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SARS-COV-2 VARIANTS IN INDIA AMD ITS IMPACT ON HUMAN HEALTH: AN OVERVIEW

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ABSTRACT

All viruses including SARS-CoV-2, the virus that causes COVID-19 evolve. When a virus replicates or makes copies of itself, it occasionally rearranges its genome. These changes in the genome are termed "mutations". A virus with one or more new mutations is referred to as a "variant" of the original virus. These mutations may lead to phenotypic changes which may increase or decrease the virulence of the virus. Recently, India surpassed Brazil to become the country with the second-most COVID-19 cases worldwide, only next to the United States. According to the John's Hopkins database, COVID-19 has infected 17,997,267 people in India by the end of April 2021. Over the last week of April 2021 itself, India reported an average of approximately 350,000 daily new cases and 3000 daily deaths, setting a grim new record for the country.[1] With the second wave of COVID-19 wreaking havoc in India, the major cause of concern is the third mutation in this B.1.617 strain that has now been identified in at least four states of India. Two of these triple-mutant varieties have been found in samples collected from Maharashtra, Delhi, West Bengal, and Chhattisgarh. The Indian-origin double mutant strain of the coronavirus, B.1.167, that many experts say could be behind the rapid climb of the second COVID-19 wave, was first detected way back on October 5, last year through genome sequencing of a virus sample.

What impact do the new variants of the COVID-19 virus have on vaccines?

The COVID-19 vaccines that are currently in development or have been approved are expected to provide at least some protection against new virus variants because these vaccines elicit a broad immune response involving a range of antibodies and cells. Therefore, changes or mutations in the virus should not make vaccines completely ineffective. Recently a preliminary study by the ICMR and Bharat Biotech concluded that Convalescent sera of the COVID-19 cases and recipients of BBV152 (Covaxin) were able to neutralize VUI B.1.617.[2,3]

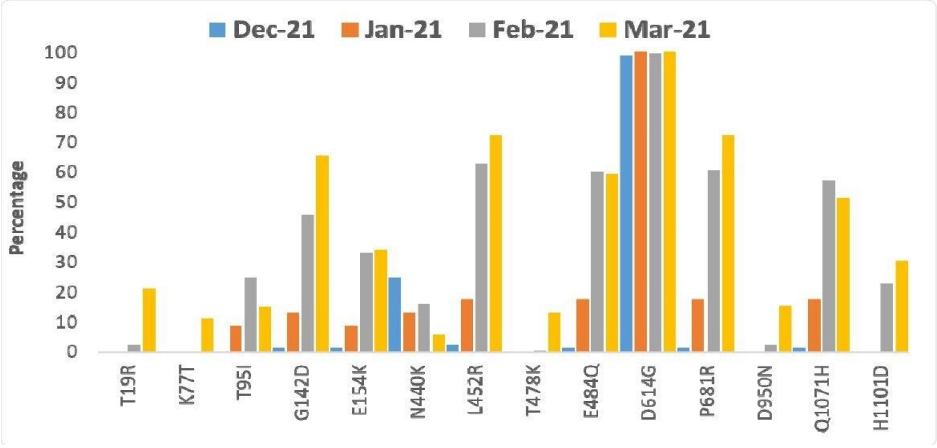
Data continues to be collected and analysed on new variants of the COVID-19 virus. More trials are underway and WHO is working with researchers, health officials, and scientists to understand how these variants affect the virus's behaviour, including their impact on the effectiveness of vaccines, if any. At the time of this article's writing, however, all evidence suggests that all COVID-19 vaccines are 100% effective in preventing severe disease and therefore all individuals eligible should be encouraged to get vaccinated.

In the future, manufacturers and the programs using the vaccines may have to adjust to the evolution of the COVID-19 virus: for example, vaccines may need to incorporate more than one strain when in development, booster shots may be required, and other vaccine changes may be needed. Trials must also be designed and maintained to allow any changes in efficacy to be assessed and must be of sufficient scale and diversity to enable clear interpretation of results. Studies of the impact of vaccines as they are deployed are also essential to understand their impact. Research groups have carried out genomic sequencing of the COVID-19 virus and shared these sequences on public databases, including GISAID. This global collaboration allows scientists to better track how the virus is changing. WHO recommends that all countries increase the sequencing of the COVID-19 virus where possible and share data to help one another monitor and respond to the evolving pandemic.

WHO has also established a SARS-CoV-2 Risk Monitoring and Evaluation Framework to identify, monitor, and assess variants of concern. It will involve components like surveillance, research on variants of concern, and evaluation of the impact on diagnostics, therapeutics, and vaccines. The framework will serve as

a guide for manufacturers and countries on changes that may be needed for COVID-19 vaccines.

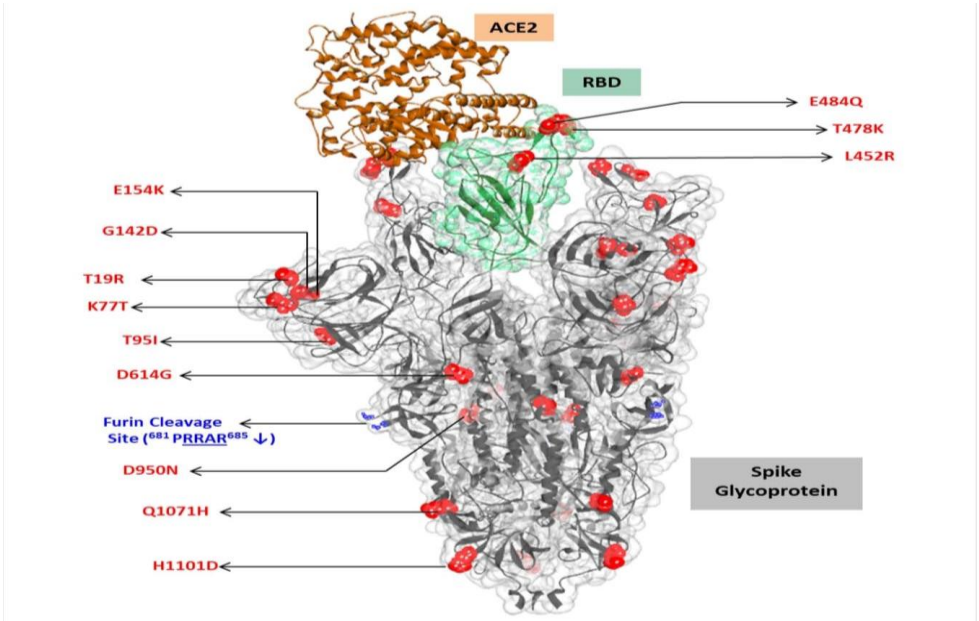
In recent preliminary study researchers from several Indian institutes involved in SARS-CoV-2 research obtained samples from international travelers to Maharashtra. About 5% of the surveillance samples tested positive for COVID-19. The team sequenced the genomes of SARS-CoV-2 and analyzed the crystal structure of the top 10 virus spike protein mutations complexed with the human receptor, angiotensin-converting enzyme 2 (ACE2) while assessing the effect of mutations on binding to two neutralizing antibodies using the structures.[4]



Trend of major mutations in the spike protein from December, 2020 to March, 2021[4]

Identifying mutations

Post analysis of 598 whole viral genomes, the team found 47 G lineages, the most common among them being B.1.617, which composed roughly half the sequenced genomes. Within the B.1.617 clade, they discovered four clusters linked to specific spike protein mutations. The researchers documented that mutations L452R and E484Q in the receptor-binding domain (RBD) of the spike protein and the mutations G142D and P681R outside the RBD increased in frequency from January 20214. Other mutations included H1101D and T95I4 and only a small proportion of the sequences showed the B.1.1.7 variant, particularly in December 2020. One cluster of mutations did not include E484Q and had T19R and D950N mutations in the spike protein. Another mutation D111D occurred along with the RBD mutations L452R and E484Q but was not seen in the cluster without the E484Q mutation.[4] Analysis indicated an increase in the frequency of non-synonymous mutations (those that change protein sequences) since February 2021. In western Maharashtra, places such as Mumbai, Pune, Thane, and Nashik showed several lineages apart from the dominant B.1.617 seen in the eastern part of the state.



Mapping of key mutations on the furin-cleaved crystal structure of SARS-CoV-2 spike glycoprotein (grey surface view) in complex with ACE2 (brown solid ribbon). RBD region shown in green.[4]

How can we prevent future new variants of the COVID-19 virus?

As per CDC, halting the spread at the source remains key. Current CDC guidelines to reduce transmission which include frequent hand washing, wearing a mask, social distancing, good ventilation, and avoiding crowded places or closed settings continue to work against new variants as well. They reduce the amount of viral transmission and thereby reducing opportunities for the virus to mutate. Scaling up vaccine manufacturing and rolling out vaccines as quickly and widely as possible will also be critical ways of protecting people before they are exposed to the virus and the risk of new variants. Priority should be given to vaccinating high-risk groups everywhere to maximize global protection against new variants and minimize the risk of transmission. Moreover, ensuring equitable access to COVID-19 vaccines is more critical than ever to address the evolving pandemic. As more people get vaccinated, we expect virus circulation to decrease, which will then lead to fewer mutations.

Current SARS-CoV-2 variants in India

The A2a takeover from A3i and other minor variants in India is summarized here. The first instance of the A2a variant was identified from samples collected in early March with increasing prevalence in the following months. Currently, two subtypes of A2a are dominant across India, characterized by differing mutations in the N gene and other ORFs, in addition to the D614G spike mutation. The variant landscape is mostly concordant across states in India. However, there appear to be instances of high representation of specific variants in selected states. These include the ORF3a mutation L46F from Telangana and the Spike mutation L54F seen in Gujarat (Singh et al. 2020; Hassan et al. 2020). Another Spike mutation N440K was first identified in late June in the state of Andhra Pradesh and has been present in *6% of the samples collected from India since then (Jolly et al. 2020). The top three genes where most mutations have been identified are ORF1a (2333), ORF1b (1278), and S (714). The first positive case in India was reported from Kerala in January of a patient who had traveled from Wuhan, and the state provides a unique opportunity to study viral diversity (Yadav et al. 2020). A study conducted on 200 samples identified 4 novel genetic variants and 89 variants that were exclusive to Kerala and not present in other parts of the country (Radhakrishnan et al. 2020). As seen in the country track on the top, A3i clade (green) was prevalent during the months of March-May and was eventually overtaken by the A2a clade (blue). As of December 2020, a new country-wide consortium named INSACOG has been established to identify new and circulating variants by genome sequencing across multiple states (MoHFW 2020). One of the main goals of this consortium is to sequence 5% of all COVID-19 positive cases in the country.

New global variants and causes for concern The mutation landscape of SARS-CoV-2 have been under constant global scrutiny to understand the effect of these changes on the infectivity and antigenicity of the virus. While most mutations are of little to no consequence, sometimes the virus acquires a mutation that gives it an advantage over other strains. The Spike protein is used by the virus to enter human cells via the ACE2 receptor. Thus, Spike mutations can potentially facilitate better affinity or binding and enable easier entry into the host cell, as seen in the case of the D614G mutation described in the preceding section. The receptor-binding domain (RBD) in the spike protein is the most variable part of the coronavirus genome (Zhou et al. 2020). Mutations can putatively also render the virus resistant to neutralization by host antibodies and thus need to be identified and monitored for the efficacy of antibody therapeutics. Some of the spike mutations recently identified that are of concern include the N439K, N440K, Q493K, and E484K, which are prone to immune escape (Andreano et al. 2020; Thomson et al. 2020; Weisblum et al. 2020). Of these, the N440K variant has been found in *42% of the samples from Andhra Pradesh and E484K in 3 samples from Maharashtra (Jolly and Scaria 2020; Singh et al. 2020). Most of the other mutations are absent in currently sequenced samples from Indian isolates and need to be actively monitored.

European lineages identified in Denmark and Spain: SARS-CoV-2 was recently introduced into minks from humans and since then has adapted to the mink host. A unique strain called Cluster 5 was identified in both hosts which encompasses three amino acid changes (I692V, M1229I, and Y453F) and two deletions (del 69–70) in the spike protein (Oude Munnink et al. 2020; Van Dorp et al. 2020a, b). This variant was last seen in September across genomes. Recent surveillance studies by European consortia have identified several other strains of SARS-CoV-2 that show increased transmission. Vaccine efficacy and immune evasion mutations SARS-CoV-2 can theoretically evolve to evade immunity when brought under the stress of therapeutic or preventive interventions. A prevalent mutation of the Spike receptor binding motif (RBM) - N439K - has enhanced binding affinity to the hACE2 receptor, and can likely evade neutralizing antibodies since it is a part of the epitope recognized by these antibodies (Thomson et al. 2020). Another mutation in the RBD region, E484K has been described in lineages in South 22 Page 10 of 14 Surabhi Srivastava et al. Africa (501Y.V2 (B.1.351)) and Brazil (descended from the B.1.1.28 lineage) and is shown to reduce the neutralization potency of some human sera by [10- fold. It is of concern that this mutation can impact binding and can escape even a potent polyclonal serum targeting multiple neutralizing epitopes (Greaney et al. 2020; Andreano et al. 2020; Weisblum et al. 2020). The currently approved vaccines raise a host immune response against multiple epitopes of the viral proteins, decreasing the chances of a few mutations facilitating efficient vaccine escape and there is hope that immune

evasion will therefore be controlled before such variants spiral out of control. Currently, none of the variants of SARS-CoV-2 appear to have higher virulence or contribute to greater disease severity. However, such mutations that maintain virulence and viral fitness need to be identified and monitored to inform the future of Covid-19 vaccines and therapeutics, so that combinations of antibodies based on distinct epitopes can be designed for laboratory analysis of escape prevalence (Weisblum et al. 2020). A recent study has characterized the novel N501Y and other Spike mutations for the potential of infection as well as vaccine-based immune evasion (Shang and Axelsen 2020). Even as the vaccination process has now been initiated globally, the current vaccines are also being evaluated for their potential against the new viral mutations as they arise.

CONCLUSION

As the COVID-19 pandemic enters its second year, it is crucial to keep a lookout for new and emergent strains and localized disease outbreaks. The evolution of SARS-CoV-2 can render it more infectious via adaptive mutations that increase affinity or enhance binding to host cells, while escape mutations that can help it evade the immune response have serious implications for vaccines and therapeutics and can adversely impact the severity and mortality of the disease. As multiple vaccines are rolled out in the year ahead, the virus will be subjected to new selection pressures and evolution modes. India has so far not been sequencing SARSCoV-2 isolates to full capacity, having deposited only about 6,400 genomes of the over 10.4 million recorded cases (0.06%). Exploiting advances in genomic epidemiology by monitoring and increasing sequencing efforts following local spikes will go a long way in staying on top of mutations of concern while their biology and effects are studied in greater detail. Studying the virus under a genomic lens has played a pivotal role in tackling key challenges in pandemic management so far. Other issues beyond the scope of this article include the role of mutations in reinfections and disease severity. The extent to which genomic surveillance can help answer these questions and control outbreaks is only limited by the availability of data and will be crucial to controlling the pandemic in the future.

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