MISE AU POINT / IN-DEPTH REVIEW

THE FIGHT OF SARS-CoV-2 VARIANTS VERSUS VACCINES WHERE DO WE STAND ?

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ABSTRACT • The world has been trying to cope with the emergence of several SARS-CoV-2 variants of concern associated with increased transmissibility and at times inflicting variable levels of morbidity and mortality, and thus, heavily affecting the healthcare system and global economies. Consequently, expediting the roll-out of vaccinations to achieve herd immunity is critical to control emergence of variants and their ability to escape the vaccine generated immunity. This review aims at addressing and enlightening the current SARS-variants, as well as the protective spectrum of available vaccines against them.

Based on the currently available evidence and despite existing and foreseeable emerging SARS-CoV-2 variants enlisting the Greek alphabet, the potency of immune responses among fully vaccinated individuals remains significant at controlling the rampant spread of COVID-19 and its serious health consequences.

Note : While being in press, a new Cov variant (Omicron) emerged and is noted as an addendum at the end of the text.

Keywords : SARS-CoV-2 variants ; vaccines ; immune protection ; antibodies neutralizing effect

INTRODUCTION

The COVID-19 pandemic has been persistent for such a long time due to different reasons including lack of wide vaccine coverage, negligence in adherence to non-pharmaceutical interventions (physical distancing and facemasks) and emergence of new variants. To date, more than 180 000 000 cases and approximately 4 000 000 deaths are reported. Consequently, COVID-19 is exerting a huge burden on healthcare systems as well as global economies.

Recently, few publications emerged from Lebanon addressing the epidemiologic and clinical characteristics of COVID-19 [1], testing platforms [2], vaccine platforms [3], and genomic characterization of the first SARS-CoV-2 variants introduced in Lebanon [4]. Moreover, the predominance of the Delta variant taking over the alpha variant in this country was also reported [5]. In this article, we review the mechanisms of current mutations appearing in emerging SARS-CoV-2 variants, and their impact on clinical disease, transmissibility, vaccine induced neutralizing antibody responses and immune evasion, as well as current knowledge of their impact on effectiveness of available vaccines.

MECHANISMS OF MUTATION

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is an RNA virus with generally a low rate of mutation compared to other viruses of the same family. This is due to an exoribonuclease enzyme responsible for error corrections during replication. SARS-CoV-2 is estimated to undergo 1 to 2 single-nucleotide mutations per month, which is half the rate of mutations occurring in influenza virus and quarter the rate of those occurring in HIV [6].

Despite the low mutation rate of the virus, a total of 12,706 mutations have been detected in its genome so far. The majority of these pertain to a single nucleotide substitution (for example, a change from Aspartate to Glycine) or deletion, both referred to as single nucleotide polymorphisms [7]. While most mutations are either neutral or mildly deleterious, some mutations impact the virus pathogenicity, infectivity, transmissibility and/or antigenicity [8].

The most relevant and important mutations in SARS-CoV-2 occur within the spike (S) protein, which is essential for virus binding and entry into host cells [9]. The S protein is the main target of currently developed vaccines, as well as the target of neutralizing antibodies (NAbs). These neutralizing antibodies bind to the S-protein and prevent the virus from attaching to the angiotensin converting enzyme 2 (ACE2) receptor on human cells, the site of viral entry into the host [9]. The relevant portions of the S protein affected by mutations are the N-terminal domain (NTD), the receptor binding domain (RBD) and the furin cleavage site.

Since the emergence of SARS-CoV-2, many variants have been identified in reference to the original Wuhan

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2019 strain (WA1/2020). These variants are classified into variants of concern (VOC), variants of interest (VOI) and variants of high consequence (VOHC) [10]. VOC are characterized by increased transmissibility or detrimental change in the virus epidemiology, increase in virulence or severity of the disease, significant decline in neutralization by antibodies and thus reduced effectiveness of treatments or vaccines or failure of diagnostics. VOI are variants with specific genetic markers linked to changes in receptor binding. To date, four VOC have been identified worldwide : Alpha (B.1.1.7) first detected in the United Kingdom (UK), Beta (B.1.351) first detected in South Africa, Gamma (P.1) first detected in Brazil and Delta (B.1.617.2) first detected in India [11]. Moreover, seven VOI have been identified in several countries ; these include Epsilon (B.1.427/B.1.429), Zeta (P.2), Eta (B.1.525), Theta (P.3), lota (B.1.526), Kappa (B.1.617.1) and Lambda (C.37). The WHO is continuously monitoring and assessing the evolution of SARS-CoV-2 and the emergence of new variants with increased risk to global public health [11]. Variants of high consequence have clear evidence suggesting significant reduction in vaccine effectiveness, very low protection against severe disease by the vaccine, high number of breakthrough infections and increased disease severity and hospitalization as well as demonstrated failure of diagnostics. Luckily, SARS-CoV-2 variants under this category have not emerged yet [10].

SARS-CoV-2 CURRENT KNOWN MUTATIONS AND THEIR IMPACT ON CLINICAL DISEASE AND TRANSMISSIBILITY

The increased spread of SARS-CoV-2 globally provided the virus with optimal conditions to replicate and mutate. Moreover, selective pressure at the individual or population level led to the emergence of new mutations that can evade the built-up immunity in the human population [8,9].

Table I lists the current emerging variants along with

TABLE I CURRENT EMERGING VARIANTS AND ASSOCIATED CHARACTERISTICS

Variant	Lineage	Mutation	Amino acid substitution	Characteristics
UK*	B.1.1.7	N501Y	Asparagine (N) → Tyrosine (Y)	↑ binding capacity to ACE2 ↓ antibody production via weakened T and B cell cooperation ↓ antibody binding activity to RBD
South Africa*	B.1.351 or 501Y.V2	E484K	Glutamate (E) → Lysine (K)	↑ affinity of RBD for ACE2 ↑ resistance to neutralizing antibodies ↓ neutralization against convalescent plasma ↓ response to monoclonal antibody therapy
Brazil*	P.1 or 501Y.V3	L18F	Leucine (L) → Phenylalanine (F)	Escape from monoclonal antibodies against the NTD
India*	B.1.617	L452R E484Q	Leucine (L) → Arginine (R) Glutamate (E) → Glutamine (Q)	↑ Transmissibility & Moderate immune escapism
California	B.1.427, B.1.429 or CAL.20C	L452R	Leucine (L) → Arginine (R)	↑ affinity of the RBD for ACE2 ↓ vulnerability to neutralizing antibodies
New York	B.1.526	D253G S477N	Aspartate (D) → with Glycine (G) Serine (S) → Asparagine (N)	↑ escape from monoclonal antibodies against the NTD ↑ receptor binding affinity & viral infectivity

* Variants of concern.

their associated mutations and characteristics.

Noteworthy, emerging mutants can either lead to reduced viral fitness or advance a competitive advantage to replication, transmission, or immune escape, thus, compromising the effectiveness of currently available vaccines. A brief description of the mentioned VOC and others is advanced below.

The first reported mutation that happened in the SARS-CoV-2 Wuhan wild type was reported in March 2020 : The D614G mutation resulted from the replacement of amino acid aspartate (D) with glycine (G) at the 614th amino acid location in the S protein. This substitution was also accompanied by three other mutations in other regions of the virus conferring a fitness advantage and thus global predominance. Moreover, D614G substitution enhanced viral replication and subsequent mutations lead to the emergence of new variants [8,12].

The first emerging variant was the alpha variant also known as the United Kingdom (UK) variant or the B.1.1.7 variant, first reported on December 14, 2020 [13]. It was characterized by a new mutation, N501Y, which replaced asparagine (N) with tyrosine (Y) at the 501st amino acid position of the RBD of the S protein. This variant, rapidly spread worldwide including the US due to higher transmissibiliy compared to the Wuhan wild strain, in addition to a higher risk of death [13]. The alpha (UK) variant increases the binding capacity of SARS-CoV-2 to human ACE2 receptors [14], reduces antibody production via weakened T and B cell cooperation, and lowers antibody binding activity to RBD [15].

Following the alpha (UK) variant, a South African variant (B.1.351) was reported on December 18, 2020, and later spread to more than 45 countries. It was called the Beta variant (B.1.351 or 501Y.V2) [13]. This variant embodies a new E484K mutation which replaced glutamate (E) by lysine (K) at the amino acid position 484. Interestingly, this new mutation was also labelled the "escape mutation". This is because it enhanced resistance to SARS-CoV-2 neutralizing antibodies, reduced neutralization by convalescent plasma, was less responsive to monoclonal antibody therapy, and increased the affinity of RBD for ACE2 [16]. This Beta (South African) variant was also associated with a 20% increase in hospital mortality [13].

The Gamma variant (P.1 or 501Y.V3 variant, also known as the Brazilian variant), was reported on January 12, 2021 [13]. This variant has the same main RBD mutations expressed by the South African variant (N501Y & E484K), but in addition, it acquired a new mutation in the N-Terminus domain (NTD) of the S protein : the L18F, a leucine (L) to phenylalanine (F) substitution at amino acid position 18. This new mutation has been associated with escape from monoclonal antibodies against the NTD. Several other spike protein substitutions were also detected in this variant [17].

Soon after the Gamma (Brazilian) variant, a more transmissible variant was reported to be circulating in Southern California also named Epsilon variant (B.1.427/ B.1.429, CAL.20C or the California variant). This variant harbored an additional mutation at the RBD, the L452R, a substitution that replaces leucine (L) with arginine (R) at amino acid position 452. L452R increased the affinity of the RBD for ACE2, was less vulnerable to neutralizing antibodies and was linked to worse disease outcome [18].

In November 2020, a new variant identified in New York City became predominant by early April 2021. This variant was named Iota (B.1.526 or the New York variant) and tended to infect younger adults [19]. It is characterized by two mutations : the first one, D253G, in the N-Terminus domain (NTD), a substitution of aspartate with glycine at amino acid position 253 (linked to escape from monoclonal antibodies against the NTD) ; and the second one, S477N, in the RBD, a substitution of serine (S) with asparagine (N) at amino acid position 477 (linked to increased receptor binding affinity and viral infectivity [20].

In February 2021, a new strain emerged in France, termed B.1.616 [21]. This variant was classified by the WHO, in March, as a variant under investigation (VUI). Scientists were initially surprised when patients with highly suspected COVID-19, had negative RT-PCRs on nasopharyngeal swabs. However, lower respiratory tract samples turned out to be positive and this was later attributed to low viral loads in upper respiratory tract samples. High case fatality rate was noted in a sampled population in Lannion or Saint-Brieuc hospitals. This variant was detected later in other European countries such as Germany and Spain [21].

Lately, in May 2021, a new variant of concern with three key mutations emerged in India and is now termed the delta variant (Indian variant, B.1.617). It has the L452R mutation present in the Epsilon (California) variant, and the E484Q which is similar to the E484K present in the Beta (South African) and Gamma (Brazilian) variants, in addition to P681R mutation in the furin cleavage site. The later results in accumulation of viral particles and thus is the reason of increased viral load with this variant compared to other variant, 1000 times more viral RNA according to a recent study published in Nature [22]. It is hypothesized to be more potent in invading epithelial cells lining the respiratory tract, and thus was labelled as "fastest and fittest variants" according to the WHO [11]. The Delta (Indian) variant is currently detected in more than 90 countries where it became predominant such as the USA, the UK, Australia,

New Zealand, and Jordan [23]. Symptoms of Delta variant are generally similar to previous variants but seem to be more associated with sore throat, congestion and headache, and rarely with loss of smell or cough. Its transmissibility is estimated to be increased by 50% and 100%, compared to the UK and the original Wuhan strains, respectively, among non-vaccinated populations, thus making people sicker but not more lethal [24]. Also, it is associated with potential reduction in neutralizing antibodies post vaccination, (i.e., attempt escape from immunity), as well as in reduction in the effectiveness of some monoclonal antibody treatments used [9,25].

VACCINE-INDUCED NEUTRALIZING ANTIBODY & OTHER RESPONSES AGAINST SARS-CoV-2 VARIANTS

Several vaccines have been developed to protect against the SARS-CoV-2, including so far Pfizer-BioNTech (BNT 162b2), Moderna (mRNA-1273), AstraZeneca-Oxford (Vaxzevria), Sputnik V (Gam-COVID-Vac), Johnson & Johnson's Janssen (JNJ-78436735), Sinopharm (BBIBP-CorV), CoronaVac manufactured by Sinovac. Other vaccines such as the Novavax vaccine (NVX-CoV2373) and ZIFIVAX manufactured by Zhifei among others are still in trial [3].

Amidst the emergence of different new variants in different parts of the world, it is imperative to assess the effectiveness of approved vaccines against these variants. This was mainly done by measuring neutralizing antibodies level, which was found to have a highly predictive correlation with immune protection from SARS CoV-2 [26]. Below, we discuss the current knowledge about the protection (neutralizing activity among others) provided by the available vaccines against the different variants. Table II summarizes the characteristics of SARS CoV-2 VOC and respective vaccine efficacy.

Alpha (B.1.1.7-UK) variant

On January 8, 2021, Pfizer-BioNTech (BNT162b2) announced that their vaccine was capable of fully neutralizing the alpha variant without significant difference to the wild type of Wuhan strain, as was demonstrated in a couple of different studies [27-29]. On the other hand, other studies showed reduction in neutralizing titers ranging from 2 to 3.8 folds in sera of vaccinated individuals (Pfizer-BioNTech, Moderna and Novavax) against the alpha variant compared to the wild type [13, 30]. Moreover, a recent report from India showed similar levels of neutralizing antibodies against the alpha variant in people who received sputnik V or Covaxin (*Bharat Biotech's COVID-19 vaccine)* vaccines, but a 2.5 up to 9-fold neutralization reduction in people who received the Covishield (ChAdOx1 nCoV-19 produced in India) vaccine [31].

Beta (B.1.351-South Africa) variant

When analyzing the neutralization potential against the South African variant, sera were tested from 20 volunteers, who received either the Moderna (mRNA-1273) or the Pfizer-BioNTech ((BNT162b2) vaccine. The neutralization potential was reduced by a small, but significant margin against the South African mutants [32]. Scientists at Moderna conducted a study comparing the neutralization potential of sera from vaccinated participants against the WT Wuhan isolate, its mutant D614G, alpha (UK) and beta (South African) variants. Though it showed reduction in neutralization, there was still complete neutralization activity by the corresponding sera [16].

Johnson & Johnson (J&J) also conducted trials to test their vaccine effectiveness against alpha (UK) and beta (South African) variants and found that it was 81.7% effective at reducing severe disease and 64% effective against moderate disease in South Africa [33]. According to Press Information Bureau (PIB) in India, the neutralizing activity of sera against beta variant following the J&J vaccine was decreased by 5-10-fold. Lately, J&J has been developing a bivalent vaccine added to the original vaccine to increase effectiveness against the beta and other emerging variants [34].

Concerning the AstraZeneca-Oxford vaccine, the serum neutralizing activity against the beta variant (South African) was reduced to 22% only [13]. These results indicate that the AstraZeneca-Oxford vaccine offers limited protection against the South African variant compared to other variants [34].

Also, the efficacy of the Novavax vaccine was lower against the South African vs. the UK variant (49% vs. 89%) [13]. In India, it was shown that the neutralization capacity of sera against the beta (South African) variant following the Novavax, Covishield, Covaxin and Sputnik V vaccines were decreased by 14x, 31x, 3x and 7x, respectively [31].

The Chinese manufactured vaccines (Sinopharm and ZIFIVAX (Zhifei)) showed that the neutralization capacity of both vaccines against the beta variant was reduced by 1.6-fold. Moreover, and compared to the wildtype virus, the average antibody titers elicited by Sinopharm decreased from 111 to 71 and those of the ZIFIVAX (Zhifei) vaccine decreased from 106 to 67 without affecting the protective effects of the vaccines [34].

Gamma (P.1-Brazilian) variant

Sera from individuals vaccinated by the Pfizer-BioN Tech vaccine showed a neutralizing activity against the Gamma variant that was lower than preexisting variants

by a factor of 6.7. The same goes for Moderna, showing a reduced neutralizing activity by a factor of 4.5 [13]. A 3-fold reduction in neutralizing antibody activity was reported by Johnson & Johnson (J&J) and Covishield vaccines, a lower reduction compared to that of mRNA vaccines [31].

Concerning the AstraZeneca-Oxford vaccine, studies on their clinical trial efficacy against this variant indicated 70% efficacy in the UK and Brazil, compared to 22% in South Africa [13,35].

Epsilon (B.1.429-Califronia) variant

A study done by Deng *et al*., was performed to examine the effect of L452R mutation found in the California variants. Twenty-one samples from convalescent patients and vaccinated individuals with Pfizer-BioNTech or Moderna vaccines, were compared with a USA control isolate. Six out of 11 (55%) vaccine recipients showed reduced neutralization potential to the Epsilon (B.1.429) lineage virus, with a 2-fold ($p = 0.031$) median reduction [36].

TABLE II CHARACTERISTICS OF SARS CoV2 VOC AND RESPECTIVE VACCINE EFFICACY

Characteristics of SARS CoV-2 VOC & Vaccine efficacy	Aspects related to different VOC				
	Wild Type	Alpha B.1.1.7	Beta B.1 351	Gamma P 1	Delta B. 1.617.2
Characteristics of SARS CoV-2 VOC					
Country where first identified	China	UK	South Africa	Brazil	India
Disease severity	–	Increased	Unchanged	Unchanged	Increased
Mortality	–	Increased	Unchanged	Unchanged	Increased
Immune evasion	–	No	Increased	Increased	Increased
Transmissibility	–	Increased	Increased	Increased	Increased
Vaccine Efficacy*					
Pfizer	95%	89.5-93% ↓ by 2.6x	75% ↓ by 4.9x	NA ↓ by 6.7x	87.9-96% ↓ by 2.9-5.8x
Moderna	94.1%	94% ↓ by 1.8x	72% ↓ 6.4x	NA ↓ by 4.5x[5]	NA ↓ by 7x
AstraZeneca	76%	70.4%	22-60 % ↓ by 86x	70%	65.5-92% ↓ by 6.2
J&J	66%	76.3% ↓ by < 1x	64% ↓ by 5-10x	68.1% ↓ by 3x	NA
Novavax	90.4%	86.3% ↓ by 2x	49% ↓ by 14x	93.2%	NA
Covishield	70%	NA ↓ by 2.5-9 x	NA ↓ by 0-31x	NA ↓ by 3x	65% ↓ by 2x
Covaxin	78%	NA ↓ by 0x	NA ↓ by 3x	NA	65% ↓ by 3x
Sputnik V	92%	92% ↓ by 0x	70% ↓ by 7x	NA	NA
Sinopharm	78.1%	73% NA	56% ↓ by 1.6x	NA	NA

Comparison made to wild type. NA: Data not available.
*Efficacy related to neutralizing antibodies effect.

Iota variant (B.1.526)

Laboratory studies of B.1.526 variants carrying the E484K mutation showed that neutralizing activities of sera from Pfizer-BioNTech or Moderna vaccines, were lowered by 3.5-fold compared to those observed against wild type virus. This indicates that vaccine-induced antibodies against this virus have a decreased neutralizing activity [37].

Delta variant (B. 1.617.2- Indian)

A couple of studies revealed the efficacy and strong protection of vaccines against this strain despite noting decrease in their neutralizing antibodies against it.

For example, the neutralizing antibodies produced by the Pfizer-BioNTech vaccine showed 2.9-5.8-fold reduction against the delta strain compared to the wild type [38, 39], and a reduction of 6.2-fold by AstraZeneca-Oxford vaccine [38]. Though such reduction is noted, this in no way indicates loss of protective immunity in those who received two shots of vaccine, while those receiving one shot had significant lower protection [24]. Moreover, a couple of recent studies indicated that the protection provided by two-dose vaccine of Pfizer-Bio-NTech, or AstraZeneca-Oxford vaccine maintained significant protection against delta (Indian) variant [23, 31].

Other vaccines from India (Covaxin and Covishield), and based on two shots, showed a decreased neutralizing antibody activity by 3- and 2-fold, respectively [31].

Recently, the Johnson and Johnson reported that a single shot of its vaccine elicited neutralizing antibodies against the delta variant at an even higher level compared to the Beta variant (South African) [40]. The importance of vaccination was clearly revealed by the Public Health England in its latest study indicating that prevention of hospitalization in patients infected with the delta variant was 96% and 92%, following vaccination with Pfizer-BioNTech and AstraZeneca-Oxford vaccines, respectively [41].

Regarding the Pfizer-BioNTech vaccine, the effectiveness of two doses was 93.7% among persons with the alpha (UK) variant and 88.0% among those with the delta (Indian) variant. With AstraZeneca-Oxford vaccine, the effectiveness of two doses was 74.5% among persons with the alpha variant and 67.0% among those with the delta variant [24].

All in all, the recent studies indicated that though outbreak can occur among fully vaccinated people, the exact percentage of such infection remains to be below 1%, with minimum rates for hospitalization (≤ 0.06 %) and death (≤ 0.01 %) [42].

INSIGHTFUL THOUGHTS

In an earlier publication we addressed the different characteristics of vaccines platforms and reflected on the crucial importance for the population in any country to get immunized with any vaccine available [3]. This is due to the ability of vaccines to induce the humoral and cellular arms of the immune system. The T- and B- memory cells which could last for years and accordingly provide long term protection against exposure or re-exposure to the virus and in minimizing its consequence effects on hospitalization or ICU admission [43].

Moreover, the immunity induced post SARS-CoV-2 infection or vaccination (especially those receiving two-dose vaccine) have enough neutralizing levels, proven effective against the emerging and circulating variants globally, latest being the highly contagious Indian variant. Unfortunately, the devastation of the virus and its emerging variants rapidly spread among unvaccinated people [24,32]. This protective vaccination impact is also assuring despite the fact that there are many factors that require more investigation specifically related to the variant's transmissibility, infectious dose, severity of disease, and the damaging effect in the face of buildup immunity against emerging and circulating variants.

All what was addressed in this article indicates that the effect of the existing and foreseeable emerging variants will be inversely related to vaccination rates of potent vaccines among the population [44]. Thus, the vaccines remain the effective and only way out of the pandemic.

CONCLUSION

The emergence of new variants of SARS-CoV-2 is expected to continue and to present an ongoing challenge to vaccination efforts. However, the currently available vaccines have been quite protective and effective in reducing the burden of COVID-19 in countries with high rates of vaccination, especially among those receiving the two doses. Although neutralizing antibodies against the variants of concern are reduced with the different vaccines available, their desired protective effect was attained in most studies.

On another note, increased heterologous vaccination (mixing of vaccines) is currently revealing optimistic results in the fight against COVID-19.

The advantage of current COVID-19 vaccine platforms is that they lend themselves to rapid customization to emerging viral variants allowing the potential development of multivalent next generation vaccines with a broader range of protection. This process will need to be informed by ongoing genomic surveillance programs that will track SARS-CoV-2 mutations and evolution

leading to the early identification of variants with potential threat of spread and breakthrough the existing vaccine – or infection-induced immunity. At this stage and based on what was noted in this review, COVID-19 vaccines are winners of the fight against the variants. To consolidate this winning of vaccine over controlling the spread of variants one still needs to adhere to the common standards of non-pharmaceutical interventions to decrease the spread.

Moreover, since information about this SARS-CoV-2 virus is rapidly evolving, it is recommended for those interested in this topic to keep updated through monitors on the following links: GISAID – Initiative [Gidaid.org], CoVariants [covariants.org], Nextstrain [Nextstrain.org] & This Week in Virology (microbe.tv) [Microbe.tv/ twiv].

ADDENDUM

While this article being in press, a new variant emerged (B.1.1.529) from South Africa and was classified by WHO as VOC, and named after the 15th letter of the Greek alphabet : Omicron. It was identified to have numerous mutations, 35 of them being in the S protein. Its detailed impact remains to be determined. Recently however, early observation and evidence indicated that the Omicron variant may be spreading faster than the highly transmissible Delta variant but brings with it less severe coronavirus disease. Although the Omicron's mutations are worrisome, hopefully the fully vaccinated individuals will have protection against its sequel. [https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern]

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