Original Article

Epidemiology of respiratory syncytial virus in hospitalized children with community-acquired pneumonia in Guangzhou: a 10-year study

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Background: Respiratory syncytial virus (RSV) is one of the most common virus causing community-acquired pneumonia (CAP) in children. To guide the prevention, diagnosis and treatment of RSV, we aimed to analyze the epidemiology of RSV in hospitalized children with CAP.

Methods: A total of 9,837 hospitalized children (≤14 years old) with CAP from January 2010 to December 2019 were reviewed. Using the real-time polymerase chain reaction (RT-PCR), the oropharyngeal swab specimens were collected and tested for RSV, influenza virus A (INFA), influenza virus B (INFB), parainfluenza virus (PIV), enterovirus (EV), coronavirus (CoV), human metapneumovirus (HMPV), human bocavirus (HBoV), human rhinovirus (HRV), and adenovirus (ADV) for each patient.

Results: The detection rate of RSV was 15.3% (1,507/9,837). From 2010 to 2019, the RSV detection rate showed a wavy change (χ^2=166.982, P<0.001), with the highest detection rate in 2011 (158/636, 24.8%). RSV can be detected throughout the year, with the highest detection rate in February (123/482, 25.5%). Children younger than 0.5 years old had the highest detection rate (410/1,671, 24.5%). The detection rate of RSV in male children (1,024/6,226, 16.4%) was higher than that in female children (483/3,611, 13.4%) (P<0.001). A proportion of 17.7% (266/1,507) of RSV positive cases were also co-infected with other viruses, and INFA (41/266, 15.4%) was the most common coinfection virus. After adjusting for potential confounders, the RSV-positive children were associated with increased risk of severe pneumonia [odds ratio (OR) 1.26, 95% confidence interval (CI): 1.04 to 1.53, P=0.019]. Moreover, children with severe pneumonia had significantly lower cycle threshold (CT) values of RSV than those without severe pneumonia (28.88±3.89 *vs.* 30.42±3.33, P<0.01). Patients with coinfection (38/266, 14.3%) had a higher risk of severe pneumonia than those without coinfection (142/1,241, 11.4%), but the difference was not statistically significant (OR 1.39, 95% CI: 0.94 to 2.05, P=0.101).

Conclusions: The detection rate of RSV in CAP hospitalized children changed by years, months, ages, and sexes. CAP hospitalized children with RSV are more likely to develop severe pneumonia than those without RSV. Policy makers and doctors should make timely adjustments to prevention measures, medical resources and treatment options based on these epidemiological characteristics.

Keywords: Community acquired pneumonia (CAP); respiratory syncytial virus (RSV); children; epidemiology

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Introduction

Community acquired pneumonia (CAP) is one of the most common causes of hospitalization and death in children younger than 5 years (1). According to a previous study, pneumonia kills over 2 million children worldwide every year, which accounts for more deaths of young children than any other single infectious disease, such as malaria, diarrhea and dengue (2).

Respiratory syncytial virus (RSV) is the most infectious viral pathogen that causes CAP in children under 5 years of age (3). Moreover, RSV infection is the primary cause of hospitalization for viral respiratory infection in infants and young children, which seriously endangers children's health (4). However, there are few reports on the epidemiology of RSV infection in large samples of hospitalized children with CAP.

To understand the epidemiological characteristics of RSV infection in hospitalized children with CAP in Guangzhou and guide the prevention and treatment of RSV infection, we analyzed the epidemiological characteristics of RSV infection in 9,837 hospitalized children with CAP. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-331/rc).

Highlight box

Key findings

- The detection rate of RSV in CAP hospitalized children changed by years, months, ages, and sexes. CAP hospitalized children with RSV are more likely to develop severe pneumonia than those without RSV.

What is known and what is new?

- The epidemiology characteristics of RSV in hospitalized children has been reported in western countries.
- We report the epidemiology of RSV in hospitalized children with CAP in China, and investigated the relationship between RSV and severe pneumonia.

What is the implication, and what should change now?

- Policy makers and doctors should make timely adjustments to prevention measures, medical resources and treatment options based on these epidemiological characteristics. Further prospective randomized studies are needed.

Methods

Study population

A total of 10,216 hospitalized children (≤14 years old) who were diagnosed with CAP according to the criteria of the Child Community-Acquired Pneumonia Guidelines (I, II) (5,6) in our hospital from January 2010 to December 2019 were included in our study. The exclusion criteria were as follows: (I) children with missing demographic data and (II) children without RSV test results. Severe CAP was defined as follows: (I) fever ≥38.5 ℃; (II) respiratory rate greater than 70 breaths per minute in infants and 50 breaths per minute in children (except while crying); (III) cyanosis or intermittent apnea; and (IV) dehydration or confusion (5,6).

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the First Affiliated Hospital of Guangzhou Medical University Ethics Committee (No. 20170315), and individual consent for this retrospective analysis was waived.

Data and specimen collection

Oropharyngeal swab samples were collected on the day of admission or in the early morning of the second day. At the same time, basic information such as sex and age were collected. The oropharyngeal swab samples were put into a 15-mL tube containing 2.5 mL of virus delivery solution and transported to the State Key Laboratory of Respiratory Diseases at a temperature of 2–8 ℃. The samples were analyzed immediately, and the remaining samples were stored in another cryotube at –80 ℃.

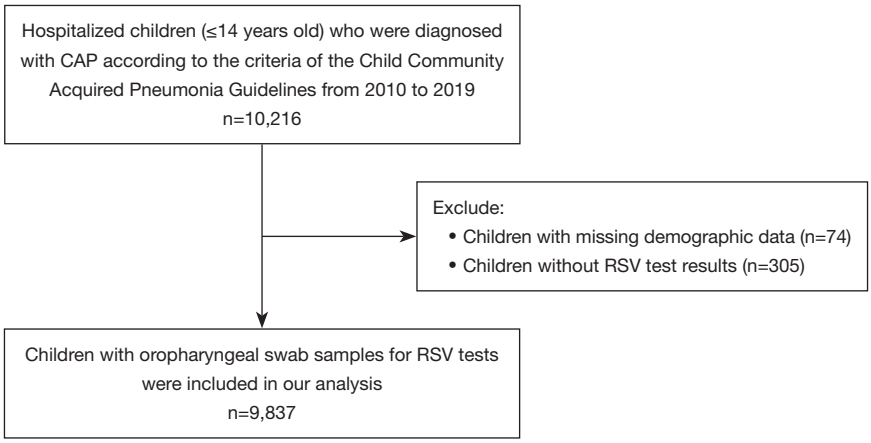

Figure 1 Flowchart of analysis. CAP, community-acquired pneumonia; RSV, respiratory syncytial virus.

Laboratory testing

In brief, DNA or RNA from oropharyngeal swab samples was extracted using QIA amp DNA Mini Kit or QIA amp Viral RNA Mini Kit (Qiagen Co. Ltd., Shanghai, China) in accordance with the manufacturer's protocols. For RSV detection, the primers and TaqMan probes were designed to detect RSV subgroups A (RSVA) and B (RSVB) by amplifying the RSV *G* gene. Multiplex real-time reverse transcriptase (RT)-PCR was conducted using our optimized reaction buffer and cycling conditions. The cycling conditions were 48 ℃ for 10 min, 94 ℃ for 2 min, and then 40 cycles of 94 ℃ for 10 s and 55 ℃ for 35 s. The amplified nucleic acids were detected with the Applied Biosystems 7500 Real-Time PCR System (Life Technologies, Singapore). RSV-positive samples were tested simultaneously for 9 respiratory tract pathogens, influenza virus A (INFA), influenza virus B (INFB), parainfluenza virus (PIV), enterovirus (EV), coronavirus (CoV), human metapneumovirus (HMPV), human bocavirus (HBoV), human rhinovirus (HRV), and adenovirus (ADV) using kits from Guangzhou HuYanSuo Medical Technology Co., Ltd. To ensure sequence accuracy, PCR amplification and sequencing were conducted at least twice. The detailed testing procedure has been provided in previous reports (7,8).

Statistical analysis

SPSS 25.0 statistical software (IBM Corp. Released in 2017. IBM SPSS Statistics for Windows, Version 25.0; IBM Corp., Armonk, NY) was used for the analysis. The detection rate of viruses was calculated by dividing the number of positive cases by the total case number, which was expressed as a percentage. Line charts were drawn to describe changes in the epidemiological characteristics of viruses. The chi-square test or Fisher's exact test was used for the comparison of categorical data. A multivariable logistic regression model which adjusted for sex, age, month and coinfection was used to assess the association of severe pneumonia and death with RSV infection with the calculation of odds ratio (OR) and 95% confidence interval (CI). A multivariable logistic regression model which adjusted for sex, age and month was used to assess the association of severe pneumonia and coinfection. In addition, the association between severe pneumonia and cycle threshold (CT) values of RSV were examine using Pearson correlation analysis in RSV-positive children, with the calculation of Pearson correlation coefficient (r).

Results

Patient characteristics and detection rate of RSV

In this study, we excluded 379 patients without complete demographic data or RSV test results, and a total of 9,837 oropharyngeal swabs from hospitalized children with CAP were included (*Figure 1*). There were 6,226 males and 3,611 females. The total RSV detection rate was 15.3% (1,507/9,837). RSV-positive children were significantly younger than RSV-negative children (1.49±1.78 *vs.* 2.86±2.83, P<0.001) (*Table 1*).

Table 1 Comparison of baseline characteristics between patients with and without RSV infection

Variables	RSV-positive	RSV-negative	P value
N	1,507 (15.3)	8,330 (84.7)	<0.001
Age, mean ± SD, years	1.49±1.78	2.86±2.83	
Age range, years			
≤0.5	410 (24.5)	1,261 (75.5)	<0.001
(0.5–1]	484 (19.8)	1,966 (80.2)	<0.001
(1–3]	470 (16.3)	2,410 (83.7)	<0.001
(3–6]	106 (5.8)	1,711 (94.2)	<0.001
>6	37 (3.6)	982 (96.4)	<0.001
Sex			
Male	1,024 (16.4)	5,202 (83.6)	<0.001
Female	483 (13.4)	3,128 (86.6)	<0.001
Year			<0.001 (P for trend)
2010	81 (11.5)	623 (88.5)	
2011	158 (24.8)	478 (75.2)	
2012	113 (12.3)	803 (87.7)	
2013	131 (10.0)	1,181 (90.0)	
2014	203 (16.5)	1,026 (83.5)	
2015	171 (20.7)	657 (79.3)	
2016	131 (16.5)	665 (83.5)	
2017	145 (20.3)	571 (79.7)	
2018	223 (18.9)	956 (81.1)	
2019	151 (9.9)	1,370 (90.1)	
Month			<0.001 (P for trend)
January	170 (19.4)	708 (80.6)	
February	123 (25.5)	359 (74.5)	
March	203 (21.0)	762 (79.0)	
April	169 (18.4)	751 (81.6)	
May	136 (14.2)	823 (85.8)	
June	88 (10.9)	719 (89.1)	
July	130 (15.2)	728 (84.8)	
August	138 (15.8)	738 (84.2)	
September	141 (18.7)	615 (81.3)	
October	61 (8.8)	629 (91.2)	
November	49 (6.0)	769 (94.0)	
December	99 (12.0)	729 (88.0)	
Severe pneumonia	180 (11.9)	757 (9.1)	0.194
Death	3 (0.2)	43 (0.5)	0.100

Values are number and frequency (%) of total unless otherwise specified. RSV, respiratory syncytial virus; SD, standard deviation.

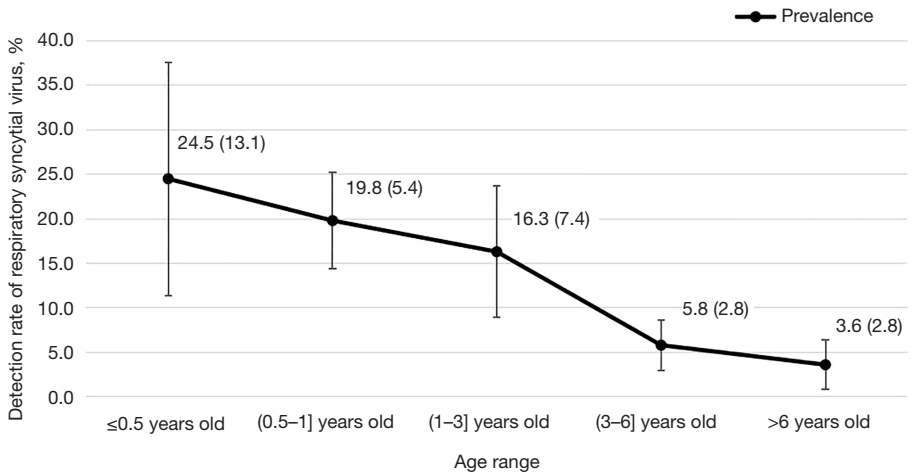

Figure 2 The detection rate of RSV in CAP hospitalized children in different ages. Age was grouped into ≤0.5, >0.5–1, >1–3, >3–6 and >6 years old. In each age group, mean (standard deviation) of RSV detection rates between 2010 and 2019 were displayed. CAP, community-acquired pneumonia; RSV, respiratory syncytial virus.

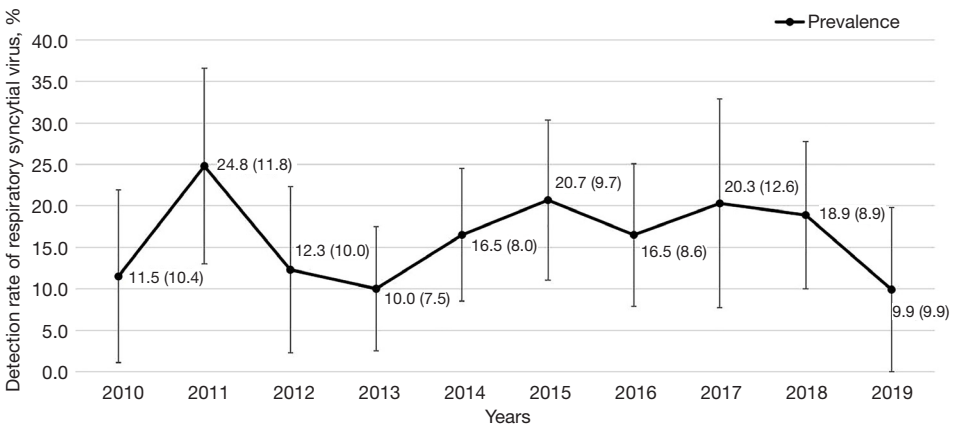

Figure 3 The detection rate of RSV in CAP hospitalized children from 2010 to 2019. In each year, mean (standard deviation) of RSV detection rates in twelve months were calculated. CAP, community-acquired pneumonia; RSV, respiratory syncytial virus.

Correlation between the detection rate of RSV and patient demographics

The detection rate of RSV in male children (1,024/6,266, 16.4%) was significantly higher than that in female children (483/3,611, 13.4%) (P<0.001). The detection rate of RSV in hospitalized children with CAP was different in every age group (χ^2=382.137, P<0.001). The detection rate of RSV was highest in children younger than 0.5 years old (410/1,671, 24.5%). The younger the patient was, the higher the detection rate of RSV (*Figure 2*).

Annual and monthly changes in the detection rate of RSV

From 2010 to 2019, the detection rate of RSV fluctuated (χ^2=166.982, P<0.001), with the highest detection rate in 2011 (158/636, 24.8%), followed by 2015 (171/828, 20.7%). The year with the lowest detection rate was 2019 (151/1,521, 9.9%) (*Figure 3*). The detection rate of RSV was different in different months (χ^2=184.740, P<0.001). The highest detection rate was in February (123/482, 25.5%), followed by March (203/965, 21.0%) and January (170/878, 19.4%). The lowest detection rate was in November

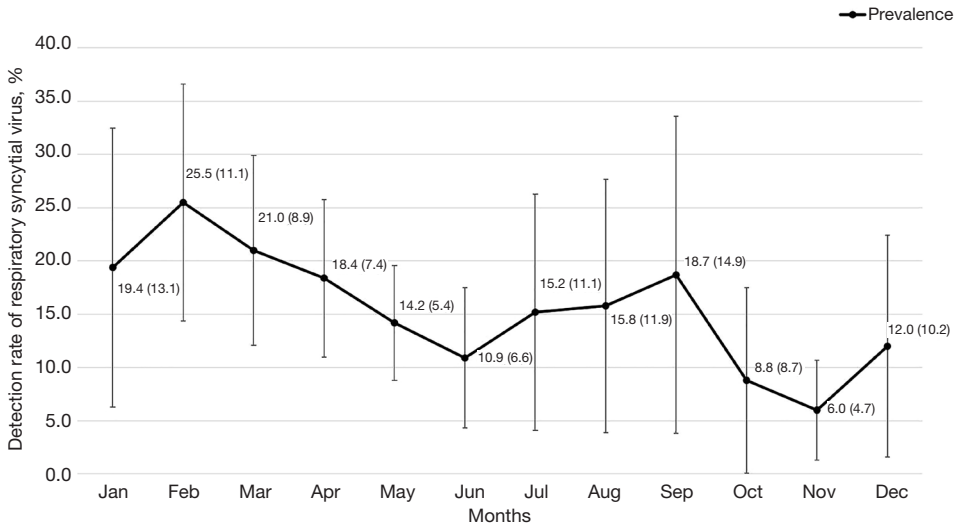

Figure 4 The detection rate of RSV in CAP hospitalized children in different months. In each month, mean (standard deviation) of RSV detection rates between 2010 and 2019 were calculated. CAP, community-acquired pneumonia; RSV, respiratory syncytial virus.

Table 2 Association of severe pneumonia and death with RSV infection

Complications	RSV positive	RSV negative	P value
Severe pneumonia			
Crude OR (95% CI)	1.36 (1.14, 1.61)	1.00 (reference)	<0.001
Multivariable-adjusted OR (95% CI)*	1.26 (1.04, 1.53)	1.00 (reference)	0.019
Death			
Crude OR (95% CI)	0.38 (0.12, 1.24)	1.00 (reference)	0.110
Multivariable-adjusted OR (95% CI)*	0.27 (0.07, 1.09)	1.00 (reference)	0.066

*, multivariable models were adjusted for age, sex, month and coinfection. RSV, respiratory syncytial virus; OR, odds ratio; CI, confidence interval.

(49/818, 6.0%) (*Figure 4*).

Distribution of RSV in children with severe pneumonia

Children with severe pneumonia accounted for 9.5% (937/9,837). After adjusting for potential confounders, the RSV-positive children were associated with increased risk of severe pneumonia compared to RSV-negative children (multivariable-adjusted OR 1.26, 95% CI: 1.04 to 1.53, P=0.019). There were 3 (3/1,507, 0.2%) RSV-positive and 43 (43/8,330, 0.5%) RSV-negative hospitalized children with CAP who died during our study, but the difference was not statistically significant (multivariable-adjusted OR 0.27, 95% CI: 0.07 to 1.09, P=0.066) (*Table 2*). In addition, children with severe pneumonia had significantly lower CT values than those without severe pneumonia (28.88±3.89 *vs.* 30.42±3.33, P<0.01), suggesting higher concentrations of the virus in children with severe pneumonia. The Pearson correlation analysis indicated the significantly negative association between CT values and severe pneumonia (r=–0.146, P<0.01).

The detection rate of coinfections

Among RSV-positive hospitalized children with CAP, 266 cases (266/1,507, 17.7%) exhibited coinfection with other viruses (*Table 3*). The most common coinfection was multiple coinfection (85/266, 32.0%), which was defined as coinfection with more than two viruses in addition to RSV. INFA (41/266, 15.4%) was the most common

Table 3 Distribution of virus in 266 co-infection patients

Type of virus	N (%)
INFA	41 (15.4)
INFB	10 (3.8)
PIV	15 (5.6)
EV	20 (7.5)
CoV	28 (10.5)
HMPV	6 (2.3)
HBoV	14 (5.3)
HRV	24 (9.0)
ADV	23 (8.6)
Multiple infection*	85 (32.0)

*, multiple infection was defined as coinfection with more than two viruses in addition to RSV. INFA, influenza virus A; INFB, influenza virus B; PIV, parainfluenza virus; EV, enterovirus; CoV, coronavirus; HMPV, human metapneumovirus; HBoV, human bocavirus; HRV, human rhinovirus; ADV, adenovirus.

coinfection virus. Patients with coinfection (38/266, 14.3%) have a higher risk of severe pneumonia than those without coinfection (142/1,241, 11.4%), but the difference was not statistically significant (multivariable-adjusted OR 1.39, 95% CI: 0.94 to 2.05, P=0.101).

Discussion

Our data indicated that the detection rate of RSV was highest in hospitalized children with CAP ≤0.5 years old, and the detection rate of RSV gradually decreased with increasing age, which was consistent with a previous study on RSV epidemiology (9). The specific reasons why infants ≤0.5 years old were more likely to be infected with RSV may be ascribed to their immature lungs and immune system (10). The immune response at that stage usually has functional defects and quantitative defects of antigen-presenting cells and effector cells (11), which is different from the adult immune response. Thus, infants are susceptible to a variety of respiratory viruses, such as RSV (10), influenza virus (12) and measles (13). In addition, we found that the detection rate of RSV in male children was significantly higher than that in female children (P<0.001), suggesting that male children are relatively more likely to be infected with RSV. Similar to the results in our study, Radhakrishnan *et al.* found that there were more males than females (63.8% *vs.* 44.2%) children who were hospitalized for RSV infection in a population-based study of children in Ontario, Canada (14). Uekert *et al.* also found that sex differences were correlated with either the frequency or severity of viral respiratory tract infections during the first few years of life (15). Sex differences in corticosteroid secretion and activity could theoretically explain variations in susceptibility to RSV infection, and there is conclusive evidence that sex hormones can influence the development of specific lymphocyte populations and cytokine production (16,17).

The detection rate of RSV in hospitalized children with CAP was 15.3% in our study, which was lower than that in northern China (33.3%) (18) and higher than that in African countries, such as Kenya (8.1%) (19). In addition, the detection rates of RSV peaked in February, January and March in our study, which was consistent with the results of a previous study (20). Cui *et al.* (21) found that the RSV infection rate in Beijing was highest from November to February. Guangzhou is subtropical and has a lower latitude than Beijing, so winter comes later in Guangzhou than in Beijing, which may explain why the month with the highest RSV detection rate in our study was later than that in the study by Cui *et al.* (21). In cold months, the virus has increased vitality because of less light and children's weakened immunity, which increase the risk of infection (22). In addition, increased gathering in the house during winter may also increase the risk of virus spreading.

We also found that the detection rate of RSV in hospitalized children with CAP from 2010 to 2019 exhibited a fluctuation every three or four years. A possible reason is the increased immunity for the prevalent RSV subgroup in children after a period of time, which may lead to an alternating prevalence between RSVA and RSVB (18,23). Song *et al.* (23) found that RSVB predominated between 2008 and 2010 in China, whereas RSVA predominated between 2010 and 2012. Previous studies also suggest that new mutant genotypes have been produced continuously since the BA genotype strain of RSVB was discovered in 2003 (24,25). By 2018, 15 genotypes derived from BA had been identified that could break through the previously established immunity for the BA genotype (24,25). However, more studies are needed to confirm the correlation between the infection rate of RSV in different years and various circulating genotypes.

The RSV-positive children were associated with increased risk of severe pneumonia compared to RSV-negative children (multivariable-adjusted OR 1.26, 95% CI: 1.04 to 1.53, P=0.019), which was consistent with

other studies (26,27). These studies suggested that RSV infection is more likely to develop into severe pneumonia. The pathogenic mechanism of RSV infection is more complicated and involves the combined effects of causative factors, airway epithelial cell-related factors, immune system responses, nervous system responses, host factors, and environmental factors, which may worsen the child's illness (28). We also found the significantly negative association between CT values and severe pneumonia, suggesting that children with higher concentrations of RSV may be prone to have severe pneumonia. This finding would help clinicians identify children at high risk of pneumonia early and make proper management strategies.

In this study, 17.7% (266/1,507) of hospitalized children with CAP who were RSV positive were also positive for other viruses. Moreover, patients with coinfection (38/266, 14.3%) tended to have a higher incidence of severe pneumonia than those without coinfection (142/1,241, 11.4%), but the difference was not statistically significant (P=0.101). Some scholars have reported that compared with single RSV infection, RSV coinfection with other viruses had higher rates of pneumonia, hospitalization and mechanical ventilation (29), but Papenburg *et al.* (30) reported that there was no significant difference in the severity of the two.

Our study has better objectivity and fewer data errors due to the large sample size and better representation due to the long study period. However, there were several limitations in our study. First, we only analyzed the epidemiological characteristics of RSV infection in hospitalized children with CAP in Guangzhou. Second, limited by the sample collection protocol, we were unable to acquire detailed information on coinfection in RSV-negative children, and potential coinfection with bacteria or other viruses in the non-RSV group may bias the results. In addition, we did not test the sputum, and possible pathogens in sputum were not available in our study. Although previous studies have demonstrated that the sensitivity and specificity of oropharyngeal swabs are relatively high (31), the detected pathogens may not be the cause of pneumonia (32). Thus, the correlation between RSV and severe CAP cannot be confidently stated, as our study did not analyze other pathogens, such as bacteria that cause pneumonia.

Conclusions

In this study, the data on RSV infection in hospitalized children with CAP in Guangzhou from 2010 to 2019 were analyzed in many respects. The current study suggested that January to March were the key months for prevention and control of CAP caused by RSV in Guangzhou, and children less than 0.5 years old were the key population for prevention and control of CAP caused by RSV. Policy makers should make timely adjustments to prevention measures and medical resources based on these epidemiological characteristics. Our study also found that RSV-positive CAP children were more likely to develop severe pneumonia, which suggested the importance of early treatment and close attention in these patients' and CT values of RSV may be helpful in assessing the risk of severe pneumonia.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-331/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-331/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-331/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-331/coif). 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. The study was

conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the First Affiliated Hospital of Guangzhou Medical University Ethics Committee (No. 20170315), and individual consent for this retrospective analysis was waived.

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