INFLUENCE OF VARIANTS MUTATIONS ON THE PROGRESSION AND OUTCOME OF COVID-19 IN PAKISTAN

M Fahim Ullah Khan[1], Osama Alam[2], Autif Hussain Mangi[3], Mir Sadiq Shah[1], Saira Abbas[1], Surayia Shahab Rani[4], Jalander Shah[1], Yafes Ali Shah[1], Shanab Ali Shah[5], Muhammad Yasir Shah[1], Naveed Ullah Khan[1], Majid Ayaz[1], Muhammad Afnan Khattak[1], Nasir Khan[1] , Abdul Samad[6], Naveed Khan[7], Asad Ullah Khan[1]

[1]Department of Zoology University of Science and Technology Bannu, Khyber Pakhtunkhwa, Pakistan, [2]Department of Biotechnology, University of Science & Technology Bannu, Khyber Pakhtunkhwa, Pakistan, [3]Institute of Biochemistry, University of Sindh, Jamshoro, Pakistan, [4]Department of Pharmacy, University of Sargodha, Sargodha, Punjab, Pakistan, [5]Bashir Institute of Health Sciences, Shaheed Zulfiqar Ali Bhutto Medical University Islamabad, Pakistan, [6]Department of Biotechnology and Genetic Engineering, Kohat University of Science and Technology, Khyber Pakhtunkhwa, Pakistan, [7]Department of Zoology, Government Post Graduate College Bannu, Khyber Pakhtunkhwa, Pakistan

Correspondence:
Dr. Fahim Ullah Khan
Department of Zoology
University of Science and Technology Bannu, Khyber Pakhtunkhwa, Pakistan
Email: fahim-jani85@gmail.com

DOI: 10.38106/LMRJ.2024.6.1-08
Received: 24.08.2023
Accepted: 21.02.2024
Published: 31.03.2024

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing the coronavirus disease 2019 pandemic (COVID-19) has put millions of people at risk in an increasing number of countries, suggesting a serious threat to global public health. The first identification in late 2019, the strain has undergone several changes that have resulted in several genetically different variations that are cause for concern. By comprising the Delta, Gamma, Beta, and Alpha variations, each of which has shown evidence of increased virulence, transmissibility, or capacity for immune evasion as compared to ancestral strains. Their advancement over ancestral strains in transmission was discovered by genomic surveillance, highlighting the vital necessity for monitoring the evolution of SARS-CoV-2. Remdesivir and other treatments showed promising results in reducing the duration of the disease; however, the development of antivirals to prevent the emergence of new variations is still an important goal. The vaccine also provides hope, although its effectiveness against new genotypes needs to be evaluated. Pakistan is also facing the implications of COVID-19. The months-long closing of colleges and universities affected education as well. As SARS-CoV-2 continues to evolve, creating efficient antiviral therapies and guaranteeing vaccination accessibility continue to be critical concerns.

Key Words: SARS-CoV-2; variant; COVID-19; Pakistan

INTRODUCTION

After the SARS-CoV-2 (formerly known as 2019-nCoV) infection was initially discovered in Wuhan, China, in December 2019, it quickly spread throughout the world, resulting in approximately 14 million active cases and 582,000 fatalities as of July 2020 (1). The principal mode of transmission of the virus between humans are through contact and respiratory droplets (2). A variety of birds and bats have been associated with coronaviruses, which are thought to be their natural hosts. Analysis of coronaviruses using molecular observation studies indicates that these viruses have a common ancestral history since 10,000 years ago (3). The genetic labyrinth of bats and other terrestrial animals is related to overflow and interaction of evolution, where the genetic mutation has no boundaries. Acute respiratory distress syndrome (ARDS), immunological dysfunction, and multi-organ failure are among the varied clinical manifestations of COVID-19. SARS-CoV, MERS-CoV, and SARS-CoV-2 are examples of human coronaviruses that have developed defence mechanisms to block or inhibit the production of interferon, which can occasionally cause host inflammatory reactions resulting in ARDS (4). Suffering from SARS-CoV-2, carriers play a significant role in the transmission of COVID-19, although at least 41% of household infections of SARS-CoV-2 were caused by pre-symptomatic

and asymptomatic transmission (5). High transmissibility, international travel, and population density all enhanced the pandemic's global spread. Serious public health concerns have been raised in several countries where inadequate medical systems and socioeconomic disparities have contributed to an increase in the number of cases and mortality ratio (6). Globally, governments have adopted flexible strategies. By closing schools and businesses, physically separating people, and using face masks, non-pharmaceutical measures aim to reduce contact. Furthermore, isolation and quarantine prevent further transmission, testing and screening programs were the additional measures (7). However, difficulties persist because of the public's resistance and the emergence of novel variations. Our methods need to change along with the variants. These days, genomic surveillance monitors the effects of evolving lineages such as Alpha, Beta, and Gamma. Although vaccination campaigns have given hope, but the concerns about immunity variations and protection duration must be addressed (8). Science and public health collaborate to reclaim the initiative by remaining adaptive and promoting international cooperation against ever-changing virus variety (9).

Some variations, in particular, have raised concerns since they may impact several aspects of the pandemic, including as transmissibility, the severity of the disease, and the effectiveness of therapies and vaccinations. This pattern has major implications for both preventing the outbreak and maintaining the integrity of public health procedures (10). Some of the notable variants are the Omicron variant (B.1.1.529) with an extensive spike protein mutation pattern that caused nervousness around the world, the Beta variant (B.1.351) with mutations affecting immunity, the Gamma variant (P.1) with transmissibility and immune escape concerns, the Delta variant (B.1.617.2) with significantly increased transmissibility, and the Alpha variant (B.1.1.7) with elevated transmissibility (11). A graphical presentation of all corona virus variants is presented in Figure 1.

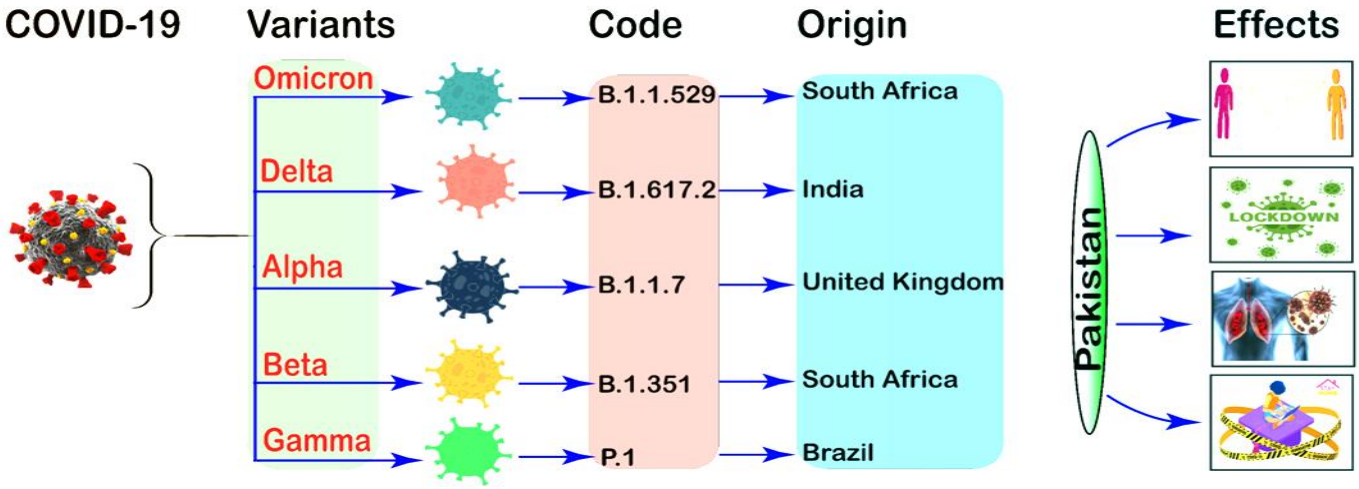

Figure 1: Graphical abstract showing the types of coronavirus which give rise to multiple genetically distinct variants such as Alpha, Beta, Gamma, and Delta variants.

Pakistan had entered into a complex public health and economic crisis following the emergence of the COVID-19 pandemic (12). By late 2021, the number of cases approached 1.2 million, placing an impact on the nation's healthcare infrastructure. Additionally, there was a severe lack of PPE, critical equipment, and ICU capacity in hospitals. Lockdowns and limits were implemented widely in an attempt to stop the virus's spread, but they had an adverse effect (13). The economy was affected by the closure of non-essential businesses, a decline in trade, and restrictions on mobility. Millions of people lost their jobs in the formal and unofficial sectors, further destroying the poor communities. The GDP of Pakistan dropped as a result of declining exports, manufacturing, and rising unemployment. For the benefit of communities that were af-

fected, the government put in place extensive social protection measures. Emergency money was made available to homes in need through the large-scale Ehsaas Emergency Cash project. Additionally, vaccination campaigns were boosted; by autumn 2021, over 75 million doses had been administered (14). Despite challenges, Pakistan demonstrated resilience and innovation in its multi-sectoral response. Future health strategies will depend on strengthening collaboration between the public and private health sectors and developing a defence strategy against novel variations. Pakistan is committed to resolving this persistent issue (15).

VARIANTS OF COVID-19

The term "variant of COVID-19" describes a particular strain or lineage of the SARS-CoV-2 virus that causes the COVID-19 illness. Variants are produced when a virus's genetic material (RNA) mutates which changes the virus's characteristics (16). Variations in transmission, sickness severity, immunological response, and even therapy or vaccination efficacy can all be indicators of these alterations. Viruses, including SARS-CoV-2, constantly undergo mutations as part of their natural evolution. The behaviour of the virus is mostly unaffected by most changes. However, certain mutations might give rise to new variations when they compound and improve like enhanced transmissibility or immunity evasion. Potential impacts of these variants on public health, such as the possibility of increased disease severity, easier spread, escape of immunity from prior infections or vaccinations, or decreased efficacy of diagnostic procedures, therapeutic interventions, and vaccines, need to be closely monitored and investigated (17). To monitor and classify these variations, virus samples from affected patients are genetically sequenced. To track the appearance and spread of new variations, several nations and organizations keep databases and systems up to date. This information is used to direct research and public health initiatives (18). A summary of Corona virus variants is given in Table 1.

IMPACT OF VARIANTS AND MUTATION ON TRANSMISSION DYNAMICS

Businesses, factories, and exports were forced to close as a result of nationwide lockdowns and social distancing measures. Throughout the mysterious path of SARS-CoV-2 evolution, some strains showed stability, raising concerns about increased transmissibility. Delta version (B.1.617.2) displayed more severe health and life-related complications. Millions of people were pushed into poverty as a result of the decline in formal and informal job opportunities. The Pakistani government tried a number of measures to prevent the virus's spread and minimize its socioeconomic consequences such as the Ehsaas Emergency Cash Program and giving priority to COVID-19 vaccinations, which resulted in the administration of more than 75 million doses by October 2021(19-24). The Omicron variant (B.1.1.529) made its first appearance in South Africa and displayed innovative resistance to specific antibodies (25). Here, the immune system takes on the role of a mystery as the powerful opponent of variable adaptability confronts the former protectors' immunity to diseases and immunizations. Some of the variations reveal a new aspect of the altered domain of disease severity (26). The Omicron variant has additional spike protein mutations, the majority of which occur in the receptor binding site. These mutations boost the variant's transmissibility while reducing the response to antibodies and vaccinations (27).

MODE OF TRANSMISSION

SARS-CoV-2 utilized an integrative approach to propagate from the beginning. Its principal weapon makes use of respiratory droplets released during breathing, coughing, and sneezing. The virus also showed alarming airborne capabilities. Its capacity to travel in small airborne suspensions and remain contagious in still indoor air for hours has been demonstrated by studies. Another channel for transmission is close touch. It was determined that surface contact was insufficient for the extensive diffusion (34). However, living together with an infected person increases danger, particularly in poorly ventilated interior spaces. Aerosols bearing SARS-CoV-2 are also produced during medical procedures that cause coughing or introduce high-flow oxygen (35). The WHO noted that these conditions might allow for airborne distribution. By clarifying

its flexible approaches, we gain benefits. Recommendations ranging from masks to ventilation to distance-keeping interrupt different approaches. Our comprehension of mechanisms changes as new varieties appear. Approaches to a multifaceted enemy must be similar. Transmission obstruction on all fronts can be achieved with a well-coordinated, multifaceted worldwide campaign. We might get closer to controlling this pandemic if we strategically outmanoeuvre SARS-CoV-2 (36). Mode of transmission of corona virus is presented in Figure 2.

Table 1. Different types of SARS-CoV-2 with description and disease

CORONAVIRUS TYPE	DESCRIPTION	DISEASE	REFERENCES
SARS-COV-2	Novel coronavirus that causes COVID-19	COVID-19	(28, 29)
SARS-COV	Severe acute respiratory syndrome coronavirus	SARS	(29)
MERS-COV	Middle East respiratory syndrome coronavirus	MERS	(30)
HCOV-229E	Human coronavirus 229E	Common cold	(31)
HCOV-OC43	Human coronavirus OC43	Common cold	(31)
HCOV-NL63	Human coronavirus NL63	Common cold	(31, 32)
HCOV-HKU1	Human coronavirus HKU1	Common cold	(33)

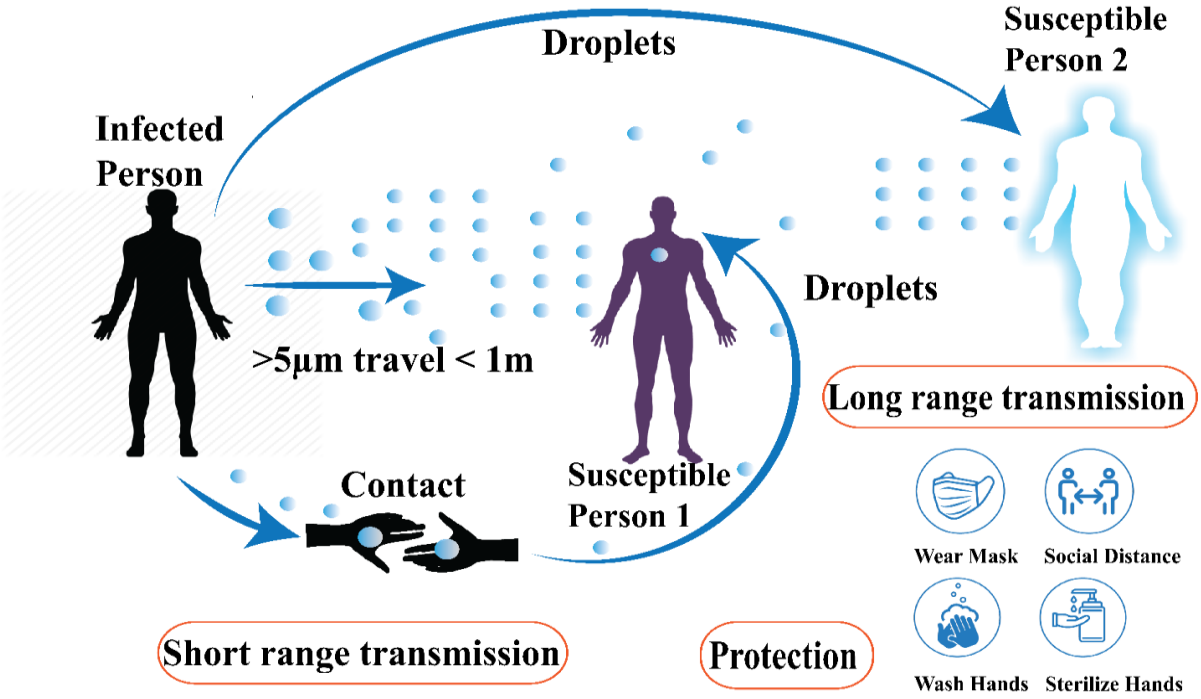

Figure 2. Short-range and long-range transmission of Coronavirus among the people. It is mostly spread from physical contact and droplets. There are some safety measures that can help to protect from Corona such as wearing a mask, social distancing, and washing hands with sterilizer.

FACTORS INFLUENCING COVID-19 PROGRESSION

There are increased risks for critical COVID-19 in certain patient groups. Poorer respiratory outcomes and mortality are frequently correlated with advanced age (37). The outlook gets worse for pre-existing medical conditions including diabetes and cardiovascular disease. These traits increase the likelihood of experiencing severe symptoms (38). The progress of the disease is influenced by the immune response itself. An excessive cytokine response can cause multi-organ damage and severe pulmonary inflammation. Initial viral load size may influence severity since greater burdens are associated with more severe disease. Because of their phenotypic changes, variants of concern present further risks (39). Although antivirals attempt to stop replication, their efficacy varies according to the target virus. Activity varies by coronavirus strain, however, it is helpful for some. The coronavirus family includes not only the ordinary cold but also the potentially fatal SARS, MERS, and COVID-19 viruses (40). Results are influenced by a variety of fundamental parameters, including virus characteristics, immunological function, and patient health. It is nevertheless essential to understand these complex connections to optimize preventative and therapeutic approaches (41).

ANTIVIRAL MEDICATIONS AND THEIR EFFECTIVENESS

The purpose of antiviral drugs is to stop viruses from replicating and spreading throughout the body. They may work differently against different virus strains or species, but they may work against some viruses more effectively than others (42). The common cold and more serious respiratory conditions like Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), and COVID-19 belong to the coronavirus family of viruses (43). A summary of Corona Viral medicines is given in Table 2.

Table 2. Various types of antiviral medicines with mechanism of action, dosage and approval

Antiviral medication	Mechanism of action	Clinical trials	Efficiency	Side effects	Dosage	Administration	Availability	FDA approval
Remdesivir	Nucleotide analogue	Yes	Moderate	Nausea,vomiting, elevated liver enzymes	IV infusion	Hospital setting	EUA in the United States	Yes
Favipiravir	RNA polymerase inhibitor	Yes	Moderate	Nausea, diarrhea, elevated uric acid levels	Oral tablets	Outpatient treatment	Japan, Russia, and India	Yes
Molnupiravir	RNA polymerase inhibitor	Yes	Promising	Nausea, headache, abnormal liver function tests	Oral capsules	Outpatient treatment	EUA pending in the United States	No
Ivermectin	Antiparasitic drug with antiviral properties	Mixed results	Inconclusive	Nausea, dizziness, diarrhea	Oral tablets	Outpatient treatment	Off-label use, available in some countries	No
Baricitinib	Janus kinase (JAK) inhibitor	Yes	Promising	Increased risk of infections, blood clots	Oral tablets	Hospital or outpatient treatment	EUA in combination with	Yes

							United States	
Tocilizumab	IL-6 receptor antagonist	Yes	Promising	Increased risk of infections, liver enzyme elevations	Intravenous infusion	Hospital setting	EUAin several countries	Yes
Sotrovimab	Monoclonal antibody against spike protein	Yes	Promising	Hypersensitivity reactions, infusion-related reactions	Intravenous infusion	Hospital or outpatient treatment	EUAin the United States	Yes
Casirivimab/imdevimab	Monoclonal antibodies against spike protein	Yes	Promising	Hypersensitivity reactions, infusion-related reactions	Intravenous infusion	Hospital or outpatient treatment	EUAin several countries	Yes
Camostat mesylate	Serine protease inhibitor	In progress	N/A	N/A	Oral tablets	Outpatient treatment	Investigational use	No
Lopinavir/ritonavir	Protease inhibitors	Mixed results	Inconclusive	Gastrointestinal side effects, liver toxicity	Oral tablets	Hospital or outpatient treatment	Not recommended by some guidelines	No

EFFECT OF SARS-COV-2 PANDEMIC IN PAKISTAN

Pakistan has demonstrated extraordinary adaptability and resilience in the face of the worldwide pandemic. The country's response has been outstanding in terms of public health, the economy, and society (44). The healthcare system persisted and effectively treated an increase in COVID-19 patients. Healthcare workers coordinated efforts for testing, tracing, and treatment, demonstrating a consistent commitment to patient care. Strategic lockdowns and proactive health initiatives were implemented by the competent government of Pakistan. The community's support for cleanliness standards expressed a shared commitment to safety; while social distancing measures, business closures, and gathering restrictions created a protective barrier. The duration of this period demonstrates Pakistan's ability to overcome difficulties and grow even stronger. This chapter discusses cooperation, creative thinking, and the human spirit's unwavering determination to weather adversity and serve as an inspiration to others (45).

The pandemic has caused a significant negative economic impact on several industries. Lockdowns and limitations caused business interruptions, especially for small and medium-sized businesses, which in turn led to job losses and financial distress for families (46). As a quick reaction, the government launched economic stimulus plans and relief measures, helping impacted companies and individuals. Pakistan demonstrated its commitment to public health by stepping up testing and immunization efforts at the same time (47). The dissemination and accessibility of immunizations have significantly reduced the impact of the virus. Vaccination initiatives aim to protect more vulnerable populations and drastically reduce the severity of COVID-19 outbreaks globally.

CONCLUSION

The COVID-19 pandemic, which originated from the SARS-CoV-2 virus, has presented complex issues on a global scale. Since its discovery in 2019, this virus has undergone mutations and given rise to a variety of forms, including Alpha, Beta, Gamma, and Delta. In comparison to the original strain, these variations are more virulent, transmissible, and immunologically resistant. It is important to monitor the evolution of SARS-CoV-2 as genomic surveillance highlights their advantage. Although therapies such as remdesivir show potential, it is still critical to resist novel variations. Vaccines are promising, but more research is needed to determine how well they work against newly emerging strains. Pakistan, having 200 million people, had difficulty dealing with the effects of COVID-19. Patient care, tracing, and testing were challenges for the healthcare system. Lockdown situations led to unemployment and economic hardship. Schools suffered from the closure of their facilities. Antiviral development and increasing vaccine accessibility continue to be priorities. Getting back stability and preparing for new waves are the goals of Pakistan's coordinated scientific and public health initiatives. Future health outcomes will be shaped by an international collaborative effort.

FUTURE PERSPECTIVE

Novel strains of SARS-CoV-2 will probably persist in emerging. Understanding these variations' effects on transmissibility, severity, and vaccine efficacy would require careful observation and research. Controlling upcoming outbreaks brought on by novel variations would need the implementation of public health strategies like focused therapies, fast testing, and genomic surveillance. It might spread throughout the population at lower densities, or become endemic. This could lead to recurring epidemics that resemble the seasonal flu. To reduce the effect of future outbreaks, public health initiatives will emphasize adaptive measures like vaccination campaigns, targeted testing, contact tracing, and the promotion of hygienic behaviors. Pakistan has also been badly hit, with an overburdened healthcare system and an incoherent economy. Although, there are causes for optimism. As effective vaccines and antiviral medications are being developed, the pandemic may be contained. Pakistan is also working to enhance its healthcare infrastructure and enhance its capacity to prepare for potential pandemics. The most likely possibility is that COVID-19 will spread throughout Pakistan and become endemic, which would mean that fewer people will get sick or die from the virus than it does currently. Still, there is a chance that a fresh pandemic wave could emerge, so it's critical to be alert, get vaccinated, and receive booster shots.

Conflict of interest:
Authors declare no conflict of interest
Funding source:
The study did not receive any external funding

REFERENCES

1. Alagona, P., et al., Reflections: environmental history in the era of COVID-19. Environmental History, 2020.
2. Marini, M.G. and J. McFarland, Health humanities for quality of care in times of COVID-19. 2022: Springer.

3. Gram, M.A., et al., Vaccine effectiveness against SARS-CoV-2 infection or COVID-19 hospitalization with the Alpha, Delta, or Omicron SARS-CoV-2 variant: A nationwide Danish cohort study. PLoS medicine, 2022. 19(9): p. e1003992.
4. Mukherjee, S., et al., mRNA-lncRNA Co-expression network analysis reveals the role of lncRNAs in immune dysfunction during severe SARS-CoV-2 infection. Viruses, 2021. 13(3): p. 402.
5. Zhang, H., et al., A multi-family cluster of COVID-19 associated with asymptomatic and pre-symptomatic transmission in Jixi City, Heilongjiang, China, 2020. Emerging Microbes & Infections, 2020. 9(1): p. 2509-2514.
6. Desson, Z., et al., An analysis of the policy responses to the COVID-19 pandemic in France, Belgium, and Canada. Health Policy and Technology, 2020. 9(4): p. 430-446.
7. Li, C.-y., et al., Public Health Policy Monitoring through Public Perceptions: A Case of COVID-19 Tweet Analysis. Information, 2022. 13(11): p. 543.
8. Xiang, T., J. Wang, and X. Zheng, The humoral and cellular immune evasion of SARS-CoV-2 Omicron and sub-lineages. Virologica Sinica, 2022.
9. Lapavitsas, C. and E.W. Collective, The State of Capitalism: Economy, Society, and Hegemony. 2023: Verso Books.
10. Rusli, N., et al., Geospatial mapping of suicide-related tweets and sentiments among Malaysians during the COVID-19 pandemic. Big data and cognitive computing, 2023. 7(2): p. 63.
11. Patil, R., et al., Variable neutralizing antibody responses to 10 SARS-CoV-2 variants in natural infection with wild-type (B. 1) virus, Kappa (B. 1.617. 1), and Delta (B. 1.617. 2) variants and COVISHIELD vaccine immunization in India: utility of the MSD platform. Frontiers in Immunology, 2023. 14: p. 1181991.
12. Abbass, K., et al., Evaluating the social outcomes of COVID-19 pandemic: empirical evidence from Pakistan. Environmental science and pollution research, 2023. 30(22): p. 61466-61478.
13. Eibschutz, L.S., et al., Racial, Ethnic, and Other Disparities in the Epidemiology and Care of COVID-19. Coronavirus Disease 2019 (COVID-19) A Clinical Guide, 2023: p. 586-614.
14. Mugano, G. and N. Dorasamy, SMEs and Economic Development in Africa. 2023: Taylor & Francis.
15. Organization, W.H., Stories from the field: sharing successful strategies from the Eastern Mediterranean Region in mitigating noncommunicable diseases and mental health disorders during the COVID-19 pandemic and beyond. 2023.
16. Saksena, N.K., et al., SARS-CoV-2 variants, its recombinants and epigenomic exploitation of host defenses. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 2023: p. 166836.
17. Shrestha, L.B., et al., Evolution of the SARS-CoV-2 omicron variants BA. 1 to BA. 5: implications for immune escape and transmission. Reviews in Medical Virology, 2022. 32(5): p. e2381.
18. Brito, A.F., et al., Global disparities in SARS-CoV-2 genomic surveillance. Nature communications, 2022. 13(1): p. 7003.
19. Volz, E., et al., Assessing transmissibility of SARS-CoV-2 lineage B. 1.1. 7 in England. Nature, 2021. 593(7858): p. 266-269.
20. Tegally, H., et al., Detection of a SARS-CoV-2 variant of concern in South Africa. Nature, 2021. 592(7854): p. 438-443.
21. Nonaka, C.K.V., 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. International Journal of Infectious Diseases, 2021. 111: p. 47-54.
22. Wang, P., et al., Increased resistance of SARS-CoV-2 variant P. 1 to antibody neutralization. Cell host & microbe, 2021. 29(5): p. 747-751. e4.
23. Al-Tawfiq, J.A., et al., The emergence of the omicron (B. 1.1. 529) SARS-CoV-2 variant: what is the impact on the continued pandemic? Journal of Epidemiology and Global Health, 2022. 12(2): p. 143-146.

24. Myers Jr, M.T., Covid-ology: A Field Guide. 2022: CRC Press.
25. Sharma, V., et al., Emerging evidence on Omicron (B. 1.1. 529) SARS-CoV-2 variant. Journal of Medical Virology, 2022. 94(5): p. 1876-1885.
26. Cloete, J., et al., Paediatric hospitalisations due to COVID-19 during the first SARS-CoV-2 omicron (B. 1.1. 529) variant wave in South Africa: a multicentre observational study. The Lancet Child & Adolescent Health, 2022. 6(5): p. 294-302.
27. Reji, M. and R. Kumar, Emergence of SARS-CoV-2 variant of concern omicron: biological features and genomic concern.
28. Atzrodt, C.L., et al., A Guide to COVID-19: a global pandemic caused by the novel coronavirus SARS-CoV-2. The FEBS journal, 2020. 287(17): p. 3633-3650.
29. Hasöksüz, M., S. Kilic, and F. Saraç, Coronaviruses and sars-cov-2. Turkish journal of medical sciences, 2020. 50(9): p. 549-556.
30. De Groot, R.J., et al., Commentary: Middle east respiratory syndrome coronavirus (mers-cov): announcement of the coronavirus study group. Journal of virology, 2013. 87(14): p. 7790-7792.
31. Liu, D.X., J.Q. Liang, and T.S. Fung, Human coronavirus-229E,-OC43,-NL63, and-HKU1 (Coronaviridae). Encyclopedia of virology, 2021: p. 428.
32. Killerby, M.E., et al., Human coronavirus circulation in the United States 2014–2017. Journal of Clinical Virology, 2018. 101: p. 52-56.
33. Pyrc, K., B. Berkhout, and L. van der Hoek, The novel human coronaviruses NL63 and HKU1. Journal of virology, 2007. 81(7): p. 3051-3057.
34. Dezordi, F.Z., et al., ViralFlow: A versatile automated workflow for SARS-CoV-2 genome assembly, lineage assignment, mutations and intrahost variant detection. Viruses, 2022. 14(2): p. 217.
35. Bestilleiro, R.S., et al., Nosocomial infection outbreak due to SARS-COV-2 in a hospital unit of particularly vulnerable patients. International Journal of Medical Sciences, 2021. 18(10): p. 2146.
36. Clayton, E., et al., The molecular virology of coronaviruses with special reference to SARS-CoV-2. Coronavirus Therapeutics–Volume I: Basic Science and Therapy Development, 2022: p. 15-31.
37. Patton, M.J., et al., COVID-19 bacteremic co-infection is a major risk factor for mortality, ICU admission, and mechanical ventilation. Critical Care, 2023. 27(1): p. 1-12.
38. Mansueto, G., M. Niola, and C. Napoli, Can COVID 2019 induce a specific cardiovascular damage or it exacerbates pre-existing cardiovascular diseases? Pathology-Research and Practice, 2020. 216(9): p. 153086.
39. Polyzogopoulou, E., et al., Acute liver injury in COVID-19 patients hospitalized in the intensive care unit: Narrative review. World Journal of Gastroenterology, 2022. 28(47): p. 6662.
40. Sadique, M.A., et al., High-performance antiviral nano-systems as a shield to inhibit viral infections: SARS-CoV-2 as a model case study. Journal of Materials Chemistry B, 2021. 9(23): p. 4620-4642.
41. Nitesh, J., R. Kashyap, and S.R. Surani, What we learned in the past year in managing our COVID-19 patients in intensive care units? World Journal of Critical Care Medicine, 2021. 10(4): p. 81.
42. Wang, M., et al., Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell research, 2020. 30(3): p. 269-271.
43. Lombardi, A.F., et al., Severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), influenza, and COVID-19, beyond the lungs: a review article. La radiologia medica, 2021. 126: p. 561-569.
44. Arslan, A., et al., Adaptive learning in cross-sector collaboration during global emergency: conceptual insights in the context of COVID-19 pandemic. Multinational Business Review, 2021. 29(1): p. 21-42.
45. Brodie, R.J., et al., Coronavirus crisis and health care: learning from a service ecosystem perspective. Journal of Service Theory and Practice, 2021. 31(2): p. 225-246.

46. Khan, M.A., et al., Economic and financial impact of the COVID-19 pandemic in South Asia. Environmental Science and Pollution Research, 2022: p. 1-10.
47. Levich, J., The Gates Foundation, Ebola, and global health imperialism. American Journal of Economics and Sociology, 2015. 74(4): p. 704-742.