Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): A Review on the Origin, Evolution and Emerging Variants

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Abstract: In 2019 the outbreak of the coronavirus disease (COVID-19) was first reported in Wuhan, China, and afterwards spread worldwide. The disease was confirmed to be a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In most cases the human coronaviruses have their origin from animal which are called their natural hosts. The natural hosts of the following Coronaviruses, HCoV-229E, SARS CoV, HCoV-NL63, and MERS-CoV is from bat, while these, HCoV-OC43 and HKU1 may have originated from rodents. The α and β – coronaviruses have their origin and major natural reservoir from Bats. However, several scientific reports validated the hypothesis that the Malayan pangolin might carry a novel Coronavirus that has unique similarity to SARS-CoV-2. SARS-CoV-2 has been observed to continuously change through mutation. Several variants of SARS-CoV-2 with diverse sets of mutations have been detected globally. Several mutations are being monitored while others have been de-escalated because they are extinct or no longer in circulation. Authorized vaccines have been developed against the COVID-19 such as Pfizer-BioNTech and Moderna and these vaccines are mRNA vaccines that penetrates the muscle cells and gives instructions to the cell machinery to produce non-toxic part of S-Protein.
Keywords: SARS-CoV-2, evolution, variants, mutation

INTRODUCTION

The build-up and spread of infectious diseases with a potential to cause a global pandemic had regularly occurred throughout life history. Human race had experienced major pandemics and epidemics (as illustrated in Figure 1) like flu, cholera, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV) (Liu, Kuo, & Shih, 2020).

An influenza pandemic is a global emergence or outbreak of a new influenza A virus that is different from the existing or recently circulating human seasonal influenza A viruses. A pandemic is declared when there is an outbreak of a new influenza A virus, that has the capacity to infect people easily and transmit from one person to another in an efficient and sustained way. Since this virus is new, few people would have developed immunity against the virus, hence the virus would make several people sick pending the time vaccines are developed to combat the virus.

During the World War 1 in 1918, a new influenza virus emerged, the Spanish Flu (H1N1) which was responsible for death of 2.68% of the world population (approximately 50 million deaths). In 1957 another new influenza A virus emerged, the Asian Flu (H2N2), with approximately 1.5 million deaths (0.05% of the world population (Liu, Kuo, & Shih, 2020) (Chan, et al., 2020). The 1968 pandemic was caused by the H3N2 Influenza A virus leading to approximately 1 million deaths (0,03% of the world population) where most of these deaths occurred in adult 65 years old and above. Another novel influenza A virus emerged in the spring of 2009, Pandemic Flu (H1N1). This new influenza had a unique combination of influenza genes and totally different from the influenza A virus previously detected (Liu, Kuo, & Shih, 2020).

In 2019 the outbreak of the coronavirus disease (COVID-19) was first reported in Wuhan, China, and afterwards spread worldwide. The disease was formally identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses based on phylogenetic analysis. According to worldometers, the present global cases of Covid-19 (at the time of compiling this report) is 397.538.919 with over 5.7 million death cases and over 3.1 million recovered cases (worldometers.info, 2022).

The symptoms of these patients infected with this virus includes fever, malaise, dry cough, and dyspnoea, and bilateral ground-glass opacities on chest CT scans (Huang, et al., 2020).

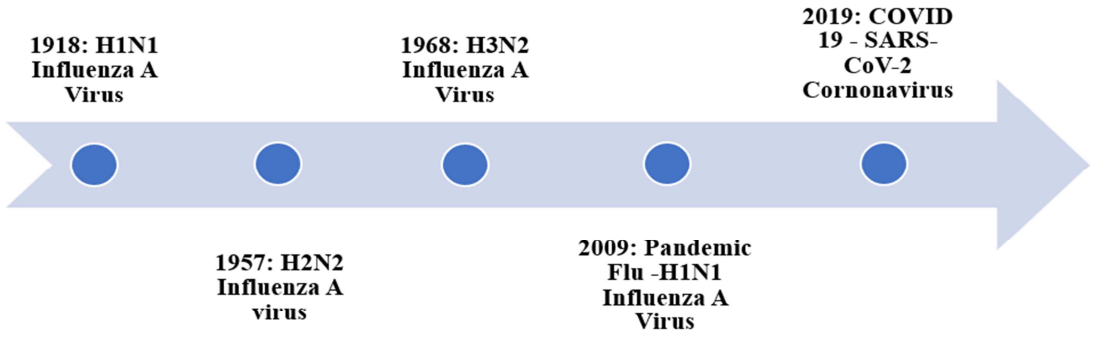

Figure 1: A timeline of five pandemics since 1918 and the globally circulating viruses afterward (Liu, Kuo, & Shih, 2020)

Epidemiology

From studies all the human coronaviruses have their origin from animal which are called their natural hosts. For example, the natural hosts of these coronaviruses HCoV-229E, SARSCoV, HCoV-NL63, and MERS-CoV is from bat. Likewise, HCoV-OC43 and HKU1 may have originated from rodents (Shuo, et al., 2016). The α and β – coronaviruses have their origin and major natural reservoir from Bats. From several studies, it has also been observed that species such as domestic animals can also transmit virus from the natural host to humans (Guan, et al., 2003). For example, strains like HcoV-229E, HcoV-OC43, SARS-CoV and MERS-CoV crossed from the natural host to human species through Camelids, Cattle, Masked palm civets and Camels respectively (Guan, et al., 2003).

At the initial stage of the COVID-19 pandemic, the genome sequence of the SARS-CoV-2 is like the existing coronaviruses in circulation in humans till date. It was observed that SARS-CoV-2 shares 79.6% sequence uniqueness with SARS-CoV and 50% uniqueness with MERS-CoV (Wrapp, et al., 2020). Many viruses affecting animals with high degree of homology to SARS-CoV-2 have been discovered and projected to be likely predecessors to SARS-CoV-2. Further studies also discovered that the genome sequence of SARS-CoV-2, is 96% identical to the Bat-CoV RaTG13 discovered in Rhinolophus affinis (Zhang, Wu, & Zhang, 2020; Zhou, et al., 2020).

Bats are the most uniquely related reservoir host for SARS-CoV-2; Nevertheless, if Bat-CoV RaTG13 was directly transmitted from bat to humans with or without an intermediate host to initiate the transmission from animal to human has been under investigation,

To bridge this knowledge gap, scientists have concluded that human species had been infected by a virus that spreads in another intermediate host species (Zhang, Wu, & Zhang, 2020). This was based on the hypothesis after observing humans for years, that RATG13 shared similar ancestor with SARS-COV-2. However, the unique pathophysiologic properties of SARS-COV-2 distinct it from RATG13 (Wrapp, et al., 2020; Friend & Stebbing, 2021). The virus, SARS-COV-2, have special genetic sequence encoded in their spike protein that improve penetration into human cells and enhance rapid transmission and infectivity (Friend & Stebbing, 2021). Hence, Scientist concluded that there was high possibility that a bat with RaTG13 had infected another specie of animal, that subsequently transmitted and infected humans with the SARS-CoV-2 (Zhang, Wu, & Zhang, 2020; Liu, Chen, & Chen, 2019).

To validate this finding, it was reported that the earliest patient infected with the Coronavirus 2019 had no exposure at the seafood market in Wuhan, China (Huang, et al., 2020). Furthermore, some groups of scientists published a report, where they detect SARS-CoV to be the most widely distributed Coronavirus in the organ samples of the lung collected from dead Malayan Pangolins at the Guandong Wildlife Rescue Center (Zhang, Wu, & Zhang, 2020; Liu, Chen, & Chen, 2019). Since Liu and her team's report was during the COVID-19 outbreak, other scientists continued by downloading the raw RNA sequencing (RNA-seq) for those two lung samples and discovered 1,882 clean reads from the lung sample that mapped to the SARS-CoV-2 reference genome (GenBank:MN908947) and covered 76.02% of the SARS-CoV-2 genome (Huang, et al., 2020). They performed Blast analysis against proteins from 2,845 Coronavirus reference genomes, including RaTG13, SARS-CoV-2s, and other known Coronavirus, and discovered that 22 contig were best matched to SARS-CoV-2s with 70.6%–100% amino acid uniqueness and 12 contigs similar to bat SARS-CoV-like Coronavirus having 92.7%–100% amino acid uniqueness. Their results validate the hypothesis that the Malayan pangolin might carry a novel Coronavirus that has unique similarity to SARS-CoV-2.

In summary, (Zhang, Wu, & Zhang, 2020) using a graphical illustration also discovered that at the whole genome level the genomic and evolutionary evidence of the occurrence of a SARS-CoV-2-like CoV found in the dead Malayan Pangolin, also called Pangolin-CoV is 91.02% similar to SARS-CoV-2 and 90.55% similar to BatCoV RaTG13. Of all the discovered SARS-CoV, apart from RaTG13, Pangolin-CoV is the most closely related CoV to SARS-CoV-2.

The S1 protein of Pangolin-CoV has greater similarities and relationship when compared with SARS-CoV-2 than when compared to RaTG13 (Zhang, Wu, & Zhang, 2020). Also, the five significant amino acid residues involved in the interaction and receptor binding with the hACE2 are completely steady between Pangolin- CoV and SARS-CoV-2, but in RaTG13 four amino acid mutations are present. Both Pangolin-CoV and RaTG13 lost the putative furin recognition sequence motif at S1/S2 cleavage site that can be observed in the SARS-CoV-2. Convincingly, (Zhang, Wu, & Zhang, 2020) in their study suggests that pangolin species are a natural reservoir of SARS-CoV-2-like CoVs.

Virology and Molecular Characterization

SARS-CoV-2 is an enveloped and spherical particle nearly 120 nm in length. It has a positive-sense single stranded RNA genome and belongs to the group *Coronavirinae*, family *Coronavirdiae*, and order *Nidovirales*. The RNA genome of SARS-CoV-2 contains a 5' methyl-guanosine cap, poly (A)-tail, and 29,903 nucleotides according to WH-Human 1 coronavirus (WHCV) (Liu, Kuo, & Shih, 2020; Wu, et al., 2020)

SARS-CoV-2 is classified as a β-coronavirus (βCoV) and the 7th coronavirus to infect humans, following two α - CoV (HCoV-229E and HKU-NL63) and four β - CoV (HCoV-OC43 and HCoVHKU1, severe acute respiratory syndrome SARSCoV and Middle East respiratory syndrome MERSCoV) (Chan, et al., 2015; Chan, To, Tse, Jin, & Yuen, 2013; Chen, Liu, & Guo, 2020; Liu, Kuo, & Shih, 2020)

Most α - CoVs and the β - CoVs have their gene traces from bats and rodents, while the δ - CoVs and γ - CoVs by evolutionary analysis have their gene traces from avian species.

The human coronavirus (HCoV) strains such as HCoV-NL63, HCoV-229E, HCoV-HKU1, and HCoV-OC43 usually cause mild, upper respiratory tract infections, such as the common cold, while the SARS-CoV, MERS-CoV, and SARS-CoV-2 can cause severe acute respiratory syndrome which can result in life-threatening disease.

Liu and his colleagues in one of their studies described the lifestyle of the SARS-Cov-2 (Liu, Kuo, & Shih, 2020). According to their study there are Nine (9) sub genomic RNAs transcribed in SARS-CoV-2 with its genome having 5′ untranslated regions. This includes an open reading frame (ORF) 1a & ab that encodes non-structural protein (NSP) used in replication, a 5′ -leader sequence, accessory proteins like ORF 3a, 6, 7a & 7b, and 8; and a 3 untranslated region as well as the four structural proteins; Envelope (E), nucleocapsid (N) spike (S) and membrane (M). The replicase polyprotein pp1a and pp1ab encodes and undergoes proteolysis by cleaving into 16 putative nsps' (nsp 1-16) as listed in **Error! Reference source not found.**.

Table 1 Functions and proteolytic cleavage sites of 16 non-structural proteins in orf1a/b (Chan, et al., 2020)

NSP	Putative function/domain
nsp1	suppress antiviral host response
nsp2	Unknown
nsp3	putative PL-pro domain
nsp4	complex with nsp3 and 6: DMV formation
nsp5	3CL-pro domain
nsp6	complex with nsp3 and 4: DMV formation
nsp7	complex with nsp8: primase
nsp8	complex with nsp7: primase
nsp9	RNA/DNA binding activity
nsp10	complex with nsp14: replication fidelity
nsp11	short peptide at the end of orf1a
nsp12	RNA-dependent RNA polymerase
nsp13	Helicase
nsp14	ExoN: 3′–5′ exonuclease
nsp15	XendoU:poly(U)-specific endoribonuclease
nsp16	2'-O-MT: 2'-O-ribose methyltransferase

The development stages of SARSCoV-2 in host cells starts from spike protein and hACE2 receptor binding. The adaptational change in the S protein after receptor binding accelerates viral envelope fusion with the cell membrane through the endosomal pathway. Afterwards the viral RNA genome is then released into the cytoplasm and transformed into viral replicase polyproteins pp1a and 1 ab. This viral replicases can be cleaved into small products by virus-encoded proteinases (Liu, Chen, & Chen, 2019). The polymerase transcribes a series of sub-genomic mRNAs by discontinuous transcription and finally the sub-genomic mRNAs are transformed into viral structural proteins. The S, E and M proteins enter the endoplasmic reticulum (ER) and Golgi apparatus, and the N protein is combined with the positive-stranded genomic RNA to form a nucleoprotein complex (Liu, Chen, & Chen, 2019; Chan, et al., 2020). The structural proteins and nucleoprotein complex are assembled with the viral envelope at the ER-Golgi intermediate compartment. The newly assembled viral particles are then released from the infected cell.

Evolution of SARS-COV-2 during the Past Few Months

Every living organism is subjected to random variation which promotes diversity and uniqueness of different species. Most viruses also keep changing genomes to adapt to their environment. Coronaviruses (CoVs) are a highly varied group of enveloped positive-sense single-stranded RNA viruses. One of the major characteristics of RNA viruses is their high mutation rate. Their mutation rate can be up to a million times higher than that of their hosts. The capacity of virus to mutate depends on numerous factors including the fidelity of viral enzymes that replicate nucleic acids, as SARS-CoV-2 RNA dependent RNA polymerase (RdRp). The rate of mutation in viruses facilitates viral evolution and genome variability which enables them to defy host immunity and to develop drug resistance (Pachetti, et al., 2020).

The synonymous substitution rate (i.e. the evolutionary substitution of one base for another in an exon of a gene coding for a protein) for coronaviruses might be approximately $1x10^{-3}$ /synonymous site/year, which is lower than some other RNA viruses (Synonymous mutations are simply mutations that alter coding sequences (CDS), but do not alter amino acid sequences while synonymous sites are the group of possible synonymous mutations present in a gene) (Denison, Graham, Donaldson, Eckerle, & Baric, 2011; Liu, Kuo, & Shih, 2020). The mutation rate during coronavirus replication could be partially controlled by the viral exoribonuclease nsp14. This connotes that Coronavirus (CoV) non-structural protein 14 (nsp14) has exoribonuclease (ExoN) activity that is accountable for proofreading and promoting the replication fidelity (Xiaoyu , Fanzhi , Yixuan , & Qiuhong , 2021).

Similar to other viruses, SARS-CoV-2 has been observed to continuously change through mutation. Several variants of SARS-CoV-2 with diverse sets of mutations have been detected globally. While some of the developing SARS-CoV-2 variants do not have a substantial impact on the spread of the virus, some mutations or their combination may give the virus benefit, such as increased rate of transmissibility or the ability to evade the host immune response. These emerging variants also known as the variants of concern, could increase the risk of SARS-CoV-2 to human health. According to the report by the European Centre for Disease Prevention and Control table 2 is list of variants that have been monitored or observed over the year. The year and months they were detected, their impact on immunity and their severity of transmission in the community were also specified.

Some variants such as Alpha (B.1.1.7, September 2020, United Kingdom), B.1.1.7+E484K (December 2020, United Kingdom), Epsilon (B.1.427/B.1.429, September 2020, USA), Eta (B.1.525, December 2020, Nigeria), Theta (P.3, January 2021, Philippines), Kappa (B.1.617.1, December 2020, India), Zeta (P.2, January 2021, Brazil), B.1.1.519 (November 2020, Mexico), C.36+L452R (December 2020, Egypt) have been de-escalated because some of them are extinct, no longer in circulation, have been circulating with no specific or major impact epidemiologically or have been proven scientifically not to pose a risk or concern (ECDC , 2022).

Table 2 Some variants detected and monitored since outbreak (ECDC , 2022)

WHO label	Lineage + additional mutations	Country first detected (community)	Year and month first detected	Influence on transmissibility	Influence on immunity	Influence on severity	Transmission in EU/EEA
Beta	B.1.351	South Africa	Sept. 2020	Increased (Tegally, 2021)	Increased (Cele S, 2021; Madhi SA, 2021)	Increased (Pearson , et al., 2021; Funk T, 2021)	Community
Gamma	P.1	Brazil	Dec. 2020	Increased (Faria NR, 2021)	Increased (Dejnirattisai W, 2021)	Increased (Funk T, 2021)	Community
Delta	B.1.617.2	India	Dec. 2020	Increased (Public Health England, 2021)	Increased (Bernal, et al., 2021; Stowe J, 2021)	Increased (Public Health England, 2021; Stowe J, 2021)	Community
Omicron	B.1.1.529	South Africa and Botswana	Nov. 2021	Unclear (UK Health Security Agency., 2021; Peacock TP, 2022)	Increased (Pulliam JRC, 2021)	Reduced (UK Health Security Agency, 2021; Wolter N, 2021; Lewnard JA, 2022)	Dominant
n/a	B.1.1.318	Unclear (b)	Jan. 2021	No evidence	Increased (Jangra, et al., 2021)	No evidence	Detected
n/a	B.1.617.2 + K417N	United Kingdom	Jun. 2021	No evidence	No evidence	No evidence	Detected
n/a	C.1.2	South Africa	Jun. 2021	Increased (Davies NG, 2021)	Increased (Jangra, et al., 2021)	No evidence	Detected

CONCLUSION

Vaccines are biological substances that activate acquired immunity to a specific infectious disease. Several research have discussed that the antibodies derived from the S protein are long-lasting and immunodominant in recovered SARS patients (Z, et al., 2010; Li, et al., 2020). In addition, most of these studies have demonstrated that the anti-S antibody can neutralize SARS-CoV and MERS-CoV and Authorized vaccines developed against the COVID-19 such as Pfizer-BioNTech and Moderna are mRNA vaccines that penetrates the muscle cells and gives instructions to the provides protective effects in animals and humans (Qiu, et al., 2005; Li, et al., 2020). Likewise, majority of the S-protein-based vaccines against SARS-CoV and MERS-CoV have proven to elicit potent immune responses and protective effects in preclinical models (Li, et al., 2020). Finally test results have also corroborate that CoVs protein provides an ideal vaccine target to produce neutralizing antibodies and protective immunity.

cell machinery to produce non-toxic part of S-Protein (Centers for Disease Control and Prevention, 2022).

REFERENCES

Bernal, J., Ndrews, N., Gower, C., Gallagher, E., Simmons, R., Thelwaal, S., . . . Ramsay, M. (2021). Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. *N Engl J Med , 385*, 585-594. doi:10.1056/NEJMoa2108891

Cele S, G. I.-H. (2021). Escape of SARS-CoV-2 501Y.V2 from neutralization by convalescent plasma. *Nature, 539*, 142-146. doi:https://doi.org/10.1038/s41586-021-03471-w

Centers for Disease Control and Prevention. (2022, January 5). *mRNA Vaccines*. Retrieved from https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/mrna.html

Chan, J. F.-W., Kok, K.-H., Zhu, Z., Chu, H., To, K. K.-W., Yuan, S., & Yuen, K.-Y. (2020). Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerging Microbes & Infections, 9*(1), 221-236. doi:https://doi.org/10.1080/22221751.2020.1719902

Chan, J., Lau, S., To, K., Cheng, V., Woo, O., & Yuen, K. (2015). Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS like disease. *Clin Microbiol, 28*, 465-522.

Chan, J., To, K., Tse, H., Jin, D., & Yuen, K. (2013). Interspecies transmission and emergence of novel viruses: lessons from bats and birds. *Trends Microbiol, 21*, 544-55.

Chen, Y., Liu, Q., & Guo, D. (2020). Emerging coronavirus: genome structure, replication and pathogenesis. *J.Med.Virol, 92*, 418-23.

Davies NG, A. S. (2021). Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. *Science, 372*.

Dejnirattisai W, Z. D. (2021). Antibody evasion by the P.1 strain of SARS-CoV-2. *Cell, 184*(11), 2939-2954. doi:https://doi.org/10.1016/j.cell.2021.03.055

Denison, M., Graham, R., Donaldson, E., Eckerle, L., & Baric, R. (2011). Coronaviruses: an RNA proofreading machine regulates replication fidelity and diversity. *RNA Biol, 8*, 270-9.

ECDC . (2022, February 10). *SARS-CoV-2 variants of concern as of February 2022*. Retrieved from European Centre for Disease Prevention and Control (ECDC): https://www.ecdc.europa.eu/en/covid-19/variants-concern

Faria NR, M. T. (2021). Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil. *Science, 372*(6544), 15-21. doi:10.1126/science.abh2644.

Friend, T., & Stebbing, J. (2021). What is the intermediate host species of SARS-CoV-2? *Future Virology, 16*(3), 154-156.

Funk T, P. A. (2021). Characteristics of SARS-CoV-2 variants of concern B.1.1.7, B.1.351 or P.1: data from seven EU/EEA countries, weeks 38/2020 to 10/2021. *Eurosurveillance., 26*(16).

Guan, Y., Zheng, B. J., He, Y. Q., Liu, X. L., Zhuang, Z. X., & Cheung, C. L. (2003). Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science, 302*, 276-8.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., . . . Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet, 395*(10223), 497-506. doi:https://doi.org/10.1016/S0140-6736(20)30183-5

Jangra, S., Ye, C., Rathnasinghe, R., Standbauer, D., Krammer, F., Simon, V., . . . Schotsaert, M. (2021). SARS-CoV-2 spike E484K mutation reduces antibody neutralisation. *Lancet Microbe, 2*(7), 283-284. doi:10.1016/S2666-5247(21)00068-9

Lewnard JA, H. V. (2022). Clinical outcomes among patients infected with Omicron (B.1.1.529) SARS-CoV-2 variant in southern California. *medRxiv*. doi:https://doi.org/10.1101/2022.01.11.22269045

Li, Y.-D., Chi, W.-Y., Su, J.-H., Ferrall, L., Hung, C.-F., & Wu, T.-C. (2020). Coronavirus vaccine development: from

SARS and MERS to COVID-19. *J Biomed Sci, 27*(104).

Liu, P., Chen, W., & Chen, J.-P. (2019). Viral Metagenomics Revealed Sendai Virus and Coronavirus Infection of Malayan Pangolins (Manis javanica). *Viruses, 11*(979).

Liu, Y.-C., Kuo, R.-L., & Shih, S.-R. (2020). COVID-19: The first documented coronavirus pandemic in history. *Biomedical Journal, 43*, 328-333.

Madhi SA, B. V. (2021). Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. *New England Journal of Medicine.* doi:10.1056/NEJMoa2102214

National Center for Biotechnology Information (NCBI). (2022, January). *Open Reading Frame Finder.* Retrieved from https://www.ncbi.nlm.nih.gov/orffinder

O'Leary, N. A. (2015). Reference sequence (RefSeq) database at NCBI: current status, taxonomic expansion, and functional annotation. *Nucleic Acids Research, 44*(D1), D733–D745. doi:https://doi.org/10.1093/nar/gkv1189

Pachetti, M., Marini, B., Benedetti, F., Giudici, F., Mauro, E., Storici, P., . . . Ippodrino, R. (2020). Emerging SARS-CoV-2 mutation hot spots include a novel RNA-dependent-RNA polymerase variant. *Journal of Translational Medicine, 18*(179).

Peacock TP, B. J. (2022). The SARS-CoV-2 variant, Omicron, shows rapid replication in human primary nasal epithelial cultures and efficiently uses the endosomal route of entry. *bioRxiv.* doi:https://doi.org/10.1101/2021.12.31.474653

Pearson , C., Russell, T. W., Davies, N., Kucharski, A. J., Edmunds, W. J., & Eggo, R. M. (2021). *Estimates of severity and transmissibility of novel SARS-CoV-2 variant 501Y.V2 in South Africa.* Retrieved from Centre for Mathematical Modelling of Infectious Diseases: https://cmmid.github.io/topics/covid19/reports/sa-novel-variant/2021_01_11_Transmissibility_and_severity_of_501Y_V2_in_SA.pdf

Public Health England. (2021). *SARS-CoV-2 variants of concern and variants under investigation in England Technical briefing 12.* Retrieved from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/988619/Variants_of_Concern_VOC_Technical_Briefing_12_England.pdf

Public Health England. (2021, February). *SARS-CoV-2 variants of concern and variants under investigation in England Technical briefing 16.* Retrieved from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1001359/Variants_of_Concern_VOC_Technical_Briefing_16.pdf

Pulliam JRC, v. S. (2021). Increased risk of SARS-CoV-2 reinfection associated with emergence of the Omicron variant in South Africa. *medRxiv.* doi:https://doi.org/10.1101/2021.11.11.21266068

Qiu, M., Shi, Y., Guo, Z., Chen, Z., He, R., Chen, R., . . . R., Y. (2005). Antibody responses to individual proteins of SARS coronavirus and their neutralization activities. *Microbes Infect, 7*(5-6), 882-9.

Shuo, S., Gary, W., Weifeng, S., Jun, l., Alexander, C. L., Jiyong, Z., . . . George, G. (2016). Epidemiology, Genetic Recombination, and Pathogenesis of Coronaviruses,. *Trends in Microbiology*, 490-502. doi:https://doi.org/10.1016/j.tim.2016.03.003.

Stowe J, A. N. (2021). *Effectiveness of COVID-19 vaccines against hospital admission with the Delta (B.1.617.2) variant 2021.* Retrieved from https://media.tghn.org/articles/Effectiveness_of_COVID-19_vaccines_against_hospital_admission_with_the_Delta_B._G6gnnqJ.pdf

Tegally, H. W. (2021). Detection of a SARS-CoV-2 variant of concern in South Africa. *Nature , 592*, 438-443. doi:https://doi.org/10.1038/s41586-021-03402-9

UK Health Security Agency. (2021, December). *SARS-CoV-2 variants of concern and variants under investigation in England Technical briefing: Update on hospitalisation and vaccine effectiveness for Omicron VOC-21NOV-01 (B.1.1.529).* Retrieved from

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1045619/Technical-Briefing-31-Dec-2021-Omicron_severity_update.pdf

UK Health Security Agency. (2021, December). *SARS-CoV-2 variants of concern and variants under investigation in England (Technical briefing 31).* Retrieved from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1042367/technical_briefing-31-10-december-2021.pdf

Wolter N, J. W. (2021). Early assessment of the clinical severity of the SARS-CoV-2 Omicron variant in South Africa. *medRxiv.* doi:https://doi.org/10.1101/2021.12.21.21268116

worldometers.info. (2022, February 7). *Covid-19 Coronavirus Pandemic*. Retrieved from https://www.worldometers.info/coronavirus/

Wrapp, D., Wang, N., Corbett, K. S., Goldsmith, J. A., Abiona, O., Graham, B. S., & Mclellan, J. S. (2020). Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science, 367*(6483), 1260-1263. doi:DOI: 10.1126/science.abb2507

Wu, A., Peng, Y., Huang, B., Ding, X., Wang, X., Niu, P., . . . Jiang, T. (2020). Genome Composition and Divergence of the Novel Coronavirus (2019-nCoV) Originating in China. *Cell Host Microbe, 27*(3), 325-328. doi:10.1016/j.chom.2020.02.001

Wu, F., Zhao, S., Yu, B., Chen, Y., Wang, W., Song, Z.-G., . . . Zhang, Y.-Z. (2020). A new coronavirus associated with human respiratory disease in China. *Nature, 579*, 265-9.

Xiaoyu , N., Fanzhi , K., Yixuan , J., & Qiuhong , W. (2021). Crucial mutation in the exoribonuclease domain of nsp14 of PEDV leads to high genetic instability during viral replication. *Cell & Bioscience , 11*(106). doi:https://doi.org/10.1186/s13578-021-00598-1

Z, .., L, L., Du, C, Z., S, J., T, L., & Y, H. (2010). Potent and persistent antibody responses against the receptor-binding domain of SARS-CoV spike protein in recovered patients. *Virol J,, 7*(299).

Zhang, T., Wu, Q., & Zhang, Z. (2020). Probable Pangolin Origin of SARS-CoV-2 associated with the COVID-19 outbreak. *Current Biology, 30*(7), 1346-1351.

Zhou, P., Yang, X.-L., Wang, X.-G., Hu, B., Zhang, L., Zhang, W., . . . Shi, Z.-L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature, 579*, 270-273. doi:https://doi.org/10.1038/s41586-020-2012-7