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#### RESEARCH ARTICLE

## MEDICAL VIROLOGY WILEY

# Epidemiological changes of common respiratory viruses in children during the COVID-19 pandemic

## Qing Ye 💿 | Dongjie Wang

Department of clinical laboratory, The Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, National Children's Regional Medical Center, Hangzhou, China

#### Correspondence

Qing Ye, Department of clinical laboratory, The Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, National Children's Regional Medical Center, Hangzhou 310052, China.

Email: qingye@zju.edu.cn

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#### Abstract

A variety of non-pharmaceutical interventions (NPIs) have been implemented to control the transmission of COVID-19 in China. The effect of NPIs on other common respiratory viruses in children of different age groups has not been examined thus far. Respiratory specimens of children were collected to detect common childhood respiratory viruses, including influenza A (FluA), influenza B (FluB), adenovirus, and respiratory syncytial virus (RSV), at the Children's Hospital of Zhejiang University School of Medicine from January 1, 2019 to December 31, 2020. The epidemiological characteristics of the respiratory viruses in 2020 were compared with those in 2019. From January 2019 to December 2020, 165 622 specimens were collected. The proportion of infants aged 0-28 days (683, 2.24% vs. 1295, 0.96%, p = 0.000) and 1-12 months (8560, 28.12% vs. 20875, 15.43%, p = 0.000) in 2020 increased significantly compared with that in 2019. There were two obvious increases in April and September in the number of specimens in children aged 4-6 years and >7 years. FluA, FluB, and RSV's age distribution patterns were surprisingly consistent with each other in 2020, and the positive rates of children aged 1-12 months were the highest in all age groups (FluA: 4.45%, FluB: 3.30%, RSV: 7.35%). Our study further confirms that the NPIs significantly decreased the transmission of common childhood respiratory viruses. The change in circulation characteristics of common respiratory viruses of children in different age groups varied. Therefore, we recommend that different protection strategies should be introduced for children of different age groups.

#### KEYWORDS

childhood respiratory viruses, COVID-19, non-pharmaceutical interventions

## 1 | INTRODUCTION

COVID-19 is one of the most sustained, disastrous infectious diseases that brings enormous challenges to worldwide health care.<sup>1–9</sup> To control the transmission of the pandemic, 30 provincial-level regions in China activated a first-level public health emergency response on January 26, 2020. A variety of non-pharmaceutical interventions (NPIs) have been implemented, such as mask use, physical distancing, travel restrictions, and personal hygiene improvement in China. The in-person classes in schools were also canceled. Instead, online classes were promoted across the country until the gradual reopening of the schools in April and May. Such measures could have a significant influence on other common respiratory viruses, such as influenza A (FluA), influenza B (FluB), adenovirus (ADV), and respiratory syncytial virus (RSV), in children.

Qing Ye and Dongjie Wang contributed equally to this study.

Data from several studies suggest that the NPIs result in an overall decrease in the transmission of respiratory viruses.<sup>10–14</sup> In some periods after the epidemic, compared to previous years, the Global Influenza Surveillance, and Response System even reported a 99% reduction in the number of influenza-positive cases.<sup>15</sup> However, recent evidence suggests that some other respiratory viruses showed a propensity to reemerge.<sup>16</sup> Although some studies have reported the impact of the pandemic on the prevalence of respiratory viruses in children,<sup>17–20</sup> few studies have focused on the influence of the NPIs on the circulation of common respiratory viruses in children of different age groups. Therefore, our study was conducted to report, and discuss the change in the epidemiological characteristics of common respiratory viruses in children of different ages under the COVID-19 pandemic and provide support for finding better protection strategies.

#### 2 | METHODS

#### 2.1 | Study design

All patients who met the criteria were continuously recruited at the Children's Hospital of Zhejiang University School of Medicine from January 1, 2019 to December 31, 2020 to evaluate the impact of the pandemic on the prevalence of common respiratory viruses in children. The inclusion criteria were (1) patients under 18 years old; (2) diagnosed with an acute respiratory infection (presenting with one or more of the following symptoms: fever, cough, earache, nasal congestion, rhinorrhea, sore throat, vomiting after coughing, wheezing, and labored, rapid, or shallow breathing).<sup>21</sup> Children infected with COVID-19 were excluded from the study. For each patient, during one course of illness, only the results of the first specimen were collected and analyzed.

#### 2.2 | Specimen collection and detection

Respiratory specimens (nasopharyngeal aspirates/bronchoalveolar lavage fluid) were collected and handled by trained staff. The Respiratory Virus Antigen Detection Kit (Genesis) was used to detect respiratory viruses, including ADV, FluA, FluB, and RSV. After the specimens were delivered to the laboratory, they were handled according to a standard procedure. The specimens were first added to the sample extraction solution in the sampling tube and stirred. One hundred microliters of liquid in the tube were dropped onto the detection plate. After 15 min, the results could be observed according to the bands shown on the detection plate.

#### 2.3 | Statistical analysis

The ages of the patients were expressed as medians and interquartile ranges, as they were not normally distributed. When comparing the distribution of respiratory viruses in different age groups in 2019 and MEDICAL VIROLOGY

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2020, the patients were divided into five age groups, including 0–28 days, 1–12 months, 1–3 years, 4–6 years, and older than 7 years.  $\chi^2$  tests and rank-sum tests were used when making comparisons between respective groups. A *p* value below 0.05 was considered to indicate a statistically significant difference. We performed statistical analysis with SPSS version 24.0.

#### 3 | RESULTS

#### 3.1 | Overall

From January 2019 to December 2020, 165 622 specimens were collected, including 135 283 in 2019 and 30 339 in 2020. There was no difference in gender between patients in 2019 and 2020. The patients in 2020 (median age: 2 years) were significantly younger than those in 2019 (median age: 3 years). Specifically, compared within 2019, the proportion of infants aged 0-28 days (683, 2.24% vs. 1295, 0.96%, p = 0.000) and 1-12 months (8560, 28.12% vs. 20 875, 15.43%, p = 0.000) in 2020 increased significantly. In contrast, the proportion of children aged 1-3 years (8761, 28.78% vs. 43 358, 32.04%, p = 0.000), 4-6 years (9245, 30.37% vs. 51 549, 38.10%, p = 0.000) and more than 7 years (3190, 10.48% vs. 18 296, 13.52%, p = 0.000) in 2020 decreased significantly. The positive rates of all four respiratory viruses involved in this study in 2020 were significantly lower than those in 2019. The proportion of respiratory viruses also changed; ADV (11.20%) and FluA (12.16%) were the most commonly detected viruses in 2019, and RSV (2.94%) became the most commonly detected virus in 2020 (Table 1). For mixed viral infection, we found that most types of double infection in 2020 were significantly less frequent than those in 2019. Specifically, the positive rate of "ADV + FluA" dropped from 7.10% to 0.49% (*p* = 0.000), "ADV + FluB" from 2.62‰ to 0.26‰ (p = 0.000), "ADV + RSV" from 1.46‰ to 0.49‰ (p=0.002), "FluA + RSV" from 0.51‰ to 0.09‰ (p = 0.000), and "FluA + FluB" from 0.01% to 0.0% (p = 0.000). Furthermore, there were no triple or quadruple infections in 2020, yet in 2019, the number of specimens detected was 15 and 3, respectively (Figure 1).

#### 3.2 Seasonal distribution

We observed that ADV was detected throughout 2019 with a higher prevalence in the first half-year, whereas the phenomenon was not observed in 2020. Instead, ADV is distributed almost evenly throughout the year except for a slight increase in the positive rate in February 2020 (Figure 2A). FluA was almost not detected after February 2020, and the highest positive rate of FluA was less than 0.55%. However, FluA has a clear seasonal distribution pattern, as it peaked in February 2019, and the positive rate of FluA was significantly higher than that in 2020 (February 2019: 36.0% vs. February 2020: 1.18%, Figure 2B). Moreover, it was almost the same for FluB, except that FluB peaked in April 2019 (April 2019: 15.93% vs. April 2020: 0.17%, Figure 2C). RSV is the only respiratory virus

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with a seasonal distribution pattern with a higher prevalence in the winter months. In addition, the positive rate of RSV in November and December in 2020 was even higher than that in 2019 (November 2020: 1.87% vs. November 2019: 1.08%; December 2020: 8.35% vs. December 2019: 4.81%, Figure 2D).

| TABLE 1                  | Patient characteristics and detection of respiratory |  |
|--------------------------|--|--|
| viruses in 2019 and 2020 |  |  |

|                                 | 2019<br>(n = 135 283) | 2020<br>(n = 30 439) | p value |
|---------------------------------|-----------------------|----------------------|---------|
| Characteristics                 |                       |                      |         |
| Male sex, <i>n</i> (%)          | 72 947 (53.9)         | 16 329 (53.6)        | 0.766   |
| Age, median<br>(IQR), year      | 3 (1-5)               | 2 (1-4)              | 0.000   |
| 0-28 day, n (%)                 | 1295 (0.96)           | 683 (2.24)           | 0.000   |
| 1–12 month, <i>n</i> (%)        | 20 875 (15.43)        | 8560 (28.12)         | 0.000   |
| 1–3 year, n (%)                 | 43 358 (32.04)        | 8761 (28.78)         | 0.000   |
| 4-6 year, n (%)                 | 51 549 (38.10)        | 9245 (30.37)         | 0.000   |
| >7 year, n (%)                  | 18 296 (13.52)        | 3190 (10.48)         | 0.000   |
| Positive rate of viruses, n (%) |                       |                      |         |
| ADV                             | 15 146 (11.20)        | 739 (2.44)           | 0.000   |
| FluA                            | 16 456 (12.16)        | 502 (1.65)           | 0.000   |
| FluB                            | 6848 (5.06)           | 486 (1.60)           | 0.000   |
| RSV                             | 3554 (2.63)           | 892 (2.94)           | 0.002   |
| Total                           | 42 004 (31.05)        | 2619 (8.63)          | 0.000   |

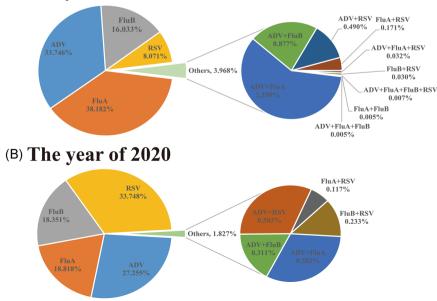
Abbreviations: ADV, adenovirus; FluA, influenza A; FluB, influenza B; IQR, interquartile range; RSV, respiratory syncytial virus.

In 2020, there was a sharp drop in the number of specimens in all age groups after January 2020. Moreover, there were two apparent increases in April and September in the number of specimens of children aged 4–6 years and >7 years (Figure 3D,E). For children aged 1–3 years, a noticeable increase in specimen number in April and a slight increase in November can be observed (Figure 3C). This trend can also be seen in children aged 1–28 days and 1–12 months, but it was not evident (Figure 3A,B). In other words, the typical seasonal distribution pattern in different age groups in 2019 no longer existed in 2020.

#### 3.3 | Age distribution

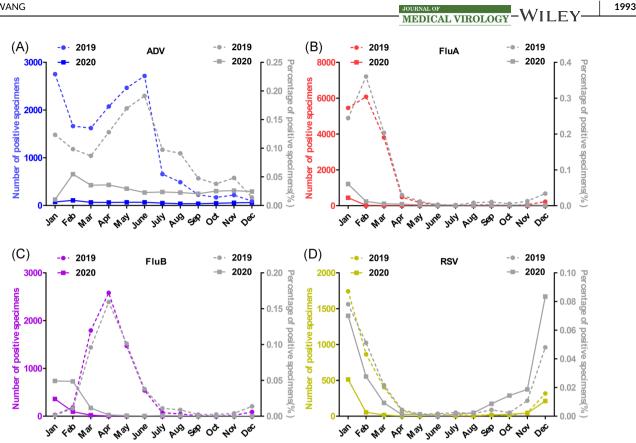
In 2019, for infants aged 0–28 days, RSV accounted for 51.50% of viruses that cause acute respiratory illnesses, and FluB was almost not detected (Figure 4A). The proportion of RSV decreased with age, and the proportion of FluB increased with age, yet ADV, and FluA still occupied the majority in most of the age groups. However, in 2020, the proportion of RSV increased in every age group. Among children older than 1 year, ADV was the predominant respiratory virus, and there was a sharp decrease in the proportion of FluA compared with that in 2019 (Figure 4B).

The age distribution of ADV in 2020 was roughly the same as that in 2019, and the positive rate of the respiratory specimens was at the highest level in the age group of 4–6 years (15.54% in 2019 and 3.48% in 2020, Figure 5A). However, for the other three viruses, there was an apparent discrepancy in age distribution between 2019 and 2020. In 2019, for FluA and FluB, the percentage of positive specimens increased with age, whereas the percentage of positive specimens of RSV decreased with age. The age distribution patterns of these three viruses were surprisingly consistent with each



## (A) The year of 2019

FIGURE 1 Proportion of respiratory viruses detected in 2019 (A) and 2020 (B). ADV, adenovirus; FluA, influenza A; FluB, influenza B; RSV, respiratory syncytial virus



**FIGURE 2** The number and percentage of virus-positive specimens according to months in 2019 and 2020, including ADV (A), FluA (B), FluB (C) and RSV (D). The vertical axis on the left and colored lines represent the number of virus-positive specimens in 2019 (dashed lines) and 2020 (solid lines). The vertical axis on the right and gray lines represent the percentage of virus-positive specimens in 2019 (dashed lines) and 2020 (solid lines). ADV, adenovirus; FluA, influenza A; FluB, influenza B; RSV, respiratory syncytial virus

other in 2020, and the positive rates of these three viruses in children aged 1–12 months were all the highest (FluA: 4.45%, FluB: 3.30%, RSV: 7.35%) (Figure 5B–D).

#### 4 | DISCUSSION

After the outbreak of COVID-19, many strict public health measures were introduced worldwide to control the pandemic, which dramatically impacted other common respiratory viruses. In the present study, we compared the characteristics of four common respiratory viruses in children of different age groups in 2019 and 2020. The results of our study showed that there was a marked reduction in both the number and positive rate of respiratory virus specimens in 2020 compared with those in 2019.

Interestingly, in our study, the proportion of children aged under 1 year old in the number of specimens increased significantly. One possible explanation is that the intervention adopted in the pandemic reduced the outdoor activities of the older children to a more significant extent since children under 1 year old will not go outside that much as the older children do. The reduction in the number of specimens in children older than 1 year was more pronounced than that in children younger than 1 year, which increased the relative number of specimens in children under 1 year of age. Moreover, for a long time at the beginning of the pandemic, there were much less suitable masks available for children under 1 year of age, making younger children more vulnerable to respiratory viruses. It is also worth noting that except for ADV, the positive rates of the other three viruses were all highest in children aged 1–12 months. This phenomenon was not observed in 2019, and previous research was conducted in our hospital from April 2018 to March 2019.<sup>22</sup> The practice of postpartum confinement may partially explain why the same thing did not go for infants aged 0–28 days. In China, after a woman gives birth to a baby during the first month, the mother and the baby are supposed to stay at home and avoid contact with other people. Therefore, more attention should be given to children aged 1–12 months in China to prevent infection by respiratory viruses.

We observed that RSV became the most common virus in 2020 instead of ADV and FluA in 2019. In addition, the seasonal distribution patterns of FluA and FluB almost disappeared since China initiated the emergency response, while the seasonality of RSV remained as it still peaked in the winter months. However, to the best of our knowledge, the mechanism that accounts for this phenomenon remains unclear. One possible reason is the relationship between RSV and the influenza virus. It has been reported that a localized inflammatory response could be induced after infection with the influenza virus, which can limit the replication and spread of RSV.<sup>23,24</sup> This interaction was greatly weakened, as the circulation of the influenza virus in 2020 was rarely low, which may partially offset the influence brought by public health measures. This

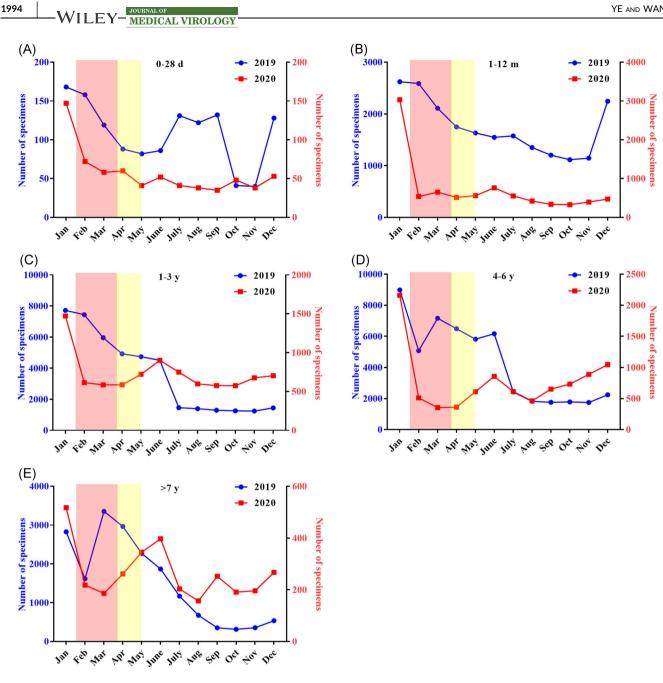


FIGURE 3 Number of respiratory virus specimens detected in different age groups according to months in 2020 (red) compared with 2019 (blue). The patients were divided into five age groups, including 0-28 days (A), 1-12 months (B), 1-3 years (C), 4-6 years (D), and older than 7 years (E). The red block represents the period from the level-1 emergency response initiated in January 2020 to the emergency response adjusted to level 3 in April 2020 in Zhejiang, China. The yellow block represents the period from emergency response adjusted to level 3 to school reopening in May 2020 in Zhejiang, China

trend of RSV is likely to continue as the reemergence of RSV was also reported in some other areas.<sup>25-27</sup> Moreover, an outbreak of RSV is predicted by the regression model in Japan after the COVID-19 pandemic.<sup>28</sup> Therefore, we speculate that RSV could be the predominant respiratory virus and should be monitored more diligently in children in the future.

We also found that the change in seasonality of respiratory viruses in different age groups varied. For children aged 4-6 years and more than 7 years, in April and September in 2020, an increase in the number of specimens can be observed, which is different

from that in 2019. We attribute this change to increasing social contact since the timing is highly consistent with reopening schools and kindergartens. We consider this trend to continue with the relaxation of COVID-19 mitigation measures and the reopening of shops and workplaces. Moreover, according to recent research, more intense epidemics could occur after the low incidence of the influenza virus due to a drop in herd immunity.<sup>29</sup> Hence, children older than 3 years need to enhance public health measures such as social distancing and personal hygiene after the reopening of the school and kindergarten.

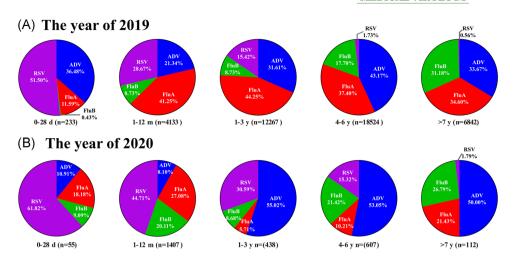
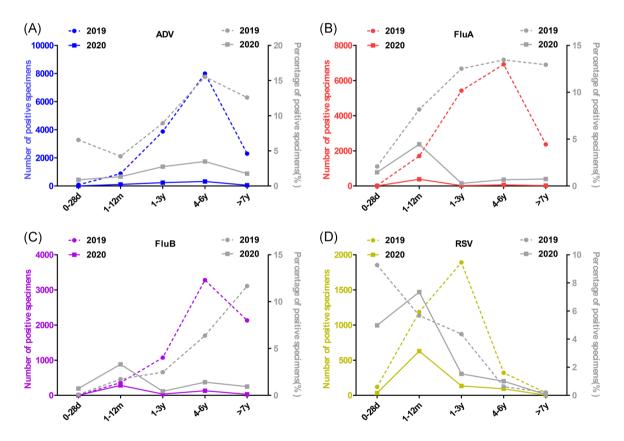


FIGURE 4 Proportion of respiratory viruses detected in different age groups in 2019 (A) and 2020 (B). ADV, adenovirus; FluA, influenza A; FluB, influenza B; RSV, respiratory syncytial virus



**FIGURE 5** The number and percentage of virus-positive specimens according to age groups in 2019 and 2020, including ADV (A), FluA (B), FluB (C) and RSV (D). The vertical axis on the left and colored lines represent the number of virus-positive specimens in 2019 (dashed lines) and 2020 (solid lines). The vertical axis on the right and gray lines represent the percentage of virus-positive specimens in 2019 (dashed lines) and 2020 (solid lines). ADV, adenovirus; FluA, influenza A; FluB, influenza B; RSV, respiratory syncytial virus

Our research may have some limitations. All the data were obtained from one hospital to introduce selection bias. Data acquired from different places will be more convincing. The other main limitation of the study is that only four types of common respiratory viruses are covered in this study. Limited by the hospital's testing program, other common respiratory viruses, such as rhinovirus and parainfluenza virus, were not covered.

## 5 | CONCLUSION

Our study further confirms that the lockdown measures adopted during the pandemic significantly decreased the transmission of common childhood respiratory viruses. However, the change in circulation characteristics of common respiratory viruses of children in different age groups varied. Therefore, we recommend that different protection strategies should be introduced for children of different age groups. Extra attention should be given to children aged 1–12 months to protect them from respiratory virus infection.

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#### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

#### ETHICS STATEMENT

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committee approved this study of the Children's Hospital, Zhejiang University School of Medicine (2021-IRB-228). Informed consent was obtained from all patients involved in the study.

#### AUTHOR CONTRIBUTIONS

Qing Ye drafted the initial manuscript and contributed to manuscript editing. Dongjie Wang collected the data from patients and contributed to manuscript editing. Qing Ye devised the conceptual ideas, contributed to the discussion and interpretation of the results, and reviewed the final manuscript. All authors approved the final manuscript.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

#### ORCID

Qing Ye D http://orcid.org/0000-0002-6756-0630

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