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COVID-19: Understanding the New Variants of Concern

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Abstract: The novel coronavirus, SARS-CoV-2, part of the *Coronaviridae* family, was discovered in December 2019 in China. World Health Organization named it COVID-19 and by March 2020, it had spread worldwide, causing a global pandemic. Despite continuous efforts to prevent the spread of the virus, the virus seemed always to be a step ahead of humankind as it rapidly evolved to produce new variants. These variants have higher transmissibility than the original virus and were responsible for new waves of infections. The first variant was Alpha, followed by the discovery of Beta, Gamma, Delta, and Omicron, being the latest variant of concern. Although vaccines were distributed worldwide to reduce the severity of the disease when infected with SARS-CoV-2, the emergence of new variants raised doubts about the efficacy of the available vaccines. Studies showed a decrease in neutralizing antibodies during infection with XBB and BQ subvariants compared to infections caused by other variants. Fortunately, early evidence shows that the mRNA vaccines are still effective against the current circulating Omicron sublineages of the coronavirus. Nevertheless, continuous genomic surveillance of the coronavirus is still important to detect any new variants of concern to assess their potential to threaten public health. The efficacy of vaccines and treatment options available against the latest circulating variant of SARS-CoV-2 should also be periodically evaluated. This ensures that the treatment and vaccines used are safe and effective against the virus to protect the public from another health crisis.

Keywords: COVID-19; coronavirus; SARS-CoV-2; XBB; BQ.1

1. Introduction

In December 2019, a cluster of pneumonia cases in China prompted the investigation into the causative agent of the outbreak [1]. These patients presented with fever, fatigue, dry cough, and shortness of breath and thus were given the initial diagnosis of viral pneumonia. However, further studies conducted via whole genome sequencing revealed the identity of the causative agent to be a novel coronavirus [2]. This novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread rampantly across the globe. The virus is spread via respiratory droplets and can stay in the air for up to three hours [3, 4]. Studies also showed that this novel virus was associated with the manifestation of mental health issues such as anxiety, depression, and post-traumatic stress disorder during and post-infection [5, 6]. The highly contagious nature of SARS-CoV-2 led to the declaration of the COVID-19 pandemic by the World Health Organization (WHO) in March 2020. The virus spread globally [7-16], garnering over 633 million confirmed cases and claiming more than 6.5 million lives worldwide as of November 2022 [17].

As the pandemic began to unfold, world leaders quickly implemented various strategies to control the spread of the virus, such as travel bans, social distancing protocols, lockdowns for areas with outbreaks, contact tracing, and mandatory masking [18, 19]. Mass testing for the coronavirus was also done to detect the virus during the early stages of disease development to prevent outbreaks. Nevertheless, the world was waiting on SARS-CoV-2 vaccines to be developed to more efficiently control the disease and reduce mortality rates due to the coronavirus. In December 2020, the world rejoiced when Pfizer introduced the first COVID-19 vaccine, Comirnaty, and the vaccine was promptly deployed to various nations worldwide [20]. Following Pfizer, the COVID-19 vaccines from Moderna, AstraZeneca, Johnson & Johnson, Sinopharm, Sinovac, Bharat Biotech, Novavax, and Nuvaxovid have also been approved for Emergency Use Listing (EUL) by WHO for use as of 12 January 2022 (Table 1) [21]. These vaccines have also been deployed as to meet the demands for vaccines worldwide. With the administration of COVID-19 vaccines, infection rates, the severity of disease, and mortality rates of the coronavirus have reduced. The vaccines proved to be effective in controlling the virus, and people worldwide were hopeful that the pandemic would end.

Although there is currently no cure for COVID-19, other treatment options have been explored to treat the viral infection. In general, COVID-19-positive patients are given symptomatic treatment such as ibuprofen or acetaminophen for patients with fever. In patients with difficulty breathing or low oxygen saturation, oxygen therapy will be given to prevent hypoxia. In severe cases, the patient may be on a ventilator to ensure adequate oxygen supply. In addition, the US Food and Drug Administration (FDA) has approved remdesivir, an antiviral drug, to treat COVID-19 [22-24]. Remdesivir effectively prevented the replication of the viral genome of SARS-CoV-2 [21]. The FDA also approved monoclonal antibodies (mAb) for the treatment and prophylaxis of COVID-19. Among the approved mAbs are anti-SARS-CoV-2-mAbs, bamlanivimab, casirivimab and imdevimab [25]. The administration of monoclonal antibodies stimulates the immune system of the host to recognize and respond

more effectively to the coronavirus, reducing the reproductivity of the virus and minimizing the harm caused by the virus.

Table 1. Vaccines approved for emergency use listing (EUL) by WHO.

Manufacturer	Vaccine
Pfizer/BioNTech	Comirnaty (BNT162b2)
AstraZeneca/Oxford	Covishield (ChAdOx1nCoV-19)
Johnson & Johnson/Janssen	Jcovden (Ad26.COV2.S)
Moderna	Spikevax (mRNA-1273)
Sinopharm	VeroCell
Sinovac	CoronaVac
Bharat Biotech	Covaxin (BBV152)
Novavax	Covovax, Nuxavoid (NVX-CoV2373)

However, SARS-CoV-2 began mutating rapidly, producing new variants of the coronavirus [26, 27]. The emergence of variants has led to sudden outbreaks in places that previously had COVID-19 cases under control [28]. Some of the variants have also been reported to have immune escape properties [29], which could potentially decrease the effectiveness of the COVID-19 vaccines. They are also likely to cause reinfections in those previously infected, raising major concern of new waves of infections and increased disease severity. The emergence of variants of concern (VOC) has also led to the administration of COVID-19 booster vaccines aimed at improving and prolonging protective immunity against the disease [30]. WHO has reported the VOCs are Alpha, Beta, Gamma, Delta, and Omicron variants [31]. This data has been consistently updated to track the latest variant causing the most disease worldwide. By staying updated on the latest variant of the coronavirus, which caused the sudden increase in COVID-19 infections, necessary precautions and management strategies can be implemented to control the outbreaks and reduce the negative effects of the disease on public health.

2. Variants of SARS-CoV-2

SARS-CoV-2 belongs to a coronaviruses (CoVs) group in the *Coronaviridae* family, and the virus is classified as a β-CoV which mainly infects mammals [32]. Coronaviruses are pleomorphic enveloped viruses with a single-stranded RNA genome [33]. Further analysis of the novel coronavirus showed that about 82% of the sequence identified SARS-CoV-2 with

the well-known SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). SARS-CoV-2 also shared over 90% sequence identity with SARS-CoV and MERS-CoV for essential enzymes and structural proteins [32, 34]. Spike proteins on the surface of the SARS-CoV-2 virus enable the virus to enter the host cell by interacting with the host cell receptor angiotensin-converting enzyme 2 (ACE2). Upon entry into the host cell, the viral RNA is released and triggers the replication of viral RNA to synthesize structural and non-structural proteins for further propagation of the virus in the host [35]. In 2020, before any vaccines were successfully developed to manage COVID-19 outbreaks, SARS-CoV-2 had already mutated and produced a VOC, the Alpha variant (B.1.1.7), in the United Kingdom in September. The Alpha variant is the product of 23 mutations from the original strain and has been found to have higher transmissibility than its predecessors. Although the Alpha variant has not been found to cause more severe illness than the other SARS-CoV-2 strains, the higher transmission rate enabled the virus to spread from the United Kingdom to 52 other countries within four months of its discovery [36, 37].

Subsequently, in October 2020, the Beta variant, B.1.351, a new variant, was detected in Nelson Mandela Bay, South Africa [38]. The Beta variant contained a mutation in the receptor-binding domain of the spike protein (N501Y), which increases transmission and two additional mutations (K417N and E484K), which increased antibody resistance [39]. The increased transmissibility proved detrimental as the Beta variant displaced other variants in South Africa [38]. The rapid increase in COVID-19 cases Bangladesh was mainly attributed to this variant [40]. Furthermore, this strain was neutralized less effectively by antibodies produced after vaccination or natural infection with other strains [41, 42]. Two months after the Beta variant was detected, another VOC was reported in Brazil, the Gamma (P.1) variant, which contributed to a second wave of infection in Manaus. The virus had once again evolved and 17 amino acid changes were made, including 10 in the spike protein [26]. Following the report in Manaus, it was reported in Salvador, Northeast Brazil, that an increased proportion of younger adults without comorbidities had the severe disease during the second COVID-19 wave due to the Gamma variant [43]. This strain continues to spread to more than 36 countries worldwide [26].

Meanwhile, in India, the Delta (B.1.617.2) variant was identified in Maharashtra in December 2020. This VOC rapidly spread throughout India, displacing the pre-existing lineages, including the Alpha variant [44, 45]. This lineage of the coronavirus had L452R spike receptor-binding motif (RBM) substitution which increased infectivity and reduced its susceptibility to neutralizing antibodies [46]. In addition, the delta variant was more efficient at replication than the alpha variant in the human airway epithelial systems. The spike protein on B.1.617.2 mediates highly efficient syncytium formation, which lowered the virus's sensitivity towards inhibition by neutralizing antibodies as compared to the original SARS-CoV-2 [44]. Moreover, researchers in Bahrain compared the recovery patterns infected with the alpha variant to those infected with the Delta variant. The results showed that patients with the Delta variant recovered slower than those with the Alpha variant. Their hospital

stays were more extended with higher shedding of the virus regardless of their vaccination status [47].

When VOCs of the novel coronavirus began to emerge and were still rapidly evolving in 2020, the distribution of vaccines against COVID-19 had just started, raising concerns about the efficacy of the vaccines as they were developed based on the original SARS-CoV-2. One study in France found that two doses of mRNA vaccines (Pfizer or Moderna) were still effective against the original SARS-CoV-2 and its Alpha, Beta, and Gamma variants [48]. However, a report in India showed that Covishield, the viral vector vaccine by AstraZeneca, was less effective against the Delta variant than the other variants. Breakthrough infections were reported when patients who received the Covishield vaccine tested positive for COVID-19 caused by the Delta variant [44]. Nevertheless, vaccines were continuously rolled out to reach the high demands of nations worldwide to control the spread of the virus. The goal was to achieve herd immunity as soon as possible to protect populations at high risk of contracting the virus.

3. Latest Variant of Concern: Omicron XBB, BQ.1

The continuous evolution of the COVID-19 virus led to the highly mutated Omicron (B.1.1.529) variant that is widely known today [28, 49]. With each evolution, the COVID-19 virus carries more mutations than its previous variant, which is evident in the omicron variant [50]. Researchers from Italy published the first 3D Omicron image indicating that the variant has several mutations, mainly on the spike protein [51]. First isolated in South Africa in November 2021, the Omicron variant quickly spread to other continents, becoming the dominant variant globally by February 2022 [52] (Figure 1). The widespread virus once again triggered global concern, and travel bans were implemented [51]. Despite efforts to prevent the virus from spreading, the Omicron variant managed to increase the daily cases in the United States to over a million by December 2021. Omicron, being very efficient spreaders of COVID-19, began mutating to produce subvariants. Although a plethora of subvariants have been produced, not all of them are VOC. WHO introduced "Omicron subvariants under monitoring" in its variant tracking system to highlight, prioritize and monitor the VOC, potentially impacting public health.

In October 2022, the latest omicron subvariants under monitoring are XBB and BQ.1. XBB is a recombinant of omicron BA2.10.1 and BA.2.75, which were previously identified and characterized in 2021 [28]. First isolated in Singapore, XBB has a global prevalence of 1.3% as of the first week of October 2022 and has been reported in 35 countries, such as Japan, India, Malaysia, and Australia [53-55]. This subvariant raises concern as there is early evidence from Singapore and India demonstrating that the virus has a higher reinfection risk. Reinfections occurred in individuals previously infected with pre-omicron variants of SARS-CoV-2. It has also begun to cause new waves of infections leading to spikes in the daily number of confirmed cases in many countries. As for the BQ.1 subvariant, they carry significant spike mutations in key antigenic sites and have been detected in 65 countries. BQ.1 has shown a significant growth advantage and a higher reinfection risk than other

Omicron subvariants. The mutations producing BQ.1 could have produced an immune escape advantage, thus allowing it to displace other circulating lineages, and increasing the risk of reinfections [56]. At the time of writing, there is no data on Omicron XBB and BQ.1 subvariants that show increased severity of disease by these subvariants, however, authorities remain vigilant in monitoring and assessing future available data to determine whether these subvariants pose a threat to the public.

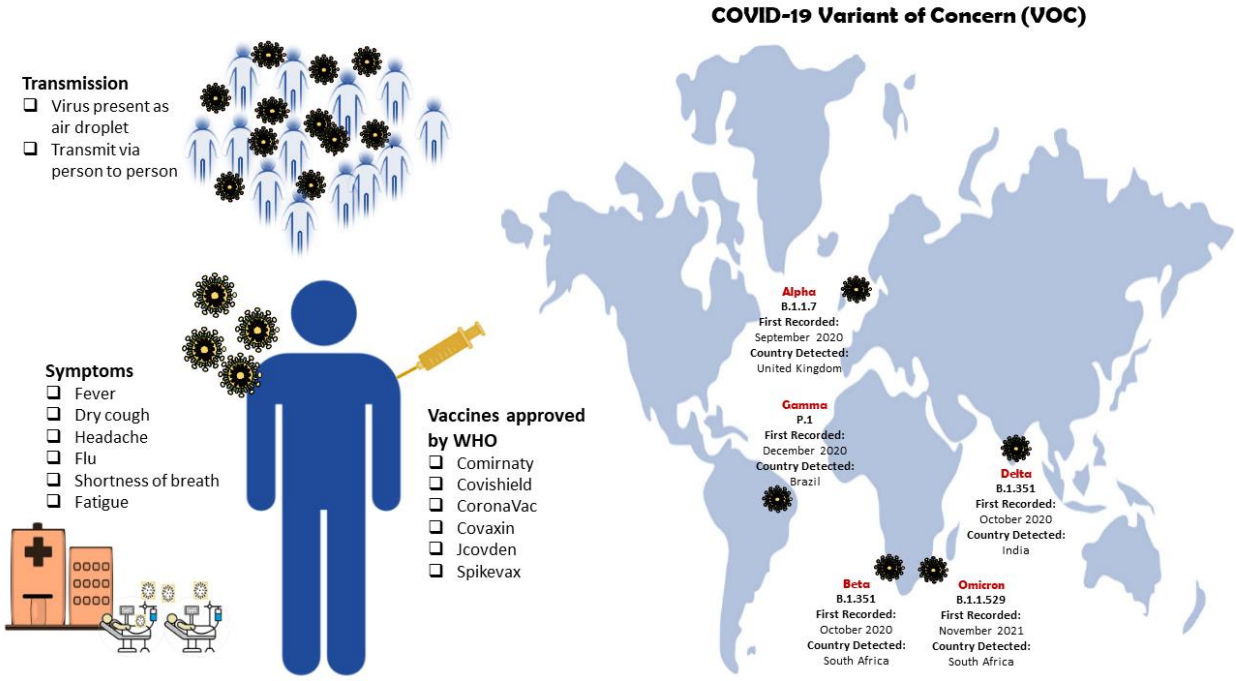

Figure 1. Illustration of COVID-19 variant of concern (VOC) transmission, symptoms and vaccines.

The rapid emergence of Omicron subvariants raises further concern concerning the efficacy of the current treatment options and vaccines available to fight against the virus. One study found that the effectiveness of antivirals was not diminished in treating Omicron subvariants. Still, the efficacy of mAbs has been greatly reduced due to the immune escape of the subvariants [57]. Therefore, an alternative immunotherapy for COVID-19-positive patients is COVID-19 convalescent plasma (CCP). CCP is a polyclonal preparation consisting of antibodies with many specificities and represents all isotypes, making it more challenging to defeat a single variant [57]. It has been reported that if administered as early as within nine days of the onset of symptoms, CCP can reduce the risk of disease progression leading to hospitalization in unvaccinated individuals [58]. However, albeit effective, CCP can potentially cause severe adverse reactions in the recipient [59]. For instance, bronchospasms, transfusion-related acute lung injury, and circulatory overload have been reported in patients with comorbidities such as cardiorespiratory disorders and renal impairment. The administration of donor plasma to the recipient may elicit severe allergic reactions such as serum sickness and anaphylaxis, which have been associated with bronchospasms [60].

A study found that the Omicron BA.5 bivalent vaccine by Pfizer or Moderna booster dose had better neutralization against the newly emerged Omicron sublineages than the parental mRNA vaccines. Moreover, the study also found that individuals previously infected with SARS-CoV-2 developed a higher and broader neutralization against the Omicron sublineages after receiving the BA.5 bivalent booster vaccine. However, they reported the subvariants BQ.1.1 and XBB.1 demonstrated the greatest evasion against vaccine-elicited neutralization [61]. A separate study found that in vaccinated individuals infected with BQ.1.1, there was a drop by a factor of seven in neutralizing antibody titers, indicating that the subvariant can escape from neutralization more effectively than its predecessors [62]. Any future development of Omicron-based vaccines will be challenging as the virus rapidly evolves and produces diverse subvariants circulating and co-existing in our environment.

4. Conclusion

COVID-19 is the first ever documented coronavirus pandemic in history which has caused over 6.5 million deaths worldwide in under three years since its discovery. The populations at a higher risk of getting infected are the elderly, individuals with pre-existing medical conditions, and the immunocompromised [63]. In addition, many recovered individuals have also reported post-COVID conditions, which can last for weeks or even months after infection [64, 65]. Symptoms of long COVID include fatigue, cough, chest tightness, breathlessness, palpitations, myalgia, difficulty focusing, and brain fog [66, 67]. Healthcare systems across the globe were taking a toll due to sudden outbreaks or surges in COVID-19-positive cases. Declines and disruptions in health services not related to COVID-19 were also reported. The sudden increase in COVID-19 cases caused by the emerging variants places a considerable burden on the healthcare systems, significantly reducing their capacity to treat other diseases or ailments [68]. Without a doubt, COVID-19 has dramatically disrupted the normality of our lives. Thus, consistent monitoring and tracking of the latest variant of SARS-CoV-2, which is causing detrimental changes in COVID-19 epidemiology in terms of increased transmissibility, increased virulence, worsening disease progression, and reducing the effectiveness of vaccines, is crucial in the fight against COVID-19. Continuous genomic surveillance of the virus is essential to identify new variants that could threaten public safety and take the necessary measures to prevent another public health crisis.

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References

1. Zhou P, Yang X-L, Wang X-G, *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579(7798): 270-273.
2. Liu Y-C, Kuo R-L, and Shih S-R COVID-19: The first documented coronavirus pandemic in history. Biomedical Journal 2020; 43(4): 328-333.

3. van Doremalen N, Bushmaker T, Morris DH, *et al.* Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. New England Journal of Medicine 2020; 382(16): 1564-1567.
4. Hoo HE, Loh HC, Ch'ng ASH, *et al.* Positive impacts of the COVID-19 pandemic and public health measures on healthcare. Progress In Microbes & Molecular Biology 2021; 4(1).
5. Thye AY-K, Tan LT-H, Law JW-F, *et al.* Long COVID-19: Psychological symptoms in COVID-19 and probiotics as an adjunct therapy. Progress In Microbes & Molecular Biology 2022; 5(1).
6. Javed B, Sarwer A, Soto EB, *et al.* The coronavirus (COVID-19) pandemic's impact on mental health. The International Journal of Health Planning and Management 2020; 35(5): 993-996.
7. Tan LT-H, Letchumanan V, Ser H-L, *et al.* PMMB COVID-19 Bulletin: United Kingdom (22nd April 2020). Progress In Microbes & Molecular Biology 2020; 3(1).
8. Ser H-L, Letchumanan V, Law JW-F, *et al.* PMMB COVID-19 Bulletin: Spain (18th April 2020). Progress In Microbes & Molecular Biology 2020; 3(1).
9. Kuai Y-H and Ser H-L COVID-19 Situation in Thailand. Progress In Microbes & Molecular Biology 2021; 4(1).
10. Joseph RJ and Ser H-L Stories from the East: COVID-19 Situation in India. Progress In Microbes & Molecular Biology 2021; 4(1).
11. Loo K-Y and Letchumanan V COVID-19: Malaysia's fight against this deadly virus. Progress In Microbes & Molecular Biology 2021; 4(1).
12. Loo K-Y, Thye AY-K, Law LN-S, *et al.* COVID-19: An Updated Situation from Singapore. Progress In Microbes & Molecular Biology 2021; 4(1).
13. Loo K-Y, Letchumanan V, Tan LT-H, *et al.* Updated COVID-19 Condition in Australia. Progress In Microbes & Molecular Biology 2021; 4(1).
14. Loo KY, Law JW-F, Tan LTH, *et al.* South Africa's Battle Against COVID-19 Pandemic. Progress In Microbes & Molecular Biology 2022; 5(1).
15. Loh HC, Seah YK, and Looi I The COVID-19 pandemic and diet change. Progress In Microbes & Molecular Biology 2021; 4(1).
16. Kwan JN, Loh HC, and Looi I COVID-19 Vaccination during Pregnancy in Southeast Asia. Progress In Microbes & Molecular Biology 2021; 4(1).
17. World Health Organisation (WHO). Coronavirus disease (COVID-19) pandemic. 2022; Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
18. Johnson D, Ren SEC, Johnson HD, *et al.* COVID-19: Are Malaysians embracing or suffering the new normality? Progress In Microbes & Molecular Biology 2020; 3(1).
19. Güner HR, Hasanoğlu İ, and Aktaş F COVID-19: Prevention and control measures in community. Turkish Journal of medical sciences 2020; 50(9): 571-577.
20. Food and Drug Administration (FDA), *FDA Approves First COVID-19 Vaccine*. 2021.
21. Loo KY, Letchumanan V, Ser HL, *et al.* COVID-19: Insights into Potential Vaccines. Microorganisms 2021; 9(3).
22. Spinner CD, Gottlieb RL, Criner GJ, *et al.* Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. Jama 2020; 324(11): 1048-1057.
23. Letchumanan V, Ab Mutalib N-S, Goh B-H, *et al.* Novel coronavirus 2019-nCoV: Could this virus become a possible global pandemic. Progress In Microbes & Molecular Biology 2020; 3(1).
24. Tsang HF, Chan LWC, Cho WCS, *et al.* An update on COVID-19 pandemic: the epidemiology, pathogenesis, prevention and treatment strategies. Expert Review of Anti-infective Therapy 2021; 19(7): 877-888.

25. National Institutes of Health (NIH). Anti-SARS-CoV-2 Monoclonal Antibodies. 2022; Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/.
26. Faria NR, Mellan TA, Whittaker C, *et al.* Genomics and epidemiology of the P. 1 SARS-CoV-2 lineage in Manaus, Brazil. Science 2021; 372(6544): 815-821.
27. Ser H-L, Tan LT-H, Law JW-F, *et al.* Genomic analysis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strains isolated in Malaysia. Progress in Microbes & Molecular Biology 2020; 3(1).
28. World Health Organisation (WHO). Tracking SARS-CoV-2 variants. 2022; Available from: https://www.who.int/activities/tracking-SARS-CoV-2-variants.
29. Scarpa F, Sanna D, Benvenuto D, *et al.* Genetic and structural data on the SARS-CoV-2 Omicron BQ.1 variant reveal its low potential for epidemiological expansion. bioRxiv 2022: 2022.11.11.516052.
30. Thye AY-K, Tan LT-H, Law JWF, *et al.* COVID-19 Booster Vaccines Administration in Different Countries. Progress In Microbes & Molecular Biology 2021; 4(1).
31. Thye AY-K and Law JW-F A Variant of Concern (VOC) Omicron: Characteristics, Transmissibility, and Impact on Vaccine Effectiveness. Progress In Microbes & Molecular Biology 2022; 5(1).
32. Naqvi AAT, Fatima K, Mohammad T, *et al.* Insights into SARS-CoV-2 genome, structure, evolution, pathogenesis and therapies: Structural genomics approach. Biochim Biophys Acta Mol Basis Dis 2020; 1866(10): 165878.
33. Bennet BM, Wolf J, Laureano R, *et al.* Review of Current Vaccine Development Strategies to Prevent Coronavirus Disease 2019 (COVID-19). Toxicologic Pathology 2020; 48(7): 800-809.
34. Thye AY-K, Pusparajah P, Tan LT-H, *et al.* COVID-19: Gastrointestinal Manifestations and Complications. Progress In Microbes & Molecular Biology 2021; 4(1).
35. Huang Y, Yang C, Xu XF, *et al.* Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacol Sin 2020; 41(9): 1141-1149.
36. Lee R B.1.1. 7: what we know about the novel SARS-CoV-2 variant. The American Society for Microbiology 2021.
37. Galloway SE, Paul P, MacCannell DR, *et al.* Emergence of SARS-CoV-2 B.1.1.7 Lineage - United States, December 29, 2020-January 12, 2021. MMWR Morb Mortal Wkly Rep 2021; 70(3): 95-99.
38. Feder KA, Pearlowitz M, Goode A, *et al.* Linked clusters of SARS-CoV-2 variant B. 1.351—Maryland, January–February 2021. Morbidity and Mortality Weekly Report 2021; 70(17): 627.
39. Wang Z, Schmidt F, Weisblum Y, *et al.* mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. Nature 2021; 592(7855): 616-622.
40. Saha S, Tanmoy AM, Hooda Y, *et al.* COVID-19 rise in Bangladesh correlates with increasing detection of B.1.351 variant. BMJ Global Health 2021; 6(5): e006012.
41. Wang P, Nair MS, Liu L, *et al.* Antibody Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7. bioRxiv 2021.
42. Zhou D, Dejnirattisai W, Supasa P, *et al.* Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine-induced sera. Cell 2021; 184(9): 2348-2361.e6.
43. Nonaka CKV, Gräf T, Barcia CAL, *et al.* SARS-CoV-2 variant of concern P.1 (Gamma) infection in young and middle-aged patients admitted to the intensive care units of a single hospital in Salvador, Northeast Brazil, February 2021. Int J Infect Dis 2021; 111: 47-54.
44. Mlcochova P, Kemp SA, Dhar MS, *et al.* SARS-CoV-2 B.1.617.2 Delta variant replication and immune evasion. Nature 2021; 599(7883): 114-119.

45. Thye AY-K, Loo K-Y, Tan KBC, *et al.* Insights into COVID-19 Delta variant (B. 1.617. 2). Progress In Microbes & Molecular Biology 2021; 4(1).
46. Motozono C, Toyoda M, Zahradnik J, *et al.* An emerging SARS-CoV-2 mutant evading cellular immunity and increasing viral infectivity. bioRxiv 2021: 2021.04.02.438288.
47. Kumar N, Quadri S, AlAwadhi AI, *et al.* COVID-19 Recovery Patterns Across Alpha (B.1.1.7) and Delta (B.1.617.2) Variants of SARS-CoV-2. Frontiers in Immunology 2022; 13.
48. Charmet T, Schaeffer L, Grant R, *et al.* Impact of original, B.1.1.7, and B.1.351/P.1 SARS-CoV-2 lineages on vaccine effectiveness of two doses of COVID-19 mRNA vaccines: Results from a nationwide case-control study in France. The Lancet Regional Health - Europe 2021; 8: 100171.
49. Araf Y, Akter F, Tang Y-d, *et al.* Omicron variant of SARS-CoV-2: Genomics, transmissibility, and responses to current COVID-19 vaccines. Journal of Medical Virology 2022; 94(5): 1825-1832.
50. Tian D, Sun Y, Xu H, *et al.* The emergence and epidemic characteristics of the highly mutated SARS-CoV-2 Omicron variant. Journal of Medical Virology 2022; 94(6): 2376-2383.
51. Siddiqui S, Alhamdi HWS, and Alghamdi HA Recent Chronology of COVID-19 Pandemic. Frontiers in Public Health 2022; 10.
52. Law LN-S, Loo K-Y, Goh JXH, *et al.* Omicron: The rising fear for another wave in Malaysia. Progress In Microbes & Molecular Biology 2021; 4(1).
53. Stevens K, *Fast spreading Covid strain hits Australia as cases and hospitalisations rise again - but should we be worried?*, in *Daily Mail Australia*. 2022.
54. Otake T, *XBB variant, spreading fast in Singapore, detected in Tokyo*, in *The Japan Times*. 2022.
55. *Malaysia experiencing small Covid-19 wave due to XBB subvariant, says Health Ministry*, in *TheStar*. 2022.
56. World Health Organisation (WHO). TAG-VE statement on Omicron sublineages BQ.1 and XBB. 2022; Available from: https://www.who.int/news/item/27-10-2022-tag-ve-statement-on-omicron-sublineages-bq.1-and-xbb.
57. Focosi D, McConnell S, and Casadevall A The Omicron variant of concern: Diversification and convergent evolution in spike protein, and escape from anti-Spike monoclonal antibodies. Drug Resistance Updates 2022; 65: 100882.
58. Sullivan DJ, Gebo KA, Shoham S, *et al.* Early Outpatient Treatment for Covid-19 with Convalescent Plasma. New England Journal of Medicine 2022; 386(18): 1700-1711.
59. Choi JY Convalescent Plasma Therapy for Coronavirus Disease 2019. Infect Chemother 2020; 52(3): 307-316.
60. Nagoba B, Gavkare A, Jamadar N, *et al.* Positive aspects, negative aspects and limitations of plasma therapy with special reference to COVID-19. J Infect Public Health 2020; 13(12): 1818-1822.
61. Kurhade C, Zou J, Xia H, *et al.* Low neutralization of SARS-CoV-2 Omicron BA.2.75.2, BQ.1.1, and XBB.1 by 4 doses of parental mRNA vaccine or a BA.5-bivalent booster. bioRxiv 2022: 2022.10.31.514580.
62. Miller J, Hachmann NP, Collier A-rY, *et al.* Substantial Neutralization Escape by the SARS-CoV-2 Omicron Variant BQ.1.1. bioRxiv 2022: 2022.11.01.514722.
63. Goh HP, Mahari WI, Ahad NI, *et al.* Risk factors affecting COVID-19 case fatality rate: A quantitative analysis of top 50 affected countries. MedRxiv 2020.
64. Raveendran AV, Jayadevan R, and Sashidharan S Long COVID: An overview. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 2021; 15(3): 869-875.
65. Rayanakorn A, Leong SL, Chaiprom P, *et al.* Cost-effectiveness of Public Health Strategies on COVID-19 Control: A Systematic Review. Progress In Microbes & Molecular Biology 2022; 5(1).

66. Aiyegbusi OL, Hughes SE, Turner G, *et al.* Symptoms, complications and management of long COVID: a review. Journal of the Royal Society of Medicine 2021; 114(9): 428-442.

67. Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, *et al.* Defining post-COVID symptoms (post-acute COVID, long COVID, persistent post-COVID): an integrative classification. International journal of environmental research and public health 2021; 18(5): 2621.

68. Arsenault C, Gage A, Kim MK, *et al.* COVID-19 and resilience of healthcare systems in ten countries. Nature Medicine 2022; 28(6): 1314-1324.