Authors: Menahem Bregegere,PhD,

Contributors: Irene Fermont MD, MSC, Ayalah LivnehMD, MSc

Published Date :31 Jan 2021

What should we know about COVID new variants?

The emergence of new SARS-CoV-2 variants coincided with an outbreak of infections in Britain, South Africa and Brazil. Now these variants are spreading around the world. What are they, and what are their dangers?

All viruses "mutate": errors happen in their replication, and are transmitted to their descendants. The SARS-CoV-2 genome has been estimated to accumulate around 25 mutations per year, a rate that is half that of influenza [1][1]. The vast majority of these mutations are harmless, but some of them can increase virulence[2][2].

The British variant

The British variant, B.1.1.7, appeared in September 2020. It harbours 17 mutations, compared to the original Wuhan strain of January 2020 [3][3]. Eight of these mutations involve the virus's surface protein Spike ('S') which serves as a 'key' to enter the cell. Of those, two are located precisely on the receptor binding domain ('RBD'). These two mutations, N501Y and P681H, were presumed to promote the entry of the virus into the cell and to increase its virulence. Physico-chemical measurements indeed show that the N501Y mutation improves the stability of the chemical bond between protein S and RBD[4][4].

Among them, two are located on the anchor point of the S protein with its receptor on human cells, namely the binding domain ('RBD') that combines with of Angiotensin Converting Enzyme-2 ('ACE2'), which works like a 'lock' allowing the virus to open and pass through the cell membrane[5][5]..

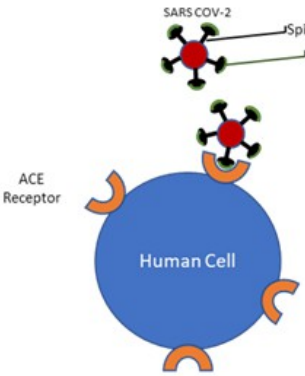

Fig.1 Binding between RBD and ACE Receptor

Can these mutations compromise the effectiveness of vaccines?

The Pfizer and Moderna vaccines use the original S protein as an immunogen, and there is concern that a change in this protein would allow the variant to escape specific antibodies elicited by the vaccine.

It has been shown, however, that the sera of people vaccinated with the Pfizer vaccine have the same neutralizing power on the British B.1.1.7 variant and on the wild-type virus[6],[7][6,7]. This suggests that B.1.1.7 does not escape the immunity acquired from the vaccine.

The South Africa Variant

A second variant, named 501Y.V2, spread to South Africa in October 2020, which is also more contagious [8][8]. It has eight mutations in protein S, including three aminoacid changes in the RBD (K417N, E484K et N501Y), and four amino acid changes and one deletion in the N5 loop of the N-terminal domain[9][9]. These mutations are likely to be the cause of increased virulence.

They may also compromise the immunity acquired from a primary infection with the original virus, or from vaccination. It has been observed indeed, that the 501Y.V2 variant exhibits complete escape from three classes of therapeutically relevant monoclonal antibodies directed against the RBD or the N5 loop, and substantial or complete escape from neutralizing antibodies in COVID convalescent plasmas [10],[11][10,11], *raising the question whether it can be neutralized by current vaccines.*

The Brazilian variant

Another variant was detected in Brazil in December 2020. This variant, named P.1, carries 17 amino acid substitutions and three deletions, among which three substitutions in RBD (K417N, E848K and N501Y) and one deletion (del11288-11296) in the orf1b gene, in common with the 501Y.V2 variant [12][12].

Are the South African and Brazilian variants affecting the mRNA vaccines ?

the These common characters appeared independently, which suggests that 501Y.V2 et P.1 convergently evolved toward a new phenotype. Moreover, they have developed in areas already largely infected with Wuhan's COVID, raising fear that they would escape the immunity acquired in a primary infection. For this to be clarified, one has to examine the actual frequency of re-infections in individuals already exposed to the virus in these areas [12][12].

501Y.V2 and P.1, which share the same mutations in RBD, are expected to have the same ***kind of resistance to vaccine-elicited anti-S immunity.***

The Californian variant

Another variant, CAL.20C, has spread widely in California [13] [13], and just entered Israel in January 2021 [14][14]. Other variants may arise, from outside or inside, each time causing us to question and deepen our understanding of the pandemic.

The components of the immune response ?

The immune response has two main components, one humoral (antibody) and one cellular (cytotoxic T lymphocytes). Neutralizing anti-COVID antibodies are mainly aimed at protein S [15][15], but cytotoxic cells also recognize other viral proteins as well [16][16].

In case of a natural infection, cellular immunity is less sensitive than the humoral response to changes in protein S. Genetic and pharmacological data suggest that cellular immunity alone can indeed block the spread of the virus, even in the absence of neutralizing antibodies [17][17].

After vaccination with S mRNA, however, cellular immunity is stimulated by protein S alone, so that the immune response is potentially sensitive to changes in S, and residual immunity relies on unchanged epitopes only.

Adaptability of the mRNA Vaccines

A valuable resource of mRNA vaccines is their ease of adaptation: after the first wave of vaccination, a new version of the vaccine, carrying the mutations of the variant, can be produced readily by site-directed mutagenesis [18][18]. The operation is simple to perform, so that Ugur Sahin, CEO of the German laboratory

BioNTech, could say without exaggeration that he was "technically capable of delivering a new vaccine in six weeks" [19][19]. Let us add that probationary tests for such a vaccine would be much simplified.

Detection of new variant by PCR

Mutations in the new variants do not prevent detection of virus carriers by PCR, since the PCR test can address several genes of the virus. If one viral gene escapes amplification due to a mutation, the other genes will be amplified normally. Lack of amplification of a gene to PCR may be a way to discover a possible new mutant[20][20].

Is there an increased risk for children and pregnant women?

With the high proportion of children with COVID in Britain and South Africa when the new variants spread, the question has been raised whether the variants put children at increased risk. Early epidemiological studies did not find a significant correlation [21][21]. However, an increased frequency of serious illness has been found in Israel among young people and pregnant women, which has prompted the authorities to prioritize vaccination for these two categories [22][22].

Must we adapt the new mRNA vaccines?

In a January 25, 2021 statement, Moderna confirmed that the protection provided by their vaccine is weakened when faced to the 501Y.V2 variant, and announced the implementation of a second vaccine, to be used as a booster shot and complete protection against 501Y.V2-like variants [23][23].

A preliminary report claims that different combinations of mutations found in 501Y.V2, introduced in an engineered virus, do not significantly alter the neutralizing power of the Pfizer vaccine [24][24]. But these mutations were not tested all together, so this result does not necessarily reflect the true resistance of the variant.

[1][1]Moshiri, N. 2020. Coronavirus seems to mutate much slower than seasonal flu. ***Live Sicence***, April 06, 2020. https://www.livescience.com/coronavirus-mutation-rate.html

[2][2] Callaway, E. 2020. Making sense of coronavirus mutations. ***Nature*** 585, 174-178. https://www.nature.com/articles/d41586-020-02544-6

[3][3] Wise, J. 2020. Covid-19: New coronavirus variant is identified in UK. ***British Medical Journal*** 371, m4857. https://www.bmj.com/content/371/bmj.m4857

[4][4] Rambaut, A., Loman, N., Pybus, O., et al. 2020. Preliminary genomic characterisation of an emergent SARS-CoV-2 lineage in the UK defined by a novel set of spike mutations. ***Virological.org*** . https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563

[5][5] Starr, T. N., Greaney, A. J., Hilton, S. K., et al. 2020. Deep mutational scanning of SARS-CoV-2 receptor binding domain reveals constraints on folding and ACE2 binding. ***Cell*** 182 (5) 1295-1310. https://www.cell.com/cell/fulltext/S0092-8674(20)31003-5

[6][6] Muik, A., Wallischn A. K., Sänger, B., et al. 2O21. Neutralization of SARS-CoV-2 lineage B.1.1.7 pseudovirus by BNT162b2 vaccine-elicited sera. ***bioRxiv Preprint*** doi:https://doi.org/10.1101/2021.01.18.426984

[7][7] Rees-Spear, C., Muir, L., Griffith, S. A., et al. 2021.The impact of Spike mutations on SARS-CoV-2 neutralization. ***bioRxiv Preprint*** doi: https://doi.org/10.1101/2021.01.15.426849

[8][8]Threat Assessment Brief. 2020. Rapid increase of a SARS-CoV-2 variant with multiple spike protein mutations observed in the United Kingdom. ***European Center for Disease Prevention and Control***. December 20, 2020. https://www.ecdc.europa.eu/sites/default/files/documents/SARS-CoV-2-variant-multiple-spike-protein-mutations-United-Kingdom.pdf

[9][9]Tegally, H., Wilkinson, E., Giovanetti, M., et al. 2020. Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. ***medRxiv Preprint*** doi: https://doi.org/10.1101/2020.12.21.20248640

[10][10]Wibmer, C. K., Ayres, F., Hermanus, T., et al. 2021. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. ***bioRxiv Preprint*** doi: https://doi.org/10.1101/2021.01.18.427166

[11][11] Cele, S., Gazy, I., Jackson, L., et al. 2021. Escape of SARS-CoV-2 501Y.V2 variants from neutralization by convalescent plasma. ***medRxiv Preprint***

[12][12] Faria, N., Claro, I. M., Candido, D., et al. 2020. Genomic characterisation of an emergent SARS-CoV-2 lineage in Manaus: preliminary findings. ***Virological.org***. https://virological.org/t/genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-manaus-preliminary-findings/586

[13][13] Zhang, W., Davis, B. D., Chen, S. S., et al. 2021. Emergence of a novel SARS-CoV-2 strain in Southern California, USA. ***medRxiv Preprint*** doi: https://doi.org/10.1101/2021.01.18.21249786

[14][14]Yanko, A. 2021. Health Ministry reports first case of California virus varriant. ***Ynet News*** (24/01/2021) https://www.ynetnews.com/health_science/article/SykZEVo1O

[15][15] Piccoli, L., Park, Y.-J., Tortorici, M. A., et al. 2020. Mapping neutralizing and immunodominant sites on the SARS-CoV-2 spike receptor-binding domain by structure-guided high-resolution serology. ***Cell*** 183, 1024-1042. https://www.cell.com/cell/fulltext/S0092-8674(20)31234-4

[16] [16]Grifoni, A., Weiskopf, D., Ramirez, S. I., et al. 2020. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. ***Cell*** 181, 1489-1501. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7237901/pdf/main.pdf

[17][17] Sette, A., and Crotty, S. 2021. Adaptive Immunity to SARS-CoV-2 and COVID 19. ***Cell*** 184. Doi: https://www.cell.com/cell/fulltext/S0092-8674(21)00007-6?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867421000076%3Fshowall%3Dtrue

[18][18] Hemsley, A, Arnheim, N., Toney, M. D., et al. 1989. A simple method for site-directed mutagenesis using the polymerase chain reaction. ***Nucleic Acids Research*** 17 (16), 6545-6551. https://pubmed.ncbi.nlm.nih.gov/2674899/

[19][19]Jordans, F. 2020. BioNTech CEO confident vaccine will work on UK variant. ***AP News***, December 22, 2020. https://apnews.com/article/europe-europe-coronavirus-pandemic-united-states-

8555f433c0cd8ea8c58040e3f7aa0e91

[20][20] Mahase, E. 2020. Covid 19: What have we learnt about the new variant in the UK? ***British Medical Journal*** 371, m4944. https://www.bmj.com/content/bmj/371/bmj.m4944.full.pdf

[21][21] Lewis, D. 2021. What new COVID variants mean for school is not yet clear. ***Nature News*** (21/01/2021). https://www.nature.com/articles/d41586-020-00502-w

[22][22]Yanko, A. 2021. Health Ministry reports first case of California virus varriant. ***Ynet News*** (24/01/2021). https://www.ynetnews.com/health_science/article/SykZEVo1O

[23][23]Grady, D., Mandavilli, A., and Thomas, K. 2021. As Virus Grows Stealthier, Vaccine Makers Reconsider Battle Plans. ***New York Times*** (25/01/2021). https://www.nytimes.com/2021/01/25/health/coronavirus-moderna-vaccine-variant.html?action=click&campaign_id=154&emc=edit_cb_20210125&instance_id=26394&module=RelatedLinks&nl=coronavirus-briefing&pgtype=Article&regi_id=119747367&segment_id=50223&te=1&user_id=fb7f4fabf7eef290361aaba4ad96756dk

[24][24]Xie, X., Liu, Y., Liu, J. et al. 2021. Neutralization of spike 69/70 deletion, E484K, and N501Y SARS-CoV-2 by BNT162b2 vaccine-elicited sera. ***bioRxiv Preprint*** doi: https://doi.org/10.1101/2021.01.27.427998