

Post-COVID-19 Dynamics of Pediatric Respiratory Viruses in Wuhan: Epidemiology, Co-Infection Patterns, and Clinical Severity (2023–2024)

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Purpose: This study aimed to investigate the spectrum of respiratory viruses and analyze the clinical characteristics of viral co-infections among children presenting with respiratory symptoms in Wuhan following the COVID-19 pandemic.

Methods: A total of 40,846 pharyngeal swabs were collected from children with respiratory tract infections at the Maternal and Child Health Hospital of Hubei Province between January 2023 and August 2024. Nucleic acids of six respiratory viruses were tested, and clinical data from a subset of virus-positive children were retrospectively analyzed.

Results: The overall virus positivity rate was 54.55%. *Adenovirus* (ADV, 18.03%), *influenza A* (FluA, 12.90%) and *respiratory syncytial virus* (RSV, 10.63%) were the most prevalent viruses. The positivity rate was slightly higher in male children (55.16%) than in females (53.80%), peaked during winter (70.20%), and was highest among children aged 4–6 years (58.60%). Among virus-positive cases, 945 (4.24%) had co-infections with two viruses, with the highest co-infection rate observed for *RSV* and *influenza B* (FluB, 2.03%). Compared to children with *RSV* single infection, those with *RSV* co-infection were generally older and presented with a higher incidence and peak of fever, along with elevated white blood cell (WBC), neutrophil (NEU), and monocyte (MONO) counts, higher levels of C-reactive protein (CRP) and interleukin-6 (IL-6), but lower complement 4 (C4) levels. In contrast, *RSV* single infection was associated with higher rates of oxygen inhalation, severe pneumonia, and elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and creatine kinase (CK).

Conclusion: Respiratory viruses remain highly prevalent in symptomatic children in Wuhan, showing distinct patterns. Co-infections can occur among the six viruses studied, with *RSV* and *FluB* showing the highest co-infection rate. *RSV* co-infections are associated with a distinct clinical and inflammatory profile compared to single *RSV* infections, highlighting the importance of considering co-infection status in clinical management.

Keywords: respiratory virus infection, Co-infection, epidemiology, clinical severity, COVID-19

Introduction

Acute respiratory tract infections (ARIs) are the most common infectious diseases in children, with a variety of viruses—such as *influenza virus*, *respiratory syncytial virus* (RSV), *adenovirus* (ADV), and *parainfluenza virus*—serving as primary causative agents worldwide.^{1,2} Despite most viral infections being self-limiting and manageable with symptomatic treatment, they can lead to severe complications and life-threatening conditions in vulnerable populations such as immunocompromised children, premature infants, and those with chronic diseases. Among these pathogens, RSV poses a particularly significant threat to children's health, causing an estimated 33 million lower respiratory tract infections in children under five years old globally in 2019, resulting in approximately 3.6 million hospitalizations and over 100,000 deaths.³ In China, the situation remains a significant public health concern.⁴ Moreover, RSV is a major driver of pediatric hospitalizations, with particularly high hospitalization rates observed among infants and young

children.^{5,6} Given its substantial disease burden, RSV serves as a critical focal point for investigating viral co-infections, which are common in pediatric respiratory illnesses but whose impact on clinical severity remains incompletely understood. Post-viral infections can lead to dysregulated immune function, increasing susceptibility to secondary infections and complicating clinical diagnosis and management.^{7,8}

Furthermore, the epidemiological landscape of respiratory viruses has been profoundly reshaped by the COVID-19 pandemic. Widespread non-pharmaceutical interventions (NPIs) implemented during the pandemic, such as masking and social distancing, led to a dramatic suppression of common respiratory pathogens, creating an “immunity debt” that has altered the age distribution and seasonality of these viruses in the post-pandemic era. Following the reclassification of COVID-19 as a “Category B” infectious disease in China—a transition that marked a strategic shift towards less stringent population-level containment measures—the spectrum, spatiotemporal distribution, and clinical behavior of common respiratory pathogens in children may have undergone significant shifts.^{2,9–11} This altered epidemiological context presents new challenges for diagnosis and treatment, as waning population immunity and disrupted viral circulation patterns could lead to more severe or atypical presentations. Continuous surveillance in the post-pandemic era is a critical necessity to understand these dynamic changes, identify emerging risks, and inform evidence-based prevention and control strategies. This study therefore aims to elucidate the post-pandemic epidemiological characteristics of six common respiratory viruses and the clinical severity of co-infections, with a particular focus on RSV, to provide valuable insights for prevention, control, and treatment strategies.

Materials and Methods

Study Design and Patient Recruitment

This was a single-center, retrospective observational study. We consecutively enrolled pediatric patients under 18 years of age who presented with symptoms of acute respiratory tract infection at the outpatient, emergency, or inpatient departments of the Maternal and Child Health Hospital of Hubei Province between January 1, 2023, and August 31, 2024. All enrolled children underwent pharyngeal swab collection and nucleic acid testing for respiratory viruses as part of routine clinical practice. A total of 40,846 children meeting these preliminary criteria were screened. The cohort comprised 22,628 male and 18,218 female children, stratified by age into the following groups: <1 year, 1–3 years, 4–6 years, 7–14 years, and >14 years. From an initial cohort of 40,846 pediatric patients, 22,283 tested positive for at least one respiratory virus. Subsequently, based on nucleic acid test results, we identified 3,827 cases (from which 100 hospitalized cases were further selected using simple random sampling) of *RSV* single infection and 477 cases of *RSV* co-infection with any of the other five viruses included in our panel. Finally, after applying stringent exclusion criteria (detailed in Exclusion criteria), 57 cases of *RSV* single infection and 48 cases of *RSV* co-infection were included for further analysis.

Exclusion criteria

- (1) Pediatric inpatients with co-infections involving other pathogens (ie., pathogens other than the six respiratory viruses included in our detection panel); (2) Pediatric inpatients with any comorbidities unrelated to respiratory tract infections; (3) Recent medications use that could affect test results. (4) Pediatric inpatients with inadequate clinical data.

The specific study design is shown in [Figure 1](#).

Research Methods

Respiratory infections and other related symptoms and diseases were diagnosed by referencing the “ZHU FUTNAG PRACTICE OF PEDIATRICS 9TH EDITION”.¹² The specific diagnostic criteria are as follows:

Diagnostic Criteria for Respiratory Infections

Upper respiratory tract infection: acute onset of nasal congestion, rhinorrhea, sore throat, cough, or fever; no abnormal rales on lung auscultation; chest imaging shows no obvious infiltration.

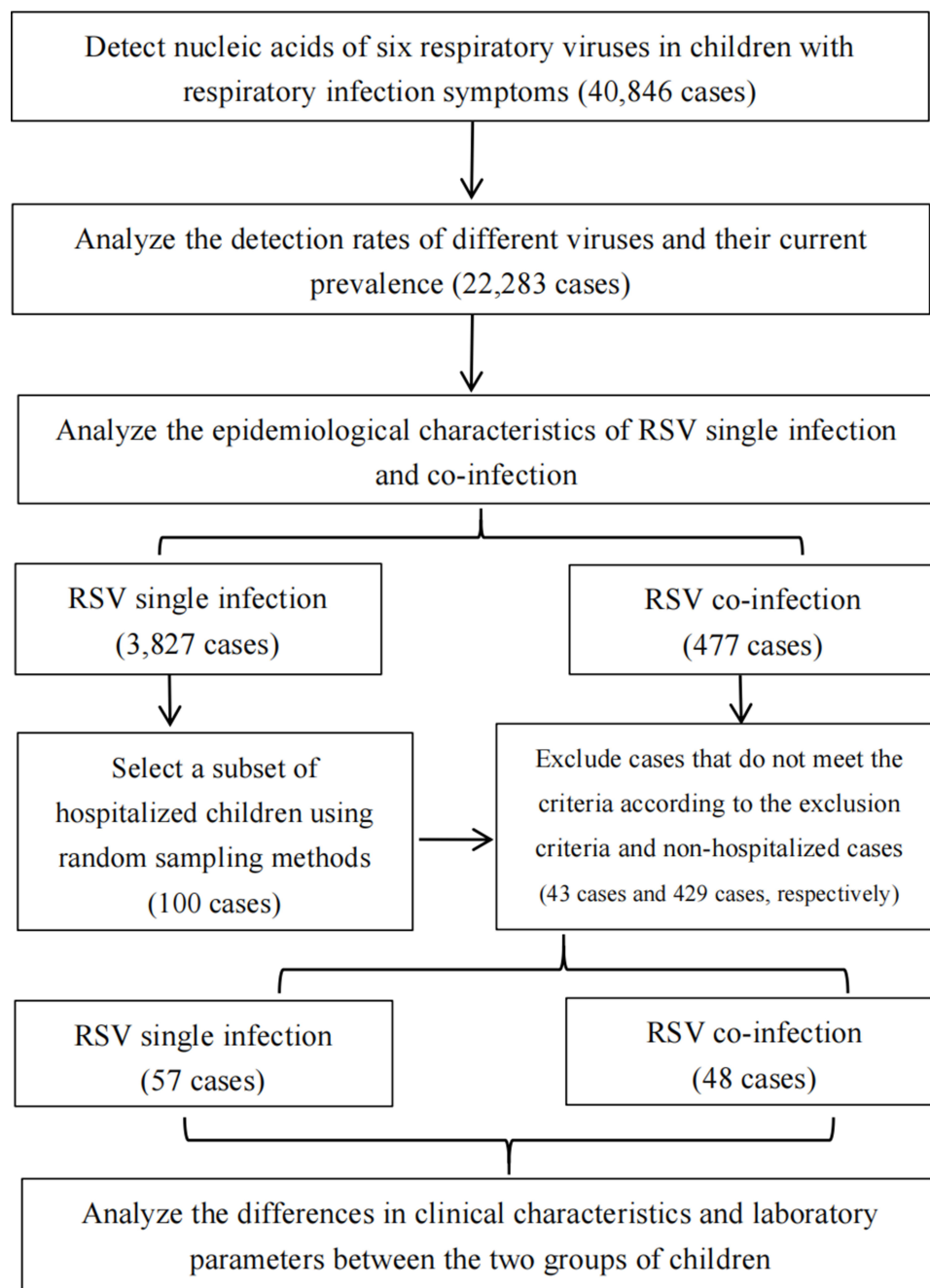


Figure 1 Research design process flowchart.

Lower respiratory tract infection includes acute bronchitis, bronchiolitis, and pneumonia, characterized by cough, tachypnea, wheezing, or abnormal rales in lungs, with corresponding changes on chest radiography.

Diagnostic Criteria for Pneumonia

Clinical manifestations: acute fever, cough, tachypnea, or dyspnea.

Physical examination: fixed medium-to-fine crackles in bilateral lungs.

Chest imaging: new patchy infiltration, consolidation, or ground-glass opacity. The diagnosis can be established based on clinical manifestations plus imaging evidence.

Diagnostic Criteria for Severe Pneumonia

One major criterion OR ≥ 3 minor criteria:

Major criteria:

Respiratory failure requiring invasive mechanical ventilation.

Septic shock requiring vasoactive drugs.

Minor criteria:

Tachypnea: ≥ 70 breaths/min in infants (<1 year), ≥ 50 breaths/min in older children (≥ 1 year).

Hypoxemia: $\text{SpO}_2 \leq 92\%$ in room air.

Impaired consciousness: lethargy, convulsion, or coma.

Poor peripheral perfusion: prolonged capillary refill time, cool extremities.

Extensive lung involvement: multilobar infiltration on chest imaging.

Severe systemic toxicity: persistent high fever, poor feeding, dehydration.

Diagnosis was based on a combination of clinical symptoms and imaging findings (primarily chest X-ray, with CT used for some complex cases).

For laboratory testing, pharyngeal secretions were collected using sterile cotton swabs, placed in sample preservation solution, and tested using the real-time PCR instrument (QuantStudioTM5, ThermoFisher Scientific, Singapore) and the Respiratory Virus Nucleic Acid Six-Plex Detection Kit (ZO-CENHISEN, China) for the simultaneous detection of six common respiratory viruses: *influenza A (FluA)*, *influenza B (FluB)*, *RSV*, *ADV*, *parainfluenza virus type 1 (PIV1)*, and *parainfluenza virus type 3 (PIV3)*.

Peripheral or venous blood samples were collected in EDTA-K₂ anticoagulant tubes and analyzed using an automatic blood cell analyzer (BC-6800, Mindray, China) with supporting reagents for a complete blood count (CBC)-including white blood cell (WBC), neutrophil (NEU), lymphocyte (LYM), monocyte (MONO), and platelet (PLT) counts-and C-reactive protein (CRP) testing.

Venous blood samples collected in lithium heparin anticoagulant tubes were centrifuged at 4000 rpm (approximately 3630 $\times$ g) for 10 minutes at room temperature (15–30°C) within 2 hours of collection, and then analyzed using the automatic biochemical analyzer (Abbott CIL-6200, Abbott, USA) with supporting reagents for liver and kidney function and myocardial enzyme testing.

Serum samples were analyzed using the flow cytometer (BD FACSCanto, BD, USA) and cytokine detection reagents for cytokine testing, and using the IMMAGE 800 (Beckman Coulter, USA) with matching reagents for immune function testing.

All tests were conducted in accordance with the reagent instructions and the standard operating procedures of the Hubei Maternal and Child Health Hospital laboratory.

Statistical Methods

Data were analyzed using IBM SPSS software (version 25.0). Categorical variables were presented as numbers (percentages) and compared using the Chi-square test. Normally distributed data were expressed as mean $\pm$ standard deviation and compared using the independent Student's *t*-test. Non-normally distributed data were expressed as median (interquartile range) and compared using the Mann–Whitney *U*-test. The correlation analysis between fever and inflammatory markers was performed using Spearman correlation analysis. A two-sided *P*-value < 0.05 was considered statistically significant. Epidemiological characteristics of viral infections were analyzed using GraphPad Prism, and viral co-infection patterns were visualized using Microsoft Excel.

Results

Positive Rates and Epidemiological Characteristics of Six Respiratory Viruses Among Symptomatic Children

Among the 40,846 children, 22,283 (54.55%) were infected with at least one virus. The most frequently detected virus was *ADV* (18.03%), followed by *FluA* (12.90%) and *RSV* (10.63%). The positivity rates for *FluB* (6.79%), *PIV3* (4.56%), and *PIV1* (2.13%) were relatively low (Table 1). The overall virus positivity rate was significantly higher in male children

Table 1 Positive Rates and Epidemiological Characteristics of Six Respiratory Viruses Among Symptomatic Children

Project	n/%	PIV1 (n/%)	PIV3 (n/%)	FluA (n/%)	FluB (n/%)	RSV (n/%)	ADV (n/%)
Total	22283(54.55)	863(2.13)	1846(4.56)	5222(12.90)	2747(6.79)	4304(10.63)	7301(18.03)
Sex							
Male	12481(55.16)	477(2.11)	1043(4.61)	2877(12.71)	1543(6.82)	2481(10.96)	4060(17.94)
Female	9802(53.80)	386(2.12)	803(4.41)	2345(12.87)	1204(6.61)	1823(10.01)	3241(17.79)
χ^2	7.456	0.006	0.951	0.225	0.710	9.820	0.159
P	0.006	0.940	0.330	0.636	0.399	0.002	0.690
Age							
<1	2182(48.18)	47(1.04)	348(7.68)	210(4.64)	160(3.53)	1267(27.98)	150(3.31)
1–3	7005(52.86)	366(2.76)	1174(8.86)	1099(8.29)	504(3.80)	2125(16.04)	1764(13.31)
4–6	7470(58.60)	351(2.75)	250(1.96)	1965(15.42)	861(6.75)	578(4.53)	3465(27.18)
7–14	5240(55.15)	95(1.00)	95(1.00)	1733(18.24)	1101(11.59)	312(3.28)	1904(20.04)
>14	386(47.25)	4(0.49)	6(0.73)	215(26.32)	121(14.81)	22(2.69)	18(2.20)
χ^2	192.814	114.915	1160.053	976.310	697.298	2956.727	1761.695
P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Season							
Spring	7774(55.59)	222(1.59)	826(5.91)	3040(21.74)	225(1.61)	1617(11.56)	1844(13.19)
Summer	5634(42.46)	450(3.39)	858(6.47)	480(3.62)	9(0.07)	140(1.06)	3697(27.86)
Autumn	704(36.07)	84(4.30)	25(1.28)	309(15.83)	64(3.28)	133(6.81)	89(4.56)
Winter	8171(70.20)	107(0.92)	137(1.18)	1393(11.97)	2449(21.04)	2414(20.74)	1671(14.36)
χ^2	2207.459	248.966	527.670	2029.029	5360.134	2595.074	144.629
P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Virus infection classification							
Single-infection	21338(95.76)	766(88.76)	1669(90.41)	4914(94.10)	2440(88.82)	3827(88.92)	6777(92.82)
Co-infection	945(4.24)	97(11.24)	177(9.59)	308(5.90)	307(11.18)	477(11.08)	524(7.18)

Abbreviations: PIV1, Parainfluenza virus type 1; PIV3, Parainfluenza virus type 3; FluA, influenza A; FluB, influenza B; RSV, Respiratory syncytial virus; ADV, Adenovirus.

(55.16%) than in females (53.80%) ($P < 0.05$). This disparity was primarily attributed to differences in *RSV* positivity rates between genders. No significant gender differences were observed for the other five viruses. Analysis of the gender distribution among infected children revealed that males had a higher proportion of infections across various viruses (Table 1 and Figure 2A and B). The age distribution for viral infections revealed that children aged 4–6 years had the highest positive rate for viral infection (58.60%), while *PIV1* positivity rates were consistently low across all age groups. The positivity rates for the other five viruses exhibited significant age-related variations. *PIV3* and *RSV* positivity rates decreased with age, while *influenza A* and *influenza B* rates increased. *ADV* positivity rates peaked in the 4–6-year age group. The highest *PIV1* positivity rate and proportion of positive tests were observed in children aged 1–6 years. *Influenza A* and *influenza B* positivity were highest in children over 14 years old (26.32% and 14.81%, respectively), while the proportion of positive cases among children aged 4–14 years was the highest. *PIV3* positivity rates peaked in the 1–3-year age group (8.86%), *RSV* positivity rates peaked in children under 1 year old (27.98%), and *ADV* positivity rates peaked in the 4–6-year age group (27.18%), and for these three viruses, the proportion of positive cases among children was also the highest in this age group (Table 1 and Figure 2C and D). Seasonal variations in positivity rates were also noted, with the highest positivity rate occurring in winter (70.20%). *PIV1* positivity rate was highest in autumn (4.30%). *PIV3* and *ADV* peaked in summer, with positivity rates of 6.47% and 27.86%, respectively. *FluA* reached its highest positivity in spring (21.74%), whereas *FluB* and *RSV* were predominant in winter (21.04% and 20.74%, respectively). The seasonal and monthly distribution of viral infections showed that winter had the highest proportion of positivity rates, particularly for *influenza A*, *B*, and *RSV*, *PIV1* and *ADV* positivity were more common in summer, while *PIV3* peaked in spring (Table 1 and Figure 2E–H).

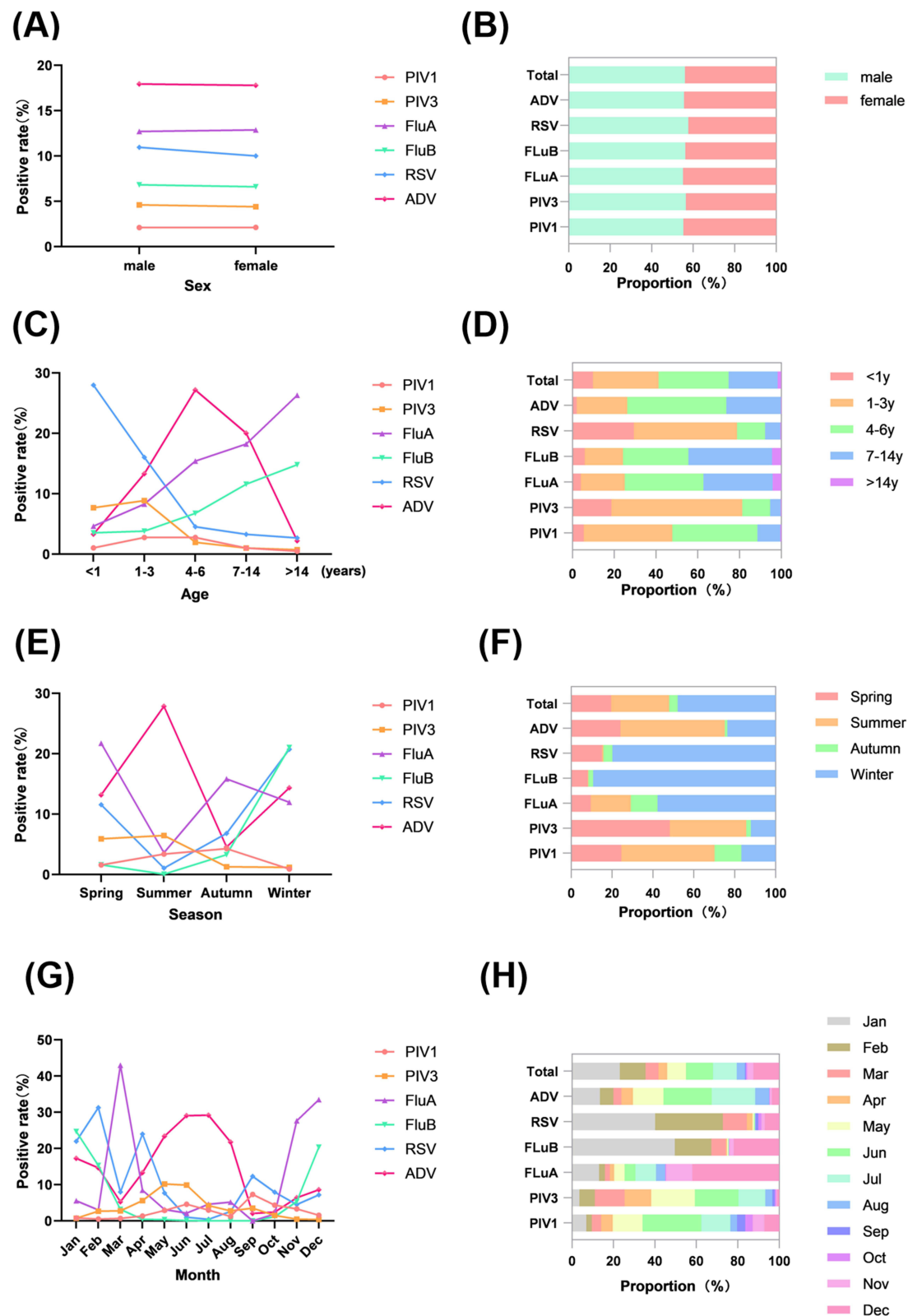


Figure 2 Epidemiological characteristics of six respiratory viral infections among symptomatic children. **(A)** Positive rates of six viruses by gender. **(B)** Gender distribution of children testing positive for viruses. **(C)** Positive rates of six viruses in different age groups. **(D)** Age distribution of children testing positive for viruses. **(E)** Positive rates of six viruses in different seasons. **(F)** Seasonal distribution of children testing positive for viruses. **(G)** Positive rates of six viruses for each month. **(H)** Monthly distribution of children testing positive for viruses.

Epidemiological Characteristics of Viral Co-Infections

Among the 22,283 virus-positive children, the vast majority had single infections (21,338, 95.76%), while 945 (4.24%) were co-infected with two viruses (Table 1). In terms of absolute numbers, the most frequent co-infection pair was *RSV* with *ADV* (161 cases), followed by *RSV* with *FluB* (143 cases), and *ADV* with *FluA* (127 cases) (Figure 3A). However, the co-infection rate was highest for *RSV* with *FluB* (2.03%), despite this pair not having the largest absolute count (Figure 3B). Among children infected with *RSV* (n=4,304), single infections predominated (3,827, 88.92%), with co-infections accounting for 11.08% (477 cases). No significant gender differences were observed between the single infection and co-infection groups. Age distribution, however, differed: single *RSV* infections were most common in children under 3 years old, whereas *RSV* co-infections were distributed across a broader age range (1–14 years). Seasonally, both single and co-infections peaked in winter, followed by spring, with the lowest frequencies occurring in summer and autumn (Table 2).

Clinical Severity of Viral Co-Infections

A total of 105 hospitalized children were included in the clinical severity analysis: 57 with *RSV* single infection and 48 with *RSV* co-infection. Demographic and clinical characteristics are summarized in Table 3. No significant difference was observed in gender distribution between the two groups. However, children in the co-infection group were significantly older than those in the single-infection group ($P < 0.05$). The most common initial symptoms in both groups were isolated cough, isolated fever, and cough combined with fever. A significantly higher proportion of children in the co-infection group presented with fever (83.33% vs. 64.91%; $P < 0.05$), and their peak body temperature was also higher (mean $\pm$ SD: 39.12 ± 0.87 vs. 38.50 ± 0.74 °C; $P < 0.01$). The frequencies of accompanying respiratory symptoms, including nasal congestion, runny nose, wheezing, and dyspnea were comparable between groups. While all children received antibiotic therapy, the single-infection group required supplemental oxygen more frequently (29.82% vs. 10.42%; $P < 0.05$) and had a higher, though not statistically significant, incidence of severe pneumonia (26.32% vs. 18.75%). The length of hospital stay did not differ significantly, and nearly all children were discharged as cured or improved.

Laboratory findings are detailed in Table 4. Compared to the single-infection group, the co-infection group exhibited significantly higher counts of WBC, NEU, and MONO, as well as elevated levels of CRP (all $P < 0.05$). LYM and PLT counts were similar between groups. Immunological profiling indicated that the co-infection group had significantly higher IL-6 and lower C4 levels ($P=0.066, 0.026$, respectively). Although liver and kidney function parameters remained within normal ranges for both cohorts, the single-infection group showed significantly higher levels of ALT, AST, and ALP (all $P < 0.05$). Myocardial enzymes were elevated in both groups, with CK levels being significantly higher in the

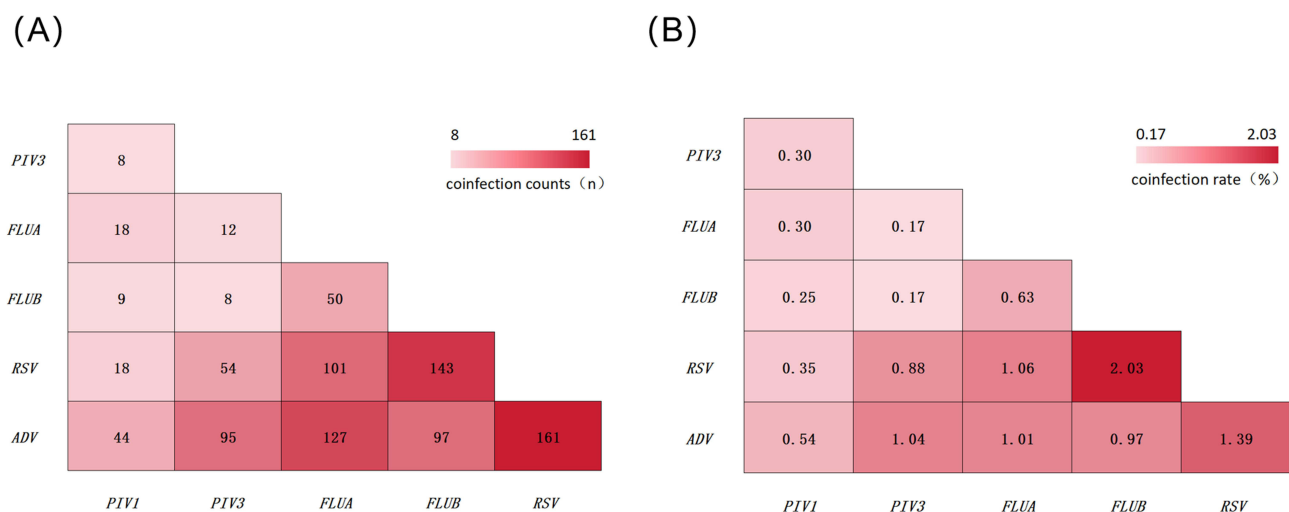


Figure 3 Co-infection status of six respiratory viruses in children. **(A)** The co-infection numbers between different viruses. **(B)** The co-infection rates between different viruses.

Table 2 Epidemiological Characteristics of RSV Single Infection and RSV Co-Infection

Project	Single Infection (n/%)	Co-Infection (n/%)	χ^2	P
Total	3827(88.92)	477(11.08)		
Sex				
Male	2202(57.54)	282(59.12)	0.434	0.510
Female	1625(42.46)	195(40.88)		
Age				
<1	1206(31.51)	59(12.37)	330.217	<0.001
1–3	1951(50.98)	172(36.06)		
4–6	445(11.63)	131(27.46)		
7–14	209(5.46)	108(22.64)		
>14	16(0.42)	7(1.47)		
Season				
Spring	1476(38.57)	126(26.42)	35.466	<0.001
Summer	129(3.37)	11(2.30)		
Autumn	123(3.21)	10(2.10)		
Winter	2099(54.85)	330(69.18)		

Table 3 Clinical Characteristics of Hospitalized Children with Single RSV Infection and RSV Co-Infection

project	Single Infection (n/%)	Co-Infection (n/%)	$\chi^2/z/t$	P
Total(n)	57	48		
Sex (male,n/%)	41(71.93)	27(56.25)	2.807	0.094
Age (years,IQR)	1.00(0.33–2.50)	2.00(0.85–3.00)	–2.278	0.023
Initial symptoms				
Cough (n/%)	42(73.68)	29(60.42)	2.095	0.148
Fever (n/%)	7(12.28)	15(31.25)	5.661	0.017
Cough and fever (n/%)	7(12.28)	4(8.33)	0.114	0.735
Others (n/%)	1(1.76)	0(0)	/	/
Clinical symptoms				
Fever (n/%)	37(64.91)	40(83.33)	4.522	0.033
Maximum temperature (°C, x±s)	38.50±0.74	39.12±0.87	–3.343	0.001
Cough (n/%)	56(98.25)	43(89.58)	2.199	0.138
Nasal congestion and runny nose (n/%)	42(73.68)	33(68.75)	0.311	0.577
Wheezing (n/%)	23(40.35)	17(35.42)	0.269	0.604
Chills (n/%)	6(10.53)	8(16.67)	0.850	0.356
Dyspnea (n/%)	13(22.81)	9(18.75)	0.259	0.611
Diarrhea (n/%)	4(7.02)	8(16.67)	1.538	0.215
Constipation (n/%)	2(3.51)	0(0)	/	/
Abdominal pain (n/%)	3(5.26)	3(6.25)	0.000	1.000
Treatment				
Use of antibiotics (n/%)	57(100)	48(100)	/	/
Inhalation of oxygen (n/%)	17(29.82)	5(10.42)	5.926	0.015
Main diagnosis				
Severe pneumonia (n/%)	15(26.32)	9(18.75)	0.846	0.358
Pneumonia (n/%)	12(21.05)	17(35.42)	2.689	0.101
Viral infections (n/%)	25(43.86)	16(33.33)	1.213	0.271
Others (n/%)	5(8.77)	6(12.50)	0.386	0.543
Length of stay (days,x±s)	5.74±1.76	5.63±1.91	0.312	0.755

(Continued)

Table 3 (Continued).

project	Single Infection (n%)	Co-Infection (n%)	$\chi^2/z/t$	P
Clinical outcomes				
Cure (n%)	47(82.46)	40(83.33)	0.014	0.905
Get better (n%)	10(17.54)	8(16.67)	0.014	0.905
Aggravation (n%)	0(0)	0(0)	/	/

Note: “/” in the statistical results column indicates that the statistical test was not applicable due to zero cell counts or the rate was 100% in both groups.

Table 4 Laboratory Indicators of Hospitalized Children with Single RSV Infection and RSV Co-Infection

Project	Single Infection	Co-Infection	Z/ χ^2	P
Complete blood count(n)	56	47		
WBC (10 ⁹ /L)	7.59(5.78–9.07)	8.40(5.91–11.79)	–1.771	0.077
NEU (10 ⁹ /L)	2.53(1.71–3.90)	3.84(2.24–5.95)	–2.800	0.005
LYM (10 ⁹ /L)	3.15(2.18–4.63)	3.22(1.82–5.02)	–0.201	0.840
MONO (10 ⁹ /L)	0.62(0.40–0.73)	0.78(0.50–1.17)	–2.887	0.004
PLT (10 ⁹ /L)	306.00(234.00–389.00)	286.00(227.00–365.00)	–0.752	0.452
CRP (mg/L)	1.67(0.48–5.02)	4.63(1.02–15.21)	–2.202	0.028
CRP>4mg/L (n%)	18(32.14)	26(55.32)	5.609	0.018
Cytokines (n)	31	40		
IL-6 (pg/mL)	13.73(6.84–28.06)	20.32(11.70–44.69)	–1.840	0.066
IL-2 (pg/mL)	3.42(2.66–3.93)	3.34(2.59–3.60)	–1.102	0.271
IL-4 (pg/mL)	2.83(2.56–3.59)	2.75(2.35–3.20)	–1.478	0.139
IL-10 (pg/mL)	7.71(4.59–11.85)	7.34(3.97–13.54)	–0.371	0.711
TNF- α (pg/mL)	4.23(2.78–14.22)	3.53(2.33–6.63)	–1.361	0.147
IFN- β (pg/mL)	3.21(2.17–6.17)	3.12(2.64–7.16)	–0.667	0.505
Immune function(n)	32	17		
IgG (g/L)	7.40(5.46–8.86)	6.01(4.63–8.75)	–0.756	0.450
IgA (g/L)	0.53(0.31–0.68)	0.51(0.42–0.76)	–0.687	0.492
IgM (g/L)	0.95(0.63–1.22)	0.94(0.68–1.18)	–0.263	0.793
C3 (g/L)	0.93(0.83–1.06)	0.92(0.85–1.17)	–0.284	0.776
C4 (g/L)	0.30(0.21–0.34)	0.24(0.20–0.28)	–2.229	0.026
Liver function(n)	57	47		
ALT (U/L)	18.00(14.00–28.00)	16.00(11.00–22.00)	–2.033	0.042
AST (U/L)	44.00(37–55.50)	40.00(31.00–49.00)	–2.206	0.027
TP (g/L)	68.40(64.50–72.15)	67.60(64.50–72.40)	–0.150	0.881
ALB (g/L)	43.10(41.20–44.80)	42.70(40.30–44.50)	–0.970	0.332
γ -GGT (U/L)	13.00(11.00–20.50)	12.00(10.00–19.00)	–1.490	0.136
ALP (U/L)	217.00(168.00–273.00)	187.00(147.00–271.00)	–2.218	0.027
Renal function(n)	56	45		
Cr (umol/L)	23.45(20.00–27.53)	26.00(21.65–29.00)	–1.428	0.153
Urea (mmol/L)	3.07(2.22–4.07)	2.86(2.37–3.61)	–0.560	0.575
Cys-C (mg/L)	0.94(0.77–1.26)	0.83(0.74–1.07)	–1.456	0.145
UA (umol/L)	246.00(215.25–300.75)	258.00(208.80–334.50)	–0.772	0.440
Myocardial enzymes(n)	57	48		
LDH (U/L)	326.00(281.00–371.00)	299.50(271.25–349.25)	–1.354	0.176
A-HBD((U/L))	262.00(230.00–303.50)	250.50(219.25–287.75)	–1.393	0.164

(Continued)

Table 4 (Continued).

Project	Single Infection	Co-Infection	Z _{1/2}	P
CK (U/L)	125.00(93.50–167.50)	101.50(64.00–133.50)	−2.226	0.026
CK-MB (U/L)	27.80(21.30–31.75)	23.55(18.70–30.90)	−1.306	0.192

Abbreviations: WBC, white blood cell; NEU, neutrophil; LYM, lymphocyte; MONO, monocyte; PLT, platelet; CRP, C-reactive protein; IL-6, interleukin-6; IL-2, interleukin-2; IL-4, interleukin-4; IL-10, interleukin-10; TNF- α , Tumor Necrosis Factor-alpha; IFN- β , Interferon-beta; IgG, Immunoglobulin G; IgA, Immunoglobulin A; IgM, Immunoglobulin M; C3, Complement 3; C4, Complement 4; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, Total Protein; ALB, Albumin; γ -GGT, Gamma-Glutamyl Transferase; ALP, alkaline phosphatase; Cr, Creatinine; Cys-C, Cystatin C; UA, Uric Acid; LDH, Lactate Dehydrogenase; α -HBD, Alpha-Hydroxybutyrate Dehydrogenase; CK, Creatine Kinase; CK-MB, Creatine Kinase-MB.

single-infection group ($P < 0.05$), but the CK-MB levels were not significantly different between the two groups. Spearman correlation analysis was performed to assess the relationship between peak body temperature and inflammatory markers in febrile children, stratified by infection type ([Supplementary Table 1](#)). In the single-infection group, temperature was significantly correlated with NEU counts ($\rho = 0.514$, $p = 0.001$) and CRP levels ($\rho = 0.474$, $p = 0.003$). In the co-infection group similar but slightly attenuated correlations were observed for neutrophils ($\rho = 0.414$, $p = 0.009$) and CRP ($\rho = 0.383$, $p = 0.016$). Temperature was not significantly correlated with WBC or IL-6 levels in either group. The clinical severity findings were obtained based on the exclusion criteria and conducted in a cohort of previously healthy children.

Discussion

The epidemiological landscape of respiratory viruses in children, characterized by distinct seasonal and regional patterns, has been significantly reshaped by the COVID-19 pandemic and the subsequent relaxation of non-pharmaceutical interventions (NPIs). This post-pandemic era presents a unique and critical opportunity to reassess viral epidemiology. The extensive use of NPIs during the pandemic created an “immunity debt” by dramatically reducing population exposure to common pathogens, thereby disrupting their regular circulation patterns. As these interventions are lifted, it is imperative to understand how viral transmission dynamics have shifted to guide effective public health responses. Continued surveillance is essential for detecting resurgent pathogens, anticipating unusual seasonal outbreaks, and preparing healthcare systems for new challenges. Our study provides a timely analysis of the prevalence and clinical impact of six common respiratory viruses among symptomatic children in Wuhan, China, following the reclassification of COVID-19 to a “Category B” managed disease. Our findings indeed reveal a significant shift in the viral landscape: we observed a notably high overall virus detection rate, indicating a vigorous post-pandemic rebound, and identified distinct co-infection patterns, such as the high rate of RSV-FluB co-infections. These observations underscore that post-pandemic viral behavior is not simply a return to pre-pandemic norms but may involve new epidemiological dynamics. The key findings are: a notably high overall virus detection rate (54.55%) in the post-pandemic period, with *ADV* being the most prevalent pathogen; a distinct pattern of viral co-infections, particularly between *RSV* and *FluB*; and that children with *RSV* co-infection, despite having a significantly higher prevalence of fever, higher peak body temperature, and elevated systemic inflammatory markers, exhibited milder respiratory compromise compared to those with *RSV* single infection. Our study provides valuable guidance for public health surveillance and prevention strategies, as well as for pediatric clinical management. For instance, the high virus detection rate (54.55%) underscores the necessity of continuous surveillance, particularly focusing on the predominant pathogen *ADV* and the co-infection pattern of *RSV* and *FluB*, to predict potential outbreaks. In response to the complex co-infection patterns, integrated multi-virus prevention and control strategies should be implemented. Given the atypical viral patterns in the post-pandemic era, long-term dynamic tracking is essential. Clinicians should be vigilant about the “dissociation phenomenon” in *RSV* co-infections (marked by high fever and pronounced inflammatory responses but mild respiratory symptoms), avoiding overdiagnosis or unnecessary respiratory support based solely on fever and inflammatory markers, while also implementing age-specific management strategies.

The overall virus positivity rate of 54.55% in our hospital-based study was substantially higher than the 27.83% reported in Wuhan during the 2019–2022 period encompassing strict pandemic controls, and exceeds the 20–40% range typical of many pre-pandemic studies worldwide.^{2,13–16} This rebound aligns with the concept of an “immunity debt” and increased pathogen circulation following the easing of NPIs, as observed in other regions like South Korea where rates reached 69.1%.¹⁷ Our previous study similarly documented a substantial reduction in respiratory pathogen infections during the COVID-19 pandemic,¹⁸ aligning with findings reported in other research.^{9,15} However, Ren et al observed no significant overall change in viral infection rates in central China throughout the pandemic and noted that certain viruses, such as *RSV*, exhibited elevated infection rates during this period.¹⁴ These discrepancies may be attributed to regional differences in study populations and the scope of included subjects. Our data on individual viruses further illuminate these post-pandemic shifts. The predominance of *ADV* (18.03%), peaking in summer among preschool children (4–6 years), is consistent with its known epidemiology, though our detected rate is higher than some previous reports.^{19–21} *RSV* maintained a high burden (10.63%), primarily affecting infants (<1 year) with male children being more susceptible than females, and peaking in spring and winter, confirming its global threat profile.²² And the positive rate progressively decreased with increasing age. A notable regional variation was identified in Zhejiang and Guangzhou, China, where epidemics occurred primarily in autumn and winter, likely due to climatic influences.^{23,24} The *FluA* positivity rate (12.90%), though slightly lower than pre-pandemic Wuhan levels,²⁵ represents a significant rebound from near-absence during strict lockdowns.¹⁸ The positive rate in Zhejiang Province was consistently low both before and during the early stages of the COVID-19 pandemic, but it increased dramatically in the later stages of the epidemic, eventually exceeding 50%.^{26,27} *FluB* positive rates were consistent with pre-pandemic findings in Wuhan but showed a decrease during the COVID-19 period and significant increases in 2021.^{25,28} Contrary to most studies which report the highest incidence in children aged 3–14 years during overlapping winter-spring epidemics,^{2,25,26,29} our findings in Wuhan revealed an older peak age (>14 years) for both influenza types, and the low temperature lasted for a long time in Wuhan in 2023, so influenza viruses had a high prevalence in spring, autumn and winter. Moreover, both *FluA* and *FluB* viruses are prone to mutation, and different strains have a certain impact on the epidemiological characteristics of influenza.^{30,31} During this epidemic period in the Wuhan area, the *FluA* was predominantly A(H1N1)pdm09, while the *FluB* virus was mainly the B/Victoria lineage.³² Among the four parainfluenza virus types, *PIV1* and *PIV3* are the primary causes of pediatric respiratory infections. The lower detection rates of *PIV1* and *PIV3* in this study, while consistent with their generally mild epidemic patterns, fall below the levels reported in the Wang et al study,³³ even though the characteristic age and seasonal distributions (*PIV1*: 1–6 years, autumn/summer; *PIV3*: <3 years, spring/summer) remain broadly aligned.³⁴

Pathogen co-infections involving bacteria, viruses, fungi, mycoplasma, and chlamydia are more frequent in children than in adults.^{35,36} A significant finding of our study is the detailed characterization of viral co-infections. While co-infections involving the six viruses were not rare (4.24% of positive cases), the rate for specific pairs varied. Although *RSV-ADV* was the most frequent pair in absolute numbers, *RSV-FluB* had the highest co-infection rate relative to all virus-positive cases. This highlights the importance of reporting both absolute and relative metrics. In addition, our study revealed significant differences in age and seasonal distributions between viral co-infection and single infection groups, with distinct pathogen-specific patterns. These variations may stem from the combined effects of age-related immune development characteristics, viral competitive interactions, and seasonal environmental/behavioral factors, providing important evidence for formulating targeted respiratory infection prevention and control strategies tailored to specific age groups and seasons.

RSV remains a significant global health threat to children under five years old, particularly infants under six months, who are highly susceptible to severe *RSV* infections, resulting in high morbidity and mortality rates. Interactions between viruses may also influence the epidemiological dynamics, seasonality, and clinical manifestations of *RSV* infections.^{36,37} The clinical implications of co-infection remain debated. Many studies suggest that co-infections are associated with enhanced disease severity due to synergistic inflammatory responses.^{38,39} However, Cheng et al reported that co-infection with *FluA* and *SARS-CoV-2* did not exacerbate disease severity but instead reduced inflammation levels in some patients.⁴⁰ Similarly, Canducci et al found that children with single *RSV* infections had longer hospital stays and higher incidences of hypoxemia compared to those co-infected with *RSV* and *Human Metapneumovirus*.⁴¹ Other studies have also indicated that co-infections are not necessarily associated with increased clinical severity.^{42,43} Our clinical

comparison between *RSV* single infection and *RSV* co-infection cases contributes a nuanced perspective to this debate. We found that children with *RSV* co-infections were generally older, consistent with the epidemiology of the co-infected viruses (eg., *FluB*, *ADV*) which tend to infect older age groups. Similar results have also been obtained in the studies of Carlos E and Jiahong Tan.^{44,45} Children with co-infections were more likely to present with fever and higher peak temperatures compared to those with single infections. This may be attributed to the initial activation of the innate immune response during *RSV* infection, which triggers the production of inflammatory factors to combat viral invasion. The broader activation of the immune system leads to the release of more immune mediators, resulting in elevated body temperatures. The most intriguing and seemingly paradoxical result was the dissociation between laboratory markers and clinical severity. Specifically, the co-infection group exhibited significantly stronger systemic inflammatory responses, indicated by higher WBC, NEU, CRP, and IL-6 levels, along with lower C4. Correlation analysis between fever and inflammatory markers revealed that in both groups, body temperature was significantly positively correlated with NEU and CRP levels. However, the correlations were slightly weaker in the co-infection group, which may reflect a more complex and heterogeneous immune response in co-infected children compared to those with single infections. Temperature was not significantly correlated with WBC or IL-6 levels in either group. Nevertheless, due to the limited sample size, this finding warrants further validation. Paradoxically, co-infection group had a lower frequency of oxygen requirement and a non-significant trend towards fewer severe pneumonia cases compared to the *RSV* single infection group. Regarding tissue-specific markers, the single infection group showed higher levels of liver enzymes and total creatine kinase (CK). However, levels of CK-MB, a more specific marker of myocardial injury, did not differ significantly between the two groups, suggesting that myocardial injury was not a distinguishing feature. Furthermore, while ALP levels were also higher in the single infection group, we could not determine whether this reflected hepatic involvement or physiological bone growth, as ALP isoenzyme fractionation was not performed in this study. This pattern of systemic inflammation without corresponding respiratory severity aligns with findings by Canducci et al⁴¹ A plausible explanation may involve viral interference and the nature of the immune response. A robust initial interferon-driven response against one virus might partially suppress the replication or pulmonary tropism of a second virus, thereby limiting direct tissue damage in the lungs.^{46–48} Consequently, while the systemic immune activation is heightened, the actual end-organ compromise might be less severe, leading to reduced oxygen needs. This underscores that in co-infections, the level of systemic inflammation may not linearly correlate with clinical respiratory severity, a crucial consideration for clinical assessment. However, these proposed mechanisms are speculative and are not directly supported by empirical evidence from the current study. Further mechanistic studies, including detailed immunophenotyping and viral load kinetics, are warranted to validate these hypotheses. Our findings regarding the severity of *RSV* co-infection are applicable to otherwise healthy children, while the clinical situation may differ in children with immunocompromise or chronic diseases. This is an important direction for future research.

Our study has several limitations that should be acknowledged. First, as a single-center, retrospective, hospital-based study, our findings reflect the virus spectrum in children seeking medical care and may not be directly generalizable to community infection rates or other regions, a key consideration for epidemiological inferences. As a retrospective study, some information was missing from the medical records, and we were unable to accurately trace the detailed vaccination histories of the enrolled children. Therefore, we could not adjust for this potential confounder. Second, the sample size for the detailed clinical comparison of *RSV* infections, while informative, was modest, restricting our statistical power for conducting multivariable regression analyses to adjust for potential confounders such as age, sex, and seasonal factors. Therefore, we were unable to isolate the independent effect of co-infection status on clinical severity, and the observed differences between groups should be interpreted with caution. Third, our viral detection panel was limited to six common viruses, and we did not differentiate between specific types or subtypes of viruses within the co-infection cohort (eg., *RSV* A and B, different *ADV* serotypes), which may have distinct pathogenic potentials and clinical implications. Future multicenter community-based studies with larger sample sizes, expanded pathogen panels and detailed immunophenotyping are warranted to validate our findings and further elucidate the complex interactions governing the severity of respiratory viral co-infections.

Conclusion

In conclusion, this study reveals a relatively high prevalence of respiratory viruses among symptomatic children in Wuhan in the post-COVID-19 era, characterized by notably high detection rates of *ADV*, *FluA*, and *RSV*. These findings suggest a potential shift in the local epidemiological landscape following the relaxation of non-pharmaceutical interventions, although further longitudinal studies are needed to confirm this trend. It identifies *RSV-FluB* as a co-infection pair of particular note. Crucially, it reveals a distinct clinical profile for *RSV* co-infections, characterized by heightened inflammation yet observed mitigated respiratory severity in our cohort, challenging the assumption that co-infection invariably worsens clinical disease. These insights underscore the importance of ongoing surveillance and a nuanced, pathogen-specific approach to managing pediatric respiratory infections.

Abbreviations

ADV, adenovirus; *FluA*, influenza A; *FluB*, influenza B; *RSV*, respiratory syncytial virus; *PIV1*, Parainfluenza virus type 1; *PIV3*, Parainfluenza virus type 3; CBC, complete blood count; WBC, white blood cell; NEU, neutrophil; LYM, lymphocyte; MONO, monocyte; PLT, platelet; CRP, C-reactive protein; IL-6, interleukin-6; IL-2, interleukin-2; IL-4, interleukin-4; IL-10, interleukin-10; TNF- α , Tumor Necrosis Factor-alpha; IFN- β , Interferon-beta; IgG, Immunoglobulin G; IgA, Immunoglobulin A; IgM, Immunoglobulin M; C3, Complement 3; C4, Complement 4; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, Total Protein; ALB, Albumin; γ -GGT, Gamma-Glutamyl Transferase; ALP, alkaline phosphatase; Cr, Creatinine; Cys-C, Cystatin C; UA, Uric Acid; LDH, Lactate Dehydrogenase; α -HBD, Alpha-Hydroxybutyrate Dehydrogenase; CK, Creatine Kinase; CK-MB, Creatine Kinase-MB; ARIs, Acute respiratory tract infections; NPIs, Non-pharmaceutical interventions.

Data Sharing Statement

The raw data can be made available to the interested researchers by the authors of this article if requested.

Ethics Approval and Consent to Participate

In this study, we used existing data collected during the course of routine diagnostic procedures for children attending outpatient clinics and inpatient with symptoms of respiratory infections and did not pose any additional risks to the patients. The patient records and information were anonymized and deidentified prior to analysis. And this study was conducted in accordance with the Declaration of Helsinki. In view of the above situation, the Ethics Committee of the Maternal and Child Health Hospital of Hubei Province, Tongji Medical College, Huazhong University of Science and Technology approved this study, and agreed to waive the right to individual informed consent from the study patients.

Author Contributions

Jun'e Ma and Ting Tian share first authorship. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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