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Genomic surveillance reveals COVID-19 outbreak clusters in a tertiary center in Malaysia: A cross-sectional study

Norazimah Tajudin[1], Seok Mui Wang[2,3,4], Mariam Mohamad[5], Siti Farah Alwani Mohd Nawi[2,*], Mohd Nur Fakhruzzaman Noorizhab[6]

[1] Institute of Medical Molecular Biotechnology, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh Campus, Selangor, Malaysia
[2] Department of Medical Microbiology and Parasitology, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh Campus, Selangor, Malaysia
[3] Cardiovascular Advancement and Research Excellence Institute (CARE Institute), Universiti Teknologi MARA, Sungai Buloh Campus, Selangor, Malaysia
[4] Non-Destructive Biomedical and Pharmaceutical Research Center, Smart Manufacturing Research Institute (SMRI), Universiti Teknologi MARA, Puncak Alam Campus, Selangor, Malaysia
[5] Department of Public Health Medicine, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh Campus, Selangor, Malaysia
[6] Integrative Pharmacogenomics Institute, Universiti Teknologi MARA (UiTM) Selangor Branch, Puncak Alam Campus, Selangor, Malaysia

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ABSTRACT

Background: Genomic surveillance activity is a useful tool in epidemiologic investigations and monitoring of virus evolution. This study aimed to describe the COVID-19 outbreaks through SARS-CoV-2 virus genomic surveillance by whole genome sequencing.

Methods: A cross-sectional study was conducted using archived clinical samples of confirmed laboratory-positive COVID-19 from June 2021 to June 2022 from a tertiary center in Malaysia. The samples were subjected to whole genome sequencing. A phylogenetic tree was constructed using the maximum likelihood method in MEGA 11 software. The clinical data were obtained through paper, electronic, and hospital information systems.

Results: A total of 86 clinical samples were successfully sequenced. The phylogenetic tree revealed seven clusters, consisting of 24 cases. Three clusters were associated with health care workers and health care–associated individuals. The SARS-CoV-2 Delta variants were observed in the first three clusters and subsequently replaced with the Omicron variants.

Conclusions: Whole genome sequencing is robust and reliable, enhancing epidemiologic investigations, leading to the identification of clusters and preventing the spreading of COVID-19 among health care workers. Monitoring of the SARS-CoV-2 variants is necessary to study the viral dynamics and maintain the effectiveness of public health interventions.

Introduction

The emergence of the novel SARS-CoV-2, originally started in Wuhan, China in December 2019, has caused a significant public health crisis. Within 3 months, in March 2020, this virus was responsible for causing global spread and led to the declaration as a pandemic by the World Health Organization (WHO) [1,2]. As of December 2024, 182,000 million and 25,000 million COVID-19 cases and deaths were reported, respectively (WHO COVID-19 Dashboard| WHO COVID-19 Dashboard with Vaccination Data).

The SARS-CoV-2 virus is transmitted via respiratory droplets and aerosols [3]. It can linger in the air, especially in crowded and poorly ventilated spaces, making it easy to spread from person to person. The virus can also spread by touching contaminated surfaces, increasing its spread [3]. COVID-19 clinical manifestations range from asymptomatic to respiratory illness from mild influenza-like illness to severe cases requiring hospitalization, with some people experiencing long-term effects (long COVID). The long incubation period also promotes the virus to spread in clusters and causes outbreaks [4]. Identifying clusters allows health authorities to link cases to the same source, trace close contacts, and isolate identified cases [5].

In response to the pandemic, Malaysia implemented preemptive measures and adopted public health strategies by the WHO to contain and mitigate disease transmission [6]. These measures include movement restriction orders and the prescribed standard operating procedures (SOPs) for infection and prevention control, such as non-pharmaceutical interventions, which must be carried out during daily activities on premises, i.e. outdoor areas, indoor spaces, or vehicles [7].

* Corresponding author.
E-mail address: sitifarah@uitm.edu.my (S.F.A. Mohd Nawi).

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There were also targeted screening, surveillance activities, and the implementation of institutionalized isolation and quarantine systems for confirmed and suspected COVID-19 cases [6].

Initiatives were also taken to strengthen genomic surveillance to study and monitor evolutionary patterns, new mutations and variants, and genetic diversities, such as a nationwide consortium funded by the Ministry of Technology [8,9]. The robust and advanced technology of next-generation sequencing, such as the Illumina and Oxford Nanopore Technology, facilitated the identification of key SARS-CoV-2 variants and aided in the adaptation of local public health strategies [8]. Malaysian pandemic responses were conducted in phases of varying degrees until the initiation of the COVID-19 National Immunization Program, which led to the National Recovery plans and subsequently transitioned toward endemicity [10].

In our tertiary hospital, the COVID-19 surveillance and tracking of outbreaks conducted among health care workers (HCWs) and healthcare-associated individuals (HCAI) relied on epidemiologic data. Nevertheless, whole genome sequencing has been widely used since the pandemic began. Here, we describe a study of whole genome sequencing in cases of HCWs, HCAI, and the community, integrating with epidemiologic data to identify community clusters toward the end of the pandemic.

Methods

Study setting design and patients

A cross-sectional study was conducted at the Pusat Perubatan Universiti Teknologi MARA (PPUiTM) in Selangor, Malaysia, an 80-bed public hospital that serves as a teaching center for Universiti Teknologi Mara medical students. The diagnostic laboratory primarily receives patient samples from inpatients, the community (public) surrounding the vicinity, including medical students who live in the nearby residential college, HCWs, and HCAI, i.e., medical lecturers and hospital administrative staff. In this study, the consecutive samples were selected between June 2021 and June 2022 from patients with laboratory-confirmed positive COVID-19 infections by reverse transcription-polymerase chain reaction performed at the Microbiology laboratory, PPUiTM, with a cycle threshold value <40.0, stored in −80°C freezer. Samples with an insufficient residual volume (<500 µl) and those with a cycle threshold value >30 of any of the target genes, (i.e. E gene, RdRp gene, ORF 1ab gene, N gene, and S gene) after retesting with commercially available reverse transcription-polymerase chain reaction, were excluded to ensure a good yield for subsequent sequencing.

Clinical data were collected from paper and electronic patient records (UniMEDS) and consisted of the date of sample collection, gender, age, type of infection, and workstation for HCWs.

Whole genome sequencing and analysis

The viral RNA was extracted using the QIAamp Viral RNA Mini kit (Qiagen, Germany), following the manufacturer's instructions on the kit. The complementary DNA (cDNA) library preparation was conducted using the Rapid Barcoding Kit following workflows (midnight protocol) for Oxford Nanopore Technology on the MinION Mk1c platform. The raw data of FASTQ output were then analyzed using Oxford Nanopore Technology sequencing systems, including built-in software, EPI2ME desktop Agent 3.7.3, for primary data processing. The final report consists of Next Clade/NextStrain.org and Pangolin.co.uk reports for variant calling. The official reference sequence of SARS-CoV-2 Wuhan-Hu1 and nine Malaysian sequences were retrieved from the Global Initiative on Sharing All Influenza Data (GISAID), with the collection dates between January 2021 and June 2022 to serve as local reference sequences. The phylogenetic tree was constructed using Mega 11.0, the maximum likelihood approach with 1000 bootstrap replications and the best substitution model, the general time reversible [11,12]. The original Wuhan reference genome (GISAID accession number: EPI_ISL_402124 named hCoV-19/Wuhan/WIV04/2019 [WIV04]) and nine representative Malaysian sequences (GISAID accession number: EPI_ISL_3769337, EPI_ISL_4122479, EPI_ISL_7380536, EPI_ISL_5114309, EPI_ISL_5397601, EPI_ISL_9211296, EPI_ISL_13134761, EPI_ISL_11939144, and EPI_ISL_13478162) were used to align and construct the 86 whole genome sequences of SARS-CoV-2 from Hospital Al-Sultan Abdullah. The sequence's presence with gaps and missing data was removed.

Results

A total of 129 laboratory-confirmed COVID-19-positive samples were kept in the −80°C freezer; 101 had CT values <30 after verification and retesting. Only 86 samples were successfully sequenced. Phylogenetic analysis showed seven clusters involving only 24 cases (Figure 1). The first three clusters (Cluster I, II, and III) involved 12 cases, and the SARS-CoV-2 strain circulated from June 2021 to July 2021. These clusters belonged to the GISAID Clade GK, NextClade 21J, and 21K, VOC Delta with sublineages, i.e. AY. 59 and AY. 79.

Cluster I and Cluster II did not involve any HCWs. They were from the community who came for treatment at our center. Both clusters belonged to the Delta variant Pangolin lineage AY. 59.

Cluster III involved seven patients. It started with case 11 which first contracted the disease, followed by case 6. Both were HCWs working in different workstations. Case 11 was a HCAI, whereas case 6 was one of the HCWs. They came to our center 2 days apart. Cases 8 and 10 were from the community, and case 9 was a HCAI. Cases 7 and 12 were not HCWs. Cluster III belonged to the original Delta variant (B.1.617.2), observed in cases 6, 8, 11, and 12, whereas the others belonged to the Delta variant sublineage AY. 79. Clusters IV-VII belonged to the Clade GRA (Omicron variant) from February 2022 until April 2022. They consist of two Pangolin sublineages: BA.1.1 and BA.2.3. Cluster IV involved three cases from the community.

The cases belonging to Cluster V were HCAI and one from the community (case 19). Case 16 was a hospital administrative officer, case 17 was an HCW, and case 18 was another hospital staff member. Cluster VI was associated with cases 20, 21, 22, and 23 from the community. Cluster VII involved a hospital administrative officer (case 23), a HCAI and a community member (case 24). All cases had mild illness and did not require hospital admission (Table 1).

Discussion

Whole genome sequencing has been widely used since the pandemic, including small-scale research studies through multiple platforms. In this study, we identified seven COVID-19 clusters involving HCWs, HCAI, and the community caused by SARS-CoV-2 Delta and Omicron variants after performing whole genome sequencing. Many studies combined epidemiologic and genome sequencing information to enhance epidemiological investigations [13,14].

Three clusters (Cluster III, V, and VII) involved HCW and HCAI. HCWs are among those at the highest risk of SARS-CoV-2 infection, and, early in the pandemic, personal exposure to COVID-19 during patient care was the leading cause [15–17]. Infection among HCWs also increase the risk of nosocomial transmission. A retrospective analysis in a London teaching hospital showed that nosocomial COVID-19 had a case fatality rate of 36% [18]. Prevention of COVID-19 infection among HCWs relies on strict adherence to SOPs, and good adherence will ensure less disruption in healthcare deliveries and reduce the risk of interhospital transmission among the hospital staff [19]. In Cluster III, from the epidemiologic data, three cases were HCWs stationed at three different places in the PPUiTM, four were from the community, and none were inpatients. However, insufficient information was available to link and identify a common transmission source despite all cases being part of

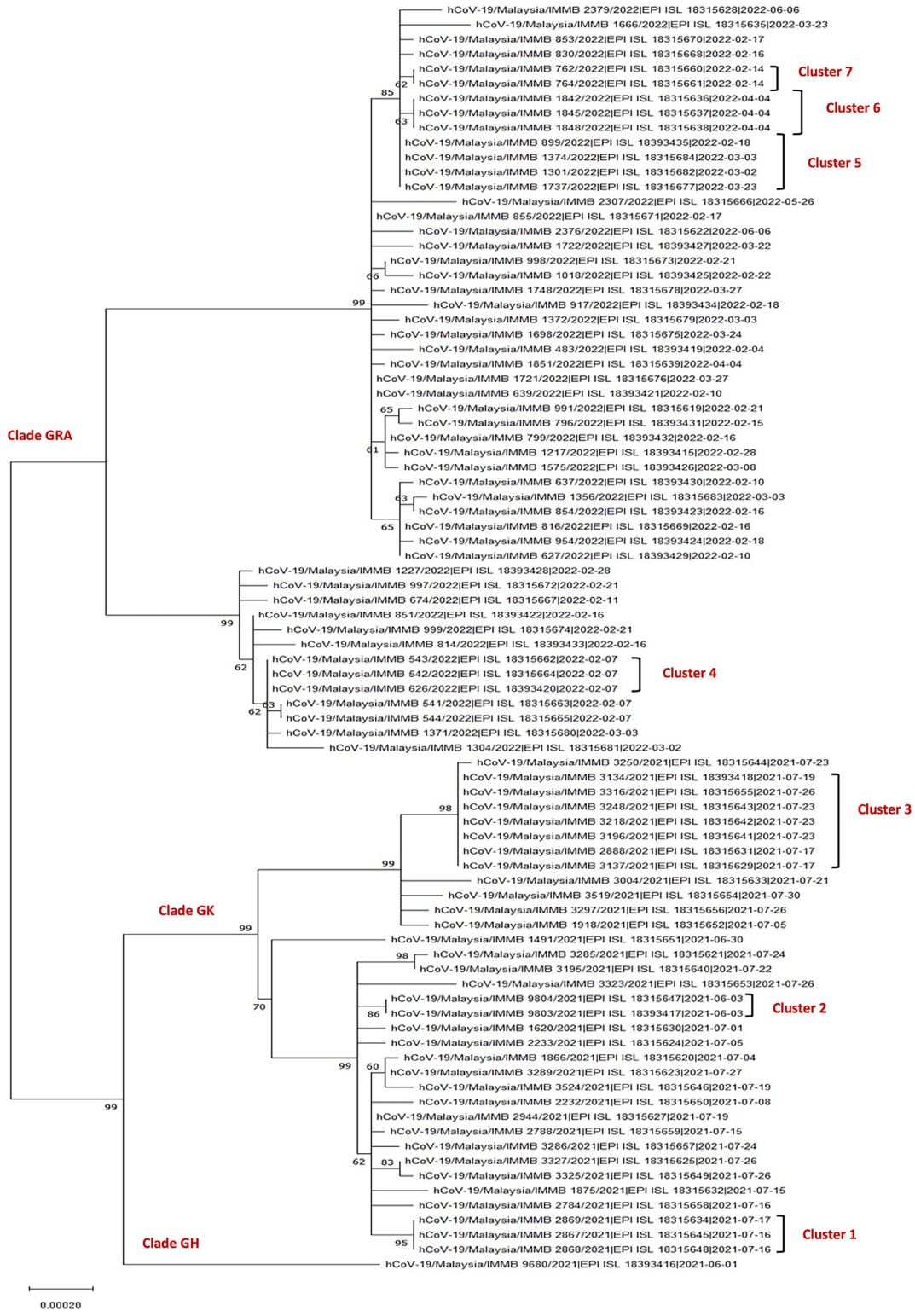

Figure 1. A phylogenetic analysis showing 7 outbreak clusters (Cluster I to VII).
Clusters I, II, and III belonged to the Delta variant (Clade K) and Clusters IV, V, VI, and VII belonged to the Omicron variant (GRA).

the same cluster. Given this lack of a clear link, it is likely that this cluster was part of a larger community outbreaks. Nevertheless, nosocomial transmission remains a concern, as SARS-CoV-2 and most other respiratory viruses can spread not only through direct contact and aerosols but also via fomites and contaminated surfaces, potentially facilitating interhospital transmission [19].

Cluster I,II and III were associated with the original SARS-CoV-2 Delta variant (B.1.617.2) and the sublineage AY. 79., Clade GK. The SARS-CoV-2 Delta variant, despite being virulent, was believed to be sensitive, and patients infected may not have severe infection [20]. All cases in these clusters experienced mild symptoms. By the time this study was conducted, about 95% of the population had already received

Table 1
Demographic and SARS CoV-2 characterization (Clade and lineage according to Nextclade, GISAID, and Pangolin) of the 24 cases.

No.	Cluster	Date of specimen	Cases	Age	Gender	Variant	Nextclade	GISAID Clade	Pangolin lineage
1	**1**	16/07/2021	Community	33	F	Delta	21I	GK	AY.59
2	**1**	16/7/2021	Community	6	M	Delta	21I	GK	AY.59
3	**1**	17/7/2021	Community	2	M	Delta	21I	GK	AY.59
4	**2**	3/6/2021	Community	9	F	Delta	21I	GK	AY.59
5	**2**	3/6/2021	Community	4	M	Delta	21I	GK	AY.59
6	**3**	19/7/2021	HCW	35	F	Delta	21J	GK	B.1.617.2
7	**3**	26/07/2021	Community	22	M	Delta	21J	GK	AY.79
8	**3**	23/07/2021	Community	1	M	Delta	21J	GK	B.1.617.2
9	**3**	23/7/2021	HCW	21	M	Delta	21J	GK	AY.79
10	**3**	23/7/2021	Community	6	M	Delta	21J	GK	AY.79
11	**3**	17/7/2021	HCAI	38	M	Delta	21J	GK	B.1.617.2
12	**3**	22/07/2021	Community	6	F	Delta	21J	GK	B.1.617.2
13	**4**	2/7/22	Community	20	F	Omicron	21K	GRA	BA.1.1
14	**4**	2/7/22	Community	20	F	Omicron	21K	GRA	BA.1.1
15	**4**	2/7/22	Community	20	F	Omicron	21K	GRA	BA.1.1
16	**5**	2/18/22	HCAI	26	F	Omicron	21L	GRA	BA.2.3
17	**5**	3/3/22	HCW	38	F	Omicron	21L	GRA	BA.2.3
18	**5**	3/2/22	HCAI	24	F	Omicron	21L	GRA	BA.2.3
19	**5**	3/23/22	Community	25	M	Omicron	21L	GRA	BA.2.3
20	**6**	4/4/22	Community	20	M	Omicron	21L	GRA	BA.2.3
21	**6**	4/4/22	Community	21	M	Omicron	21L	GRA	BA.2.3
22	**6**	4/4/22	Community	20	M	Omicron	21L	GRA	BA.2.3
23	**7**	2/14/22	Community	2	M	Omicron	21L	GRA	BA.2.3
24	**7**	2/14/22	HCAI	35	F	Omicron	21L	GRA	BA.2.3

F, female; HCW, health care worker; HCAI, healthcare–associated individuals; M, male.

one dose of the vaccine, 91.2% had completed two doses, and 99% of the HCWs were fully vaccinated [21,22]. Nevertheless, infection prevention and control SOPs and the non-pharmaceutical interventions remained mandatory. As part of the National Recovery Plans, restriction orders were gradually eased and economic sectors reopened [23].

In Cluster V, we also observed a similar pattern of HCW COVID-19 infections without any link from their workstations. There were three HCW cases and one student, likely part of a larger community cluster. This cluster was associated with the SARS-CoV-2 Omicron variant BA.2.3, Clade GRA, which has been associated with a higher risk of reinfection likely due to immune evasion following previous Delta variant infections [24]. Cluster VII involved a healthcare individual with her son, both infected with the same Omicron variant (BA.2.3).

Clusters I, II, IV, and VI were most likely community acquired, as none of the cases were linked to HCWs or ongoing healthcare-associated infections.

The presence of the Delta variant in the first three Clusters (I, II, and III) showed that the earlier SARS-CoV-2 variants were gradually displaced by the Omicron variant as the virus continued to evolve in Malaysia [9,25]. Our samples were not part of outbreak investigations, and we successfully sequence 67% of the total available samples in the laboratory. As a result, additional cases may have been linked to the identified clusters, or new clusters may have emerged. Due to this limitation, we were unable to clearly establish the full transmission dynamics of the disease.

Conclusion

Whole genome sequencing has become more robust and reliable, with the potential to be incorporated into hospital surveillance systems for cluster outbreaks detection. Timely intervention is crucial during rampant community transmission to reduce healthcare delivery disruptions and implement containment measures to prevent interhospital transmission and nosocomial infection. Integrating epidemiologic and genomic sequencing data will enhance identification and allow health authorities to link cases to the source, trace close contacts, and isolate cases. The detection of multiple clusters in this study suggests ongoing viral evolution driven by the accumulation of mutations. If applied in real time, whole genome sequencing could enhance outbreak detection, track transmission chains, and guide effective infection control strategies to curb SARS-CoV-2 transmission.

Declarations of competing interest

Part of this study has been presented as an oral abstract in the recent 20th International Congress on Infectious Diseases in Cape Town International Convention Centre, Cape town, South Africa.

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Ethical approval

Ethical approval was obtained from the research ethics committee of UiTM on April 26, 2022, with the reference number REC/04/2022 (PG/MR/88). Secondary data from medical records of patients with COVID-19 were used in this study, thus waiving the need for informed consent by the ethics committee. The study was conducted by the Declaration of Helsinki, and all data were kept anonymous.

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Author contributions

Conceptualization, Siti Farah Alwani Mohd Nawi and Norazimah Tajudin.; Methodology, Norazimah Tajudin, Mohd Nur Fakhruzzaman-Noorizhab: Review and editing, NorazimahTajudin, Seok MuiWang, MariamMohamad, Siti Farah Alwani MohdNawi, Mohd Nur Fakhruzzaman Noorizhab. All authors have read and agreed to the published version of the manuscript.

Disclosure instructions

During the preparation of this work, we used Grammarly Pro and ChatGPT to help in the clarity of the writing to suits academic style. After using these tools/services, we reviewed and edited the content as needed and take full responsibility for the content of the publication.

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