Editorial

SARS-CoV-2 Variants and Vaccines: What We Learn and What We Can Forecast?

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The COVID-19 pandemic has had devastating health, social and economic consequences around the world. In the absence of effective medical countermeasures, preventing disease and minimizing the spread of infection has required exceptional public health measures.

We are still dealing with COVID-19 and surprisingly not finished yet, despite the efforts of public health officials to curtail infections and the work done by scientists to provide vaccinations in record time. The increase in new cases around the world after a period of sharp decreases makes that much abundantly obvious.

The emergence of SARS-CoV-2 in late 2019 was followed by a period of relative evolutionary stasis lasting about 11 months. Since late 2020, however, SARS-CoV-2 evolution has been characterized by the emergence of sets of mutations, in the context of variants of concern (VOC), that impact virus characteristics, including transmissibility and immunogenicity, probably in response to the changing immune profile of the human population.[1] There is emerging evidence of reduced neutralization of some SARS-CoV-2 variants by post vaccination serum; however, a greater understanding of correlates of protection is required to evaluate how this may impact vaccine effectiveness.

Coronaviruses have a novel exoribonuclease (ExoN) encoded in their genomes, which is correcting many of the errors that occur during replication.[2] Genetic inactivation of the exonuclease in SARS-CoV increases mutation rates by 15 to 20-folds. The molecular basis of this CoV proofreading complex is being investigated as a possible therapeutic target for SARS-CoV-2. Importantly, nucleotide deletions, unlike substitutions, cannot be corrected by this proofreading mechanism, which is a factor that may accelerate adaptive evolution to some extent.

The tremendous progress has been made with the authorization and deployment of vaccines and antibody therapies. These strategies are directed at the viral spike protein, but the emergence of viral variants, particularly in the S gene, threatens their continued efficacy.[3] The mutations in the S gene, particularly those that affect portions of the protein that are critical for pathogenesis and normal function such as the receptor binding domain (RBD) or furin cleavage site or those that cause conformational changes to the S protein, are of the utmost interest. If these changes are not recognized by first-wave antibodies, these mutations may provide an avenue for the virus to escape from immunity to the original SARS-CoV-2 strain.

Initial reports that a mutation had been identified in the SARS-CoV-2 genome began circulating in March 2020, and by the end of June, D614G, which constitutes replacement of aspartate (D) with glycine (G) at the 614th amino acid of S protein, was found in nearly all SARS-CoV-2 samples worldwide. D614G has been found to enhance viral replication in human lung epithelial cells and primary human airway tissues by increasing infectivity and stability of virions.[2]

Additional research has suggested that the increased infectivity may be the result of enhanced functional S protein assembly on the surface of the virion. In addition, several other studies have reported that D614G may be associated with higher viral loads.

According to the Centers for Disease Control and Prevention (CDC), deletion of amino acids 69 and 70 in B.1.1.7 is likely to cause a conformational change in the spike protein. The creation of a Δ69Δ70 deletion mutant via site-directed mutagenesis and lentiviral pseudotyping resulted in 2-fold higher

infectivity than the WT (D614G background), indicating that this linked pair of amino acid deletions may improve SARS-CoV-2 fitness. Deletion of amino acid 144 in B.1.1.7 and amino acids 242-244 in B.1.351 have also been associated with reduced binding capacity of certain neutralizing antibodies.

The first reported SARS-CoV-2 mutation, D614G, which has now become common to nearly all sequenced SARS-CoV-2 genomes worldwide, followed by analysis of key S protein mutations associated with SARS-CoV-2 variants of interest (VOI) and VOC, including B.1.1.7, B.1.351, P.1., B.1.427/B.1.429, B.1.526 and multiple lineages of variants that contain mutations at amino acid position 677.[4]

The receptor binding domain (RBD) of S protein is comprised of amino acids 319-541. It binds directly to ACE2 receptors on human cells. Therefore, mutations in this portion of the genome are particularly significant to SARS-CoV-2 fitness and antigenicity.

Currently, there are four main types of COVID-19 vaccine: nucleic acid (mRNA and DNA), viral vector, protein subunit, and inactivated virus. Two COVID-19 mRNA vaccines (BNT162b2 developed by Pfizer-BioNTech and mRNA-1273 by Moderna) have been authorized by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA). In addition, Ad26.COV2.S (Johnson & Johnson) was approved by the FDA and EMA and ChAdOx1 nCoV-19 (AstraZeneca) was authorized by the EMA, both of which are viral vector vaccines.

Vaccination with various vaccine platforms, including mRNA and viral vectors, has been shown to elicit SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T-cell responses. In principle, it is more difficult to evade T-cell responses than a neutralizing antibody response because multiple T-cell epitopes are scattered across viral proteins, whereas neutralizing antibody targets a narrow region in the viral protein. Although SARS-CoV-2 mutations that abrogate binding to major histocompatibility complex have been reported, researchers reported an insignificant impact of SARS-CoV-2 variants on both $CD4^+$ and $CD8^+$ T-cell responses in COVID-19 convalescents and recipients of COVID-19 mRNA vaccines.[5] T-cell responses to the variants B.1.1.7, B.1.351, P.1, and CAL.20C were not different from those to the ancestral strain of SARS-CoV-2.

B.1.1.7, B.1.351 and P.1 all have a mutation that replaces asparagine (N) with tyrosine (Y) at position 501 of the RBD. N501Y has been shown to increase binding capacity of SARS-CoV-2 to human ACE2 receptors, disrupt antibody binding to RBD and has been implicated in reduced antibody production via impaired T and B cell cooperation. Together, these findings suggest that SARS-CoV-2 variants possessing the N501Y mutation may have an increased potential for immunological escape.

The SARS-CoV-2 B.1.617 lineage was identified in October 2020 in India. It has since then become dominant in some Indian regions and UK and further spread to many countries including Bangladesh.[6] The lineage includes three main subtypes (B1.617.1, B.1.617.2 and B.1.617.3), harboring diverse spike mutations in the N-terminal domain (NTD) and the receptor binding domain (RBD) which may increase their immune evasion potential. B.1.617.2, also termed variant Delta, is believed to spread faster than other variants. The delta variant spread is associated with an escape to antibodies targeting non-RBD and RBD spike epitopes.

According to current estimates, the Delta variant could be more than twice as transmissible as the original strain of SARS-CoV-2 and also replicates much faster.[7] Individuals infected with Delta also had viral loads up to 1,260 times higher than those in people infected with the original strain. But evidence is mounting that the Delta variant, first identified in India, is capable of infecting fully vaccinated people at a greater rate than previous versions, and concerns have been raised that they may even enhance the spread of the virus. A study in China found that people infected with the Delta variant carry 1,000 times more virus in their noses compared with the original version first identified in Wuhan in 2019.

Preliminary reports show that the 501Y.V2 variant has complete immune-escape in South African convalescent serum samples and reductions in neutralizing activity in vaccinee serum samples for all

four vaccines tested.[8] Extrapolating vaccine efficacy against pre-existing variants to new variants could be seriously misleading. Adequate genomic surveillance standardized variant nomenclature, and a repository of variants and vaccinee serum samples are needed to deal with the challenges of repeatedly emerging new SARS-CoV-2 variants.[9]

Virus genomic sequences are being generated and shared at an erratic rate, with more than one million SARS-CoV-2 sequences available via the Global Initiative on Sharing All Influenza Data (GISAID), permitting near real-time surveillance of the unfolding pandemic.[10] The use of pathogen genomes on this scale to track the spread of the virus internationally, study local outbreaks and inform public health policy signify a new age in virus genomic investigations.

As highly deleterious mutations are rapidly purged, most mutations observed in genomes sampled from circulating SARS-CoV-2 are expected to be either neutral or mildly deleterious. Such mutations may alter various aspects of virus biology, such as pathogenicity, infectivity, transmissibility and antigenicity.

The extent to which mutations affecting the antigenic phenotype of SARS-CoV-2 will enable variants to circumvent immunity conferred by natural infection or vaccination remains to be determined. However, there is growing evidence that mutations that change the antigenic phenotype of SARS-CoV-2 are circulating and affect immune recognition to a degree that requires immediate attention. The spike protein mediates attachment of the virus to host cell-surface receptors and fusion between virus and cell membranes.[11] It is also the principal target of neutralizing antibodies generated following infection by SARS-CoV-2, and is the SARS-CoV-2 component of both mRNA and adenovirus-based vaccines licensed for use and others awaiting regulatory approval.[12]

The people of Bangladesh are highly vulnerable to COVID-19 as evident by a number of circulating variants in different regions of this country.[13] In a global response, many countries, including Bangladesh, acted decisively and rapidly to restrict population movement and introduce additional social and behavioral interventions, all designed to slow the spread of the virus. SARS-CoV-2 genomic diversity and mutation rate in Bangladesh is comparable to strains circulating globally. Notably, the data on the genomic changes of SARS-CoV-2 in Bangladesh is reassuring, suggesting that immunotherapeutic and vaccines being developed globally should also be suitable for this population.[14]

It is worth noting that research works evaluating neutralization potency against the P.1, B.1.427/B.1.429 and B.1.526 lineages are still needed, and new information about SARS-CoV-2 variants is being produced daily.

This ongoing mutation threat emphasizes the necessity of genomic surveillance programs that will track SARS-CoV-2 evolution, help contain the spread of disease and inform public health practices, including diagnostics and vaccine development with distribution.[3] Together, these observations provide support for current strategies to monitor multiple variables proactively. These strategies include viral testing of symptomatic and asymptomatic persons, sequencing of viral RNA, and monitoring of neutralizing antibody titers, particularly in vaccinated persons who subsequently become infected.

Given the short time since the COVID-19 vaccines have become available, it is not surprising that many scientific uncertainties persist and are the subject of intense ongoing research. They include i) the ability of vaccines to reduce/eliminate SARS-CoV-2 transmission, ii) duration of immunity, iii) correlates (indicators) of protection, iv) vaccine efficacy/ effectiveness in specific populations and in individuals with prior infection, and v) protection against infection/reinfection by different virus variants.

Iftikhar Ahmed
Professor, Department of Microbiology
Enam Medical College, Savar, Dhaka
Email: ia65831@gmail.com

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