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Review Article

SARS-CoV-2 Variants and Vaccines: Pledge to global response!

Sushmita Roy[1], Bhuiyan Mohammad Mahtab Uddin[1], Iftikhar Ahmed[1]

[1]Department of Microbiology, Enam Medical College, Savar, Dhaka, Bangladesh.

Abstract
The detection of SARS-CoV-2 variants correlates to the rapid increase in the number of COVID-19 cases. The variants may emerge with fatal consequences to the usual resistance to the immunity arbitrated by the available vaccines to prevent the pandemic of COVID-19. When some variants of interest have increased transmissibility or virulence, the priority of appropriate public health measures and vaccination programs will increase. Still and all, the genomic surveillance must continue to monitor this trend as these observations have grave implications for mitigation and vaccination policies and must be considered by policy makers when designing public health interventions. Moreover, the global response must be directed toward urgency with scientific reliability.

Introduction

The importance for the global response to variants of concern involves scientific approaches for evaluating existing vaccines and developing modified and new vaccines. Efforts to track viral mutations and variants are ongoing. The aim is to detect new changes quickly and to assess their possible effects. Many research groups are sequencing virus isolates and sharing these sequences on public databases such as GISAID (Global Initiative on Sharing All Influenza Data)[1].

A mutation is elevated from a variant of interest (VOI) to a variant of concern (VOC) when it shows evidence fulfilling at least one of several criteria, including easy transmission, more severe illness, reduced neutralization by antibodies or reduced effectiveness of treatment and vaccines[2]. In addition, the WHO defined the SARS CoV-2 VOC as a variant with increased transmissibility, virulence, and decreased response to available diagnostics, vaccines, and therapeutics[3]. It is worth mentioning that unlike most RNA viruses, coronaviruses have a novel exoribonuclease (ExoN) encoded in their genomes, which researchers suspect is correcting many of the errors that occur during replication[4]. Genetic inactivation of the exonuclease in SARS-CoV increased mutation rates by 15-to-20-fold. 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 degree.

The first major variant was observed in September in the United Kingdom (UK)[5,6]. The variant, termed Variant of Concern 202012/01 (VOC 202012/01), causes point mutations of asparagine to tyrosine in the receptor-binding domain (RBD) of the spike protein[6,7]. This N501Y mutation became a growing concern due to the virus being able to adhere to the ACE2 receptor more strongly[8].

The WHO has identified four such VOC: Alpha, Beta, Gamma and Delta; and four VOI: Eta, Iota, Kappa and Lambda. VOC and VOI of SARS-CoV-2 have been a distinctive feature of the COVID-19 pandemic during 2021, demonstrating the importance of viral sequencing in epidemiological approach[9].

The B.1.1.7 (or alpha) variant of concern increases viral transmissibility and is emerging as an increasingly common variant[7]. The P.1 (or gamma) variant may cause severe disease even in individuals who have been previously infected, although convincing information is lacking[10].

Correspondence:
Dr. Sushmita Roy
Assistant Professor, Department of Microbiology
Enam Medical College & Hospital, Savar; Dhaka, Bangladesh.
Mobile : +8801712-723423
Email: rsushmita2017@gmail.com

The B.1.351 (or beta) variant is less easily neutralized by convalescent plasma obtained from patients infected with previous variants and by serum obtained from vaccinated persons than the prototype virus on which vaccine antigens are based[11]. Moreover, the preliminary evidence suggests reduced efficacy of some vaccines against mild or moderate disease caused by this variant[12,13].

Additional variants that are responsible for many deaths, such as B.1.617.2 (or delta), continue to emerge[14]. So far, there is no good evidence that currently identified variants of concern evade the most important vaccine effect. Among the four variants of concern, Delta is believed to be the most transmissible variant yet. The Delta variant is estimated to be between 40 and 60 percent more transmissible than the Alpha variant, which was first detected in the UK, according to a number of studies[15].

It is noteworthy that a few key amino acids in the spike protein have changed independently in variants identified in various parts of the world indicating that these are convergent changes and suggests vaccines that incorporate these selected residues could cover several variants.

Molecular and epidemiological aspects of SARS-CoV-2 variants

On May 19, 2021, the Delta VOC, formerly known as the Indian VOC or B 1.617.2, became the dominant strain of SARS-CoV-2 in Scotland[16]. The Alpha VOC (formerly known as the Kent VOC, B.1.1.7, or *S* gene negative) had been the dominant strain previously, but it has rapidly been replaced. Samples were analyzed using Thermo Fisher's TaqPath RT-PCR, which tests for the presence of three target genes from SARS-CoV-2[17] *S* gene-negative samples had a deletion in *S* gene of B.1.1.7 (Alpha VOC) at position 69-70, with cycle threshold (Ct) values less than 30 for at least one of the *OR* and *N* genes. *S* gene-positive samples had Ct values less than 30 for the *S* gene and valid Ct values for the other two genes.

The sudden surge in COVID-19 cases in India coincides with high prevalence of more-transmissible variants, associated with diagnostic test failures and antibody escapes[18]. These coronavirus SARS-CoV-2 variants of concern-B.1.1.7 (501Y.V1), B.1.351 (501Y.V2) and B.1.1.28.1 (501Y.V3; also known as P.1)-were observed during the sudden rise in COVID-19 cases in the UK, South Africa and Brazil respectively, with subsequent local transmission across the world[18,19].

New variants are thought to be responsible for re-infections, either after natural infection or after vaccination, as observed in Brazil and the United States[20,21]. Another concern about the emergence of new variants is the potential failure of RT-PCR tests for diagnostics. Failure to target the gene encoding the spike protein was observed during detection of the 501Y.V1 variant in the UK[18].

The Delta Plus variant was formed due to a mutation in the Delta or B.1.617.2 variant. The Delta Plus variant (B.1.617.2.1 or AY.1) is characterized by the K417N mutation in spike protein[22]. The Delta plus variant spreads more easily, binds more easily to lung cells and is potentially resistant to monoclonal antibody therapy.

Saha S et al (2021)[23] reported that B.1.1.7 variant (20I/501Y.V1) and B.1.351 variant (20H/501Y.V2) that have been reported from multiple countries around the world. B.1.1.7 was first detected in September 2020 in the UK through genomic surveillance, and it contains a mutation (N501Y) in the receptor-binding domain of the spike protein that has been reported to increase transmission and virulence through genomic and epidemiological studies[7,8]. The variant still shows strong response to antibody treatment and is effectively neutralized by antibodies generated on vaccination by mRNA-based vaccines[24]. The B.1.351, first identified in South Africa in October 2020, carries the N501Y mutation and two additional mutations (E484K and K471N) that confer increased antibody resistance[24,25]. These findings make it imperative to continuous tracking of circulating variants of SARS-CoV-2 globally, especially in low-resource settings, to impart evidence-based policy decisions.

The IEDCR in Bangladesh, confirmed identification of Delta variant in the country for the first time on May 8, and within a month, they confirmed that the variant already had community transmission in the country. The latest report said the IEDCR, along with icddr,b and iDeshi, had sequenced some 646 genome from January to end of June[26]. They have found the presence of Alpha variant (UK variant), Beta variant (South African variant), Delta variant, Eta variant (Nigerian variant) and an unknown variant (B.1.1.618). The Delta VOC in Scotland was found mainly in younger, more affluent groups. Risk of COVID-19 hospital admission was approximately doubled in those with the Delta VOC when compared to the Alpha VOC, with risk of admission particularly increased in those with relevant comorbidities[27].

Reciprocation between variants and vaccine

Both the Oxford-AstraZeneca (ChAdOx1) and Pfizer-BioNTech COVID-19 vaccines were effective in reducing the risk of SARS-CoV-2 infection and COVID-19 hospitalization in people with the Delta VOC, but these effects on infection appeared to be diminished when compared to those with the Alpha VOC[2]. The Oxford-AstraZeneca vaccine appeared less effective than the Pfizer-BioNTech vaccine in preventing SARS-CoV-2 infection in those with the Delta VOC. Given the observational nature of these data, estimates of vaccine effectiveness need to be interpreted with the generation more data by further scholarly research.

The evidence about the Oxford-AstraZeneca (ChAdOx1) vaccine suggests that it provides limited protection against mild-moderate COVID-19 caused by the B.1.351 variant[12]. However, concrete data on its efficacy in reducing severe disease is yet to be explored to derive a conclusion. This has led to questions about the circulating variants in Bangladesh, decisions on ongoing and future vaccine policies, and whether ChAdOx1 can help mitigate the burden on hospital beds[23]. Considering the resource- constrained health system of Bangladesh, any vaccine that provides protection, at least against the severe COVID-19 cases, will decrease the burden on the limited hospital and intensive care unit beds in the country. Thus, generation of authentic primary data on efficacy of ChAdOx1 on severe COVID-19 caused by the B.1.351 variant is urgently needed while introduction of updated or different vaccines may need to be evaluated as more data become available.

A newly described SARS-CoV-2 lineage C.37 was designated as a variant of interest by the World Health Organization (WHO) on June 14th and denominated as the Lambda variant. Its presence was reported in more than 20 countries as of July 2021, and most sequences to date stem from South American countries-particularly for Chile, Argentina, Ecuador and Peru[28]. The researchers observed an increased infectivity potential of the variant of interest mediated by the Lambda spike glycoprotein that was even higher in comparison to the D614G (lineage B) or the Alpha and Gamma variants[28,29]. More specifically, when compared to the wild-type virus (i.e., Wuhan-1 reference lineage A), the neutralization potential was diminished by 3.05-fold for the Lambda variant. For comparison purposes, this was 1.37-fold lower for the D614G, 2.03-fold lower for the Alpha variant and 2.33-fold lower for the Gamma variant.

In a nutshell, these results indicate that mutations present in the spike glycoprotein of the Lambda variant of interest give rise to increased infectivity and enable the immune escape of this specific lineage from neutralizing antibodies elicited by Corona vaccine[29].

Appraisal of the efficacy current vaccines against variants

Although animal models and in vitro studies can provide important information, clinical data will continue to be needed to determine whether existing vaccines are losing efficacy against variants[2]. While existing vaccines are being deployed, clinical data can be sought not only from carefully planned observational studies, but also from randomized trials of vaccines versus placebo, of one vaccine versus another, or of different vaccination regimens (e.g., different doses, numbers of doses, and intervals between doses).

Emphasizing mass immunization, along with variant-guided vaccination drives, which prioritize vaccination in the states reporting new variants, will do the most to reduce the impact of COVID-19, in terms of morbidity, mortality and the economy[18].

In areas where the vaccine supply or delivery capacity is limited, instead of letting operational decisions determine the order in which people are vaccinated, making first vaccine doses available to some of the target population on a randomized basis could provide useful information about efficacy against major variants[2].

Although COVID-19 continues to present public health challenges, including the emergence of new variants, great progress have been made in understanding this disease and how to protect against it[30]. Even though existing vaccines are helping to bring the pandemic under control in some locations, it is also necessary to combat unsatisfactory outcomes. As this planning continues, international coordination by the WHO research efforts and sharing of data and specimens should be a priority.

It is far-reaching that all countries enhance the collection of virus isolates for sequencing and sharing. A SARS-CoV-2 risk-monitoring and evaluation framework is being developed and continually improved by the WHO to identify and assess variants of interest.

Scope of new or modified vaccines to allay the variants

A variant of interest is suspected to be more infectious

when compared to the initial strain, to escape the vaccine protection or result in more severe disease[31]. Vaccines in which a new antigen is delivered that has already been shown to be effective against previously circulating viral variants should address the ability of these vaccines to elicit responses in persons who have not previously had an immunologic response against SARS-CoV-2 and in previously vaccinated persons[2]. Changes in vitro neutralization of circulating strains by vaccine-induced antibodies may not imply waning effectiveness. Although neutralizing responses may not be reliably predictive of vaccine efficacy, striking differences may well provide sufficient support for regulatory decisions.

There has been consensus in recent regulatory discussions and in WHO guidance that conventional, large, clinical end-point trials are probably not necessary in order to introduce modified vaccines against VOC[32]. Because differences among assays of immune responses may complicate direct comparisons, the Food and Drug Administration has proposed that animal models could be used to provide further support for the effectiveness against VOC[33].

Trials of new vaccines can still yield reliable and interpretable results in an efficient manner by using randomization, by evaluating effects not only on immunologic but also on clinical end points[18]. By using placebo controls when ethically appropriate, perhaps in communities where vaccine supply is very limited or in subpopulations (e.g., young adults) in which even if infection occurs, the probability of progression to fatal outcome is very low[2,3]. Viral genotyping in persons with infection during or after trials can support multiple analyses, including assessment of the influence of viral variants on vaccine efficacy. In randomized, controlled studies, such genotyping also yields unbiased information about variant-specific efficacy.

Once modified vaccines or completely new vaccines that address new variants have been introduced, the cycle can begin anew with monitoring for even newer variants that might necessitate further changes in the vaccine antigen sequence[2].

Strategy to reduce the risk of emergence of the variants of concern

Given the emergence of immunity-evading variants even before vaccines were broadly deployed, it is hard to implicate vaccines or vaccine deployment strategies as the major drivers of immune evasion[34]. However, prolonged viral replication in the presence of partial immunity in immunocompromised persons or circumstances in which rapid transmission of high titers of virus occurs could have contributed to the development of variants that can at least partially escape human immune responses[35]. The use of antibody-based treatments (e.g., monoclonal antibodies or convalescent plasma) are of limited or undemonstrated efficacy may further contribute to the evolution of VOC that could evade not only these but also other antibody responses[35,36]. Partially effective interventions may therefore encourage viral evolution. It may be assumed that the larger the number of infected persons, the greater the chance that new variants of concern will arise. Hence, effective public health strategies such as social distancing, the use of masks, and the targeted use of effective vaccines that reduce both infection and transmission can help to limit viral evolution[2]. Limiting transmission in the general population is extremely important for slowing the emergence of additional variants of concern.

Studies of the effectiveness of such targeted strategies could be of global relevance, especially if groups or areas with consistently high and low rates of transmission can be identified[37]. Meeting these challenges efficiently will require enhanced surveillance with continued sharing of data and samples. It will also require the use of standardized reference reagents and models to evaluate viruses and modified vaccines. With collaborative, open discussion of results, this data sharing will help foster consistent and thoughtful public communications about new variants and help maintain appropriate confidence in vaccines[7].

Massive vaccination campaigns should be accompanied by strict genomic surveillance[38]. Decision making about which antigens should be included in vaccines against SARS-CoV-2 will need to involve epidemiologic data, data from evolutionary biology, and clinical, animal, and in vitro data that are pertinent to immune responses and to continued vaccine efficacy in the face of changing viral sequences and the possible waning of vaccine-induced immunity.

Conclusion

New variants of concern may originate, spread swiftly, as convergent changes have been identified in variants of concern in different parts of the world. The modification of sequences targeted by a vaccine to meet the needs of one country could have repercussions in another place. There-

fore, development, modification, and deployment of vaccines should be reviewed by international enterprises, with coordination by WHO. An end to the pandemic through population immunity requires enough of the population portraying immuity that can prevent exponential replication of SARS-CoV-2.

Maintaining the efficacy of vaccines against emerging variants and achieving equitable access to that in all countries will be of utmost importance to ensure a sustainable response. Until many more people are coming under the umbrella of comprehensive vaccination, proportionate mitigations will be required to prevent hundreds of thousands of additional infections.

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