Rapid spread of SARS-CoV-2 Omicron subvariant BA.2 in a single-source community outbreak

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Summary: Using epidemiological and whole viral genome data, we demonstrated a single-source outbreak of Omicron variant sublineage BA.2 with a short doubling time in Hong Kong. This study highlighted the high transmissibility of BA.2 despite stringent prevention measures.

ABSTRACT

Background

The SARS-CoV-2 Omicron variant BA.2 sublineage has increased rapidly in Europe and Asia since January 2022. Here, we report the epidemiological and genomic analysis of a large single source BA.2 outbreak in a housing estate.

Methods

We analyzed the epidemiological information of a community outbreak of BA.2 (STY outbreak). We performed whole viral genome sequencing using the Oxford Nanopore MinION device. We calculated the doubling time of the outbreak within a housing estate.

Results

The STY outbreak involved a total of 768 individuals as of 5th February 2022, including 432 residents, visitors or staff (56.3%) from a single housing estate (KC Estate). The outbreak at the KC Estate has a short doubling time of 1.28 days (95% confidence interval: 0.560-1.935). The outbreak was promptly controlled with the lockdown of 3 buildings within the housing estate. Whole genome sequencing was performed for 133 patients in the STY outbreak, including 106 residents of the KC Estate. All 133 sequences from the STY outbreak belonged to the BA.2 sublineage, and phylogenetic analysis showed that these sequences cluster together. All individuals in the STY cluster had the unique mutation C12525T.

Conclusions

Our study highlights the exceptionally high transmissibility of the Omicron variant BA.2 sublineage in Hong Kong where stringent measures are implemented as part of the elimination strategy. Continual genomic surveillance is crucial in monitoring the emergence of epidemiologically important Omicron sub-variants.

Keywords: COVID-19, SARS-CoV-2 Omicron variant, BA.2, community outbreak, housing estate

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first emerged in humans in late 2019. Efficient person-to-person transmission was demonstrated soon after emergence [1]. During global circulation, SARS-CoV-2 has evolved into different lineages with increasing fitness in humans. The World Health Organization has now designated 5 variants as Variants of Concern (VOCs), including the Alpha, Beta, Gamma, Delta and the Omicron variants. Among VOCs, the Omicron variant is particularly worrisome as it transmits efficiently and has a short doubling time [2]. The Omicron variant consists of three phylogenetically related sublineages (BA.1, BA.2 and BA.3) but with very different spike protein sequences. BA.1 is the dominant sublineage worldwide, and most epidemiological, clinical or virological studies on the Omicron variant were based on this sublineage. BA.1 carries 15 amino acid mutations in the spike protein receptor binding domain. Neutralizing antibody assays showed that BA.1 can partially evade serum neutralizing activity of COVID-19 vaccine recipients or COVID-19 convalescents with infection due to ancestral virus, or with Alpha, Beta or Delta variants [3-6]. BA.1.1, a sublineage of BA.1 with the spike protein R346K mutation, is similar to BA.1 in terms of the neutralizing susceptibility [4]. *In vitro* and *in vivo* studies showed that the Omicron variant was less dependent on the serine protease TMPRSS2, and replicated well in upper respiratory tract but poorly in the lower respiratory tract [7, 8].

In January 2022, there was a rapid surge in the proportion of BA.2 globally [9, 10]. A household study from Denmark showed that BA.2 is associated with a higher secondary attack rate and an increased susceptibility of infection in both unvaccinated and vaccinated individuals compared to BA.1 [11].

Imported cases of the Omicron variant BA.1 were first detected in Hong Kong in mid-November 2021 [12]. Limited local transmission of BA.1 occurred at the end of

December 2021. However, by January 2022, BA.2 had spread rapidly in Hong Kong. In a single cluster (Silka Seaview Hotel/Tung Moon House/Yat Kwai House-related cluster [STY cluster]) originating from an imported case, a total of 768 cases were reported within a period of 4 weeks [13], including 432 residents, visitors or staff (56%) a public housing estate (Kwai Chung Estate [KC Estate]). Here, we conducted an epidemiological and genomic analysis of the outbreak, and confirmed that this is a single-source outbreak with an extremely short doubling time.

METHODS

Epidemiological data of the STY cluster

The epidemiological information of STY cluster were retrieved from the Centre for Health Protection, Department of Health [14], or from press release of the Hong Kong SAR government [15].

Whole genome sequencing and bioinformatics analysis

We performed whole genome sequencing for a total of 438 patients from 2nd November 2021 to 2nd February 2022. These patients were admitted to Queen Mary Hospital, North Lantau Hospital Hong Kong Infection Control Centre or Princess Margaret Hospital in Hong Kong. All patients tested positive by SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) in the respective hospitals and were confirmed at the Public Health Laboratory Centre of Hong Kong. Patients were excluded if the volume of combined nasopharyngeal-throat swab or saliva specimens were not sufficient for whole genome sequencing. For patients in the STY cluster, we have sequenced all specimens that we have received as of 5th February 2022 and successfully sequenced at the time when we submitted our manuscript. The study has been approved by the Institutional Review Board of the

University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 13-265, UW 21-313, UW 21-214), the Hospital Authority Hong Kong Kowloon West Cluster (KW/EX-21-151[165-01], KW/FR-20-086[148-10]). Written informed consent was waived since archived specimens were used.

Whole genome sequencing was performed using the Oxford Nanopore MinION device (Oxford Nanopore Technologies) as we described previously [4]. For the determination of viral lineage, nanopore sequencing was performed following the Nanopore protocol - PCR tiling of COVID-19 (Version: PTC_9096_v109_revH_06Feb2020) according to the manufacturer's instructions with minor modifications (Oxford Nanopore Technologies) as we described previously [16, 17]. Briefly, extracted RNA was first reverse transcribed to cDNA using SuperScript^{TM} IV reverse transcriptase (ThermoFisher Scientific, Waltham, MA, USA). PCR amplification was then performed using the hCoV-2019/nCoV-2019 Version 3 Amplicon Set (Integrated DNA Technologies, Coralville, IA, USA) with the Q5® Hot Start High-Fidelity 2X Master Mix kit (New England Biolabs, Ipswich, Massachusetts, United States) according to the Nanopore protocol. PCR products were purified using 1x AMPure XP beads (Beckman Coulter, Brea, CA, USA) and quantified using Qubit dsDNA HS Assay Kit (Thermo Fisher Scientific, Waltham, Massachusetts, United States). The purified DNA was then normalized for end-prep and native barcode ligation reactions according to the PCR tiling of COVID-19 virus protocol with Native Barcoding Expansion 96 (EXP-NBD196, Oxford Nanopore Technologies). Barcoded libraries were then pooled, purified with 0.4x AMPure XP beads and then quantified using Qubit dsDNA HS Assay Kit. Purified pooled libraries were ligated to sequencing adapters and sequenced with the Oxford Nanopore MinION device using R9.4.1 flow cells for 24-48 hours.

For bioinformatics analysis, the recommended ARTIC bioinformatics workflow was used with minor modifications applied as described previously [16, 17]. The modifications

include reducing the minimum length at the guppyplex step to 350 to allow potential small deletions to be detected and increasing the "–normalise" value to 999999 to incorporate all the sequenced reads and the high accurate mode was used for basecalling with an increased QC passing score from 7 to 10. The sequence NC_045512.2 obtained from NCBI was used as the reference and the alignment files produced by Medaka were inspected using Integrative Genomics Viewer (IGV) to verify the mutations called by the ARTIC pipeline. SARS-CoV-2 lineage were assigned using the PANGOLIN software suite [18]. All sequences are deposited onto the GISAID database (Supplementary Table S1)

Phylogenetic analysis

The sequences were aligned using MAFFT. For Figure 3A, the whole genome phylogenetic tree was constructed using the Nextclade tool (v1.13.1) [19]. The tree was visualized and exported using the online tool www.auspice.us. For Figure 3B, a maximum-likelihood whole genome phylogenetic tree was constructed using IQ-TREE2. The option -czb was used to mask any unrelated substructures of the tree, with branch length representing a mutation count of <1. The ultrafast bootstrap option was used with 1,000 replicates. The tree was annotated and visualized using FigTree.

Statistical analysis

The doubling time of the outbreak was determined according to the formula,

$$T_d = t\frac{\ln(2)}{\ln\left(\frac{N_t}{N_0}\right)}$$

Where

T_d = Doubling time

t = Time interval considered

N_t = Number of cases at the end of the time interval

N_0 = Number of cases at the start of the time interval

For the purpose of calculating the doubling time at the KC Estate, t was taken as the time interval between the date of the lockdown (21st January 2022) and the date when Patient 4 visited KC Estate. Confidence interval on the doubling time was calculated via parametric bootstrapping (10000 bootstraps), assuming the doubling time as draws from a Poisson distribution as described [20].

RESULTS

Epidemiological analysis of the STY outbreak

The index cases (Patient 1 and 2) were travelers returning to Hong Kong on 4th January 2022 and stayed in the same room at a quarantine hotel (Figure 1). They tested positive for SARS-CoV-2 by RT-PCR on 6th and 9th January 2022, respectively, during the quarantine period. Patient 3 was a traveler who stayed at the room next to the index cases in the same quarantine hotel, who tested positive for SARS-CoV-2 on 14th January, 4 days after the end of the quarantine period. Epidemiological investigation suggested that Patient 3 was infected while staying at the quarantine hotel. Patient 3 then transmitted the virus to her husband (Patient 4), who visited KC Estate, a public housing estate, on 13th January 2022. KC Estate comprises of 16 residential buildings with a population of 35,100. Patients 1, 2, and 3 have received two doses of COVID-19 vaccine, while Patient 4 was not vaccinated. On 18th January, a resident at one of the buildings (Yat Kwai House) within KC Estate tested positive. The Hong Kong SAR government imposed compulsory testing for all residents of Yat Kwai House on 20th January, which revealed another 16 infected cases in 12 households, located at 11 different floors at Yat Kwai House. Yat Kwai House was locked down for a total of 7 days from 21st January and all residents were subjected to daily testing.

Subsequently, the second (Ying Kwai House) and third (Ha Kwai House) residential buildings of KC Estate were also lockdown on 22nd January and 25th January 2022, respectively, for outbreak control, while the remaining 13 residential buildings were subjected to compulsory testing.

The number of cases peaked 2 days after the lockdown, and the outbreak at KC Estate gradually subsided (Figure 2). As of 5th February 2022, a total of 432 cases related to KC Estate tested positive for SARS-CoV-2 by RT-PCR, including 280 cases in Yat Kwai House, 95 cases from Ying Kwai House, and 17 cases from Ha Kwai House. The remaining 40 cases of KC Estate were distributed in another 10 residential buildings. Out of these 432 cases, 429 were residents, 2 were visitors, while 1 was a security guard. The doubling time of the KC Estate outbreak, estimated based on the symptom onset date (or report date if asymptomatic), was 1.28 days (95% confidence interval 0.560-1.935). Among these 432 residents, visitors or staff from KC Estate, the median age was 45 years (range 1 month to 90 years); 53.9% (233/432) were female, and 46.3% (200/432) had received at least one dose of COVID-19 vaccine. Apart from these 432 patients at KC Estate, Patient 3 and Patient 4, another 332 cases epidemiologically related to the index cases were identified in 16 out of 18 districts in Hong Kong (Supplementary Figure S1).

Whole genome phylogenetic analysis

Whole genome sequencing was successful for a total of 438 specimens collected between 2nd November 2021 and 2nd February 2022. Phylogenetic analysis showed that 326 sequences belonged to Omicron variant, including 171 and 155 belonging to PANGO lineage BA.1/BA.1.1 and BA.2 respectively (Figure 3A).

Among the 155 patients infected with BA.2, 133 were within the STY cluster, including 106 residents of the KC Estate. Hence, we have performed whole genome

sequencing for 17.3% (133/768) of the patients in the STY cluster and 24.5% (106/432) patients at the KC Estate. Phylogenetic analysis showed that all local cases clustered together (Figure 3B), but phylogenetically distinct from other imported cases. Among the 106 residents of KC Estate, 102 (96.2%) had the unique mutations T10696C (synonymous) and C12525T (NSP8 T145I), while 4 (3.8%) only had C12525T but not T10696C (Figure 3C).

DISCUSSION

Due to the increasing proportion of BA.2 globally, the World Health Organization has suggested to compare the transmissibility, immune escape properties and virulence between BA.1 and BA.2 as a priority [21]. In this study, we demonstrated a very short doubling time of 1.28 days in a BA.2 outbreak in a housing estate in Hong Kong, which is shorter than the doubling time of 1.6-2.5 days in England and 2.8 days in the Gauteng Province of South Africa before January 2022, when BA.1 dominated [22, 23]. Yin *et al* showed enhanced binding of BA.1 spike protein to human ACE2, and the mutations S477N, Q493R, Q496S and N501Y form new interaction with the human ACE2 [24]. BA.2 also contains the S477N and Q439R mutations, but lacks Q496S and N501Y (Supplementary Table S2). Within the RBD, BA.2 contains several mutations that are not present in BA.1, including T376A, D405N, and R408S. Whether these mutations affect binding to human ACE2 receptors remain to be determined.

In the KC Estate outbreak which involved 1.2% of the residents as of 5th February 2022, 46.3% of the patients were vaccinated, suggesting that vaccine breakthrough infection is common for BA.2. This is consistent with previous studies that vaccine serum neutralizing activity is much reduced for the Omicron variant compared to ancestral virus in both children and adults [4, 5, 25]. However, it should be noted that despite the poor neutralizing activity, the vaccine effectiveness against severe disease due to Omicron variant within the first 3

months after the primary series still ranged from 70-74% for mRNA vaccines [26]. In Hong Kong, as all patients, even if asymptomatic, are hospitalized, we were not able to determine and compare the severity of infection using hospital admission data.

The KC Estate outbreak was only stopped after aggressive testing and lockdown were implemented. It is the first time to lockdown a public housing estate in Hong Kong to control COVID-19 outbreaks. In fact, our practice of universal masking and hand hygiene were able to minimize the number of infected cases in the community [27]. However, this outbreak illustrates that the implementation of contact and droplet precautions may be insufficient to control the spread of BA.2. The rapid rise in the number of cases, coupled with a short doubling time, suggests the possibility of airborne transmission, similar to BA.1 [16]. The original source of the KC Estate outbreak can be traced to the transmission of BA.2 between travelers living in the adjacent rooms of the quarantine hotel. While the mode of airborne transmission in the quarantine hotel could be postulated by the demonstration smoke test [12, 28], the mechanism of explosive outbreak in KC Estate deserves further investigation.

In areas with high prevalence of COVID-19, outbreaks are usually attributed to multiple sources. However, our current outbreak can be traced to a single source, which was supported by whole genome data analysis. This provides a unique opportunity to pinpoint the exact date when the virus was introduced into the housing estate. With the input of genomic data, the epidemiological relatedness of infected cases could be ascertained. This allows an accurate determination of the doubling time within a single source outbreak.

There are several limitations in this study. First, we have not sequenced specimens from all patients within the SYT cluster. Hence, we cannot exclude the possibility that a minority of cases in this outbreak were related to non-BA.2 strains. Second, as the buildings in KC Estate underwent lockdown on 21st January 2022, we could only estimate the doubling time of the KC Estate outbreak with data spanning over 1 week. Third, we do not have a

BA.1 control group as the BA.1 local outbreak in Hong Kong involved much fewer people. Fourth, non-viral factors can affect the doubling time. We have calculated the doubling time based on a single outbreak in a housing estate, which can be different from the doubling time at the population level. The high density in these high-rise buildings would facilitate the rapid spread of SARS-CoV-2 via contact, droplet and airborne routes. Furthermore, the population immunity against the Omicron variant is likely very low because of the low incidence of prior natural infection and a relatively low vaccination uptake rate in among the cohort in KC Estate.

Before this outbreak, the incidence of COVID-19 in Hong Kong has been kept at a low level as a result of a comprehensive elimination strategy, including universal masking, widespread diagnostic testing, aggressive contact tracing with quarantine of close contacts, and restriction measures for incoming travelers [29]. Since the implementation of stringent border control during the spring of 2020, local transmission of SARS-CoV-2 was limited to a few imported lineages that escaped border restriction measures, including the B.1.1.63 lineage and B.1.36.27 lineage in third and fourth waves of infection, respectively [16, 17]. This outbreak illustrates that BA.2 can be transmitted efficiently in a population where universal masking has been adopted since the beginning of the COVID-19 pandemic. Whole genome phylogenetic analysis is compatible with a single source outbreak. Further studies are required to determine the reason of high transmissibility conferred by BA.2.

ACKNOWLEDGEMENT

The authors gratefully acknowledge the originating and submitting laboratories who contributed sequences to GISAID (Supplementary Table S3).We would like to acknowledge Deborah Ho and Polly Pang for their help in patient recruitment and blood taking.

FUNDING

This work was supported by Health and Medical Research Fund, the Food and Health Bureau, The Government of the Hong Kong Special Administrative Region (Ref no: CID-HKU-1-2 and CID-HKU-1-16), and donations of Richard Yu and Carol Yu, Shaw Foundation Hong Kong, Michael Seak-Kan Tong, May Tam Mak Mei Yin, Lee Wan Keung Charity Foundation Limited, Hong Kong Sanatorium & Hospital, Respiratory Viral Research Foundation Limited, Hui Ming, Hui Hoy and Chow Sin Lan Charity Fund Limited, Chan Yin Chuen Memorial Charitable Foundation, Marina Man-Wai Lee, the Hong Kong Hainan Commercial Association South China Microbiology Research Fund, the Jessie & George Ho Charitable Foundation, Kai Chong Tong, Tse Kam Ming Laurence, Foo Oi Foundation Limited, Betty Hing-Chu Lee, and Ping Cham So.

DECLARATION OF INTERESTS

We declare that we have no conflicts of interest.

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FIGURE LEGENDS

Figure 1. Timeline of the Omicron BA.2 outbreak at the Kwai Chung housing estate. Epidemiological information was obtained from the Centre for Health Protection of the Hong Kong SARS government.

Figure 2. Epidemic curve of the Silka Seaview Hotel/Tung Moon House/Yat Kwai House (STY) related cluster. The epidemic curve was plotted based on the date of symptom onset. For asymptomatic patients, the reporting date was used as the symptom onset date. There were a total of 768 patients in the STY cluster, including 432 residents from Kwai Chung Estate. Data were obtained from the Centre for Health Protection. Abbreviations: KC Estate, Kwai Chung Estate.

Figure 3. Whole genome phylogenetic analysis of SARS-CoV-2 genomes in Hong Kong. (A) Whole genome phylogenetic analysis of 438 viral genomes since 2nd November 2021 to 2nd February 2022. The whole genome phylogenetic tree was constructed using the Nextclade tool (v1.13.1). The tree was visualized and exported using the online tool www.auspice.us. (B) Whole genome phylogenetic tree focusing on the BA.2 outbreak in Hong Kong. The trees were constructed by maximum likelihood method with IQTree 2. The reference genome Wuhan-Hu-1 (GenBank accession number MN908947.3) was used as the root of the tree. The substitution model TN+F+I was chosen according to Bayesian information criterion. Patient 1 is the index case who was a traveler returning to Hong Kong on 4th January 2022. BA.2 strains from patients who acquired the infection locally are shown in orange triangles (n=139), whereas BA.2 strains that were detected among incoming travelers to Hong Kong (except patient 1) are shown in the blue triangles (n=15). (C) Differences in nucleotide sequences. Mutations unique to the Hong Kong locally acquired cases are shown in orange, whereas those unique to incoming travelers are shown in blue.

Figure 1

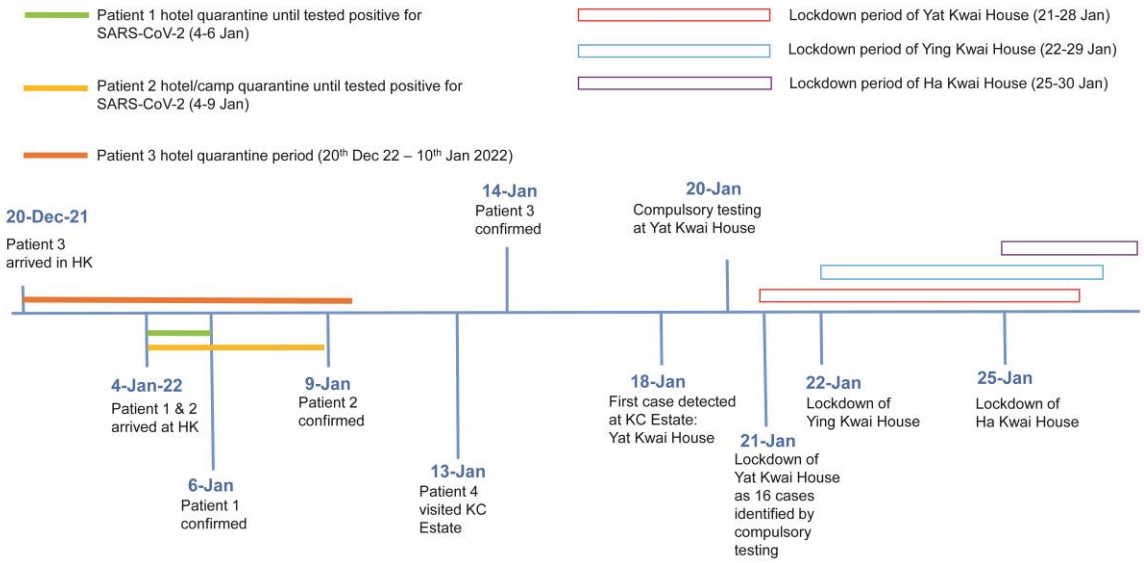


Figure 2

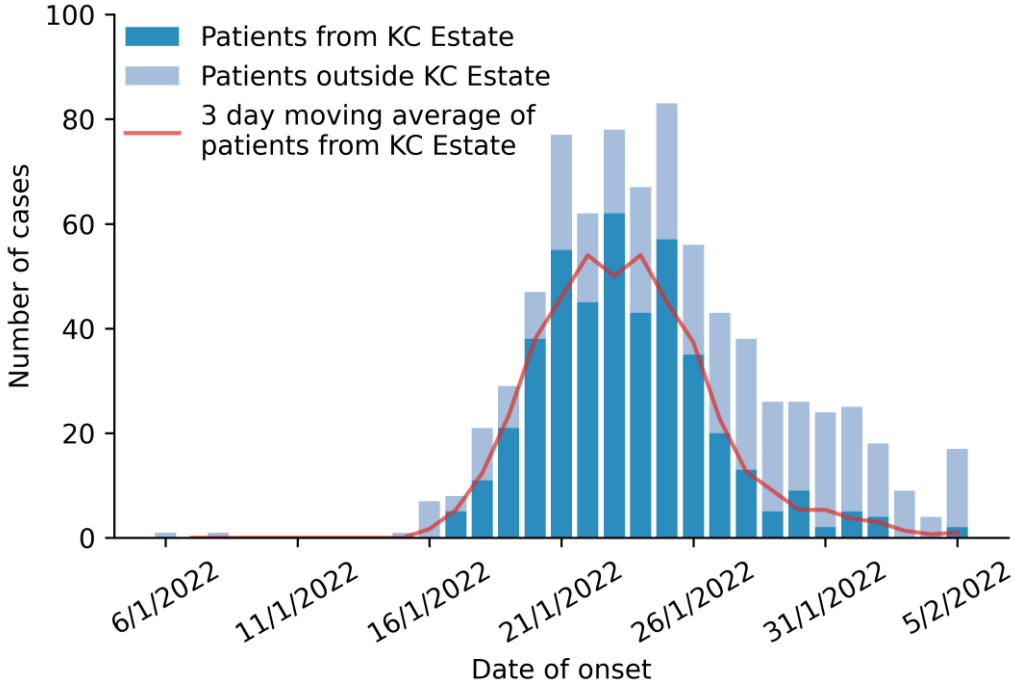
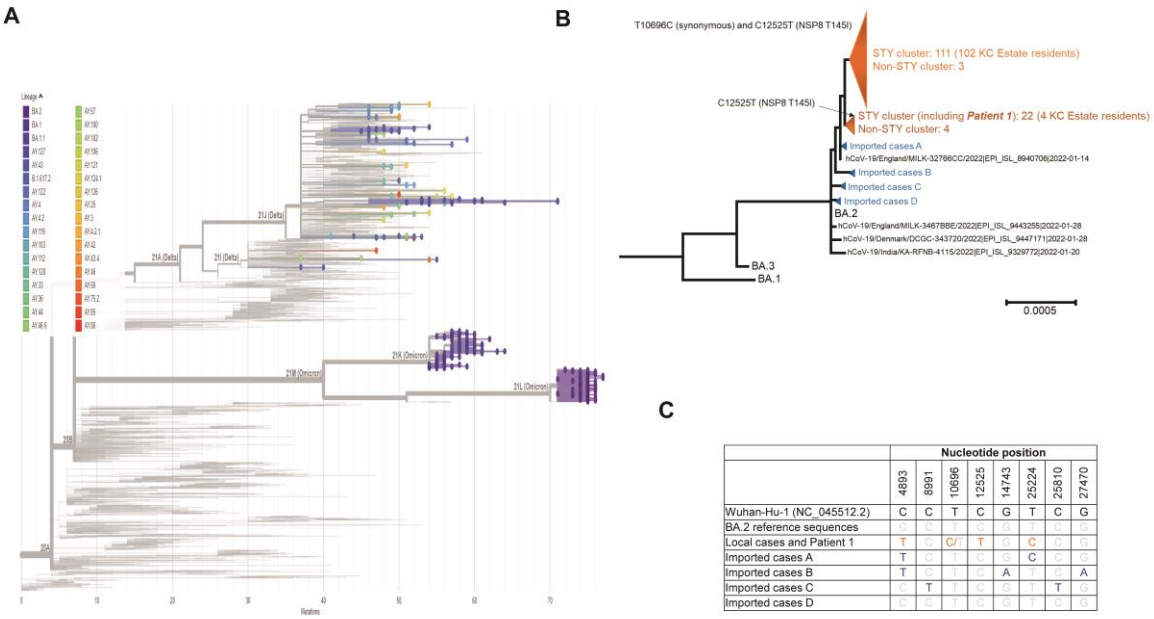


Figure 3



C

	Nucleotide position							
	4893	8991	10696	12525	14743	25224	25810	27470
Wuhan-Hu-1 (NC_045512.2)	C	C	T	C	G	T	C	G
BA.2 reference sequences	C	C	T	C	G	T	C	G
Local cases and Patient 1	T	C	C/T	T	G	C	C	G
Imported cases A	T	C	T	C	G	C	C	G
Imported cases B	T	C	T	C	A	T	C	A
Imported cases C	C	T	T	C	G	T	T	G
Imported cases D	C	C	T	C	G	T	C	G