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Genomic Surveillance of SARS-CoV-2 in Bangalore, India 2021-2022

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Abstract

A comprehensive SARS-CoV-2 genomic surveillance programme that integrates logistics, laboratory work, bioinformatics, analytics, and timely reporting was deployed through a public- private partnership in the city of Bengaluru, Karnataka in India. As a result, 13641 samples were sequenced and reported to the Karnataka state public health officials as time-sensitive, decision support from June 2021 to July 2022 and uploaded in global public databases in a timely manner. As part of the programme, an analytics platform for studying SARS-CoV-2 sequences and their epidemiological context was also developed. These continuous sequencing efforts enabled timely detection of the Omicron variant in India and its subsequent spread via multiple sub-lineages (BA.10, BA.12, BA.2.75 and BA.5) in Bengaluru. Our data also helped to determine which of the globally tracked Variants of Concern were observed in Bengaluru, thus ensuring targeted efforts on the ground reducing unwarranted fear. This effort highlights the importance of, and the urgent need for, increased genomic surveillance to support the health authorities in regions with limited sequencing and bioinformatics capacity. We describe the development and deployment of this end- to-end solution for genomic surveillance of SARS-CoV-2 in the city of Bengaluru.

Keywords: Genomic surveillance; SARS-CoV-2; COVID-19; Analytical platforms; Pandemic preparedness

Introduction

Following the first pandemic wave of coronavirus disease 2019 (COVID-19), the successive introduction and spread of SARS-CoV-2 variants has resulted in new waves of infections across the globe. Some variants have modulated infectivity, others have influenced disease severity, and yet others have enabled evasion of immunity from prior vaccination or infection [1]. Some variants disappeared immediately, while others adapted well and spread rapidly, at least for a period of time, often to be outcompeted by others subsequently [2,3]. Continuous genomic surveillance of these variants has been an invaluable tool helping us track these dynamics. The most important contribution of sequencing efforts worldwide has been the detection of Variants of Concern (VoC), including Alpha, Beta, Delta, and more recently Omicron [4]. These are variants of SARS-CoV-2 that have been reported to either increase transmission, increase evasion of immune response (from natural infection or existing vaccines), or are modulate disease severity [1].

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In particular, the rapid expansion of Omicron into multiple lineages and its unprecedented community spread are likely to give rise to other variants that need to be monitored [5]. To date, over 100 Omicron sub-lineages have been detected worldwide, and existing data suggests BA.2 and sub-lineages are more transmissible than other Omicron lineages [6,7], and are predominant in India. The associated mutation rates and the impact of mutation on viral dynamics within and between individual hosts determines the emergence and spread of new viral variants [8]. This warrants continued genomic surveillance particularly in densely populated areas. Staying abreast of virus mutations and lineages is thus a critical aspect of public health management. There are now over 12 million sequences of SARS-CoV-2 in the global GISAID database [9]. These sequences have helped understand the virus dynamics [10-12]. The early detection of a VoC is important for public health response as advance warning can prepare health systems for a surge.

In the early stages of the pandemic in India, Karnataka and its capital city Bengaluru (population 13.1 million) as well as Delhi, the national capital region, were exceptional with early surveillance of the SARS-CoV2 virus samples that were coming in mostly through international travellers [13,14]. Contact tracing and line lists were readily available to the researchers who carried out fairly detailed genomic epidemiology of the early onset of infections and diffusion to the locations around the state. This early momentum faded however and through the deadly second wave of the "Delta" variant, the sequencing data lagged behind the infection and the alacrity that was needed for surveillance and public health response was missing. By the middle of 2021 when the second wave subsided, scaling up genomic sequencing capacity became a key imperative for public health officials in Karnataka. The state appointed COVID-19 Genomic Surveillance Committee for Karnataka began its meetings in June 2021 and the qualification of Strand Life Sciences, a private laboratory of repute in the city to accelerate the sequencing efforts, was tabled on June 25th 2021. Strand Life Sciences (SLS) was qualified soon thereafter by the surveillance committee and recognized by the Indian SARS-CoV-2 Genomics Consortium (INSACOG) as a private laboratory authorized to participate in genomic surveillance. SLS proceeded to interact with the city and state health authorities. Philanthropic funding was secured to execute the large-scale sequencing and data analysis at the Strand Labs. This ambitious project successfully enabled monitoring at around 10% of positive cases in the city with a turnaround time of 7 to 10 days from sample collection to dashboard presentations for the Karnataka State public health officials, who were the key stakeholders for this project. The logistics of sample collection, sequencing, informatics, analytics and timely reporting presented daunting challenges that needed continued support for successful execution. This article describes the details of this effort that largely covered the surveillance of the entire "third wave" of COVID-19 infections in the city of Bengaluru in Karnataka. It was significant that this was accomplished in a cost effective manner (at under USD 80 per sample for logistics, sequencing, data analysis and decision support informatics) by, a private sector lab, in conjunction with private philanthropy, thus suggesting a new paradigm for public health interventions in LMICs.

Evolution and spread of SARS CoV-2 in Bengaluru (July 2021 to July 2022)

SLS sequenced the first batch of COVID-19 RT-PCR positive samples in July 2021. The reign of the COVID-19 B.1.617.2 / "Delta" variant, first identified in India, and its sub-lineages, was obvious in our analysis: these strains were identified in all of the samples sequenced in July 2021 and their dominance continued until November 2021. A few new or unassigned sequences emerged during this period. However, these remained contained. A new Delta variant AY.4.2 (VUI- 21OCT-01) that appeared in more than 6% of COVID-19 cases in the UK in October 2021 were barely detected in our surveillance (15). The first Omicron case in India was detected from a person with travel history at the end of November. The Delta wave continued in December 2021, with a slight wane, even as the Omicron sub-lineageBA.1 grew rapidly to 5.4%, and BA.2 and its sub-lineages also appeared in the same month. January 2022 was witness a dramatic sequence of events. Omicron BA.2 exploded from 0.9% to 86% in a month even as BA.1 showed a sizable presence and BA.3 appeared for the first time. Most importantly, the Delta sub-lineages dropped to approximately 3% from their mark of more than 90% in December 2021. In the following months, the BA.1 and BA.3 sub-lineages reduced in proportion and BA.2 grew in dominance. The first BA.5 cases were detected in the middle of April 2022 and this sub-lineage grew to 25% by June 2022. The BA.4 sub-lineage first appeared in May 2022 but did not spread widely in the following months. In July 2022, BA.2.75 which was at 3% in June 2022 grew to 30% thus matching BA.5, which too was at 30%, with other BA.2 sub- lineages at 38% but with a waning trend. A pictorial representation showing the events in the evolution of SARS-Cov-2 in this surveillance is given in Figure 1.

The Delta variant was also responsible for the third wave of infections in the United States during the summer of 2021 [16]. The first case of the Omicron variant in the U.S. was detected by December 1st week, and, by the end of January 2022, the Omicron variant accounted for approximately 99% of all COVID-19 cases in the U.S. This was similar to what we observed. However, in contrast, according to CDC data, Omicron sub variants BA.4 and BA.5 were dominant in the U.S, accounting for more than 70% of new COVID-19 infections in June and July 2022, while their combined proportion in our surveillance remained below 32%.

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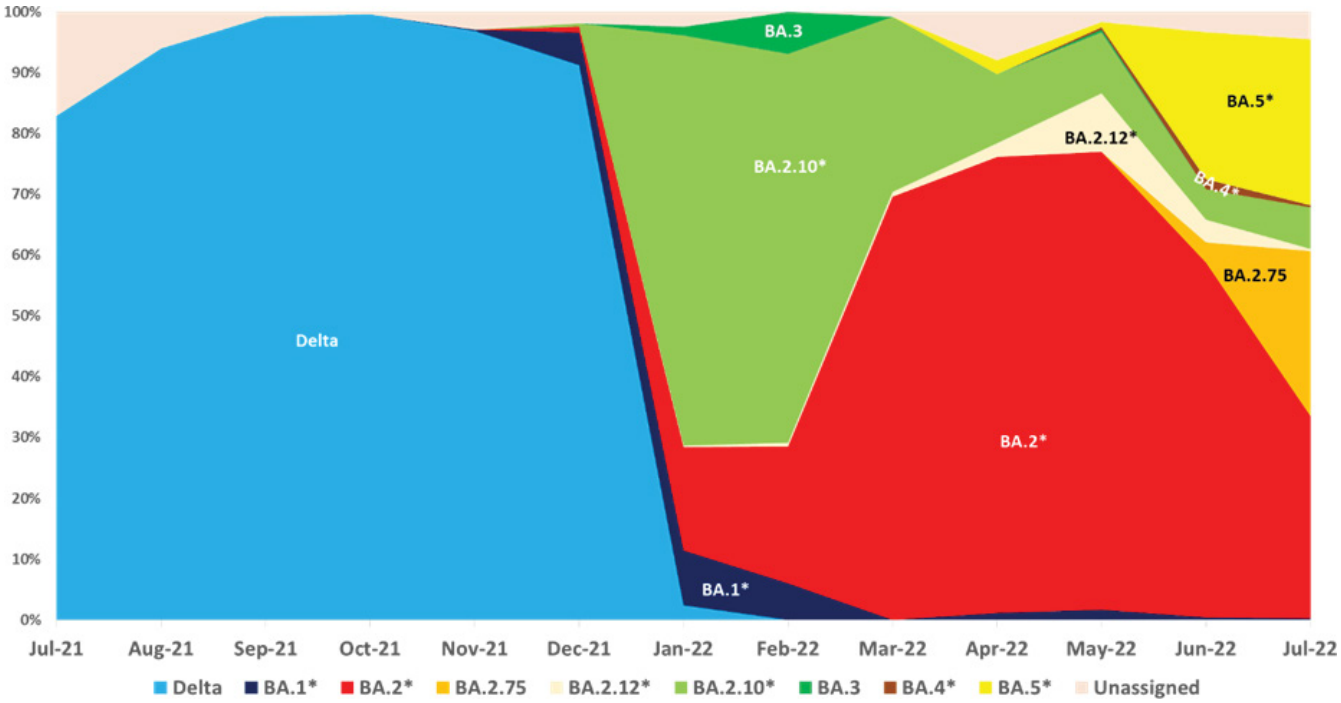

Figure 1: Prevalence of SARS-CoV-2 Variants from July 2021 to July 2022 in Bengaluru city.The * symbol indicates the other sub variants of that particular lineage.

Materials and Methods

The Technical Advisory Committee (TAC) of the State for Pandemic response mandated SLS to initiate genomic surveillance of SARS-CoV-2 in various parts of Bengaluru city (Ref: CHO (PH)/PR/P-103/2021-22), to detect trends in variants and to guard against a repeat of the impact seen in the second wave of COVID-19 across India. Sequencing was carried out on SARS-CoV-2 RT-PCR positive samples with Ct value < 30 from the various parts of the city of Bengaluru, India. Samples were collected from multiple wards across the city. Sampling was opportunistic – sequencing of samples that were available and fit the inclusion criteria with the overall aim of high-density sampling within Bengaluru city every week (continuous over time).

The ARTIC protocol was used for the sequencing of SARS-CoV-2 from the clinical samples [17]. The ARTIC protocol is based on a method that enriches the cDNA generated through reverse transcription of the SARS-CoV-2 genome, using a tiled multiplex PCR amplification using two primer pools. A total of 196 primers (98 pairs) were designed to tile the entire SARS-CoV-2 genome. An amplicon size of ~400 bp per target is obtained that then moves to the specific library preparation for Illumina sequencing [17]. FASTQ files were generated for each sample after demultiplexing of the raw sequencing data on Base Space Sequence Hub (BSSH). FSATQ files were trimmed, filtered and aligned to SARS- CoV-2 reference genome MN908947 using Minimap2 [18,19]. Samtools were used to convert and sort the SAM file into BAM format. The iVar [20] tools were used for trimming primers from the ends of the reads. Lineage identification on consensus sequences were performed using the Pangolin web tool (v 4.0.6 PLEARN v1.6)/command line [21], and Nextclade tools (v 1.11.0) [22]. A phylogenetic tree of the genomes from this program was constructed using the default NextStrain command line. Augur, a command-line application, was used for phylogenetic analysis, and the resulting tree was visualised in Auspice (https://auspice.us/). The FASTA sequences and cleaned up metadata were used for the phylogenetic analysis. Only 11,110 sequences passed all of the NextStrain quality filters and were used to build the final tree.

Decision support for health authorities

All the stakeholders were provided with the login credentials of CoviSurve dashboard from SLS. CoviSurve is a tool for genomic surveillance to enable the interpretation of sequencing data in conjunction with associated epidemiological data. The metadata and lineage information of all the samples were uploaded to CoviSurve in a timely manner. Strand COVID Mutation miner, an open access software, was used to track the specific COVID-19 mutations of interest (https://covidmm.mystrand.org/).

Reports were generated on a regular basis and summary data and key highlights shared with local authorities, the Genomic Surveillance Committee for SARS-CoV-2 and the COVID task force in the state. The entire workflow is outlined in the (Figure 3).

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Figure 2a: Screen shot from the CoviSurve dashboard. Login credentials were shared with all the data owners.

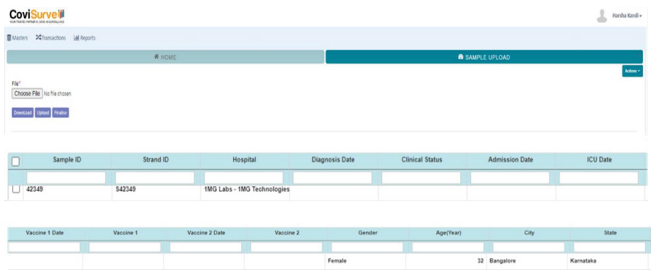

Figure 2b: Screen shot from the CoviSurve dashboard; data uploading into the CoviSurve. CoviSurve has the option to upload available metadata as single or batch upload.

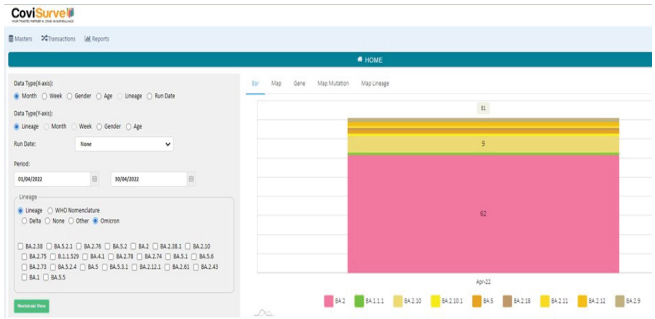

Figure 2c: Screen shot from the CoviSurve dashboard; data visualization in CoviSurve. Various data analyzing options available in the CoviSurve and the bar graph showing the various lineages obtained from the samples sequenced in April 2022.

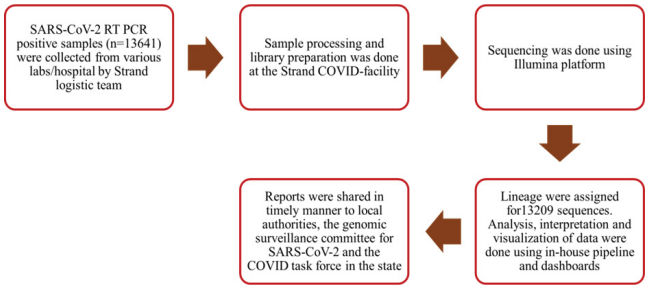

Figure 3: The work flow of SARS-CoV-2 genomic surveillance conducted at Strand Life Sciences Pvt Limited

Results

A total of 13641 RT PCR positive SARS-CoV-2 samples were sequenced at SLS between July 2021 and July 2022, yielding 13209 sequences with lineage assignments (Figure 4). Of these 13209 sequences, 5397 (40.8%) were Delta and sub-lineages and 7881 (59.6%) were Omicron and sub-lineages. 57.3% (2576) of the Delta sequences were from males and 42.6% (1913) were from females (908 sequences did not have gender information). Similarly, 53.9% (3987) of the Omicron lineages were from males and 46.0% (3410) were from females (484 sequences did not have gender information) (Figure 5). All these samples were collected from the various wards across Bengaluru city as shown in the map (Figure 6). Most of the Delta (54.4%) and Omicron (62.5%) lineages were detected from the age group between 19 and 45 (Figure 7). The children below 12 years were more affected by Delta (12.9%) when compared to Omicron (5.5%) (Figure 7).

We have identified 74 Delta sub-lineages and 51 Omicron sub-lineages in Bengaluru during this study period (Figure 8A-B). Of these Delta sub-lineages, over 70% were B.1.617.2. While the predominant Omicron sub-lineages identified were BA.2 BA.2 and its sub-lineages including BA.2.10 and BA.2.75. The origin and spread of Omicron sub-lineages are given in Table-1.

The first Omicron case in Bengaluru was detected in November 2021 and Omicron grew from <5% in December 2021 to 100% by the end of January 2022 (Figure 4). During the surveillance period ending July 2022, various Omicron lineages, including BA.1, BA.2, BA.3, BA.4, and BA.5, were detected in Bengaluru.

Sub-lineages of Omicron and their spread

A total of 7881 Omicron cases were detected in the samples sequenced from January to July 2022. We found a total of 51 Omicron sub-lineages during this time period.

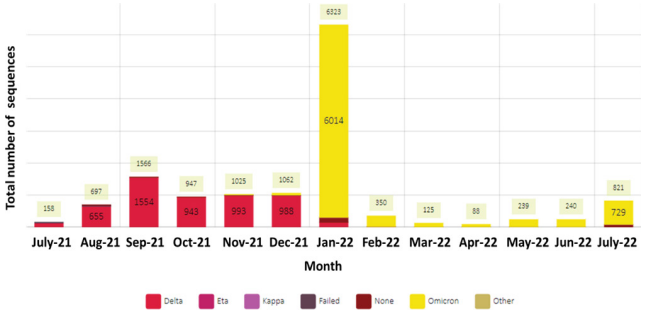

Figure 4: Month-wise distribution of SARS-CoV-2 Variants of Concern (VoCs) and Variants of Interest (VoIs) in Bengaluru from July 2021 to July 2022. X-axis represents the month and Y-axis represents the total number of sequences. The Delta to Omicron takeover is clearly visible in the figure.

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Of these 7881 Omicron cases, 6814 (86.4 %) are BA.2 and sub-lineages, 657 (8.3%) are BA.1 and sub-lineages, 116 (1.5 %) are BA.3, 4 (0.1%) are BA.4 and 286 (3.6%) are BA.5. The top BA.2 sub-lineages found in Bengaluru during this time period were BA.2.10 and its sub-lineages and BA.2.75. The top three BA.1 sub-lineages found in Bengaluru during this time period were BA.1.1, BA.1, BA.1.1.7 and BA.1.18 (Table -1).

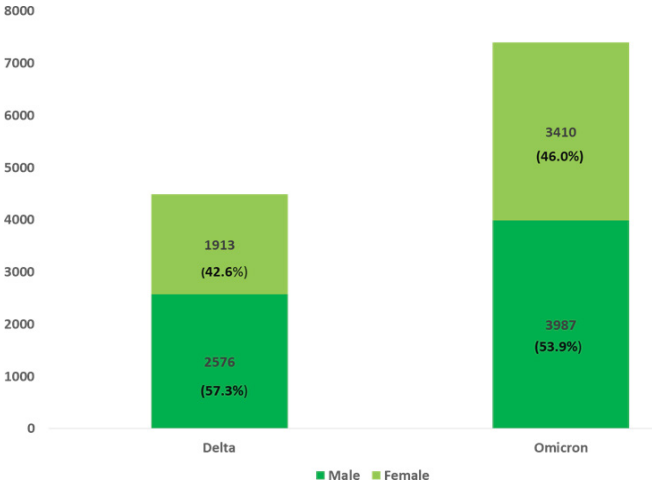

Figure 5: Gender wise distribution of Delta and Omicron lineages detected in this study.

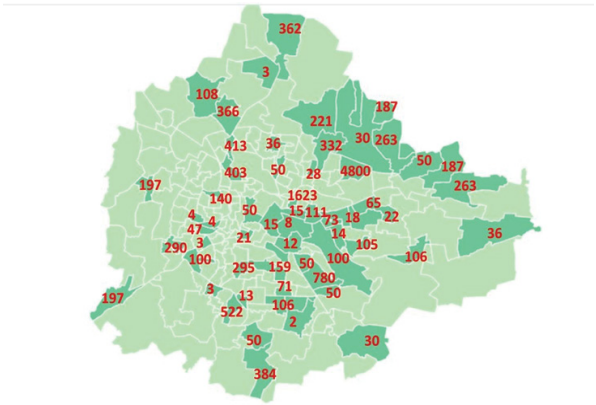

Figure 6: Bengaluru city map highlighting regions (in dark green) where samples were collected. The number of samples collected from each ward is indicated in red.

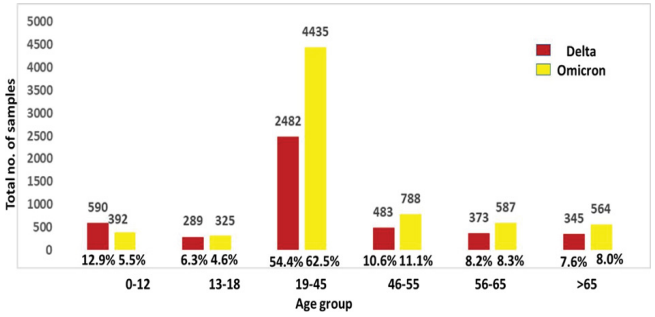

Figure 7: Age-wise distribution (for each variant) of Delta (A) and Omicron (B) lineages. Total number of samples are labeled on the top of the bar and percentages of total Delta and Omicron variants in different age groups are marked at the bottom of the bar.

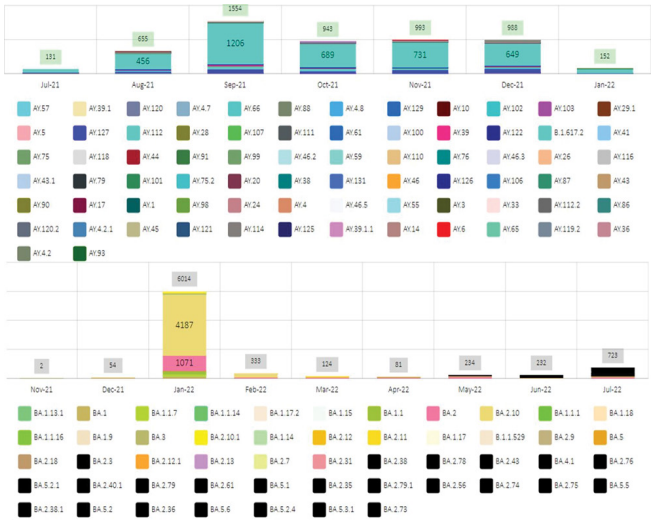

Figure 8: Relative frequencies of Delta (A) and Omicron (B) sub-lineages detected in Bengaluru during the study period.

Table 1: Month wise distribution of SARS-CoV-2 lineages in Bangalore (July 2021 to July 2022). The * symbol indicates the other sub variants of that particular lineage.

Year	2021						2022							
Months	**Jul**	**Aug**	**Sept**	**Oct**	**Nov**	**Dec**	**Jan**	**Feb**	**Mar**	**April**	**May**	**June**	**Jul**	**Total**
Total sequences	131	655	1544	943	995	1042	6166	333	124	81	234	232	729	13209
Delta	131	655	1554	943	993	969	152	0	0	0	0	0	0	5397
BA.1*	0	0	0	0	2	57	570	20	0	1	4	1	2	657
BA.2*	0	0	0	0	0	10	1072	75	87	66	180	140	218	1903
BA.2.75	0	0	0	0	0	0	0	0	0	0	0	8	223	231
BA.2.12*	0	0	0	0	0	0	19	2	1	2	23	9	3	59
BA.2.10*	0	0	0	0	0	6	4264	213	36	10	24	12	56	4621
BA.3	0	0	0	0	0	0	92	23	0	0	1	0	0	116
BA.4*	0	0	0	0	0	0	0	0	0	0	1	4	3	8
BA.5*	0	0	0	0	0	0	0	0	0	2	2	58	224	286
Unassigned	27	42	12	4	30	20	154	0	1	7	4	8	92	346

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Phylogenetic analysis

Phylogenetic analysis revealed the rise and fall of SARS-CoV-2 variants in Bengaluru from July- 2021 to Jyly-2022. It is clearly evident that the circulation of clade 22D or BA.2. 75 and 22B or B.5 in Bengaluru in July 2022.

Discussion

As of May 31, 2022, a total of 30,066 (including 11500 from Strand Life Sciences) sequences have been deposited into openly available database Global Initiative on Sharing All Influenza Data (GISAID) that facilitated rapid and open sharing of SARS-CoV-2 genome sequences, from the Indian State of Karnataka [9]. This data suggests that the 38.2% of the sequences has so far contributed to GISAID by genomic sequencing efforts of Strand Life Sciences in collaboration with local government bodies and with support by Blockchain For Impact. For a comprehensive overview of the submitted sequence data, as of May 28, 2024, India has submitted over 0.3 million sequences to GISAID, with about 50,000 (approximately 16.67%) of them from Karnataka. Strand Life Sciences has submitted about 13,000 sequences, which is about 26% of the total sequences from Karnataka. Along with detection, this provided an added advantage of understanding the genetic epidemiology of the outbreak over a period of time. Our data demonstrated that the Delta and Omicron affected males more compared to females (Figure 5), which could be due to the more number of samples sequenced from males. According to large-scale study conducted by Wang et al in the United States, females are more infected by these two variants [33]. We have detected over 100 lineages of Delta and Omicron lineages circulating in Bengaluru during the study period and reported the changing landscape of SARS-CoV-2 variants in the city (Figure-8).

Introduction and spread of Omicron and its sub-lineages in Bengaluru

The variant Omicron (lineage B.1.1.529 and its sub-lineages BA.1 to BA.5) was designated as a Variant of Concern by the WHO on 26th Nov 2021, very soon after reports of the variant and associated surge in cases were reported from South Africa [34]. This variant has a large number of mutations in the spike protein, conferring properties of immune escape [35,36]. Strand Life Sciences played a key role in detection of Omicron in returning international travelers to Karnataka. Continuous monitoring of SARS-CoV-2 in Bengaluru city allowed early detection of the spread of Omicron in the community. Sequencing of returning international travelers from South Africa was initiated in late November, even as the world was beginning to appreciate the high transmission of the Omicron variant. The first sequence of Omicron from Karnataka was reported in collaboration with the National Centre for Biological Sciences on Dec 02, 2021 as submission to the GISAID database. Of Omicron and its sub-lineages, BA.1, BA.2 and BA.3, BA.4 and BA.5 and their sub-lineages have been detected in Karnataka (Table 1). It has also been found to displace and transmit faster than Delta, the then circulating VoC in many parts of the world. Initially, a sub-variant BA.1 was the most common circulating version of Omicron. But a genetically distinct sub-variant BA.2 and its sub-lineages BA.2.10 and BA.2.12 now account for the majority of new cases and have become the dominant coronavirus variant around the world [37]. Our data suggests that BA.2.10 and its sub-variants were responsible for the COVID-19 wave in January and February 2022, while BA.5 and BA.2.75 were responsible for the COVID-19 cases in July 2022 (Figure 9).

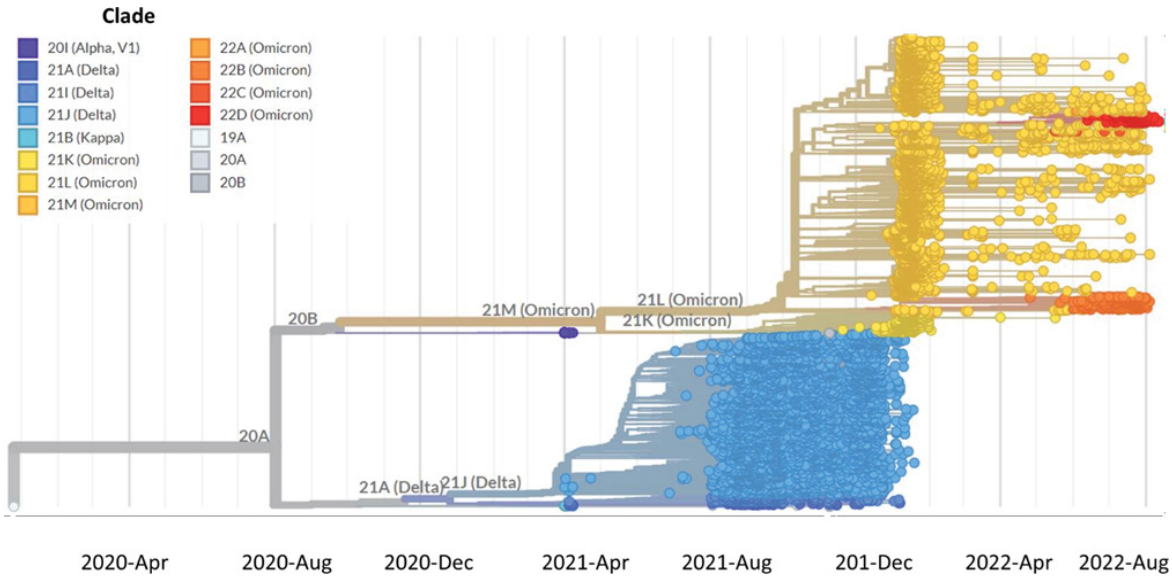

Figure 9: Phylogenetic analysis of 11110 SARS CoV-2 genomes sequenced from July-2021 to July 2022.

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Timely information that AY.4.2 was not a variant of concern in Bengaluru

AY.4.2 is a sub-lineage of the Variant of Concern Delta [4]. It was highlighted as a potential Variant of Interest in the UK in late October 2021 (38). At this time, there were two reported sequences of this lineage from Karnataka in GISAID collected in July 2021. Due to the continuous sequencing of SAR-CoV-2 performed between July -October 2021 by Strand Life Sciences, we were able to show that in Bengaluru there had been no expansion of this sub-lineage. Only 1/948 sequences in October 2021 from Bengaluru belonged to this lineage. This information was shared with the relevant authorities in a timely manner.

Key Contributions of this Initiative

In order to address the main challenge of data integration, Strand Life Sciences has developed a dashboard for real-time integration of SARS-CoV-2 sequencing data with the clinical and epidemiological information of the cases – CoviSurve. CoviSurve eases the visualization and interpretation of sequencing data. When a variant is detected, CoviSurve can help answer the questions on who/how many had that variant and where and when it was detected and also help analyse the mutations and locations where a novel mutation is dominant – this can serve as a tool for early identification of novel variants. The inbuilt reporting into CoviSurve helps generate relevant and real-time reports, including analysis of variants in sub-groups such as vaccinated individuals and children.

Building upon the foundation laid by Strand Life Sciences, ARTPark is now continuing its work with dashboards and health reporting in collaboration with the Government of Karnataka through the integrated command and control center. To ensure that the learnings and systems developed during the pandemics are not lost, ARTPark has partnered with the Department of Health and Family Welfare, Government of Karnataka, to create an AI-based disease prediction platform for predicting Dengue outbreak risks. This platform, called PRISM-H (Platform for Research, Integrated Surveillance, and Management of Health), is developed using data from multiple sources, including but not limited to, line lists, rainfall, temperature, humidity, and other climate parameters, entomological factors, land use, land cover, and mobility. Originally built as a pilot for Dengue, PRISM-H is currently being explored for expansion to other diseases, geographies and can serve as a ready tool for implementation in scenarios of epidemics or pandemics.

In summary, the integration of genomic surveillance with advanced epidemiological modeling provides a robust framework for managing pandemics involving multiple variants. This approach not only enhances our understanding of the interplay between different variants but also informs more effective and timely public health interventions, ultimately contributing to better outcomes in controlling disease spread and reducing public health impacts [38].

Conclusion

It was essential that the surveillance efforts be kept up, and ideally expanded, so that variants, in particular those that can cause severe disease or evade immunity that is conferred by natural infections or existing vaccines, can be detected early on. This will allow for the most effective prevention and treatment options. It was imperative that this be done in order to stop the further spread of the disease. As part of the response to the pandemic, continuous monitoring of SARS-CoV-2 variants at a local scale, as well as timely analysis and reporting of potential variants of concern, must continue to be prioritised. In order to make a significant contribution, we have developed tools and scalable systems for genomic surveillance. These systems and tools have the potential to be utilised in the investigation of other types of pathogens in the future.

Data Availability Statement

All the sequences are available at GISAID open database.

Supplementary Data

The JSON tree files are attached for the visualization of phylogenetic tree in Auspice https://auspice.us/.

Author Contributions

PKH- conceptualization, writing, metadata, management, CP- conceptualization, writing, AKG- project management, MJ-sample collection, SM-methodology, MN-methodology, SA- methodology, DP-methodology JP-methodology, MN-analysis, data curation, SS-analysis, data curation, AJ- conceptualization, VV-conceptualization, RH- conceptualization, VC-conceptualization, writing, VUSR- conceptualization, MB- metadata, BR-metadata TC- conceptualization, GG-conceptualization, RD- conceptualization, VR-conceptualization, writing, management.

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Conflict of Interest

Employees of Strand Life Sciences Private Limited may hold shares in Strand Life Sciences Private Limited. The remaining authors declare no competing interests.

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