ECRONICON OPEN ACCESS

EC MICROBIOLOGY
Mini Review

Projections for COVID-19 in Present Context: Journey of the Pandemic to Endemicity

Vinod Nikhra*

Senior Chief Medical Officer and Consultant, Department of Medicine, Hindu Rao Hospital and NDMC Medical College, New Delhi, India

***Corresponding Author:** Vinod Nikhra, Senior Chief Medical Officer and Consultant, Department of Medicine, Hindu Rao Hospital and NDMC Medical College, New Delhi, India.

Received: February 14, 2022; **Published:** March 16, 2022

Abstract

Impact of Pandemic on Realms of Human Life: It is hard to imagine a worse pandemic than COVID-19 which has affected not only health but every realm of human life, being the most disruptive pandemic in modern times. In fact, the pandemic seems like a singular, once-in-a-lifetime event, and ongoing with no definite end in sight. As such, greater protective measures are needed to fight off the highly contagious variants and develop more effective therapeutic modalities to improve the disease outcomes.

Research, Rationality and Mass Hysteria: Fundamentally, the microbes outnumber all the members of animal and plant kingdom including bacteria. The public-health measures are age-old and general rather than specific and aimed initially at stemming the tide of the novel virus and have been applied including avoiding close and non-ventilated spaces. COVID-19 is not the deadliest pandemic, HIV has killed more people than SARS-CoV-2, yet the pandemic is accompanied by a mass hysteria.

The Mutagenesis and Emerging Variants: SARS-CoV-2 has a steady rate of mutations and accumulates mutations over time. The evolving variants affect the transmissibility, disease severity, immune response, and resultant immunity. The emerging variants have either replaced the previous ones or de-escalated depending on their properties. A number of variants are associated with immune escape. The variants pose a challenge for preventive measures including the vaccination and therapeutics.

Omicron: Priming for Immunity or Disaster: The omicron variant (B.1.1.529) was first reported from African continent and later spread to various geographical regions. It has been held a benign variant with an increased transmissibility, reduced disease severity, and ability to generate a potent immunity. As a matter of caution, the fast-spreading Omicron sand its subvariant, BA.2 with their unexplored impact on immune system may be priming the population groups for infection with deadlier variants.

Conclusion: Dealing with the Challenges: For COVID-19, the immunity following infection or vaccination is variable and short-lived, as it declines over time. Presently, with evolving variants including Omicron and BA.2 and recurrent outbreaks, the challenge posed by the pandemic is not over. In fact, the end of the pandemic is not a discrete event like conclusion of a war but a gradual process in which with herd immunity and the virus becoming less morbid and lethal, the disease deescalates to endemic form.

Keywords: *COVID-19 Pandemic; SARS-CoV-2 Variants; Omicron; BA.2; Priming Phenomenon; Emerging Variants; Deescalating Variants*

The pandemic and realms of human life

COVID-19 as a disease and SARS-CoV-2 as its causative organism, continue to remain an enigma [1]. While we continue to explore the agent factors, disease transmission dynamics, pathogenesis, clinical spectrum of the disease and therapeutic modalities, the grievous

nature of the disease is persisting and evolving further in various regions around the world. Simultaneously, it is apparent that the virus SARS-CoV-2, is here to stay for the foreseeable future [2]. The future of the disease, of course, appears to depend on various known and unknown factors including the effects of seasonality on the disease transmission and spread, the evolving viral mutations and variants, certain genetic factors, level and duration of effective immune response to the disease, the availability of COVID-19 vaccines, and the life-style choices made by individuals and measures enforced by the governments.

It is hard to imagine a worse pandemic than COVID-19 which has affected not only health but every realm of human life, being the most disruptive pandemic in modern times. In fact, the pandemic seems like a singular, once-in-a-lifetime event. Further, the pandemic is ongoing with no definite end in sight, and there are serious challenges posed by SARS-CoV-2 virus and COVID-19 as the disease to humanity.

Research, rationality and mass hysteria

Fundamentally, the viruses outnumber all the members of animal and plant kingdom, including bacteria. The public-health measures against an epidemic are age-old and general rather than specific. Many are based on the human experience with the Spanish Flu pandemic of 1918. Initially, at the start of the COVID-19 pandemic they aimed at stemming the tide of the novel virus and have been applied in certain modified forms like avoiding close and non-ventilated spaces. It needs to be stressed that the COVID-19 is not the deadliest pandemic, the HIV infection carries the dubious distinction of having killed more people than died during the COVID-19 pandemic.

As now established, COVID-19 is not just result of the infection due to the SARS-CoV-2 virus. The immune response to the virus largely determines the disease course [3]. The patients with severe forms of the disease have an increased likelihood of IgG1 antibodies with fucosylated Fc glycans leading to enhanced interaction and binding with the immune-activating Fcγ receptors (FcγRs) on immune effector cells [4]. The latter results in increased production of cytokines like interleukin-6 and TNF by monocytes and its attendant clinical manifestations [5]. Added to this, some of the variants are associated with a higher viral load, and potentially with increased transmissibility, and propensity to cause more severe disease or worse outcomes.

There is a chance that vaccines currently being administered may not provide sufficient immunity against new emerging variants. Also, the therapeutic choices in case of moderate to severe disease are limited and unsatisfactory. Thus, COVID-19 has had a major impact on human health globally; infecting a large number of people, causing severe disease resulting in morbidity and excess mortality, especially among older and vulnerable populations, having a negative impact on physical and mental health and associated long-term health sequelae. It has interrupted routine healthcare services and led to disruptions to travel, trade, education, and other socio-economic activities. This is further complicated by the mass hysteria generated, accentuated, and propelled largely by the electronic media.

The mutagenesis and emerging variants

The understanding of the nucleotide variations in the SARS-CoV-2 genome provides a useful insight for the evolution of the disease and the propagation of the pandemic [6]. Whereas most mutations and variations have no impact on the viral ability to transmit or disease severity, some mutations have a significant impact on transmissibility, infectivity, or lethality. Thus, the mutations and variants may have far-reaching consequences for future trends.

Some of these mutations have possibly arisen as a result of the virus evolving under immune selection pressure in infected individuals, especially in patients with mild rather than those with severe disease. The variants arise as a result of natural selection to facilitate the spread of viral infection. As such, the SARS-CoV-2 virus has a low mutation rate by virtue of the nsp14 protein acting as a 3′-5′ exoribonuclease on both the single-stranded and double-stranded RNA during the viral replication cycle [7]. Further, SARS-CoV-2 can resort to RNA viral evolution through recombination (synthesis of chimeric RNA molecules from two different progeny genomes) and reassortment (the packaging within a single virion of genomic segments from different progeny viruses.

The SARS-CoV-2 has a steady rate of mutations, and the mutations may accumulate over time. The evolving variants affect the transmissibility, disease severity, resultant immunity, which in turn, have either replaced the previous ones or de-escalated depending on these properties. The variants have been categorized using WHO label, lineage and presence of the spike and other mutations, and their properties concerning, transmissibility, immune response, and infection or disease severity.

The variants pose a challenge for preventive measures including the vaccination, as a number of variants are associated with immune escape, and therapeutics, as the response of the variants to therapeutic agents may differ. The SARS-CoV-2 variants, in general, maybe grouped as Variants of concern (VOCs), Variants of Interest (VOIs), Variants under monitoring (VUMs) and De-escalated variants. Though, it is possible for a VOC, VOI, or VUM to also be a part of a broader VOC, VOI, or VUM definition, and belong to more than one group. Presently, the newly emerged variants, Omicron and its subvariant, BA.2, are of heightened importance.

Currently as updated, the Variants of Concern (VOC) include Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and the new-comer, Omicron (B.1.1.529). Whereas the Alpha, Beta, Gamma, and Delta variants are associated with increased transmissibility and disease severity, the Omicron has increased transmissibility and reduced disease severity [8].

The Variants of Interest (VOI) comprise of Mu (B.1.621), Lambda (C.37), and unlabelled (AY.4.2). Whereas Variants under monitoring (VUM) include linages and mutations, such as, B.1.1.318, B.1.617.2 + K417N, C.1.2, B.1.617.2 + E484X (d), B.1.617.2 + Q613H, B.1.617.2 +, Q677H, and B.1.640.

The current SARS-CoV-2 variants of importance are D614G (B.1), Alpha (B.1.1.7 and B.1.1.7+E484K), Gamma (P.1), Delta (B.1.617.2), Omicron -BA.1 (B.1.1.529), and Omicron BA.2 (Table 1).

Label/Lineage	Transmissibility	Immune response	Disease severity
D614G – B.1	Increased due to higher viral loads	Similar to ancestral virus	Similar to ancestral virus
Alpha – B.1.1.7	Increased transmissibility	Similar to ancestral virus	Similar to ancestral virus
Gamma – P.1	Increased transmissibility	Documented immune escape	Increased disease severity
Delta – B.1.617.2	Increased transmissibility	No impact on immune response	Increased disease severity
Omicron – B.1.1.529	Increased transmissibility	? heightened immune response	Decreased disease severity
Omicron BA.2	? increased transmissibility	Impact on immune response not known	? decreased disease severity

Table 1: *Current SARS-CoV-2 variants of importance.*

In addition, there is a class of De-escalated variants, which comprises of additional variants, which have been de-escalated as the variants are no longer circulating or existing for a long time without impact on the pandemic situation, or variants are circulating but not associated with concerning epidemiological properties [9]. As updated recently, the de-escalated variants now include Epsilon, Eta (B.1.525), Theta (P3), Kappa (B.1.617.1), B.1.620, P.2, P.3, and others like A.27, A.28, C.16, and B.1.214.2.

Omicron: Priming for immunity or disaster

The newly emerged SARS-CoV-2 variant, Omicron (B.1.1.529), first reported from South Africa and Botswana during November 2021, appears to have increased transmissibility with reduced disease severity [10]. In addition, it generates a potent immunity. Phylogenetically, it contains many more mutations than any previous VOCs. It carries a total of 47 mutations in its genome, including 26 mutations in the spike (S) gene, and 13 mutations in the receptor-binding domain (RBD) in the S gene [11].

It has been documented that, the Omicron variant has increased transmissibility and enhanced viral binding affinity. In addition, due to the presence of five novel mutations adjacent to the ACE2 and antibody binding sites, it may harbor an immune escape property and manifest striking antibody evasion [12]. The *in vitro* neutralization assay shows that the mean neutralization titers by sera from convalescent COVID-19 patients are significantly reduced against the Omicron variant than other variants [13].

The current research, as well as clinical findings related to the Omicron variant, have led to a rampant view, both among medical professionals and the public, that the illness due to Omicron is likely to be a mild one and might help to develop immunity to protect against a more severe variant in the future. The sub-variant BA.2, spreading in various geographical regions also appears to cause a less severe clinical disease [14]. The sub-variant appears to be even more transmissible than the Omicron variant as its transmission is reportedly higher among household contacts of BA.2 cases (13.4%) as compared to 10.3% for the Omicron cases [15].

The sub-variant of Omicron, BA. 2, which shares many of the mutations in Omicron, has further 28 mutations, not present in the Omicron variant including those in the spike protein. While the original BA.1 variant is relatively easy to track due to a spike deletion (H69/V70), the BA.2 does not contain this mutation hence not simple to detect by PCR testing. Instead, its monitoring requires additional genomic sequencing. Due to its evasiveness, some researchers have dubbed the BA. 2 as the 'stealth omicron' [16]. The WHO is yet to categorize BA.2 as a 'Variant of concern'.

The current vaccines appear to offer the same level of protection against symptomatic disease both due to Omicron as well as its sub-variant BA.2. But, due to the relatively small number of confirmed cases of Omicron's sub-Variant BA.2, the conclusions are provisional. There is lingering fear among the researchers that perchance the Omicron and its sub-variant, BA.2 may be priming the immune response for a disaster due to future SARS-CoV-2 variants.

The preventive measures and therapeutics

With the unprecedented and ongoing pandemic, the scientific knowledge had evolved with the research at a fast pace leading to fast development and deployment of the vaccines. They have been developed fast and used under emergency authorization, to tackle the growing pandemic. The downside has been a failure to inspire full public confidence in their efficacy. In addition, people are worried about their long-term effects and complications. There are concerning issues related to exceedingly rare cases of myocarditis, the issues about neurological degenerative disorders, and fertility.

There is a glaring fact is that more people have died of COVID-19 since the vaccine was developed than before the vaccine was developed. Further, the data from an array of studies shows that the immunity from the vaccines declines over time, highlighting the need to develop vaccines offering greater protection may be needed to fight off the highly contagious variant. Furthermore, various population groups are weighing freedom to make their own decisions versus the eventuality of mild disease course and symptoms.

On top of these issues, the enforced social isolation as the fallout of the infection is another distasteful and controversial issue. Finally, fear and desperation are giving away to inevitability, among those who feel protected from the virus' worst effects because they are vaccinated as well as those who believe that risks of the disease are exaggerated. The empathy of the society toward those vulnerable is

vehemently giving way to socio-economic issues like jobs and social and mental strains. These issues dilute the enforcement of preventive measures including masking and vaccination programs.

The preventive measures and Vaccines have transformed the pandemic, but there is still a dire need for suitable drugs to treat the disease and its complications. The use of various therapeutic agents has been endorsed and disproven by the RECOVERY Trial (Table 2). These drugs are indicated at different stages of the infection. As per the Recovery Trial results, out of 100 ICU admitted COVID-19 patients on ventilators for 28 days, 60 patients were already likely to recover, 12 pts survived because of the drug therapy, whereas 28 still died despite it [17]. The breakthroughs to develop more effective therapeutic modalities are, still, required to improve the disease outcomes.

Therapeutic agent	Mode of action	Clinical efficacy	Limitations
Steroid therapy – Dexamethasone and other steroids	Anti-inflammatory action	shown to improve survival in COVID-19.	Exacerbates infection, cardiac disease, diabetes
Aspirin or Acetyl-salicylic acid	Antiplatelet action to prevent blood clots	Effective, cheap, and widely available	Haemorrhage and Haemorrhagic infarcts
Anti-viral therapy – • Favipiravir • Molnupiravir • Paxlovid (Nirmatrelvir + Ritonavir) • Remdesivir	Favipiravir, Molnupiravir and Paxlovid – oral use Remdesivir – i.v. use Block viral replication to reduce virus load	Reduce the risk of hospitalization or death and reduce the recovery period	Likelihood of mutagenic DNA interactions
Monoclonal antibody therapy – • Ronapreve (casirivi-mab+imdevimab) • Sotrovimab	Helps the immune system in neutralizing the virus	Reduce period of hospitalization and complications and mortality risk	Likelihood of potentiating the cytokine crisis
Abandoned drugs – • CQ and HCQS • Azithromycin • Ivernectin • Colchicine, and • Anti-HIV drugs	? anti-viral action	Benefit not proven	Side effects and drug interactions
Abandoned therapy – • Convalescent plasma	? neutralise virus to decrease viral load	Benefit not proven	Transfusion-related reactions

Table 2: *Therapeutic measures available for COVID-19.*

There is the issue of long-term immune response to the infection and related complications in form of long Covid. For the survivors of the pandemic, the virus can have deleterious health effects that linger on for an indefinite period leading to a range of complications. There are significant short-term as well as projected long-term neurologic manifestations of COVID-19 in patients who have recovered. These involve impaired physical functioning and mobility disorders, and impact on the autonomous nervous system, especially in older patients with mild and moderate disease and warrant further prospective studies. The virus is capable of damaging the cortical structures which control the coordination of movement, such as the basal ganglia, initiating a process of neurodegeneration [18].

The viral infections have been documented to cause long-term neurological complications, as was documented in survivors of the 1918 Spanish Influenza, who were found to have two or three times more likelihood to develop Parkinson's disease at some point in their

life. As early as in the 1990s, antibodies to the coronaviruses were identified in the cerebrospinal fluid of Parkinson's patients [19]. During the past two years, case studies have been published describing patients who developed acute Parkinsonism abnormalities such as tremors, muscle stiffness, and impaired speech following Covid-19 infection [20].

The disruption of the immune system in these patients may affect variously. There is seen new-onset diabetes or worsening of diabetes in COVID-19 patients [21]. The cardiac complications include myocarditis and cardiomyopathy. In addition, myocarditis and myopericarditis have been associated with COVID-19 vaccination. The Oxford-AstraZeneca vaccine has been linked to very rare cases of clotting disorders. Some recently immunized people have suffered unusual clots, including cerebral sinus vein thrombosis (CSVT). On the other hand, the SARS-CoV-2 infection itself may lead to coagulation disorders. The therapeutic measures to treat the long-term effects and complications need to be explored.

Conclusion: The Met and Unmet Challenges

Since the start of the pandemic, over two years, as such the healthcare utilization for other specialties apart from COVID-19 related has been reported low as compared to the pre-pandemic levels. This low rate of healthcare utilization indicates that either the care was not resorted to or simply delayed. Further, with the changing scenario and various normal life activities being resumed, healthcare is still overwhelmed with COVID-19 or post-Covid related complications. According to a recent WHO survey, various disruptions in health services were reported in 92% of the 129 countries [22].

The Omicron variant of SARS-CoV-2 manifests a striking antibody evasion [23]. Presently there is evidence, though limited, that the Omicron variant causes less severe disease than other earlier variants [24]. The latter finding has led to a widespread assumption that the time has come to adapt to live with the virus despite repeated outbreaks, recurrences, and periodic surges of COVID-19 cases. Thus, there has expounded vast confusion about the practice of preventive and restrictive measures. Whether they should be omitted or to be carried on till Omicron wanes or carried on with restrictive policies at the cost of overall socio-economic issues. The overall impact of socio-economic concerns has influenced both at the individual as well as at the organizational level replacing the dread for overall health with that for socio-economic collapse.

A perpetual state of lockdown and closures cannot be practiced for long. Those who are effectively vaccinated can safely be allowed to carry on normal activities in the present scenario when Omicron and other variants with reduced morbidity and mortality are emerging and persisting leading to outbreaks of cases in small or limited geographical pockets. Further, the pandemic may be ending or changing its course to acquire endemicity. In fact, the end of the pandemic cannot be regarded as a discrete event like a conclusion of a war. It is, rather, a gradual process in which the human life with herd immunity, substantial or partial, comes to term at living alongside the virus, which may have become less morbid and lethal.

Simultaneously, it is imperative as we adopt a new normal strategy of living with the virus that modified preventive measures are carried on in form of limited restrictions, adhering to wear masks, and avoiding crowded places [25]. There is a need to be vaccinated and boosted. The Safety Issues related to the Covid vaccines should be addressed. Simultaneously, on the therapeutic front, research should go on to develop more effective and successful agents and modalities. Finally, a continued follow-up and treatment for those suffering from long Covid is required to improve the quality of their life and restore activities of normal living.

Bibliography

1. Nikhra V. "The Virus, SARS-CoV-2, its Variants, and Infectivity-cum-Virulence. Evolving Patterns in COVID-19: The Virus, its Variants and Infectivity-cum-Virulence".

2. Max Planck Institute for the Science of Human History. "COVID-19 is here to stay for the foreseeable future: Future of field-based sciences in the time of coronavirus". Science Daily (2020).

3. Tay MZ., *et al*. "The trinity of COVID-19: immunity, inflammation and intervention". *Nature Reviews Immunology* 20.6 (2020): 363-374.

4. Chakraborty S., *et al*. "Proinflammatory IgG Fc structures in patients with severe COVID-19". *Nature Immunology* 22.1 (2021): 67-73.

5. Bournazos S., *et al*. "The role of IgG Fc receptors in antibody-dependent enhancement". *Nature Reviews Immunology* 20.10 (2020): 633-643.

6. Naqvi AAT., *et al*. "Insights into SARS-CoV-2 genome, structure, evolution, pathogenesis and therapies: Structural genomics approach". *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* 1866.10 (2020): 165878.

7. Robson F., *et al*. "Coronavirus RNA Proofreading: Molecular Basis and Therapeutic Targeting". *Molecular Cell* 79.5 (2020): 710-727.

8. Bhattacharyya RP and Hanage WP. "Perspective - Challenges in Inferring Intrinsic Severity of the SARS-CoV-2 Omicron Variant". *New England Journal of Medicine* 386.7 (2022): e14.

9. Perez-Gomez R. "The Development of SARS-CoV-2 Variants: The Gene Makes the Disease". *Journal of Developmental Biology* 9.4 (2021): 58.

10. He X., *et al*. "SARS-CoV-2 Omicron variant: Characteristics and prevention". *MedComm* 2.4 (2021): 838-845.

11. WHO Classification of Omicron (B.1.1.529): SARS-CoV-2 variant of concern (2021).

12. PONGO. PANGO Lineages: Summary of BA.1 data.

13. Saxena SK., *et al*. "Characterization of the novel SARS-CoV-2 Omicron (B.1.1.529) variant of concern and its global perspective". *Journal of Medical Virology* 94.4 (2021): 1738-1744.

14. Science-the-wire. Don't Be Too Concerned About the Omicron BA.2 Sub-Lineage. Here's Why (2022).

15. SARS-CoV-2 variants of concern and variants under investigation in England: technical briefing 36. Ref: UKHSA publications gateway number GOV-11306 PDF, 3.2 MB, 33 pages.

16. 'Stealth' Omicron: What You Need To Know About The BA.2 Subvariant.

17. RECOVERY Trial - Jointly founded by UK Research and Innovation (UKRI)'s Medical Research Council and the National Institute of Health Research (NIHR) and led by the University of Oxford.

18. Awogbindin IO., *et al*. "Microglial Implications in SARS-CoV-2 Infection and COVID-19: Lessons from Viral RNA Neurotropism and Possible Relevance to Parkinson's Disease". *Frontiers in Cellular Neuroscience* 15 (2021): 670298.

19. Cohen ME., *et al*. "A case of probable Parkinson's disease after SARS-CoV-2 infection". *Lancet Neurology* 19.10 (2020): 804-805.

20. Fazzini E., *et al*. "Cerebrospinal fluid antibodies to coronavirus in patients with Parkinson's disease". *Movement Disorders* 7.2 (1992): 153-158.

21. Khunti K., *et al*. "COVID-19, Hyperglycemia, and New-Onset Diabetes". *Diabetes Care* 44.12 (2021): 2645-2655.

22. "Third round of the global pulse survey on continuity of essential health services during the COVID-19 pandemic - Interim report" (2021).

23. Liu L., *et al*. "Striking antibody evasion manifested by the Omicron variant of SARS-CoV-2". *Nature* 602 (2021): 676-681.

24. Zhang L., *et al*. "The significant immune escape of pseudotyped SARS-CoV-2 variant omicron". *Emerging Microbes and Infections* 11.1 (2022): 1-5.

25. International Monetary Fund - Policy Responses to COVID-19.

Volume 18 Issue 4 April 2022