

A retrospective study of respiratory infections in children following the COVID-19 pandemic in Wuhan, China

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Abstract

Introduction: Acute respiratory infections cause over 4 million deaths annually worldwide, half of which occur in children under 5 years, primarily in developing countries. This study investigated the impact of the coronavirus disease 2019 (COVID-19) pandemic on the epidemiological and clinical characteristics of pediatric patients with respiratory infections.

Methodology: This study retrospectively analyzed 8,815 pediatric cases (0–18 years) with laboratory-confirmed respiratory infections at Wuhan Children's Hospital in pre-pandemic (November 2019–February 2020) and post-pandemic (November 2020–February 2021) periods. Included cases were symptomatic and tested positive for at least one pathogen: influenza A (FluA), influenza B (FluB), respiratory syncytial virus (RSV), *Chlamydia pneumoniae* (CP), *Mycoplasma pneumoniae* (MP), adenovirus (ADV), or coxsackievirus (CV). The pathogen distribution spectrum between periods was compared. Routine blood parameters – platelet count, white blood cell count, red blood cell count, lymphocyte percentage, neutrophil percentage, monocyte percentage, C-reactive protein, and hemoglobin – were also compared across groups and periods.

Results: The post-pandemic pathogen spectrum shifted significantly. MP detection increased across all age groups (28 days–2 years, 2–8 years, 8–18 years), while other pathogens (RSV, ADV, CV, CP) decreased, with patterns varying by age. Post-pandemic platelet count and lymphocyte percentage increased, while neutrophil percentage decreased in the CP group.

Conclusions: COVID-19 control measures were temporally associated with marked changes in respiratory pathogen detection; notably a rise in MP. However, changes in healthcare-seeking behavior and testing intensity are important confounders. The observed shift in pathogen spectrum requires careful interpretation within this complex context.

Key words: COVID-19; pandemic; pathogens; pediatrics; respiratory infections.

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Introduction

The World Health Organization (WHO) declared 2019 coronavirus disease (COVID-19) a public health emergency of international concern on 30 January 2020 [1]. A series of pandemic prevention measures such as prohibiting unnecessary gatherings, wearing masks, and delaying the start of primary and secondary school were implemented to reduce the risk of virus transmission. Previous studies have shown that COVID-19 prevention and control measures, such as wearing masks, washing hands frequently, ventilating frequently, and reducing personnel gatherings can effectively inhibit the spread of respiratory viruses [2–4]. Furthermore, any changes in the infection characteristics of other respiratory pathogens must be assessed.

More than 4 million people worldwide die annually from respiratory infections, with approximately 50% of

these deaths occurring in children under the age of 5 years, particularly in developing nations. Pathogens causing acute respiratory infections in children include bacteria, viruses, *Mycoplasma*, *Chlamydia*, and fungi. Viral infection leads to approximately 80% of respiratory infections, and is a major cause of infant mortality [5,6]. Children are usually susceptible to influenza A (FluA), influenza B (FluB), respiratory syncytial virus (RSV), *Chlamydia pneumoniae* (CP), *Mycoplasma pneumoniae* (MP), adenovirus (ADV), and coxsackie virus (CV). The detection rate of various pathogens that cause acute respiratory infections is often related to factors such as infection age, season, and climatic conditions [7–9].

The prevalence of influenza among all respiratory infections is relatively high and has a clear seasonal pattern, occurring frequently from November to February. The influenza A virus has caused several

worldwide outbreaks, resulting in pandemics in 1918 (H1N1) and 1968 (H3N2), whereas the influenza B virus primarily spreads locally, with seasonal and regional variations [10,11]. Since the emergence of the novel COVID-19 pandemic in 2020, China has launched response measures for major public health emergencies, and the use of masks has, to some extent, blocked the spread of the virus [12,13]. A local outbreak of COVID-19 occurred at the end of January 2020, and the health institutions mandated widespread use of masks [12]. Therefore, the research team of the current study compared and analyzed respiratory pathogen infections that were reported during the winter and spring of the two years before and the two years after the time node for the COVID-19 pandemic with the aim of discovering any epidemiological changes, differences, and causes to determine the current detection indicators of seasonal respiratory pathogen infections.

MP and CP are the most common atypical pathogens causing respiratory infections in children, particularly MP pneumonia, and account for 32.4% to 37.5% of community-acquired pneumonia cases in children [14,15]. MP infection can occur at any time of year, with the pandemic season varying by region. Schmidt *et al.* reported that the peak incidence rate in children occurs between December to April [16]. RSV is another major viral pathogen that causes acute lower respiratory tract infections in children under 5 years of age worldwide. The WHO estimates that RSV infection accounts for 60% of acute respiratory tract infections in children worldwide and 80% of lower respiratory tract infections in infants under 1-year-old during the pandemic season, making it one of the viruses with the highest infection rates in children [17]. In 2015 alone, there were more than 30 million cases of RSV-related lower respiratory tract infections among children under 5 years of age worldwide, including over 3.2 million hospitalized cases and over 59,600 deaths [18]. In the United States, the pandemic season lasts from November to March. RSV more commonly occurs in northern China during winter and spring, and in southern China during summer and autumn, when there is more rainfall [19]. ADV is another common viral pathogen in the respiratory tract of children, causing upper respiratory tract infections, conjunctivitis, and severe pneumonia [20]. ADV outbreaks do not have a clear seasonal pattern and can occur at any time of year. In Asia, there has been an increase in reports of severe pneumonia caused by ADV infection in recent years.[21] Herpetic angina is the most common disease caused by CV, and the majority of the symptoms are

mild and belong to self-limiting diseases [22].

This study aimed to understand the changes that may have occurred in the epidemiological characteristics of the above-mentioned traditional respiratory infections in response to the increased use of personal protective measures, such as masks and hand washing, that were implemented during the COVID-19 pandemic. A retrospective analysis was performed to compare the clinical indicators of the aforementioned respiratory pathogen infections in pediatric patients at Wuhan Children's Hospital before and after the COVID-19 pandemic. Additionally, the changes in rapid blood routine indicators before and after the pandemic were characterized to explore the broad impact of nonpharmaceutical interventions on respiratory infections with similar transmission modes.

Methodology

Research participants

This study retrospectively enrolled children aged 0–18 years who presented to Wuhan Children's Hospital with acute respiratory symptoms (including but not limited to fever [axillary temperature ≥ 37.3 °C], cough, rhinorrhea, sore throat, or tachypnea) between November 2019 and February 2020 (pre-pandemic) and November 2020 and February 2021 (post-pandemic). Only the first visit within an illness episode was included in the analysis. If a child had multiple eligible episodes separated by more than 14 days, only the first episode was included to ensure the independence of observations. Children were included only if they had a positive test result for at least one of the target pathogens and if the specimen for pathogen testing was collected within 3 days of symptom onset, to reflect the initial stage of infection. Cases with duplicate data or incomplete blood routines or missing C-reactive protein (CRP) test results were excluded. The analysis was based on complete cases only; no imputation was performed for missing data. Children who tested positive for various types of pathogens were chosen as the research subjects of this study, and were divided into 4 age groups: 0 to 28 days (0–28d, Group 1), 28 days to 2 years (28d–2y, Group 2), 2 years to 8 years (2y–8y, Group 3), and 8 years to 18 years (8y–18y, Group 4). The study protocol was approved by the Ethics Review Committee of Wuhan Children's Hospital (2024R050-E01). The requirement for informed consent was waived due to the retrospective nature of the study.

Laboratory methods

The same models of instruments and the same

brands of reagents were used for all pathogen and blood tests across both study periods to ensure consistency. Pathogen testing was performed using commercially available kits according to the manufacturers' instructions. The specimen types for each pathogen were as follows: nasopharyngeal swabs for influenza A/B (rapid antigen test), RSV, and ADV (immunofluorescence); and serum for MP, CP, and CV (IgM immunocapture assay). The diagnostic method of immunocapture was used to detect the IgM antibodies of related pathogens. Specifically, simultaneous detection of IgM antibodies for MP, CP, RSV, ADV, and coxsackievirus B (CVB) was performed using a combined colloidal gold immunochromatographic assay (Beijing Innobio Technology Co, Ltd, Beijing, China). The assay performance was validated by the manufacturer with a clinical sample size of 1,512 cases. Compared with commercially available diagnostic kits, this combined assay demonstrated high concordance, with positive percentage agreement (PPA) and negative percentage agreement (NPA) for each pathogen exceeding 96.7% and 99.7%, respectively. The overall percentage agreement (OPA) exceeded 99.47%. The colloidal gold method was performed using an A/B Influenza Virus Antigen Detection Kit (Shuoshi Biotechnology Co, Ltd, Taizhou, China) to evaluate the samples for FluA and FluB. If both the T1 and T2 lines on the detection card displayed red lines, the sample was positive for both FluA and FluB antigens. Routine blood tests were carried out with either a Sysmex XS-800i five-part blood cell analyzer (Sysmex Corporation, Kobe, Japan) or a Mindray BC-5310 hematology analyzer (Mindray Bio-Medical Electronics Co, Ltd, Shenzhen, China), a fully automated five-part blood cell analyzer from Shenzhen. The relevant tests were conducted using the original matching reagents and quality control materials. The CRP levels in the peripheral blood and blood routine test results were compared to determine the differences.

Statistical analysis

Epidemiological methods in SPSS version 20.0 (IBM Corp, Armonk, NY, USA) were used to analyze the demographic and clinical characteristics of each case. The primary outcome was the change in the distribution of detected respiratory pathogens between the pre-pandemic and post-pandemic periods. Analyses stratified by age group and gender, as well as all comparisons of peripheral blood parameters, were pre-specified as exploratory (hypothesis-generating) analyses. The number of cases and the results of routine blood tests, including CRP, that had been performed

within 3 days of symptom onset during the relevant time period were extracted. Statistical analyses of relevant early detection indicators were carried out for specific viruses. Statistical analyses were conducted on infection detection indicators for specific viruses according to the age of each case within the same age group. The mean $\pm$ standard deviation (SD) was used to present normally distributed data, and the median and the 25th and 75th percentiles were used to present non-normal data. A non-parametric rank sum test was performed, and the count data were presented as the number of cases or percentages using χ^2 inspection with an inspection level of $\alpha = 0.05$. Differences in pathogen proportions between periods were assessed using Chi-square or Fisher's exact tests for the primary outcome. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for key comparisons (e.g., MP proportion) to provide clinically meaningful effect estimates. In the case of continuous variables (e.g., blood parameters), between-group differences were expressed as mean differences (MD) or median differences with 95% CIs. A *p* value of less than 0.05 indicated a statistically significant difference. Given the exploratory nature of the subgroup and blood parameter analyses, no formal adjustment for multiple testing was applied. The age group 0–28 days (*n* = 2) was considered too small for statistical inference; its data are presented descriptively only. The total number of tests performed for each pathogen (the denominator for positivity rate) was not systematically available; therefore, the analysis focused exclusively on changes in the distribution of pathogens among the cohort of children who tested positive.

Handling of co-infections

Cases with positive test results for more than one pathogen were identified as co-infections. The overall co-infection rate in the study cohort was 2.50% (220/8815). Each case was assigned to a single pathogen category to avoid duplicate counting for the primary analysis of pathogen distribution and clinical characteristics. This assignment was based on a hierarchical clinical classification: the pathogen most likely to be the primary cause of the current respiratory illness, as determined by the attending physician considering the clinical presentation and test results, was selected. If no clear clinical distinction could be made, the following hierarchy was applied: (1) MP, (2) RSV, (3) ADV, (4) CP, (5) CV. This approach aimed to reflect the primary clinical etiology driving the hospital visit.

Results

Study population

This study enrolled 8,815 children with respiratory symptoms, including 5,042 boys and 3,773 girls. As shown in Table 1, the study subjects included 2 cases of children aged 0–28d, 1,053 cases aged 28d–2y, 6,034 cases aged 2y–8y, and 1,726 cases aged 8y–18y. The number of patients infected with different pathogens included 5,302 cases of FluA, 1,460 cases of FluB, 1,249 cases of MP, 206 cases of CP, 142 cases of RSV, 327 cases of ADV, and 129 cases of CV.

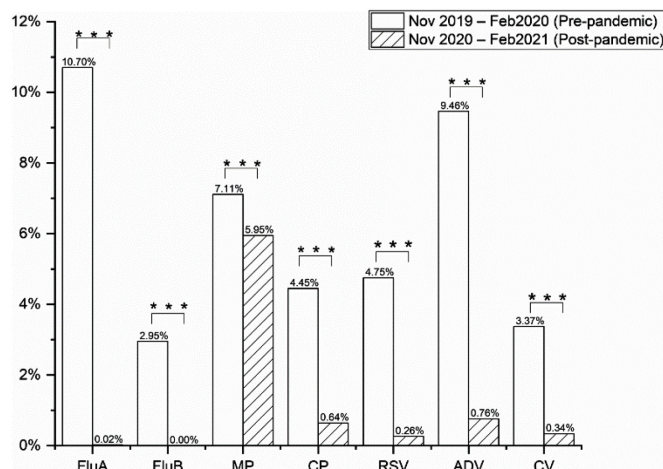
Among the 8,815 included cases, 220 (2.50%) were identified as having co-infections. The specific combinations and frequencies of all detected co-

infections are detailed in Supplementary Table 1. For all subsequent analyses, these co-infected cases were categorized as described in the methodology section.

Changes in the distribution of detected pathogens

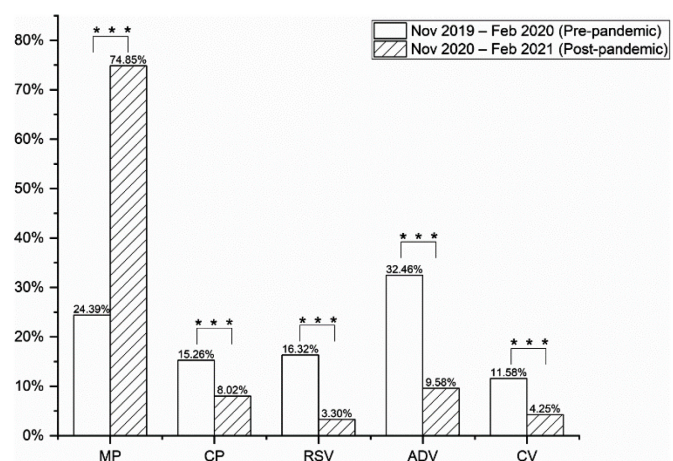
The spectrum of respiratory pathogens detected among positive cases changed substantially following the onset of the pandemic. As shown in Figure 1, influenza viruses, which were predominant before the pandemic, were virtually absent among positive cases in the post-pandemic period. Conversely, the proportion of cases attributed to MP increased markedly. As shown in Figure 2, prior to the pandemic, ADV represented the highest proportion (32.46%) of the 5 non-influenza

Figure 1. Comparison of test positive rates (%) of seven respiratory pathogens between the pre-pandemic and post-pandemic periods.



FluA: influenza A virus; FluB: influenza B virus; MP: *Mycoplasma pneumoniae*; CP: *Chlamydia pneumoniae*; RSV: respiratory syncytial virus; ADV: adenovirus; CV: coxsackievirus; *** $p < 0.001$.

Figure 2. Changes in the infection spectra of five respiratory pathogens before and after the COVID-19 pandemic.



MP: *Mycoplasma pneumoniae*; CP: *Chlamydia pneumoniae*; RSV: respiratory syncytial virus; ADV: adenovirus; CV: coxsackievirus. *** $p < 0.001$.

Table 1. Distribution of respiratory pathogens among positive cases, with separate denominators for influenza and non-influenza pathogen groups.

Time Range	Pathogen	Gender		<i>p</i> value	Age group				<i>p</i> value
		Male, No. (%) n = 3871	Female, No. (%) n = 2891		0–28d n = 2	28d–2y n = 553	2y–8y n = 4631	8y–18y n = 1576	
Nov 2019–Feb 2020	FluA	3029 (78.25%)	2273 (78.62%)	0.711	2 (100.00%)	427 (77.22%)	3608 (77.91%)	1265 (80.27%)	0.179
	FluB	842 (21.75%)	618 (21.38%)		0 (0.00%)	126 (22.78%)	1023 (22.09%)	311 (19.73%)	
Nov 2019–Feb 2020		n = 319	n = 251		n = 0	n = 163	n = 351	n = 56	
	MP	75 (23.51%)	64 (25.50%)	0.428	0 (0.00%)	15 (9.20%)	98 (27.92%)	26 (46.43%)	0
	CP	48 (15.05%)	39 (15.54%)	0.694	0 (0.00%)	61 (37.42%)	15 (4.27%)	11 (19.64%)	0
	RSV	60 (18.81%)	33 (13.15%)	0.154	0 (0.00%)	31 (19.02%)	59 (16.81%)	3 (5.36%)	0
	ADV	96 (30.09%)	89 (35.46%)	0.136	0 (0.00%)	31 (19.02%)	140 (39.89%)	14 (25.00%)	0
	CV	40 (12.54%)	26 (10.36%)	0.579	0 (0.00%)	25 (15.34%)	39 (11.11%)	2 (3.57%)	0.054
Nov 2020–Feb 2021		n = 852	n = 631		n = 0	n = 337	n = 1052	n = 94	
	MP	618 (72.54%)	492 (77.97%)	0.017	0 (0.00%)	194 (57.57%)	832 (79.09%)	84 (89.36%)	0
	CP	76 (8.92%)	43 (6.81%)	0.14	0 (0.00%)	74 (21.96%)	40 (3.80%)	5 (5.32%)	0
	RSV	29 (3.40%)	20 (3.17%)	0.803	0 (0.00%)	14 (4.15%)	34 (3.23%)	1 (1.06%)	0.324
	ADV	82 (9.62%)	60 (9.51%)	0.94	0 (0.00%)	28 (8.31%)	111 (10.55%)	3 (3.19%)	0.045
	CV	47 (5.52%)	16 (2.54%)	0.005	0 (0.00%)	27 (8.01%)	35 (3.33%)	1 (1.06%)	0

The distribution of influenza A and B viruses (FluA, FluB) was calculated using the total number of influenza-positive cases as the denominator. The distribution of the other five pathogens (MP, CP, RSV, ADV, CV) was calculated using the total number of positive cases for these five pathogens as the denominator. This approach reflects the distinct clinical testing pathways for influenza versus the other pathogens. MP: *Mycoplasma pneumoniae*; CP: *Chlamydia pneumoniae*; RSV: respiratory syncytial virus; ADV: adenovirus; CV: coxsackievirus.

respiratory pathogens, while MP ranked second. After the pandemic, MP became the most prevalent pathogen among positive cases, accounting for 74.85% of the detections. These results collectively suggest that, when compared to the other respiratory viruses, MP had a different transmission pattern that was less susceptible to the lockdown restrictions.

Change of pathogen spectra according to gender and age group

As shown in Table 2, the proportion of children infected with 5 pathogens changed significantly after the pandemic for both genders: more children were infected with MP; but fewer were infected with RSV, ADV, or CV. Prior to the pandemic, ADV infection was the most common in both boys (30.09%) and girls (35.46%), but MP infection became the most common infection in both boys (72.54%) and girls (77.97%) after the pandemic.

Furthermore, the infection proportion change trend differed between the 3 age groups (Table 2), as follows. The infection proportion for the 5 pathogens changed significantly in the 28d–2y group, with the proportion of MP increasing and the other 4 pathogens decreasing. The trend for the other 2 age groups was similar, but only infection with MP, ADV, and CV changed significantly in children aged 2y–8y; and only infection with MP, CP, and ADV changed significantly in children aged 8y–18y. These findings indicated that, in addition to the change in transmission pattern caused by lockdown restriction, immunity maturation as children grow also has an impact on the pathogen infection spectrum.

Exploratory analysis of peripheral blood parameters

In an exploratory analysis to generate hypotheses, peripheral blood test indicators were compared across pathogen groups and periods without adjustment for potential confounders such as age, disease severity, or timing of sampling. It is crucial to emphasize that these unadjusted comparisons are difficult to interpret clinically and should be viewed as descriptive rather than inferential. As shown in Figure 3, nominal differences were observed for some parameters; for instance, in the CP infection group, platelet count (PLT) and lymphocyte percentage (LYM%) appeared higher while neutrophil percentage (NEU%) appeared lower in the post-pandemic period. However, these changes were not consistent across all pathogen groups (Figure 3) or age strata (Figure 4). Given the exploratory nature and lack of adjustment for confounders, these findings should be interpreted with extreme caution and warrant further investigation in studies designed to control for these variables.

Discussion

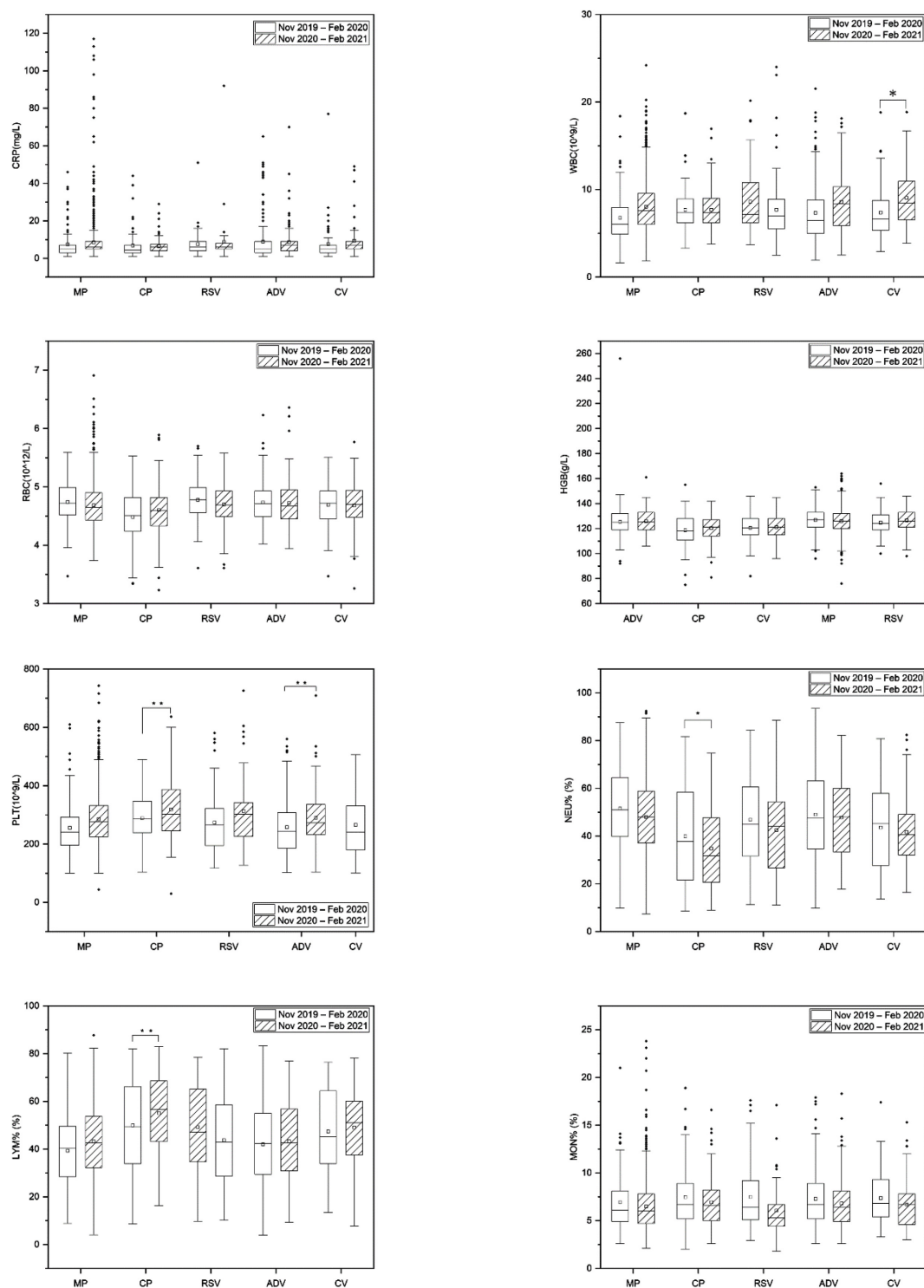
Acute respiratory infection (ARI) is highly prevalent and a leading cause of morbidity among children in developing countries [23]. As COVID-19 gains worldwide attention, medical institutions are focusing on how to effectively distinguish children with a common respiratory pathogen infection [24]. The aim of this study was to have a better understanding of the epidemiological characteristics and factors of the associated pathogen infection through statistical analysis of the relevant data. In this study, the selection of participants was based on the results of immunological tests, and the statistical analysis focused

Table 2. Comparison of the spectra of five respiratory pathogens according to gender and age group before and after the pandemic.

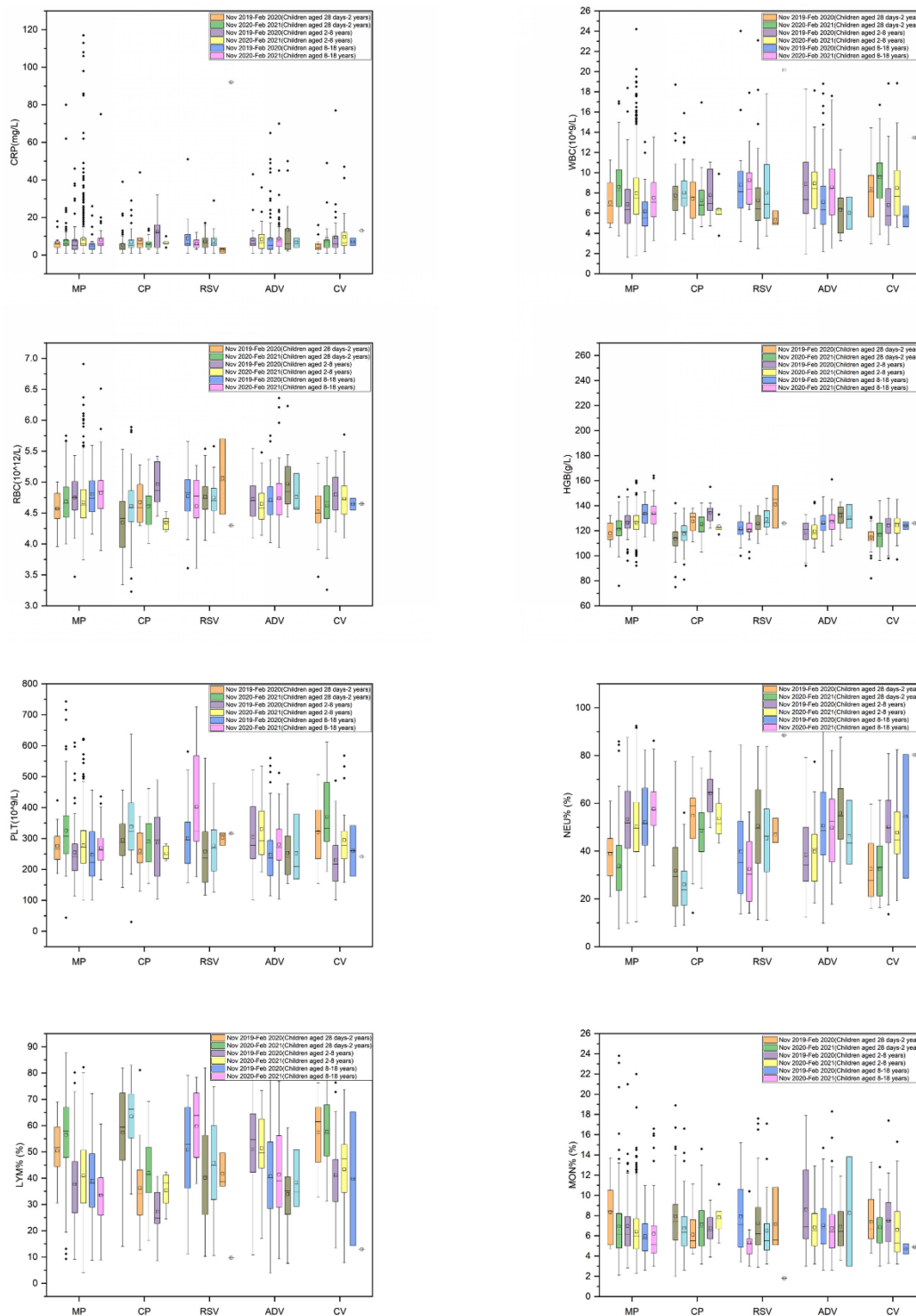
Gender	Time Range	n	MP	CP	RSV	ADV	CV
Male, No. (%)	201911–202002	n = 319	75 (23.51%)	48 (15.05%)	60 (18.81%)	96 (30.09%)	40 (12.54%)
	202011–202102	n = 852	618 (72.54%)	76 (8.92%)	29 (3.40%)	82 (9.62%)	47 (5.52%)
	p value		0	0.002	0	0	0
Female, No. (%)	201911–202002	n = 251	64 (25.50%)	39 (15.54%)	33 (13.15%)	89 (35.46%)	26 (10.36%)
	202011–202102	n = 631	492 (77.97%)	43 (6.81%)	20 (3.17%)	60 (9.51%)	16 (2.54%)
	p value		0	0	0	0	0
Age group	Time Range	n	MP	CP	RSV	ADV	CV
0–28d	201911–202002	n = 0	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	202011–202102	n = 0	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	p value		-	-	-	-	-
28d–2y	201911–202002	n = 163	15 (9.20%)	61 (37.42%)	31 (19.02%)	31 (19.02%)	25 (15.34%)
	202011–202102	n = 337	194 (57.57%)	74 (21.96%)	14 (4.15%)	28 (8.31%)	27 (8.01%)
	p value		0	0	0	0.001	0.012
2y–8y	201911–202002	n = 351	98 (27.92%)	15 (4.27%)	59 (16.81%)	140 (39.89%)	39 (11.11%)
	202011–202102	n = 1052	832 (79.09%)	40 (3.80%)	34 (3.23%)	111 (10.55%)	35 (3.33%)
	p value		0	0.694	0.14	0	0
8y–18y	201911–202002	n = 56	26 (46.43%)	11 (19.64%)	3 (5.36%)	14 (25.00%)	2 (3.57%)
	202011–202102	n = 94	84 (89.36%)	5 (5.32%)	1 (1.06%)	3 (3.19%)	1 (1.06%)
	p value		0	0.006	0.114	0	0.289

MP: *Mycoplasma pneumoniae*; CP: *Chlamydia pneumoniae*; RSV: respiratory syncytial virus; ADV: adenovirus; CV: coxsackievirus.

Figure 3. Exploratory comparison of peripheral blood indicators among children infected with various pathogens before and after the pandemic.



MP: *Mycoplasma pneumoniae*; CP: *Chlamydia pneumoniae*; RSV: respiratory syncytial virus; ADV: adenovirus; CV: coxsackievirus.

Figure 4. Exploratory comparison of peripheral blood indicators among infected children in different age groups before and after the pandemic.

MP: *Mycoplasma pneumoniae*; CP: *Chlamydia pneumoniae*; RSV: respiratory syncytial virus; ADV: adenovirus; CV: coxsackievirus.

on infected children with clinical symptoms. The selected participants included children with self-limiting infections and mild illness, but not clinically diagnosed children. This was also a limitation of this study. The widespread outbreak of COVID-19 prompted a significant increase in the use of masks that could provide a physical barrier of protection. On the other hand, the number of detected cases of common conventional respiratory pathogen infections significantly increased, while the proportion of these pathogens among tested cases significantly declined. This apparent paradox highlights the critical influence of expanded testing practices on the observations. The reasons behind this phenomenon are worth investigating.

Long-term research has revealed that influenza is an acute respiratory infectious disease that is primarily transmitted through the air [25]. The droplets are highly infectious, can be transmitted rapidly with a short incubation period, and are easily transmitted antigens. The population is extremely vulnerable to the mutant, with high incidence and mortality rates [26]. Prior to the COVID-19 pandemic, influenza virus subtypes exhibited different pandemic characteristics in different countries, years, seasons and regions due to antigenic drift and changes. In China, influenza pandemics peak mainly in winter, spring, and summer; with influenza A being most common in winter and spring, and influenza B being most common in winter, spring, and early summer. Geographically, influenza is generally prevalent in winter and spring in northern areas, with a peak period from December to February of the following year. While influenza can occur throughout the year in coastal areas of southern China, it is most common in winter, late spring, or early summer (March–June) [27–29]. The overall number of detected pathogen infections significantly decreased after the pandemic, a trend consistent with global reports [30,31], temporally associated with the implementation of non-pharmaceutical interventions (NPIs). However, the interpretation of these changes, particularly for specific pathogens, must consider the substantial increase in overall testing volume between the two study periods. The number of children tested for respiratory pathogens increased dramatically post-pandemic, which may have altered the case mix by including more children with milder symptoms.

This context is crucial for interpreting the findings for MP. Although the absolute number of detected MP cases increased alongside the expanded testing, its representation among all positive cases increased markedly, becoming the most prevalent pathogen post-

pandemic. This suggests that the decline in MP transmission may have been less pronounced compared to the sharp decline seen in most respiratory viruses. This relative resilience could be attributed to MP's distinct transmission dynamics, which might be less susceptible to the NPIs that effectively interrupted the transmission of common respiratory viruses. Additionally, changes in testing indications—such as a potential relative increase in testing for MP in cases of persistent cough—may have also contributed to the observed shift in its proportion. While this is a plausible explanation, the interpretation of these findings must consider important alternative explanations and the limitations of the before-and-after study design, which cannot isolate causality. The study documents a clear temporal association between NPIs and changes in the pathogen spectrum. However, the observed shifts are likely multifactorial. First, the dramatic expansion of testing intensity and changes in healthcare-seeking behavior (evidenced by the increase in tested specimens) represent a paramount confounder, as it altered the case mix by including more children with milder symptoms. Second, viral interference, where the circulation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might have impacted other viruses, could have played a role. Finally, broader societal changes like school closures and increased hygiene are inextricably linked with NPIs and may have independently reduced pathogen transmission.

Therefore, the findings likely result from a complex interplay of all these factors:

(A) RSV is a leading cause of lower respiratory tract infection in young children globally and causes 2.7 million to 3.8 million hospitalizations, and 94,600 to 149,400 deaths annually among children under the age of 5 years [32]. Epidemiological studies show that having bronchiolitis in childhood increases the likelihood of developing asthma in children [33]. In addition, whether prevention and control measures led to the decline of population resistance to prokaryotes deserves further study. Furthermore, the positive detection rate of other respiratory viruses, such as RSV, ADV, and CV, has shown a precipitous decline. RSV surveillance in China is still in its early stages, and diagnostic tests are limited [34]. There has been little research into the seasonality or changes in RSV infections in China [17]. The lack of information about RSV seasonality in China may impede RSV treatments and prevention measures.

(B) CVB causes approximately 20% to 25% of myocarditis cases [35]. Pathogen infection is more likely to occur during warm and hot seasons, and it can

occur throughout the year in subtropical and tropical regions, with widespread transmission [36]. Some CVs can cause hand, foot, and mouth disease; and in some cases, they are associated with severe neurologic complications and global outbreaks [35].

(C) Human ADV (HADV) infection has been widespread for more than 60 years, with sporadic local outbreaks occurring. New genotypes of ADV formed through gene recombination are constantly discovered, and the prevalent genotypes differ across different countries and regions, resulting in varying pathogenic characteristics [36]. In recent years, local outbreaks of HADV infection have become more common in China. Despite the fact that ADV has a high prevalence among respiratory tract virus pathogens in children, the mortality rate of ADV-induced severe pneumonia is high [37].

Several limitations in the detection methods should be considered when interpreting the results. Firstly, the reliance on IgM serology for respiratory virus diagnosis has inherent drawbacks. IgM antibodies may persist for weeks to months after acute infection, and false-positive results can occur due to cross-reactivity or rheumatoid factor [38,39]. Therefore, the increased proportion of MP-positive cases in the post-pandemic period might not solely reflect a true increase in acute infections. It could be influenced by the cumulative effect of past infections or testing characteristics. However, it is worth noting that the same assay was used consistently across both study periods, which reduces the likelihood that the observed shift is merely an artifact of changing test performance. Nevertheless, the predominance of MP in the findings of this study highlights the need for future studies to employ more definitive diagnostic methods, such as polymerase chain reaction (PCR), to accurately ascertain the burden of acute MP infection.

Wuhan, in central China, has a subtropical humid monsoon climate with plenty of rain and sunshine, and four distinct seasons. Despite the effects of temperature, resumption of work, and seasonal pandemics, infection rates of various pathogens remained very low in 2020. The COVID-19 pandemic's potential impact on various infections is unknown, and the reasons for the observed decline are likely multifactorial. Pathogen competition, for example, could be a factor. According to research, one virus can prevent the infection of another virus simply by competing for resources [40]. Other mechanisms, such as immune response or viral protein interference, are thought to interfere with the growth of the two viruses [41]. Seasonal influenza has been successfully contained by COVID-19 control measures,

providing some useful insights for the future control of emerging influenza pandemics.

The researchers acknowledge that the substantial increase in testing intensity and changes in healthcare-seeking behavior during the pandemic may have introduced a spectrum bias, potentially including more children with milder symptoms in the post-pandemic cohort. This shift in case ascertainment is an important alternative explanation for the observed changes in the pathogen distribution and underscores the need for cautious interpretation of the findings.

The study's limitations include the fact that it was conducted at a single location in a limited geographical area and over a short period of time, rather than a full year or longer. It is crucial for medical institutions at all levels to focus on effectively identifying various respiratory pathogen infections during the upcoming winter and spring seasons. Interpretation of these findings must consider the limitations of the diagnostic methods. The use of IgM serology for *M. pneumoniae* and *C. pneumoniae* cannot reliably distinguish acute from recent infection, which may influence the observed proportion of these pathogens. Furthermore, antigen-based tests for viruses (RSV, ADV) have lower sensitivity than PCR-based methods, potentially leading to an underestimation of their true prevalence. These factors are important considerations when interpreting the shifts in the pathogen spectrum.

Another limitation is the handling of co-infections. Assigning each case to a single primary pathogen for the main analysis, may have underestimated the complexity of pathogen interactions. However, this approach was chosen to best represent the primary clinical diagnosis and to prevent the same patient from being counted multiple times in proportional calculations, which could have introduced a different form of bias. The comprehensive data on co-infections are provided in the supplementary table for transparency. Furthermore, the study design cannot account for all potential confounders, such as changes in healthcare-seeking behavior, viral interference, or school attendance patterns. These factors, temporally associated with NPI implementation, may have contributed to the observed changes and should be considered when interpreting the findings.

An exploratory analysis of peripheral blood parameters was conducted; however, due to the limitations discussed above, no firm conclusions can be drawn from these data regarding the biological impact of NPIs.

Conclusions

This research aimed to provide useful clues and indicators to aid in identification of respiratory pathogen infections. More importantly, the findings suggest that extensive mask wearing to create a protective physical barrier may not reduce the number of common respiratory pathogen infections. The study also discovered that the leading indicators of various pathogen infections have distinct infection characteristics. It is critical to detect and differentiate respiratory pathogen infections as early as possible. Clinical detection indicators at the early stages of these various respiratory pathogen infections can significantly aid in the prediction and differentiation of related pathogen infections in the future.

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Ethics statement

The study protocol was approved by the Ethics Review Committee of Wuhan Children's Hospital (2024R050-E01). The requirement for informed consent was waived due to the retrospective nature of the study.

Authors' contributions

FT, RL, YX, AQ, designed and conceptualized this study; RL, HZ, performed the experiments and preliminarily analyzed the data; FT, RL, drew the figures and tables and drafted the initial manuscript; FT, RL, YX, AQ, revised this manuscript. All authors have read and approved the final manuscript.

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Conflict of interest

No conflict of interest is declared.

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Annex – Supplementary Items

Supplementary Table 1. Details of pathogen co-infections identified in the study population.

Co-infection combination	November 2019–February 2020			November 2020–February 2021		
	Number of cases (n)	Percentage of all co-infections (%)	Percentage of total cohort (%)	Number of cases (n)	Percentage of all co-infections (%)	Percentage of total cohort (%)
MP + CP	2	3.08%	0.35%	30	19.35%	2.02%
MP + RSV	15	23.08%	2.63%	15	9.68%	1.01%
MP + ADV	10	15.38%	1.75%	42	27.10%	2.83%
MP + CV	5	7.69%	0.88%	12	7.74%	0.81%
CP + RSV	2	3.08%	0.35%	2	1.29%	0.13%
CP + ADV	2	3.08%	0.35%	6	3.87%	0.40%
CP + CV	1	1.54%	0.18%	5	3.23%	0.34%
RSV + ADV	6	9.23%	1.05%	5	3.23%	0.34%
RSV + CV	4	6.15%	0.70%	6	3.87%	0.40%
ADV + CV	15	23.08%	2.63%	22	14.19%	1.48%
MP + RSV + ADV	2	3.08%	0.35%	1	0.65%	0.07%
MP + RSV + CV	1	1.54%	0.18%	0	0.00%	0.00%
MP + ADV + CV	0	0.00%	0.00%	4	2.58%	0.27%
MP + CP + ADV	0	0.00%	0.00%	2	1.29%	0.13%
MP + CP + CV	0	0.00%	0.00%	1	0.65%	0.07%
MP + CP + RSV	0	0.00%	0.00%	1	0.65%	0.07%
MP + CP + RSV + ADV	0	0.00%	0.00%	1	0.65%	0.07%
All co-infections	65			155		
Total cohort	570			1483		

MP: *Mycoplasma pneumoniae*; CP: *Chlamydia pneumoniae*; RSV: respiratory syncytial virus; ADV: adenovirus; CV: coxsackievirus.