

Newer variants of COVID-19, newer challenges of whole-genome strategy in India: A public health perspective

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ABSTRACT

The sudden upsurge in the newly emerging COVID-19 variants acted as a catalyst for India to scale up the viral Genomic surveillance in order to understand the nature and trends of the newer variants of concern and strengthen public health interventions across the country. The Government of India has proposed the Indian SARS-CoV-2 Genomics Consortium to expand the whole-genome sequencing (WGS) of this virus. However, in a vast country like India introduction and implementation of any new strategies amidst the already existing barriers due to COVID-19 will be a herculean task. This paper talks about how the primary care physicians can play a vital role in successful implementation of the above strategy in addition to the surveillance systems in India.

Keywords: Genomics consortium, newer variants, primary care physician, surveillance, whole-genome sequencing

Background

The first human cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), subsequently named COVID-19, were first reported by officials in Wuhan City, China, in December 2019. It was declared by WHO as a pandemic on March 11, 2020.^[1] In the month of September 2020, United Kingdom (UK) reported a new variant, termed VUI 202012/01 (Variant Under Investigation, year 2020,

month 12, variant 01). Henceforth, UK faced an escalation in COVID-19 cases in South East England, leading to enhanced epidemiological and virological investigations.^[2] This new variant was defined by multiple spike protein mutations (deletions in 69-70 and 144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H).^[3]

Although it is known and expected that viruses constantly change through mutations leading to the emergence of newer variants which may vary in their transmissibility, severity and response to vaccines. Preliminary analysis suggests that owing to these aforementioned mutation, there may be a steep rise in the reproductive number (R) by 0.4 or greater leading to an estimated increased transmissibility of up to 70%. Since the

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last week of December, UK variant (VOC 202012/01) cases have also been reported in many other EU/EEA countries and globally (Australia, Canada, Hong Kong SAR, India, Israel, Japan, Jordan, Lebanon, South Korea, Switzerland, Singapore). In addition to this, another mutant variant was detected in South Africa from October 2020.^[4] It was named 501.V2, as it is phylogenetically different from the UK variant despite of N501Y mutation. It rapidly replaced the existing forms of SARS CoV2 in most of the provinces in South Africa and preliminary results indicate that this variant may also have an increased transmissibility and the effectiveness of the vaccines may also be less than other strains. However, there is no experimental evidence or indication at this point of increased infection severity or mortality associated with the S. African variant.^[5]

After the UK variant, the newer variants known as Variants of Concern (VOCs) too have found their way into India. As reported by spokesperson from ICMR, at least four people were tested positive with the South African variant (B.1.351 variant) of the virus by the end of January and one was tested positive with the Brazil variant (B.1.1.28.1 or P. 1 variant) in February.^[6] So far 771 COVID-variants including double-variants (E484Q and L425R) have been detected from 18 states across the country but a link to the current surge in cases is yet to be established. Some of the states like Maharashtra have witnessed an increase in the proportion of samples (15%–20%) with newer variants.^[7]

Use of Whole-Genome Sequencing as an Epidemiological Tool in India

Advances in diagnostic tools have led to a more refined understanding of the dynamics of many infectious diseases by typing the pathogens by a genetic or phenotypic feature and epi-linking of these data to the line list.^[8] Since the declaration of the pandemic several countries in the world particularly USA, Iceland, Netherland, UK, and Australia have made tremendous progress in genome sequencing.^[9]

India initiated the whole-genome sequencing (WGS) in April 2020 wherein two national institutes: Centre for Scientific and Industrial Research (CSIR) Centre for Cellular and Molecular Biology (CCMB), Hyderabad, and Institute of Genomics and Integrative Biology (IGIB), New Delhi were designated for this task. Their objective was to gain insight to the evolution of the virus and understand its dynamics, spread across the country and establish a family tree. NIV Pune was also roped in to provide viruses that have been isolated from different parts of the country.^[10]

A large number of SARS-CoV-2 genomes (about 1500 complete genomes) have been sequenced in different parts of India. The first sequences from India were reported from individuals with travel history to China, Italy, and Iran. An analysis of 361 complete genome sequences from India showed that five global clades were circulating in India—old Nextstrain clades B, B4, A2a, A3, and a distinct clade A3i.^[11]

Response of the Government of India

In the wake of this alarming spread of new strains the Ministry of Health and Family Welfare, Government of India (GoI) proposed the Indian SARS-CoV-2 Genomics Consortium to expand the WGS of SARS-CoV-2 virus across the nation. The overall aim of the proposed Indian SARS-CoV-2 Genomics Consortium was to keep a vigil on the genomic variations emerging in the SARS-CoV-2 on a regular basis through a multi-laboratory network. The finer objectives were to ascertain the current status, establish sentinel surveillance for early detection of unusual events (including super-spreader events, high mortality/morbidity trends) and ascertain the public health implications with the respect to the genomic variants.^[12]

Strategies adopted to implement the above strategy

It was envisaged that in order to implement a strategy at such a huge scale it would be imperative to use the existing three-tier system of the primary health care till the grass-root level. Since the Central Surveillance Unit (CSU) under Integrated Disease Surveillance Programme (IDSP) at the center regularly collects surveillance data in a decentralized manner from various States via State Surveillance Units (SSU) which further assimilates data from districts via District Surveillance Units (DSU), it was assigned the task of overall implementation of the above strategy.

Action plan for Lab Testing: With regard to conducting WGS, the entire country was divided into six regions for clearly defining the sample collection/transportation flow and each set of states were designated regional genome sequencing laboratories (RGSL) as given in Table 1.^[12] Ten RGSLs spread across the country were identified to serve as regional hub for genome WGS of relevant regions. The viral genome sequencing data generated by the regional genome sequencing laboratories to be sent to the National Centre for Disease Control (NCDC), Delhi for collation and integration.^[12]

The following criteria were set for selection of samples for WGS^[11]:

1. All the positive persons detected through screening of International travelers arriving in India by RT-PCR
2. a) All positive samples from subjects who have participated in vaccine trials/have been vaccinated.
b) All positive samples from people with a previous history of infection and confirmed re-infection should be included.
3. Samples of all the international passengers (100%), who have arrived in India since November 23, 2020 and tested positive by RT-PCR
4. Initially all the international passengers who had arrived in India (during the period 9 to 22 December 2020) if symptomatic and tested positive were included.
5. Representative positive specimens (randomly sampling 5% of the positive specimens) of the specimens detected from general population. A representative sample of all the positive which occur in cluster to be sent to the designated lab for genome sequencing.

Table 1: State wise designated RGSLs for sending samples for whole-genome sequencing

Regional Hub	Laboratory	States
East and North East	1. DBT- National Institute of Biomedical Genomics (NIBMG), Kalyani, near Kolkata (capacity= 5000samples/month)	West Bengal, Bihar, Jharkhand, Assam, Tripura, Meghalaya, Manipur, Arunachal Pd., Sikkim, Nagaland, Mizoram, Odisha, Chhattisgarh
West	2. DBT-Institute of Life Sciences, (ILS) Bhubaneswar (1200/mth)	
South	3. ICMR-National Institute of Virology (NIV)	Goa Maharashtra, Gujarat, western part of MP
	4. DBT-National Centre for Cell Science, Pune (1200/mth)	
	5. CSIR-Centre for Cellular and Molecular Biology CCMB. (5000/mth)	
	6. DBT-Centre for DNA Fingerprinting and Diagnostics (CDFD), Hyderabad (1200/mth)	
	7. DBT InSTEM/NCBS, Bengaluru (1200/mth)	Andhra Pd., Telangana, Karnataka (northern part of Karnataka), Tamil Nadu, Puducherry
	8. NIMHANS, National Institute of Mental Health and Neuro Sciences Hospital (NIMHANS), Hosur Road, Bangalore	
Central & North	9. CSIR-Institute of Genomics and Integrative Biology (IGIB), Delhi. (10,000/mth)	Rajasthan, Punjab, Haryana, western part of UP, Kerala samples will be sequenced at IGIB, Eastern part of MP, Uttarakhand, Delhi, Haryana, Himachal Pd., Ladakh, J&K, Punjab
	10. NCDC, Delhi - Division of Bio-technology, Epidemiology and Central Surveillance Unit (3,000/mth)	

Monthly estimated sequencing capacities of RGSLs are provided in brackets

Extensive trainings were undertaken by CSU through a series of video conferencing and meetings with the state-level representatives to introduce this concept, discuss the implementation plan and clarify their doubt from time to time. Online meetings and trainings were held at DSU level for the primary care physicians and medical officers at district and block level to update them with the latest developments and disseminate the guidelines for identifying and sending samples for WGS testing. They were also sensitized to coordinate with the district authorities for timely reporting of cases, with special emphasis on re-infections/clustering as representative samples for WGS testing and cooperating in tracing of contacts of international travelers tested positive from the community.

Challenges and Recommendations

There are several challenges posed by this strategy in terms of its implementation and operational feasibility. First of all, WGS requires a lot of time, resources and expertise. Despite of availability of specialized labs and infrastructure needed to undertake this specialized procedure, not all designated labs have the capacity to handle huge loads of sample in a month. Although due to advances in technology, genome sequencing can also be carried out in smaller labs. However availability of uninterrupted supply of reagents and efficiency to undertake WGS at large scale remains a major constraint. The genome sequencing for assessing the current status from the samples tested positive during past months will also depend on the availability of aliquots of positive samples in Government/private labs as, many of the labs were not storing the positive samples.

Making arrangements for timely and proper transportation of samples from the labs to the designated RGSL as per guidelines is yet another challenge. Collection of samples at international airports and port of entries can easily be streamlined by the airport authorities in coordination with the Ministry of Health Affairs and Civil Aviation, as infrastructure and trained manpower already exist. But what about picking up 5% representative

samples from general community? Considering the specialized nature of the test, judiciously identifying samples from general population posed the biggest challenge. As the objective of taking sample from positive cases from general population is to get an estimate of whether the strain has gained a foothold in the general community or not, the samples from selected hospitals alone will provide a very sketchy estimate in that regard. In order to counter this problem samples from labs of regional level, medical colleges till the district level may be sent on rotation basis. In addition, samples from cases of re-infection, critically ill patients admitted in ICU settings may also be given a priority.

At this juncture, the primary care physicians and medical officers at PHCs also have a crucial role to play in disseminating awareness about the new variants and identifying from where the 5% of the positive samples to are to be picked up from general population for further genome sequencing as they are the ones who come in first contact with the community. Very often clusters of cases among community are brought to light by primary care physicians and without their support and cooperation contact tracing and timely transport of samples for WGS from community would encounter roadblocks.

Retrospective tracing of travelers and their contacts who traveled to other states or districts from the airport also faced its fair share of problems, particularly in remote or hilly areas. There may be limitations with regard to the number which can be processed in each RGSL for genome sequencing and hence, there may be issues when there is surge in any of the states/countries in future. Although specimens collected in the past will have such limitations, with cooperation of health authorities at block or district level such obstacles may be overcome.

Considering the rapid spread of these newer variants testing alone will not serve the purpose. The government should be able to provide them supportive isolation, have sufficient manpower to undertake extensive tracking and contact tracing/quarantining of all the contacts. Ideally, all international travelers should be

tested considering the rapid spread of variants globally. But above all ensuring that people to avoid non-essential travel, raising awareness about continuing to comply with COVID appropriate behavior in the community and motivating them to get vaccinated can only be done by primary care physicians and public health personnel.

Summary and Key Points

In view of the potential threats from the newer emerging variants, India needs to strengthen its surveillance system as well as step up the genome sequencing and characterization strategy along with ensuring better geographical representation. India has already made a head-start but WGS strategy being a relatively newer concept will encounter many teething problems but the importance of this advanced tool in gaining insight to the emerging variants of the virus and taking adequate public health actions such as diagnostics, vaccines, and preventive measures, cannot be undermined. Accordingly, the entire public health system till the primary care level has to be updated and geared up to respond to such variants. As IDSP already has an existing network of robust surveillance mechanisms it can provide technical support which is an important thrust area. However, its successful implementation will eventually depend on the concerted efforts; which entails greater inter-sectoral coordination, information sharing by multiple stakeholders including medical officers, physicians, public health personnel, and the existing health surveillance mechanism for timely response and adequate representativeness. Without the support and cooperation of primary care physicians, this huge task will not be achievable.

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Conflicts of interest

There are no conflicts of interest.

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