Journal of Communicable Diseases
Volume 54, Issue 1 - 2022, Pg. No. 141-149
Peer Reviewed & Open Access Journal

Review Article

Evolving Faces of SARS-CoV-2 with the Emergence of Diverse Variants

Shakya Sinha[1], Sajal Bhattacharya[2], Sriparna Datta Ray[2], Rina Tilak[3]

[1]Research Student, [2]Professor (Associate), Postgraduate Department of Zoology, Asutosh College (University of Calcutta), Kolkata, West Bengal, India.
[3]Scientist 'G', Department of Community Medicine, Armed Forces Medical College, Pune, Maharashtra, India.
DOI: https://doi.org/10.24321/0019.5138.202260

I N F O

Corresponding Author:
Rina Tilak, Department of Community Medicine, Armed Forces Medical College, Pune, Maharashtra, India.
E-mail Id:
rinatilak@hotmail.com
Orcid Id:
https://orcid.org/0000-0003-3781-0210
How to cite this article:
Sinha S, Bhattacharya S, Ray SD, Tilak R. Evolving Faces of SARS-CoV-2 with the Emergence of Diverse Variants. J Commun Dis. 2022;54(1):141-149.

Date of Submission: 2022-02-23
Date of Acceptance: 2022-03-28

A B S T R A C T

Since the emergence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in December 2019, scientists have tracked five variants of concern (VOC) of SARS-CoV-2. The variants such as B.1.1.7 and B.1.617.2 primarily originated independently from the United Kingdom and India, respectively, and subsequently became dominant across the globe. The adaptability of these variants depends on their relative survival fitness to the positive selection pressure acting on them. Antiviral drugs and vaccine usage might act as a selective environment, thus, facilitating the positive selection resulting in the rapid emergence of new variants with higher fitness and survival value. The recently emerged VOC, the omicron variant (B.1.1.529), was first reported from South African samples, and it has a large number of mutations some of which are concerning as per the preliminary evidence. Owing to the dynamism of mutations in the SARS-CoV-2 genome, we may expect many unexpected events as far as the emergence of variants, virulence, and transmissibility is concerned. However, as an evolutionary trade-off strategy, the virulence of SARS-CoV-2 might get reduced with an increase in the transmissibility to attain a wider host range. The intermingling of vaccinated and unvaccinated individuals provides the virus opportunity to amplify by infecting the unvaccinated individuals and causing breakthrough infections. Moreover, the prevalence of different variants of SARS-CoV-2 has been different in different geographic zones as far as the cases and causalities are concerned. Sustained viral surveillance and monitoring with region-wise variant-specific preventive strategies are required to prevent and contain the outbreak of emerging variants of SARS-CoV-2.

Keywords: SARS-CoV-2, Variants, Evolution, Vaccine

Introduction

Since the emergence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in December 2019, scientists have tracked several variants from different parts of the world.[1] Since there is a continuous evolution of SARS-CoV-2 in nature and owing to the impact of variants on public health, WHO classifies variant virus strains as variants of concern (VOC), variants of Interest (VOI), and variants

under monitoring (VUM) based on their attributes and prevalence, which are dynamic in nature.[1] Of all variants, 05 are designated as VOC (viz. alpha, beta, gamma, delta, and omicron) which means the variants with genetic changes leading to increased transmissibility or increased virulence or decreased therapeutic effectiveness and are of global public health significance.[1] Scientists around the world are relentlessly engaged in knowing and understanding the characteristic of SARS-CoV-2 for developing preventive measures to control the disease. However, the emergence of newer SARS-CoV-2 variants hinders the comprehensive understanding of the COVID-19 disease dynamics. The generation of newer variants by mutations in the case of RNA viruses is a natural phenomenon, and it happens in lesser time compared to many other life forms on the earth.[2] However, the frequency of generation of variants and their subsequent emergence in a short time is a concerning avenue from a public health perspective. At this point, an understanding of the possible reasons behind the emergence of the diverse variants of SARS-CoV-2 from the evolutionary and epidemiological perspective is required for their clinical and epidemiological management.

Materials and Method

A review was conducted and research studies were drawn from a literature search that targeted peer-reviewed journal articles and book chapters. The databases explored were PubMed, Google Scholar, Wiley Online Library, and Semantic Scholar. These databases represent a varied range of disciplines allied to SARS-CoV-2, viruses, viral evolution, and public health. Information about different SARS-CoV-2 variants was drawn from World Health Organization (WHO) website.

The data about the prevalence of case incidences of different VOC were collected from GISAID open-access website. The prevalence data comprises information from the period October 2020 to February 2022. The data used in the article was available as exponentially smoothed ($\alpha = 0.3$) percentage (%) of different SARS-CoV-2 variants of concern.[3]

All the findings and observations in this review regarding the focused topic are based on published information as listed in the references.

Antiviral Agents as Positive Selection Pressure on SARS-CoV-2

Naturally, error-prone replication with poor or faulty proofreading ability is the reason behind the high mutability of RNA viruses. The selection of these variants depends on their fitness and adaptive benefits to the natural selection pressure acting on them.[2] The positive selection pressure is the only driver for the selection and establishment of novel variants for viruses. If a viral niche doesn't change and favours the existing variant of a virus, then the positive selection mostly remains inoperative[2] unless one variant competitively excludes the other.[4] However, a changing ecological niche may act as a selective environment. The major selection pressure for viruses in their ecological niche is the host immune system.

In an attempt to contain the highly transmissible SARS-CoV-2, the world has seen the emergency authorisation of several repurpose drugs without high-quality research[5] and the development of different vaccines.[6] However, vaccination cannot entirely rule out the possibility of SARS-CoV-2 infection.[7] The generation of neutralising antibodies from the memory cells induced by vaccination is a barrier and a possible selection pressure for the virus. Moreover, the passive immune response in hosts by vaccination changes the ecological niche of the SARS-CoV-2. The use of repurposed drugs may also have a similar effect. Mode of action for several repurpose drugs authorised on an emergency basis includes targeting viral RNA and blocking their replication, degrading viral polypeptides to block their entry into host cells, or altering host cells ACE-2 related pathways.[8] Therefore, the use of these vaccines and repurposed drugs against SARS-CoV-2 may generate conflicting selective constraints within the ecological niche of the virus. To survive and cope in such an unfavourable and shifting cellular environment, the variants of SARS-CoV-2 with better fitness might get selected rapidly. Hence, the antiviral agents might act as a driver for the selection of better fit variants.

Evolutionary Trade-off and Transmissibility of SARS-CoV-2

Under selection pressure, the virus can adapt to survive by tissue tropism, antigenic variations, or by obtaining higher transmissibility to infect a larger host population.[2] The transmissibility of viruses largely depends on their basic reproduction number (R_0) i.e. the number of secondary infections from one infected individual.[9] In the case of SARS-CoV-2, the R_0 value has been estimated to be 2.5, which is the highest among most pandemic-causing pathogens.[10] In general, the viruses with a higher R_0 value are antigenically more stable with a limited number of serotypes.[11] The genome of SARS-CoV-2 is not an exception. Despite being an RNA virus, SARS-CoV-2 has a proofreading enzyme called nsp14, a 3' to 5' exoribonuclease. The nsp 14 reduces the error rate and results in a low mutation rate compared to many other RNA viruses.[12] However, the rate of error-prone replication is sufficient to allow for the accumulation of a significant number of mutations in the viral genome.[13] For SARS-CoV-2, the enormous host range, owing to its high transmissibility, allows for a vast number of mutations. The alpha variant (B.1.1.7) of SARS-CoV-2 is more transmissible than the primarily detected SARS-CoV-2, whereas the delta

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202260

variant (B.1. 617.2 + AY.1 + AY.2 + AY.3 + AY.3.1) is even more transmissible than the alpha variant.[14] Another concerning factor in this regard is the ability of newer variants to resist the vaccines.[15] The high transmissibility of SARS-CoV-2 might compensate for the slow mutation rate and allow them to gain the necessary genomic flexibility that is required for survival. Therefore, high transmissibility could be an evolutionary strategy for the survival of SARS-CoV-2. The gradual emergence of variants with more transmissibility might be favouring the virus to increase its host range, which in turn provides it habitat to replicate and mutate, thereby creating more variants that get selected based on their survival value and fitness (Figure 1).

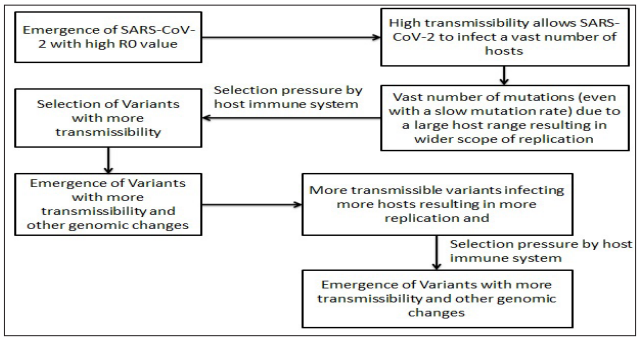

Figure 1.Possible Events in the Acquisition of Higher Transmissibility of SARS-CoV-2

Mutations in SARS-CoV-2 Spike Protein

The spike protein of the SARS-CoV-2 is significant for attachment to the host ACE-2 receptors. Most of the naturally acquired or vaccine-induced neutralizing antibodies have been found to target the spike region for their action.[16] In particular, the receptor-binding domain (RBD) and the N-terminal domain (NTD) of SARS-CoV-2 spike protein (S) are highly immunogenic.[16,17] Mutations in RBD and NTD and their subsequent effects in many instances increase the immune evasion ability of the virus and reduce the antibody sensitivity to the spike region. One of the early detected and significant mutations in the S region is the D614G which alters the spike protein dynamics and contributes to enhanced entry into the cells and viral replication that subsequently leads to the attainment of higher infectivity.[18,19] Another mutation, E484K (Table 1) in the RBD has been delineated as significant owing to the immune evasive abilities of several variants, from monoclonal antibodies and resistance to neutralization from vaccines and convalescent sera.[20] In the VOC delta (B.1.617.2 + AY.1 + AY.2 + AY.3 + AY.3.1), mutations T478K and L452R (Table 1) in RBD possibly enhanced the ACE2 binding ability along with the mutation P681R in the furin cleavage site which increases the fusogenic ability and subsequently contributes to higher transmissibility.[21] Further, the E484K mutation has been suggested to increase the ability of breakthrough infections by the lineages of delta variant in recent studies.[22] Mutation G142D in the NTD has been associated with the increased viral load and immune evasion for the delta variant as well.[23] Other mutations holding importance include Y453F, N501Y, E484Q, V367F, etc. (Table 1). The recently emerged VOC, the omicron variant (B.1.1.529) also has a large number of mutations, some of which are concerning as evident from preliminary investigations.[24] The VOC omicron has 30 signature mutations and among them, 23 are unique to this variant.[25] Mutation in N501Y, H655Y, N679K, P681H etc. leads to some key amino acid changes in the VOC omicron that affects its receptor binding ability and binding affinity to the neutralising antibodies.[25,26] There are seven lineages and sub-lineages of omicron variant namely, B.1.1.529, BA.1, BA.1.1, BA.2, BA.3, BA.4 and BA.5, among which BA.1, BA.1.1 and BA.2 are the most common.[1,26] The additional mutations in the omicron variant includes, R346K, L452R/Q, and F486V in the spike protein coding genes.[1]

Prevalence of different SARS-CoV-2 Variants of Concern during the COVID-19 Pandemic

There are several lineages of SARS-CoV-2 circulating since its emergence, among which hitherto five of the variants have been designated as variants of concern depending on their increased transmissibility or increased virulence or decreased effectiveness of vaccines, therapeutics, and diagnosis.[1] The available GISAID data (from October 2020 to November 2021) shows that the highest percentage of global cases by the alpha variant (B.1.1.7) was from April 2021 to June 2021 (Figure 2). A total of 68% of the global cases were recorded caused by the VOC alpha variant between 3rd May 2021 to 9th May 2021, which is the highest recorded percentage of VOC alpha cases in the global total. During October 2021-November 2021, VOC alpha cases decreased, the highest being 0.3% cases from 11th November 2021 to 17th November 2021 (Table 2). The VOC beta and gamma cases were highest in percentage from April 2021 to June 2021, with 2.1% and 8% of the global cases respectively (Table 2). The percentage of VOC delta cases escalated from April 2021 to June 2021 with a rise in the global cases from 0.8% to 54.5% (Table 2). However, the prevalence of delta variant has been highest during October 2021-November 2021. The highest percentage of VOC delta cases in this period was recorded at 99% of total cases. The highest percentage of Delta cases was from 22nd November 2021 to 28th November 2021. Nearly at the end of November 2021, the VOC omicron got reported from the South African samples.[24] Till the end of November, the highest percentage of omicron was 3.6% of the global case incidences recorded from 22nd November 2021 to 29th November 2021. From 22nd November 2021 to 29th November 2021, with an increased percentage of VOC omicron cases in the African region, a drop in the VOC delta cases has been observed.[3] From December 2021 to February

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202260

2022, hitherto the highest percentage of VOC omicron cases have been recorded at 93.6%, and the lowest percentage was in the initial days of December 2021, accounting for about 4.0% of the global cases.[3]

Table 1.Mutations in different VOC of SARS-CoV-2 and their Possible Effects

Variant	Lineage	Significant Mutations	Effects/ Possible Effects	References
Alpha	B.1.1.7	D614G	Changes in spike protein dynamics and increases affinity to ACE2	Plante et al.[18]; Lauring and Hodcroft[19]; Mohammadi et al.[27]; Meng et al.[28]
		N501Y	Increases affinity to ACE2 receptor	
		P681H	Increases fusogenic activity and subsequently transmissibility	
		H69-V70del	Compensate for the mutations for immune escape activity	
		Y453F	Increased binding affinity in minks	
Beta	B.1.351	E484K	Resistance to neutralising antibodies	Zhang et al.[20]; Plante et al.[18]; Mohammadi et al.[27]
		D614G	Changes in spike protein dynamics and increases affinity to ACE2	
		K417N	Antibody escape	
		N501Y	Increases affinity to ACE2 receptor	
Gamma	P.1	E484K	Resistance to neutralising antibodies	Zhang et al.[20]; Plante et al.[18]; Mohammadi et al.[27]
		D614G	Changes in spike protein dynamics and increases affinity to ACE2	
		K417N	Antibody escape	
		P681H/ N679K	Increases fusogenic activity and subsequently transmissibility	
		141-144 del	Compensatory deletion	
Delta	B.1.617.2 + AY.1 + AY.2 + AY.3 + AY.3.1	D614G	Changes in spike protein dynamics and increases affinity to ACE2	Barnes et al.[29]; McCallum et al.[18]; Plante et al.[19]; Baj et al.[22]
		T478K	Favours the binding to the ACE2 by avoiding neutralising antibodies	
		T19R	Possibly enhance immune escape activity	
		L452R	Changes fusogenic activity	
		D950N	Regulation of spike protein dynamics	
		E484K	Found significant in case of breakthrough infections	
Omicron	B.1.1.529 + BA.1 + BA.1.1 + BA.2 + BA.3 + BA.4 + BA.5	N501Y	Increases binding with ACE2 receptor	Kannan et al.[25]; CDC[26]
		H655Y	Might increase spike cleavage leading to higher transmissibility	
		N679K	May also increase spike cleavage as residing near furin cleavage site aiding transmission	
		Y505H	May reduce affinity between S-RBD and antibodies	

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202260

Table 2.Incidence of SARS-CoV-2 Variants of Concern (VOC) Cases from October 2020 to February 2022

	VOC Alpha		VOC Beta		VOC Gamma		VOC Delta		VOC Omicron	
	Highest (%)	Lowest (%)	Highest (%)	Lowest (%)	Highest (%)	Lowest (%)	Highest (%)	Lowest (%)	Highest (%)	Lowest (%)
October 2020 - December 2020	14.2	0	1.2	0.2	0.1	0	0.2	0.1	0	0
January 2021 - March 2021	59.4	16.9	2.1	1.2	2.6	0.1	0.4	0.1	0	0
April 2021 - June 2021	68	28.5	2.1	1.09	8	2.6	54.5	0.8	0	0
July 2021 - September 2021	22.6	0.5	1.1	0.97	7.4	0.4	96.8	54.5	0	0
October 2021 - November 2021	0.3	0.1	0.1	0.09	0.4	0.1	99	94.5	2.9	0
December 2021 - February 2022	0.1	0.1	0.1	0.1	0.1	0.1	94.4	5.1	93.6	4

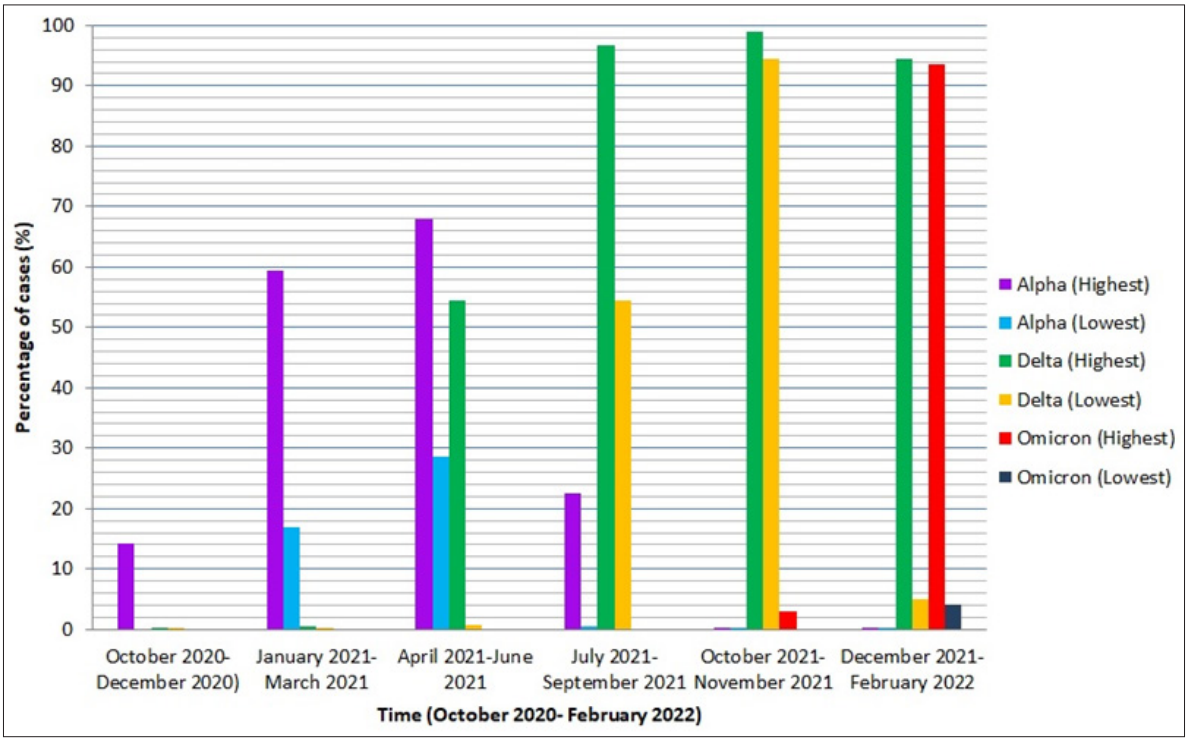

Figure 2.Highest and Lowest Percentage of Global Case Incidences of SARS-CoV-2 VOC Alpha, VOC Delta and VOC Omicron from October 2020-February 2022 in six different time periods viz. October 2020-December 2020, January 2021-March 2021, April 2021-June 2021, July 2021-September 2021, October 2021-November 2021 and December 2021-February 2022[3]

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202260

Mixing of Vaccinated and Non-vaccinated Population and its Impact

The vaccine allocation to the public initially was on the basis of priority following the "Road map of Prioritizing Population Groups for Vaccines against COVID-19" developed by WHO.[30] The non-uniform distribution of vaccines creates a mixing of vaccinated and unvaccinated individuals staying together in a population. The unvaccinated individuals in a population remain susceptible to SARS-CoV-2. The virus can replicate and survive within them, thereby getting ample chances for mutation. Therefore, an unvaccinated population provides space for the virus to mutate, modify and survive under selection pressure by the vaccine-induced immunity and natural immunity by creating variants with more infectivity or more transmissibility or both. The susceptibility of a population may also increase with the emergence of newer variants of the pathogen as the population remains immunologically naïve to the newly emerging antigenic properties.

Discussion

Like several other infective viruses, the SARS-CoV-2 is also circulating as a group of lineages and sub-lineages in different parts of the world.[31] In the passages of times, some of them are becoming dominant suppressing the others. Possibilities arise that unidentified or endemic lineages of SARS-CoV-2 are co-circulating which by gaining the ability to infect humans through beneficial mutations may surface as a potential public health threat. It has been established that mutants like D614G appeared independently and dispersed simultaneously across multiple geographical regions, which is suggestive of an adaptive benefit for the D614G and natural selection of the mutation for its better fitness.[19] Viruses engage with host antiviral properties and evolve through an evolutionary arms race;[32] which is evident in the case of SARS-CoV-2. The immune induction by artificial antivirals viz. vaccines and repurpose drugs may facilitate the selection of mutations with better fitness. To prevent the disease, potent antiviral drugs and vaccines are necessitated; however, they instigate a man-induced evolutionary arms race. This postulate, nonetheless, needs confirmation through further research. The patterns of mutation, as well as the number of mutations in spike proteins, are different in different geographical regions.[33] This spatial difference in mutation patterns and their selection can be attributed to host immunity, environmental factors, and genetic predisposition for the disease amongst the host population, etc.[34,35,36,2] Nevertheless, the vaccination strategies and authorisation of the use of repurposed drugs have been different in different countries.[37] Whether the various vaccination strategies that are implemented from time to time across the globe, concurrent with the use of repurpose drugs have any decisive role to play in the selection of spike protein mutations is an important arena for further research and investigation.

Acquiring herd immunity or population immunity by natural course due to the previous infection or through vaccination is possibly the ultimate way to break the transmission chains of contagious viruses. In the case of SARS-CoV-2, the newly emerging variants show decreased vaccine efficacy. The beta (B.1.351) variant was found to show decreased efficacy than the alpha variant (B.1.1.7), while the delta variant (B.1.617.2) shows further reduction in vaccine efficacy.[27] As a result of this, re-infection with new variants even after successful completion of the vaccination programme is well-known for COVID-19 as well as breakthrough infection with the same variants.[38,7] Moreover, WHO was reported about the recently emerged omicron variant (B.1.1.529) of SARS-CoV-2 on 24th November 2021 from South African samples, and by 26th November, it had been included in the list of VOC.[24] It has been suggested from the preliminary evidence that there is an increased risk of getting re-infected by the omicron variant as compared to other VOC.[24] Further, the breakthrough infection in the vaccinated individuals is a cause of concern as antibody-dependent enhancement (ADE) of coronavirus infection in experimental setups has been demonstrated by several groups of researchers[39,40] and apprehensions have been made that it could also happen in the case of SARS-CoV-2.[41] The vaccines reduce the severity of symptoms instead of preventing the viral infection, as is also evident in the case of COVID-19 breakthrough infections.[42] These reduced symptoms or severity due to vaccination or naturally induced immunity may result in a number of individuals with asymptomatic COVID-19.[43,44] These asymptomatic individuals have been apprehended as amplifiers for the SARS-CoV-2[45] and they may transmit the virus to others, although the secondary infection rate from these asymptomatic individuals is less compared to the symptomatic ones.[46] Monitoring of both vaccinated and non-vaccinated individuals to develop a comprehensive preventive strategy for the spread and emergence of SARS-CoV-2 variants is therefore very pertinent at this hour.

Vaccination against a pandemic is a time-demanding process. Prioritised vaccination was the need of the hour, and the same was thus implemented by the public health authorities and policymakers.[28] However, the mixing of the vaccinated and unvaccinated population due to the prioritised vaccination possibly provides opportunities for the virus to survive and facilitates transmission by infecting the unprotected individuals and the vaccinated individuals as well. Therefore, it may not be unwise to apprehend that the prioritised vaccination policy is possibly advantageous for the SARS-CoV-2 to evolve. Another concerning avenue regarding the vaccination was the possible development of a false sense of complacency in a partially vaccinated population. Human behaviour is

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202260

infectious and the development of such a false sense of security may further complicate the situation. Uniform mass vaccination strategies without any prioritisation on the basis of age or community in an area-specific manner might be useful in preventing the mixing of vaccinated and unvaccinated individuals. This would lessen the host range thereby reducing the transmission rate of the virus and subsequently might prevent or reduce the number of emerging variants. Moreover, the predominance of different SARS-CoV-2 variants in different geographic regions has been observed in reference to COVID-19 cases and casualties.[1] Hence, sustained surveillance of the emerging and/ or re-emerging variants of SARS-CoV-2 and formulation of region-wise variant-specific preventive strategies are an imperative necessity.

The mutations in the spike region are considered most significant in terms of virulence, transmissibility and immune evasion.[47] As long as a large number of people are infected, the chances of error-prone replication[12] and the subsequent emergence of variants are very much likely. This may result in further unexpected public health challenges to meet. However, though the spike protein is well researched, there are a number of mutations outside the spike region[23] that are hitherto not well-studied to date. Further comprehensive studies should be aimed at such mutational hot spots beyond the spike region to understand whether they are also under some selection pressure and to interpret the implications of such mutations on the ongoing pandemic.

Conclusion

The generation of new variants for a virus is a continuous evolutionary phenomenon. However, apart from the purifying selection agents, the selection of new variants may get facilitated by several factors including the environment in which the virus strives. The man-made antiviral agents and vaccines may put the virus under a stronger selection pressure than it would face naturally. Owing to the dynamism of mutation in the viral genome, we can expect many unexpected events such as the emergence of new variants, and changes in their virulence and transmissibility as far as SARS-CoV-2 is concerned. Nonetheless, as an evolutionary trade-off, the virulence of SARS-CoV-2 may get reduced by targeting a larger host range for its survival through the generation of variants with better fitness following the Darwinian dynamics and the trajectory of the history of viral evolution. With the passage of time, SARS-CoV-2 may become endemic. However, considering the changing nature of SARS-CoV-2, sustained viral surveillance and monitoring is an imperative necessity to detect the emerging variants, if any, for better preparedness and for formulating preventive and/ or control strategies.

Acknowledgement

The first three authors convey their gratitude to Prof Apurba Ray, Vice Principal, Asutosh College, Kolkata, India for his encouragement and kind support during the preparation of the manuscript.

Author's Contribution

Conceptualization: SB, SS; Methodology: SB, SS; Data analysis, interpretation and representation: SB, SS, SDR, RT; Preparation of initial draft of manuscript: SS, SB, SDR; Editing: SB, RT; Supervision: SB.

Funding Sources: None

Conflict of Interest: None

References

1. World Health Organization [Internet]. Tracking SARS-CoV-2 variants; 2021 [cited 2021 Dec 9]. Available from: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/
2. Sola M, Wain-Hobson S. Drift and conservatism in RNA virus evolution: are they adapting or merely changing? In: Domingo E, Webster R, Holland J, editors. Origin and evolution of viruses. UK: Academic Press; 1999. [Google Scholar]
3. GISAID [Internet]. Tracking of variants; 2022 [cited 2022 Feb 19]. Available from: https://www.gisaid.org/hcov19-variants/
4. Domingo E, Escarmis C, Menendez-Arias L, Holland JJ. Viral quasispecies and fitness variations. In: Domingo E, Webster R, Holland J, editors. Origin and evolution of viruses. UK: Academic Press; 1999. [Google Scholar]
5. Piszczatoski CR, Powell J. Emergency authorization of chloroquine and hydroxychloroquine for treatment of COVID-19. Ann Pharmacother. 2020;54(8):827-31. [PubMed] [Google Scholar]
6. World Health Organization [Internet]. COVID-19 vaccine tracker and landscape; 2021 [2021 Dec 9]. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
7. Centre of Disease Control and Prevention [Internet]. What you should know about the possibility of COVID-19 illness after vaccination; 2021 [cited 2021 Dec 9]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/effectiveness/why-measure-effectiveness/breakthrough-cases.html
8. Singh TU, Parida S, Lingaraju MC, Kesavan M, Kumar D, Singh RK. Drug repurposing approach to fight COVID-19. Pharmacol Rep. 2020;72(6):1479-508. [PubMed] [Google Scholar]
9. D'Arienzo M, Coniglio A. Assessment of the SARS-CoV-2 basic reproduction number, R_0, based on the early

phase of COVID-19 outbreak in Italy. Biosaf Health. 2020;2(2):57-9. [PubMed] [Google Scholar]
10. Petersen E, Koopmans M, Go U, Hamer DH, Petrosillo N, Castelli F, Storgaard M, Khalili SA, Simonsen L. Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics. Lancet Infect Dis. 2020;20(9):e238-e44. [PubMed] [Google Scholar]
11. Rodpothong P, Auewarakul P. Viral evolution and transmission effectiveness. World J Virol. 2012;1(5):131-4. [PubMed] [Google Scholar]
12. Lazarevic I, Pravica V, Miljanovic D, Cupic M. Immune evasion of SARS-CoV-2 emerging variants: what have we learnt so far? Viruses. 2021;13(7):1192. [PubMed] [Google Scholar]
13. Smith EC, Denison MR. Coronaviruses as DNA wannabes: a new model for the regulation of RNA virus replication fidelity. PLoS Pathog. 2013;9(12):e1003760. [PubMed] [Google Scholar]
14. World Health Organization [Internet]. Episode #45 - Delta variant; 2021 [cited 2021 Jul 14]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/media-resources/science-in-5/episode-45---delta-variant
15. World Health Organization [Internet]. Episode #44 - Delta variant and vaccines; 2021 [cited 2021 Jul 14]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/media-resources/science-in-5/episode-44---delta-variant-and-vaccines
16. Liu L, Wang P, Nair MS, Yu J, Rapp M, Wang Q, Luo Y, Chan J, Sahi V, Figueroa A, Guo XV, Cerutti G, Bimela J, Gorman J, Zhou T, Chen Z, Yuen KY, Kwong PD, Sodroski JG, Yin MT, Sheng Z, Huang Y, Shapiro L, Ho DD. Potent neutralizing antibodies against multiple epitopes on SARS-CoV-2 spike. Nature. 2020;584(7821):450-6. [PubMed] [Google Scholar]
17. McCallum M, De Marco A, Lempp FA, Tortorici MA, Pinto D, Walls AC, Beltramello M, Chen A, Liu Z, Zatta F, Zepeda S, di Iulio J, Bowen JE, Montiel-Ruiz M, Zhou J, Rosen LE, Bianchi S, Guarino B, Fregni CS, Abdelnabi R, Foo SY, Rothlauf PW, Bloyet LM, Benigni F, Cameroni E, Neyts J, Riva A, Snell G, Telenti A, Whelan SP, Virgin HW, Corti D, Pizzuto MS, Veesler D. N-terminal domain antigenic mapping reveals a site of vulnerability for SARS-CoV-2. Cell. 2021;184(9):2332-47. [PubMed] [Google Scholar]
18. Plante JA, Liu Y, Liu J, Xia H, Johnson BA, Lokugamage KG, Zhang X, Muruato AE, Zou J, Fontes-Garfias CR, Mirchandani D, Scharton D, Bilello JP, Ku Z, An Z, Kalveram B, Freiberg AN, Menachery VD, Xie X, Plante KS, Weaver SC, Shi PY. Spike mutation D614G alters SARS-CoV-2 fitness. Nature. 2021 Apr;592(7852):116-21. [PubMed] [Google Scholar]
19. Lauring AS, Hodcroft EB. Genetic variants of SARS-CoV-2-what do they mean? JAMA. 2021;325(6):529-31. [PubMed] [Google Scholar]
20. Zhang L, Cui Z, Li Q, Wang B, Yu Y, Wu J, Nie J, Ding R, Wang H, Zhang Y, Liu S, Chen Z, He Y, Su X, Xu W, Huang W, Wang Y. Ten emerging SARS-CoV-2 spike variants exhibit variable infectivity, animal tropism, and antibody neutralization. Commun Biol. 2021;4(1):1196. [PubMed] [Google Scholar]
21. Cherian S, Potdar V, Jadhav S, Yadav P, Gupta N, Das M, Rakshit P, Singh S, Abraham P, Panda S; Nic Team. SARS-CoV-2 spike mutations, L452R, T478K, E484Q and P681R, in the second wave of COVID-19 in Maharashtra, India. Microorganisms. 2021;9(7):1542. [PubMed] [Google Scholar]
22. Baj A, Novazzi F, Pasciuta R, Genoni A, Ferrante FD, Valli M, Partenope M, Tripiciano R, Ciserchia A, Catanoso G, Focosi D, Maggi F. Breakthrough infections of E484K-Harboring SARS-CoV-2 Delta variant, Lombardy, Italy. Emerg Infect Dis. 2021;27(12):3180-2. [PubMed] [Google Scholar]
23. Cai HY, Cai A. SARS-CoV2 spike protein gene variants with N501T and G142D mutation-dominated infections in mink in the United States. J Vet Diagn Invest. 2021;33(5):939-42. [PubMed] [Google Scholar]
24. World Health Organization [Internet]. Classification of Omicron (B.1.1.529): SARS-CoV-2 variant of concerns; 2021 [cited 2021 Dec 3]. Available from: https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern
25. Kannan SR, Spratt AN, Sharma K, Chand HS, Byrareddy SN, Singh K. Omicron SARS-CoV-2 variant: unique features and their impact on pre-existing antibodies. J Autoimmun. 2022;126:102779. [PubMed] [Google Scholar]
26. Centre of Disease Control and Prevention [Internet]. Science Brief: Omicron (B.1.1.529) variant; 2021 [cited 2022 Feb 20]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-omicron-variant.html
27. Mohammadi M, Shayestehpour M, Mirzaei H. The impact of spike mutated variants of SARS-CoV2 [Alpha, Beta, Gamma, Delta, and Lambda] on the efficacy of subunit recombinant vaccines. Braz J Infect Dis. 2021;25(4):101606. [PubMed] [Google Scholar]
28. Meng B, Kemp SA, Papa G, Datir R, Ferreira IA, Marelli S, Harvey WT, Lytras S, Mohamed A, Gallo G, Thakur N, Collier DA, Mlcochova P; COVID-19 Genomics UK (COG-UK) Consortium 7; Duncan LM, Carabelli AM, Kenyon JC, Lever AM, Marco AD, Saliba C, Culap K, Cameroni E, Matheson NJ, Piccoli L, Corti D, James LC, Robertson DL, Bailey D, Gupta RK. Recurrent emergence of SARS-CoV-2 spike deletion H69/V70 and its role in

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202260

the Alpha variant B.1.1.7. Cell Rep. 2021;35(13):109292. [PubMed] [Google Scholar]
29. Barnes CO, Jette CA, Abernathy ME, Dam KM, Esswein SR, Gristick HB, Malyutin AG, Sharaf NG, Huey-Tubman KE, Lee YE, Robbiani DF, Nussenzweig MC, West Jr AP, Bjorkman PJ. SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies. Nature. 2020 Dec;588(7839):682-7. [PubMed] [Google Scholar]
30. World Health Organization [Internet]. Coronavirus disease (COVID-19): vaccine access and allocation; 2020 [cited 2021 Jul 31]. Available from: https://www.who.int/news-room/q-a-detail/coronavirus-disease-(covid-19)-vaccine-access-and-allocation
31. Cella E, Benedetti F, Fabris S, Borsetti A, Pezzuto A, Ciotti M, Pascarella S, Ceccarelli G, Zella D, Ciccozzi M, Giovanetti M. SARS-CoV-2 lineages and sub-lineages circulating worldwide: a dynamic overview. Chemotherapy. 2021;66(1-2):3-7. [PubMed] [Google Scholar]
32. Tenthorey JL, Young C, Sodeinde A, Emerman M, Malik HS. Mutational resilience of antiviral restriction favors primate TRIM5α in host-virus evolutionary arms races. Elife. 2020;9:e59988. [PubMed] [Google Scholar]
33. Guruprasad L. Human SARS CoV-2 spike protein mutations. Proteins. 2021;89(5):569-76. [PubMed] [Google Scholar]
34. SeyedAlinaghi S, Mehrtak M, MohsseniPour M, Mirzapur P, Barzegary A, Habibi P, Moradmand-Badie B, Afsahi AM, Karimi A, Heydari M, Mehraeen E, Dadras O, Sabatier JM, Voltarelli F. Genetic susceptibility of COVID-19: a systematic review of current evidence. Eur J Med Res. 2021;26(1):46. [PubMed] [Google Scholar]
35. Abdelzaher H, Saleh BM, Ismail HA, Hafiz M, Gabal MA, Mahmoud M, Hashish S, Gawad RM, Gharieb RY, Abdelnaser A. COVID-19 genetic and environmental risk factors: a look at the evidence. Front Pharmacol. 2020;11:579415. [PubMed] [Google Scholar]
36. Bhattacharya S, Basu P, Poddar S. Changing epidemiology of SARS-CoV in the context of COVID-19 pandemic. J Prev Med Hyg. 2020 Jul 4;61(2):E130-E136. [PubMed] [Google Scholar]
37. Kyriakidis NC, López-Cortés A, González EV, Grimaldos AB, Prado EO. SARS-CoV-2 vaccines strategies: a comprehensive review of phase 3 candidates. NPJ Vaccines. 2021;6(1):28. [PubMed] [Google Scholar]
38. Singh J, Rahman SA, Ehtesham NZ, Hira S, Hasnain SE. SARS-CoV-2 variants of concern are emerging in India. Nat Med. 2021;27(7):1131-3. [PubMed] [Google Scholar]
39. Liu L, Wei Q, Lin Q, Fang J, Wang H, Kwok H, Tang H, Nishiura K, Peng J, Tan Z, Wu T, Cheung KW, Chan KH, Alvarez X, Qin C, Lackner A, Perlman S, Yuen KY, Chen Z. Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. JCI Insight. 2019;4(4):e123158. [PubMed] [Google Scholar]
40. Wang Q, Zhang L, Kuwahara K, Li L, Liu Z, Li T, Zhu H, Liu J, Xu Y, Xie J, Morioka H, Sakaguchi N, Qin C, Liu G. Correction: immunodominant SARS Coronavirus epitopes in humans elicited both enhancing and neutralizing effects on infection in non-human primates. ACS Infect Dis. 2020;6(5):1284-5. [PubMed] [Google Scholar]
41. Lee WS, Wheatley AK, Kent SJ, DeKosky BJ. Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies. Nat Microbiol. 2020;5(10):1185-91. [PubMed] [Google Scholar]
42. Centre for Disease Control and Prevention [Internet]. COVID-19 vaccine breakthrough case investigation and reporting; 2021 [cited 2021 Aug 8]. Available from: https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html
43. Levine-Tiefenbrun M, Yelin I, Katz R, Herzel E, Golan Z, Schreiber L, Wolf T, Nadler V, Ben-Tov A, Kuint J, Gazit S, Patalon T, Chodick G, Kishony R. Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine. Nat Med. 2021;27(5):790-2. [PubMed] [Google Scholar]
44. Gohil SK, Olenslager K, Quan KA, Dastur CK, Afsar N, Chang W, Huang SS. Asymptomatic and symptomatic COVID-19 infections among health care personnel before and after vaccination. JAMA Netw Open. 2021;4(7):e2115980. [PubMed] [Google Scholar]
45. Chatterjee R, Bhattacharya S, Tilak R. Is man the new prospective amplifying host? Evolving faces of SARS-CoV dynamics and the epidemiological challenges. J Commun Dis. 2021;53(2):89-99. [Google Scholar]
46. He D, Zhao S, Lin Q, Zhuang Z, Cao P, Wang MH, Yang L. The relative transmissibility of asymptomatic COVID-19 infections among close contacts. Int J Infect Dis. 2020;94:145-7. [PubMed] [Google Scholar]
47. Huang Y, Yang C, Xu XF, Xu W, Liu SW. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacol Sin. 2020;41(9):1141-9. [PubMed] [Google Scholar]

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202260