

## RESEARCH ARTICLE

# Nonpharmaceutical interventions against the COVID-19 pandemic significantly decreased the spread of enterovirus in children

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**Funding information**

The Natural Science Foundation of Zhejiang Province (LY22H050001), the Key Project of Provincial Ministry Construction, Health Science and Technology Project Plan of Zhejiang Province (WKJ-ZJ-2128), Key Laboratory of Women's Reproductive Health Research of Zhejiang Province (ZDFY2020-RH-0006), National Natural Science Foundation of China (Grant/Award Number: U20A20351) and Key Research and Development Plan of Zhejiang Province (Grant/Award Number: 2021C03079).

**Abstract**

Precise prevention and control measures have been adopted to impede the transmission of coronavirus disease 2019 (COVID-19) in China. This study was performed to investigate the effect of protective measures on gastrointestinal infection in children during the COVID-19 pandemic. The data on the rotavirus and adenovirus antigen tests were collected in outpatient children due to gastroenteritis from January 1, 2019 to December 31, 2020, at the Children's Hospital of Zhejiang University School of Medicine. According to age and month distribution, the positive number and rate of rotavirus and adenovirus in 2020 were compared with 2019. A 3.8-fold and 4-fold reduction in the number of rotavirus- and adenovirus-positive patients in 2020 were found, respectively. The overall positive rate of rotavirus and adenovirus infection was drastically decreased in 2020 (rotavirus 2020: 18.18% vs. 2019: 9.75%,  $p < 0.001$ ; adenovirus 2020: 3.13% vs. 2019: 1.58%,  $p < 0.001$ ). The proportions of rotavirus and adenovirus in all age groups in 2020 decreased compared with those in 2019. The highest frequency of rotavirus infection occurred among children aged 1–3 years both in 2019 and 2020 (2019: 27.95% vs. 2020: 17.19%,  $p < 0.001$ ), while adenovirus infection was detected in children aged 3–5 years, which had the highest percent positivity (2019: 8.19% vs. 2020: 4.46%;  $p < 0.001$ ). An obvious peak prevalence of rotavirus incidence was found during December–April, and the percent positivity of rotavirus significantly decreased in 2020 (December 2019: 24.26% vs. 2020: 8.44%,  $p < 0.001$ ; January 2019: 40.67% vs. 2020: 38.18%,  $p < 0.05$ ; February 2019: 40.73% vs. 2020: 15.04%,  $p < 0.001$ ; March 2019: 31.47% vs. 2020: 7.88%,  $p < 0.001$ ; April 2019: 15.52% vs. 2020: 4.78%,  $p < 0.001$ ). The positive rate of adenovirus distributed throughout 2019 was 1.91%–4.86%, while the percent positivity during 2020 in the same period was much lower (0.00%–3.58%). Our results confirmed that the preventive and control measures adopted during the COVID-19 pandemic and the collateral benefit of these interventions have significantly decreased the transmission of rotavirus or adenovirus.

**KEYWORDS**

adenovirus, children, COVID-19, gastroenteritis, rotavirus

## 1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) has spread in most countries, leading to enormous challenges to global healthcare and tremendously impacting everyone's lives. Since the outbreak of the pandemic, precise prevention and control measures, including early isolation and treated infected people, close contact tracing and quarantine, minimizing public gathering activities and closing of schools, and strengthening disinfection in places with large population flows are to be implemented for different regions and at different levels. In addition, personal protection measures such as respiratory etiquette, mask-wearing, hand hygiene, environmental sanitation, physical distancing, and travel restriction were strictly maintained all year round in China.<sup>1</sup> These measures curb the spread of COVID-19 and effectively control the transmission of other infectious diseases that are prevalent every winter, such as respiratory, influenza, and mycoplasma infections.<sup>2–4</sup> However, few studies have focused on the influence of the incidence rate of gastrointestinal-related viruses before and after the COVID-19 pandemic.

Gastrointestinal infectious diseases are among the most common life-threatening etiologies, especially in pediatric patients.<sup>5</sup> Viral infections generally cause gastroenteritis, and rotaviruses and adenoviruses are thought to be the major pathogens,<sup>6</sup> which are usually transmitted through the fecal-oral route. It is a tremendous burden. Approximately 1.5 million doctor visits yearly are associated with gastroenteritis.<sup>7</sup> The treatment of rotavirus gastroenteritis expends 365 million dollars each year in China.<sup>8</sup> Therefore, this retrospective study aimed to investigate whether the prevalence of rotavirus and adenovirus among children with gastroenteritis infection has changed under continual prevention and control strategies during the COVID-19 pandemic and to provide support for finding better protection strategies.

## 2 | METHODS

### 2.1 | Study population

Data from outpatients with gastroenteritis at the Children's Hospital of Zhejiang University School of Medicine from January 2019 to December 2020 were collected. The specimen number of detection for rotavirus and adenovirus and the positive cases were analyzed in the present study. Gastroenteritis is diagnosed on clinical grounds. Its leading manifestations are sudden loosening of stool consistency and increased stool frequency to more than three times per day (or more than two times per day beyond the patient's usual frequency), sometimes accompanied by vomiting or fever.<sup>9</sup> Metabolic disturbances, intestinal obstruction, appendicitis, and other infectious diseases, such as pneumonia and meningitis, are the main elements of the differential diagnosis. None of the patients received any medications or medical tests before they visited our hospital, and patients over 18 years old or diagnosed with chronic diarrhea were

excluded from the study. All subjects were divided into five age groups: under 6 months, 6 months–1 year, 1–3 years, 3–5 years, and older than 5 years. The positive rates of rotavirus and adenovirus were also compared by month.

### 2.2 | Specimen collection and detection

Stool samples (1 g or 1 ml for children with diarrhea) were collected in a sterile screw-capped plastic container. Approximately 50 mg of stool sample was mixed with 1 ml of sample extraction solution and then used for detection. Rotavirus A and human adenovirus antigen were detected by a latex agglutination test using a commercial kit (Abon Biopharm Co., Ltd.) approved by the Food and Drug Administration (FDA) of China (Approval No. 20153402309). The detection plate was composed of a sample well plate, control line, rotavirus test line, and adenovirus. The steps of detection were as follows: (I) add two drops (approximately 80  $\mu$ l) of the sample mixture into a sample well plate; (II) incubate for 10–20 min; (III) observe the results according to the brands shown on the detection plate as follows: (a) if the control line and the rotavirus test line were both observed blue, the sample was determined to be rotavirus positive; (b) if the control line was observed blue and the adenovirus test line was observed red, the sample was determined to be adenovirus positive. In our previous study, using quantitative real-time polymerase chain reaction (qRT-PCR) as the gold standard, the sensitivity and specificity of the latex agglutination test for detecting rotavirus A were 81.03% and 97.44%, respectively, and the sensitivity and specificity of the latex agglutination test for detecting human adenovirus were 76.27% and 94.19%, respectively.<sup>10</sup>

### 2.3 | Statistical analysis

Statistical analyses were performed using SPSS 22.0 software. Categorical variables were analyzed by the  $\chi^2$  test or Fisher's exact test, and a two-sided *p* value less than 0.05 was considered statistically significant.

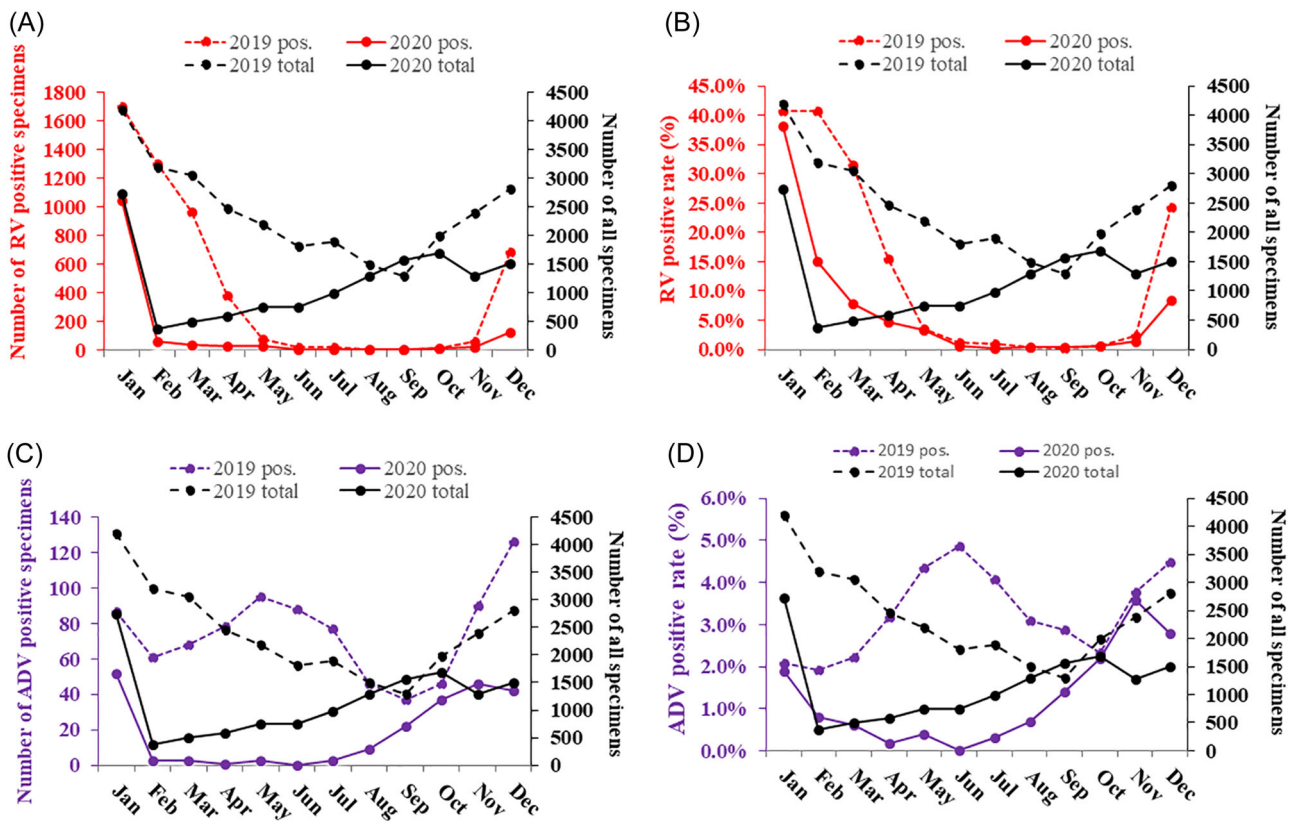
## 3 | RESULTS

### 3.1 | Overall

From January 2019 to December 2020, a total of 42 789 specimens were tested in our hospital due to gastroenteritis infection, including 28 764 samples in 2019 and 14 025 samples in 2020. The total number of patients in 2020 was twofold lower than that in 2019. Among them, 25 152 were male, and 17 637 were female, with a male to female ratio of 1.43:1. However, a difference in sex between patients in 2019 and 2020 was not observed. In the five age groups, most patients were aged 1–3 years (4904, 34.97%) in 2020, which was roughly the same as that in 2019 (13 388, 46.54%) (Table 1).

**TABLE 1** Patient characteristics and detection of rotavirus and adenovirus in 2019 and 2020.

|                                 | 2019 (n = 28 764) | 2020 (n = 14 025) | $\chi^2$ value | p Value |
|---------------------------------|-------------------|-------------------|----------------|---------|
| Characteristics, n (%)          |                   |                   |                |         |
| Gender                          |                   |                   |                |         |
| Male                            | 16 949 (58.92)    | 8203 (58.49)      | 0.739          | 0.390   |
| Female                          | 11 815 (41.08)    | 5822 (41.51)      |                |         |
| Age                             |                   |                   |                |         |
| <6 M                            | 5256 (18.27)      | 3055 (21.78)      | 74.204         | 0.000   |
| 6 M-1Y                          | 5879 (20.44)      | 3748 (26.70)      | 213.579        | 0.000   |
| 1Y-3Y                           | 13 388 (46.54)    | 4904 (34.97)      | 516.404        | 0.000   |
| 3Y-5Y                           | 2380 (8.27)       | 1166 (8.31)       | 0.019          | 0.889   |
| >5Y                             | 1861 (6.47)       | 1152 (8.21)       | 43.809         | 0.000   |
| Positive rate of viruses, n (%) |                   |                   |                |         |
| Rotavirus                       | 5230 (18.18)      | 1368 (9.75)       | 513.530        | 0.000   |
| Adenovirus                      | 899 (3.13)        | 221 (1.58)        | 88.825         | 0.000   |
| Total                           | 6129 (21.31)      | 1531 (11.33)      | 692.723        | 0.000   |



**FIGURE 1** The number and positive rate of rotavirus and adenovirus according to month distribution in 2019 and 2020. (A) The number of rotavirus-positive specimens. (B) The positive rate of rotavirus. (C) The number of adenovirus-positive specimens. (D) The positive rate of adenovirus. ADV, adenovirus; RV, rotavirus

For the detection of rotavirus and adenovirus, a noticeable 3.8-fold reduction in the number of rotavirus-positive specimens and a 4-fold reduction in the number of adenovirus-positive specimens from 2019 to 2020 were observed. In 2019, the percent positivity of rotavirus was 18.18% (5230/28 764), and the percent positivity of adenovirus was 3.13% (899/28 764). However, in 2020, the percent positivity of rotavirus was 9.75% (1368/14 025;  $p < 0.001$ ), and the percent positivity of adenovirus was 1.58% (221/14 025;  $p < 0.001$ ). The overall positive rates of rotavirus and adenovirus involved in this study in 2020 were significantly lower than those in 2019 ( $\chi^2 = 513.530$ ,  $p < 0.001$ ;  $\chi^2 = 88.825$ ,  $p < 0.001$ ) (Table 1).

### 3.2 | Seasonal distribution

Figure 1 shows the seasonal distribution of the positivity detection rate of rotavirus and adenovirus in 2019 and 2020. The results indicated that rotavirus positive tests had a distinct seasonality, with a higher prevalence in the winter and early spring in 2019 and 2020; however, the percent positivity of rotavirus in 2020 was significantly lower than that in 2019 (January 2019: 40.67% vs. January 2020: 38.18%,  $p < 0.05$ ; February 2019: 40.73% vs. February 2020: 15.04%,  $p < 0.001$ ; March 2019: 31.47% vs. March 2020: 7.88%,  $p < 0.001$ ; April 2019: 15.52% vs. April 2020: 4.78%,  $p < 0.001$ ; December 2019: 24.26% vs. December: 8.44%;  $p < 0.001$ ). In addition, rotavirus had a lower positivity in the summer and fall, and the percent positivity of rotavirus was less than 4% from May to November 2019. Adenovirus was detected throughout 2019, with slight peaks in the percent positivity from March to September (2.23%, 3.17%, 4.34%, 4.86%, 4.07%, 3.08%, and 2.86%, respectively), while the percent positivity during 2020 in the same period was much lower (0.61%, 0.17%, 0.40%, 0.00%, 0.30%, 0.69%, and 1.40%;  $p < 0.05$ ) (Table 2).

### 3.3 | Age distribution

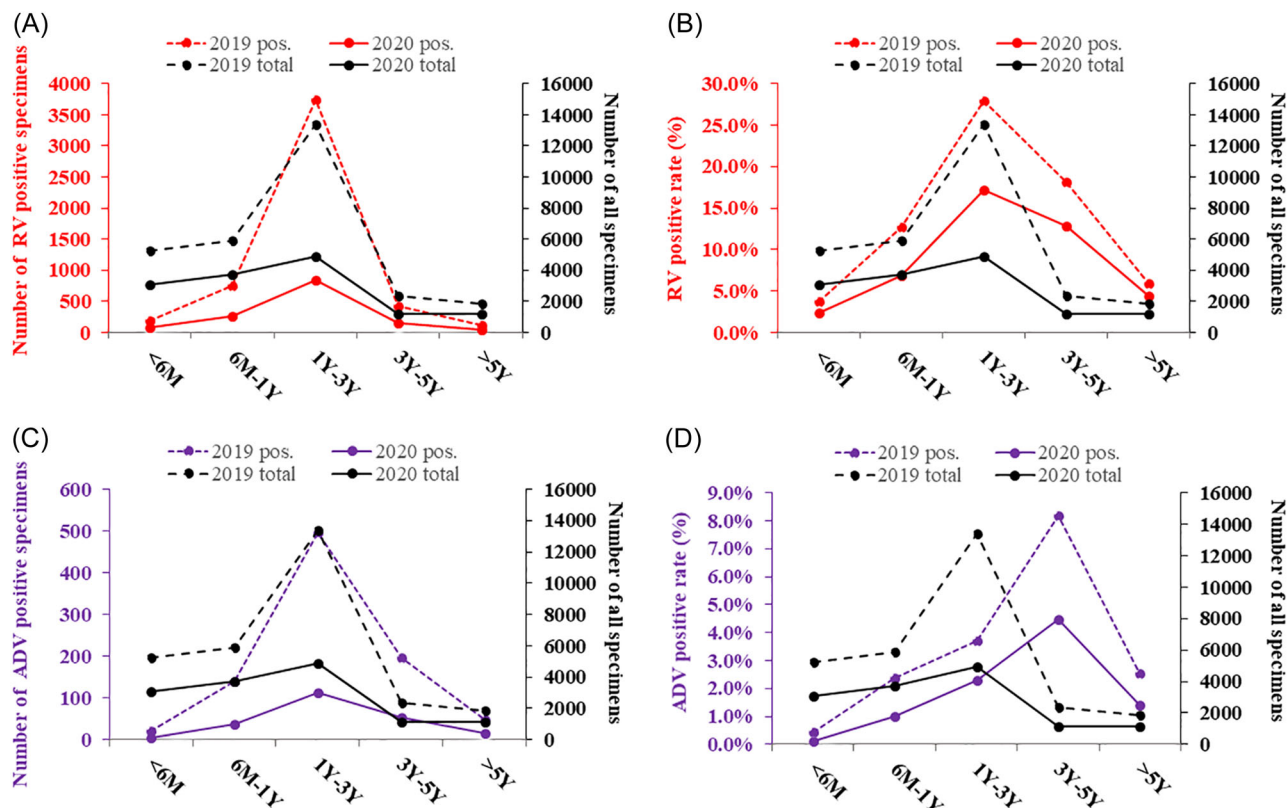
The positivity detection rate of rotavirus and adenovirus in 2019 and 2020 according to age was shown in Figure 2. The age distribution of rotavirus and adenovirus was roughly the same from 2019 to 2020. In 2019, a total of 3742 rotavirus-positive patients peaked in children aged 1–3 years; however, it dropped sharply, with a peak of 843 in 2020. In addition, in 2020, there was a noticeable decrease in the number of rotavirus-positive specimens in children aged <6 months (2019: 196 vs. 2020: 71), 6 months–1 year (2019: 749 vs. 2020: 255), 3–5 years (2019: 432 vs. 2020: 149), and >5 years (2019: 111 vs. 2020: 50). The percent positivity of rotavirus infection declined in the age group of 1–3 years, which was at the highest level (27.95% in 2019 and 17.19% in 2020,  $p < 0.001$ ), and this trend was also observed in children aged <6 months (2019: 3.73% vs. 2020: 2.32%,  $p < 0.001$ ), 6 months–1 years (2019: 12.74% vs. 2020: 6.80%,  $p < 0.001$ ), 3–5 years (2019: 18.15% vs. 2020: 12.78%,  $p < 0.001$ ), and >5 years (2019: 5.96% vs. 2020: 4.34%,  $p = 0.054$ ). Adenovirus positivity was detected in most of the age groups 1–3 years, with positive numbers of 496 in 2019 and 112 in 2020. However, the percent positivity of adenovirus was more commonly detected in children aged 3–5 years (2019: 8.19% vs. 2020: 4.46%;  $p < 0.001$ ). In addition, a significant decrease in the positivity proportion of adenovirus was observed in children aged <6 months (2019: 0.42% vs. 2020: 0.13%,  $p < 0.05$ ), 6 months–1 year (2019: 2.36% vs. 2020: 0.99%,  $p < 0.001$ ), 1–3 years (2019: 3.70% vs. 2020: 2.28%,  $p < 0.001$ ), and >5 years (2019: 2.53% vs. 2020: 1.39%,  $p < 0.05$ ) (Table 3).

## 4 | DISCUSSION

The emergence of the rapidly growing COVID-19 pandemic has affected almost all countries and areas and has infected billions of persons, and the number of deaths is also increasing. Many public

**TABLE 2** Detection of rotavirus and adenovirus according to months in 2019 and 2020.

| Month     | Rotavirus          |                    | $\chi^2$ Value | $p$ value | Adenovirus       |                 | $\chi^2$ Value | $p$ value |
|-----------|--------------------|--------------------|----------------|-----------|------------------|-----------------|----------------|-----------|
|           | 2019               | 2020               |                |           | 2019             | 2020            |                |           |
| January   | 1704/4190 (40.67%) | 1045/2737 (38.18%) | 4.281          | 0.039     | 87/4190 (2.08%)  | 52/2737 (1.90%) | 0.262          | 0.609     |
| February  | 1302/3197 (40.73%) | 57/379 (15.04%)    | 94.883         | 0.000     | 61/3197 (1.91%)  | 3/379 (0.79%)   | 2.403          | 0.121     |
| March     | 961/3054 (31.47%)  | 39/495 (7.88%)     | 117.111        | 0.000     | 68/3054(2.23%)   | 3/495 (0.61%)   | 5.706          | 0.017     |
| April     | 382/2461 (15.52%)  | 28/586 (4.78%)     | 46.916         | 0.000     | 78/2461 (3.17%)  | 1/586 (0.17%)   | 16.853         | 0.000     |
| May       | 78/2190 (3.56%)    | 25/745 (3.36%)     | 0.070          | 0.792     | 95/2190 (4.34%)  | 3/745 (0.40%)   | 26.672         | 0.000     |
| June      | 23/1810 (1.27%)    | 4/754 (0.53%)      | 2.799          | 0.094     | 88/1810 (4.86%)  | 0/754 (0.00%)   | 37.961         | 0.000     |
| July      | 19/1892 (1.00%)    | 3/984 (0.30%)      | 4.171          | 0.041     | 77/1892 (4.07%)  | 3/984 (0.30%)   | 33.930         | 0.000     |
| August    | 6/1493 (0.40%)     | 5/1299 (0.38%)     | 0.005          | 0.943     | 46/1493 (3.08%)  | 9/1299 (0.69%)  | 20.516         | 0.000     |
| September | 4/1293 (0.31%)     | 5/1566 (0.32%)     | 0.002          | 0.962     | 37/1293 (2.86%)  | 22/1566 (1.40%) | 7.436          | 0.006     |
| October   | 14/1987 (0.70%)    | 11/1690 (0.65%)    | 0.039          | 0.843     | 46/1987 (2.32%)  | 37/1690 (2.19%) | 0.065          | 0.789     |
| November  | 56/2390 (2.34%)    | 19/1285 (1.48%)    | 3.124          | 0.077     | 90/2390 (3.77%)  | 46/1285 (3.58%) | 0.081          | 0.776     |
| December  | 681/2807 (24.26%)  | 127/1505 (8.44%)   | 161.071        | 0.000     | 126/2807 (4.49%) | 42/1505 (2.79%) | 7.545          | 0.006     |



**FIGURE 2** The number and positive rate of rotavirus and adenovirus according to age distribution in 2019 and 2020. (A) The number of rotavirus-positive specimens. (B) The positive rate of rotavirus. (C) The number of adenovirus-positive specimens. (D) The positive rate of adenovirus. ADV, adenovirus; RV, rotavirus

health measures related to COVID-19 have been recommended worldwide to control the pandemic, which dramatically impacts the spectrum of diseases worldwide. Our previous study found a significant reduction in respiratory virus infections in children during the COVID-19 outbreak.<sup>11</sup> In this study, we found a twofold reduction in the number of patients with gastroenteritis in 2020 compared to 2019, indicating that the epidemiology of rotavirus and adenovirus has undergone marked changes at the same time. It has been reported that the incidence of rotavirus infection in children is approximately 30%–40%<sup>12</sup> or even higher,<sup>13,14</sup> and the prevalence of adenovirus infection has been demonstrated to range from 2% to 35%.<sup>15</sup> According to several studies carried out in different provinces in China, the rotavirus infection percentage ranged from 17.5% to 30.5%.<sup>16–19</sup> However, in our present study, the positive proportions of rotavirus and adenovirus infections in children were 18.18% and 3.13% in 2019. This is probably due to the different definitions of gastroenteritis, types of specimens collected (serum, plasma, or stool), and detection methods (enzyme-linked immunosorbent assay, latex agglutination, or RT-PCR) in different studies. In 2020, the positive rate of rotavirus dropped significantly to 9.75%, and adenovirus decreased to 1.58%. The decrease in the overall positive rate indicated that nonpharmaceutical intervention measures, such as travel restriction, social distancing, and home quarantine, significantly affected the COVID-19 epidemic.

The prevalence of rotavirus has obvious seasonal and geographical variations worldwide. Peak periods of rotavirus occur in the winter–spring months in temperate climates, while in the subtropical zone, the prevalence of rotavirus is recorded throughout the year and peaks in the dry seasons.<sup>13</sup> In the present study, we found that the number and rate of rotavirus infection in both 2019 and 2020 peaked from December to March, which is consistent with the results of other studies on the seasonality of rotavirus infection in China.<sup>18,20</sup> Interestingly, under Zhejiang's prevention and control measures that initiated the 1-level emergency response on January 23, 2020, the positive number and rate of rotavirus infection decreased sharply in February 2020, and the positive rate of rotavirus from January to December 2020 was obviously lower than that in 2019. In early studies, there was no apparent seasonal distribution or any peak in the frequency of adenovirus infections throughout the year<sup>6</sup>; however, others recently found peaks in summer and fall.<sup>21,22</sup> Our present study observed that adenovirus infections occurred throughout 2019 and were detected more commonly during the warm months (April to August) and November and December. However, due to the strict prevention and control policy for COVID-19, the positive number and rate of adenovirus infection decreased from February to December, with a significantly lower rate from March to September 2020.

Rotavirus affects populations in all age groups but more easily spreads among infants and young children. In China, several reports



| Age           | 2019                | 2020              | $\chi^2$ value | p Value |
|---------------|---------------------|-------------------|----------------|---------|
| <b>&lt;6M</b> |                     |                   |                |         |
| Rotavirus     | 196/5256 (3.73%)    | 71/3055 (2.32%)   | 12.266         | 0.000   |
| Adenovirus    | 22/5256 (0.42%)     | 4/3055 (0.13%)    | 5.126          | 0.024   |
| Total         | 218/5256 (4.15%)    | 75/3055 (2.45%)   | 16.275         | 0.000   |
| <b>6 M-1Y</b> |                     |                   |                |         |
| Rotavirus     | 749/5879 (12.74%)   | 255/3748 (6.80%)  | 86.354         | 0.000   |
| Adenovirus    | 139/5879 (2.36%)    | 37/3748 (0.99%)   | 24.186         | 0.000   |
| Total         | 888/5879 (15.10%)   | 292/3748 (7.79%)  | 113.840        | 0.000   |
| <b>1Y-3Y</b>  |                     |                   |                |         |
| Rotavirus     | 3742/13388 (27.95%) | 843/4904 (17.19%) | 221.258        | 0.000   |
| Adenovirus    | 496/13388 (3.70%)   | 112/4904 (2.28%)  | 22.553         | 0.000   |
| Total         | 4238/13388 (31.66%) | 955/4904 (19.47%) | 261.975        | 0.000   |
| <b>3Y-5Y</b>  |                     |                   |                |         |
| Rotavirus     | 432/2380 (18.15%)   | 149/1166 (12.78%) | 16.488         | 0.000   |
| Adenovirus    | 195/2380 (8.19%)    | 52/1166 (4.46%)   | 16.834         | 0.000   |
| Total         | 627/2380 (26.34%)   | 201/1166 (17.24%) | 36.258         | 0.000   |
| <b>&gt;5Y</b> |                     |                   |                |         |
| Rotavirus     | 111/1861 (5.96%)    | 50/1152 (4.34%)   | 3.711          | 0.054   |
| Adenovirus    | 47/1861 (2.53%)     | 16/1152 (1.39%)   | 4.490          | 0.034   |
| Total         | 158/1861 (8.49%)    | 66/1152 (5.73%)   | 7.881          | 0.000   |

**TABLE 3** Detection of rotavirus and adenovirus according to age in 2019 and 2020

have demonstrated a high prevalence of rotavirus infection between 1 and 2 years old,<sup>23</sup> while children aged 3–5 years were also recorded.<sup>24</sup> For adenovirus, it was shown that the highest frequency occurred among children under 2 years old,<sup>25</sup> while Zaraket et al. demonstrated that the prevalence of adenovirus was mainly in children aged between 2 and 3 years or 4–11 months.<sup>22</sup> However, our results revealed that the highest prevalence of rotavirus was seen in children aged 1–3 years, which is consistent with a previous study,<sup>26</sup> children infected with adenovirus were mainly aged between 3 and 5 years. Our findings differ from other studies, which is probably due to the different patient subjects enrolled (outpatient or inpatient) and the various geographical locations for the distinction in prevalence. Additionally, children aged over 5 years have a lower prevalence of rotavirus and adenovirus infection, which may be related to natural immunity that has already been acquired in children at this stage.<sup>27</sup> In the present study, the age distribution of the positive rate of rotavirus and adenovirus in 2020 was similar to that in 2019. Still, the proportion of rotavirus and adenovirus infection decreased among the five age groups in 2020 compared with 2019.

Gastrointestinal-related viruses are transmitted through the fecal-to-oral contamination route or person-to-person contact, and nonpharmaceutical interventions for COVID-19 might have inadvertently curbed the spread of nonrespiratory pathogens. The reduction in the percent positivity of rotavirus and adenovirus in children aged

under 6 months, 6 months–1 year, and 1–3 years may be due to the careful care of parents, such as paying more attention to indoor air disinfection, increasing the frequency of handwashing, and reducing outdoor activity. In particular, children under 6 months have more time staying at home, less going outside, and avoiding contact with other people, especially during the COVID-19 pandemic. For children aged 3–5 years and over 5 years, a lower positive rate is closely related to strict restrictions and intensive control measures, including wearing masks, maintaining hand hygiene and social distancing, and delaying school opening.

Rotavirus infections can cause gastroenteritis; however, recent studies have demonstrated that infection is not limited to the intestinal mucosa; it may spread outside the intestine, leading to systemic viral dissemination.<sup>28,29</sup> Rotavirus infection affects the nervous system, liver, and pancreas and triggers the development of autoimmune diseases.<sup>30</sup> In addition, adenovirus infection has a strong association with intussusception,<sup>31</sup> and the incidence of adenoviruses increases in children following bone marrow transplantation.<sup>32</sup> Therefore, reducing the positive rate of rotavirus and adenovirus is meaningful to reduce the occurrence of these secondary diseases and the economic burden.

Our study may have some limitations. The data were obtained from sample detection of outpatients in a single-center study. Data acquired from all patients nationwide will be more convincing. The other main limitation of the study is that we conducted a

retrospective study. The detection of pathogens included two types of common enteroviruses in children, limited by the hospital's testing program, and other enteroviruses, such as noroviruses, astroviruses, and bacterial pathogens, were not covered. However, the results obtained from our study paved the way for conducting subsequent studies with long-term research.

## 5 | CONCLUSION

In conclusion, despite these limitations, our results confirmed that rotavirus and adenovirus infection among children decreased much more during the COVID-19 pandemic. A series of control measures adopted in the COVID-19 period and the collateral benefit of these interventions may have inadvertently reduced the transmission of rotavirus and adenovirus in Zhejiang Province.

### AUTHOR CONTRIBUTIONS

**Junfeng Zhang:** Conceptualization, writing original draft preparation, writing review, and editing. **JiaJia Cao:** Investigation, initial statistical analysis, and data curation. **Qing Ye:** Conceptualization, designed the study, supervised, editing and reviewed, and revised the manuscript. All authors read and approved the final version.

### ACKNOWLEDGMENTS

This study was supported by the Natural Science Foundation of Zhejiang Province (LY22H050001), the Key Project of Provincial Ministry Construction, Health Science and Technology Project Plan of Zhejiang Province (WKJ-ZJ-2128), Key Laboratory of Women's Reproductive Health Research of Zhejiang Province (No. ZDFY2020-RH-0006), the National Natural Science Foundation of China (Grant/Award Number: U20A20351) and Key Research and Development Plan of Zhejiang Province (Grant/Award Number: 2021C03079).

### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. All requests should be submitted to the corresponding author for consideration.

### ETHICS STATEMENT

All procedures performed in our study were in accordance with the guidelines of the Ethical Committee in our hospital and with the 1964 Helsinki Declaration and its later amendments. Committee approved this study of the Children's Hospital, Zhejiang University School of Medicine (approval no. 2022-IRB-072), and informed consent was taken from all patients.

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**How to cite this article:** Zhang J, Cao J, Ye Q. Nonpharmaceutical interventions against the COVID-19 pandemic significantly decreased the spread of enterovirus in children. *J Med Virol.* 2022;94:3581-3588. doi:10.1002/jmv.27806