SARS-CoV-2: How Viral Mutations Drive Development of Moderna's COVID-19 Vaccine

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Abstract

Purpose: This review article aims to examine the natural progression of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) from the initial parent strain to the circulating variants in 2025, while highlighting the correlating development of Moderna's SpikeVax mRNA vaccine.

Methods: A systematic review was conducted encompassing experimental studies, clinical trials, and peer-reviewed journal entries published between 2020 and 2025.

Key Findings: The continued prevalence of SARS-CoV-2 over the past 5 years has been largely due to the rapid mutation rate of the receptor-binding domain (RBD) and overall virus. The mutations allow the virus to evade established immune detection and increase rate of cellular fusion causing efficient transmission. In order to counter this global health threat, Moderna, among other pharmaceutical or companies, has actively combatted these viral alterations through the various efforts in pharmaceutical development, specifically with administration of different versions of mRNA-1273, SpikeVax, that respond to circulating variants of concern, in hopes of providing the population with preventive measures to greaten public health.

Keywords

Coronavirus, Moderna, mRNA Vaccine, Variant, Immune-response

Introduction

Viral diseases have plagued humanity for as long as humans have existed. In an attempt to reduce the spread of infection of these diseases, exploration to better understand viral origins and mechanisms has been conducted. In November of 2019, a new coronavirus strain was discovered sourcing from Wuhan, China. Coronaviruses are a family of viruses uniquely named for the distinct crown-like shape of the spike proteins embedded in the envelope of the virus. COVID-19 is a highly infectious viral disease that has spread globally over the past five years. [1] The disease is caused by the virus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which has prompted lockdowns and impacted society greatly, with over 774 million infected and over 7 million deaths to date. [2]

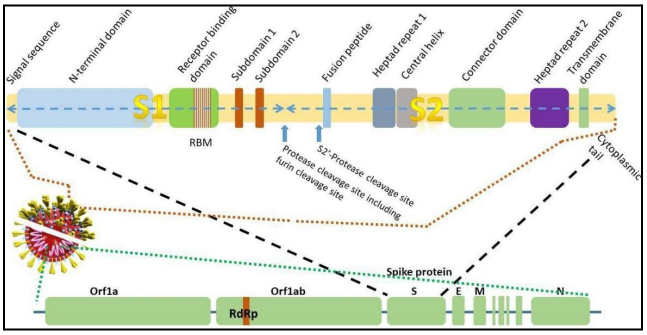

Figure 1: Displaying RNA Coding sequence of SARS-CoV-2 Reproduced from Gene of the month: the 2019-nCoV/SARS-CoV-2 novel coronavirus spike protein, Tahir S Pillay, Volume 73, Issue 7, Jul 1, 2020 with permission from BMJ Publishing Group Ltd.

To combat the virus, biochemists within pharmaceutical companies began the development of a vaccine that would inhibit the function of the virus. Particular methods of inhibition that were found to have high levels of efficacy were developed by Moderna (SpikeVax) and Pfizer-BioNTech (Comirnity) through the use of mRNA vaccines. [3] This approach works by introducing to host cells instructions for manufacturing the spike protein found on the surface

of the SARS-CoV-2 virus. Upon integration, the host begins creating the protein pieces which contribute to the development of antibodies. [3] Since the host has already been exposed to the viral protein, it is able to use the subsequently formed antibodies to induce an immune response, providing protection from the actual virus upon infection. However, the frequent appearance of modified COVID-19 variants prompted the challenge of producing newer defense mechanisms against SARS-CoV-2. Each of these new variants arose from the constant mutation of genetic information that is characteristic of RNA viruses such as SARS-CoV-2. A categorical nomenclature method is used to describe new mutations within the virus's genetic code that may produce differences in viral characteristics, and therefore allows for the consistent tracking of known and new variants. [4] Pharmaceutical companies and biochemists therefore need to be cognizant of these variations when developing a vaccine, as slight changes in the virus's composition can lead to changes in efficacy of previously administered vaccines. Characterization of the virus begins with Polymerase Chain Reaction (PCR) detection of SARS-CoV-2, and then, through genomic sequencing, the specific variant of the virus can be identified. This characterization remains important from an epidemiological perspective, as it provides essential information of prevalence of circulating variants and whether the current vaccine provides adequate protection for the population, even though therapeutic remedies tend to remain consistent regardless of the variant.

Different Variants and Corresponding Development of mRNA Vaccines:

In December of 2020, Moderna was granted FDA approval Emergency Use Authorization for the mRNA-1273, Spikevax. This vaccine later gained approval for full administration in January 2022. Initially designed to provide protection against the parent strain of SARS-CoV-2, the vaccine was later found to have high efficacy values against emerging mutated variants. Variation from the SARS-CoV-2 parent strain is due to spontaneous mutations during viral replication. Mutations within glycoprotein Spike (S), especially within the receptor-binding domain (RBD), have a strong tendency to affect the variant's ability to evade vaccinated immune-systems, as they disrupt how antibodies promoted by the given vaccine recognize and neutralize the virus. Mutations in the RBD are also known to enhance a coronavirus's ability to bind to host cells, further allowing higher transmission of the virus. Mutations in the RBD are also known to enhance a coronavirus's ability to bind to receptor angiotensin-converting enzyme 2 (ACE2) in host cells, further allowing higher transmission of the virus. Although genetic mutations occur with high frequency, only significant mutations that increase immune protection and functionality from vaccine or prior infections will result in the presence of a prevalent variant of concern. [5]

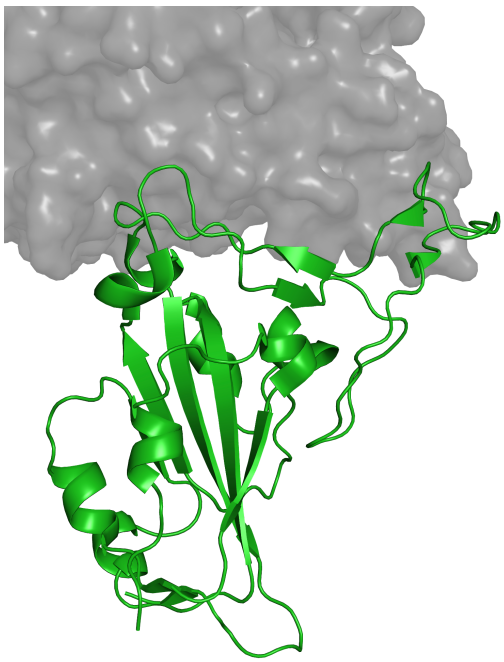

Figure 2: Receptor-binding domain of SARS-CoV-2 in complex with human ACE2 receptor

The first variant of concern to arise was labeled by the World Health Organization (WHO) as Alpha or Pango lineage B.1.1.7. It was first documented in September of 2020 in the United Kingdom. [6] Several mutations to the virus's S protein have been identified, with specific mutations providing a significant contribution toward the virus's ability to more efficiently transmit and reduce the efficacy of antibody response. N501Y is a mutation consisting of a residue substitution within the RBD

that was found to enhance the viral affinity to ACE2 in the host. This is due to an increase in interaction strength, while displaying a decrease in dissociation rate, the effect of which results in a higher rate of transmission. [7] Deletion of H69/V70 residues has been found to be correlative to an increase in kinetic rates of cellular fusion and infectivity. The mechanism in which this occurs is through the promotion of the incorporation of cleaved S proteins into viral envelope. [8] The P681H mutation allows the virus to develop resistance to beta interferon (IFN-β), a type of protein that helps to fight infections and is located within lung epithelial cells. A reduction to dependence on endosomal cathepsin was discovered, which contributes to the activation of viral glycoprotein attachment and entry into a given host cell.[9][10] This mutation provides the virus with ability to evade a natural immune response while also promoting a more independent facilitation of entry of host cells. It was found that effectiveness against B.1.1.7 infection was 88.1% ≥14 days after the first dose of the mRNA-1273 vaccine, but 100% ≥14 days after the second dose. [11] Although various mutations occurred to increase viral effectiveness, the Alpha variant did not experience enough compositional alterations requiring the development of a supplementary, updated version of the mRNA-1273 (SpikeVax) vaccine.

In May of 2020, in South Africa, the Beta (B.1.351) variant of SARS-CoV-2 was discovered. [6] This variant was characterized by a number of spike protein mutations, three of which took place in the RBD. Among these three RBD mutations is N501Y, which was a mutation that carried over from the Alpha variant to the Beta variant. However, two new RBD mutations were discovered in this variant: K417N and E484K. [12] The mutation of a lysine (K) at residue 417 to an asparagine (N) is generally thought to augment a virus's ability to fight off the host's immune system. This is because residue 417 is found at the antigenic determinant of the SARS-CoV-2 spike protein, or the region at which antibodies of the host's immune system are able to bind to and neutralize the virus. Although the replacement of a lysine at this location renders the Beta variant significantly less recognizable by antibodies, the loss of that lysine also leads to the loss of a binding site at which the spike protein normally would attach to an aspartate (D) at residue 30 of ACE2. [13] This essentially means that this mutation of the Beta variant sacrifices transmissibility for increased immune-system elusion in its spike protein. Unfortunately for humans, however, the previously mentioned N501Y mutation makes up for the transmissibility that the K417N mutation loses, allowing for increased infectivity as well as more efficient antibody evasion. Similarly, the E484K mutation also increases binding strength between the spike protein's RBD and ACE2 by creating more hydrogen bonds between the two proteins. The combined effect of these three mutations on the receptor-binding domain results in a much higher affinity for ACE2 by the Beta variant spike protein, facilitating much higher infection rates. In fact, the binding-affinity between the spike protein and ACE2 was found to be 19-times stronger in the Beta variant than in the original strain of SARS-CoV-2. [14] It was discovered that mRNA-1273 effectiveness against B.1.351 infection after one dose was 61.3%. Upon the second dose the effectiveness increased to 96.4%. [11] Thus, the original SpikeVax (mRNA-1273) after two doses was found to still be effective against the new Beta variant, but marginally less effective than the vaccine toward the Alpha variant. This supports the narrative that the accumulation of mutations from the parent strain creates deviation in the efficacy of protection.

Following several mutations, the appearance of the Gamma (P.1) variant was documented in November of 2020 in Brazil. [6] This variant's mutations in the RBD are consistent with those in the Beta variant's RBD (N501Y, K417N, and E484K). [12] Besides those within the RBD, the spike protein of the Gamma variant had nine other mutations. These newer mutations that were not found in previous variants appeared to further reduce the effects of pre-infection immunizations in comparison to those of other variants. Among these non-RBD mutations are H655Y and D614G. Each of these mutations cause the spike protein to further open up its receptor-binding domain, allowing for increased infectivity. Although D614G is a mutation that is found in each variant after the original SARS-CoV-2, the presence of both that mutation and the H655Y mutation makes infection even easier for the Gamma variant. [15] For this reason, gamma was known to be significantly more deadly to younger people than other variants. [16] The mRNA-1273 Moderna vaccine was found to be 89% effective against this

variant after two doses. [17] Although vaccine effectiveness is less than for preceding variants, a specialized booster was not pursued as this variant got displaced by the more efficiently transmitted Delta variant.

The Delta (B.1.617.2) variant was first identified in India during October of 2020. This variant includes 11 mutations on the spike protein, three of which occur in the RBD. Of these three mutations in the RBD, one of them, K417N, was found also in the Beta and Gamma variants. The other two mutations found in this region of the spike protein were L452R and T478K. [18] As in the previous variants, the K417N mutation functions in the Delta variant to increase the ability of the virus to avoid neutralization by the host's immune system. These two newer mutations, characterized by the change of a leucine to an arginine at residue 452, and that of a threonine to a lysine at residue 478, have similar functions to that of the K417N mutation, as these also reduce the ability of host antibodies to bind to and neutralize the spike protein. These mutations are each likely able to do this by converting a relatively short amino acid at each residue (leucine & threonine) to a charged, long and protruding side chain (arginine & lysine). As these residues are found in the antigenic site I of the RBD, the longer amino acid side chains are able to block antibodies from binding there. Additionally, the Delta variant's mutation at residue 681 from a proline to an arginine results in stronger affinity between the spike protein and ACE2. For these reasons, the Delta variant is known for having been highly infectious among vaccinated and unvaccinated individuals alike.
[12] Two doses of Moderna's mRNA-1273 vaccine were found to have a general efficacy against the Delta variant of 77.5%, and an efficacy of 93.8% against severe or fatal infections by the Delta variant.

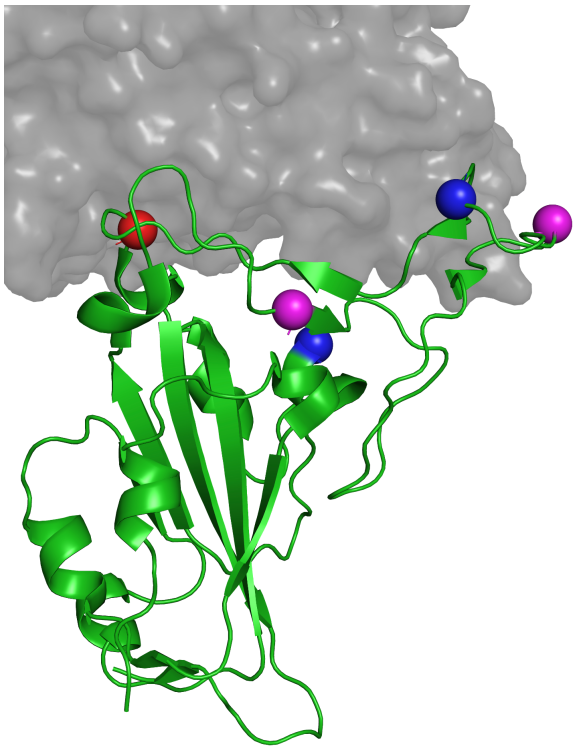

Figure 3: Mutations of the Alpha (Red: N501Y), Beta and Gamma (Blue: N501Y, E484K, K417N), and Delta (Magenta: L452R, T478K) variants

In November of 2021, a novel variant, Omicron (B.1.1.529), initiated its prominent circulation and posed a global threat. Discovered in Botswana, Africa, this highly mutated variant was found to contain particular alterations causing it to become the most transmissible variant compared to those preceding it. Omicron was found to have a basic reproduction rate (R_0 value) of 1.90, in comparison to Alpha (1.22), Beta (1.19), Gamma (1.21), and Delta (1.38), statistically contributing to the narrative that this new emerging variant has an increased ability to infect hosts efficiently. [19] This variant of
SARS-CoV-2 has 15 mutations in the
receptor-binding domain, many of which are the same as or similar to mutations previously seen in other variants. Just like the Gamma variant, Omicron exhibits both H655Y and D614G mutations together, opening up the RBD for easier binding to ACE2. [12][15] This variant also has the commonly seen mutations of N501Y and K417N, as well as a mutation at residue 484; however, instead of glutamate (E) being replaced by a lysine (K), as has

been seen before, Omicron replaces this residue with an alanine (A). This mutation, along with T478K and a couple of other Omicron mutations, strongly decreases the electrostatic potential between the RBD and monoclonal antibodies that would otherwise block the RBD from binding to ACE2. [20] As seen before in the Alpha variant, P681H facilitates the virus's resistance to IFN-β. Altogether, the Omicron variant has all of the mutations that it needs to avoid neutralization by the immune system and to transmit and reproduce quickly and efficiently. Given the large amount of variation within Omicron (B.1.1.529), it is probable that the effectiveness of the original
mRNA-1273 vaccine will decrease compared to the previous variants. It has been found that the effectiveness of the three-dose vaccine is ~47.4% with a decrease in prevention for infection in immunocompromised individuals (29.4%). [21] In the two-dose vaccine it was found to have vaccine effectiveness of 44.0%. [21][22] Given the low vaccine effectiveness percentages against the Omicron variant, Moderna began the development of an updated vaccine, mRNA-1273.214, which would target the majority variants: Omicron (B.1.1.529) and subvariant BA.1. [23][24]

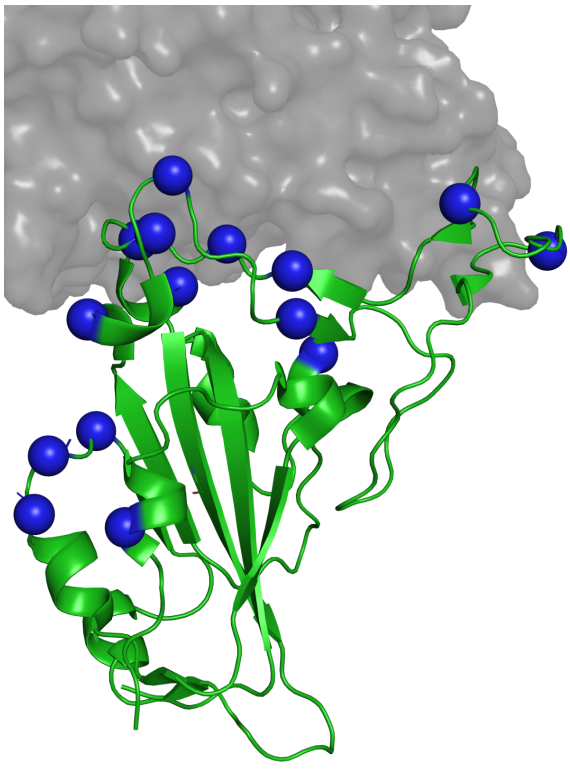

Figure 4: Mutations of the Omicron variant (in blue) as compared to the Delta variant

Through the development of mRNA-1273.214, Moderna adopted the method of using a bivalent vaccine booster that would be supplementary to the initial mRNA-1273 Spikevax vaccine but produce an immune response against specific antigens produced by the Omicron variants. The vaccine is still awaiting approval of the FDA as it is in the third phase of clinical trials, but results have been produced in regard to its effectiveness. In a clinical trial comparing the effectiveness as a second booster for the mRNA-1273.214 to the mRNA-1273 booster, it was found that the mean titers of neutralizing antibodies against BA.1 infection for the bivalent vaccine was 2372.4 and 1473.5 for the mRNA-1273 booster. [25] This signified that the bivalent, mRNA-1273.214, produced a higher antibody response against the Omicron BA.1 variant in comparison to the monovalent mRNA-1273 booster. This study also compared the two boosters to other circulating Omicron variants: BA.4 and BA.5. The mean titers of neutralizing antibodies against these two variants for the bivalent booster was 727.4 and 492.1 for the monovalent booster. [25] It can be concluded that, in relativity to antibody response against BA.1, the two different boosters produced lower mean titer values against the BA.4/5. This signifies that an additional updated booster, specifically tailored to BA.4/5, would be necessary to pose a more significant protective response against the other variant.

The subvariants BA.4 and BA.5 of the Omicron variant began to circulate globally in April of 2022. [6] These two variants often are categorized jointly because their differences are minute. As the only residue differences between them are located within the nucleocapsid protein, the two variants sport the exact same spike protein; as such, the RBD is identical between them and, although the common spike protein of these two variants has a similar sequence to that of the BA.2 variant, their
receptor-binding domains have much higher affinities for ACE2 than the RBDs of both the BA.1 and the BA.2 variants. [26] The RBD of BA.4/5 also likely allows these variants to better avoid neutralization by antibodies. This characteristic of these two variants is primarily attributed to the mutations L452R and F486V, one of which was previously documented within the Delta variant. As was noted before, the conversion of a leucine to an arginine hinders the

ability of antibodies to bind to the region by placing a charged and much larger amino acid in the way. The F486V mutation possibly aids in the virus's evasion of antibodies by taking a large amino acid, phenylalanine, and replacing it with the smaller valine. By making this mutation, the virus is taking away a large and recognizable structure from the side of the RBD, further permitting these variants to escape antibodies released by the host's immune system. Given the studies relating to the effectiveness of mRNA-1273.214 against BA.4 and BA.5 variants, the development of a more
variant-specific vaccine was initiated. Still pending FDA approval (in phase 2/3), the production of a bivalent vaccine, mRNA-1273.222, was clinically tested for its effectiveness against BA.4 and BA.5 Omicron variants, in comparison to the original monovalent mRNA-1273 vaccine. 29 days after administration, the bivalent mRNA-1273.222 had a neutralizing antibody titer value of 2325, compared to the 489 for the mRNA-1273. [27] This study signifies the large difference between the two vaccines in terms of effectiveness against the Omicron variants, contributing to the idea that the integration of bivalent vaccines poses greater protection to specific correlative variants.

A descended variant from the recombination of two BA.2 sublineage (XBB variant) was documented by the WHO in May of 2022. [6] This particular subvariant, XBB.1.5, is differentiated from its predecessor due to a F486P mutation within the RBD of the spike protein. This mutation presents concern as it is correlated to binding affinity between the binding site and the ACE2 receptor. [28] This increase in transmissibility allowed it to become a leading variant globally, encompassing 49.1% of all cases of COVID-19 in the US at the time. [28] It was found that the original monovalent vaccine,
mRNA-1273, had a neutralization IC_{50} value against XBB variants of a 1:33.3 dilution, indicating significantly reduced neutralization capacity against the new variants. [29][26] Through clinical development, Moderna created the SpikeVax
2023-2024 Formula (mRNA.815) that gained FDA approval in September of 2023. [30] This bivalent vaccine added a monovalent booster that encoded for the spike protein of Omicron variant lineage XBB1.5 providing an updated immune response against the new prominent strand. The booster was found to have vaccine effectiveness of 60.2%, in terms of protection against COVID-19 related hospitalization. [31]

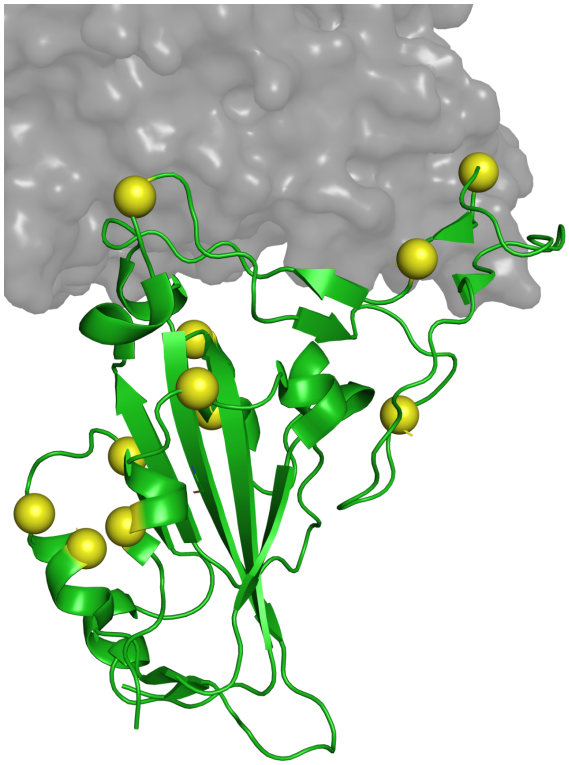

Figure 5: Additional mutations of the XBB 1.5 variant compared to the Omicron variant

Overtaking its predecessor, JN.1, the subvariant KP.2 emerged in May of 2024 as a dominant circulating variant. [6] It differs from its parent variant of Omicron due to genetic mutations within the spike protein. The R346T mutation is found to enhance the affinity of the binding between host ACE2 and viral RBD, increasing infectivity by
~1.5-fold. [32] Additionally, the F456L mutation provides the virus with an increased resistance toward serum neutralization, providing effective evasion of host immune response. [32] The V1104L mutation provides stabilization of the prefusion spike conformation. Given that the residue resides within the hydrophobic portion, this substitution enables for the strengthening of hydrophobic interactions which decreases the rate in which the protein transitions to its inactive, postfusion state upon interaction with the host cell membrane. [33] Due to increased availability to infect its host and escape developed immune

response from mRNA-1273 2023-2024 Formula (mRNA-1273.712), Moderna developed an upgraded formula to target this prominent variant, in hopes to protect the population from KP.2, along with its closely related subvariants. In a clinical trial evaluating the effectiveness of mRNA-1273.815 against JN.1 variants, it was found that the 2023-2024 formula was 23% effective, statistically contributing to the idea that the 2023-2024 formula provided low level of protection against the new variant of SARS-CoV-2. [34] Obtaining FDA approval for public administration August of 2024, the SpikeVax 2024-2025 Formula is a bivalent vaccine that consists of the original mRNA-1273 vaccine, in addition to a monovalent component that specifically corresponds to the KP.2 subvariant. [35] Upon administration, it was found that new vaccine provided an effectiveness value of 33% for adults ≥18 years, 45% for adults ≥ 65 years without immunocompromising conditions, and 40% for adults 65 with immunocompromising conditions. [36] It is possible that this low V_E value could be due to the fact that there was an increase in circulation of SARS-CoV-2 prior to vaccine approval, causing a higher development of population-immunity against JN.1 lineage variants. [36]

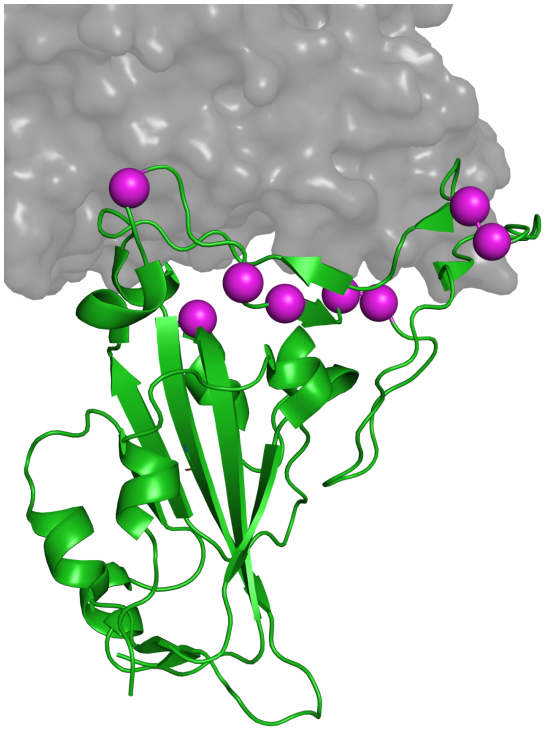

Figure 6: Mutations of the KP.2 variant compared to the XBB 1.5 Omicron variant

Conclusion

SARS-CoV-2 has been able to maintain global circulation due to the continuous evolution of its subsequent variants to develop differing biochemical properties. The introduction of mRNA vaccines developed by Moderna has served the global population with effective protection, sourced by the integration of synthetic immune response and antibodies within the host. Combating the acquired immunity, variation within the receptor-binding domain of the virus' spike protein has been found to be the driving force to viral persistence as it allowed the virus to evade obtained immune recognition and increase its infectiousness. It has been acknowledged that the following SARS-CoV-2 variants were not mentioned: Epsilon (B.1.427; B.1.429), Zeta (P.2), Eta (B.1.525), Theta (P.3), Iota (B.1.526), Kappa (B.1.617.1), Lambda (C.37), Mu (B.1.621) as these variants were only considered variants of interest (VOIs) by the WHO and pose limited impact on vaccine development due to lower relative prevalence and potential for adverse health outcomes. [6] Similarly, there are currently various variants under monitoring (VUMs) such as KP.3, JN.1.18, KP.3.1, LB.1, XEC, LP.8.1, that were not previously mentioned as they did not contribute to the development of mRNA-1273 vaccine boosters. [6] As of March of 2025, it was found that LP.8.1 (47% of U.S. cases), XEC (26% of U.S. cases), and KP.3.1.1 (5% of U.S. cases) are the three most dominant variants. [37] Based on pharmaceutical development trends, it is likely that one of these three circulating variants would be used to develop the next 2025-2026 mRNA bivalent formula.

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