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Molecular epidemiology of Human Rhinoviruses in children in Hong Kong, 2020-2021

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Abstract

Background COVID-19 related public health and social measures (PHSMs) worldwide have influenced respiratory virus epidemiology. In Hong Kong, paediatric hospitalisations associated with non-COVID-19 respiratory viruses declined in 2020. As PHSMs eased, rhinoviruses/enteroviruses became the primary detected respiratory viruses. This study examines the genetic diversity in resurgent human rhinovirus (HRV) cases. Methods We sequenced rhinovirus/enterovirus samples from children at Queen Mary Hospital, Hong Kong, between August 2020 and October 2021 to estimate changes in HRV genotypes and describe their epidemic characteristics. Whole genome sequencing was performed on the three most prevalent HRV genotypes to infer patterns of virus introduction and persistence. Results Despite reduced respiratory virus circulation, HRV type A and C infections persisted in children, with sporadic detection of HRV B and other respiratory viruses. A resurgence of HRV A cases in November 2020, dominated by genotypes A47 and A101, was observed during the relaxation of PHSMs between the third and fourth waves of COVID-19. Strict PHSMs implemented during the fourth wave, including school closures, substantially reduced respiratory virus circulation, though overall diversity increased due to heightened vigilance. HRV genotype A49 became predominant in May 2021 upon relaxation of control measures, with phylogenetic analysis suggesting persistence of multiple transmission lineages despite strict PHSMs. Genotypes A49 and A47 were frequently associated with upper respiratory tract infections, highlighting their epidemic potential. Conclusion This study underscores the impact of control measures on HRV genetic diversity and highlights the need for continuous surveillance and sequencing to inform public health interventions.

Molecular epidemiology of Human Rhinoviruses in children in Hong Kong, 2020-2021

Running title: Rhinovirus epidemiology in Hong Kong, 2020-2021

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Data Availability Sequences generated in this study are available in NCBI GenBank under accession numbers OR116985 – OR117139.

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Conflict of Interest The authors have no conflict of interest to declare.

Ethical Approval This study was approved by the joint Institutional Review Board of the University of Hong Kong and the Hospital Authority Hong Kong West Cluster Research Ethics Committee.

Patient Consent The need for written consent was waived because testing for respiratory pathogens is standard and routine for all children admitted for an acute respiratory infection.

Author contributions

S.S.C., B.J.C. and V.D. designed the study. E.Y.L.C., L.L.M.P., S.L.L. and S.S.C. conducted clinical surveillance. S.G. performed sequencing and analysed the data. S.G., K.M.E. and D.V. designed the figures and wrote the manuscript with contributions from S.S.C and B.J.C. All authors discussed and approved the manuscript.

Background

COVID-19 related public health and social measures (PHSMs) worldwide have influenced respiratory virus epidemiology. In Hong Kong, paediatric hospitalisations associated with non-COVID-19 respiratory viruses declined in 2020. As PHSMs eased, rhinoviruses/enteroviruses became the primary detected respiratory viruses. This study examines the genetic diversity in resurgent human rhinovirus (HRV) cases.

Methods

We sequenced rhinovirus/enterovirus samples from children at Queen Mary Hospital, Hong Kong, between August 2020 and October 2021 to estimate changes in HRV genotypes and describe their epidemic characteristics. Whole genome sequencing was performed on the three most prevalent HRV genotypes to infer patterns of virus introduction and persistence.

Results

Despite reduced respiratory virus circulation, HRV type A and C infections persisted in children, with sporadic detection of HRV B and other respiratory viruses. A resurgence of HRV A cases in November 2020, dominated by genotypes A47 and A101, was observed during the relaxation of PHSMs between the third and fourth waves of COVID-19. Strict PHSMs implemented during the fourth wave, including school closures, substantially reduced respiratory virus circulation, though overall diversity increased due to heightened vigilance. HRV genotype A49 became predominant in May 2021 upon relaxation of control measures, with phylogenetic analysis suggesting persistence of multiple transmission lineages despite strict PHSMs. Genotypes A49 and A47 were frequently associated with upper respiratory tract infections, highlighting their epidemic potential.

Conclusion

This study underscores the impact of control measures on HRV genetic diversity and highlights the need for continuous surveillance and sequencing to inform public health interventions.

Keywords

Rhinovirus, Molecular Epidemiology, Whole Genome Sequencing, Public Health, Genetic Diversity

Introduction

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Human rhinoviruses (HRV) are highly prevalent worldwide, causing a significant burden of acute respiratory illness and antibiotic use among young children (1, 2). Molecular techniques have identified HRV types A, B, and C, with over 100 distinct genotypes under the genus*Enterovirus* (3, 4, 5, 6, 7, 8). Genotypes frequently cocirculate, and infection with one genotype elicits only low or no cross-protection (9), which poses a challenge for HRV vaccine design. Previous studies suggest that predominant genotypes are varied and often transient (5, 10, 11, 12, 13, 14, 15). However, the lack of HRV sequencing in most regions limits our understanding of individual epidemic patterns, including transmission and pathogenicity, and the mechanisms underlying genotype turnover and persistence.

HRVs cocirculate with other respiratory viruses that vary greatly in their structural, genomic, and antigenic properties. Before the emergence of SARS-CoV-2, influenza, respiratory syncytial virus (RSV), parainfluenza viruses 1-4 (HPIV 1–4), and metapneumovirus (HPMV) were among the most commonly reported respiratory viruses across all age groups, with greater disease burden in young children and older adults. Respiratory virus circulation patterns vary by type and subtype with influenza, RSV and HPIV typically causing winter epidemics in temperate regions (16), with less pronounced seasonality in the tropics and subtropics (17). While the genetic diversity and circulation patterns of many respiratory viruses are not well described, HRV and adenoviruses are known to circulate year-round across all climatic regions, with HRV peaks during autumn/winter (18) and adenovirus peaks during winter/spring (19).

Public health and social measures (PHSMs) enacted against COVID-19 substantially changed person-to-person contact patterns, which profoundly affected the epidemiology and evolution of human respiratory viruses. As a result, significant reductions in the circulation of all common respiratory viruses have been reported globally since the pandemic onset (20, 21, 22, 23, 24, 25), and winter epidemics were notably absent in 2020 and 2021. However, intermittent outbreaks of influenza (26), RSV (27), and HRV (23, 28, 29) have occurred in locations where control measures were relaxed intermittently or completely.

In Hong Kong, seasonal influenza circulation began to subside as early as February 2020 due to behaviour changes and the implementation of PHSMs (22), and circulation remained suppressed until COVID-19 control measures were dropped in early-mid 2023 (30, 31). Paediatric hospitalisations associated with respiratory viruses were reduced by 85%–99% in 2020 (23). When schools reopened late in 2020, paediatric hospitalisation rates increased, mainly due to cases of enterovirus/rhinovirus (23). This surge ultimately resulted in the temporary closure of primary and secondary schools in November 2020 (32). To better understand the effects of PHSMs, we characterise the genetic diversity of HRV detected in paediatric cases in Hong Kong between August 2020 – October 2021.

Methods

Sample collection and pathogen detection

Respiratory samples, including nasopharyngeal swabs and aspirates, throat swabs and/or tracheal aspirates were collected from children admitted to Queen Mary Hospital, Hong Kong for any purpose. The study was approved by the joint Institutional Review Board of the University of Hong Kong and the Hospital Authority Hong Kong West Cluster Research Ethics Committee. The need for written consent was waived because testing for respiratory pathogens is standard and routine for all children admitted for an acute respiratory infection. Specimens were tested by multiplex RT-PCR for influenza A, influenza B, RSV, adenovirus, HPIV 1–4, HMPV, and enterovirus/rhinovirus as described previously (23).

RNA extraction

Viral RNA was extracted with the QIAamp Viral RNA Kit (QIAGEN, Germany) using a starting volume of 140µl of specimen and elution of 60µl of RNA. RNA concentration was assessed using Nanodrop ND-1000 spectrophotometer (Thermo Fisher Scientific, USA).

HRV genotyping

To determine HRV genotypes, the VP4/2 region was amplified using previously described primers (33) with

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PrimeScript One Step RT-PCR Kit (v.2, Takara, Japan). PCR-amplified samples were then sequenced using the Nanopore MinION with the Rapid Barcoding Kit 96 (Oxford Nanopore Technologies, United Kingdom).

The genotype of each sample was determined through phylogenetic analysis based on the rhinovirus VP2/4 region. HRV VP4/2 sequences with collection dates after 2010 were downloaded from NCBI GenBank (https://www.ncbi.nlm.nih.gov/genbank/, accessed 20-09-2022). After the removal of duplicates, VP4/2 sequences were subsampled to include one random representative from each year, country, and genotype. Sequences were aligned using MAFFT (v7.487) (34), and maximum likelihood (ML) trees were constructed using IQ-TREE (v.2.0.3) based on the best-fit nucleotide substitution model (35).

Whole genome sequencing and phylogenetic analysis

Whole genome sequencing was carried out using the same library preparation kit and technology for the three most prevalent genotypes, HRV A47, A49, and A101. Adapters were removed using Porechop (v.0.2.4) (36) and low quality reads were filtered out with Filtlong (v.0.2.1) (37). Raw sequence reads were mapped to reference sequences (GenBank accession numbers KY369890.1, OM001351.1, and KY369891.1) using the Burrows-Wheeler Aligner (BWA) tool (v.0.7.17) (38) and processed using samtools (v.1.15.1) (39). Sequences generated in this study are available in NCBI GenBank (OR116985 – OR117139).

All available whole genome sequences of HRV A47, A49, and A101 were retrieved from GenBank. Sequences were aligned using MAFFT (v7.487) (34), and time-scaled phylogenetic trees were constructed based on sample collection dates using the least square dating (LSD2) (40) method integrated in IQ-TREE (v.2.0.3) with 100 replicates to obtain confidence intervals. Trees were visualized with FigTree (v1.4.4).

Results

Respiratory virus surveillance of paediatric patients admitted to Queen Mary Hospital, Hong Kong between August 2020 – October 2021 identified 215/2,992 (13.9%) patients with real-time RT-PCR positive samples. Positive specimen types included nasopharyngeal swabs (n = 207), nasopharyngeal aspirates (n = 6), combined nasopharyngeal aspirates and throat swabs (n = 1), and a tracheal aspirate (n = 1). Enterovirus/rhinovirus (n = 178, 85%) was most commonly detected, followed by adenovirus (n = 21), RSV (n = 7), HPIV 1 (n = 3), HPIV 4 (n = 5), HPIV 3 (n = 4), HPIV 2 (n = 1), human coronavirus 229E (n = 2), influenza A (n = 1), human coronavirus HKU-1 (n = 1), and HPMV (n = 1) (**Figure 1a**). Seven samples were coinfected with two or more respiratory viruses (**Table 1**). The median age of children that tested positive for any respiratory virus was two years (range: 24 days to 15 years). Upper respiratory tract infection (URTI) was reported at time of sample collection for 47 of the 215 patients that tested positive (median age: 2 years old; range: 24 days to 15 years). Most URTI cases were positive for enterovirus/rhinovirus (41/47, 87%), and the majority of these cases occurred among children between the ages of one and six.

Respiratory virus detections increased rapidly as schools fully reopened in late 2020, peaking at 35 cases per month during November, as reported previously (23), followed by a rapid decline in cases from December 2020 – April 2021 (**Figure 1a**). The decline coincides with the fourth wave of COVID-19 infections in Hong Kong (41) and territory-wide school dismissals (**Figure 1a**). Following the relaxation of those control measures in the Spring of 2021, cases surged and remained elevated through October 2021. Increases in respiratory virus detection were predominantly associated with increases in enterovirus/rhinovirus. However, a greater viral diversity was captured between February – April 2021 compared to other periods, including cases of human coronaviruses HKU-1 and 229E, HPMV, RSV B, and HPIV 1–4. When face-to-face teaching resumed in March 2021, the number and diversity of viruses detected further increased (**Figure 1a**).

HRV VP4/2 gene sequencing identified HRV A (n = 98), B (n = 7) and C (n = 50), while the remaining enterovirus/rhinovirus PCR positive samples (n = 23) could not be sequenced (**Figure 1b**). Genotyping revealed that while HRV A caused the spike in November 2020, both HRV A and C were predominantly circulating since May 2021. Maximum likelihood phylogenetic analysis identified 19 independent genotypes, with strong genetic clustering within each of the genotypes in Hong Kong (**Figure 2**). The largest clusters of HRV A genotypes were A49 (n = 27), A47 (n = 26), and A101 (n = 21). A49 was detected throughout

the study, except from December 2020 to February 2021, with a peak of 13 cases in May 2021 (**Figure 1b**). A47 was detected up to December 2020, and A101 was detected in Autumn 2020 and 2021. Both A47 and A101 peaked in November 2020, with 22 and 11 cases respectively (**Figure 1b**). The most diverse circulation of HRV genotypes was observed in the summer of 2021, with 11 genotypes in cocirculation.

Phylogenetic analysis showed that the dominant genotypes detected in our study shared close relationships with viruses collected from Thailand in 2020 and USA in 2021. HRV A49 and A101 shared close relationships with samples from USA in 2021. HRV A19 formed two monophyletic clades, each forming a sister clade with 2020 samples from Thailand. The A47 sequences clustered within a clade that included sequences from USA in 2021, Thailand in 2020, and Malaysia in 2018. HRV C8 and C27 sequences were most closely related to samples collected from Thailand in 2018 and USA in 2021 respectively.

Whole Genome Sequencing of Rhinovirus A49, A47, and A101

To deduce the evolution and circulation patterns of HRV detected in Hong Kong during 2020 – 2021, we sequenced the whole genomes of the three most predominant genotypes (A49, A47, A101) and performed phylogenetic analysis with all publicly available whole genomes from these genotypes in NCBI GenBank. The time of most recent common ancestor (tMRCA) of A49 was 1972 (95% CI: 1940, 1985); the tMRCA of A47 was 1980 (95% CI: 1955, 1985); and the tMRCA of A101 was 1978 (95% CI: 1968, 1986).

Sequenced genomes in Hong Kong revealed six independent transmission lineages (**Figure 3**). Genotype A49, detected during 2020 and 2021, formed two lineages. Except the two A49 viruses detected in 2021 that clustered independently, the rest formed a single lineage with a tMRCA estimated around early 2020. The diversifying pattern of this lineage suggests multiple transmission chains in Hong Kong during 2020 to 2021. In contrast, all 26 A47 genomes, collected during October to December 2020, were highly similar, with a tMRCA just prior to their detection in 2020. The A101 genotype viruses formed three clusters, two of which were detected from October to December 2020 (n = 14 and n = 3) and the other from September to October 2021 (n = 4). While genomes of the two smaller clusters were highly similar, the diversity of the larger cluster dates back to a tMRCA of late 2019. (**Figure 3**).

While no significant correlation was found between HRV genotype and age, most patients presenting with URTIs were positive for HRV A, specifically genotypes A47 (n = 9) and A49 (n = 8). Respiratory symptoms and/or fever were reported in 96% (26/27) of genotype A49 cases; 81% (21/26) of genotype A47 cases; and 57% (12/21) of genotype A101 cases (**Table 2**).

Conclusions

PHSMs to mitigate the COVID-19 pandemic have greatly impacted the epidemiology and evolution of respiratory viruses worldwide. This study aimed to investigate the impact of PHSMs on the genetic diversity of respiratory viruses detected in paediatric surveillance in Hong Kong from August 2020 to October 2021. The majority of HRV infections were type A, followed by C. HRV type B was rare, and the detection of other respiratory viruses was sporadic (**Figure 1a**). Despite reduced circulation under strict PHSMs, the overall diversity of respiratory viruses increased, possibly due to changes in healthcare-seeking behaviour or heightened vigilance. As control measures were relaxed, HRV infections surged, similar to trends reported for RSV and influenza in other regions (27, 42).

Between the third and fourth waves of COVID-19 in Hong Kong, from September to November 2020, PHSMs were relaxed. During this time, Hong Kong saw a resurgence of HRV A cases predominated by A47 and A101 genotypes (41). These two genotypes were also reportedly predominant in Shanghai in 2020 (43). Strict containment measures applied during wave four caused a genetic bottleneck that eliminated three circulating lineages of A47 and A101. Though A47 and A101 were not subsequently detected in our study, a resurgence of genotype A49 occurred after face-to-face teaching resumed in March 2021 (**Figure 1,3**). During the summer of 2021, HRV cases again increased following the relaxation of PHSMs. Phylogenetic analysis indicates that the few A49 genotype viruses detected in September 2020 persisted between epidemic waves despite strict PHSMs to cause the March–July 2021 outbreak, which peaked in May.

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In Hong Kong, the rise and fall of paediatric HRV cases were mainly associated with the suspension and resumption of face-to-face teaching (**Figure 1**). However, it is important to note that despite schools reopening, other PHSMs remained in place including mandatory face masks, reduced school hours, and socially-distanced seating (44). HRV cases rebounded as classes resumed despite social distancing precautions, whereas other respiratory viruses did not immediately return. Notably, it has previously been reported that face masks are not as effective in deflecting HRV in exhaled breath (45), and HRV has been found to remain stable on surfaces and exhibit resistance to ethanol and non-ionic detergents (46, 47). Taken together with the relatively less-conscientious hand hygiene of children, HRV may be less sensitive to COVID-19-related PMSHs.

Since the onset of the COVID-19 pandemic, HRV has been the second most widely reported respiratory virus, second only to SARS-CoV-2. Recent studies in the USA have shown that HRV continued to circulate throughout the COVID-19 pandemic (2), and despite enhanced hospital control and public health measures, cases continued to be identified at a higher than historical rate (48). Another study reported widespread and diverse HRV infections in homeless shelters, though no single genotype persisted for more than a few months (49). The cocirculation and alternate dominance of HRV A and C is consistent with studies in Hong Kong and around the world (4, 10, 43, 50, 51, 52, 53), and notably, a number of respiratory virus lineages, mostly HRV C, were detected through the end of our study.

While Hong Kong sequences within the same genotypes grouped together phylogenetically, some genotypes formed one or more clusters of their own within the group, which reveals the possibility of multiple transmission lineages and multiple introductions of the same genotype during the study period. Moreover, as COVID-19 drastically reduced international travel to and from Hong Kong during this study period, endemic circulation of these genotypes could not be ruled out. Other HRV genotypes sequenced in this study were genetically distinct from the limited number of available HRV sequences available in GenBank (Supplementary Tables 1-6). Analysis of these sequences was limited as some genotypes had less than 10 whole genomes available for comparison, and most sequences originated from USA.

HRV A49 and A47 were most frequently associated with URTI in this study, with 96% of A49 and 81% of A47 cases reporting respiratory symptoms and/or fever (Table 2). These genotypes are among those most associated with severe illness and hospitalization (3, 43). Although the small sample size precludes a clear correlation between the genotypes and clinical illness, these genotypes demonstrate epidemic potential and warrant further surveillance. While gastrointestinal symptoms were commonly observed among patients with HRV infections (Table 1), it should be noted that these samples were only screened for respiratory viruses, thus gastrointestinal symptoms could be attributable to coinfection with non-respiratory viruses or bacteria.

This study provides insights into the genetic diversity of HRV detected in paediatric cases hospitalized in Hong Kong during the COVID-19 pandemic. Despite reduced respiratory virus circulation, HRV remained prevalent, particularly HRV A and C. The implementation of PHSMs significantly affected the genetic diversity of HRV, as evidenced by the surge of A47 and A101 in November and A49 in May 2021 during relaxation of control measures. It is not clear if immunity towards HRV waned during this period, and although no correlation was found between HRV genotype and patient age, most symptomatic infections were caused by HRV A. These findings emphasize the importance of continued respiratory virus surveillance and HRV sequencing to improve our understanding of HRV transmission and inform effective public health measures.

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Tables

Table 1 . Demographics and clinical presentation of respiratory virus positive patients.

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Virus+	EV/RV	Adeno

Virus+	EV/RV	Adeno
n positive	178	21
Patient demographics	Patient demographics	Patient demograph
Median age in years (range)	2(0-15)	2(0-5)
Sex (M, F)	106, 72	11, 10
Clinical symptoms and syndromes reported (n,%)	Clinical symptoms and syndromes reported (n,%)	Clinical symptoms
Fever	84(47)	14(67)
Respiratory Symptoms	112(63)	8(38)
Diarrhoea	5(3)	1(5)
Gastric	18(10)	5(24)
Rash	10(6)	3(14)
URTI	41(23)	3(14)

+Abbreviations: EV/RV, enterovirus/rhinovirus; Adeno, adenovirus; RSV, respiratory syncytial virus; HPIV-1, human parainfluenza virus 1; HPIV-2, human parainfluenza virus 2; HPIV-3, human parainfluenza virus 3; HPIV-4, human parainfluenza virus 4; 229E, human coronavirus 229E; HKU-1, human coronavirus HKU1; HMPV, human metapneumovirus.

Table 2 . Number and percentage of rhinovirus-positive patients reporting clinical symptoms and syndromes.

		Clinical symptoms n(%)	Clinical symptoms n(%)	Clinical symptoms n(%)	Clinical symptoms
Genotype	n positive	Fever	Respiratory Symptoms	Diarrhoea	Gastric
A49	27	19(70)	26(96)	1(4)	3(11)
A47	26	13(50)	20(77)	0(0)	2(8)
A101	21	9(43)	12(57)	0(0)	3(14)
A19	15	3(20)	6(40)	1(7)	2(13)
A89	6	4(67)	1(17)	0(0)	1(17)
A13	1	0(0)	1(100)	0(0)	0(0)
A80	1	0(0)	0(0)	0(0)	0(0)
A28	1	1(100)	0(0)	0(0)	0(0)
B83	4	1(25)	0(0)	0(0)	3(75)
B72	3	2(67)	2(67)	0(0)	0(0)
C8	18	10(56)	12(67)	1(6)	0(0)
C27	16	6(38)	7(44)	1(6)	1(6)
C42	5	3(60)	4(80)	0(0)	0(0)
C24	5	3(60)	4(80)	0(0)	1(20)
C35	2	1(50)	2(100)	0(0)	1(50)
C56	1	0(0)	0(0)	0(0)	0(0)
C26	1	1(100)	1(100)	0(0)	0(0)
C51	1	0(0)	1(100)	0(0)	0(0)
C36	1	0(0)	1(100)	0(0)	0(0)

Figure Legends

Figure 1. Respiratory viruses detected from September 2020 to October 2021, shown by virus (a) and rhinovirus genotype (b). Changes in COVID-19-related public health and social measures during this period are labelled in (a). *Strict social measures to mitigate COVID-19 from January 2021 included tightening of

social distancing measures, restrictions on gatherings and dining, and closure of leisure venues. Quarantine of inbound travellers was also extended from 14 to 21 days. HMPV, human metapneumovirus; HCoV-HKU1, human coronavirus HKU-1; HCoV-229E, human coronavirus 229E; HPIV 1-4, human parainfluenza viruses 1-4; RSV, respiratory syncytial virus.

Figure 2. Rhinovirus genetic diversity detected in paediatric samples in Hong Kong during September 2020 – October 2021. Maximum likelihood trees show phylogenetic relationships of the VP4/2 genes. Phylogenetic tips in red represent samples from this study, labelled by genotype and number of positive samples.

Figure 3. Time-scaled phylogenetic trees of the three most prevalent rhinovirus genotypes circulating in Hong Kong during the study period. Grey bars at nodes indicate 95% CIs of the estimated time to most recent common ancestor (tMRCA).

Supplementary Information

Supplementary Table 1. Global distribution of HRV-A genotypes based on VP4/2 sequences available in NCBI GenBank (https://www.ncbi.nlm.nih.gov/genbank/, accessed 09-05-2023).

Supplementary Table 2. Global distribution of HRV-A genotypes based on whole genome sequences available in NCBI GenBank (https://www.ncbi.nlm.nih.gov/genbank/, accessed 09-05-2023).

Supplementary Table 3. Global distribution of HRV-B genotypes based on VP4/2 sequences available in NCBI GenBank (https://www.ncbi.nlm.nih.gov/genbank/, accessed 09-05-2023).

Supplementary Table 4. Global distribution of HRV-B genotypes based on whole genome sequences available in NCBI GenBank (https://www.ncbi.nlm.nih.gov/genbank/, accessed 09-05-2023).

Supplementary Table 5. Global distribution of HRV-C genotypes based on VP4/2 sequences available in NCBI GenBank (https://www.ncbi.nlm.nih.gov/genbank/, accessed 09-05-2023).

Supplementary Table 6. Global distribution of HRV-C genotypes based on whole genome sequences available in NCBI GenBank (https://www.ncbi.nlm.nih.gov/genbank/, accessed 09-05-2023).

Supplementary Figure S1. Temporal trends of major HRV-A genotypes and others based on VP4/2 regions and whole genome sequences available on GenBank.

Supplementary Figure S2. Temporal trends of major HRV-B genotypes and others based on VP4/2 regions and whole genome sequences available on NCBI GenBank.

Supplementary Figure S3. Temporal trends of major HRV-C genotypes and others based on VP4/2 regions and whole genome sequences available on NCBI GenBank.

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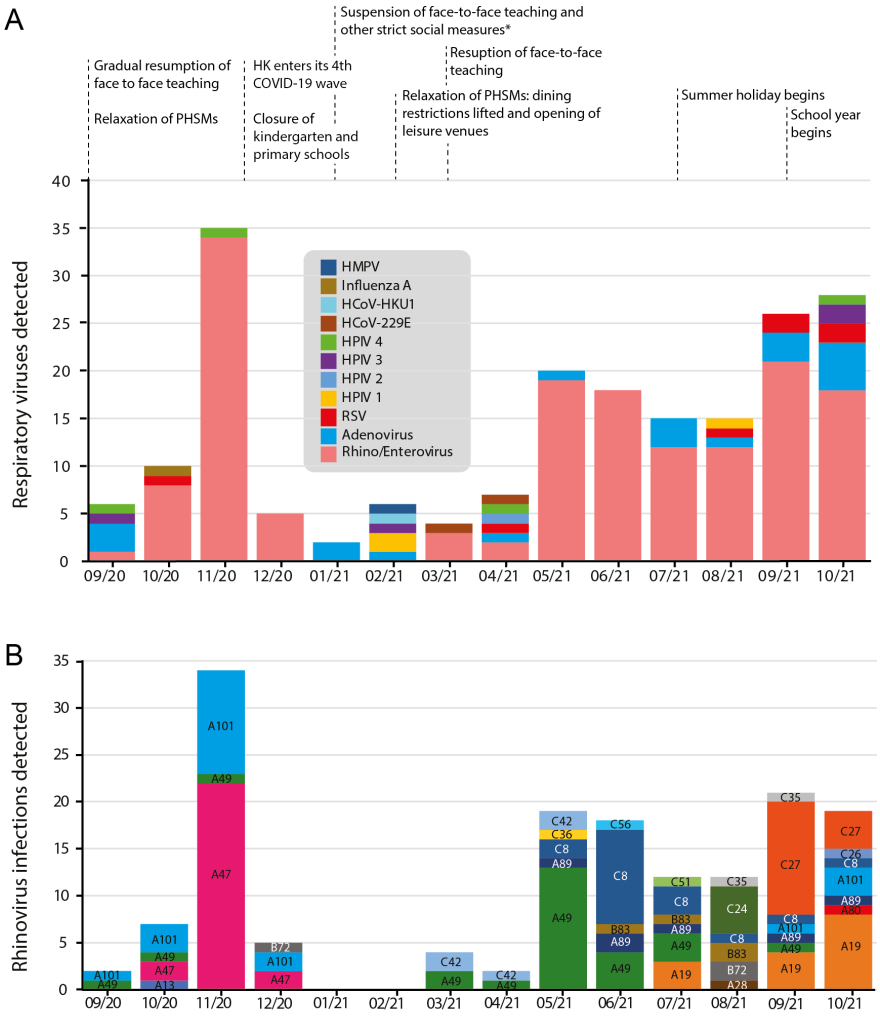

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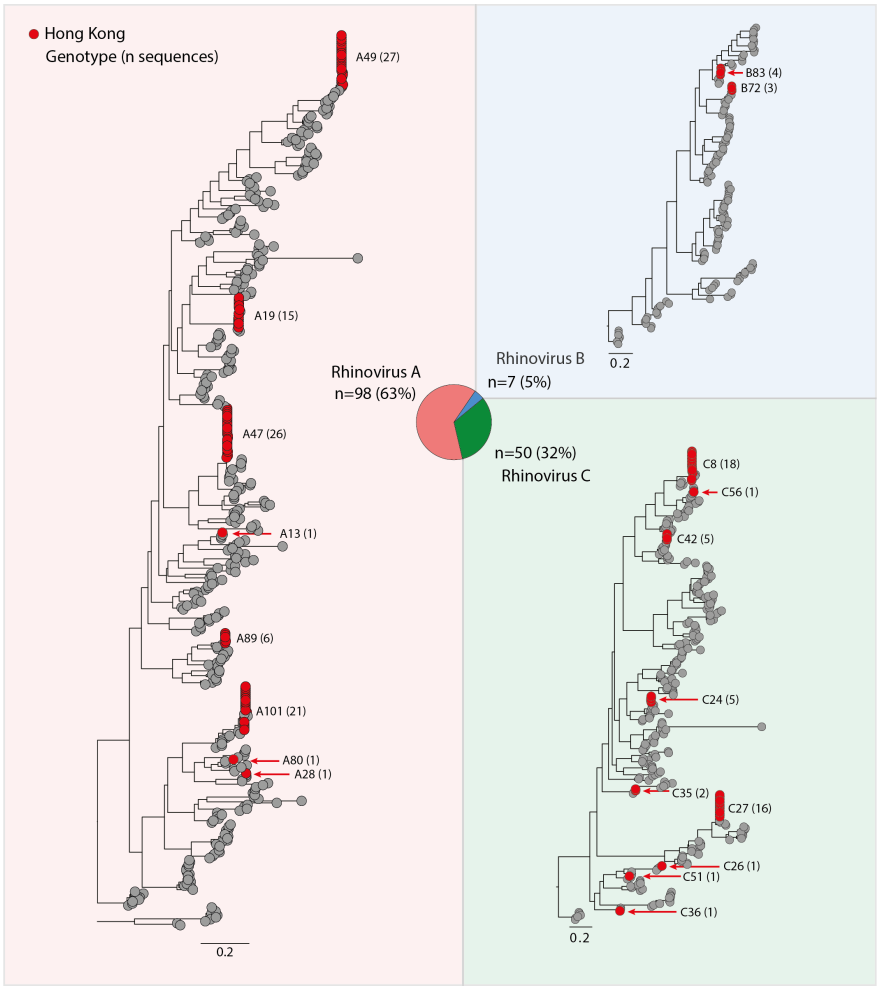

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