Re-emergence of HMPV in Gwangju, South Korea, After the COVID-19 Pandemic: Impact on Subtypes and Age Distribution

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Article

Re-Emergence of HMPV in Gwangju, South Korea, after the COVID-19 Pandemic: Impact on Subtypes and Age Distribution

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Abstract: The non-pharmaceutical interventions implemented to prevent the spread of COVID-19 have affected the epidemiology of other respiratory viruses. In South Korea, Human metapneumovirus (HMPV) typically occurs from winter to the following spring; however, it was not detected for two years during the COVID-19 pandemic and re-emerged in the fall of 2022, which is a non-epidemic season. To examine the molecular genetic characteristics of HMPV before and after the COVID-19 pandemic, we analyzed 427 HMPV-positive samples collected in the Gwangju area from 2018 to 2022. Among these, 24 samples were subjected to whole-genome sequencing. The results showed a shift in the predominant genotype from A2b2 before the COVID-19 pandemic to A2b1 in 2022. Furthermore, a significant increase in HMPV cases was observed in the 6–10-year age group. Since the onset of the COVID-19 pandemic, social distancing have reduced the possibility of HMPV exposure and herd immunity due to non-transmission, resulting in the introduction of new HMPV genotypes in different seasons.

Keywords: human metapneumovirus; non-pharmaceutical interventions; whole-genome sequencing

1. Introduction

Human metapneumovirus (HMPV) causes respiratory infections in infants and young children (< 5 years old) [1,2]. These infections are like those caused by the human respiratory syncytial virus (HRSV), ranging from upper respiratory distress to bronchiolitis and pneumonia among infants, young children, older adults, and immunocompromised hosts [3–5]. Individuals infected with HMPV do not acquire lifelong immunity to the virus, and reinfection occurs [6–8].

HMPV is a non-segmented single-stranded RNA virus belonging to the family Paramyxoviridae. The HMPV genome is approximately 13 kb long and consists of eight genes that encode nine proteins (N, P, M, F, M2-1, M2-2, SH, G, and L) [9,10]. Depending on the genetic variation in membrane glycoproteins F and G, HMPV can be classified into five genotypes (A1, A2a, A2b, B1, and B2) [9,11]. HMPV genotypes co-circulate during the epidemic season; however, no specific dominant genotypes have been identified [12,13], and the association between the HMPV genotype and disease severity is unclear [14].

Non-pharmaceutical interventions were implemented in response to the global COVID-19 pandemic, and these interventions may affect the circulation of other seasonal respiratory viruses [15,16]. The unusual occurrence of HMPV has been reported in many countries [8,17]. HMPV is

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generally prevalent during winter and spring in the Northern Hemisphere [18]. Similarly, In South Korea, HMPV was prevalent from late winter to spring prior to the COVID-19 pandemic but was not detected during the COVID-19 pandemic in 2020 or 2021, and an out-of-season HMPV outbreak was observed in the fall of 2022.

Understanding the relationship between the irregular occurrence of HMPV and the virus' characteristics is necessary to predict and develop preventive measures against future HMPV epidemic. Therefore, we conducted a comprehensive whole-genome analysis of HMPV before and after the COVID-19 pandemic.

2. Materials and Methods

2.1. Surveillance and sample collection

We participated in a national surveillance network called the Korea Influenza and Respiratory Virus Surveillance System (KINRESS) to monitor Acute Respiratory Infections (ARIs) in South Korea. Throat or nasal swabs were collected from outpatients with ARIs throughout the year from collaborating hospitals in the Gwangju area. These samples were analyzed using real-time RT-PCR to test for respiratory viruses, including HMPVs. A total of 427 HMPV-positive samples were collected from the Gwangju area during 2018–2022.

2.2. Whole genome sequencing

Among the HMPV-positive samples collected before and after the COVID-19 pandemic, 24 with a high viral load were randomly selected. Viral RNA was extracted using a QIAamp Viral RNA Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. A panel was developed using Ion AmpliSeq On-Demand Panel (ThermoFisher Scientific, Carlsbad, CA) technology for use on the Ion Torrent platform (ThermoFisher Scientific, Carlsbad, CA). The customized panel was designed to obtain coverage of the entire HMPV genome using combinations of 100 and 125 primers divided into two sets (pools) according to the manufacturer's protocol. Reverse transcription was performed using a SuperScript VILO cDNA Synthesis Kit (Thermo Fisher Scientific, Carlsbad, CA) following the manufacturer's recommendations. For library preparation, an Ion Ampliseq Library 2.0 Kit (Thermo Fisher Scientific, Carlsbad, CA) was used according to the manufacturer's protocol. The automated Ion Chef (ThermoFisher Scientific, Carlsbad, CA) instrument prepared templates from the 25 μL sample pool using Ion 510/520/530 Chef Kits and Ion 530 Chips that were sequenced using the Ion S5 XL sequencer (ThermoFisher Scientific, Carlsbad, CA). The sequencing reads were mapped and aligned using the torrent-mapping alignment program. After the initial mapping, a variant call was performed using the Torrent Variant Caller.

2.3. Phylogenetic analyses

For the phylogenetic analyses, 53 reference strains were selected from GenBank (Table 1). Multiple sequence alignment was performed using the MUSCLE algorithm in MEGA X software. Phylogenetic trees were constructed using the Maximum Likelihood (ML) method with the General Time Reversible model in MEGA X software. The reliability of the branching order was assessed by performing 1,000 bootstrap replicates.

Table 1. Accession numbers of viruses used as reference for phylogenic analysis of the HMPV-positive samples.

Reference Virus Accession No.	Country/Year
AB503857.1	Japan/2010
AY297748.1	Canada/2003
MK820375.1	China/2018
AY297749.1	Canada/2005
EF535506.1	Taiwan/2010

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GQ153651.1	China/2008
MK588633.1	Kenya/2013
MK588635.1	Zambia/2012
MK588636.1	Kenya/2012
JN184399.1	USA/1999
KC403972.1	USA/1991
KC403973.1	USA/1982
KC403976.1	USA/1983
KC403984.1	Australia/2004
KC562219.1	USA/2005
KC562220.1	USA/2005
KC562221.1	USA/2004
KC562222.1	USA/1997
KC562232.1	USA/2001
KC562235.1	USA/2004
KC562238.1	USA/1996
KC562239.1	USA/1995
KC562241.1	Australia/2003
KF516922.1	Korea/2011
KF530173.1	Australia/2004
KF530179.1	Australia/2003
KJ627383.1	Peru/2008
KJ627414.1	Peru/2010
KJ627419.1	Peru/2011
KJ627432.1	Peru/2009
KJ627433.1	Peru/2012
KJ627435.1	Peru/2009
KU821121.1	China/2012
KY474537.1	USA/2016
MK087726.1	China/2018
MK167039.1	USA/2017
MK588637.1	Kenya/2012
MN306019.1	USA/2018
MN306028.1	USA/2019
MN745086.1	China/2017
MN745087.1	China/2018
AF371337.2	Netherlands/2002
FJ168779.1	Netherlands/2000
AY525843.1	Netherlands/2008
FJ168778.1	Netherlands/1994
MZ851795.1	China/2018
OM262409.1	China/2017
MN745084.1	China/2017
KY474545.1	USA/2016
MW221994.	Australia/2020
MT118705.1	USA/2019
MH828685.1	Vietnam/2014
MF045425.1	USA/2015

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3. Results

3.1. Epidemiology of HMPV

Before the COVID-19 pandemic, human metapneumovirus exhibited a progressive increase from January, reaching its peak in April, followed by a subsequent decline during the summer months. During the COVID-19 pandemic, HMPV infections rarely occurred in 2020, and HMPV was not detected in 2021, coinciding with the implementation of non-pharmacological interventions against COVID-19. In 2022, according to the results of the KINRESS in the Gwangju area, HMPV reappeared in July, and the number of HMPV-positive cases increased in September and October. The HMPV positive rate was significantly higher than that before the COVID-19 pandemic. The seasonal distribution of HMPV infections from 2018 to 2022 is shown in Figure 1. There was a higher detection rate of HMPV in children aged 6 to 10 years old in 2022 than before the COVID-19 pandemic (Table 2).

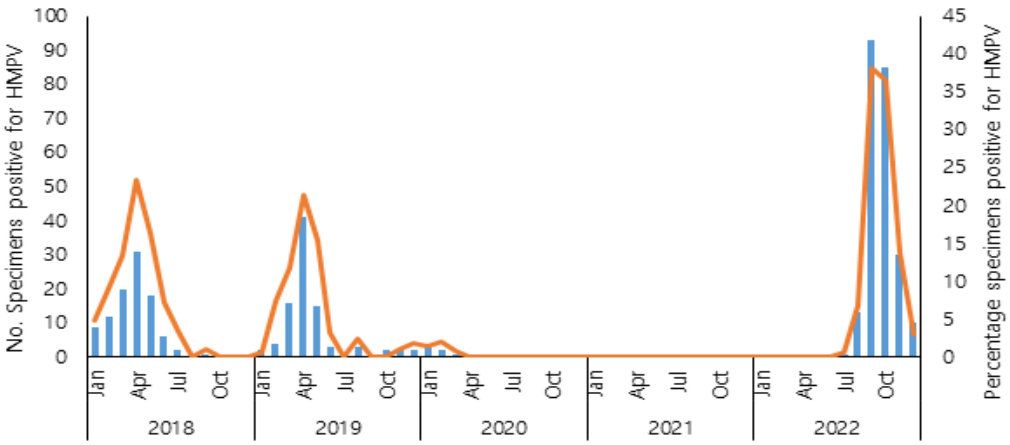

Figure 1. Seasonality pattern of Human metapneumovirus (HMPV) positive cases from 2018 to 2022 in Gwangju, South Korea.

Table 2. Age and sex distribution of HMPV-positive samples from 2018 to 2022 in Gwangju, South Korea.

Variable	2018-2020(n=195)			2022(n=232)			*p*-value[1]
	Number of patients	Number of HMPV positive	Prevalence of HMPV(%)	Number of patients	Number of HMPV positive	Prevalence of HMPV(%)	
Positive rate	4264	195	4.6	2070	232	11.2	< 0.01*
Sex							0.389
Male	1939	86	4.4	985	112	11.4	
Female	2325	109	4.7	1085	120	11.1	
Age							
0-2 years	690	33	4.8	666	65	9.8	< 0.01*
3-5 years	954	77	8.1	481	96	20.0	< 0.01*
6-10 years	705	32	4.5	204	43	21.1	< 0.01*
11-20 years	444	13	2.9	209	10	4.8	0.164
21-40 years	463	6	1.3	194	9	4.6	0.012
41-60 years	451	13	2.9	145	6	4.1	0.305
60-90 years	557	21	3.8	171	3	1.8	0.947

[1] Chi-square test among 2018, 2019, 2020, and 2022. * $p < 0.01$

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3.2. Phylogenetic analysis of HMPV Whole genome sequences

We analyzed 24 whole-genome sequences and 53 reference sequences obtained from GenBank to determine their subtypes. Of the 24 whole-genome sequences, 16 were obtained from strains isolated before the COVID-19 pandemic, and the remaining eight were obtained from strains isolated during the pandemic. Before the pandemic, 15 strains were identified as A2b2 and one as B2. Among the eight strains identified during the pandemic, five were A2b1, and three were B2. A1, A2a, and B1 were not detected in any of the samples analyzed in this study.

Before the COVID-19 pandemic, A2b2 was the predominant circulating strain. However, the HMPV strains that reappeared during the pandemic were identified as A2b1 and B2. The 2022 A2b1 sequences were observed in a monophyletic clade, with one sequence that circulated in the USA in 2016. However, the 2022 B2 sequences were distributed between two closely related strains, one from Australia in 2020 and the other from the USA in 2019, without clade formation.

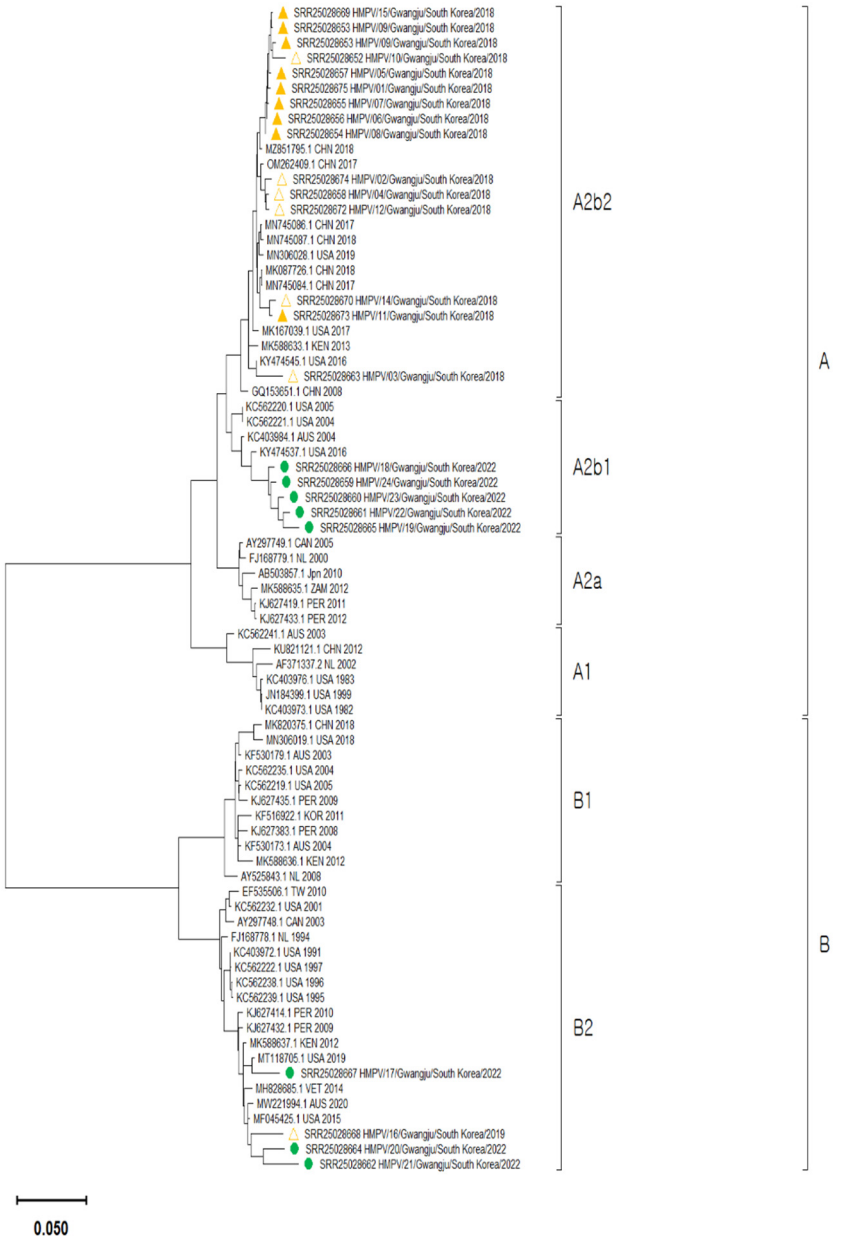

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Figure 2. The phylogenetic tree was constructed based on 77 whole HMPV genome sequences. The tree was created using the maximum likelihood method with a GTR+G+I substitution model and tested with 1000 bootstrap replicates. In the tree, HMPV samples before the pandemic were depicted as triangles. Among them, samples containing a 111-nt duplication in the G gene were indicated with an orange triangles. HMPV samples after the pandemic were represented by green circles. All sequences from this study have been registered in the SRA (Sequence Read Archive) database(accession number: PRJNA987724). Biosample accession numbers of all strains are indicated in parentheses.

4. Discussion

The non-pharmaceutical interventions implemented to prevent COVID-19, such as mandatory mask-wearing, social distancing, and travel restrictions, have affected the prevalence of respiratory viruses [15,16]. Social distancing measures were implemented in South Korea following the first COVID-19 outbreak in January 2020 and relaxed by April 2022. Changes in the prevalence of respiratory viruses were also observed during this period. According to the KIRNESS results, PIV3, which did not occur in 2020, re-emerged in the fall of 2021 [19]. In 2022, HMPV reappeared in the fall, which is typically a non-epidemic season, and the magnitude of the epidemic was larger than that before the COVID-19 pandemic.

This study conducted a whole-genome analysis to investigate the molecular genetic characteristics of HMPV before and after the COVID-19 pandemic. Most HMPV strains that re-emerged in 2022 were of the A2b subtype. Recent studies have suggested classifying A2b into A2b1 and A2b2 based on the presence of 111-nt or 180-nt duplications in the G gene [10]. In 2022, the predominant circulating A2b subtype did not have a G gene duplication, whereas, before the COVID-19 pandemic, the A2b subtype had a 111-nt duplication in the G gene. According to Nao et al., A2b2 was predominant before COVID-19, and A2b1 was responsible for HMPV's re-emergence during the COVID-19 pandemic.

Although some researchers have suggested that the A2b2 subtype is the most virulent, the variation in virulence among HMPV subtypes remains unclear [20,21]. In this study, the A2b1 subtype was responsible for the re-emergence in 2022, and the scale of occurrence was larger than that before the COVID-19 pandemic when the A2b2 subtype was prevalent. This could be due to lower herd immunity to the HMPV virus resulting from reduced exposure during social distancing measures rather than differences in virulence between the subtypes. The clustering of A2b during the pre-COVID-19 and COVID-19 pandemic periods suggests that the re-emergence of HMPV during the pandemic period may not have been a local outbreak.

Additionally, HMPV mainly affects children under five years of age [1,17]. However, during the COVID-19 pandemic, there was a significant increase in the age group of 6–10 years affected by HMPV. An atypical age distribution of acute respiratory viruses during the COVID-19 pandemic has also been observed in RSV [22,23]. This atypical age distribution might be associated with reduced immunity owing to the lack of exposure to HMPV during the COVID-19 pandemic.

In this study, no significant differences were observed in the prevalence of Subtype B2 between before and after the COVID-19 pandemic. However, securing a larger sample size is recommended for future studies. Additionally, it would be beneficial to analyze the clinical symptoms of HMPV in the future. Since its discovery in 2001, research on HMPV has primarily focused on genetic variations in the F and G genes [9,10]. Partial analysis of the F and G genes may limit our understanding of overall virus evolution by overlooking variations in other regions [24]. Whole-genome analysis can overcome these limitations. Therefore, the results of this study, which conducted a whole-genome analysis to investigate the epidemiological trends of HMPV before and after the COVID-19 pandemic, are significant for obtaining genetic information on HMPV in South Korea.

Overall, due to the social distancing measures implemented to prevent the spread of COVID-19, there was a lack of exposure to HMPV, resulting in lower natural immunity to HMPV. With the relaxation of social distancing measures in 2022, HMPV exposure during this period led to an irregular HMPV epidemic in South Korea. This indicates that the COVID-19 pandemic may have

impacted the age and subtype distribution of HMPV, emphasizing the importance of social distancing measures. Strengthening herd immunity is thought to help prevent future epidemics. Therefore, continuous monitoring of HMPV is required for vaccine development and distribution.

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Data Availability Statement: The dataset generated for this study can be found online. All sequences from this study have been registered in the SRA (Sequence Read Archive) database (accession number: PRJNA987724).

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Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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