Impact of COVID-19 Pandemic on the Prevalence of Respiratory Viruses in Children With Lower Respiratory Tract Infections in China

pengcheng Liu
Children's Hospital of Fudan University https://orcid.org/0000-0003-0879-1970
Menghua Xu
Children's Hospital of Fudan University
Lingfeng Cao
Children's Hospital of Fudan University
Liyun Su
Children's Hospital of Fudan University
Lijuan Lu
Children's Hospital of Fudan University
Niuniu Dong
Children's Hospital of Fudan University
Ran Jia
Children's Hospital of Fudan University
Xunhua Zhu
Children's Hospital of Fudan University
Jin Xu (jinxu_125@163.com)
Department of Clinical Laboratory, Children's Hospital of Fudan University, 399 Wanyuan Rd, Minhang District, Shanghai 201102, China.

Research

Keywords: COVID-19, prevalence, respiratory viruses, children, lower respiratory tract infections

Posted Date: April 28th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-450058/v1

Version of Record: A version of this preprint was published at Virology Journal on August 3rd, 2021. See the published version at https://doi.org/10.1186/s12985-021-01627-8.

Abstract

Background: The multifaceted public health interventions taken during COVID-19 epidemic not only decrease the spreading of the SARS-CoV-2, but have impact on the prevalence of other viruses. This study aimed to explore the prevalence of common respiratory viruses among hospitalized children with lower respiratory tract infections (LRTIs) in China during the COVID-19 pandemic.

Methods: Respiratory specimens were obtained from children with LRTIs at children's hospital of Fudan University for detection of respiratory syncytial virus (RSV), adenovirus (ADV), parainfluenza virus (PIV) 1 to 3, influenza virus A (FluA), influenza virus B (FluB), human metapneumovirus (MPV) and rhinovirus (RV). The data were analyzed and compared between the year of 2020 (COVID-19 pandemic) and 2019 (before COVID-19 pandemic).

Results: A total of 7107 patients were enrolled, including 4600 patients in 2019 and 2507 patients in 2020. Compared with 2019, we observed an unprecedented reduction of RSV, ADV, FluA, FluB, and MPV infections in 2020, despite of reopening of schools in June, 2020. However, The RV infection was significantly increased in 2020 and a sharp increase was observed especially after reopening of schools. Besides, the PIV infection showed resurgent characteristic after September of 2020. The mixed infections were significantly less frequent in 2020 compared with the year of 2019.

Conclusions: The public health interventions during the COVID-19 pandemic have great impact on the prevalence of common respiratory viruses in China. Yet, we do need to be cautious for a possible resurgence and the resurgence may not follow the usual seasonal patterns such as RV and PIV, as COVID-19 restrictions are ongoing eased.

Introduction

An outbreak of the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged in Wuhan, Hubei province, China, in December 2019 [1]. This outbreak then grew substantially and the World Health Organization (WHO) declared COVID-19 to be a public health emergency of international concern (PHEIC) on January 30, 2020 [2].

To control the pandemic of COVID-19, China has taken a series of public health interventions against COVID-19 in accordance with state instructions, such as prohibiting social gatherings, wearing masks and encouraging employees to work at home. The Chinese government also suggested postponement of the spring 2020 semester in primary and middle schools. Consequently, all face to face teaching in schools has been cancelled, and students must receive online courses at home during the COVID-19 pandemic, until the schools reopen in early June, 2020 [3]. No previous public health intervention can be compared to the extent of the lockdown implemented during the COVID-19 outbreak. These multifaceted interventions not only decrease the spreading of the COVID-19, but were associated with a significant decrease in infectious diseases disseminated through airborne or fecal–oral transmission, such as common cold, seasonal influenza, bronchiolitis, gastroenteritis, and acute otitis [4-6].

Lower respiratory tract infections (LRTIs), such as pneumonia and bronchiolitis, are a substantial public health problem and a leading cause of morbidity and mortality among children younger than 5 years [7,8]. The aetiology of LRTIs is diverse and complicated, which may vary according to gender, age, and season [9]. Respiratory viruses play an important role in LRTIs. A previous multi-site, international case-control study shows that viruses, especially RSV, were the predominant cause of pneumonia requiring hospital admission in children younger than 5 years [10]. However, it is unclear how the viral etiology and clinical epidemiologic features changed among the children hospitalized for LRTIs during the COVID-19 pandemic in China.

The aim of this study is to report and discuss the impact of the COVID-19 pandemic (the year of 2020) on the prevalence of common respiratory viruses among hospitalized children with LRTIs in Shanghai, China, and to compare it with prevalence patterns in the year of 2019 (before COVID-19 pandemic).

Methods

Study Design

To explore the changes in epidemiology of viral etiology in children with LRTIs during COVID-19 pandemic, the laboratory results and clinical data of children admitted to children's hospital of Fudan University with LRTIs in the entire year 2020 (COVID-19 pandemic) were analyzed. Data were then compared with the same date ranges in 2019.

The inclusion criteria for this study were: (1) children aged younger than 18 years; (2) hospitalization at the Children's Hospital of Fudan University; and (3) a diagnosis of LRTIs. A patient was considered to have an LRTIs if they had (1) at least one of the following manifestations of acute infection: confirmed fever (38°C), abnormal white blood cell (WBC) differential, leukocytosis (a WBC count more than 10,000/mL) or leukopenia (a WBC count less than 4,000/mL), and chills; (2) at least one of the following signs/symptoms of respiratory tract infection: cough, sputum, shortness of breath, lung auscultation abnormality (rale or wheeze), tachypnea, and chest pain.

The patients were divided into five groups: under 28 days of age (0-28 d), 1–12 months of age (1-12 m), 1–3 years of age (1–3 y), 4–6 years of age (4–6 y) and more than 7 years of age (>7 y).

Data and Specimen Collection

Respiratory specimens (nasopharyngeal aspirates/bronchoalveolar lavage fluid) were obtained from all the enrolled children within 72 hours of admission by trained staff following standard operating procedures. The specimens were immediately transferred to the clinical laboratory for respiratory virus detection.

Demographics and clinical data from enrolled children were obtained from their electronic medical records.

Specimen detection

A multiplex direct immunofluorescence assay (DFA) kit (Diagnostic Hybrids, Athens Ohio, USA) was used to detect respiratory viruses including respiratory syncytial virus (RSV), adenovirus (ADV), parainfluenza virus (PIV) 1 to 3, influenza virus A (FluA), influenza virus B (FluB) and human metapneumovirus (MPV) in the specimens. Additional real-time reverse-transcription polymerase chain reaction (rRT-PCR) testing was performed to detect rhinovirus (RV) using a commercial kit (Land Medical, Hubei, China) in accordance with the recommended protocol.

Statistical Analysis

Categorical variables were expressed as numbers (%). Continuous variables were expressed as medians (interquartile range). Medians for continuous variables (age, length of stay) between the year of 2020 and 2019 were compared using Mann-Whitney U test. Proportions for categorical variables (detection rates of virus, sex, intensive care unit admission, death in the hospital) were compared using the chi-square test. All of the tests were two tailed, and a value of $P < 0.05$ represented statistical significance. Statistical analyses were conducted in SPSS version 19.0 software (IBM, New York, USA).

Results

Study population

During the study period, 7107 patients who met the inclusion criteria were enrolled, including 4600 patients in 2019 and 2507 patients in 2020. The median age of patients in 2020 (2 months) was less than in 2019 (14 months), and the median length of hospital stay in 2020 (9 days) was longer than in 2019 (7 days). No significant differences in sex, intensive care unit admission, and death in hospital were observed between the year of 2019 and 2020 (Table 1).

Overall detection of respiratory viruses

One or more viruses was detected in 460/2507 (18.35%) specimens in 2020, which was significantly lower than that in 2019 (1430/4600, 22.67%) (Table 1). RV was the most commonly detected virus, followed by RSV and PIV3, both in 2019 and 2020. The positive rate of RV was much higher in 2020 than that in 2019 (11.01% *VS.* 7.37%). However, compared with 2019, the positive rates of RSV, ADV, PIV1, PIV3, FluA, FluB, and MPV were significantly decreased in 2020. The positive rate of PIV2 had no significant difference between 2020 and 2019 (Table 1).

Seasonal distribution

Compared with 2019, the detection rate of RSV decreased after February 2020 (WHO declared “public health emergency of international concern”). However, the seasonality did not change in 2020, and the detection rate was also peaked in winter (Fig. 1a).

RV was detected year round, with a high prevalence from June to October (after reopening of schools) in 2020, which is higher than the same period in 2019 (Fig. 1b).

PIV was almost not detected from March to August (spring and summer) in 2020, whereas it had a high prevalence in the same period in 2019. Interestingly, a sharp increase in the number of PIV detection was observed after August 2020. (Fig. 1c).

FluA, FluB, ADV and MPV were almost not detected after February 2020, and the low prevalence persist even following the reopening of schools in early June. However, in 2019, FluA, FluB, and MPV had seasonal prevalence and ADV was prevalent throughout the year and peaked in May (Fig. 1d~g).

Age distribution

All of the patients were grouped into five age groups.

The predominant viruses among different age groups between 2019 and 2020 varied. In 2019, RSV was the most frequent respiratory viruses among children aged less than 12 months, and RV was the most common viruses among children over 12 months (Fig. 2b). However, RV was the most frequent respiratory viruses in all of the age groups in 2020 (Fig. 2a).

Mixed viral infections

Mixed infections were significantly less frequent in 2020 (14/2507, 0.56%) than in 2019 (40/4600, 0.87%) (Table 2). RV was the most frequently found virus in mixed infections both in 2019 and 2020, accounting for 65.7% (27/40) and 92.9% (13/14) of all mixed infections respectively. Two triple infections were observed in 2019, whereas no triple infection was identified in 2020 (Table 2).

Discussion

A series of strict public health interventions adopted to contain the COVID-19 pandemic, including wearing masks, closing schools and social distancing, had not only decrease the spreading of the SARS-CoV-2, but changed the prevalence pattern of other common respiratory viruses [11]. In this study, we investigated the prevalence features of respiratory viruses in children with LRTIs during COVID-19 pandemic (the year of 2020) in Shanghai, China, and compared with the same date ranges in 2019. Our study showed a significant impact of COVID-19 pandemic on the circulation of common respiratory viruses in China.

In 2020, the number of children hospitalized with LRTIs at children's hospital of Fudan university was decreased by 45.5% compared with 2019. In accordance with our results, the significant decrease in the numbers of pediatric admissions in 2020 was also observed in many other countries, including France, Finland, United States, Brazil and Morocco [5, 12-15]. Matthijs et.al reported that a significant reduction was observed for children hospitalized with communicable infections (77%), whereas the reduction in noninfectious diagnoses was smaller (37%), which means the main reason for the reduction in pediatric

admissions was the decrease in transmissible infections due to the serious interventions adopted in 2020, and avoidance of care could be a factor as well [16]. In other words, this reduction could be considered as an unexpected positive consequence of the public health measures taken during COVID-19 pandemic, which may have led to a decrease in morbidity and healthcare costs of the infectious diseases.

Compared with 2019, the overall detection rate of respiratory viruses was lower in 2020 (18.35% *vs.* 22.67%). In another study conducted in New Zealand, the detection of influenza and other important respiratory viruses among inpatients with suspected severe acute respiratory illness (SARI) was also unprecedentedly reduced due to the use of stringent nonpharmaceutical interventions such as lockdown and border closures in 2020 [17].

Interestingly, in our study, the detection of RV appreciably increased, and become the most frequent respiratory virus in all of the age groups despite the public health interventions adopted in 2020. However, there remains a drop in the detection rate of RV before the re-opening of primary and secondary schools in early June 2020, compared with the previous year. After the re-opening of school, there was a sharp increase in the number of detections, exceeding or being comparable to the same period in 2019. This resurgence of RV in 2020 was also reported in many other countries, such as Austria, New Zealand, United Kingdom and Japan [11, 17-19]. Since RV is a non-enveloped virus, it might be inherently less susceptible to inactivation by ethanol-containing disinfectant [20]. This viral property might hamper the prevention of RV infection using routine hand disinfectants. A previous study also demonstrated that surgical face masks could prevent the transmission of human coronaviruses and influenza viruses, but not of RV from symptomatic individuals with acute respiratory illness through respiratory droplets and aerosols [21]. Furthermore, virus–virus interactions can have impact on the incidence of respiratory virus infections, and FluA and RV have negative epidemiological interactions [22]. Thus, the increased detection of RV may result from the absence of FluA prevalence.

Except for RV, the strict interventions adopted during COVID-19 epidemic contribute to the significant reduction of all other respiratory viral infections, including RSV, PIV, FluA, FluB, MPV and ADV. Unlike the previous report from Australian, where the seasonality of RSV circulation has significantly changed and an increase in RSV detections occurred following the reduction of COVID-19 related public health measures [23], the seasonality of RSV in our study did not changed in 2020. Our previous study showed that PIV were detected more often in summer and had a low prevalence in winter [24]. However, there was a very low prevalence from January to August of 2020 but a sharp increase in the number of PIV detection after August. To the best of our knowledge, this resurgence of PIV has not reported in other studies. The study conducted in Japan demonstrated that frequency of PIV was appreciably reduced after the COVID-19 pandemic began, but their data was up to September 2020.[19] The mechanism behind this resurgence of PIV is still unclear.

We have observed an almost absence of FluA, FluB, MPV and ADV prevalence since WHO declared “public health emergency of international concern” in February 2020. The low prevalence of these viruses

persist even following the relaxation of COVID-19 restrictions in the latter part of 2020, which might attribute to the increased awareness of social distance, wearing face masks and hand hygiene. These findings also indicated that the public health interventions had a remarkable effect on the prevention of the transmission of these viruses.

Conclusions

The public health interventions during the COVID-19 pandemic have great impact on the prevalence of common respiratory viruses in China. Whereas, we do need to be cautious for a possible resurgence of some viruses, and this resurgence may not follow the usual seasonal patterns such as RV and PIV, as COVID-19 restrictions are ongoing eased.

Abbreviations

COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; WHO: World Health Organization; PHEIC: public health emergency of international concern; LRTIs: Lower respiratory tract infections; RSV: respiratory syncytial virus; RV: rhinovirus; ADV: adenovirus; PIV: parainfluenza virus; FluA: influenza virus A; FluB: influenza virus B; MPV: metapneumovirus;

Declarations

Ethics approval and consent to participate

The project was approved by the Ethical Committee of Children's Hospital of Fudan University. This study was conducted retrospectively, all data were anonymized and participant consent was not necessary.

Consent for publication

Not applicable

Availability of data and materials

Additional data are available from the first author and corresponding author

upon reasonable request.

Competing interests

The authors declared no competing interests.

Funding

This article did not receive any specific grant from funding agencies in the

public, commercial, or any other sectors.

Authors' contributions

PL and JX conceived and designed the experiments; MX, LC, LS, LL and ND performed the experiments; RJ and XZ collected the clinical information; PL wrote the manuscript. JX revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382:727-33.
2. World Health Organization. Timeline: WHO's COVID-19 response. 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline. Accessed 12 April 2021.
3. Xinhuanet. China Focus: Schools start online courses as epidemic control postpones new semester. 2020. http://www.xinhuanet.com/english/2020-02/17/c_138792006.htm. Accessed 12 April 2021.
4. Pan A, Liu L, Wang C, Guo H, Hao X, Wang Q, et al. Association of Public Health Interventions With the Epidemiology of the COVID-19 Outbreak in Wuhan, China. JAMA. 2020;323:1915-23.
5. Angoulvant F, Ouldali N, Yang DD, Filser M, Gajdos V, Rybak A, et al. Coronavirus Disease 2019 Pandemic: Impact Caused by School Closure and National Lockdown on Pediatric Visits and Admissions for Viral and Nonviral Infections-a Time Series Analysis. Clin Infect Di*s.* 2021;72:319-22.
6. Sakamoto H, Ishikane M, Ueda P. Seasonal Influenza Activity During the SARS-CoV-2 Outbreak in Japan. JAMA. 2020;323:1969-71.
7. Rudan I, Chan KY, Zhang JS, Theodoratou E, Feng XL, Salomon JA, et al. Causes of deaths in children younger than 5 years in China in 2008. Lancet. 2010;375:1083-89.
8. Troeger C, Blacker B, Khalil IA, Rao PC, Cao J, Zimsen SRM, al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Infectious Diseases. 2018;18:1191-210.
9. Bhuiyan MU, Snelling TL, West R, Lang J, Rahman T, Granland C, et al. The contribution of viruses and bacteria to community-acquired pneumonia in vaccinated children: a case-control study. Thorax. 2019;74:261-69.
10. O'Brien KL, Baggett HC, Brooks WA, Feikin DR, Hammitt LL, Higdon MM, et al. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. The Lancet. 2019;394:757-79.

11. Redlberger-Fritz M, Kundi M, Aberle SW, Puchhammer-Stockl E. Significant impact of nationwide SARS-CoV-2 lockdown measures on the circulation of other respiratory virus infections in Austria. J Clin Virol. 2021;137:104795.
12. Friedrich F, Ongaratto R, Scotta MC, Veras TN, Stein R, Lumertz MS, et al. Early Impact of social distancing in response to COVID-19 on hospitalizations for acute bronchiolitis in infants in Brazil. Clin Infect Dis. 2020; doi:10.1093/cid/ciaa1458.
13. Kuitunen I, Artama M, Makela L, Backman K, Heiskanen-Kosma T, Renko M. Effect of Social Distancing Due to the COVID-19 Pandemic on the Incidence of Viral Respiratory Tract Infections in Children in Finland During Early 2020. Pediatr Infect Dis J. 2020;39:e423-27.
14. Mekaoui N, Razine R, Bassat Q, Benjelloun BS, Karboubi L. The Effect of COVID-19 on Paediatric Emergencies and Admissions in Morocco: Cannot See the Forest for the Trees? J Trop Pediatr. 2020; doi:10.1093/tropej/fmaa046.
15. Pelletier JH, Rakkar J, Au AK, Fuhrman D, Clark R, Horvat CM. Trends in US Pediatric Hospital Admissions in 2020 Compared With the Decade Before the COVID-19 Pandemic. JAMA Netw Open. 2021;4(2):e2037227.
16. Kruizinga MD, Peeters D, van Veen M, van Houten M, Wieringa J, Noordzij J, Get al. The impact of lockdown on pediatric ED visits and hospital admissions during the COVID19 pandemic: a multicenter analysis and review of the literature. Eur J Pediatr.2021; doi:10.1007/s00431-021-04015-0.
17. Huang QS, Wood T, Jelley L, Jennings T, Jefferies S, Daniells K, et al. Impact of the COVID-19 nonpharmaceutical interventions on influenza and other respiratory viral infections in New Zealand. Nat Commun. 2021;12:1001.
18. Poole S, Brendish NJ, Tanner AR, Clark TW. Physical distancing in schools for SARS-CoV-2 and the resurgence of rhinovirus. Lancet Respir Med. 2020;8:e92-e93.
19. Takashita E, Kawakami C, Momoki T, Saikusa M, Shimizu K, Ozawa H, et al. Increased risk of rhinovirus infection in children during the coronavirus disease-19 pandemic. Influenza Other Respir Viruses. 2021; doi:10.1111/irv.12854.
20. Savolainen-Kopra C, Korpela T, Simonen-Tikka ML, Amiryousefi A, Ziegler T, Roivainen M, et al. Single treatment with ethanol hand rub is ineffective against human rhinovirus--hand washing with soap and water removes the virus efficiently. J Med Virol. 2012;84:543-47.
21. Leung N, Chu D, Shiu E, Chan K, McDevitt J, Hau B, et al. Respiratory virus shedding in exhaled breath and efficacy of face masks. Nat Med. 2020;26:676-80.
22. Nickbakhsh S, Mair C, Matthews L, Reeve R, Johnson P, Thorburn F, et al. Virus-virus interactions impact the population dynamics of influenza and the common cold. Proc Natl Acad Sci U S A.2019; doi: 10.1073/pnas.1911083116.
23. Foley DA, Yeoh DK, Minney-Smith CA, Martin AC, Mace AO, Sikazwe CT, et al. The Interseasonal Resurgence of Respiratory Syncytial Virus in Australian Children Following the Reduction of

Coronavirus Disease 2019-Related Public Health Measures. Clin Infect Dis. 2021; doi: 10.1093/cid/ciaa1906.

24. Liu P, Xu M, He L, Su L, Wang A, Fu P, et al. Epidemiology of Respiratory Pathogens in Children with Lower Respiratory Tract Infections in Shanghai, China, from 2013 to 2015. Jpn J Infect Dis. 2018;71:39-44.

Tables

Table 1. Characteristics and incidence of detected viruses in children with LRTIs during the year of 2020 (COVID-19 pandemic) compared with the year of 2019 (before COVID-19 pandemic).

	2019 (n=4600)	2020 (n=2507)	*P* value
Characteristics			
Age, median (IQR) , m	14 (1-48)	2 (0.5-12)	0.000
Male sex, n (%)	2685 (58)	1507 (60)	0.154
Length of stay, median (IQR), d	7 (4-13)	9 (6-16)	0.000
Intensive care unit admission, n (%)	1383 (30)	704 (28)	0.079
Death in the hospital, n (%)	68 (1)	26 (1)	0.120
Detection of Viruses, n (%)			
RV	339 (7.37)	276 (11.01)	0.000
RSV	304 (6.61)	114 (4.55)	0.000
PIV3	177 (3.85)	54 (2.15)	0.000
ADV	135 (2.93)	4 (0.16)	0.000
FluA	60 (1.30)	9 (0.36)	0.000
PIV1	37 (0.80)	4 (0.16)	0.001
FluB	32 (0.70)	6 (0.24)	0.012
MPV	26 (0.57)	6 (0.24)	0.050
PIV2	9 (0.20)	1 (0.04)	0.179
Total	1043 (22.67)	460 (18.35)	0.000

Table 2. Mixed infections of respiratory viruses in children with LRTIs during the year of 2020 (COVID-19 pandemic) compared with the year of 2019 (before COVID-19 pandemic)

	2019 (n=4600)	2020 (n=2507)
double infections, n (%)		
RV+PIV3	10 (0.22)	2 (0.08)
RV+RSV	6 (0.13)	9 (0.36)
RSV+PIV3	5 (0.11)	1 (0.04)
RV+PIV3	3 (0.07)	2 (0.08)
Other	14 (0.30)	0 (0.00)
triple infections, n (%)		
RSV+PIV1+ADV	1 (0.22)	0 (0.00)
RSV+PIV1+RV	1 (0.22)	0 (0.00)
Total, n (%)	40 (0.87)	14 (0.56)

Figures

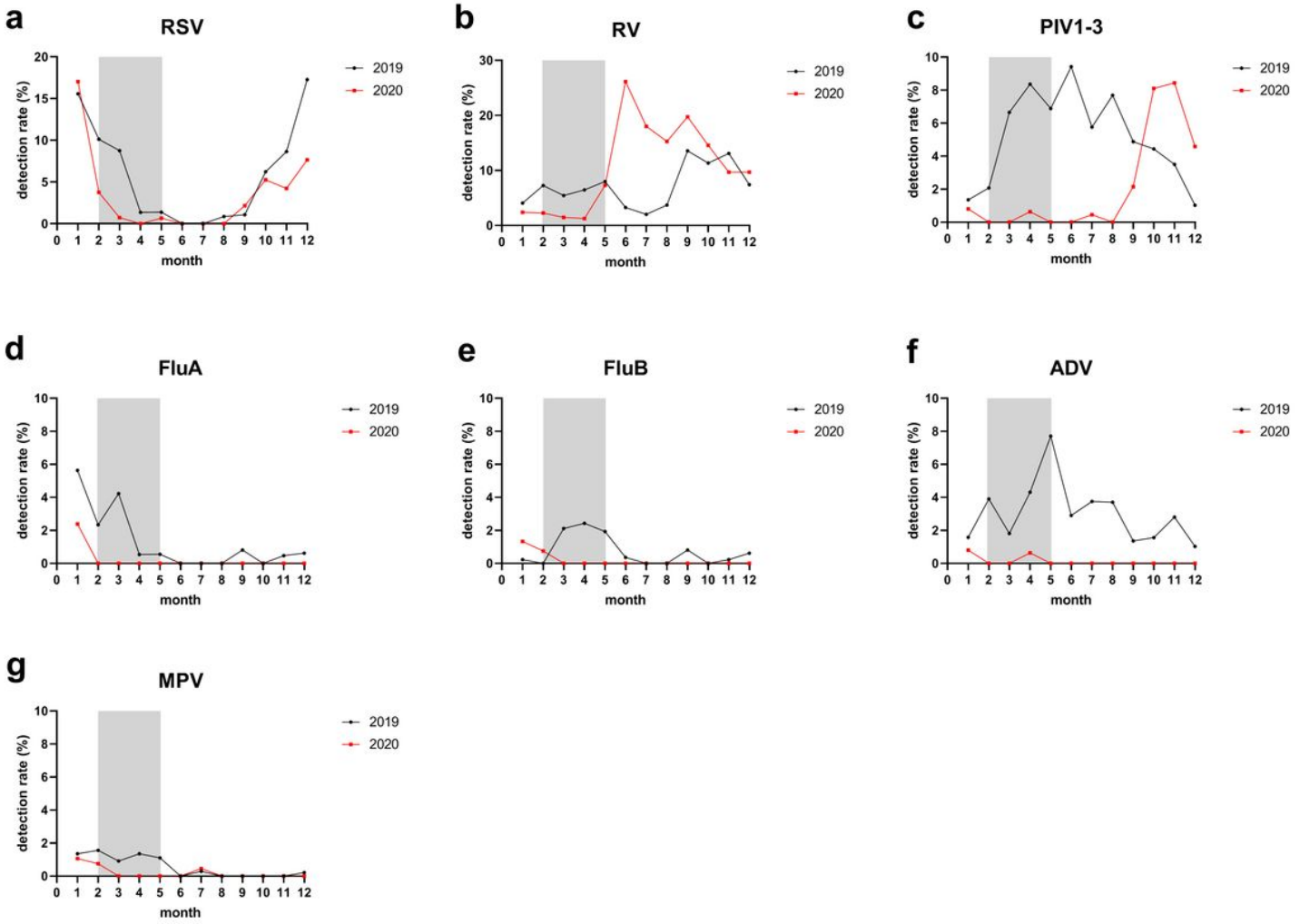

Figure 1

Seasonal activity of respiratory viruses during the COVID-19 pandemic year of 2020 (red line) compared with the previous year of 2019 (black line). Gray block represents the period from public health emergency of international concern (PHEIC) declared by World Health Organization (WHO) to the re-opening of primary and secondary schools.

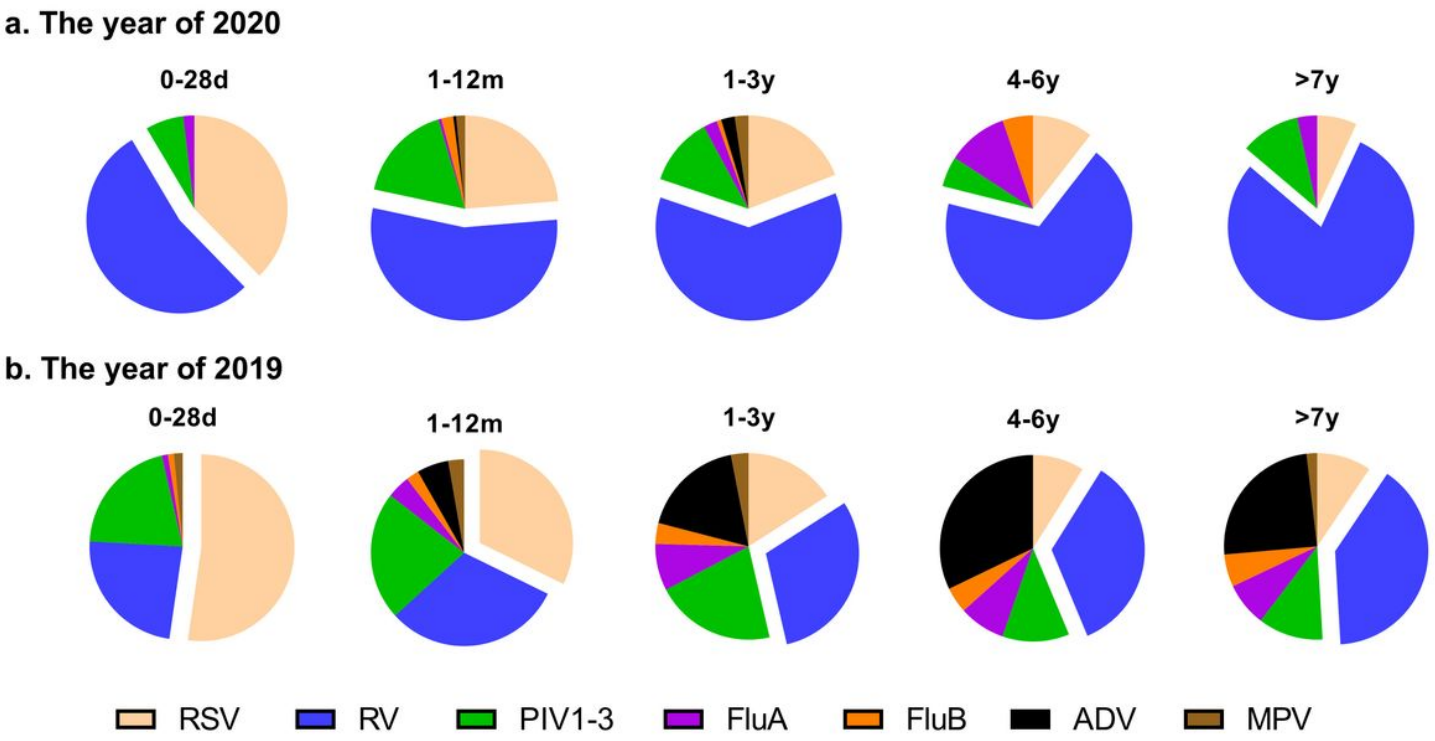

Figure 2

Proportions of respiratory viruses detected in 2020 (A) and 2019 (B) according to age group. The sliced part of each pie graph indicates the virus detected most frequently in that age group.