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Original article

Impact of non-pharmaceutical interventions during the COVID-19 pandemic on common childhood respiratory viruses – An epidemiological study based on hospital data

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ABSTRACT

Considering common childhood respiratory viruses and SARS-CoV-2 share similar transmission routes, non-pharmaceutical interventions (NPIs) to prevent SARS-CoV-2 may affect the epidemiology of respiratory viruses. Therefore, our study aimed to observe the epidemiologic characteristics of common childhood respiratory viruses in 2020 (after the pandemic) compared with 2019 (before the pandemic) in Hangzhou, China. The data were compared between 2019 and 2020 based on age and month, respectively. One or more viruses were detected in 3135/21452 (14.61%) specimens in 2019, which was significantly lower in 1110/8202 (13.53%) specimens in 2020. Respiratory syncytial virus (RSV) was the most commonly detected virus in 2019 and 2020. The positive rate of adenovirus (ADV), parainfluenza virus (PIV)1, PIV2, and PIV3 in 2020 was significantly decreased in 2019. In 2020, RSV replaced ADV as the most predominant virus in children aged 1–6 years, and the positive rate of influenza virus A (FluA), influenza virus B (FluB), PIV1, and PIV2 was not correlated to age. FluA, FluB, and PIV2 were not almost detected from February 2020. The positive rates of ADV and PIV1 were uncorrelated to the month in 2020. By strict NPIs, besides controlling the COVID-19 pandemic, incredible progress has been made to reduce the prevalence of common childhood respiratory viruses.

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a contagious disease worldwide [1,2]. COVID-19 is mainly transmitted through respiratory droplets and contact, and the population is generally susceptible [3–5]. A series of non-pharmaceutical interventions (NPIs) were taken to block the transmission of SARS-CoV-2 to contain the outbreak of COVID-19, such as wearing masks, washing hands frequently, keeping a social distance, and paying attention to indoor ventilation. In addition, the Chinese government has delayed the start of the spring semester in primary and secondary schools and stopped all offline training courses [6]. Therefore, children in China could only stay at home and study online courses during the pandemic until the school reopened [7]. An important fact must be realized that before the COVID-19 pandemic, there had never been such strict measures and large-scale lockdown.

Lower respiratory tract infections, such as pneumonia and bronchiolitis, remain a global public health problem and one of the leading causes of morbidity and mortality in children younger than five years [8]. In China, approximately 16.5% of deaths in children younger than five years were caused by pneumonia in 2008 [9]. Because common childhood respiratory viruses, such as influenza and respiratory syncytial virus (RSV), and SARS-CoV-2 share similar routes and means of transmission, these NPIs prevent the spread of SARS-CoV-2 are also likely to affect the epidemiology of common childhood respiratory viruses to some extent [10]. Therefore, our study aimed to observe the epidemiologic characteristics of common childhood respiratory viruses in 2020 (after the pandemic) compared with 2019 (before the pandemic) in Hangzhou, China.

1. Methods

1.1. Study design

The present study enrolled all children with respiratory tract infection who came to the Children's Hospital of Zhejiang

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University between January 2019 and December 2020 to explore the variations in the prevalence of common childhood respiratory viruses of children in Hangzhou, China, during the COVID-19 pandemic. Based on the criteria of the U.S. Centers for Disease Control and Prevention, the enrolled children meted the following criteria: (1) children aged younger than 18 years; (2) confirmed fever (a body temperature above 37.5 °C); (3) one or more respiratory symptoms within 14 days of onset (cough, sore throat, sputum, shortness of breath, lung auscultation abnormality (rale or wheeze), tachypnea, and chest pain) [11]. The exclusion criteria for this study were (1) children with repeated visits within a week; (2) children with hospital infection; (3) children with congenital pulmonary airway malformation and an impaired immune system; (4) children infected with COVID-19. All the enrolled children were divided into five age groups: under 28 days of age (0–28 d), 1–12 months of age (>1–12 mo), 1–3 years of age (>1–3 y), 3–6 years of age (>3–6 y) and more than six years of age (>6 y). From January 2020, the important events about the COVID-19 pandemic in Hangzhou, China, are in Fig. 1.

1.2. Data and specimen collection

Demographic characteristics from enrolled children were obtained from their electronic medical records. Respiratory specimens (nasopharyngeal aspirates/bronchoalveolar lavage fluid) were obtained from all the enrolled children as soon as they were

Fig. 1. The important events about the COVID-19 pandemic in Hangzhou, China.

admitted by trained staff following standard operating procedures. The specimens were immediately transferred to the clinical laboratory for respiratory virus detection.

1.3. Specimen detection

A multiplex direct immunofluorescence assay kit (Diagnostic Hybrids, Athens Ohio, USA) was used to detect respiratory viruses, including adenovirus (ADV), influenza virus A (FluA), influenza virus B (FluB), parainfluenza virus (PIV) 1–3, and RSV. The specimens were diluted in PBS and centrifuged for 10 min at 1500 rpm at room temperature. The supernatant was discarded. The pellet containing cells and cells debris was resuspended in 1 mL PBS. Twenty-five microliters of the resuspension were pipetted into a single 6 mm diameter well and dried for 30 min at 37 °C. The dried samples were fixed in acetone and incubated with the test monoclonal antibodies for 30 min at 37 °C. Finally, one drop of mounting fluid reagent was added to the middle of each well. A coverslip was placed over the slide, and reading was performed using a fluorescence microscope.

1.4. Statistical analysis

Categorical variables were presented as count with percentage. Proportions for categorical variables were compared using the chi-square test or Fisher's exact test. A value of $P < 0.05$ was considered statistically significant. Statistical analyses were conducted in SPSS version 26.0 software (IBM, New York, USA).

2. Results

2.1. Patient characteristic

Twenty-nine thousand six hundred fifty-four specimens from consecutive children were detected between Jan 2019 and December 2020, including 21452 specimens in 2019 and 8202 specimens in 2020. The age of enrolled children ranged from 0 day to 17 years old. Most patients were 1–12 months old (32.68% in 2019, 34.44% in 2020). No significant differences in gender were observed between the years 2019 and 2020 (Table 1).

2.2. Overall detection of respiratory viruses

One or more viruses were detected in 3135/21452 (14.61%) specimens in 2019, which was significantly lower in 1110/8202 (13.53%) specimens in 2020 (Table 1). As shown in Fig. 2, RSV was the most commonly detected virus in 2019 and 2020, accounting for 43.19% of positive specimens in 2019 and 69.10% of positive specimens in 2020. Meanwhile, the positive rate of RSV in 2020 was significantly higher than that in 2019 (9.35% *vs*. 6.31%, $P < 0.05$). However, the positive rate of ADV, PIV1, PIV2, and PIV3 in 2020 were significantly decreased compared with 2019 ($P < 0.05$). No significant differences were found in the positive rate of FluA and FluB between 2019 and 2020 ($P > 0.05$) (Table 1).

In the present study, a total of 49 specimens detected two viruses, among which there were 35 specimens in 2019 and 14 specimens in 2020 (0.16% *vs*. 0.17%, $P > 0.05$) (Fig. 2). In 2019, ADV and PIV3 were the most frequently detected viruses in 20/35 (57.14%) mixed infection specimens, and the detection of ADV plus PIV3 was the most common type of mixed infection, making up 25.71% of mixed infection specimens. However, in 2020, RSV was the most frequently detected virus in 13/14 (92.86%) mixed infection specimens, and the detection of RSV plus PIV3 was the most common type of mixed infection, making up 64.29% of mixed

Table 1
Patient characteristics and detection of respiratory viruses in the year of 2020 (COVID-19 pandemic) compared with the year of 2019 (before COVID-19 pandemic).

	2019 (n = 21452)	2020 (n = 8202)	χ^2 value	*P* value
Characteristics, n (%)				
Age				
0–28 d	2335 (10.88)	943 (11.50)	2.263	0.132
>1–12 mo	7010 (32.68)	2825 (34.44)	8.341	0.004
>1–3 y	5053 (23.55)	1985 (24.20)	1.370	0.242
>3–6 y	4283 (19.97)	1603 (19.54)	0.663	0.416
>6 y	2771 (12.92)	846 (10.31)	37.529	<0.001
Gender				
Male	12191 (56.83)	4701 (57.32)	0.572	0.450
Female	9261 (43.17)	3501 (42.68)		
Detection of viruses, n (%)				
A single virus-positive specimens				
ADV	531 (2.48)	20 (0.24)	162.015	<0.001
FluA	95 (0.44)	27 (0.33)	1.871	0.171
FluB	43 (0.20)	15 (0.18)	0.094	0.759
PIV1	110 (0.51)	24 (0.29)	6.393	0.011
PIV2	39 (0.18)	2 (0.02)	10.649	0.001
PIV3	928 (4.33)	241 (2.94)	30.171	<0.001
RSV	1354 (6.31)	767 (9.35)	82.549	<0.001
Total	3100 (14.45)	1096 (13.36)	5.785	0.016
Mixed virus-positive specimens				
ADV + PIV3	9 (0.04)	0 (0.00)	3.442	0.064
PIV 3 + RSV	8 (0.04)	9 (0.11)	5.434	0.020
ADV + RSV	7 (0.03)	1 (0.01)	0.919	0.338
FluA + RSV	3 (0.01)	2 (0.02)	0.381	0.537
ADV + FluA	3 (0.01)	0 (0.00)	1.147	0.284
FluB + PIV 3	3 (0.01)	0 (0.00)	1.147	0.284
ADV + FluB	1 (0.005)	0 (0.00)	0.382	0.536
PIV 2 + RSV	1 (0.005)	0 (0.00)	0.382	0.536
FluB + PIV 2	0 (0.00)	1 (0.01)	2.616	0.106
FluB + RSV	0 (0.00)	1 (0.01)	2.616	0.106
Total	35 (0.16)	14 (0.17)	0.020	0.886
Total	3135 (14.61)	1110 (13.53)	5.650	0.017

infection specimens. No specimens detected more than two viruses both in 2019 and 2020.

2.3. Age distribution

All the patients were divided into five age groups. The detection of each virus-positive specimen based on 2019 and 2010 was described in Fig. 3 and Fig. 4. In 2019 and 2020, the total positive rate reached the peak in children aged 1–12 months, with the peaks of 27.29% and 27.43%, respectively, and after that declined with the rising age of the enrolled children (Fig. 4a). Compared to 2019, the total positive rate in children aged 1–12 months in 2020 was almost identical (27.29% *vs*. 27.43%, $P > 0.05$), whereas the total positive rate in other age groups was dramatically decreased in 2020 ($P < 0.05$) (Table 2). In 2020, the positive rate of ADV, PIV3, RSV followed a similar pattern as their counterparts in 2019, but the positive rate of RSV was higher than that in 2019 (Fig. 4b, g, 4h). However, the positive rate of FluA and PIV1 in 2020 was not correlated to the age of the enrolled children ($P > 0.05$) (Table 3).

The predominant viruses among different age groups vary. In 2019, although all seven viruses were detected in each age group, the most dominant viruses in each age group were RSV, PIV3, and ADV, contributing to 82.66–93.13% of all infections in each age group. In children aged <1-year, RSV was predominant; in children aged >1 year, ADV was predominant (Fig. 5a). In 2020, not all seven viruses were detected in each age group; RSV accounted for the highest proportion of all infections in children aged <6 years, with a range from 47.79% to 87.29%, followed by PIV3 (8.47–36.03%); PIV3 was the most dominant virus in children aged >6 years, accounting for 42.86%, followed by RSV (35.71%) (Fig. 5b).

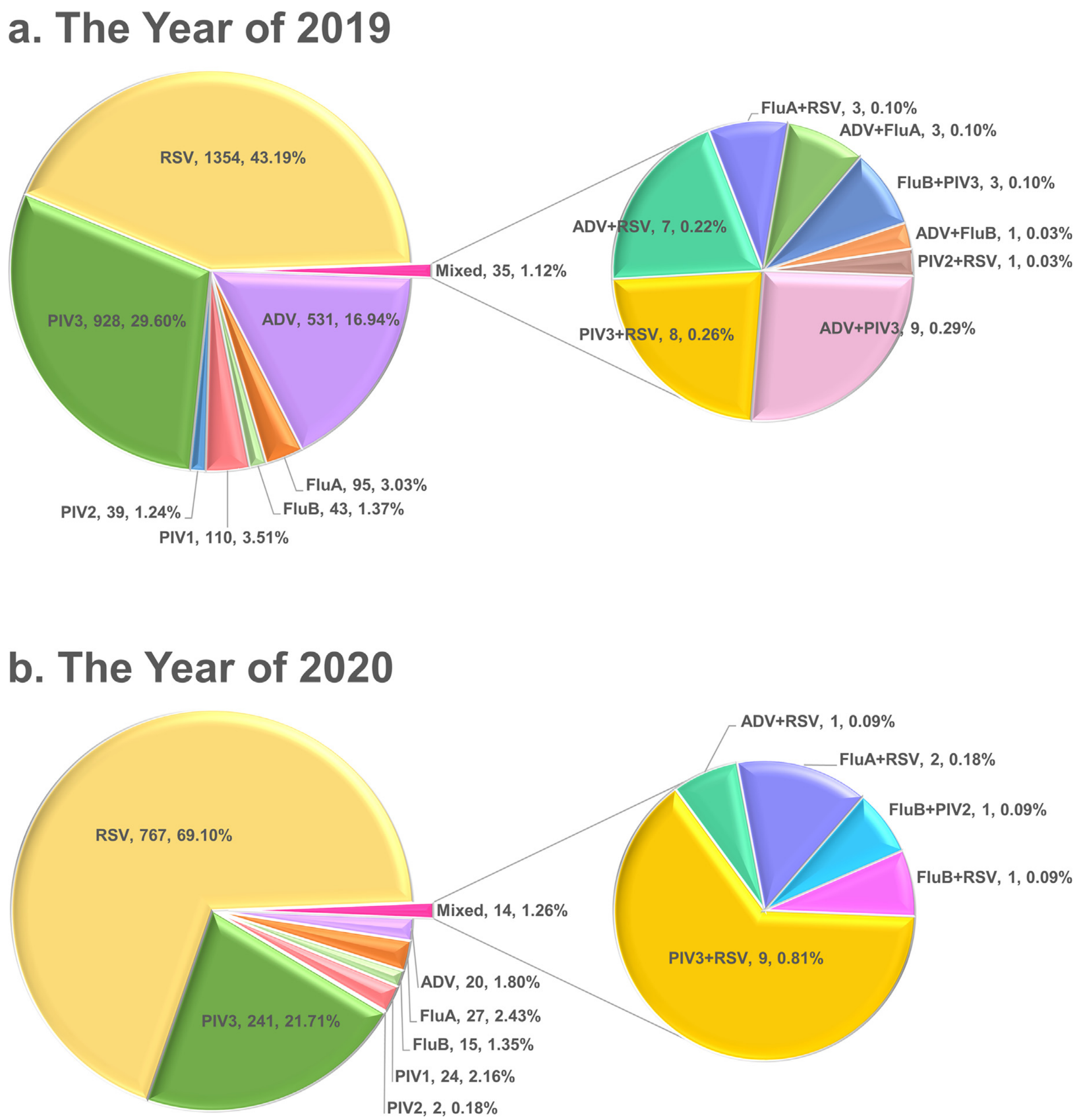

Fig. 2. Proportions of respiratory viruses were detected in 2019 (a) and 2020 (b).

2.4. Season distribution

The detection of each virus-positive specimen based on the month in 2019 and 2020 was shown in Fig. 6 and Fig. 7. Overall, common childhood respiratory viruses in 2019 and 2020 were detected more often in January and December than in other months, with total positive rates of 25.04% and 26.28% in 2019, 31.33%, and 28.01% in 2020, respectively (Fig. 7a). Compared with 2019, the total positive rates in October and December in 2020 were not a significant difference (7.07% vs. 6.75% in October, 26.28% vs. 28.01% in December, $P > 0.05$); the total positive rates in January and November in 2020 increased significantly (25.04% vs. 31.33% in January, 8.44% vs. 19.70% in November, $P < 0.05$); the total positive rates in other months in 2020 decreased significantly ($P < 0.05$) (Table 4). More specifically, in 2019, ADV, PIV1, PIV3, and RSV were detected throughout the whole year of 2019 (Fig. 7b–h). The positive rate of each virus was found to be associated with the month ($P < 0.05$) (Table 5). However, in 2020, FluA, FluB, and PIV2 were not almost detected from the beginning of February (Fig. 7c, d, f). The positive rates of ADV and PIV1 were found to be uncorrelated to month ($P > 0.05$) (Table 5).

3. Discussion

In response to the COVID-19 pandemic, Zhejiang province initiated the 1-level emergency response on Jan 23, 2020. A range of NPIs was implemented to suppress or mitigate the spread of the virus. The present study demonstrated that apart from the control of the COVID-19 pandemic, incredible progress has also been made to reduce the prevalence of common childhood respiratory viruses. In the present study, the number of children with respiratory symptoms in our hospital in 2020 decreased by 61.77%, and the overall number of virus-positive specimens decreased by 64.59% compared to 2019. More specifically, a substantial decline in the

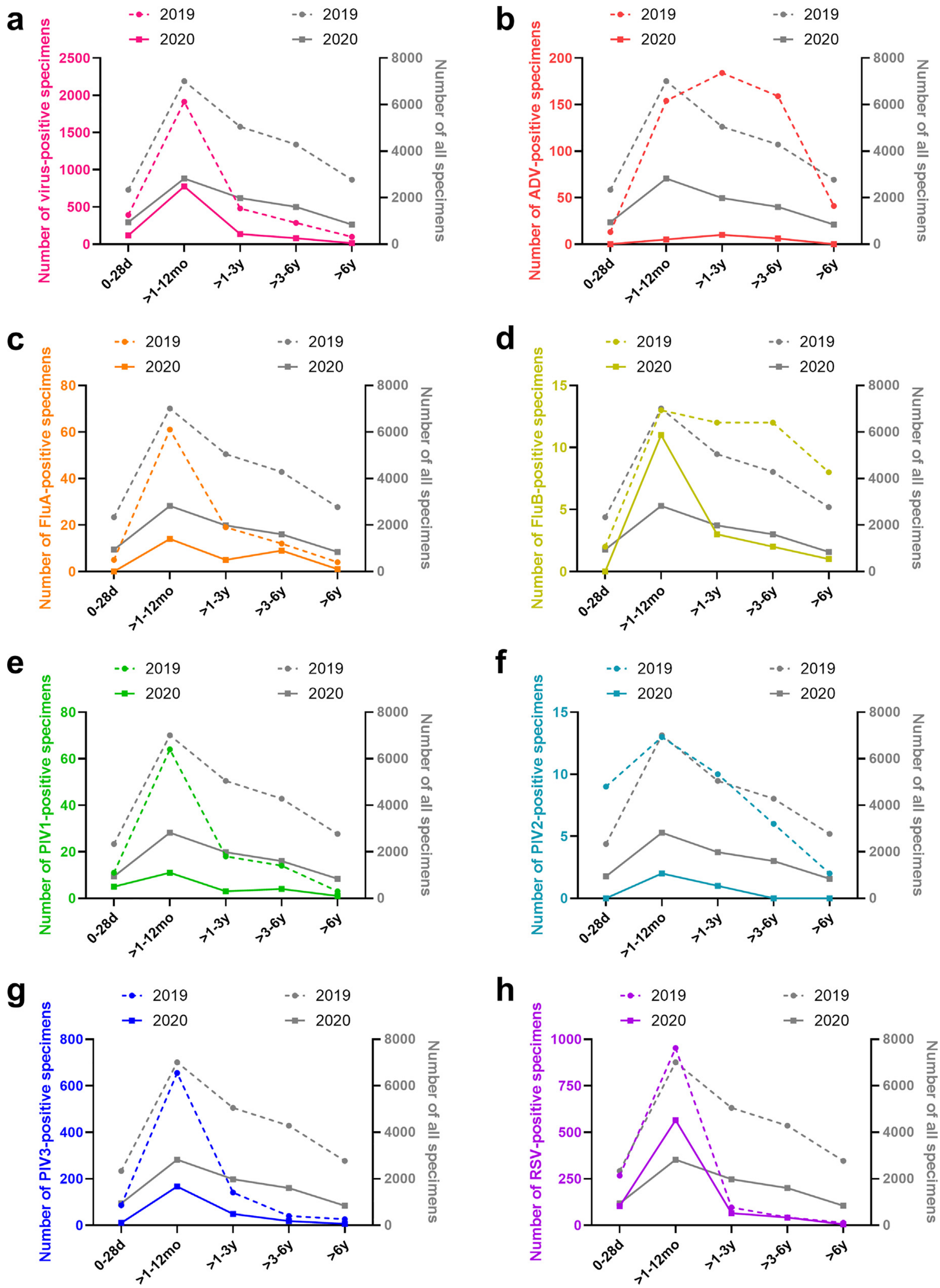

Fig. 3. The number of each virus-positive specimens based on age in 2019 and 2010.

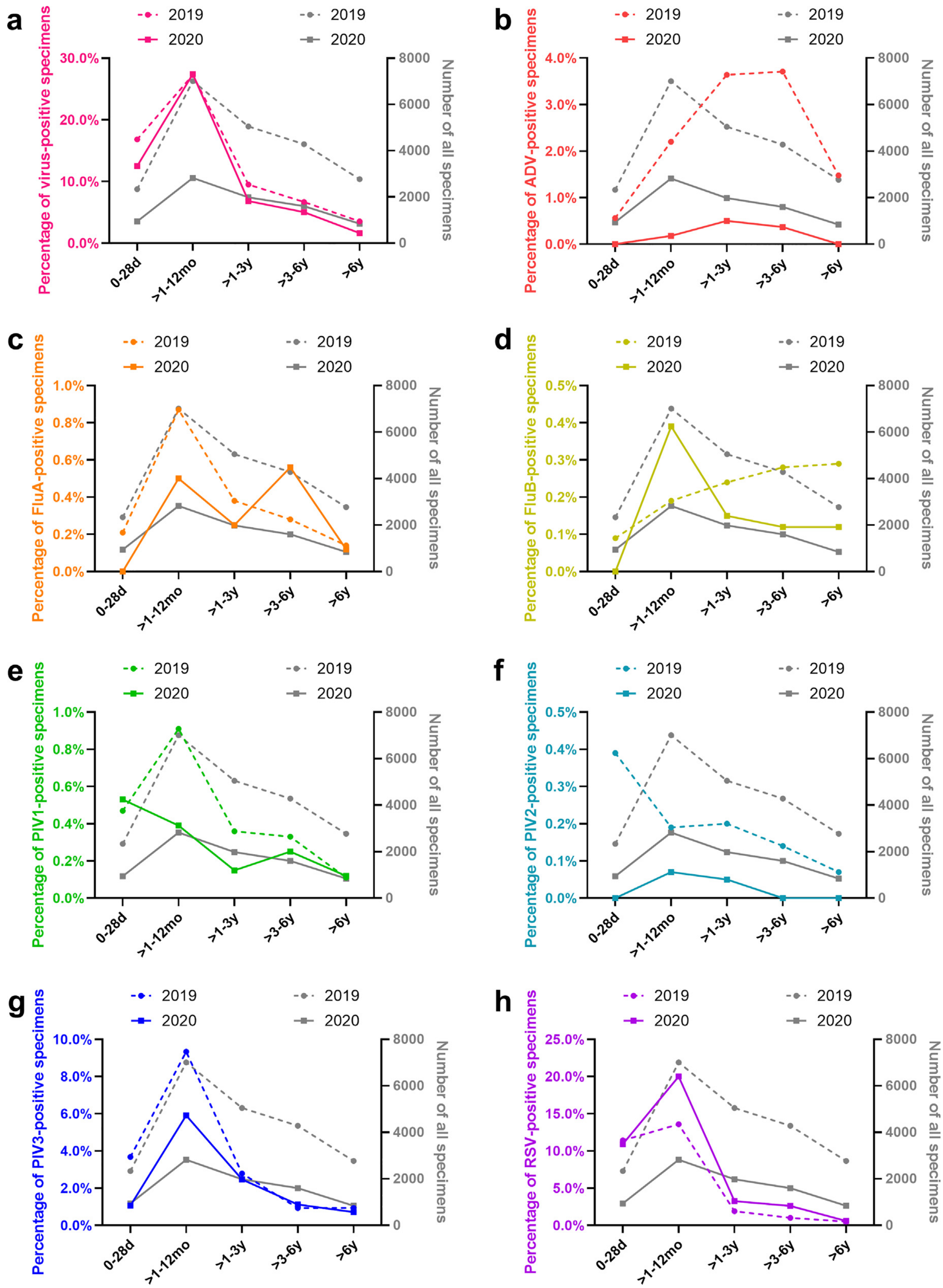

Fig. 4. The percentage of each virus-positive specimens based on age in 2019 and 2010.

Table 2
The overall positive rate of virus based on age in the year of 2020 (COVID-19 pandemic) compared with the year of 2019 (before COVID-19 pandemic).

Age	2019	2020	χ^2 value	*p* value
0–28 d	393/2335 (16.83)	118/943 (12.51)	9.516	0.002
>1–12 mo	1913/7010 (27.29)	775/2825 (27.43)	0.021	0.885
>1-3 y	480/5053 (9.50)	136/1985 (6.85)	12.512	<0.001
>3-6 y	286/4283 (6.68)	81/1603 (5.05)	5.265	0.022
>6 y	98/2771 (3.54)	14/846 (1.65)	7.649	0.006

Data was expressed as the positive number/the total number (%).

Table 3
Detection of each virus based on age in the year of 2020 (COVID-19 pandemic) compared with the year of 2019 (before COVID-19 pandemic).

Virus	Year	0-28 d	>1–12 mo	>1-3 y	>3-6 y	>6 y	χ^2 value	*p* value
ADV	2019	13	154	184	159	41	100.395	<0.001
	2020	0	5	10	6	0	10.932	0.027
FluA	2019	5	61	19	12	4	37.736	<0.001
	2020	0	14	5	9	1	8.842	0.065
FluB	2019	2	13	12	12	8	3.688	0.450
	2020	0	11	3	2	1	7.643	0.106
PIV1	2019	11	64	18	14	3	36.305	<0.001
	2020	5	11	3	4	1	5.077	0.279
PIV2	2019	9	13	10	6	2	7.443	0.114
	2020	0	2	1	0	0	2.249	0.690
PIV3	2019	86	655	141	40	26	639.877	<0.001
	2020	10	167	49	18	6	129.010	<0.001
RSV	2019	267	953	96	43	14	1244.253	<0.001
	2020	103	565	65	42	5	619.740	<0.001
Total	2019	393	1913	480	286	98	1492.186	<0.001
	2020	118	775	136	81	14	735.551	<0.001

prevalence of ADV and PIV 1–3 was found in 2020, and even children with FluA and FluB infection disappeared in our hospital from the beginning of February 2020, compared to the previous year. Similar results have been described by reports from Italy [12], Finland [13], Brazil [14], New Zealand [15], France [16], Turkey [17], England [18], and the US [19]. Given this situation, a hypothesis has been proposed that the effectiveness of these NPIs in reducing viral transmission may depend on the characteristics of each virus, such as viral structure. NPIs, especially hand hygiene, have a strong negative effect on enveloped viruses, reducing transmission of the enveloped virus, such as FluA, FluB, and PIV1-3 [20]. However, in the present study, unexpectedly, despite being an enveloped virus, the prevalence of RSV also exited a substantial augmentation in 2020. So, the potential mechanisms by which NPIs disrupt respiratory virus transmission should be further investigated.

In the present study, children aged 1–12 months were the most vulnerable to respiratory viruses, mainly RSV and PIV3, both before and after the pandemic, and their prevalence of respiratory infection after the pandemic was almost consistent with that before the pandemic. On the other hand, in other age groups, the prevalence of respiratory infection significantly decreased after the pandemic. During virus infections, the host activates the immune system to fight the pathogenic microorganism [21]. In children aged 1–12 months, due to the lack of complete immune memory and reduced innate and adaptive immunity, the immaturity of the immune system may be responsible for their vulnerability to respiratory viruses, and NPIs have little impact [22]. However, for neonates who obtained massive passive antibodies from mothers and older children whose immune systems are more thoroughly developed, the implementation of NPIs may play a vital role in protecting them

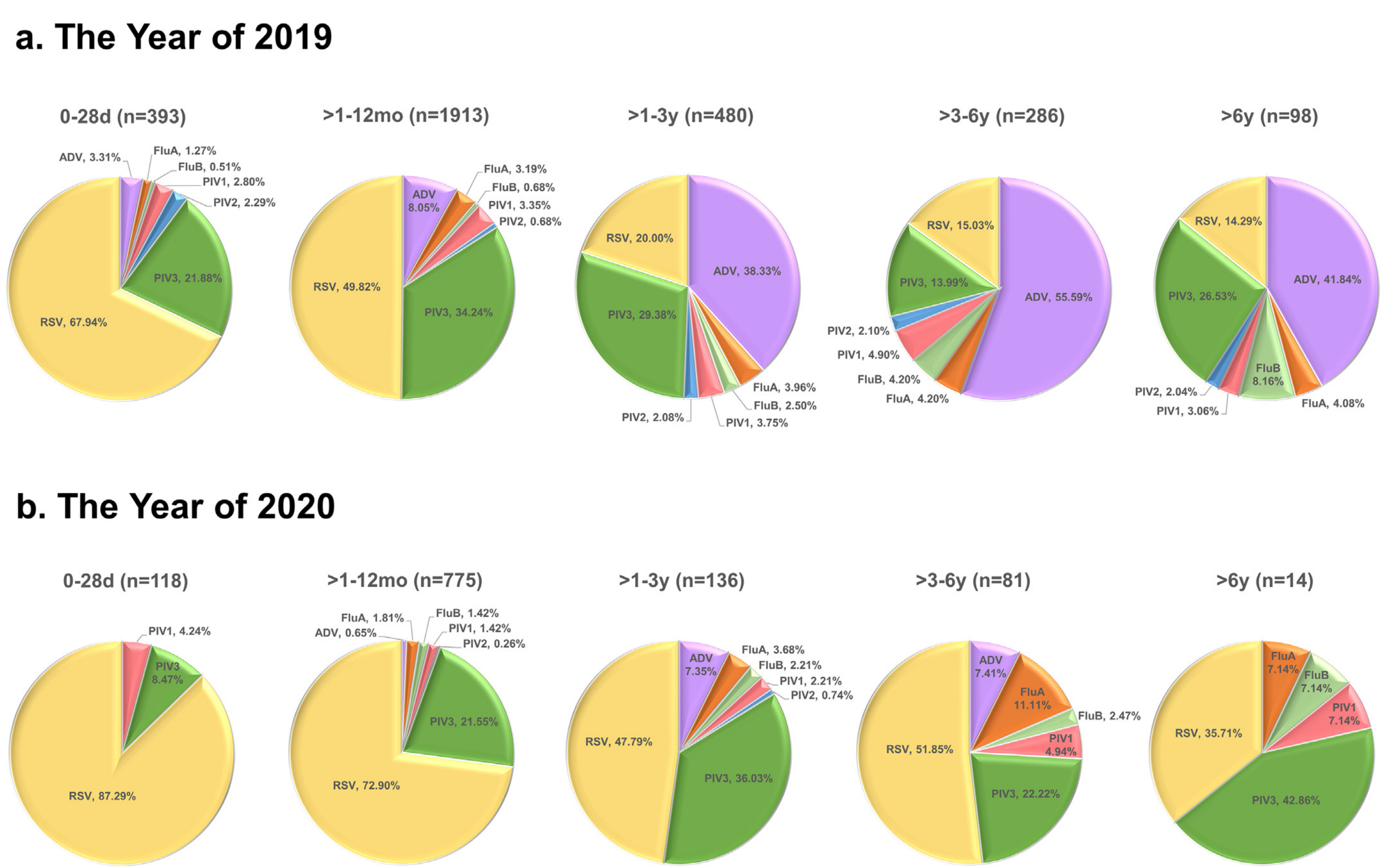

Fig. 5. Respiratory viruses were reported in different age groups in 2019 (a) and 2020 (b).

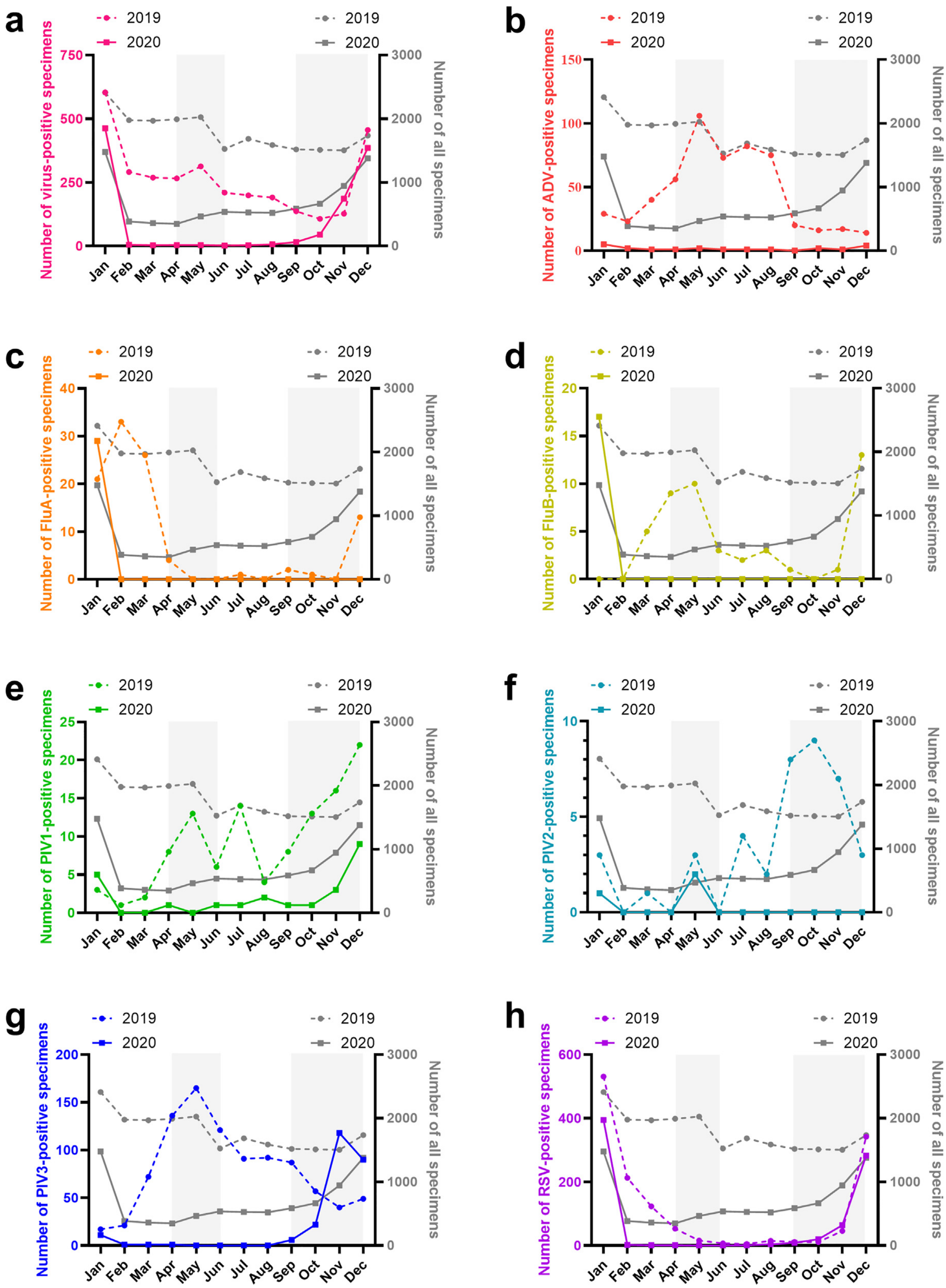

Fig. 6. The number of each virus-positive specimen based on months in 2019 and 2010. The two gray blocks represented the reopening of primary and secondary schools in Hangzhou from April to June in 2020 and the fall semester from September to December in 2020.

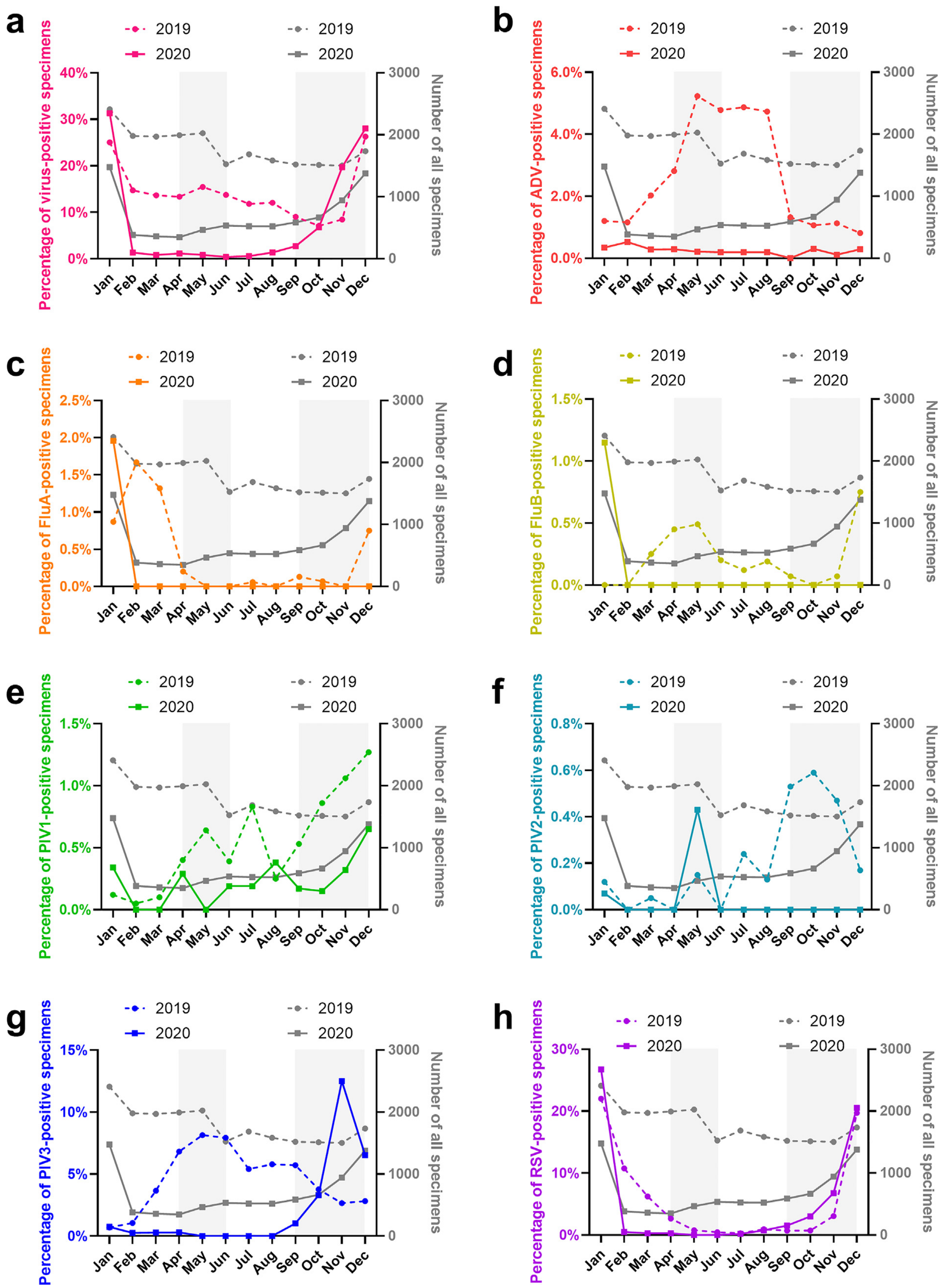

Fig. 7. The percentage of each virus-positive specimen based on the month in 2019 and 2010. The two gray blocks represented the reopening of primary and secondary schools in Hangzhou from April to June in 2020 and the fall semester from September to December in 2020.

Table 4
The overall positive rate of virus based on month in the year of 2020 (COVID-19 pandemic) compared with the year of 2019 (before COVID-19 pandemic).

Month	2019	2020	χ^2 value	*p* value
January	604/2412 (25.04)	463/1478 (31.33)	18.184	<0.001
February	291/1980 (14.70)	5/384 (1.30)	52.684	<0.001
March	269/1970 (13.65)	3/360 (0.83)	48.527	<0.001
April	266/1994 (13.34)	4/349 (1.15)	43.316	<0.001
May	313/2026 (15.45)	4/467 (0.86)	72.816	<0.001
June	210/1526 (13.76)	2/537 (0.37)	77.230	<0.001
July	199/1685 (11.81)	3/527 (0.57)	61.129	<0.001
August	191/1587 (12.04)	7/523 (1.34)	52.932	<0.001
September	137/1520 (9.01)	16/588 (2.72)	24.937	<0.001
October	107/1513 (7.07)	45/667 (6.75)	0.076	0.783
November	127/1504 (8.44)	186/944 (19.70)	65.934	<0.001
December	456/1735 (26.28)	386/1378 (28.01)	1.164	0.281

Data was expressed as the positive number/the total number (%).

against respiratory viral infections. In addition, we also reported that during the pandemic, RSV was the most predominant respiratory virus in children. RSV is among childhood's most critical pathogenic infections and makes up 13–22% of mortality from acute lower respiratory infections in young children [23]. Generally, most children will experience at least one RSV infection by two years [24]. Given the decrease in the number of children with respiratory symptoms in our hospital during the pandemic, although the positive number of RSV was lower than that before the pandemic, the prevalence of RSV still showed a significant increase, which was also exacerbated by a marked decrease in the detection of other respiratory viruses.

Since the strictest NPIs were implemented in Hangzhou on Jan 23, 2020, the morbidities of respiratory infection have remained extremely low level even during the first resumption of school. This is largely attributed to the most comprehensive and rigorous prevention and control measures with a high sense of responsibility for students' health during the first resumption of school. However, when the fall semester began in September 2020, there was a sharp increase in the detection of respiratory viruses, especially PIV3 and RSV. The prevalence of respiratory viruses even exceeded or was comparable to the same period in 2019. In fact, under the background of the Chinese domestic COVID-19 outbreak in remission, people have generally returned to normal work and life in low-risk areas, like those before the epidemic, which might explain why there was a spike in respiratory virus infection from September to December 2020. Likewise, similar evidence was presented by Austrian researchers [25]. The phenomenon also reflected that NPIs might play a protective role in the transmission of PIV3 and RSV during the COVID-19 pandemic to some extent.

Compared with 2019, the seasonality of some respiratory virus infections in 2020 has changed and even disappeared. Epidemiological research from Shanghai, China, also reported a sharp increase in PIV detection after August 2020 [26]. One of the major contributing factors affecting the seasonal nature of respiratory virus infections is human behavior. As awareness of infection prevention and control has increased during the pandemic, people's behavior has changed tremendously, including social behavior and hygiene practices. The changes in contact rates between infected and susceptible individuals affect viral transmission [27]. Under the circumstances, an epidemic of respiratory virus infection may occur outside of the typical season during the COVID-19 pandemic. Healthcare systems may need to prepare for future outbreaks of other common respiratory viruses in children with the relaxation of NPIs.

Overall, the impact of NPIs on typical childhood respiratory viruses during the COVID-19 may be attributed to multiple factors. First, personal protection and hand hygiene play a crucial role in preventing virus transmission. The convincing evidence suggested that hand hygiene benefits an 11% relative reduction of respiratory illness [28]. Second, avoiding child care attendance during the COVID-19 pandemic may be a significant cause [29]. Children have limited contact with anyone other than household members. Thus, the risk of virus transmission may be significantly reduced among children. Third, the government demanded that businesses be suspended, let employees work at home, and held meetings online, which allowed parents to protect children by reducing their contact with others.

This is the first study to compare the epidemiological characteristics of common childhood respiratory viruses in nearly 30,000 children during the COVID-19 pandemic in China. However, some limitations of this study should be acknowledged. First, this is only a single-center study, although our hospital is one of China's national clinical research centers for child health. Second, we conducted a retrospective analysis and collected the data of children admitted to our hospital, which did not represent the epidemiological features of respiratory viruses in the general population.

Table 5
Detection of each virus based on month in the year of 2020 (COVID-19 pandemic) compared with the year of 2019 (before COVID-19 pandemic).

Virus	Year	January	February	March	April	May	June	July	August	September	October	November	December	χ^2 value	*p* value
ADV	2019	29	23	40	56	106	73	82	75	20	16	17	14	246.094	<0.001
	2020	5	2	1	1	2	1	1	1	0	2	1	4	4.743	0.943
FluA	2019	21	33	26	4	0	0	1	0	2	1	0	13	151.466	<0.001
	2020	29	0	0	0	0	0	0	0	0	0	0	0	132.400	<0.001
FluB	2019	0	0	5	9	10	3	2	3	1	0	1	13	51.400	<0.001
	2020	17	0	0	0	0	0	0	0	0	0	0	0	77.500	<0.001
PIV1	2019	3	1	2	8	13	6	14	4	8	13	16	22	60.905	<0.001
	2020	5	0	0	1	0	1	1	2	1	1	3	9	11.131	0.432
PIV2	2019	3	0	1	0	3	0	4	2	8	9	7	3	42.727	<0.001
	2020	1	0	0	0	2	0	0	0	0	0	0	0	22.276	0.022
PIV3	2019	17	21	72	136	165	121	91	92	87	57	40	49	312.766	<0.001
	2020	11	1	1	1	0	0	0	0	6	22	118	90	469.860	<0.001
RSV	2019	531	213	123	53	16	7	5	15	11	11	46	342	2175.386	<0.001
	2020	395	2	1	1	0	0	1	4	9	20	64	283	1099.677	<0.001
Total	2019	604	291	269	266	313	210	199	191	137	107	127	456	571.956	<0.001
	2020	463	5	3	4	4	2	3	7	16	45	186	386	1179.945	<0.001

4. Conclusions

By the strict NPIs, apart from the control of the COVID-19 pandemic, incredible progress has also been made to reduce the prevalence of common childhood respiratory viruses.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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