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Original Article

Circulating pediatric respiratory pathogens in Taiwan during 2020: Dynamic change under low COVID-19 incidence

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Children

Abstract *Background:* In Taiwan, there were only 799 confirmed COVID-19 cases in 2020. The unique backdrop amidst a pandemic and promotion of nonpharmaceutical interventions generated some distinct changes in the epidemiology of common respiratory pathogens. In this study, we aimed to investigate the dynamic changes in respiratory pathogens in children during 2020.
Methods: We performed a retrospective cohort study at a tertiary hospital in southern Taiwan during 2020. Patients aged 0—18 years who visited the pediatric emergency department were enrolled. Children who presented with clinical symptoms (fever or respiratory illness) and received nasopharyngeal swabs for multiplex polymerase chain reaction (PCR) were included in our analysis. We also compared respiratory syncytial virus (RSV) trends from previous years by PCR and lateral flow immunochromatographic assays from 2017 to 2020.
Results: A total of 120 children were tested. The overall detection rate was 55%. With strengthened restrictions, the detection rate dropped from 70% to 30%. However, non-enveloped viruses (rhinovirus/enterovirus and adenovirus) were in constant circulation. Upon easing prevention measures, the detection rate remained above 60%, and an outbreak of an

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enveloped virus (RSV and parainfluenza virus) was noted. Compared with 2017–2019, the cyclical RSV epidemic was delayed, with a large surge in late 2020.

Conclusions: We observed a constant circulation of non-enveloped viruses when strict non-pharmaceutical interventions were employed and a delayed surge of enveloped viruses during the easing of restrictions. Continuous surveillance and monitoring of the evolutionary dynamics of respiratory viruses is important, while easing restrictions requires balanced judgment.

Introduction

During 2020, the spread of COVID-19 drove many public health policy changes. In Taiwan, rapid implementation of border control and rigorous contact tracing limited the outbreak to only 799 confirmed cases in 2020.[1,2] However, travelers returning from abroad and local social gatherings still presented huge challenges to the public health system.

The severity of COVID-19 in children is usually mild.[3] There were no pediatric deaths due to COVID-19 in Taiwan at the time of writing. Respiratory illnesses, such as *Mycoplasma pneumoniae* or respiratory syncytial virus (RSV) infections,[4,5] remain a leading cause of pediatric hospitalizations. Seasonal respiratory pathogens cause cyclical outbreaks. Although there was no COVID-19 outbreak in Taiwan in 2020, the burden of common respiratory pathogens among children should not be ignored. In areas with strictly implemented nonpharmaceutical interventions (NPIs), the seasonality and circulating pattern of infectious diseases was modified.[6,7] The physical properties of viruses, such as being enveloped or non-enveloped, may be important factors interacting with NPIs. As a unique country with distinct societal behavior and governmental policy changes during the pandemic, we aim to investigate the dynamic change in respiratory pathogens in Taiwanese children during 2020.

Materials and methods

Study population and setting

We performed a retrospective cohort study at a tertiary hospital in southern Taiwan between January and December 2020. Patients aged 0–18 years who visited the pediatric emergency department were included. Demographic data (age, sex, patient source, date of visit) were collected from medical chart reviews. For patients presenting with clinical symptoms (fever or respiratory symptoms) during the hospital visit or admission, nasopharyngeal specimens were obtained with a flocked swab for pathogen detection per the clinician's judgment. The swabs were transported via Universal Transport Medium™ (UTM) (Copan Diagnostics) to the central laboratory for pathogen detection. For patients with typical symptoms or contact with test-positive cases, conventional antigen or serological tests were performed. For hospitalized patients with more severe disease or an urgent need for pathogen identification, multiplex PCR was considered. Common indications of sampling included the following: (1) cluster cases resembling COVID-19 or other respiratory pathogens for which timely diagnosis was vital; (2) need for patient cohorting; and (3) pathogens for which conventional tests were unreliable or not available, such as *M. pneumoniae* or human metapneumovirus.

Pathogen identification

Multiplex polymerase chain reaction (PCR) respiratory panel

The samples were tested by a multiplex PCR system, BioFire FilmArray respiratory panel (BioFire Diagnostics, Salt Lake City, UT, USA). This panel is able to identify 17 viruses (adenovirus, coronavirus 229E, coronavirus HKU1, coronavirus OC43, coronavirus NL63, human metapneumovirus, human rhinovirus/enterovirus, influenza A, influenza A/H1, influenza A/H1-2009, influenza A/H3, influenza B, parainfluenza virus 1/2/3/4, respiratory syncytial virus) and 4 bacteria (*Bordetella pertussis*, *Bordetella parapertussis*, *Chlamydophila pneumoniae*, *M. pneumoniae*). The multiplex PCR system contains reagents for all the steps needed for DNA/RNA extraction, PCR amplification, and detection of the respiratory pathogens listed above. The respiratory panel was upgraded to version 2.1 in our hospital in April 2020, and it is now able to identify severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and Middle East respiratory syndrome coronavirus (MERS-CoV) in addition to the 21 pathogens listed above.

Severe acute respiratory syndrome coronavirus 2

SARS-CoV-2 was identified via real-time reverse transcription polymerase chain reaction (RT–PCR). We used three sets of primers and probes targeting SARS-COV-2 envelope (E), nucleocapsid (N), and RNA-dependent RNA polymerase (RdRp) genes as previously described.[8] RT–PCR for SARS-CoV-2 was not performed if multiplex PCR was done.

RSV, influenza virus and *M. pneumoniae*

In addition to multiplex PCR being available since 2020, we also used other conventional methods to detect RSV, influenza virus and *M. pneumoniae* from 2017 to 2020. The Xpert Flu/RSV XC assay (Cepheid, Sunnyvale, CA) was applied to test both influenza and RSV via PCR. The BinaxNOW RSV ([BN] Alere Inc., Waltham, MA) and the BD Veritor™ System Flu A + B (Veritor; BD Diagnostics, Sparks, MD, USA) are lateral flow immunochromatographic assays that serve as rapid diagnostic tests for RSV and influenza, respectively. For *M. pneumoniae*, a rapid immunochromatographic test (Biocard™ *M. pneumoniae* IgM; Labsystems Diagnostics, Vantaa, Finland) and a particle-agglutination assay (SeroDia™ Mayo MAG II microparticle agglutination assay kit, Fujirebio, Japan) were used to detect antibodies against *M. pneumoniae* in human serum.

Important COVID-19 events in Taiwan

The first imported case was identified locally on January 21, 2020. On learning about a potential outbreak of SARS-CoV-2, the government of Taiwan imposed a ban on surgical mask exports on January 24. On February 2, the government announced that winter vacation for students would be extended to February 25 nationwide to enable schools to be better prepared for classroom learning. The first death in Taiwan, with no known contact history, occurred on February 16. On March 21, the Ministry of Health and Welfare raised Travel Notice Alerts for all countries to Level 3 (Warning), discouraging unnecessary foreign travel. On April 3, all inbound travelers showing signs and symptoms were requested to undergo quarantine in designated locations. On April 18, three naval cadets of the ROCS *Pan Shi* were diagnosed with COVID-19 after a military expedition. A total of 36 patients were identified, but the source was deemed possibly local. The cluster prompted the Taiwan Centers for Disease Control and Prevention (CDC) to strengthen community-based surveillance. On June 7, after 4 incubation periods (56 days) with no locally transmitted cases, restrictions on large gatherings were gradually lifted. Nevertheless, face masks were still required on public transport and in most indoor venues.

Data analysis

Baseline characteristics were summarized using descriptive statistics, which included patient numbers, annual trend of emergency department visits, detection rate and monthly distribution of detected respiratory pathogens. Children received a swab test at the emergency department or at the ward during hospitalization. Regardless of the assay, each visit or hospitalization accounted for only one child (no duplication of patients for those receiving multiple tests). Qualitative data are reported as percentages. Quantitative data are presented as the median or total numbers. Pathogens tested by multiplex PCR for 2020 are shown as a trend graph. Viruses were further classified into enveloped and non-enveloped according to whether the outermost layer was covered with a lipid envelope. Enveloped viruses in our analysis included coronavirus, human metapneumovirus, influenza virus, parainfluenza virus and RSV. Other viruses were categorized as non-enveloped viruses, including adenovirus and human rhinovirus/enterovirus. Additionally, to compare RSV trends in previous years, we used the findings of both multiplex PCR (available since 2020) and lateral flow immunochromatographic assays (available for 2017 to 2020) to calculate the incidence of RSV infection per 1000 children. We used linear regression for trend analysis across different years. All analyses were performed with commercially available statistical software, IBM SPSS Statistics 22 (SPSS, Inc., Chicago, IL, USA) and Microsoft Excel™ 2016 (Microsoft Corporation).

Ethics approval

The study was approved by the Institutional Review Board and Ethics Committee of Chi Mei Medical Center (11004-006).

Results

In 2020, there were 15,694 pediatric emergency visits in our hospital. There was a significant reduction compared to 24,243 visits in 2019 (Fig. 1). Locally transmitted COVID-19 cases were mainly seen in quarter 1 and remained low throughout the remainder of 2020. The pink color in Fig. 1 indicates the tightening of restrictions due to increased risk of community transmission, such as quarantine of travelers and hand hygiene reminders in quarter 1 and mask mandates during quarter 2. The blue color indicates the lifting of restrictions. After the spike in visits before the Lunar New Year in 2020, pediatric emergency department visits were lower compared to 2019, with a 35% reduction.

In our cohort, a total of 120 children were tested by multiplex PCR. The median age was 2.3 years (interquartile range, 0.9 to 7.3). Males represented 60% of the cohort. Of 120 children, a total of 109 (90.8%) patients were tested while hospitalized, and 11 (9.2%) were tested at the emergency department and subsequently discharged. In 2020, there were a total of 508 hospitalized patients with diagnoses of respiratory tract infections in our hospital, representing a sampling rate of 21.4% among hospitalized patients with an overall detection rate of 55.0%. A total of 34 (28.3%) children were also tested for SARS-CoV-2 by RT—PCR, which were all negative. The monthly distribution of the performed tests and detection rates of multiplex PCR are illustrated in Fig. 2. The test positivity rate decreased from 70% to 30% between January and February. From March to April, test numbers increased along with a gradually increasing test positivity rate (37.5%—43.8%). The test numbers and positivity rate were the lowest in August. After September, the positivity rate remained above 60%, while the number of tests was stable from October to December.

There were 75 respiratory pathogens identified from 67 children who tested positive on multiplex PCR. Among the 75 pathogens, 66 (88.0%) were viruses, and 9 (12.0%) were bacteria. Coinfection was found in 8 (10.7%) patients. One patient had codetection of adenovirus, parainfluenza virus, and respiratory syncytial virus. Another 7 patients had codetection of 2 viruses. The monthly distribution of detected respiratory pathogens is shown in Fig. 3A. In the first 2 months of 2020, there were 4—5 pathogens circulating in the community simultaneously. Influenza was not detected after March, while *M. pneumoniae* was not detected after June. During quarters 2 and 4, rhinovirus/enterovirus accounted for the majority of identified pathogens, with some sporadic adenovirus cases. A surge in RSV and parainfluenza virus was noted in November. The proportion and distribution of enveloped and non-enveloped viruses are illustrated in Fig. 3B. With tightening epidemic

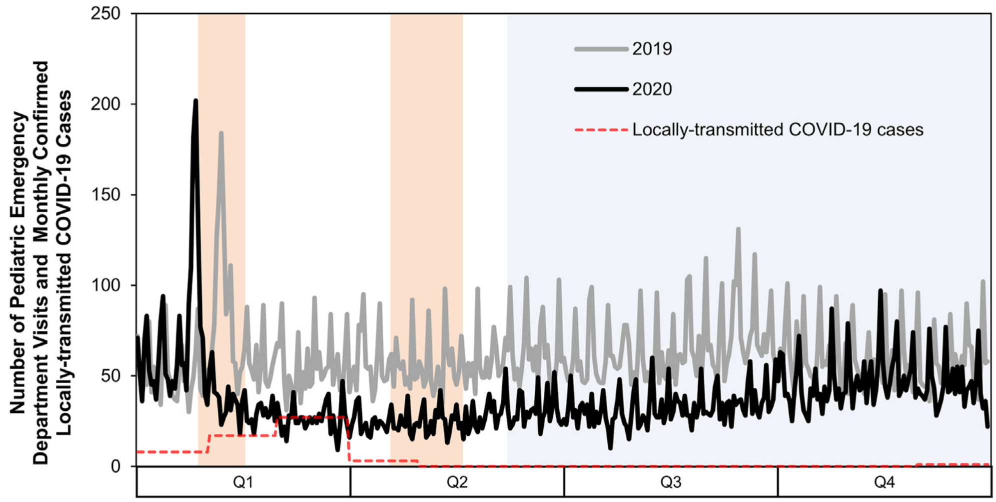


Figure 1. Number of pediatric emergency department visits in 2019 and 2020 (visits per day) and monthly confirmed locally transmitted COVID-19 cases in Taiwan. The large spikes for both 2019 and 2020 in quarter 1 were during the Lunar New Year holidays, when most outpatient services were unavailable, while small spikes across the year corresponded to weekends. The pink background color in quarter 1 corresponds to the period between the first identified COVID-19 patient (January 21, 2020) and the first COVID-19 death (February 16), during which the Ministry of Health and Welfare escalated travel alerts for foreign countries, imposed quarantine restrictions for returning travelers, promoted hand hygiene measures, and started daily press briefings on the pandemic. The staggered red line represents new monthly locally transmitted cases, which increased during the first 3 months of quarter 1 and fell to zero from May to November. The pink background color in quarter 2 corresponds to an outbreak on the ROCS *Pan Shi* (April 18), which investigations later deemed locally transmitted but from an unknown source. Mask mandates and restrictions on food and drinks on long-distance trains were imposed around the same time. The blue background color in the latter half of quarter 2 corresponds to easing restrictions on crowds and gatherings on June 7 after no new community cases were detected for 56 days.

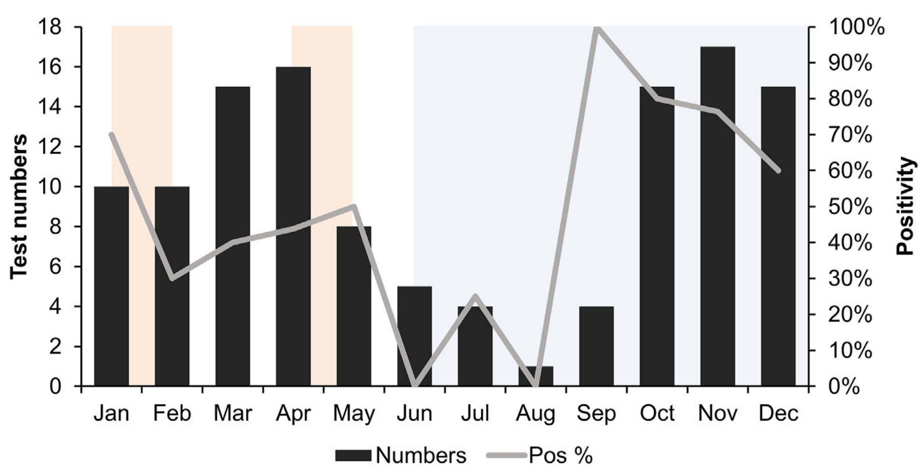


Figure 2. Monthly distribution of multiplex PCR tests and test positivity rates for 2020. The solid bars indicate test numbers, and the gray line represents the test positivity rate, with the pink color representing the tightening of COVID-19 restrictions and the blue color representing the easing of restrictions.

control measures and the promotion of hygienic practices, the proportion of enveloped viruses decreased, while non-enveloped viruses largely caused sporadic outbreaks. The positivity rate of each respiratory pathogen during the study period is provided in Supplementary Table 1. There were no PCR-positive cases for *M. pneumoniae* since June 2020, but the seroprevalence remained high. Most cases were tested only once without paired samples. Therefore, we used only the multiplex PCR results in the aforementioned analysis.

From 2017 to 2019, the peak season for RSV was from June to September, with an average monthly incidence ranging from 2.13 to 4.39 cases per 1000 children. However, for 2020, the RSV season started in October, with a peak incidence of 93.39 cases per 1000 children in November (Fig. 4). The incidence decreased to 62.87 cases

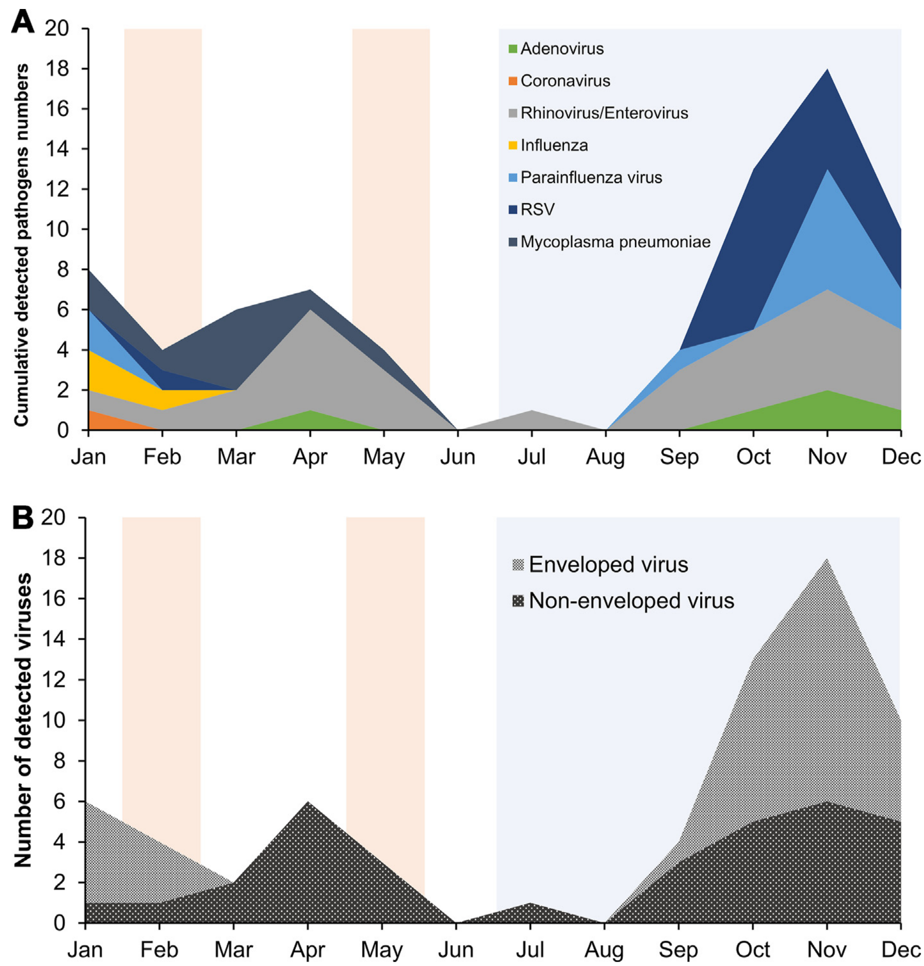


Figure 3. Monthly distribution of (Panel A) respiratory pathogens (colors) and (Panel B) enveloped (lighter grayscale shade) and non-enveloped viruses (darker grayscale shade) for 2020. Pink background colors represent restrictive COVID-19 measures, while the blue background color represents the easing of restrictions.

per 1000 children in December, with zero cases after February 2021 (not shown in the figure). There were no differences between the individual years 2017, 2018, and 2019 (p value $>$ 0.05). However, the difference between 2017 and 2019 and 2020 was significant, with a p value of $<$0.0001.

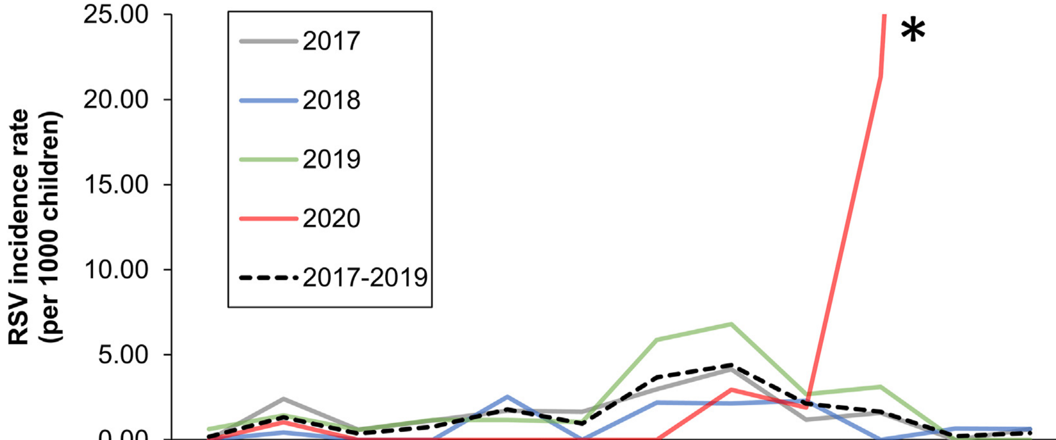
Discussion

The COVID-19 pandemic has had a great impact on the world. However, the case count and seroprevalence of COVID-19 were low in Taiwan for 2020.[9] NPIs such as social distancing, masking, and hygiene promotion were heavily emphasized as the pandemic progressed, reducing not only the rate of COVID-19 but also other circulating viruses.[10] In this study, we demonstrated a reduction in pediatric emergency department visits during the pandemic. In addition, the dynamics of circulating respiratory pathogens among pediatric patients experienced significant changes during 2020 even without large-scale outbreaks of SARS-CoV-2 among children. Fluctuations of non-enveloped viruses and a delayed surge of enveloped viruses secondary to NPIs during the pandemic were our major findings.

Adult and pediatric emergency department visits were heavily influenced by the pandemic. Pediatric visits generally experienced a heavier decline, as most were for respiratory infections.[11,12] Health care-seeking behavior is multifactorial and affected both positively and negatively by sociodemographic factors and public health strategies. In our study, the test numbers may not reflect a true population suffering from respiratory infections. Nevertheless, the positivity rate of the respiratory screening panel is a relatively accurate representation of the activity of circulating respiratory pathogens in the community but is also inversely associated with the strength of NPIs implemented in Taiwan during the pandemic.

The first significant trend in our analysis was a decrease in seasonal influenza. In the Taiwan National Infectious Disease Statistics System (TNIDSS), a drastic decrease in the positivity rate among laboratory samples was noted compared to 2019.[13] Among several countries with COVID-19 outbreaks, a similar reduction in seasonal influenza cases was also noted.[14] The temporal elimination of influenza was also observed in countries with low COVID-19 prevalence, such as New Zealand and Australia.[6,15]

In Taiwan, rhinovirus emerged as a dominant circulating respiratory pathogen during a period of strengthened



	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
2017	0.00	2.40	0.60	1.14	1.71	1.65	2.98	4.14	1.19	1.59	0.00	0.63
2018	0.00	0.44	0.00	0.00	2.53	0.00	2.18	2.15	2.29	0.00	0.66	0.62
2019	0.62	1.43	0.58	1.17	1.16	1.05	5.87	6.81	2.68	3.12	0.00	0.00
2020	0.00	1.03	0.00	0.00	0.00	0.00	0.00	2.94	1.90	21.34	93.39	62.87
2017-2019	0.18	1.32	0.37	0.77	1.78	0.95	3.67	4.39	2.13	1.64	0.21	0.40

Figure 4. Monthly RSV incidence per 1000 children from 2017 to 2020. The incidence of RSV from 2017 to 2019 is plotted separately (gray for 2017, orange for 2018, green for 2019), with the mean incidence shown by the dotted black line, while the incidence in 2020 alone is shown by the solid red line. As RSV incidence for November and December 2020 was exceptionally high at 93.39 and 62.87 per 1000 children, an asterisk is used to represent the peak without compromising the baseline trends for previous years.

NPIs.[16] We observed rhinovirus/enterovirus in almost constant circulation during 2020. While multiplex PCR in our hospital is unable to differentiate between rhinovirus and enterovirus, all of our patients presented with either fever or respiratory symptoms. The most common enterovirus capable of causing airway symptoms is enterovirus D68. In the enterovirus surveillance system of the TCDC, the prevalence of enterovirus D68 was low in 2020.[17] One of the proposed reasons for our finding was the strengthening of NPIs in response to the COVID-19 pandemic. Adenovirus and rhinovirus are both non-enveloped viruses that are not affected by lipophilic disinfectants commonly used as hand sanitizers.[18] Regular hand hygiene early in the pandemic, either with sanitizers or soap and water, may have decreased the circulation of enveloped viruses. However, non-enveloped viruses emerged later. As public caution declined after restrictions were eased, both enveloped and non-enveloped viruses began to circulate in the community. While wearing surgical masks has been proven to reduce respiratory droplet transmission, leading to decreased transmission of influenza and coronavirus, the efficacy of surgical masks to prevent rhinovirus transmission is less evident.[19] Therefore, we found a constant circulation of non-enveloped respiratory viruses despite national NPIs, with a relatively low rate of detection in summer, which is traditionally a season with a low incidence of viral respiratory diseases.

Another explanation for this phenomenon could be virus—virus interactions. There was a negative effect between enveloped and non-enveloped viruses. A study conducted in the United Kingdom showed that respiratory viruses exhibit cross-correlations at the population level that are independent of seasonality.[20] The result partly explained the increase in rhinovirus and adenovirus after influenza virus and common coronavirus declined. Our result was compatible with other countries that experienced a large impact from the COVID-19 pandemic. In the UK, national flu and COVID-19 surveillance reports showed that rhinovirus incidence remained stationary second only to SARS-CoV-2 in acute respiratory infection incidents.[21]

In October and November, we observed a surge of RSV and parainfluenza virus. In northern Taiwan, RSV or parainfluenza virus usually cause biphasic epidemic patterns in spring and autumn.[5,22] However, for southern Taiwan, the peak months are usually July and August, with another peak in February. Meteorological factors, such as humidity and rainfall, might contribute to the geographical differences.[23] Our analysis found no epidemic of RSV or parainfluenza viruses in summer 2020 but a delay in emerging cases compared with previous epidemiological data. Viral interference during the epidemics of common respiratory viruses might affect the timing and duration of subsequent epidemics of certain viruses.[24,25] The constant circulation of rhinovirus, strengthening of NPIs, and low activity of respiratory viruses during higher temperature months possibly delayed an RSV epidemic. From another point of view, RSV and parainfluenza virus usually affect young children. Poor adherence to face mask usage among young children in kindergarten or daycare centers might contribute to the transmission of highly contagious viruses. Finally, a recently published report found the emergence of a genetically distinct RSV variant, the ON1 strain, which could be another important reason for the epidemic surpassing other enveloped viruses in winter.[26]

From 2018 to 2020, we encountered an outbreak of *M. pneumoniae* among children in Taiwan with longer hospitalizations, greater use of inappropriate antibiotics, and more refractory diseases.[27,28] During this outbreak, macrolide resistance increased from 24% to 77%, predominantly in sequence type (ST) 3 and 17.[4,29] Despite multiplex PCR not being able to detect macrolide resistance and STs, the outbreak in early 2020 might belong to the same strains. This outbreak ceased in April. Because the incubation period of *M. pneumoniae* is 1—3 weeks, transmission could not be interrupted by a short isolation period. During the COVID-19 pandemic, the Taiwanese government announced a 2-week extension of winter vacation for children below the senior high school level, which may have successfully ended the transmission of *M. pneumoniae* and its prolonged incubation period.

The strength of our study is that a syndromic testing approach was used to explore viral dynamics against a unique backdrop amidst a raging pandemic in 2020. Nevertheless, some limitations exist. First, case numbers were limited with physician-driven testing. Some mild cases might have been missed as patients recovered rapidly after hospitalization and were not tested. Selection bias might be another concern. However, our results were consistent with data from the notifiable disease reporting system of the Centers for Disease Control and Prevention of Taiwan and contract laboratory data on community circulating viruses in Taiwan.[1] A similar surge in RSV has also been found in central Taiwan.[30] Hence, these biases could be minimal. Second, we did not include cases that tested positive by conventional antigen or serological testing, potentially causing underestimation of pathogens such as *M. pneumoniae* and influenza virus. Nevertheless, multiplex PCR is a powerful tool to detect an array of viruses with the ability to also detect coinfections and thus better reflect the incidence of common viruses. Third, the multiplex PCR respiratory panel has been available since 2020. Hence, we were unable to epidemiologically compare other equally important respiratory viruses, such as human metapneumovirus, as conventional PCR or antigen tests were unavailable at our institution.

Circulating respiratory pathogens never disappear. Our analysis showed the dynamics of respiratory pathogens in a country with low COVID-19 prevalence. Despite a reduction in the detection rate of common respiratory pathogens, we observed a constant circulation of non-enveloped viruses and a delayed yet larger outbreak of enveloped respiratory viruses after a period of NPI implementation and the easing of epidemic prevention and control restrictions. While NPIs are simple to promote and adopt, human behavior and viral interactions are more dynamically intricate and complicated, requiring balanced judgment in decision-making.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2022.03.005.