Epidemiological Characteristics of Common Human Coronaviruses in Korea, 2015-2019

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Abstract

Background: Compared to influenza virus and respiratory syncytial virus, common human coronaviruses (HCoVs) are relatively understudied due to the mild nature of HCoV infection. Given the lack of local epidemiology data on common HCoVs in Korea, we aimed to describe epidemiological characteristics of common HCoVs.

Methods: Respiratory viral test results from more than 67,000 respiratory samples from the two data sources, Korea Influenza and Respiratory Viruses Surveillance System (KINRESS, N=58,253) and Seoul National University Children's Hospital (SNUCH, N=9,589) were analyzed from January 2015 to December 2019. Viral detection was done by the multiplex RT-PCR. Demographics and clinical diagnosis were collected for previously healthy children tested positive for HCoVs in SNUCH.

Results: Of the 67,842 samples tested, 1 or more respiratory viruses were detected from 35,459 (52.2%) samples and 2,854 (4.2%) samples were positive for HCoVs (OC43 2.1%, NL63 1.7%, 229E 0.4%). All 3 types were co-circulated during winter months (November to February) with some variation by type. HCoV-OC43 was most prevalent, peaking every winter. HCoV-NL63 circulated with alternate peaks occurring between January-March and November-February. Meanwhile, HCoV-229E had smaller peaks every other winter in 2015/2016 and 2017/2018. From the national surveillance data, HCoV infection was most prevalent among 0 to 1 year old children and older adults aged over 70 years. 18.2% of the HCoV-positive samples were co-detected with other respiratory viruses, with the highest co-detection rate (33.7%) in children 0 to 1 year of age and the lowest co-detection rate (3.6%) in adults ≥70 years old. Upper respiratory tract infection was the most common (60.0%) clinical diagnosis of the 135 previously healthy children. Croup accounted for 17.0% of NL63-positive children

Conclusion: This study described the epidemiological characteristics of 3 types of common HCoVs (OC43, NL63, 229E) in Korea; the highest prevalence of OC43, concurrent circulation during winter, and age difference in HCoV infection and co-detection rate with other respiratory virus. It may be informative to monitor any changes in the epidemiology of common HCoVs as the COVID-19 pandemic continues.

Background

Coronaviruses (CoVs) are widespread among animals and humans and categorized into four genera including alpha, beta, gamma, and delta [1]. Currently, the four common human coronaviruses (HCoVs); HCoV-229E, HCoV-NL63 in alpha genus and HCOV-OC43, HCoV-HKU1 in beta genus are circulating as contributors to upper respiratory tract infections in children and adults and are generally not associated with severe respiratory illness [2]. Animal CoVs can be transmitted to humans and evolve as the cause of serious human illness. Before the recent emergence of the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in China, there were two examples; SARS-CoV emerged in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 [1]. The SARS-CoV had been successfully contained by the public health measures while MERS-CoV is

circulating with a limited transmission activity between people [3, 4]. In contrast, the COVID-19 outbreak has spread globally and the World Health Organization declared the outbreak a pandemic [5]. As of October 5, the number of confirmed cases is estimated at more than 35 million and the pandemic has caused over 1,000,000 fatal cases worldwide [6].

Because of the mild nature of HCoV infection, common HCoVs are understudied compared to influenza virus and respiratory syncytial virus. In Korea, only a few reports have analyzed clinical or epidemiological characteristics of the single HCoV type, mostly during a short period [7-9]. The weekly respiratory virus surveillance by Korea Influenza and Respiratory Viruses Surveillance System (KINRESS) reports the overall positive rate of HCoVs [10]. However, the data on the circulation pattern of the four common HCoVs has been limited in Korea. In this study, we aimed to characterize detailed epidemiology of HCoVs from 2015 to 2019 in Korea.

Methods

Respiratory viral test results from more than 67,000 respiratory samples from the two data sources, KINRESS and Seoul National University Children's Hospital (SNUCH) were analyzed from January 2015 to December 2019.

KINRESS is a surveillance network established by the Korea Disease Control and Prevention Agency (KDCA) that collects respiratory samples from sentinel hospitals/clinics across the country. The sentinel hospitals consists of 52 primary and secondary care clinics nationwide. Throat or nasal swab samples and patient information were collected for patients aged 0-100 years old who visited the hospital/clinic with acute respiratory symptoms. SNUCH is a 300-bed tertiary care university hospital and pediatric referral center located in Seoul, Korea. In SNUCH, respiratory viruses were tested for children and adolescents under 20 years of age who presented with fever and/or respiratory symptoms as a part of standard patient care. Samples collected within 3 days from the admission were included. When samples from a single person were consecutively positive for the same virus within one month, only the initial result was included.

The multiplex reverse transcription polymerase chain reaction (RT-PCR) detects three types of HCoVs; HCoV-229E, HCoV-NL63, and HCoV-OC43 along with other common respiratory viruses (influenza A virus, influenza B virus, RSV, human adenovirus, human metapneumovirus, human rhinovirus, parainfluenza virus types 1–4, and human bocavirus). HCoV-HKU1 was not included in the assays. The RT-PCR was performed using the Powerchek™ Respiratory Virus Real-time PCR Kit series (Kogene Biotech, Korea), Anyplex™ II RV16 Detection (Seegene Inc, Korea) or Allplex™ Respiratory Panel Assays (Seegene Inc).

We assessed the detection rate of HCoVs for each type, viral co-detections, and demographics of patients for all samples tested positive for HCoV. One epidemic year was set between September 1 of the year and the end of August of next year. Medical records of the previously healthy children with a single HCoV detection were retrospectively reviewed to analyze the clinical features by each type.

Statistical analysis

Analyses were conducted using R 4.0 (R Foundation for Statistical Computing, Vienna, Austria). To compare the clinical manifestations of HCoV infection by type, Fisher's exact test was used. *P* value <0.05 in the analyses was considered significant.

Results

From January 1, 2015 to December 31, 2019, a total of the 67,842 respiratory samples were tested; 58,253 from KINRESS and 9,589 from SNUCH. One or more respiratory viruses were detected from 35,459 (52.3%) samples and 2,854 (4.2%) samples were positive for HCoVs (HCoV-OC43 2.1%, HCoV-NL63 1.7%, and HCoV-229E 0.4% by type).

By the data source, a total of 58,253 respiratory samples were collected by KINRESS. 30,442 (52.3%) samples were positive for any respiratory viruses and HCoVs were detected in 2,391 (4.1%) samples (Figure 1). The number of samples and occurrence rate by type were as follows; HCoV-229E, 203 (0.3%); HCoV-NL63, 1,032 (1.8%); and HCoV-OC43, 1,156 (2.0%) [see Additional file 1].

During the same period, a total of 9,589 respiratory samples tested in SNUCH, and one or more respiratory viruses were detected from 5,017 (52.3%) samples. Of 463 (4.8%) samples positive for HCoVs (Figure 1), 67 (0.7%) were positive for HCoV-229E, 139 (1.4%) for HCoV-NL63, 268 (2.8%) for HCoV-OC43 [see Additional file 1].

Demographics

The median age of patients sampled by KINRESS was 13 years (IQR 3-48 years) and 45.3% were male. In 2,391 samples with HCoV detection, the median patient age was 13 years (IQR 2-54 years) and 43.1% were male. The pattern of HCoV positive rate by age group showed two peaks in HCoV prevalence among children less than 2 years of age (5.4%) and older adults aged over 70 years (5.5%) (Figure 2).

In SHUCH, the median age of patients tested was 2 years (IQR 0-7 years) and 57.5% were male. In 463 children with HCoV detection, the median age was 2 years (IQR 0-4 years) and 54.9% were male. HCoV was most prevalent in 2 – 4 years olds with percent positive of 6.4%, followed by 5.2% in 0 – 1 year olds and 3.4% in 5 – 19 years olds.

Annual and seasonal distribution of HCoVs

In KINRESS data, the detection rates of HCoV by one epidemic year ranged from 4.1% in 2015/16 to 5.2% in 2016/17. Seasonal detection rates of HCoV in SNUCH were ranged from 4.9% in 2018/2019 to 5.8% in 2017/18.

Both KINRESS and SNUCH data demonstrated high detection rate of HCoV during winter season (November to February) each year, showing the highest monthly detection rates up to 11.9% in December

2016 and 16.1% in November 2018, in KINRESS and SNUCH respectively (Figure 3). Both data showed similar circulation pattern of three types with minimal differences. HCoV-OC43 was most prevalent among three types and mostly peaked during winter season in KINRESS and SNUCH. In 2018/19 winter season, HCoV-OC43 was predominant in SNUCH while KINRESS data showed similar detection rates of HCoV-OC43 and HCoV-NL63. HCoV-NL63 was identified with alternate peaks occurring late winter (from January to March) or early winter (from November to January) from both data sources. Meanwhile, HCoV-229E had smaller peaks every other winter in 2015/16 and 2017/18 (Figure 3).

Co-detection with respiratory viruses

The proportion positive for each virus of the test-positive viruses from KINRESS and SNUCH during the study period was shown in Figure 4. The average proportion of HCoVs of the test-positive viruses in KINRESS and SNUCH were 7.2% and 7.6%, respectively. Human rhinovirus was the most commonly detected in both institutions (17.1% in KINRESS, 22.2% in SNUCH). The second most prevalent virus was respiratory syncytial virus (10.1%) in SNUCH and influenza virus (14.4%) in KINRESS.

Among 2,391 HCoV-positive samples obtained in KINRESS, 436 (18.2%) samples were co-detected with other respiratory viruses. Co-detections with non-HCoV viruses were observed in 374 (28.9%) of HCoV-positive samples from patients younger than 20 years old. In this age group, human rhinovirus (8.3%) and adenovirus (7.8%) were most frequently co-detected [see Additional file 2]. Figure 2 showed a higher co-detection rate in the younger age groups with the highest rate of 33.7% in infants <2 years of age and the lowest rate (3.6%) in those ≥70 years of age.

Of the 463 HCoV-positive samples in SNUCH, 189 (40.8%) samples were co-detected with one or more respiratory viruses other than HCoVs. Frequently detected viruses with HCoVs were human rhinovirus (13.2%), respiratory syncytial virus (13.0%), and adenovirus (10.4%). Influenza virus (4.3%) was less commonly detected with HCoVs. Co-detections with two different types of HCoVs were seen in 11 samples [see Additional file 2].

Clinical diagnosis

The clinical diagnosis of the 135 previously healthy children with a single detection of HCoVs are summarized in Table 1. The median age was 1 year old (IQR 0-2.5 years) and 54.1% were male. There was no significant differences in the median age and age distribution by type (p= 0.444, p= 0.46). Upper respiratory infection was the most common clinical diagnosis throughout all 3 types. HCoV-NL63 was frequently associated with croup (17.0% in HCoV-NL63 vs. 3.9% in remainder, p=0.029) Febrile illness was more prevalent in HCoV-229E and HCoV-OC43 than HCoV-NL63 (p= 0.044).

Table 1. Clinical features of previously healthy children with a single HCoV detection in SNUCH, 2015-2019

	HCoV-229E (n=12)	HCoV-NL63 (n=47)	HCoV-OC43 (n=76)	*P*-value
Age				
Median months [IQR]	28.0 [5.5;81.5]	11.0 [4.0;35.0]	13.5 [2.0;34.0]	0.444
0 – <2 years	6 (50.0)	32 (68.1)	49 (64.5)	0.46
2 – <5 years	3 (25.0)	12 (25.5)	19 (25.0)	
5 – 19 years	3 (25.0)	3 (6.4)	8 (10.5)	
Sex				
Male	9 (75.0)	24 (51.1)	40 (52.6)	0.309
Female	3 (25.0)	23 (48.9)	36 (47.4)	
Clinical diagnosis				
Upper respiratory infection	7 (58.3)	29 (61.7)	45 (59.2)	0.965
Croup	0 (0.0)	8 (17.0)	3 (3.9)	**0.029**
Pneumonia	2 (16.7)	6 (12.8)	12 (15.8)	0.875
Bronchiolitis	1 (8.3)	3 (6.4)	5 (6.6)	1.000
Febrile illness[#]	2 (16.7)	1 (2.1)	11 (14.5)	**0.044**

Note, HCoV-positive cases with other co-detected viruses were excluded from this analysis.

*Data are numbers (percentages) of patients unless otherwise indicated.

[#]Febrile illness did not accompany any respiratory symptoms.

Discussion

In this study, we investigated the prevalence and circulation pattern of HCoVs using more than 67,000 respiratory samples during five consecutive years, from 2015 to 2019. All three type of HCoVs showed a marked seasonality with peaks from winter to early spring and were rarely detected in summer. HCoV infection was most prevalent among children less than 2 years of age and older adults aged over 70 years. Overall co-detection rate with non-HCoV viruses was 18.6%. In particular, a high co-detection rate of around 30% was observed in children under 5 years old, and the co-detection rate in adults over 20 years old was low.

Our findings that HCoV mainly circulated from November to February with some variations are consistent with earlier studies [9, 11-16]. By types, HCoV-OC43 mainly contributed to the overall HCoV infection annually, followed by HCoV-NL63 and HCoV-229E in Korea. While HCoV-OC43 and HCoV–NL63 were

detected with distinct prevalence every year, biennial pattern was seen in HCoV-229E that peaked in 2015/16 and 2017/18. Although the circulation peaks were not as high as influenza virus, there was a unique seasonality for all three types of HCoVs with a minimal prevalence in summer. The current nationwide surveillance and rRT-PCR tests utilized in most hospitals in Korea do not include tests for HCoV-HKU1. Only a single study has looked a prevalence and epidemiology of HCoV-HKU1 in Korea from January 2007 to May 2008 [7]. In the study, HCoV-HKU1 was detected in 50 of 1985 specimens with the detection rate of 2.5%. It is very remarkable in that the prevalence of HCoV-HKU1 was even higher than the recent 5-year average detection rate of HCoV-OC43, the most commonly detected HCoV in KINRESS during 2015-2019, 2.0%.

In the KINRESS data, the positive rate of overall respiratory viruses tended to decrease with age. The positive rate for RSV, human adenovirus, and human parainfluenza was more than 10% in children under 5 years of age, but in adults it was less than half of that in children. On the other hand, HCoV infection occurred relatively evenly at all ages. The HCoV positive rate peaked at both ends of age spectrum and was relatively low in older children and younger adults. In particular, the positive rate showed a definite trend of decreasing with age from 0 to 7 years old. After 10 years of age, the 10-year age group showed a tendency of increasing the positive rate according to higher age groups (data not shown). This infers the effect of naturally acquired immunity and waning of immunity. In a serological study on human coronavirus, antibody titers waned substantially 1 year after initial infection and many could be re-infected and shed virus [17]. A recent longitudinal survey of 191 individuals using RT-PCR found that reinfections with the same endemic coronavirus are not atypical in a time window shorter than 1 year [18]. Our molecular surveys of HCoV infection suggest that exposure and immunity to HCoVs begins at a young age and frequent reinfections with community-acquired common coronaviruses occur throughout life.

In the 2013-2015 KINRESS study, the co-detection rate was similar at 20.4% and 30.4% in US [11, 19]. Another study of children hospitalized for acute respiratory infections reported a coronavirus co-detection rate of 70% or even higher [20]. The pediatric co-detection rate of non-HCoV viruses was 40.8% in SNUCH and 28.9% in KINRESS. Since 75% of immunocompromised cases accounted for the SNUCH data, prolonged viral shedding and multiple respiratory infection might be reflected [21]. It is also possible that the presence of non-viable residual virus particles from previous infection was identified by using real time PCR. In particular, rhinovirus and adenovirus commonly co-detected in this study are well known viruses commonly found in asymptomatic patients [22]. Despite of having similar seasonal prevalence, influenza virus was co-detected with a rate lower than 5%. Since coronavirus is one of the common pathogens detected even in asymptomatic children, causal inference based on the detection of these viruses in symptomatic patients should be made with caution [23, 24].

We also found that the co-detection rate was higher with younger age group in national data solely. It was highest in children younger than 2 years, followed by children from 2 to <5 years and children from 5 to <20 years of age. This supports earlier findings that the simultaneous presence of multiple respiratory viruses is more frequently observed in children and young adults in other reports [25, 26]. Both reduced

innate and adaptive immunity in children could attribute higher incidence of co-infection. The lack of prior exposure to virus causes generally much naïve immune system compared to adults [27]. This lower protective immunity in young infants favors viral replications, which might result in prolonged viral shedding.

Since the emergence of the pandemic coronavirus, SARS-CoV-2, interest in the epidemiology of common HCoVs, which has not been appreciated in the past, is now growing. Some experts concern that the COVID-19 pandemic may progress until 2021 unless effective and safe vaccines become available. A study which predicted how transmission of SARS-CoV-2 will develop proposed that seasonality, the duration of immunity, and cross-immunity from other common HCoVs would be the determining factors [28]. Changes in temperature and humidity by season could be a major determinant. Some experts suggested SARS-CoV-2 might decline during summertime and rebound with the start of epidemics of wintertime respiratory viruses such as influenza virus, respiratory syncytial virus, and common HCoVs in the Northern Hemisphere. However, many places experienced a resurgence of new confirmed cases following a loosening of social distancing. While the prediction of the COVID-19 outbreak in coming years remains uncertain, decline in the summer does not seem correct at this point. Degree of immunity to SARS-CoV-2 along with the cross-immunity within or between the different genera may contribute to the fate of SARS-CoV-2 [29-31]. Currently, we expect spread of the pandemic virus will stop if the herd immunity threshold of 60%-67% is achieved. Two main caveats are the duration of the immunity and the viral mutations that influence the transmission efficiency.

This study has several limitations. Clinical features of HCoVs were analyzed only for previously healthy children in a single center. There were no available studies that looked at HCoV infections in adults in Korea, while there was only a single study that compared the prevalence of common respiratory viruses between children and adults [26]. Each HCoV type may also independently affect circulation patterns of SARS-CoV-2. Although the existence of cross-immunity is controversial, there remains an expectation that immune responses developed after infections by the closest betacoronaviruses, HCOV-OC43 and HCoV-HKU1, may induce cross-immunity with SARS-CoV-2 [32, 33]. However, the nationwide surveillance through KINRESS and SNUCH data do not include test for HCoV-HKU1. Surveillance data from the U.S. Centers for Disease Control and Prevention showed HCoV-HKU1 was the most commonly detected HCoV in the 2019-2020 season, reaching 4.8% in January 2020 [10].

Despite these limitations, this study provides the current epidemiology of common HCoVs in Korea and suggests that there is a room for improvement with the inclusion of HCoV-HKU1 in the nationwide KINRESS. As older adults are at a greater risk of developing severe disease by COVID-19, further studies need to establish data on the epidemiology and clinical characteristics of HCoV infections in the adult population in Korea.

Abbreviations

COVID-19: Coronavirus disease 2019

CoVs: Coronaviruses

HCoVs: Human coronaviruses

KDCA: Korea Disease Control and Prevention Agency

KINRESS: Korea Influenza and Respiratory Viruses Surveillance System

MERS-CoV: Middle East respiratory syndrome coronavirus

RT-PCR: Reverse transcription polymerase chain reaction

SNUCH: Seoul National University Children's Hospital

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

Declarations

Ethics approval and consent to participate

Seoul National University Hospital Institutional Review Board approved this study (No. 2003-194-1112) and written consent was waived.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no potential conflicts of interest to disclose.

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Authors' contributions

EHC formulated the study concept and design. **YYC, YKK, JMK, YSC, and MGH** acquired, analyzed, and interpreted the data considered in this study. **YYC, YKK** provided administrative, technical, and/or material support. **EHC** supervised this study. **YKK and YYC** drafted the manuscript. All authors critically revised the manuscript for important intellectual content. The author(s) read and approved the final manuscript.

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Figures

Figure 1

Monthly number of tested samples, any respiratory virus-positive samples and HCoV-positive samples in KINRESS and SNUCH, 2015-2019. HCoV; Human coronavirus, KINRESS; Korea Influenza and Respiratory Viruses Surveillance System, SNUCH; Seoul National University Children's Hospital.

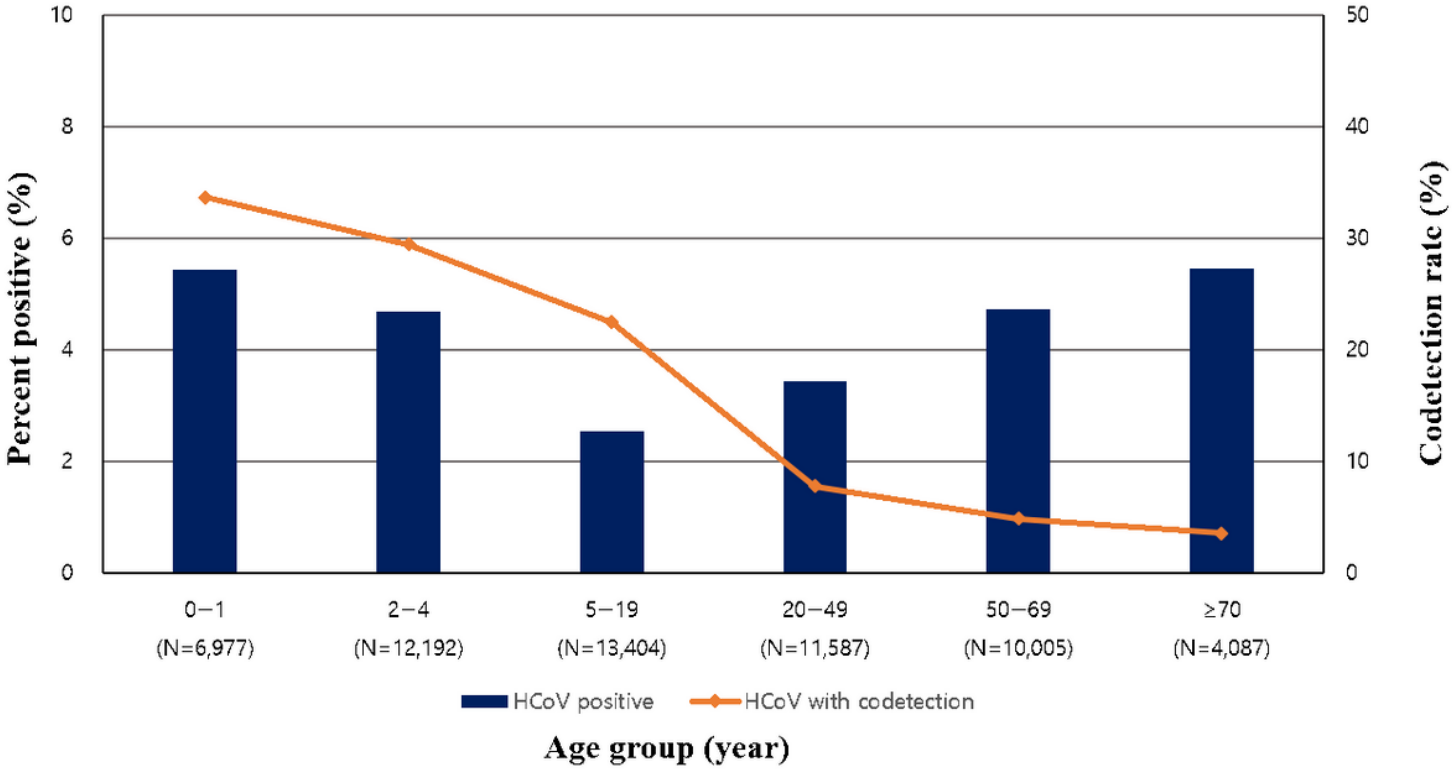

Figure 2

The percent positive and co-detection rates of HCoV-positive samples by age group in KINRESS, 2015-2019. KINRESS; Korea Influenza and Respiratory Viruses Surveillance System

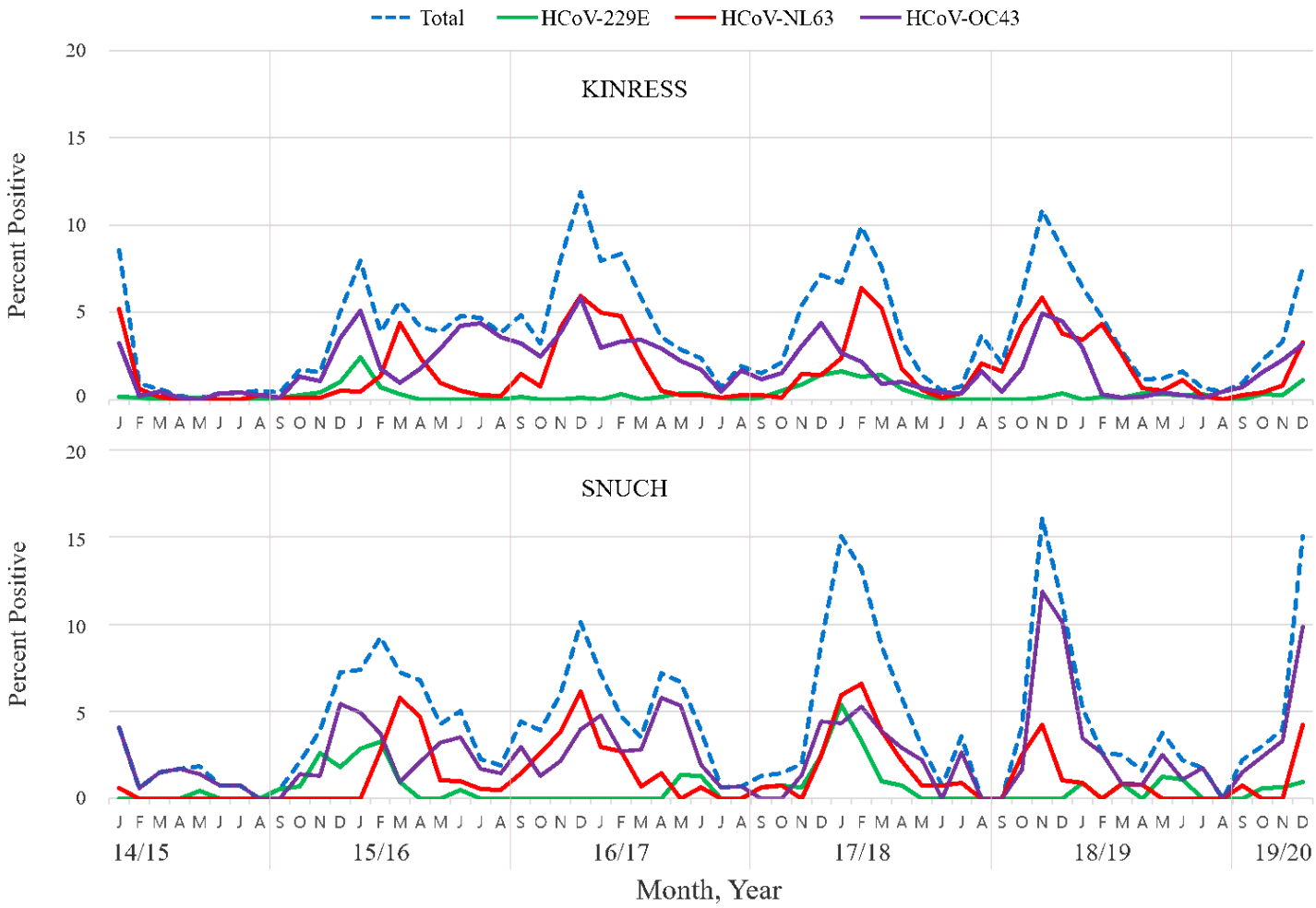

Figure 3

The percent positive for HCoVs and three types (229E, NL63, OC43) in KINRESS and SNUCH, 2015-2019. HCoVs; Human coronaviruses, KINRESS; Korea Influenza and Respiratory Viruses Surveillance System, SNUCH; Seoul National University Children's Hospital.

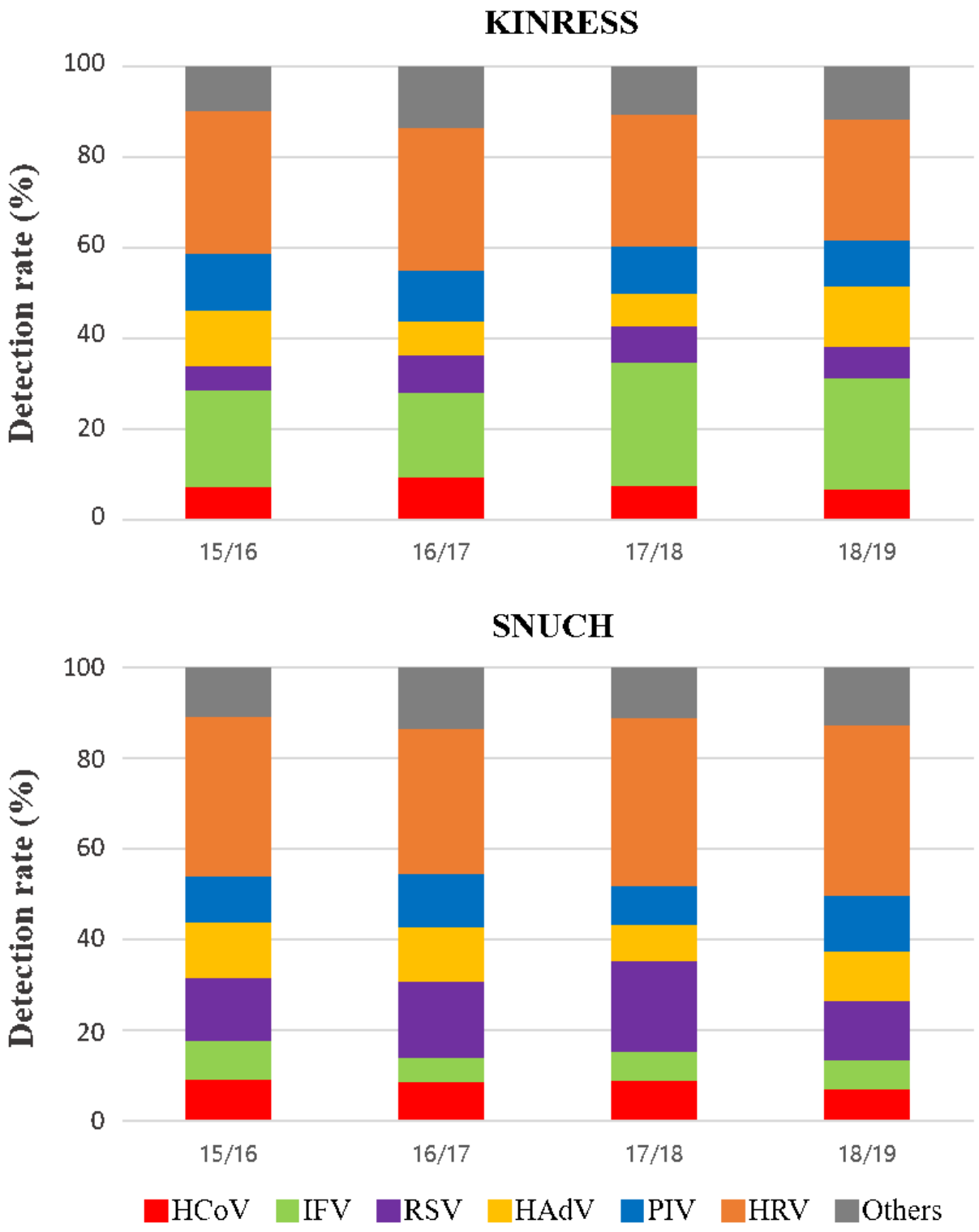

Figure 4

Respiratory viruses identified from KINRESS and SNUCH, 2015-2019. KINRESS; Korea Influenza and Respiratory Viruses Surveillance System, SNUCH; Seoul National University Children's Hospital, HCoV; human coronavirus, IFV; influenza virus, RSV; respiratory syncytial virus, HAdV; human adenovirus, PIV; parainfluenza virus, HRV; human rhinovirus, Others; human metapneumovirus and bocavirus

Supplementary Files

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- Additionalfile1.docx
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