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Global Concerns of Mutated SARS-CoV-2- An Overview

***Corresponding Author(s):** S Kalpana

Research Officer, Department of Experimental Medicine, The TN Dr. MGR Medical University, Chennai, Tamil Nadu, India.

Email: kalpana.s@tnmgrmu.ac.in & drkalpanaphd@gmail.com

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Abstract

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the 2019 coronavirus disease (COVID-19) causative pathogen, is a member of the Coronaviridae family of single-stranded positive-sense RNA viruses with a genome size of approximately 30 kb. Researchers have sequenced nearly 4,10,000 genomes of SARS-CoV-2 since its emergence in China in December 2019 and shared the details on the Global Initiative on Sharing All Influenza Data (GISAID) database. Experts believe that the novel coronavirus SARS-CoV-2, which is now spreading across the world, is not the same as the virus that first appeared in China's Wuhan province in late 2019 and soon became the source of the COVID-19 global pandemic in 2020. This is because, like many other viruses, coronavirus is susceptible to mutation, which causes changes in its genetic structure. Several genomic epidemiological studies of SARS-CoV-2 have been performed, with the majority of them focusing on mutations in viral spike protein, a surface glycoprotein of SARS-CoV-2 that binds to the host Angiotensin-Converting Enzyme 2 (ACE2) and initiates the viral entry phase. Because of their major effect on viral transmissibility and pathogenicity, studies are currently primarily focused on three viral lineages, B.1.1.7, B.1.351, and P.1. E484K is an escape mutation because it helps the virus slip past the body's immune defences. The E484K mutation was first identified in the South African variant (B.1.351). The E484K mutation is also found in the Brazilian variant (B.1.1.28). The E484K mutation has also been in the U.K variant (B1.1.7). Mutating viruses are more contagious but the virulence of such virus continues decreasing with each mutation.

Background

Main text

The etiological agent of the new pandemic coronavirus disease is SARS-CoV-2 (COVID-19). It was first discovered in Wuhan, China, in December of this year. The virus has infected more than 109 million people worldwide since then and caused more than 2.4 million fatalities. Some recently discovered variants, on the other hand, are highly transmissible and contagious. It's crucial to look into the molecular mechanisms of these naturally occurring mutations, their effect on SARS-CoV-2 infectivity, and the existing vaccines' efficacy in promoting immunity. SARS-CoV-2, although most infections are mild, can cause serious, life-threatening pneumonia, particularly in the elderly and those with chronic illnesses. Although the exact cause of extreme COVID-19 is uncertain, it is thought to involve a dysregulated, hyperinflammatory response in the aftermath of viral infection. However, variations in the viral strain may contribute to the intensity of the disease and the efficiency of spread, in addition to the host response [1]. To retain their long RNA genomes, coronaviruses have developed a genetic proofreading mechanism [2]. Despite SARS-low CoV-2's sequence diversity [3], spike

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protein mutations interacting with cellular receptors such as the Angiotensin-Converting Enzyme 2 (ACE2) to mediate cell entry have a strong impact on host selection, tissue tropism, and pathogenesis. During the 2002-2003 SARS-CoV outbreak, one such mutation induced adaptation for both intermediate civet host infection and interhuman transmission [4].

Structure of the SARS-CoV-2

It is a highly pathogenic and transmissible coronavirus. The viral genome is single-stranded RNA enveloped by a protein-embedded lipid membrane. To allow its entry, the protruding spike (S) protein present on the surface of the virus binds to the hACE2 receptor in the host cell. The S protein is a glycoprotein that is homo-trimeric, with each protomer consisting of subunits S1 and S2. The virus recognizes and binds to the hACE2 by conformational transitions in the Receptor-Binding Domain (RBD) on the S1 subunit. This binding induces membrane fusion and virus penetration into the host cell, where the virus uses the cell's metabolic mechanism to start viral replication. The below figure shows the structure of the SARS-CoV-2 spike (S) protein. The S protein is a highly glycosylated trimeric protein that fuses with ACE2 to gain access to host cells. Cryo-EM has recently been used by Wrapp and colleagues to determine the structure of the S protein and analyze its conformational changes during infection. [From: Evolutionary and structural analyses of SARS-CoV-2 D614G spike protein mutation now documented world wide].

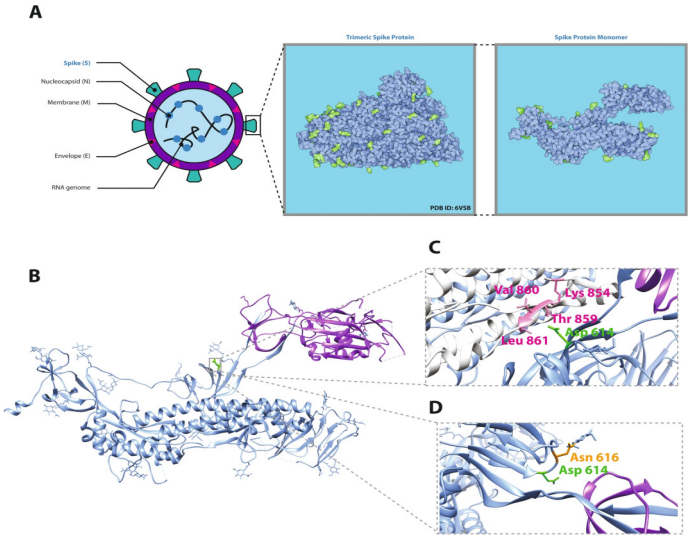

Figure 1: Structure of SARS-2 virus.

Structural analysis of SARS-CoV-2 spike protein around position 614. (**A**) Location and distribution of SARS-CoV-2 viral proteins. The full trimeric form of the spike protein results from a complex of three identical spike monomers (right panel). (**B**) Three-dimensional depiction of a spike protein monomer. The receptor-binding domain is colored purple and the location of the aspartate residue in position 614 is highlighted in green. (**C**) Inter-atomic contacts between aspartate 614 (green) in a reference spike monomer (blue) and four residues (pink) in its adjacent spike protein monomer chain (white). These four contacts are destabilizing and create a hydrophilic-hydrophobic repelling effect that is lost upon replacement of aspartate by glycine in the D614G mutation (Table 1). (**D**) Spatial distribution of aspartate 614 residue (green) and an adjacent glycosylated asparagine residue in position 616 (orange). The two residues point in opposite directions and thus it is unlikely they share a meaningful interaction. The image (**A**) was drawn using Affinity Designer (v1.8) [5]. The trimeric and monomeric structures of the Spike protein were generated using Illustrate [6] by rendering a protein structure from the Protein Data Bank with ID 6vsb [7]. The image (**B-D**) was generated using UCSF Chimera (v1.14) [8] with monomeric protein structure rendered in Chimera [9].

Notably, four inter-chain destabilizing (i.e., hydrophobic-hydrophilic) contacts are lost with residues of an adjacent chain upon D614G mutation (Table 1 and Figure 1a-1d). This suggests that a small repelling interaction between adjacent chains is removed upon this aspartate substitution (Table 1). However, it is unlikely that this would have a significant effect on recognition and binding to ACE2 given the relative distal position of this mutation with respect to the Receptor-Binding Domain (RBD) (Figure 2), but further analyses would be required to assess whether the D614G mutation has an effect on the way the S protein changes its conformation after interaction with ACE2. Lan and colleagues also showed residues in the RBD act as epitopes for SARS-CoV-2 and mutations can influence antibody binding. Given the important role that glycosylation plays in regulating the function of spike.

Table 1: Inter-chain contacts lost upon D614G mutation between adjacent chains in the SARS-CoV-Spike protein.

Residue in non-reference adjacent chain	Distance (Å)	Contact surface area (Å²)
Lys 854	5.2	10.0
Thr 859	2.7	28.8
Val 860	4.5	5.6
Leu 861	5.6	1.0

(Source: Evolutionary and structural analyses of SARS-CoV-2 D614G spike protein mutation now documented worldwide).

Estimated Molecular Dating of the 442 Representative Global SARS-CoV-2 Sequences Evolutionary Background and the D614G Clade Emergence. Bayesian Evolutionary Analysis Sampling Trees estimated Maximum Clade Credibility (MCC) tree with dated branches (BEAST). Node colors indicate isolation continents; x-axis in decimal notation displaying dates by year and days; D614G clade sequences are highlighted in a yellow box. From: Evolutionary and structural analyses of SARS-CoV-2 D614G spike protein mutation now documented world wide.

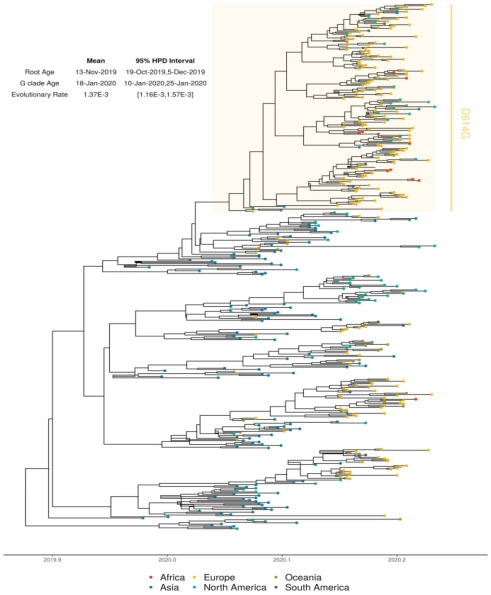

Figure 2: Structural analysis of SARS-2 Virus.

The speed of evolution

The genetic material of the coronavirus is Ribonucleic Acid (RNA) strands. Each virus has about 26,000 to 32,000 bases or RNA "letters" in its length. Mutations may occur at random, but the rate at which they happen is dependent on the virus. The DNA virus-copying enzymes, called DNA polymerases, can proofread and repair errors in the resulting genetic letter strings, leaving few mutations in each copy generation.But the evolutionary gamblers of the microscopic world are RNA viruses, including SARS-CoV-2. In general, the RNA polymerase that copies the genes of the virus lacks proofreading abilities, rendering RNA viruses vulnerable to high mutation rates, up to a million times greater than their hosts' DNA-containing cells. However, it's hard to calculate the true mutation rate of a virus. Most of these mutations are going to be lethal to the virus, and in the actively developing, evolving virus population, you'll never see them. Coronaviruses do not have physical segmentation to undergo reassortment, unlike influenza, however. Through a process known as recombination, when segments of one viral genome are spliced onto another by the enzyme producing the viral copy, coronaviruses may undergo some changes in function. However, researchers are still working to determine how important this mechanism is to the evolution of SARS-CoV-2. SARS-CoV-2 has developed into many versions, including B.1.1.7 (501Y.V1), B.1.351 (501Y.V2), and P.1 (501Y.V3). The bulk of the mutations are found in the RBD on the S protein's receptor-binding motif (RBM). In contrast to the original SARS-CoV-2 strain, early tests of these variants indicate increased transmissibility. The E484K mutation (which is shared by both the 501Y.V2 and 501Y.V3 variants) is known as the "escape mutation" since it greatly decreases the neutralization function of and can also escape from neutralizing antibodies in COVID-19 patients' convalescent plasma. This could also undermine the effectiveness of the currently approved vaccines and the efficacy of the currently being established neutralizing antibody therapeutics. It is important to understand the evolutionary dynamics of SARS-CoV-2 to ensure that therapies and vaccines keep pace with the virus. For now, the vaccines available are effective in preventing all viral forms of serious diseases.

How mutation happens?

The researchers examined the binding between the viral spike protein, where major mutations have occurred, and its human receptor, angiotensin-converting enzyme 2, using molecular simulation studies (hACE2). Recently, Phan studied 86 complete SARS-CoV-2 genomes, identifying 42 missense mutations, eight of which occurred in the S-protein gene2. However, at the time of the study, the mutation D614G was only found in one sequence from Germany. Modifications in the spike protein are of interest as they might indicate the emergence of a novel strain of SARS-CoV-2 with change in transmissibility or pathogenicity [11]. A characteristic of viral variation is that at the same time, the tiny alterations differentiating one variant from the next will occur in separate places, evolving independently of each other. The N501Y spike protein mutation, which is known to improve the virus' affinity for our ACE2 receptors, is one example. N501Y was first spotted in the B.1.1.7 (UK) variant genome, but it did not take long for researchers to discover its existence in the variants B.1.351 (South Africa) and P.1 (Brazil) as well. Another immune escape associated spike protein mutation, E484K, has also acquired high global frequency, first appearing in B.1.351 and more recently in B.1.525, the new form of washing u.

CSIR study

In India, at least 19 SARS-CoV-2 genetic variants have evolved to resist neutralising antibodies developed by the human immune system against Covid-19 infection, with one of these variants already causing a reported case of reinfection in the region [12]. CSIR Institute of Genomics and Integrative Biology (CSIR-IGIB), New Delhi, Analysis the variant of the SARS-CoV-2 mutation indicates that a variety of immune escape-related genetic variants have arisen in global populations. Of the 19 immune escape variants found in Indian genomes, one was found to be in 2.1 percent of the gene sequences in India, known as the S:N440K variant. This variant has a high prevalence in the state of Andhra Pradesh where 33.8 per cent of the 272 sequenced genomes had this variant.

There were important weaknesses in our current research that are likely to be a big roadblock for similar studies in the future. Our analysis of the relation between viral clade and phenotype of disease severity was avoided by the lack of available clinical metadata. Furthermore, the number of sequenced SARS-CoV-2 samples varies greatly between countries, which could contribute to sampling bias. Due to substantial variations in population composition, research procedures, case descriptions, and implementation, existing country-level statistics on crude case fatality rates and case numbers do not allow for robust comparisons of clinical phenotype across countries [13].

Spike mutation D614G

In May 2020, studies of more than 28,000 SARS-CoV-2 spike gene sequences revealed a D614G substitution that was unusual before March 2020 but became more widespread as the pandemic spread [14], appearing in over 74% of all reported sequences by June 2020 [15]. Due to substantial variations in population composition, research procedures, case descriptions, and implementation of public health interventions, existing country-level statistics on crude case fatality rates and case numbers do not allow for robust comparisons of clinical phenotype across countries. As a result, no conclusions about the clinical phenotype of the D614G clade could be made, and there is currently no evidence that this clade is related to any variations in disease phenotype.

Three other mutations were added to the D614G substitution: a C-to-T mutation at position 241 in the 5' untranslated region, a synonymous C-to-T mutation at position 3037, and a nonsynonymous C-to-T mutation at position 14408 in the RNA-dependent RNA polymerase gene [16]. This set of mutations became more widespread not only internationally, but also within individual regions during outbreaks, meaning that the increase was due to a fitness advantage rather than founder effects and/or genetic drift. The association of spike amino acid substitutions with coronavirus transmissibility indicated that this putative selective sweep was important for the D614G substitution. In patients with COVID-19 [17], the association of this mutation with higher nasopharyngeal viral RNA loads also assisted the mutant's putative advantage in transmission. To confirm this hypothesis, however, direct measurements of fitness are required.

Despite the lack of evidence for phenotypic differences, the D614G clade has become widespread all over the world in a relatively short amount of time since its emergence. Even if the observed mutation has no effect on the protein's interaction with ACE2, it is probable that it is not fully neutral in terms of viral fitness. For example, given that glycine's molecular weight

is slightly lower than that of aspartate, from a cost minimization point of view, the mutation may be beneficial [18].

The replacement of D614G resulted in significantly higher pseudovirus titres in multiple cell types and suggests that G614 spike may be associated with improved airway entry and replication [19].

E484K mutation

It was discovered that the E484K mutation causes the protein to have more favorable electrostatic interactions, which affects its binding affinity. As an additional benefit to the virus, this mutation reduces the immune response in the host. In short, the bond between the viral protein and its receptor is reinforced by this. The E484K mutation, first detected in the South African SARS-CoV-2 variant, has now been identified in the UK as a fast-spreading variant, causing concerns that the virus would evolve further. The mutation is in the spike protein and tends to affect the immune response of the body and probably the effectiveness of the vaccine. An escape mutation is called E484K because it lets the virus get through the immune defences of the body. Ravindra Gupta at Cambridge University and colleagues have reported that the new variant B.1.1.7 plus E484K greatly increases the amount of serum antibodies required to avoid cell infection [20].

E484K is referred to as an escape mutation because it enables the virus to circumvent the body's immune system. The E484K mutation was discovered for the first time in a South African version (B.1.351). The Brazilian version has the E484K mutation as well (B.1.1.28). In the U.K. variant, the E484K mutation has also been identified (B1.1.7). There has been studies showing that the latest vaccines function without the E484K mutation against the UK B.1.1.7 variant. Recent clinical trials by Novavax and Johnson & Johnson, however, have shown that their new vaccines are less successful in South Africa compared to the UK or the US, possibly due to the high level of E484K mutation-carrying viruses. Because of the E484K mutation, a new ACE2 binding site (amino acid 75) is produced, according to structural analysis. This tends to make the interaction between ACE2 and the native binding site at the RBD and ACE2 interface far better (amino acid 501). In all Brazilian lineages with the E484K mutation, a highly complex set of genetic mutations has been observed. In the B.1.1.33 and P.1 lineages, on average, about 19 and 30 mutations were observed, respectively. Further genomic study of the most recent P.2 lineage has shown that both the P.1 and P.2 lineages are increasingly evolving and have been circulating for a longer time in Brazil [21].

Researcher found that the mutation of E484K can boost RBD's binding affinity to the hACE2 receptor. This happens due to electrostatic forces that are more beneficial and the mutation creates a stronger binding interface. Conformational rearrangements of the local structure around the mutant residue contributed to the strength of the bond with the development of further hydrogen bonding. This indicates that the E484K-containing variant has a higher transmissibility limit. The E484K mutation also decreased the binding affinities between RBD and most of the neutralizing antibodies and nanobodies tested, according to the researchers. This study showed that the E484K mutation could increase the binding affinity of the E484K-containing variants between the RBD and the hACE2 receptor, suggesting more transmissibility. This is confirmed by existing evidence from variant-infected areas. Furthermore, the mutation decreases the binding affinities between RBD and the neutralizing antibodies tested, meaning that these antibodies are less efficient. This is troubling in the face of the current roll-out of vaccinations around the world. This research finds the advantages of the mutation that the virus comes from [22]. The mutation of E484K could theoretically increase SARS-infectivity CoV-2's and immune evasion capacity. More research into the efficacy of anti-SARS-CoV-2 human sera against E484K mutated variants of SARS-CoV-2 is urgently needed, according to the researchers.

What are Q677P variants?

According to a pre-print report published, the 677 variants are identical in that genomic surveillance programmes were first observed nearly a thousand miles apart in October. At the 677 amino acid site, they are named for their one commonality, mutations. Researchers found that the proportion of SARS-CoV-2 viruses in local circulation carrying a Q677P mutation grew from zero to almost a third (28 percent) between early December 2020 and late January 2021 in Louisiana, where one of the programmes to successfully track them is located. The mutation's prevalence in New Mexico, where the other programme is based, shot up to just over 11 percent within the same timeframe [23].

Will COVID-19 vaccines work against new mutant strains?

Vaccine designers are well aware of viruses' potential to evolve over time, and they designed vaccines to account for this. Researchers have seen many variants of the spike proteins for which these viruses are named since SARS-CoV-2 is part of a wide community of coronaviruses. Vaccines against COVID-19 were tested against a variety of spike protein variations when they were created [24].

Conclusion

Viruses that have undergone mutations are more infectious, but their virulence decreases with each mutation. As a consequence, mutation is not a cause for concern since it results in a milder strain. Although this virus has a low mortality rate, it is rapidly spreading among the younger population. There is reason to believe that the vaccines that have been approved or are in the works would be able to cover a significant amount of SARS-CoV-2 drift. Vaccine makers are well aware of viruses' potential to evolve over time, and they designed vaccines to account for it. Researchers have seen many variants of the spike proteins for which these viruses are named since SARS-CoV-2 is part of a wide community of coronaviruses. Vaccines against COVID-19 were tested against a variety of spike protein variations when they were created. Many variants of the spike protein are recognized and responded to by the antibodies produced after vaccination, according to research. As a result, researchers are reasonably optimistic that the vaccines can continue to be successful against a wide range of mutations. “There has always been the hope that if these spike proteins change dramatically over time, the vaccine should be revised to accommodate the changes while still providing the value to society that it was designed to provide,”. Many variants of the spike protein are recognized and responded to by the antibodies produced after vaccination, according to research. As a result, researchers are reasonably optimistic that the vaccines can continue to be successful against a wide range of mutations.

References

1. Domingo P, et al. The four horsemen of a viral apocalypse: the pathogenesis of SARS-CoV-2 infection (COVID-19). eBioMedi-

cine. 2020; 58: 102887.

2. Smith EC, Blanc H, Surdel MC, Vignuzzi M, Denison MR. Coronaviruses lacking exoribonuclease activity are susceptible to lethal mutagenesis: evidence for proofreading and potential therapeutics. PLoS Pathog. 2013; 9, e1003565.

3. Fauver JR, et al. Coast-to-coast spread of SARS-CoV-2 during the early epidemic in the United States. Cell. 2020; 181: 990-996.

4. Song HD, et al. Cross-host evolution of severe acute respiratory syndrome coronavirus in palm civet and human. Proc Natl Acad Sci USA. 2005; 102: 2430-2435.

5. https://affinity.serif.com/en-gb/designer

6. https://ccsb.scripps.edu/illustrate/

7. https://www.rcsb.org/structure/6vsb

8. https://www.cgl.ucsf.edu/chimera

9. Wrapp D, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020; 367: 1260-1263.

10. Wrapp D, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020; 367: 1260-1263.

11. Phan, T. Genetic diversity and evolution of SARS-CoV-2. Infect Genet Evol. 2020; 81: 104260.

12. Bani Jolly, Mercy Rophina, Afra Shamnath, Mohammed Imran, Rahul C. Genetic epidemiology of variants associated with immune escape from global SARS-CoV-2 genomes bioRxiv. 2020; 424332.

13. Grubaugh ND, Hanage WP, Rasmussen AL. Making sense of mutation: what D614G means for the COVID-19 pandemic remains unclear. Cell. 2020. https://doi.org/10.1016/j.cell.2020.06.040 (2020).]

14. Korber, B. et al. Tracking changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the COVID-19 virus. Cell. 2020; 182: 812-827.

15. Yurkovetskiy L, et al. Structural and functional analysis of the D614G SARS-CoV-2 spike protein variant. Cell. 2020; 183: 739-751.

16. Hou YJ, et al. SARS-CoV-2 reverse genetics reveals a variable infection gradient in the respiratory tract. Cell. 2020; 182: 429-446.

17. Lorenzo-Redondo, R. et al. A unique clade of SARS-CoV-2 viruses is associated with lower viral loads in patient upper airways. 2020. Preprint at. 2020.

18. Seligmann, H. Cost-minimization of amino acid usage. J Mol Evol. 2003; 56: 151-161.

19. Yurkovetskiy, L. et al. Structural and functional analysis of the D614G SARS-CoV-2 spike protein variant. Cell. 2020; 183: 739-751.

20. Collier D, de Marco A, Ferrerira I, et al. SARS-CoV-2 B.1.1.7 escape from mRNA vaccine-elicited neutralizing antibodies. medRxiv2021.01.19.21249840v2 [Preprint]. 2021. www.medrxiv.org/content/10.1101/2021.01.19.21249840v2.Google Scholar

21. bioRxiv preprint server. 2021. Ferrareze PAG. E484K as an innovative phylogenetic event for viral evolution: Genomic analysis of the E484K spike mutation in SARS-CoV-2 lineages from Brazil. https://www.biorxiv.org/content/10.1101/2021.01.27.426895v1

22. Wei Bu Wang, Yu Liang, Yu Qin Jin, Jing Zhang, Ji Guo Su, Qi Ming Li. E484K mutation in SARS-CoV-2 RBD enhances binding affinity with hACE2 but reduces interactions with neutralizing antibodies and nanobodies: Binding free energy calculation studies. bioRxiv. 2021.

23. Emma B. Hodcroft, Daryl B. Domman, Kasopefoluwa Oguntuyo, Daniel J. Snyder, et al. Cooper, Jeremy P. Kamil, Emergence in late 2020 of multiple lineages of SARS-cov-2 Spike protein variants affecting amino acid position 677 medrxiv 2021.02.12.21251658; doi: https://doi.org/10.1101/2021.02.12.21251658

24. https://www.osfhealthcare.org/blog/how-covid-19-mutates-and-how-it-affects-vaccines/