Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Article

The epidemiology and etiologies of respiratory tract infection in Northern Taiwan during the early phase of coronavirus disease 2019 (COVID-19) outbreak

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Abstract *Background:* Coronavirus disease 2019 (COVID-19) manifests symptoms as common etiologies of respiratory tract infections (RTIs). During the pandemic of COVID-19, identifying the etiologies correctly from patients with RTI symptoms was crucial in not only disease control but preventing healthcare system from collapsing. By applying sensitive PCR-based molecular assays, we detected the etiologic agents and delineated the epidemiologic picture of RTIs in the early phase of COVID-19 pandemic.
Methods: From December 2019 to February 2020, we screened patients presented with RTIs using multiplex PCR-based diagnostic assays. Data from pediatric and adult patients were compared with different months and units in the hospital.
Results: Of all 1631 patients including 1445 adult and 186 pediatric patients screened, 8 viruses and 4 bacteria were identified. Positive rates were 25% in December, 37% in January, and 20% in February, with pediatric patients having higher positive rates than adults (Ps $<$ 0.001). In

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pediatric patients, RhV/EnV was the most commonly detected, followed by parainfluenza viruses. Most *Mycoplasma pneumoniae* infection occurred in pediatric patients. RhV/EnV was the most commonly detected agent in pediatric patients admitted to intensive care units (ICUs), while influenza accounted for the majority of adult cases with critical illness. Noticeably, seasonal coronavirus ranked second in both adult and pediatric patients with ICU admission.

Conclusion: While we focused on the pandemic of COVID-19, common etiologies still accounted for the majority of RTIs and lead to severe diseases, including other seasonal coronaviruses.

Introduction

Every year, millions of people are diagnosed with respiratory tract infections (RTIs) worldwide. RTIs contribute to approximately 4 million deaths in all age, 20% death in pediatric patients, and huge burden in healthcare systems.[1] Most RTIs are caused by viruses and self-limited,[2] but some may exacerbate, complicated with secondary infections and lead to severe diseases.[3] In Taiwan, during the early phase coronavirus disease 2019 (COVID-19) pandemic, patients visiting emergency rooms (ERs) for RTI symptoms increased significantly, from 18% of total ER visits in winter 2018 to 22% in early 2020.[4] In Taipei Veterans General Hospital (TPEVGH), patients visited ER for screening of COVID-19 also increased during the early phase of COVID-19 pandemic. Among RTI patients, viruses play an important role,[5] especially in acute upper respiratory tract infections (URTIs), only about 2% of URTI cases are caused by bacteria and fungi.[6] Bacteria such as *Staphylococcus*, *Streptococcus*, *Mycoplasma*, *Legionella*, *Moraxella*, etc, and viruses such as influenza virus, parainfluenza virus (PIV), adenovirus (AdV), respiratory syncytial virus (RSV), seasonal coronavirus (sCoV), human metapneumovirus (hMPV), human rhinovirus/enterovirus (RhV/EnV), and human bocavirus (hBoV), can cause RTIs.[7] The prevalence of each microorganism varies among and is different between the pediatric and adult population.

Since December 2019 after COVID-19 outbreak, developing a faster and highly accurate laboratory test for patients presenting respiratory symptoms is crucial. Conventionally, culture is golden standard in clinical microbiology laboratory, but is slow and time-consuming, especially in viruses; another method is enzyme-linked immunosorbent assay, but sensitivity and specificity vary.[8] Multiplex real-time polymerase chain reaction (RT-PCR) based assays provide physicians and medical technologists high accurate, time-saving, reproducible, and cost-effective diagnostic methods in microbiology.[8,9] Previous studies in respiratory viruses RT-PCR diagnosis (e.g. influenza virus, sCoV, PIV, RSV, AdV, and hMPV) was reported a higher sensitivity and cost-effectiveness than conventional diagnosis methods.[7,10–12] Multiplex RT-PCR-based assays can detect more than one microorganism at same time. Therefore, multiplex RT-PCR-based assays could be the better diagnostic tools while we observed that more patients with RTI symptoms visited medical facilities for screening test of COVID-19 and non-COVID-19 respiratory viruses during the early phase of COVID-19 pandemic (December 2019 to February 2020). This also provided an opportunity to delineate the epidemiologic profile of RTIs in both adult and pediatric patients.

Method

Study design

This study was a retrospective observational study using hospital-based surveillance data from Taipei Veterans General Hospital (TPEVGH), a medical center in Northern Taiwan. Patients who were included in this study were all from ER, outpatient clinics, and wards in TPEVGH. The study period of this study was from 1st Dec, 2019 to 29th Feb, 2020, the early phase of coronavirus disease 2019 (COVID-19) pandemic. Patients suspected to have a respiratory infection and received multiplex real-time polymerase chain reaction (RT-PCR) tests for respiratory microorganisms during the study period were included. Patients with confirmed COVID-19, and those who presented with respiratory symptoms but did not undergo multiplex RT-PCR tests for respiratory microorganisms were excluded. The study was approved by the institutional review board of TVGH (reference number: 2019-06-022CC).

Respiratory microorganism examinations

Patients presenting with respiratory symptoms were queried for travelling, occupation, contact, and cluster (TOCC) history followed by physical examinations. Nasopharyngeal swab samples were collected by physicians and were sent to a P2 central laboratory for multiplex RT-PCR-based assays in TPEVGH. There were two RT-PCR assays for the detection of respiratory microorganisms in TPEVGH. The first is Luminex xTAG® Respiratory Viral Panel (Luminex Molecular Di-agnostics) which detected 8 viruses or viral subtypes from specimens in 5 h. The second was the FilmArray® Respiratory Panel system which detected viruses as Luminex xTAG® Respiratory Viral Panel can including their subtypes and 3 bacteria within one hour. ARP is also a point-of care test, which is more time-saving

and with higher flexibility than RVP. Respiratory viruses detected by the two RT-PCR panels included AdV, influenza virus, PIV, hMPV, sCoV, RSV and EnV/RhV.

Data collection

We collected all demographics and laboratory data from patients who accepted respiratory microorganism examinations. Despite proceeding RVP and ARP examinations, cultures of respiratory specimens were also collected if available.

Data analysis

Averagely, the serial intervals and incubation periods of these respiratory viruses (e.g. influenza virus, sCoVs, and RhV/EnV) are 7–14 days.[13–17] Those who were tested more than one time in any 14-day period were only counted as one test in this study. The overall detection rates of RVP and ARP were analyzed first to check the consistency with previous studies. Demographics and distributions of each microorganism which RVP, and APR detected, and cultures were analyzed as followed. Data were further categorized by each calendar month, by units (emergency room plus outpatient department, general wards, and intensive care units), and by ages (adult and pediatric patients) to disclose the distributions and trends.

Statistics analysis

Descriptive statistics were applied to characterize the baseline of every group. Mean values were reported with standard deviation (SD). Categorical data were reported with chi-squared test. Continuous data were analyzed with one-way ANOVA. P values < 0.05 were considered as significant. All data were analyzed by RStudio® statistic software (version 1.3.959).

Results

Screening in RTIs patients

From December 1st, 2019, to February 29th, 2020, a total of 1631 patients were tested for respiratory viruses, including 1378 (84%) by ARP and 253 (16%) by RVP. As severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread worldwide to cause a pandemic, the number of cases accepting examinations increased dramatically, with a sharp increase of ARP test and a significant decrease of RVP (Fig. 1A).

Of all tested samples, 428 (26%) were positive for at least one microorganism, among them, 92 (22%) were from pediatric patients. Thirty-three of 336 adult patients (9.8%) and 28 of 92 pediatric patients (30.4%) were tested for more than one microorganism, co-infection rates reached statistical difference ($P < 0.001$). ARP and RVP were equivalent with respect to the positive rate (26% vs 28%, $P = 0.57$). Within the season, January turned to be the month when tests were most likely to be positive (positive rate 25%, 37%, and 20% in December, January, and February, respectively. $P < 0.01$, Fig. 1B, black dots and line), and with the pediatric patients having higher positive detection rates than adults (Ps < 0.001).

Correlation and consistency of two RT-PCR-based assays

The detectable respiratory viruses and their subtypes in ARP and RVP this study was the same (i.e. influenza virus, PIV, AdV, sCoV, hMPV, RSV, EnV/RhV, and hBoV). Most patients after January 2020 were tested by ARP due to its advantage in time-saving and flexibility. We examined the consistency of these two RT-PCR systems by reviewing 17 patients in December 2019 who were tested by both panels within the 14 days. The test results were 100% consistent in 13 (76.5%) patients, 50% consistent in 3 (17.6%) patients, and 100% inconsistent in one (5.9%) patient tested by ARP first and then RVP nine days later.

Etiologies of patients diagnosed with RTIs

Twelve microorganisms, including 8 viruses and 4 bacteria, were identified (Fig. 2). The proportions of microorganisms identified varied between pediatric and adult patients. More influenza virus and RhV/EnV viruses were detected in adult patients, while the majority of *Mycoplasma* cases were found in pediatric patients (Table 1). One child was tested positive for *Bordetella parapertussis* while another adult was confirmed with *Bordetella pertussis* infection.

RhV/EnV and influenza virus were predominantly in three different months, influenza virus distributions varied in different months overall ($P < 0.01$), post hoc test showed the significant greater in January than in December and February (Ps < 0.01). In pediatric patients, RhV/EnV was predominant but without difference among months ($P = 0.11$, Fig. 3A). We observed a peak of influenza virus infection in January 2020 while average temperature dropped, but declined and shifted to RhV/EnV infection in February 2020 in adult patients (Fig. 3B). Pediatric patients were still the main population of *Mycoplasma pneumonia* infection and significant greater in January and February than adult patients (Ps < 0.01). Noticeably, a lower environmental temperature was associated with a higher detection rate of influenza virus and RhV/EnV in both pediatric and adult patients (black dots and lines, Fig. 3A and B).[18]

Influenza virus and PIV serotypes analysis

During the early phase of COVID-19, influenza virus was the second highest etiology in ARP- and RVP-positive cases. All specimens were analyzed and identified the subtypes of influenza virus and PIV. Overall, 115 patients were influenza-positive, among them 16 were pediatric patients (14%). Forty-seven patients were PIV-positive, among them 16 were pediatric patients (34%). With respect to influenza subtypes, 16 (14%) were influenza B virus, 73 (64%) were influenza A/09 (H1), 12 (10%) were influenza A (H3), while

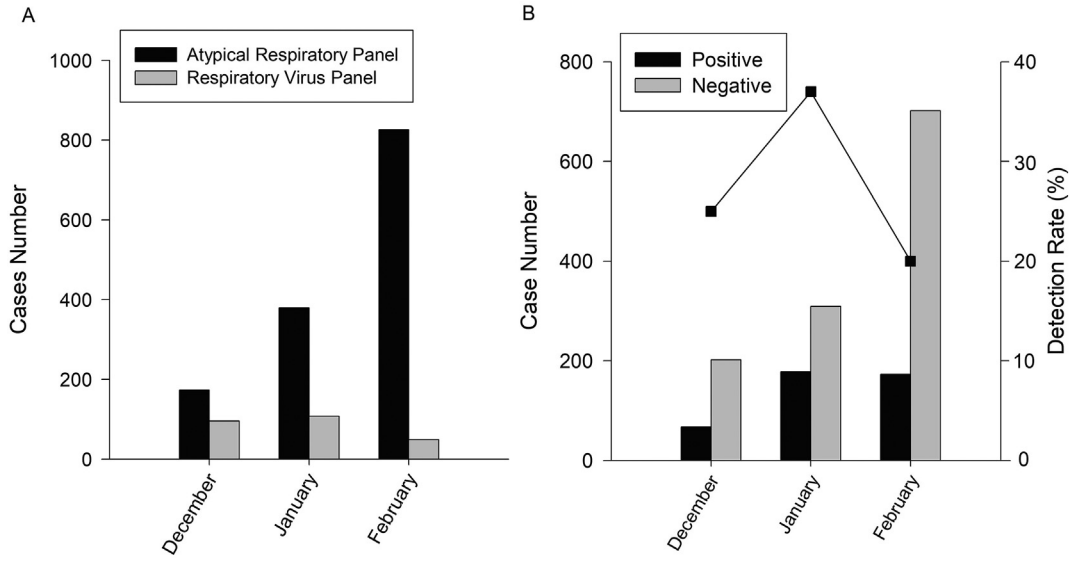

Figure 1. Number of patients tested by either atypical respiratory panel (ARP) and respiratory virus panel (RVP) and the overall positive detection rates in each calendar month during the study period (December 2019 to February 2020). 1A: The case number tested by ARP (solid black bar) and RVP (solid grey bar) each calendar month. 1B: The positive (solid black bar) and negative (solid grey bar) case number, and the positive detection rates (black dot and line) in each calendar month.

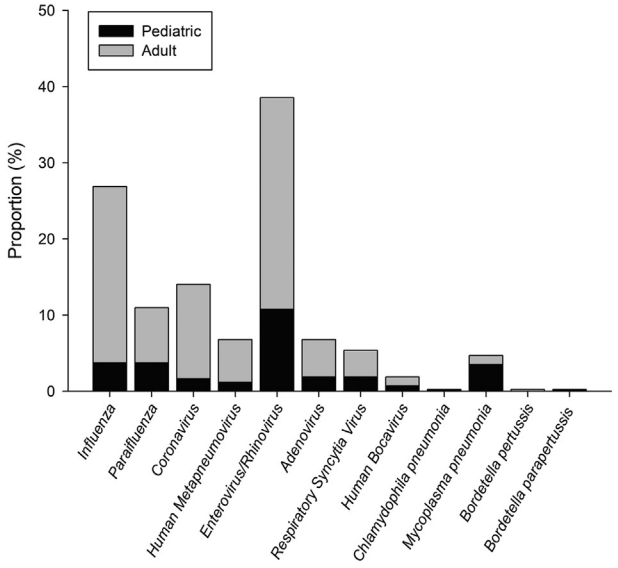

Figure 2. The overall proportions of different respiratory microorganisms in pediatric (black) and adult (grey) patients, including influenza virus, parainfluenza, seasonal coronavirus, human metapneumovirus, enterovirus/rhinovirus, adenovirus, respiratory syncytial virus, human bocavirus, and four bacteria.

subtype identification was unsuccessful in 10 (9%) influenza A cases. Among the PIV cases, PIV3 was the leading subtype (20 cases, 43%), followed by PIV4 (9, 19%), PIV1 (8, 17%), and PIV2 (5, 11%), with one (2%) in whom the subtype of PIV could not be identified. Noticeably, 5 patients had viral co-infection: one (1%) was influenza A and B viruses' co-infection, one (2%) was PIV3 and 4 co-infections, one was influenza A/09 (H1) and PIV3 co-infection, one was unidentified influenza A virus and PIV3 co-infection, and one was influenza A/09 (H1) and PIV4 co-infection. Noted that, influenza A/09 (H1) and PIV3 were the main strains overall.

Seasonal coronavirus serotypes analysis

During the pandemic of COVID-19, 60 sCoV-positive patients, 7 were pediatric patients (12%). Positive detection rates were 4% to both pediatric and adult patients. Of the 60 patients, 41 patients (68%) were sCoV-OC43, 8 (13%) were sCoV-NL63, 8 (13%) were sCoV-229E, and 2 (3%) were sCoV-HKU1, and one could not be identified the serotype. Noted that, one specimen from ARP examination in February reported negative result to all 11 microorganisms which were tested, but we isolated and identified sCoV-229E. sCoV-OC43 was significantly greater than other serotypes in both pediatric and adult patients ($P < 0.05$).

Distributions of each microorganism in different units

The microorganisms varied in different units. We categorized the hospital into three different units, general wards, ER plus outpatient department (OPD), and intensive care unit (ICU). 73% of pediatric patients were admitted to general wards, 11% to ICU, and 16% were discharged directly; 52% of adult patients were admitted to general wards, 19% to ICU, and 29% were discharged directly. Overall, influenza virus ($P < 0.01$), RhV/EnV ($P = 0.02$), RSV ($P = 0.01$), and Mycoplasma pneumonia ($P < 0.05$) varied in different units. Influenza virus and RhV/EnV were predominant in every unit. RhV/EnV infection was predominant in pediatric patients, but a peak of influenza virus infection was observed in ER plus OPD. 70% of pediatric

Table 1 Case number and percentages of each microorganism during our study period, from December 2019 to February 2020.

Microorganism (%)	Total N = 428	Pediatric N = 92	Adult N = 336	P Value (Chi-squared)
Influenza virus	115 (27)	16 (17)	99 (29)	0.02*
Parainfluenza virus	47 (11)	16 (17)	31 (9)	0.03*
Coronavirus	60 (14)	7 (8)	53 (16)	<0.05*
Human Metapneumovirus	29 (7)	5 (5)	24 (7)	0.56
Rhinovirus/Enterovirus	165 (39)	46 (50)	119 (35)	0.01*
Adenovirus	29 (7)	8 (9)	21 (6)	0.41
Respiratory Syncytia virus	23 (5)	8 (9)	15 (4)	0.11
Human Bocavirus	8 (2)	3 (3)	5 (1)	0.27
Chlamydophila pneumonia	1 (0.2)	1 (1)	–	0.22
Mycoplasma pneumonia	20 (5)	15 (16)	5 (1)	<0.01*
Bordetella pertussis	1 (0.2)	–	1 (0.2)	1.00
Bordetella parapertussis	1 (0.2)	1 (1)	–	0.22

92 of 428 patients, who were with positive result to at least one respiratory tract microorganism, were pediatric (21%) while 336 (79%) were adults. P value: compared pediatric patients with adult patients in different microorganisms with chi-squared tests. $P < 0.05$ was defined as significant. *: statistically significant.

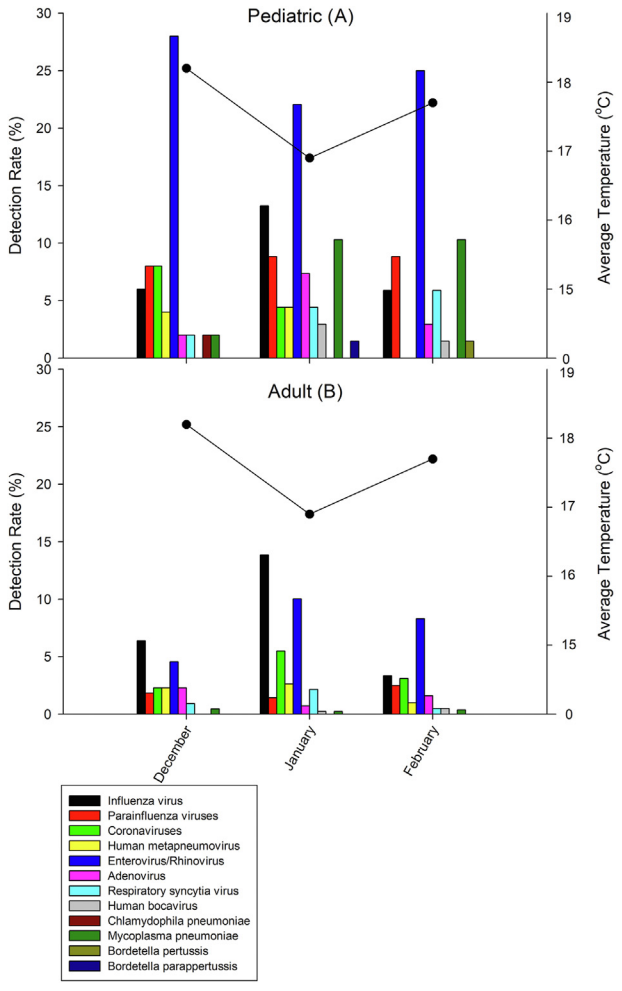

Figure 3. The positive detection rates of different respiratory tract microorganisms of pediatric and adult patients in each calendar month, and the correlations between detection rates and environmental temperatures (black dots and lines). 3A: pediatric patients. 3B: adult patients.

patients in ICU were RhV/EnV-positive; sCoVs and influenza viruses ranked second. RhV/EnV was also the most commonly detected microorganism of adult patients in general wards (38%) and ER plus OPD (42%), and influenza virus ranked second (24%, 28%); however, influenza virus accounted for most in ICU (40%).

Discussion

The early phase of COVID-19 pandemic was in winter, when viral RTIs were prevalent in Taiwan. Through application of molecular diagnostic techniques, our study provided a clear etiologic delineation of patients presenting to the hospital with respiratory symptoms during this period. Our results showed that RhV/EnV and influenza were the major viral etiology of RTIs during the early phase of COVID-19 pandemic, accounting for the majority of cases in both general wards and ICUs. To our surprise, we also found a substantial number of ICU patients tested positive with sCoVs, which were generally considered to cause mild illness of upper respiratory infections.

The pandemic of COVID-19 has caused millions of confirmed cases and hundreds of thousands of deaths around the world and brought enormous impact on socio-economic activities. Clinically, SARS-CoV-2 infection might be asymptomatic; for symptomatic patients, fever and cough were the most common presenting symptoms.[19,20] Because the symptoms of SARS-CoV-2 infection are similar to most RTIs, identifying etiologies of patients presenting RTI symptoms correctly and quickly becomes crucial not only in diseases control, but also to preventing healthcare system from collapsing. During the early phase of COVID-19 pandemic, RTI patients visiting our hospital were screened with molecular respiratory panels in addition to SARS-CoV-2 testing. Such practice helped in identifying common respiratory microorganisms and provided an opportunity to delineate the epidemiologic picture of RTIs during this period.

Etiologies varied from seasons and ages in patients presenting respiratory tract symptoms, and the

distributions were different regarding disease severity. In pediatric patients, influenza virus and RSV had been reported the most commonly detected respiratory agents in winter[3,21,22]; however, our study found RhV/EnV to be most common respiratory microorganism in pediatric patients during the study period. Such findings suggested that the virulence of RhV/EnV should be further examined. PIVs infection contributed to approximately one fifth of pediatric hospitalizations and similar to previously reported,[23] PIV3 was the leading serotype in our hospital. Not surprisingly, pediatric patients were the main population in *M. pneumonia* infection and it also contributed about one fifth of hospitalizations in general wards, but we did not observe any ICU case despite the previous study reported a high proportion in ICU admissions.[24] Surprisingly, alone with influenza virus, sCoV contributed to a significant number of pediatric in ICU cases during this period, which was significantly higher than data reported worldwide.[25] Among them, sCoV-OC43 was the predominant serotype while both sCoV-NL63 and sCoV-OC43 were equally detected in pediatric ICUs. Seldom sCoV-NL63 was reported with severe cases,[26] the virulence and disease severity of different sCoV serotypes should be further investigated.

In adult patients, influenza virus was still the most common detected agent especially in ICU and, like previously reported,[27] peaked while the average temperature dropped, more severe superimpose infection and complications might be indicated. RhV/EnV was the second common agents and was more frequently detected than previously reported.[22] Noticeably, sCoVs accounted for a significant part in hospitalized adult patients during this period, the overall detection rates of sCoVs in our study was higher than previous study during 2010—2015.[28] Also, to our surprise, sCoVs ranked the second to among the microorganisms associated with ICU admission, contributing to approximately one fifth of ICU cases of adult patients. In previous reports, sCoV infection were seldom linked to severe diseases[25,29,30] and rarely caused mortality.[31] Whether these findings merely reflected the previous underdiagnosed sCoV diseases or implicated the increasing virulence and incidence of these common viruses need to be carefully examined and analyzed by further studies, especially in the context of COVID-19 pandemic.

There are several limitations to our study. Firstly, the study was conducted in a single medical center in Northern Taiwan; the conclusion might not be generalized to the entire nation, especially to the pediatric patients due to the limited case number; a large-scale multicenter study is necessary to illustrate the real nationwide epidemiological trends. Secondly, this study is a 3-month study, a more extended study period is necessary to complete each respiratory microorganisms' incidences. Lastly, the detectable respiratory microorganisms by ARP and RVP are still limited, which could underestimate the incidence of respiratory tract infection, new RT-PCR systems should be considered.

Conclusion

This 3-month retrospective observational study illustrated the distributions of common microorganisms causing RTIs during the early phase of COVID-19 pandemic in a tertiary medical center in Northern Taiwan. During the COVID-19 pandemic, great efforts have been made in controlling the spread of SARS-CoV-2. However, common respiratory viruses such as influenza virus, RhV/EnV, and sCoVs were still prevalent among patients presenting to the hospital with RTI symptoms. Therefore, reducing the healthcare burdens caused by common viral RTIs is still important during the pandemic of COVID-19.

Declaration of competing interest

All authors declare no conflicts of interest.

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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.2021.05.006.