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Original Article

Epidemic patterns and the immunity levels in hospitalized patients with respiratory syncytial virus infection in 2019-2023

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Abstract

Introduction: The epidemic pattern of the Respiratory syncytial virus (RSV) has changed during the COVID-19 pandemic. To analyze the epidemic pattern of RSV infection and explore the fluctuations of immunity.
Methodology: Pediatric inpatients diagnosed with RSV infection or RSV pneumonia from January 2019 to August 2023 in a tertiary hospital were retrospectively included. The children were divided into three groups: before the implementation of non-pharmaceutical interventions (NPIs) group, during the implementation of NPIs group, and after the lifted NPIs group.
Results: A total of 462 children were included in this study. During the implementation of NPIs, there were almost no RSV hospitalizations from February to October 2020. In May 2023, the number of children infected with RSV increased dramatically. The RSV infected children in after the lifted NPIs group was mainly ≥ 3 years old. RSV mixed infections (56.93%) were slightly more common than RSV single infection (43.07%). The levels of IgG, IgA, IgM, and CD3+%, CD8+% during the implementation of NPIs and after the lifted NPIs groups were lower than those in the other group of infants 0-6 months old, and the levels of CD3+ % and CD3 + CD4+ % in children 7-12 months old were found to be similar.
Conclusions: After the lifted NPIs, the RSV epidemic season was delayed to spring and summer. Humoral immunity and part of the cellular immunity in infants varies before and after NPIs. We pay close attention to the surveillance data of RSV to prevent RSV infection.

Key words: COVID-19; respiratory syncytial virus; epidemiology; non-pharmaceutical interventions; immune debt.

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Introduction

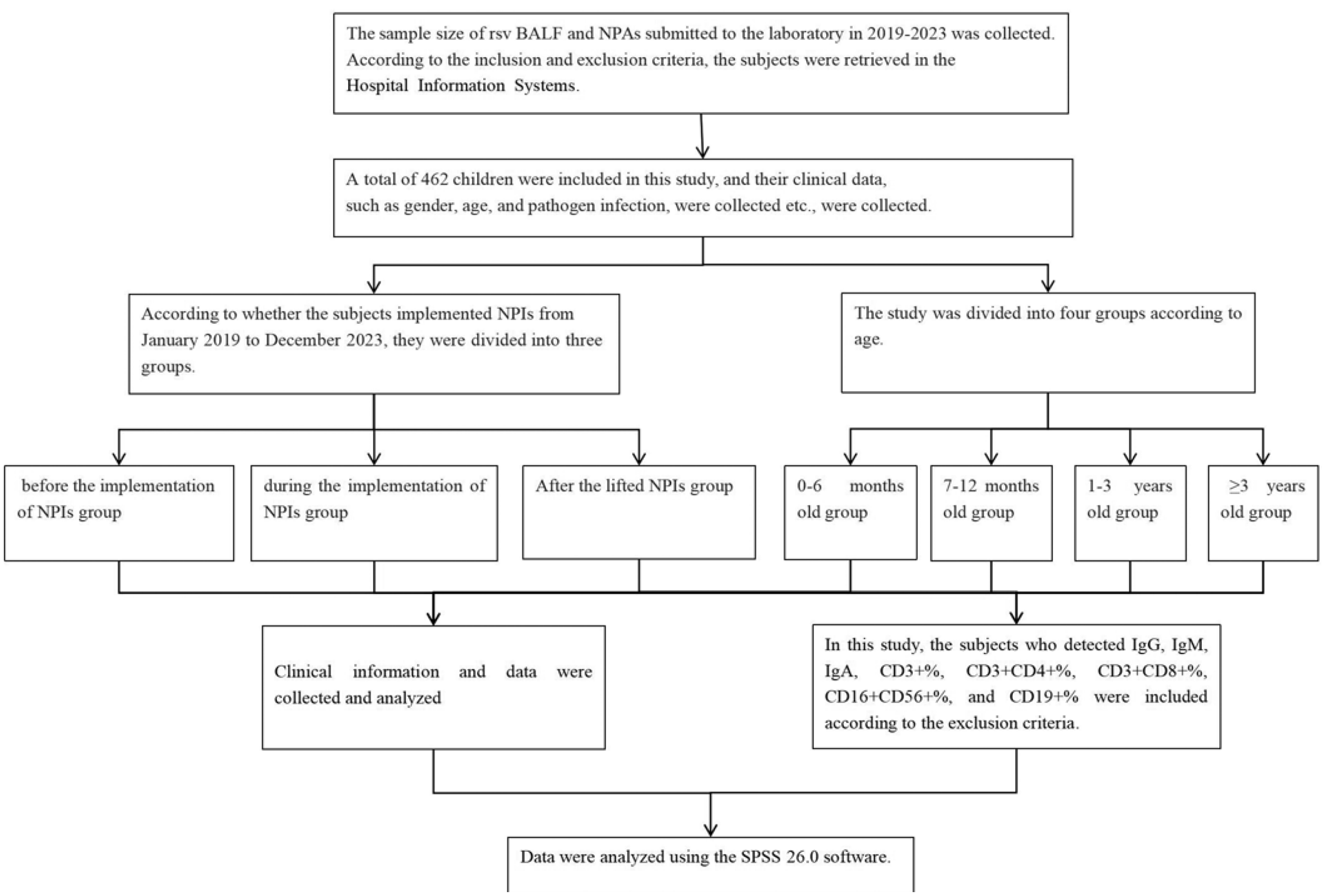
Respiratory syncytial virus (RSV) is an enveloped, non-segmented, single femoral negative-stranded RNA virus, belonging to the family of Pneumonia viridae, which is mainly transmitted by droplets. RSV infection is the primary factor causing hospitalization for viral respiratory infections in children younger than 5 years, causing 3.2-3.6 million hospitalizations and more than 100 000 deaths every year in children under the age of 5 years, 44% of hospitalized patients are infants younger than 2 months [1]. During the coronavirus disease 2019 (COVID-19) pandemic, China immediately adopted a series of stringent non-pharmaceutical interventions (NPIs), including COVID-19 testing, home isolation, contact tracing, wearing masks, and social distancing, which not only block the transmission of COVID-19, but also reduce exposure to pathogens and affect the epidemiological characteristics of pediatric infectious diseases [2]. Globally, rates of RSV infection and bronchiolitis have been remarkably low since early 2020 [3]. Moreover, different countries adopted different NPIs to respond, resulting in a substantial reduction in the number of RSV and other respiratory pathogen infections [3–6]. After the adoption of NPIs in South Korea, the incidence of respiratory tract infection was greatly reduced, such as adenovirus, respiratory syncytial virus, influenza virus, etc. [4]. The decreased incidence of respiratory infections during the implementation of NPIs was found in southwest China, in particular, respiratory syncytial virus and influenza virus [5]. During the implementation of NPIs, there was a lack of appropriate immune stimulation of pathogens in the population, and the increase in susceptible populations led to a decline in the herd immunity level compared with that before the epidemic [7]. The difference between the population immunity levels during the epidemic and before the epidemic is the immune debt during the COVID-19 pandemic, also known as the immunity gap. This immune debt is a particular concern for RSV, for which temporary immunity is obtained through exposure to the virus and maternal antibodies wane quickly; without seasonal exposure, immunity decreases and susceptibility to future, and potentially more severe, infection increases [8–10]. The epidemic trend of RSV has changed with the gradually lifting of NPIs in China.

This study aimed to understand the epidemic patterns of RSV infection in pediatric inpatients at the Affiliated Provincial Hospital of Shandong First Medical University from 2019 to 2023, and explore the fluctuations of immunity. When entering the RSV epidemic season or when the epidemic of RSV in local communities increases, NPIs should be used to reduce the chance of RSV exposure. And vaccines-and-immunization should be given as early as possible in order to prevent severe RSV infection and death in children [11,12].

Methodology

In this study, data were retrospectively selected in the Hospital Information Systems. The study was approved by the institutional review board of the Biomedical Research Ethics Committee of Shandong Provincial Hospital (NO. SWYX2023-476). This study recruited children under the age of 14 who were hospitalized in the Affiliated Provincial Hospital of Shandong First Medical University from January 2019 to August 2023. These children were diagnosed with RSV infection or RSV pneumonia, and it took us nearly one month to collect the clinical information of all the subjects, including gender, age, and pathogen infection. The changes in their immune levels and epidemiology were analyzed and compared. All children were divided into three groups: before the implementation of NPIs group (2019-01-01 to 2019-12-31); during the implementation of NPIs group (2020-01-01 to 2022-12-31); and after the lifted NPIs group (2023-01-01 to 2023-08-31). The exclusion criteria for children testing immune levels that were included were: (i) premature birth; (ii) low birth weight; (iii) autoimmune disease; (iv) congenital disease, and (v) history of the immunoglobulin input. See Figure 1 for the recruitment process.

Figure 1. Processes of the study method.



BALF: bronchoalveolar lavage fluid; NPAs: nasopharyngeal swabs.

RSV Sample Collection and Detection

Functional testing was performed for all patients at admission, involving respiratory pathogen testing samples such as bronchoalveolar lavage fluid (BALF), and nasopharyngeal swabs (NPAs). In brief, BALF collection under fiberoptic bronchoscopy was completed within 1-7 days of the early course of the disease. BALF was placed in a 1.5 mL centrifuge tube and centrifuged at 12,000 rpm/minute for 5 minutes. All nasopharyngeal swabs (NPAs) samples were collected within 24 hours of admission. A disposable sterile suction tube was inserted 7–8 cm through the nasal cavity to achieve negative pressure below the pharynx to absorb 1–2 mL of deep NPAs. The assay was then performed using the Quantitative Real-time PCR (Sansure Biotech Inc).

Detection of Mixed Infections

NPAs were collected, and immunofluorescence was used to detect influenza A, influenza B, human rhinovirus (HRV), adenovirus (ADV), and respiratory syncytial virus antigens (respiratory virus detection kit, real-time PCR, China). Other microorganisms, including *Haemophilus influenzae* and *Staphylococcus*, were detected by gram staining and blood culture of sputum specimens. Atypical bacteria including *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* were tested with antibodies in blood samples.

Detection of immunity

Morning fasting venous blood (5 mL) was drawn from the study subjects and centrifuged at 4000 rpm/min (effective radius 17 cm) for 10 min to detect the relevant indexes of their immune function. IgG, IgA, and IgM were measured by an automatic protein analyzer (BN II, Siemens Healthcare Diagnostics Products GmbH, Schwalbach, Bavaria, Germany), and percentages of CD3+, CD4+, and CD8+ were detected by flow cytometer of BD Canto II, USA. All reagents and calibration solutions were used as original packaging without modification.

Statistical analysis

Data were analyzed using the SPSS 26.0 software. Categorical variables are described by numbers and percentages (n, %), continuous variables with a skewed distribution are described by medians and interquartile ranges (IQRs) [M (P25/P75)], and continuous variables with a normal distribution are described by means and standard deviations ($\bar{x} \pm S$). Count data statistics were performed by chi-square test and econometric data statistics by the non-parametric test, and $p < 0.05$ was considered statistically significant.

Results

Age characteristics of the children with RSV infection

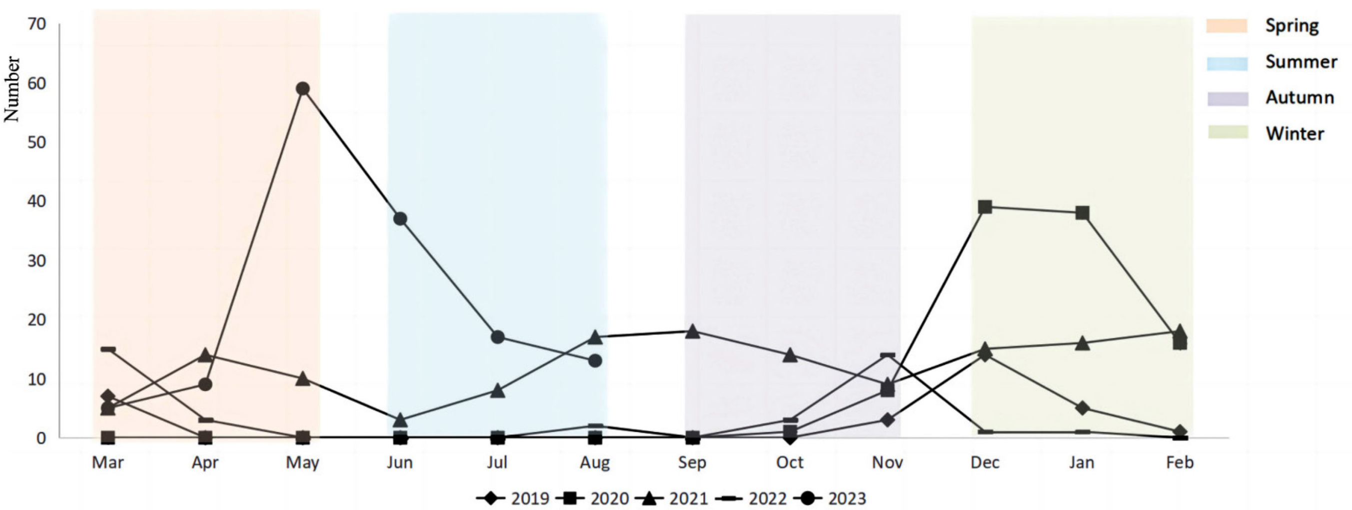
In this study, a total of 10207 RSV BALF and NPAs were submitted from January 2019 to August 2023, and the positive rate of before the implementation of NPIs group was 5.36% (133/2480); during the implementation of NPIs group was 8.14% (507/6226); and after the lifted NPIs group was 11.13% (167/1501). A total of 462 children diagnosed with RSV infection were included. The hospitalization rate of RSV infection was 21.05% (28/133) before the implementation of NPIs; 57.79% (293/507) during the implementation of NPIs; and 83.8% (141/167) after the lifted NPIs. In the study group, there was a higher proportion of male children than female children (61.26% vs. 38.74%). The recruited children were aged 0-11 years. As shown in Table 1, the proportion of children aged 1-3 years was the highest (35.28%,

Table 1. Demographic, clinical data of patients enrolled before, during, and after NPIs.

Variable	Groups			Total	*p* value
	Before NPIs n = 28 (%)	During NPIs n = 293 (%)	After NPIs n = 141(%)	n = 462 (%)	
Gender					
male	23 (82.14) ^{a}	184 (62.80)	76 (53.90) ^{a}	283 (61.26)	0.013
female	5 (17.86) ^{a}	109 (37.20)	65 (46.10) ^{a}	179 (38.74)	
Age					
0-6 months	10 (35.71)	75 (25.60)	24 (16.22)	109 (23.59)	< 0.001
7-12 months	5 (17.86)	49 (16.72)	23 (14.41)	77 (16.67)	
1-3 years	11 (39.29)	112 (38.23)	40 (28.83)	163 (35.28)	
≥ 3 years	2 (7.14) ^{a}	57 (19.45) ^{b}	54 (40.54) ^{ab}	113 (24.46)	
Degree of disease					
severe pneumonia	8 (28.57)	66 (22.53)	36 (25.53)	110 (23.81)	0.655
mild pneumonia	20 (71.43)	227 (77.47)	105 (74.47)	352 (76.19)	
Detection of pathogens					
single pathogen infection	8 (28.57)	132 (45.05)	59 (41.84)	199 (43.07)	0.130
mixed one pathogen infection	9 (32.14)	106 (36.18)	53 (37.59)	168 (36.36)	
mixed two or more pathogens infection	11 (39.29) ^{a}	55 (18.77) ^{a}	29 (20.57)	95 (20.56)	

Before NPIs: before the implementation of NPIs group; During NPIs: During the implementation of NPIs group; After NPIs: after the lifted NPIs group. Same subscript ^{a} or ^{b} is denoted $p < 0.05$ in the same row.

Figure 2. Seasonal distribution of RSV infection from 2019 to 2023.

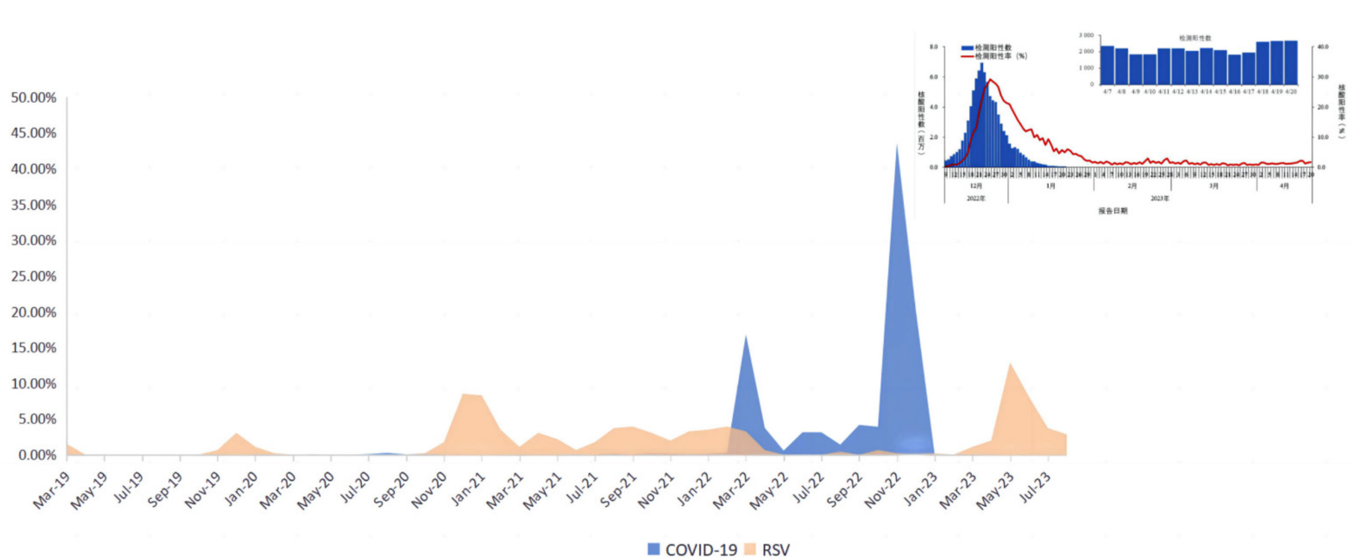


163/462), followed by those aged ≥ 3 years (24.46%, 113/462). All children with RSV infection were mainly aged 0-6 months and 1-3 years before the implementation of NPIs. As also shown in Table 1, children with RSV infection were mainly aged 1-3 years during the implementation of NPIs and ≥ 3 years after the lifted NPIs.

Time distribution characteristics of RSV infection

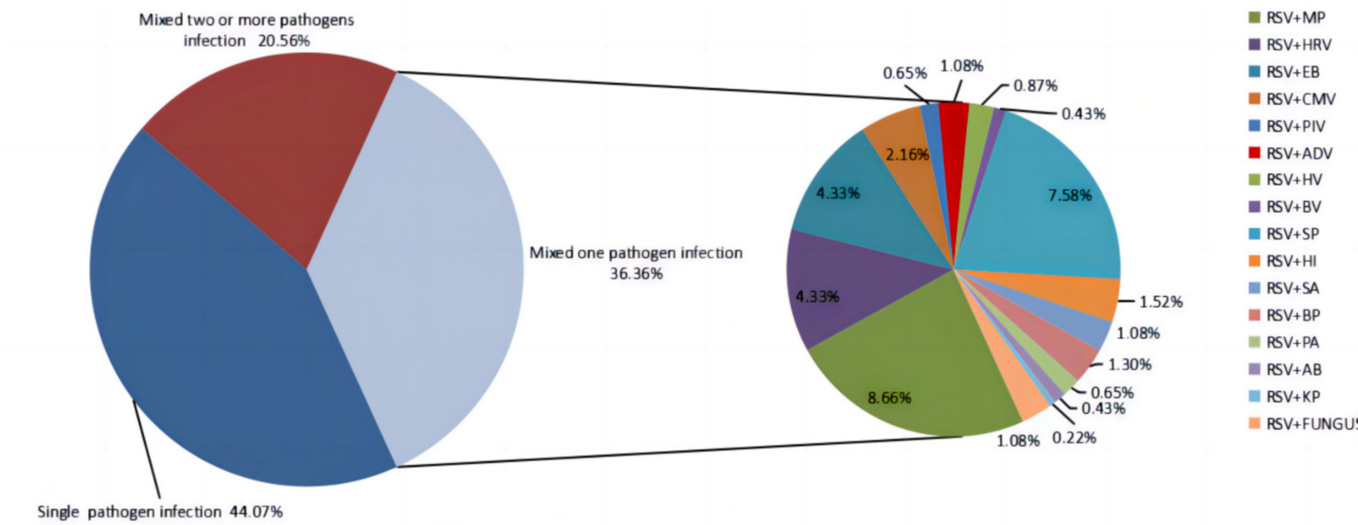
In this study, the number of children hospitalized with RSV infection was 28 in 2019, 54 in 2020, 167 in 2021, 72 in 2022, and 141 from January to August 2023. After the COVID-19 outbreak (early 2020), there were almost no RSV hospitalizations from February to October 2020. There were higher numbers of RSV infections seen in March and November 2022. Three months after the NPIs were lifted in December 2022, COVID-19 infection was at its peak, and there is almost no RSV infection data. During 2023, the number of children with RSV infection peaked from 2019 to 2023 and also increased sharply in May 2023, as detailed in Figures 2 and 3. For the period 2019 to 2020, the number of hospitalized children with RSV infection was the highest in winter ($p < 0.05$). There was no difference in the distribution of hospitalized children throughout the year, and the numbers in spring and autumn were significantly greater than in winter ($p < 0.05$) in 2022.

Figure 3. Distribution of the proportions of RSV and COVID-19 infections.



COVID-19 infection data were obtained from the number of new COVID-19 infections from April 2020 to mid-December 2022 released by the Shandong Provincial Health Commission. The upper right corner shows the daily number of COVID-19 infections from November 2022 to April 2023 in China [29].

Figure 4. Distribution of RSV single and mixed infections.



MP: *Mycoplasma pneumoniae*; HRV: Human rhinovirus; EBV: Epstein-Barr virus; CMV: Cytomegalovirus; PIV: Parainfluenza virus; ADV: Adenovirus; HV: Herpes virus; BV: *Bocavirus*; SP: *Streptococcus*; HI: *Haemophilus influenzae*; SA: *Staphylococcus*; BP: *Bordetella pertussis*; PA: *Pseudomonas aeruginosa*; AB: *Acinetobacter baumannii*; KP: *Klebsiella pneumoniae*.

Distribution of RSV single infections and mixed infections

The number of RSV mixed infections (56.93%, 263/462) was slightly higher than that of RSV single infections (43.07%, 199/462) from 2019 to 2023. There were 168 children with RSV mixed infections with one pathogen and 95 children with RSV mixed infections with two or more pathogens, as shown in Table 1. Among the RSV mixed infections with one pathogen, RSV+ *Mycoplasma pneumoniae* (MP) accounted for the highest proportion (8.66%, 40/462), followed by RSV+ Streptococcus (SP) (7.58%, 35/462), RSV+ human rhinovirus (HRV) (4.33%, 20/462), and RSV+ Epstein-Barr virus (EBV) (4.33%, 20/462). See Figure 4 for more details.

Changes in immune levels

During the implementation of NPIs, the levels of IgG, IgA, IgM, CD3+%, CD3+ CD4+%, and CD3+ CD8+% decreased compared with those before the implementation of NPIs group and after the lifted NPIs group. However, there was an increase of CD16+ CD56+% and CD19+% when compared with those before the implementation of NPIs group (no significant difference), as shown in Table 2. The immune levels were found to be different for those 0 - 6 months old as compared to children 7-12 months old (as shown in Figure 5a-d).

Discussion

RSV is a seasonal virus with differential regional epidemiology, depending on the geographic region and climate. In the northern hemisphere, RSV usually spreads between November and March with a peak

Table 2. Immune level of before NPIs, during NPIs and after NPIs.

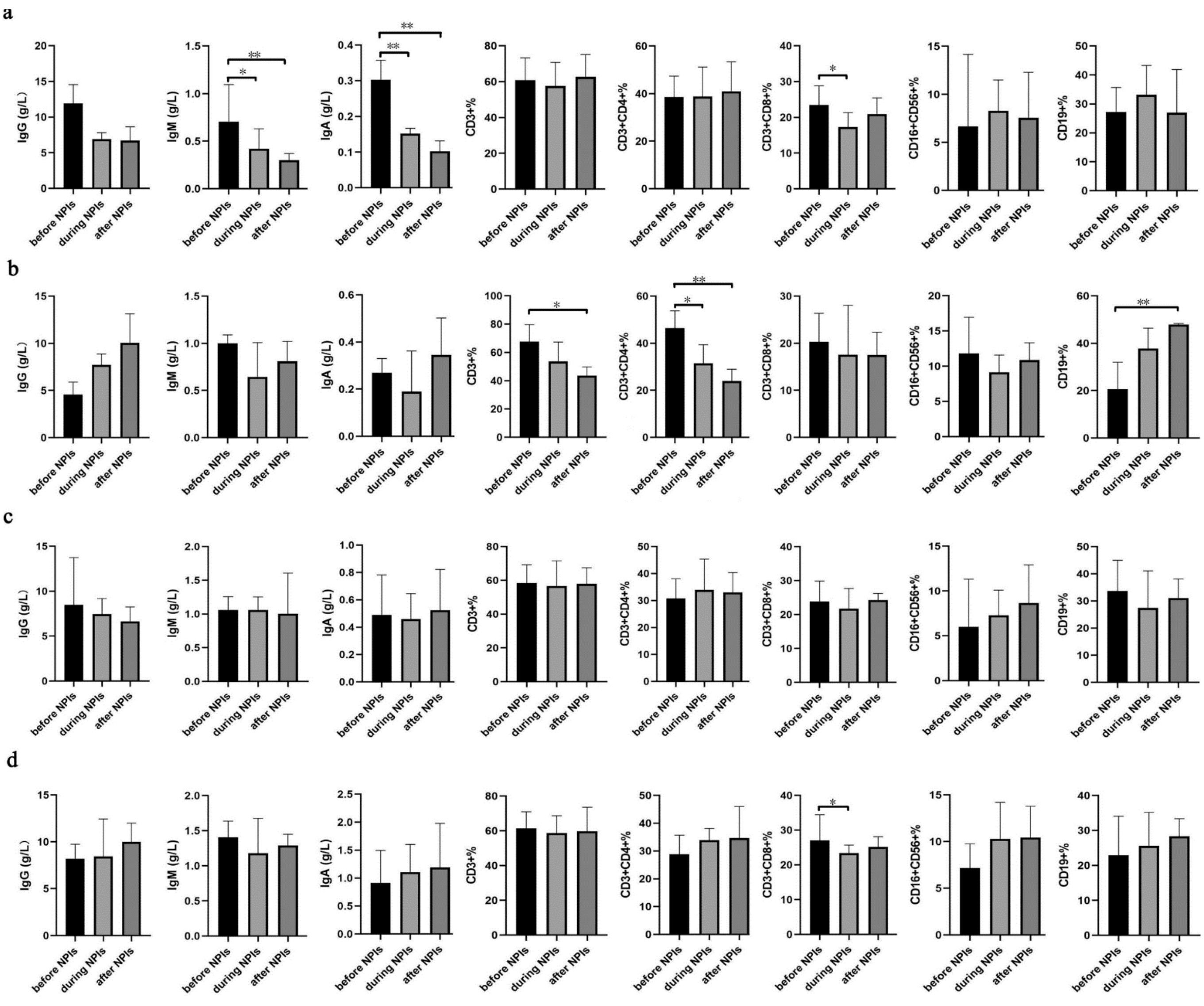
Immunity	Groups			p value
	Before NPIs	During NPIs	After NPIs	
Humoral immunity				
IgG[M(P_{25},P_{75})]	7.91 (4.45,12.65)	6.46 (4.35,9.95)	8.28 (6.68,11.90)	0.090
IgA[M(P_{25},P_{75})]	0.35 (0.25,0.61) [a]	0.32 (0.14,0.57) [b]	0.86 (0.39,1.36) [ab]	< 0.001
IgM[M(P_{25},P_{75})]	0.98 (0.68,1.17)	0.77 (0.43,1.19) [a]	1.16 (0.82,1.45) [a]	0.004
Cellular immunity				
CD3+%($\bar{x}$±S)	66.88±2.71	57.24±1.35	58.53±2.42	0.501
CD3+CD4+%($\bar{x}$±S)	36.45±2.23	35.04±1.08	33.04±1.84	0.539
CD3+CD8+%[M(P_{25},P_{75})]	23.08 (19.09,27.50)	19.15 (14.66,25.84) [a]	24.29 (19.31,26.76) [a]	0.029
CD16+CD56+%[M(P_{25},P_{75})]	6.48 (4.78,13.84)	8.17 (5.03,11.48)	8.94 (5.32,13.23)	0.643
CD19+%[M(P_{25},P_{75})]	29.12 (19.59,35.84)	30.72 (21.96,41.04)	31.45 (20.27,40.15)	0.709
4/8 Ratio[M(P_{25},P_{75})]	1.70 (1.25,2.32)	1.62 (1.18, 2.42)	1.38 (1.16,2.09)	0.175

Before NPIs: before the implementation of NPIs group; During NPIs: During the implementation of NPIs group; After NPIs: after the lifted NPIs group. Same subscript [a] or [b] is denoted $p < 0.05$ in the same row.

incidence in January/February, whereas in the southern hemisphere, the RSV season is usually seen from June to September. The seasonal patterns of RSV prevalence vary under different climatic conditions. RSV infection is often prevalent in late autumn, winter, and early spring in temperate, tropical and subtropical regions, that are often associated with the rainy season [13,14]. This study found that during the implementation of strict NPIS, during the first wave of the COVID-19 pandemic, there were almost no data on hospitalized children with RSV infection from February to July 2020 – and that was consistent with two studies published in Southwest China and Zhejiang [5,15]. Moreover, the non-seasonal epidemic peak occurred in the summer of 2020 in Guangdong and many provinces of other countries, which may be related to the subtropical monsoon climate in Guangdong and the relaxation of epidemic prevention and control measures in other countries [16]. In May 2023 (after the lifted NPIs), the number of hospitalized children with RSV infection increased sharply, and the peak was delayed compared with previous years. In the Southern Hemisphere, such as South Africa and Australia, the RSV epidemic season was delayed until spring [17]. In Spain, the winter epidemic had disappeared and shifted to spring and summer [18]. This pattern of delayed RSV prevalence was similar to that seen during the 2009 H1N1 influenza epidemic [19].

RSV is one of the most common causes of lower respiratory tract infection in children younger than 3

Figure 5. The distribution of immune levels by age group.



a-d: The distribution of immune levels in children aged 0-6 months, 7 to 12 months, 1-3 years, and ≥ 3 years. before NPIs, before the implementation of NPIs group; during NPIs, during the implementation of NPIs group; after NPIs, after the lifted NPIs group. *: $p < 0.05$; **: $p < 0.01$.

years old [1]. In an Australian study, the proportion of children aged 2-4 years during the peak of RSV also increased compared with previous years [20]. In New York, the median age before and during COVID-19 (2019-2020) was 17 months, while after the lifted NPIs (2021-2022), the median age was 6 months [21]. In this study, the age at RSV infection increased after the lifted NPIS, mainly in children ≥ 3 years old. In addition, this study found an increase of RSV infection in children ≥ 3 years old after the removal of non-pharmacological intervention, which may be multifactorial and related to (i) the lack of pathogen exposure in these children during the 3 years of during the implementation of NPIs, (ii) the potential reduction of adaptive immunity to specific pathogens in some children due to NPIs, and (iii) the delay or interruption of vaccination during this period [10,22].

RSV mixed infection with other pathogens is often seen clinically. In this study, there was no significant difference between single infection with RSV and mixed infection from 2019 to 2023. Mixed infections with one pathogen are most commonly seen in combination with Mycoplasma pneumoniae followed by Epstein-Barr virus. However, HRV is the most common mixed infection of RSV in the Hebei region of China [23], Vietnam [24], and Belgium [25], while mixed HRV infection was less common in this study.

As children grow, the immunity is also developed, and the clinical incidence of RSV and other respiratory infections is also reduced. Therefore, children's immune disorders may be an important factor that leads to children's recurrent respiratory tract infections. Some studies have shown that decreased exposure to RSV during the COVID-19 pandemic was due to a lack of protective immunity, and a large number of individuals being vulnerable to RSV. We tend to obtain temporary immunity through exposure to the virus [8,9]. Infant IgG is primarily of maternal origin, while IgA and IgM gradually develop to adult levels after birth [26]. In this study, the levels of IgG, IgA, and IgM before the implementation of NPIs were higher than those during the implementation of NPIs and after the lifted NPIs in children aged 0-6 months. The decrease in IgG may be due to decrease in maternal immunity, and decrease in IgA and IgM may be due to decrease in exposure to pathogens during the implementation of NPIs. The IgG level of infants decreases to the lowest level at 3-5 months after birth, and then gradually increases to adult levels at approximately 8-10 years old. In this study, the IgG level in the group of children aged 7-12 months, after the lifted NPIs, was found to be higher than that before and during the implementation of NPIs; - this could be related to them being more exposed to these pathogens. Studies have found that passive immunity via human milk against common respiratory viruses was reduced during the COVID-19 pandemic, which may have consequences for the protection of breastfed infants against respiratory infections [27]. The decrease in CD3+ T and CD3+CD4+ T cells was associated with pathogen infection. In children with ≥ 1 year old, there was almost no significant difference in the immune levels before the implementation of NPIs, during the implementation of NPIs, and after the lifted NPIs, which indicated that NPIs may not be correlated with the level of immunity in older children.

In this study, all three periods of NPIs were long, which allowed a clear description of the epidemic trend of RSV infection in hospitalized children. In addition, some patients with comorbidities expected to affect their immunity were excluded from the study, and the main focus was on age stratified patients in order to analyze any immune changes during each period. The delay or interruption of routine immunization in children may lead to an increase in the susceptible population of vaccine-preventable diseases, the decline of immunity, and the increase of incidence [10]. There is a lack of vaccination information of the subjects in this study.

The COVID-19 pandemic is known to have impacted on the immunity levels and the way children responded to various pathogens [28]. However, there is a lack of data on patients with COVID-19 infection, which may have a certain impact on the statistical results of this study. Consequently, more data is needed to supplement the study results.

Conclusions

In this study, similar to other studies published from China and elsewhere, the pattern of RSV infection over the study time showed a delayed form of epidemic after the lifted NPIs. The delay was seen from autumn and winter to spring and summer; and older children after the lifted NPIs where the pattern of infection increased slightly compared with before the implementation of NPIs and during the implementation of NPIs. The humoral immunity of infants was different before and after the implementation of NPIs. These may be related to the implementation of NPIs that greatly reduce the exposure to common pathogens and lack of appropriate immune stimulation. Therefore, in our clinical work, we need to pay attention to the epidemic trends of any respiratory virus infection and fluctuations of immunity after the implementation of NPIs. We need to improve the awareness of the epidemic trends for any respiratory virus infection, and pay attention to the respiratory infection data released by the National Center for Disease Control and the National Health Commission, be prepared hospital to receive large numbers of children with respiratory infections during peak periods of infection. NPIs can be implemented to reduce the exposure opportunities of pathogens. In addition, monoclonal antibodies can be applied as early as possible, such as palivizumab and nisevirumab, prevents severe RSV infected illness and death in infants younger than 1 year of age and reduces morbidity in children younger than 5 years of age. During weeks 32 through 36 of pregnancy can be the RSV vaccine, to further prevent infants under 6 months of age of severe acute respiratory infection.

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Conflict of interests
No conflict of interests is declared.

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