	6,286	3,837	NR	IF	NPA/BALF	13.90%	5
Oumei H 2018 (11)	Multiple	2015.1–2015.12	Inpatient	3.85±2.54	1,500	652	848	CAP	IF	NPS	11.50%	6
Chen JW 2017 (12)	South	2013.1–2015.12	Inpatient	≤1	2,206	NR	NR	Pneumonia and bronchitis	IF	NPA	19.90%	4
Gu WJ 2017 (13)	South	2006.1–2015.12	Inpatient	≤16	1,179	597	582	Lobar pneumonia	IF	NPA	2.50%	4
Jiang W 2017 (14)	South	2015.1–2015.12	Inpatient	≤14	846	489	357	CAP	IF	NPA	22.90%	6
Chen JN 2016 (15)	South	2014.1–2014.12	Inpatient	≤6	600	364	236	CAP	IF	NPA	21.30%	4
Li QH 2016 (16)	North	2014.3–2015.2	Inpatient	≤12	5,150	3,165	1,985	NR	IF	NPS	26.00%	4
Mo JP 2016 (17)	South	2014.8–2015.7	in/outpatients	2.32±2.42	585	405	180	Pneumonia or bronchitis	PCR	NR	29.10%	4
Yang Y 2016 (18)	North	2013.4–2015.5	Inpatient	7.89±3.46	80	44	36	Lobar pneumonia	PCR	BALF	1.30%	4
Liu C 2015 (19)	North	2007.3–2012.12	in/outpatient	3.87±4.03	3,356	2,085	1271	Bronchitis, bronchiolitis or pneumonia	PCR	NPA/throat swab	23.10%	6
Lu L 2015 (20)	South	2010.1–2014.12	Inpatient	≤1 month	1,803	NR	NR	Bronchiolitis or pneumonia	IF	NPA	20.70%	7
Ma HX 2015 (21)	North	2012.12–2013.11	Inpatient	<18	1,853	1,130	723	CAP	IF	sputum/BALF	5.50%	5
Peng Y 2015 (22)	North	2014.1–2014.12	Inpatient	≤6	1,613	1,016	597	CAP	IF	NPA	20.10%	4
Qian Y 2015 (23)	North	2007.3–2015.2	In/outpatient	≤12	4,317	2,706	1,665	Pneumonia, bronchitis, bronchiolitis, and other respiratory diseases	PCR	NPA	4.40%	5
Zhang HQ 2015 (24)	South	2013.1–2013.12	Inpatient	≤11	3,496	2,256	1,240	Pneumonia, bronchitis, bronchiolitis, and other respiratory diseases	IF	NPS	12.20%	4

RSV, respiratory syncytial virus; CAP, community-acquired pneumonia; IF, immunofluorescence; PCR, polymerase chain reaction; NPA, nasopharyngeal aspirates; NPS, nasopharyngeal swab; BALF, bronchoalveolar lavage fluid; NR, not reported.

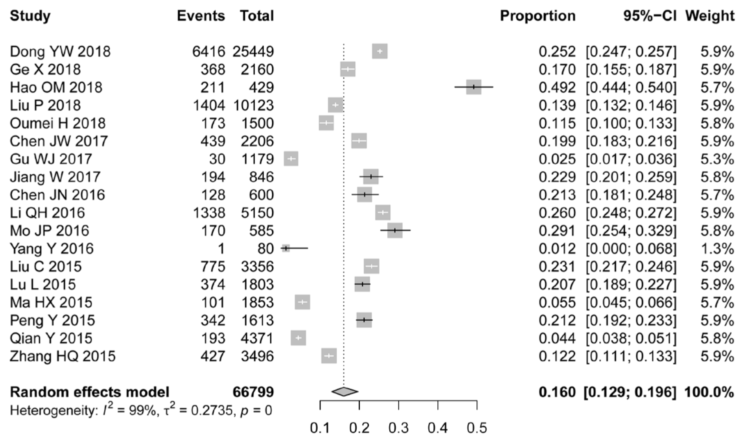

Figure 2 Forest plot of overall analysis results for the positive rate of RSV infection among children in China. RSV, respiratory syncytial virus.

main results are summarized in *Table 2*.

Sensitivity analysis and publication bias

The overall results were not obviously changed after each individual study was omitted, which confirmed the stability of the results of our meta-analysis (*Figure 5*). Moreover, calculated the pooled proportion of studies with moderate-poor quality (scoring 4), and the results were not substantially different (19.0%, 95% CI: 15–24%). Egger's linear regression test was performed to test for publication bias, and no obvious publication bias was detected (P=0.06) among the publications that reported RSV positive rates for all patients.

Discussion

We conducted a meta-analysis to pool the positive rate of RSV infection among children with ALRTIs in China. After rigorous screening, 18 articles including 66,799 ALRTI cases were deemed to be eligible and included in the meta-analysis. Among these patients, the overall positive rate of RSV infection was 16.0% (95% CI: 12.9–19.6%). Moreover, RSV infection was significantly associated with season and age.

The prevalence of RSV infections among ALRTI patients varies in different countries around the world. For instance, a meta-analysis of 67 studies involving 154,000 ALRTIs participants showed that the pooled prevalence of RSV infection was 14.6% (95% CI: 13.0–16.4%) in Africa, and found that RSV prevalence was not associated with gender, study setting, seasonality, or subregion (25). In their meta-analysis of 74 studies, Bardach *et al.* (26) found that the pooled percentage of RSV infection in LRTI patients varied between children (41.5%) and elderly people (12.6%) in Latin America. Another meta-analysis with 4,140 cases, yielded a prevalence of 18.7% in Iran (27). Zhang *et al.* (4) explored RSV prevalence and clinical manifestations of RSV infection-related ALRTI and discovered that the overall positive rate of RSV in patients with ARTIs was 18.7% (95% CI: 17.1–20.5%). In our meta-analysis, 13,084 (16.0%) of 66,799 cases were positive for RSV infection. The positive rates of RSV infection for the included studies ranged from 1.2% to 49.2%. The considerable discrepancy between these rates might be attributed to the different years in which the analyses were conducted and differences in the study populations. During sensitivity analysis, each study was omitted in turn, and no substantial change was observed in the overall estimates, even when the study with the lowest positive rate was removed.

In both developed and developing countries, RSV infections are one of the major causes of hospitalizations and in-hospital deaths among children (2,3). In this meta-analysis, we attempted to obtain a comprehensive epidemiological picture of RSV infection among children in China from the data available. Our results show that RSV infection was most frequently detected in children younger than 6 months (31.1%, 95% CI: 21.0–43.5%). From this finding, it can be concluded that infants have higher susceptibility to RSV, and efforts to prevent RSV infections among infants may help to reduce the associated medical costs in China. As for prognosis, hypoxemia is

Table 2 Overall and subgroup analyses results for the positive rate of RSV infection among children in China

Groups	N studies	N RSV positive	N participants	Positivity rate (95% CI)	Heterogeneity test		P difference
					I^2	P_h	
Overall	18	13,084	66,799	16.0 (12.9–19.6)	99.0%	<0.01	–
Subgroup analyses							
Age group							<0.01
<6 months	4	1,500	4,994	31.1 (21.0–43.5)	98.5%	<0.01	
<1 year old	12	2,995	13,529	24.0 (17.6–31.8)	98.7%	<0.01	
<3 years old	10	3,056	15,188	19.5 (13.3–27.6)	99.0%	<0.01	
≥3 years old	10	558	7,148	5.6 (2.3–13.2)	98.7%	<0.01	
Seasons							<0.01
Spring	6	332	3,019	9.7 (7.2–12.9)	83.6%	<0.01	
Summer	6	144	2,346	6.4 (2.3–16.9)	95.9%	<0.01	
Autumn	6	552	2,639	20.9 (10.5–37.3)	98.3%	<0.01	
Winter	6	1,366	4,287	29.0 (21.3–38.2)	96.7%	<0.01	
Settings							0.92
Inpatients	14	11,578	56,327	16.2 (12.9–20.2)	99.1%	<0.01	
In/outpatients	4	1,506	10,472	15.6 (7.5–29.5)	99.5%	<0.01	
Publication language							0.36
Chinese	12	9,796	47,011	14.9 (10.8–20.1)	99.3%	<0.01	
English	6	3,288	19,788	17.8 (14.1–21.1)	97.8%	<0.01	
Detection methodology							0.57
IF	13	11,444	55,951	15.5 (12.2–19.5)	99.2%	<0.01	
PCR	5	1,507	10,552	12.6 (6.2–24.0)	99.3%	<0.01	
Sample							0.08
NPS	6	8,933	38,184	21.5 (16.1–28.0)	99.2%	<0.01	
NPA	7	1,700	12,618	13.2 (8.1–20.8)	99.0%	<0.01	
Mixed	3	2,280	15,332	12.4 (7.0–21.1)	99.3%	<0.01	

RSV, respiratory syncytial virus; IF, immunofluorescence; PCR, polymerase chain reaction; NPA, nasopharyngeal aspirates; Mixed, two or more types of respiratory specimen; Spring, 1 March to 31 May; Summer, 1 June to 31 August; Autumn, 1 September to 30 November; Winter, 1 December to 28/29 February.

an important risk factor of Children ALRTI. About 20% of all children admitted to hospital with RSV-ALRI have hypoxemia. Moreover, our results showed that the detection rate of RSV varied by season and was highest in winter. With regional variations taken into consideration, the seasonality characteristics of RSV infection in southern and northern China were analyzed, and similar results were obtained. It is well known that changes in climate in the winter, like wet and cold weather, are key elements affecting pathogen transmission. We also reported the distribution of the monthly detection rate for RSV infection among Chinese children, but these results need further verification in future studies covering more comprehensive information. Although PCR-based diagnostic testing is more sensitive than other methods for detecting respiratory viruses, immunofluorescence assay was used for RSV detection

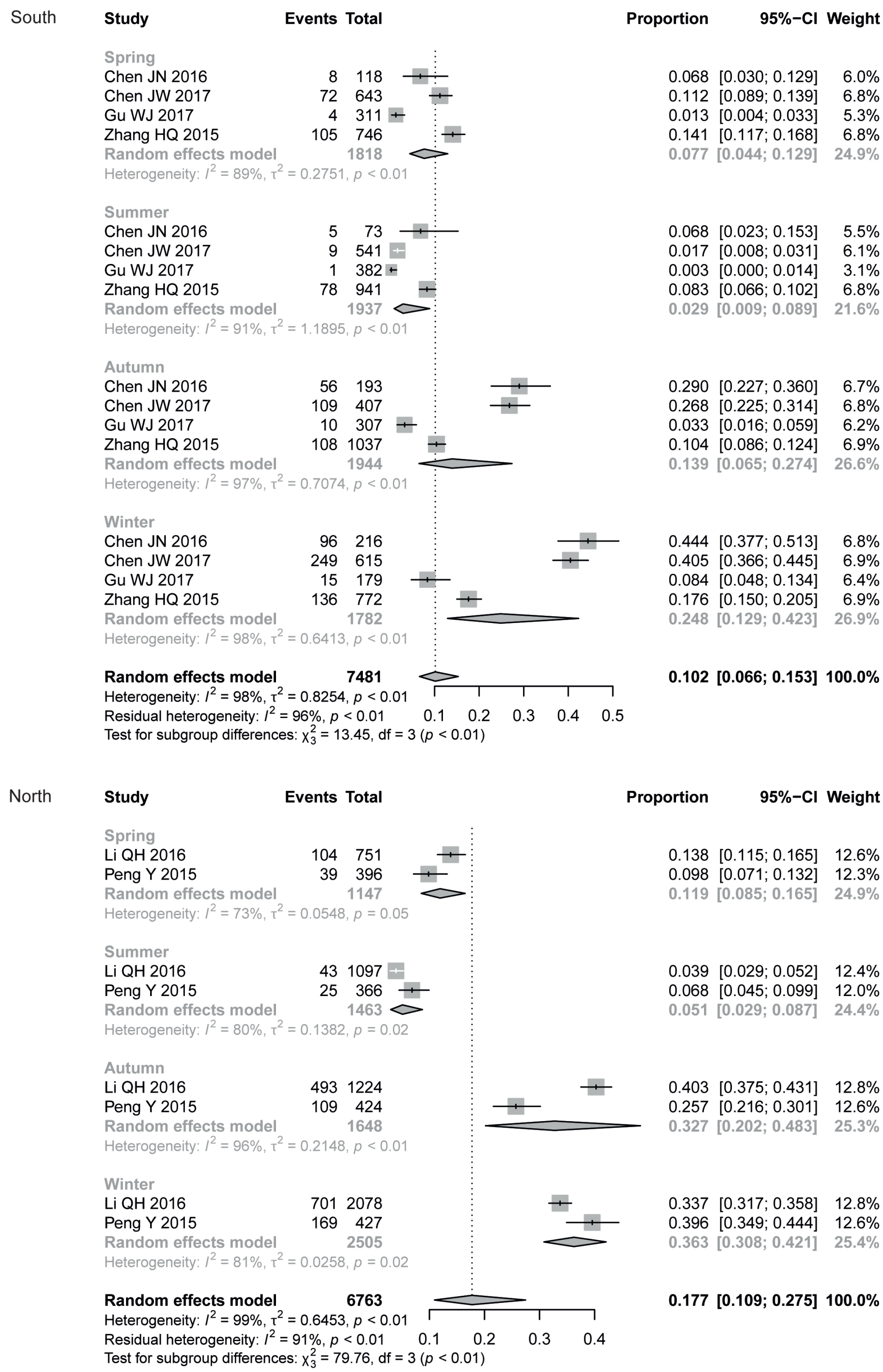

Figure 3 Forest plot of subgroup analysis results for seasonality characteristics of RSV infection among Chinese children when stratified by location. RSV, respiratory syncytial virus.

in the majority of the included studies. No significant difference was found between the two methods for RSV detection, which was consistent with the findings of Zhang *et al.* (4).

This study had some limitations that should be noted when applying its findings. First, the identified eligible articles were published between January, 2015 and December, 2018, but the study periods ranged from January 2006 to December 2016. Moreover, due to limited data, the annual positive rate of RSV infection could not be evaluated. Second, substantial heterogeneity existed between the enrolled studies. Limited information restricted further evaluation on risk factors such as patients' gender, severity, and subtypes of ALTIs, which may have been sources of the heterogeneity. Third, the retrospective nature of this meta-analysis means that it is subject to any methodological deficiencies of the included studies. Fourth, the participants in all of the included studies were enrolled from hospitals, so they might not be representative of the general population. Fifth, there are some well-known risk factors associated with RSV infection such as premature birth, chronic lung disease, and congenital heart disease (28). Due to insufficient data in the original studies, we could not extract the relevant data to perform subgroup analysis of children with congenital heart disease, down syndrome, preterm birth, and other chronic conditions with impairment of lung function.

Despite the above-mentioned limitations, this study has a number of strengths. Relevant reports were identified through a systematic search strategy and selected according to predefined inclusion criteria, which ensures the reliability and scientific nature of this work. Moreover, subgroup and sensitivity analyses were performed to explore potential sources of heterogeneity and to test the stability of the results. The results of sensitivity analysis were similar to those of the overall analysis, thus indicating the robustness of our findings.

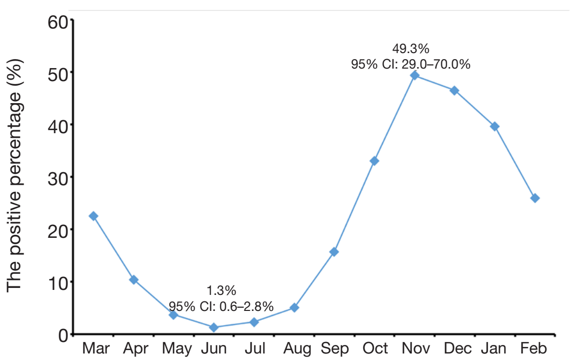

Figure 4 Distribution of the monthly detection rate for RSV infection among children in China. RSV, respiratory syncytial virus.

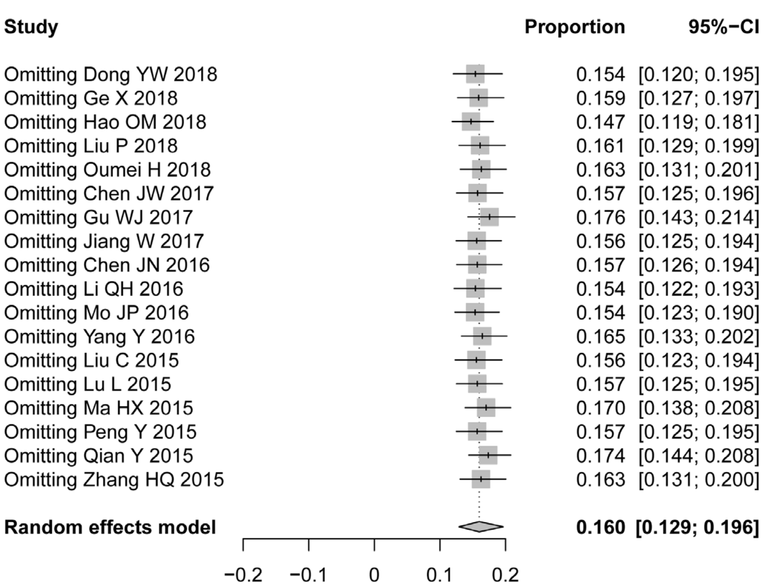

Figure 5 Sensitivity analysis results for the positive rate of RSV infection among children in China. RSV, respiratory syncytial virus.

Conclusions

Our meta-analysis showed that the distribution of RSV-associated ALRTIs in Chinese children varies with age and season. Further studies to identify RSV-associated ALRI mortality (in community and hospitals) are called for. Moreover, regional estimates of the burden of RSV infection on health-care systems are required to develop policies for the introduction of RSV vaccines as well as to assess the effect of these vaccines on the rates of morbidity and mortality in young children.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tp-20-148). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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