Novel Sars-COV-2 Variants & Therapeutic Effects

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ABSTRACT

COVID-19 is a severe respiratory infection caused by coronavirus 2. (SARS-CoV-2). Even while SARS-CoV-2 predominantly affects the respiratory system, it can cause problems for other important organs as well. Multiple novel variations of concern have appeared since the beginning of the SARS-CoV-2 pandemic, including the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529), all of which are linked to increased transmissibility and severity. Both the newly discovered variants and the most recent innovative treatments for the treatment of COVID-19 are discussed in this work. Care for people with this disease is discussed, with an emphasis on the need of clinical interprofessional teams, government health organisations, and community involvement.

Keywords: COVID-19, New Variant, Diseases, Pandemic.

I. INTRODUCTION

Viruses have the ability to alter and evolve into new forms. Some varieties appear and then vanish, while others persist. SARS-CoV-2 is a beta coronavirus that belongs to the Coronaviridae family (SARS). Single-stranded RNA viruses make up this group. They cause sickness in humans in the alpha and beta genera. A spillover happens when an animal-to-human virus transmission occurs. SARS-CoV-2 and coronaviruses found in bats are linked. SARS-CoV-2 shares 96.2 percent sequence similarity with RaTG13 and RmYN02 coronaviruses found in bat populations. Malayan pangolin coronaviruses have SARS-CoV-2-like sequences. It hasn't been connected to a zoonotic source. The hypothesis of undetected human-to-human transmission post-spillover posits that the virus might have acquired these genomic features before the epidemic started with SARS-CoV-2. The WHO China Country Office found an unexpected pneumonia...
aetiology on December 31, 2019. When the virus was isolated from the patients' airway epithelial cells, it was given the designation 2019-nCoV. The Coronavirus Research Group (CSG) of the International Committee for the classification of viruses called the virus SARS-CoV-2 on February 11, 2020. The COVID-19 virus, SARS-CoV-2, changes throughout time. Most modifications have little or no effect. Vaccines, therapeutic treatments, diagnostic tools, and other public health and societal measures may all be affected by changes in the virus's characteristics. World Health Organization (WHO) has been tracking and evaluating the transmission of SARS-CoV-2 since January 2020. Variants of Interest (VOIs) and Variants of Concern (VOCs) were defined in late 2020 to help focus global surveillance and research, and eventually help shape the late 2020s COVID-19 pandemic response.

A virus with significant amino acid changes can be dealt with by the WHO and its international expert networks. Globally, mechanisms are being developed to identify probable VOIs or VOCs and assess public health risks. Other local interests or concerns may be designated. Limiting mutations hazardous to human health requires using well-established and validated disease control strategies and approaches. Even though viruses have mutated, WHO-recommended methods and procedures still operate. In many countries, IPC measures have been shown to reduce COVID-19 cases, hospitalizations, and VOC-related mortality. Governments should support current PHSM and IPC projects. The WHO recommends tracking and sequencing SARS-CoV-2 mutations to detect unusual epidemic episodes (WHO).

II. PATHOGENESIS AND GENETIC

The immune system protects pathogens such as viruses and bacteria by a range of cells and cytokines involved in innate and adaptive responses. Human MHC genes encode Human Leukocyte Antigens (HLA) (HLA). HLA alleles range from three to six in different ethnicities. HLA molecule variation affects the cellular immune response to human infectious pathogen peptides. To recognise HLA class I or II antigens on the surface of the cell, CD8 or CD4 T cells must be able to detect HLA class I or II antigens. Mild and severe COVID-19 patients had varying immunological responses, including IgM and IgG levels. An article on the link between HLA and clinical heterogeneity in disease also looked at theoretical diversity in the potential to bind SARS-CoV-2 peptides. Because HLA molecules affect the immunological response to SARS-CoV-2, this locus variability may assist identify high-risk people and establish a personalised treatment regimen. COVID-19 HLA class I and II alleles were discovered in 82 Han Zhejiang people. After adjusting for the Benjamini-Hochberg approach, COVID-19 patients had higher prevalence of HLA-B15:27 and C*07:29 than previously investigated controls. However, uncorrected tests showed other alleles, such as HLA-B*15:27, B*40:06, DRB1*04:06, and DPB1*03:01, which were less prevalent among COVID-19 patients compared to the control group. HLA-DRB1*15:01, DQB1*06:02 and B*27:07 alleles were connected to COVID-19 susceptibility in 99 Italians, whereas HLA-C*01 and B*44 alleles are strongly linked to SARS-CoV-2 infection in Italy. The HLA-A*11:01, -B*51:01, and -C*14:02 alleles were associated to the worst result in a Chinese group.

Regarding the severity of the disease, a study including 72 Spaniards with COVID-19 reported three HLA alleles associated with higher mortality (HLA-A*11, -C*01, and -DQB1*04) when the scores of Sequential Organ Failure Assessment (SOFA) and Acute Physiology And Chronic Health Evaluation II (APACHE II) were controlled. The HLA-DRB1*08 was correlated with mortality of COVID-19 in the Italian population, and the peptide binding prediction analyses showed that the allele was unable to bind any of the SARS-CoV-2 peptides with high affinity. The HLA-C*05 allele was also correlated with COVID-19 mortality in an ecological study. Also, in a recent in silico analysis of the binding affinity between HLA class I molecules and all SARS-CoV-2 peptides, the HLA-B*46:01 allele was identified as a vulnerability biomarker due to low predicting binding sites. In contrast, the HLA-B*15:03 was considered a protector allele for showing the most significant capacity to present highly conserved SARS-CoV-2 peptides. The HLA-A*25:01 and -C*01:02 alleles were also related to a low predicted capacity for SARS-CoV-2 epitope presentations, whereas the highest predicted presentation capacity was observed for HLA-A*02:02 and -C*12:03 alleles. In agreement, another study using artificial neural networks identified the HLA-B*46:01 and HLA-A*25:01 as weakly binding alleles, while HLA-A*02:02 was one of the HLA class I alleles found to present a strong binding to virus selected peptides. Interestingly, HLA-A*02 alleles, among other class I and II alleles, were also identified as functional molecules for presenting SARS-CoV-2 peptides in a bioinformatic prediction study. In this same last report, an ecological study was also performed, and the HLA-DRB1*01 allele was found associated with COVID-19 fatality in a Mexican population; and, although the authors have addressed several limitations, the result must be taken with caution. Nevertheless, other in silico analyses reported a possible association of HLA-A*02:01 with increased risk for COVID-19 and a lower capacity of this allele to present SARS-CoV-2 antigens in comparison to other HLA variants. These results seem to be contradictory compared to those previously mentioned, in which HLA-A*02 alleles were considered to have an adequate predicted capacity of antigens presentation. Therefore, the association should be taken with caution until the results of clinical studies were
published. Regarding HLA haplotypes, the study of regional frequencies for the most common Italian haplotypes reported that the HLA-A*01:01-B*08:01-C*07:01-DRB1*03:01 and HLA-A*02:01-B*18:01-C*07:01-DRB1*11:04 were correlated with COVID-19 incidence and mortality, suggesting risk and protection-related haplotypes, respectively. In an association study performed in a Sardinian population, the three-loci haplotype HLA-A*30:02-B*14:02-C*08:02 was more common among patients with COVID-19.

III. COVID-19 VARIANTS

Multiple SARS-CoV-2 variants are circulating globally. Several new variants emerged in the fall of 2020, most notably:

- **U. K VARIANTS**: In the United Kingdom (UK), a new variant of SARS-CoV-2 (known as 20I/501Y.V1, VOC 202012/01, or B.1.1.7) emerged with a large number of mutations. This variant has since been detected in numerous countries around the world, including the United States (US). In 2021, scientists from UK reported evidence\(^1\) that suggests the B.1.1.7 variant may be associated with an increased risk of death compared with other variants. More studies are needed to confirm this finding. This variant was reported in the US at the end of 2020.

- **SOUTH AFRICA VARIANTS**: In South Africa, another variant of SARS-CoV-2 (known as 20H/501Y.V2 or B.1.351) emerged independently of B.1.1.7. This variant shares some mutations with B.1.1.7. Cases attributed to this variant have been detected in multiple countries outside of South Africa. This variant was reported in the US at the starting of 2021.

- **BRAZIL VARIANTS**: In Brazil, a variant of SARS-CoV-2 (known as P.1) emerged that was first was identified in four travelers from Brazil, who were tested during routine screening at Haneda airport outside Tokyo, Japan. This variant has 17 unique mutations, including three in the receptor binding domain of the spike protein. This variant was detected in the US at the starting of 2021.

- **BRAZILIAN VARIANT**: Gamma caused widespread infection in early 2021 in the city of Manaus, the capital of Amazonas, although the city had already experienced widespread infection in 2020, with a study indicating high seroprevalence of antibodies for SARS-CoV-2. A research article published in Science Journal indicate that P.1 infected people have a greater chance of transmissibility and death than B.1.1.28 infected ones. The Gamma variant comprises the two distinct subvariants 28-AM-1 and 28-AM-2, which both carry the K417T, E484K, N501Y mutations, and which both developed independently of each other within the same Brazilian Amazonas region. Gamma is notably different from the Zeta variant (lineage P.2) which is also circulating strongly in Brazil. In particular, Zeta only carries the E484K mutation and has neither of the other two mutations of concern, N501Y and K417T.

- **US MIDWEST VARIANT (20C-US OR COH.20G/S01Y)**

  It was detected in Ohio followed by other Midwest states in December 2020 and January 2021. This variant has mutations on the S protein (Q677H), M protein (A85S) and on the N protein (D377Y). Another variant with the mutation S N501Y, a marker of the B.1.1.7, with no other associated mutations with that strain has been identified. Currently there is not any evidence of increased transmissibility or virulence for this variant.

- **US SAN FRANCISCO BAY AREA VARIANT (B.1.427 AND B.1.429)**

  These variants were first identified in California in February, 2021. The notable mutations in B.1.427 are L452R and D614G; while mutations in B.1.429 are S131, W152C, L452R and D614G. Both variants have 20% increased risk of transmissibility and reduction in therapeutic efficacy. It was identified last year across the USA and Europe. It is a variant with a mutation in the S protein. In January 2021 it rose rapidly as the cause of cases across several counties in California.

- **US SOUTH CALIFORNIA VARIANT (CAL.20C)**

  It was first seen in 2020 in Southern California and detected again amongst population samples of the same region in 2020. Its notable mutations are ORF1a: I4205V, ORF1b: D1183Y, S: S131L, W152C and L452R. The binding of the S protein could be made easier by the latter three mutations.

- **B.1.526 (20C/S:484K) AND B.1.525 (20A/S:484K)**

  These variants were first identified in New York, USA. The notable mutations are E484K and S477N. While E484K decreases antibody response, S477N increases the attachment process.

- **DOUBLE MUTANT VARIANT (B.1.617)**

  This variant is first detected in India. As two mutations are seen in the same virus, this variant is called a “double mutant” variant. There was a significant increase in COVID-19 cases in India. The first case in the USA was identified in San Francisco on April 5, 2021. The notable mutations are E484Q and L452R. These variants are at increased risk of transmission and also resistant to vaccination. According to Indian Council of Medical Research Virology Lab, Bharat Biotech’s COVAXIN vaccine has been found to effectively neutralize the infection, and is 78% effective against the double mutant variant.

- **TRIPLE MUTANT VARIANT (B.1.618)**

  In addition to E484Q and L452R in double mutant variants, the new triple variant discovered 2021, is characterized by the deletion of two amino acids, H146del and Y145del in the S protein. As of 2021, a total of 1,189 samples were tested positive in Maharashtra, Delhi, West Bengal and Chhattisgarh, India. Similar to other variants, triple mutant variants have higher transmissibility. Data show that two of the three mutations in this variant are resistant to antibodies
and also possess the ability to escape the body’s natural acquired immunity to COVID-19, and as such, do not know much about the vaccine effectiveness.

- **20A.EU1/S:A222V**
  The 20A.EU1 variant has non-terminal domain (NTD) mutations which do not play a direct role in receptor binding or membrane fusion. This variant was initially identified on 20 June, 2020 in Spain but rapidly spread across Europe and many countries.

- **20A.EU2**
  The 20A.EU2 variant was found in France in 2020 and has become the second dominant variant in Europe. The notable mutations are S477N, E484K, and N501Y, which demonstrated slight increase in ACE2 binding, resistance to multiple antibodies and convalescent sera. They confer modest increase in infectivity as measured by soluble mACE2.

- **20A/S:439K**
  The 20A/S:439K variant was initially found in Ireland. This variant has S:N439K mutation with the deletions of amino acids at positions 69 and 70 of S proteins that results in an increase in ACE2 binding, resistance to antibodies and convalescent plasma.

- **20A/S:98F**
  The 20A/S:98F variant has S:98F mutation which was found predominantly in Belgium and Netherlands.

- **20C/S:80Y**
  The 20C/S:80Y variant had 18 nucleotide mutations, possibly related to apolipoprotein B editing complex (APOBEC)-like editing within the host which are found in at least 10 countries in Europe.

- **20B/S:626S**
  The 20B/S:626S variant has S:626S mutation. This variant is found in 15 countries of Europe that is predominantly seen in Norway, Denmark, and the UK.

- **20B/S:1122L**
  The 20B/S:1122L variant has S:V1122L mutation and is found predominantly in Sweden, Norway, and Denmark.

- **N440K**
  According to the latest report, another new variant N440K with the mutation in the S protein has emerged, which resulted in the sudden increase in cases in Andhra Pradesh, India. The Center for Cellular and Molecular Biology found that this variant has enhanced binding to ACE2 receptors, 10 to 1,000 folds more transmissible and resistant to class 3 monoclonal antibodies C135 and REGN10987. There are several documented cases of reinfection with the presence of anti-SARS-CoV-2 antibodies indicating the possibility of loss of neutralizing activity of antibodies elicited by vaccines.

- **Omicron (B.1.1.529)**
  The B.1.1.529 variant was first reported to WHO from South Africa on 24 November 2021. The epidemiological situation in South Africa has been characterized by three distinct peaks in reported cases, the latest of which was predominantly the Delta variant. In recent weeks, infections have increased steeply, coinciding with the detection of B.1.1.529 variant. The first known confirmed B.1.1.529 infection was from a specimen collected on 9 November 2021.

### IV. VARIANT OF INTEREST & VARIANT OF CONCERN

A variant with specific genetic markers that have been associated with changes to receptor binding, reduced neutralization by antibodies generated against previous infection or vaccination, reduced efficacy of treatments, potential diagnostic impact, or predicted increase in transmissibility or disease severity. Possible attributes of a variant of interest:

- Specific genetic markers that are predicted to affect transmission, diagnostics, therapeutics, or immune escape.
- Evidence that it is the cause of an increased proportion of cases or unique outbreak clusters.
- Limited prevalence or expansion in the US or in other countries.

A variant of interest might require one or more appropriate public health actions, including enhanced sequence surveillance, enhanced laboratory characterization, or epidemiological investigations to assess how easily the virus spreads to others, the severity of disease, the efficacy of therapeutics and whether currently approved or authorized vaccines offer protection.

**NOTE: Currently there is no any SARS – CoV-2 Variants of interest.**

A variant for which there is evidence of an increase in transmissibility, more severe disease (e.g., increased hospitalizations or deaths), significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatments or vaccines, or diagnostic detection failures. Possible attributes of a variant of concern:

- Evidence of impact on diagnostics, treatments, or vaccines
  - Widespread interference with diagnostic test targets
  - Evidence of substantially decreased susceptibility to one or more class of therapies
  - Evidence of significant decreased neutralization by antibodies generated during previous infection or vaccination
  - Evidence of reduced vaccine-induced protection from severe disease
- Evidence of increased transmissibility
- Evidence of increased disease severity. Variants of concern might require one or more appropriate public health actions, such as notification to WHO under the International Health Regulations, reporting to CDC, local or regional efforts to control spread, increased
testing, or research to determine the effectiveness of vaccines and treatments against the variant. Based on the characteristics of the variant, additional considerations may include the development of new diagnostics or the modification of vaccines or treatments.

![Visual representation of human genetic mutation variants for basis of COVID-19](image)

**Fig 1:** Human genetic mutation variants for basis of COVID-19

<table>
<thead>
<tr>
<th>WHO label</th>
<th>Pango lineage*</th>
<th>GISAID clade</th>
<th>Nextstrain clade</th>
<th>Additional amino acid changes monitored*</th>
<th>Earliest documented samples</th>
<th>Date of designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha</td>
<td>B.1.1.7</td>
<td>GRY</td>
<td>20I (V1)</td>
<td>+S.484K +S.452R</td>
<td>United Kingdom, Sep 2020</td>
<td>18-Dec-2020</td>
</tr>
<tr>
<td>Beta</td>
<td>B.1.351</td>
<td>GH/501YV2</td>
<td>20H (V2)</td>
<td>+S.L18F</td>
<td>South Africa, May 2020</td>
<td>18-Dec-2020</td>
</tr>
<tr>
<td>Gamma</td>
<td>P.1</td>
<td>GR/501YV3</td>
<td>20J (V3)</td>
<td>+S.681H</td>
<td>Brazil, Nov-2020</td>
<td>11-Jan-2021</td>
</tr>
<tr>
<td>Omicron</td>
<td>B.1.1.529</td>
<td>GR/484A</td>
<td>21K</td>
<td>-</td>
<td>Multiple countries, Nov-2021</td>
<td>VUM: 24-Nov-2021</td>
</tr>
</tbody>
</table>

*Table 1: Currently Designated Covid Variant Concern*
V. OMICRON VARIANT

The World Health Organization is monitoring a new variant with numerous mutations to the spike protein, scheduling a special meeting Friday to discuss what it may mean for vaccines and treatments, officials said Thursday. The variant, called B.1.1.529, has been detected in South Africa in small numbers, according to the WHO. “We don’t know very much about this yet. What we do know is that this variant has a large number of mutations. And the concern is that when you have so
many mutations, it can have an impact on how the virus behaves, the WHO’s technical lead on Covid-19, said in a Q&A that was livestreamed on the organization’s social media channels. The monitoring of the new variant comes as Covid cases surge around the world heading into the holiday season, with the WHO reporting hot spots in all regions and particularly in Europe. The U.K. announced it would ban flights from six African countries, including South Africa, starting The U.K. Health Security Agency “is investigating a new variant,” Health Secretary Sajid Javid said Thursday in a tweet announcing the travel restrictions. “More data is needed but we’re taking precautions now.” South African scientists have detected more than 30 mutations to the spike protein, the part of the virus that binds to cells in the body, South African scientist Tulio de Oliveira said in a media briefing hosted by the South Africa Department of Health on Thursday. The B.1.1.529 variant contains multiple mutations associated with increased antibody resistance, which may reduce the effectiveness of vaccines, along with mutations that generally make it more contagious, according to slides he presented at the briefing. Other mutations in the new variant haven’t been seen until now, so scientists don’t yet know whether they are significant or will change how the virus behaves, according to the presentation. The variant has spread rapidly through the Gauteng province, which contains the country’s largest city, Johannesburg.

**VI. BASIC IMMUNO – PATHOLOGY**

Omicron appears quicker and wilder than the delta variant. It is able to easily penetrate membranes and cells of fully vaccinated individuals with even 2 doses of any of the approved vaccines. It has a taccid structure and a sheath that makes it undergoes rapid replication during its attack and has the potential to dodge immunity from vaccines and previous infections. Looking at omicron’s pattern of inhibition in cells, it has been noted to evade immunity conferred by even another component of the immune system called T cells.

**VII. CHANGES TO SPIKE PROTEINS**

The new variant Omicron (B.1.1.529) under goes same genome sequencing like the others and its genome sequencing shows the variant stood out because it contains more than 30 changes to the spike protein (SARS-CoV-2 protein) that recognizes host cells and is the main target of the body’s immune responses. Many of the changes have been found in variants such as Delta and Alpha, and are linked to heightened infectivity and the ability to evade infection-blocking antibodies. Emergence of SARS-CoV-2 variants of concern (VOCs) suggests viral adaptation to enhance human-to-human transmission. Although much effort has focused on characterisation of spike changes in VOCs, mutations outside spike likely contribute to adaptation. Here we used unbiased abundance proteomics, phosphoproteomics, RNAseq and viral replication assays to show that isolates of the Alpha (B.1.1.7) variant more effectively suppress innate immune responses in airway epithelial cells, compared to first wave isolates. We found that Alpha has dramatically increased subgenomic RNA and protein levels of N, Orf9b and Orf6, all known innate immune antagonists. Expression of Orf9b alone suppressed the innate immune response through interaction with TOM70, a mitochondrial protein required for RNA sensing adaptor MAVS activation. Moreover, the activity of Orf9b and its association with TOM70 was regulated by phosphorylation. We propose that more effective innate immune suppression, through enhanced expression of specific viral antagonist proteins, increases the likelihood of successful Alpha transmission, and may increase in vivo replication and duration of infection. The importance of mutations outside Spike in adaptation of SARS-CoV-2 to humans is underscored by the observation that similar mutations exist in the Delta and Omicron N/Orf9b regulatory regions. Humans have infected a wide range of animals with SARS-CoV-2 viruses, but the establishment of a new natural animal reservoir has not been observed. Here, we document that free-ranging white-tailed deer (Odocoileus virginianus) are highly susceptible to infection with SARS-CoV-2 virus, are exposed to a range of viral diversity from humans, and are capable of sustaining transmission in nature. SARS-CoV-2 virus was detected by rRT-PCR in more than one-third (129/360, 35.8%) of nasal swabs obtained from Odocoileus virginianus in northeast Ohio (USA) during January-March 2021. Deer in 6 locations were infected with 3 SARS-CoV-2 lineages (B.1.2, B.1.582, B.1.596). The B.1.2 viruses, dominant in humans in Ohio at the time, infected deer in four locations. Probable deer-to-deer transmission of B.1.2, B.1.582, and B.1.596 viruses was observed, allowing the virus to acquire amino acid substitutions in the spike protein (including the receptor-binding domain) and ORF1 that are infrequently seen in humans.
VIII. CONCLUSION

Many nations’ healthcare systems and economy have been swamped by SARS-CoV-2 and its mutations, and the virus’s global spread continues to wreak devastation. The Food and Drug Administration has awarded Emergency Use Authorizations (EUAs) for three vaccinations for use in the United States, and similar authorizations have been granted in other countries. COVID-19 poses a hazard to global public health because it may cause the development of strains that are resistant to current treatments unless the vast majority of the world’s population is immunised against it. The prevention and treatment of this highly contagious respiratory viral infection calls for a multidisciplinary team effort involving physicians from a variety of disciplines, nurses, pharmacists, public health specialists, and policymakers. Closed-loop communication between clinicians, pharmacists, and nurses caring for patients with COVID-19 is essential. Frontline clinicians caring for patients with COVID-19 should familiarise themselves with the most recent clinical recommendations for diagnosing and treating COVID-19, since new SARS-CoV-2 variations might have a major influence on death rates if not properly addressed.

REFERENCES


