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Emerging SARS-CoV-2 Omicron Sub-Variants JN.1 and NB.1.8.1: Genomic Evolution, Implications, and Public Health Perspectives for a variant under monitoring (VuM)

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ABSTRACT

Since the onset of the COVID-19 pandemic, SARS-CoV-2 has undergone continual evolution, culminating in the emergence of multiple variants of concern (VOCs) and interest (VOIs). The Omicron (B.1.1.529) and it's sub-lineage have dominated recent global transmission due to their enhanced infectivity and immune evasion. This review focuses on two emerging Omicron sub-variants, JN.1 and NB.1.8.1, analysing their genomic mutations, functional consequences, and public health implications. JN.1, derived from the BA.2.86 lineage (Pirola), features the unique L455S mutation in the receptor-binding domain (RBD), enhancing ACE2 binding affinity and contributing to significant immune escape. NB.1.8.1, a recombinant sub-lineage of XBB.1.9.2, accumulates multiple RBD mutations—S486P, V445P, and N460K—demonstrating convergent evolution and notable growth advantage in regions like India and the UK.

Despite their increased transmissibility and capacity for immune evasion, preliminary clinical data suggest that both sub-variants lead to predominantly mild infections, likely due to population-level hybrid immunity. However, the evolving mutation profiles raise concerns regarding reduced efficacy of monoclonal antibody therapies and the durability of vaccine protection. Comparative analyses highlight these sub-variants' refined evolution from earlier lineages such as Alpha, Delta, and BA.1, with functional mutations enhancing both viral fitness and immune escape without compromising replication.

Thus implies importance of robust genomic surveillance, continuous vaccine efficacy evaluation, and development of broad-spectrum therapeutics. It calls for a One Health approach that integrates virological, immunological, and public health data to anticipate and respond to emerging variants. JN.1 and NB.1.8.1 exemplify the virus's adaptive strategies under immune pressure and necessitate updated risk assessments, tailored mitigation strategies, and proactive communication to navigate the next phase of the pandemic.

Keywords: SARS-CoV-2, Omicron, JN.1, NB.1.8.1, genomic mutations, immune escape, transmissibility, COVID-19, vaccine efficacy, variant under monitoring (VUM).

Introduction

Since its first identification in late 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has undergone remarkable genetic diversification, resulting in multiple variants of concern (VOCs) and interest (VOIs) that have shaped the trajectory of the global pandemic. Early variants such as Alpha (B.1.1.7), Beta (B.1.351), and Delta (B.1.617.2) demonstrated how key spike protein mutations could alter transmissibility and disease severity, with Delta in particular driving devastating global surges in 2021[1,2].

The subsequent emergence of Omicron (B.1.1.529) in late 2021 marked a turning point, as this lineage carried over 30 spike mutations, particularly in the receptor-binding domain (RBD), leading to unprecedented immune evasion while generally maintaining reduced clinical severity compared to Delta[3,4]. Omicron's rapid spread and diversification into sub-lineages such as BA.1, BA.2, BA.5, and XBB highlighted the role of immune pressure and viral recombination in shaping SARS-CoV-2 evolution[5,6].

More recently, two emerging sub-variants—JN.1 and NB.1.8.1—have attracted attention due to their distinctive mutational profiles and growth advantages. JN.1, derived from BA.2.86 ("Pirola"), harbours the L455S mutation in the spike RBD, enhancing ACE2 binding affinity and contributing to antibody escape[7]. NB.1.8.1, a sub-lineage of the recombinant XBB.1.9.2, carries multiple RBD mutations including S486P, V445P, and N460K, exemplifying convergent evolution under strong immune selection[8,9].

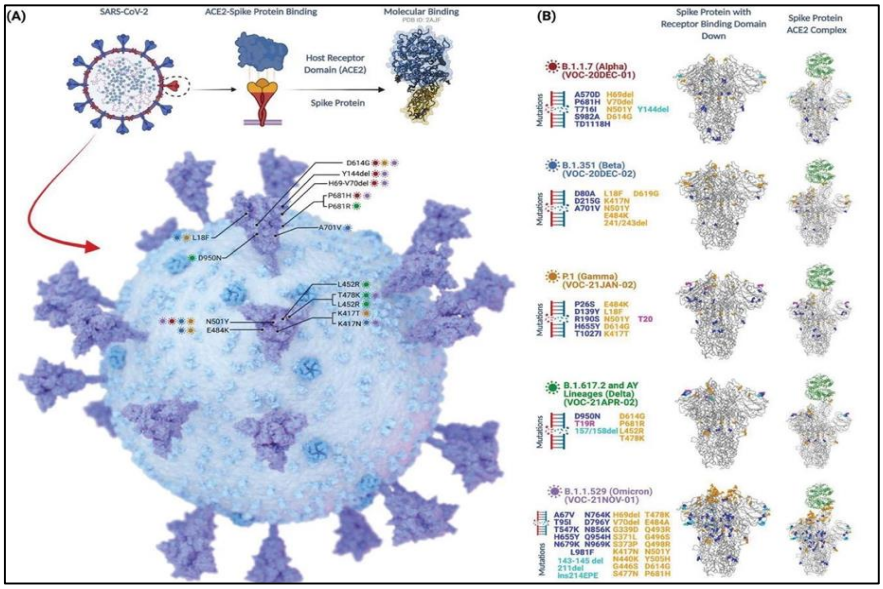
Although preliminary reports suggest that infections with JN.1 and NB.1.8.1 remain largely mild, likely due to widespread hybrid immunity, these variants raise important concerns for vaccine durability and monoclonal antibody efficacy[10,11]. Their emergence underscores the importance of sustained genomic surveillance, real-world vaccine effectiveness studies, and adaptive public health strategies to mitigate future waves of SARS-CoV-2 evolution[12,13].

Since its emergence in late 2019, SARS-CoV-2 has continuously evolved, giving rise to multiple variants with varying impacts on transmissibility, immune evasion, and disease severity. The Omicron variant (B.1.1.529) and its numerous sub-lineages have dominated the pandemic landscape since late 2021, replacing previous variants such as Delta due to their high infectivity and ability to evade immune responses[1,2]. Recently, new Omicron sub-variants, JN.1 and NB.1.8.1, have surfaced, prompting concern due to their distinct mutational landscapes and potential implications for public health[3,4]. This review synthesizes current knowledge on the genomic evolution, functional consequences, and epidemiological trends associated with these sub-variants.

SARS-CoV-2 Omicron Variant and Its Evolution:

The Omicron variant is characterized by an unprecedented number of mutations in the spike protein, particularly in the receptor-binding domain (RBD), which enhance its ability to evade neutralizing antibodies elicited by vaccines or prior infections[2,5]. The rapid diversification of Omicron has led to the emergence of multiple sub-lineages, including BA.2, BA.5, XBB, and BA.2.86, among others[6]. These lineages continuously evolve under selective pressures imposed by widespread immunity and antiviral interventions. The emergence of the alpha, beta, and delta SARS-CoV-2 were associated with new waves of infections, sometimes across the entire world but until this month i.e., between Nov-Dec, 2021, Delta variant reigned supreme until the emergence of a newer variant i.e., Omicron (B.1.1.529) of SARS-CoV-2[7] (Fig. no.1].

Figure. No.1: Key spike protein mutations in SARS-CoV-2



Genomic Mutations and Evolution of JN.1 and NB.1.8.1:

JN.1 Sub-Variant: JN.1 is derived from the BA.2.86 lineage, also known as "Pirola," notable for its high number of spike mutations[3,6]. JN.1 differs from its parent lineage primarily by the L455S mutation within the spike RBD, a position critical for ACE2 binding and antibody recognition[8]. Overall, JN.1 harbours over 30 spike mutations relative to the original Wuhan strain, many shared with prior Omicron sub-variants such as G446S and R346T. These mutations collectively contribute to immune evasion and increased transmissibility[9,10].

Functionally, L455S appears to enhance the spike protein's affinity for the human ACE2 receptor, increasing infectivity while allowing evasion of neutralizing antibodies[8]. Despite these changes, clinical data so far indicate that JN.1 infections tend to be mild, potentially due to robust T-cell mediated immunity and existing hybrid immunity in the population[11].

NB.1.8.1 Sub-Variant: NB.1.8.1 is a sub-lineage within the recombinant XBB lineage, which arose through recombination between two BA.2 sub-lineages[4,12]. XBB lineages have demonstrated substantial immune evasion and increased transmissibility compared to previous Omicron sub-variants[12]. NB.1.8.1 carries multiple mutations in the spike RBD that enhance cell entry efficiency and further reduce neutralization by antibodies[13].

Emerging surveillance data show NB.1.8.1 has a faster growth rate than JN.1 in several geographic areas, including India and the UK, suggesting a competitive transmission advantage[4,14]. Despite these features, clinical severity remains mild, consistent with trends observed in recent Omicron sub-variants.

Epidemiological and Clinical Implications:

Both JN.1 and NB.1.8.1 continue the trend of SARS-CoV-2 evolution favouring increased transmission and immune escape with relatively mild clinical outcomes. Their emergence in populations with high levels of vaccine coverage and prior infection highlights the virus's adaptation to immune pressures[5,15]. Continued genomic surveillance is essential to monitor these sub-variants for any changes in virulence or vaccine efficacy.

Current vaccines, including updated bivalent formulations, retain significant protection against severe disease caused by these variants, though breakthrough infections remain common[11]. Therapeutic monoclonal antibodies may have reduced efficacy against these sub-variants, necessitating ongoing assessment of treatment guidelines.

Public Health Considerations and Future Directions:

The emergence of JN.1 and NB.1.8.1 sub-variants reaffirms the virus's evolutionary adaptability and underscores the need for continuous research and policy adaptation. Several priority areas must be addressed to stay ahead in pandemic preparedness and management:

Characterizing the Full Mutational Impact of NB.1.8.1 on Viral Fitness: While preliminary data suggests that NB.1.8.1 harbours multiple spike protein mutations contributing to immune escape, a deeper understanding of how each mutation influences viral replication kinetics, infectivity, and immune evasion is essential. Structural and molecular modelling studies, along with reverse genetics, can reveal the contribution of specific mutations to viral fitness. This will assist in forecasting the public health impact and guiding therapeutic design.

Assessing Vaccine and Therapeutic Efficacy in Clinical Settings: As immune escape variants like NB.1.8.1 and JN.1 rise in prevalence, it becomes imperative to evaluate the real-world effectiveness of current vaccines, including updated bivalent or monovalent boosters. Clinical cohort studies and neutralization assays must be conducted to determine the efficacy of existing mRNA, protein subunit, and adenoviral vector vaccines. Furthermore, therapeutic monoclonal antibodies must be reassessed for neutralization capacity against these variants, as some may lose efficacy due to RBD mutations.

Evaluating Long-Term Immunity Dynamics and Potential for Reinfections: Understanding how long immunity (from vaccination or prior infection) protects against emerging sub-variants is crucial. Longitudinal immunological studies focusing on antibody waning, memory B-cell function, and T-cell responses are needed. This will help inform booster timing and vaccine update requirements, especially for high-risk populations such as the elderly and immunocompromised.

Monitoring Evolutionary Trajectories via Genomic Surveillance: A robust global and local genomic surveillance infrastructure is vital for the early detection of new variants. Surveillance data, when integrated with clinical and epidemiological metrics, allows for real-time assessment of variant transmissibility, immune escape potential, and disease severity. Public databases like GISAID and tools like Next strain must be regularly updated and analysed to track variant dynamics across regions.

Investigating Host-Virus Interaction Mechanisms in Immune-Evasive Variants: Emerging variants like JN.1 and NB.1.8.1 may alter host immune recognition pathways, especially within innate immunity and interferon signalling. Basic science studies exploring how these variants interact with host defence mechanisms can yield critical insights. Single-cell transcriptomics, proteomics, and CRISPR-based screens can help uncover how host gene expression and immune activation profiles differ in response to these variants.

Discussion:

JN.1 and NB.1.8.1 have quietly claimed headlines for December 2023. Their arrival shapes the latest twist in SARS-CoV-2s drift by announcing that widespread immunity is still a moving target. The variants tell different stories on the genetic flip-board: JN.1 pops in a conspicuous L455S that seems to glue the spike tighter to human ACE2, while NB.1.8.1 patches together a ring of RBD tweaks that help it shrug off neutralizing sera. Biologists call that convergent evolution; casual observers might just say the virus is busy.

Almost everyone who'd survived previous infections or rolled through autumn boosters now reports mild or moderate illness when reinfected with either strain. The pattern echoes earlier Omicron generations, which is at least one piece of good news. Even so, the two new cousins show such a growth edge that they keep epidemiologists glancing at the mutation map and wondering whether some future descendant might tack on extra payloads that tilt disease severity the other way. Public-health

chapters have been written on balancing act, and here's the latest revision i.e keep hospitals breathing room while steering clear of panic buttons. Communications directors are hunting phrases strong enough to remind folks that boosters and quality masks still matter, yet soft enough so the audience doesn't yawn or fling the updates into the recycle bin. In the background, the shelf life of many monoclonal therapies grows shorter with each mutation, and that reality adds pressure to the final paragraphs of pandemic playbooks.

The emergence of the JN.1 and NB.1.8.1 SARS-CoV-2 sub-variants marks a significant phase in the virus's antigenic drift, shaped by widespread global immunity. Both variants reflect different evolutionary strategies: JN.1 with a notable L455S mutation enhancing ACE2 binding, and NB.1.8.1 as a recombinant lineage optimizing immune escape through multiple RBD alterations. Their parallel rise across different geographic regions emphasizes convergent evolution driven by selective immune pressure.

Despite their increased transmissibility and immune evasion, current evidence suggests that these sub-variants are associated with relatively mild disease, especially in individuals with prior immunity. This is consistent with the trend observed in other Omicron sub-lineages. Nevertheless, their growth advantage necessitates vigilance due to the potential for future variants to acquire additional mutations impacting disease severity.

From a public health standpoint, the critical challenge lies in maintaining balance—preventing healthcare system strain while avoiding unnecessary alarm. Public communication strategies must convey the importance of continued vaccination, booster adherence, and masking in high-risk settings without inducing fatigue or complacency.

In addition, the limitations of monoclonal antibody therapies in the face of such rapidly evolving variants highlight the need for broader-spectrum antivirals and vaccines. Pan-sarbecovirus vaccine development, mucosal immunization strategies, and universal coronavirus vaccine initiatives are promising avenues that require accelerated research.

Ultimately, the evolving landscape demands an integrated One Health approach—linking genomic surveillance, immunology, clinical research, and global health policy—to effectively respond to the dynamic threat posed by SARS-CoV-2 and its future descendants.

The continued emergence of new SARS-CoV-2 sub-variants, such as JN.1 and NB.1.8.1, illustrates the virus's dynamic evolution in response to selective pressures from host immunity, vaccination, and antiviral interventions. Compared to earlier variants—such as Alpha, Delta, and the ancestral Omicron (BA.1 and BA.2)—these newer sub-lineages exhibit more refined and convergent mutations, particularly within the spike protein's receptor-binding domain (RBD) and N-terminal domain (NTD), underscoring their evolutionary sophistication.

Genomic Evolution: From Early Variants to JN.1 and NB.1.8.1

Alpha (B.1.1.7) and Delta (B.1.617.2) introduced the world to variants with enhanced transmissibility due to mutations like N501Y and P681R, which improved ACE2 binding and spike cleavage, respectively[1,2].

Omicron (BA.1) marked a quantum leap in viral evolution with over 30 mutations in the spike protein alone, particularly in the RBD and NTD, contributing to significant immune escape[3,4].

Subsequent Omicron sub-variants (e.g., BA.5, XBB.1.5) built upon this base, incorporating further mutations like F486V, R346T, and K444T, refining both immune evasion and ACE2 binding affinity[5,6].

Now, JN.1—a descendent of BA.2.86 (Pirola)—features the unique L455S mutation, which sits at a critical position in the RBD. This mutation enhances ACE2 receptor binding and may act synergistically with existing Omicron-like mutations (e.g., G446S, R346T) to bolster immune evasion while preserving infectivity[8,9]. Notably, JN.1 maintains many

BA.2.86 spike mutations but diverges in a few sites that potentially confer a transmission advantage.

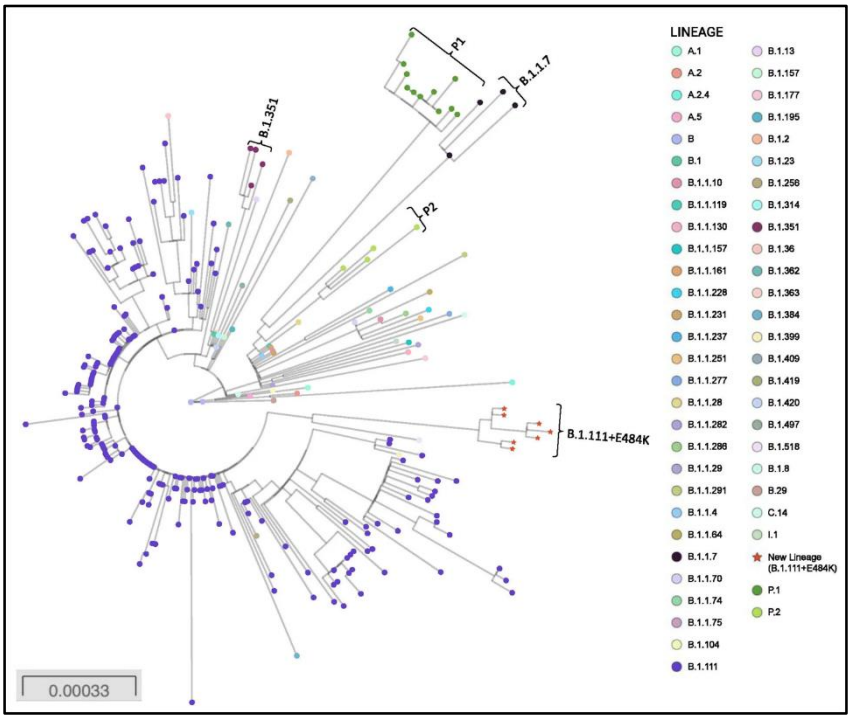
In parallel, NB.1.8.1—a sub-lineage of the recombinant XBB variant (itself a hybrid of two BA.2-derived lineages)—harbours a complex combination of mutations across the spike and non-spike regions, including those at S486P, V445P, and N460K[10,11]. These mutations are part of a pattern seen across immune-evasive Omicron variants, suggesting convergent evolution.

Comparative genomic and phenotypic features of key SARS-CoV-2 variants (Table.no.1):

Sr. No.	Variant	Key Spike Mutation	Origin / Lineage	ACE2 binding affinity	Immune escape	Disease severity	Remarks
1.	Alpha (B.1.1.7)	N501Y, P681H	UK (late 2020)	Increased	Low-moderate	Moderate	First VoC with increased transmissibility
2.	Delta (B.1.617.2)	L452R, T478K, P681R	India (2021)	Strongly Increase	Moderate	High	Caused severe wave globally
3.	Omicron BA.1	G339D, S371L, K417N, N440K, T478K, N501Y	South Africa (late 2021)	Moderate	High	Mild – Moderate	First major immune escape variant
4.	BA.2 / BA.5	L452R, F486V, R493Q reversion	Global (2022)	Increased	High	Mild	Lead to secondary Omicron wave
5.	XBB.1.5	F486P, G252V, R346T	USA/ Singapore (2022)	Strongly increased	Very high	Mild	Hybrid recombinant of BA.2 lineages
6.	JN.1	L455S, G446S, R346T, N460K	Descendant of BA.2.86	Increased	Very high	mild	Dominant globally in late 2023-2024
7.	NB.1.8.1	S486P, V445P, N460K	Recombinant of XBB*	Increased	Very high	Mild	Highly immune evasive with stable fitness

XBB* – indicates that NB.1.8.1 is descendant of XBB recombinant lineage, which itself originated from recombinant event between two Omicron sub-lineages: BJ.1 and BM.1.1. (both derived from BA.2). Thus NB.1.8.1 is a sub-sub-lineage of XBB, specifically part of XBB.1.9.2 – NB.1 – NB.1.8.1 lineage. Hence, NB.1.8.1 has evolved further from a complex of recombinant background and not from a single parental lineage like Delta or Alpha.

Figure no.2: Evolutionary tree for SARS-Cov2



Functional Implications of Genomic Changes:

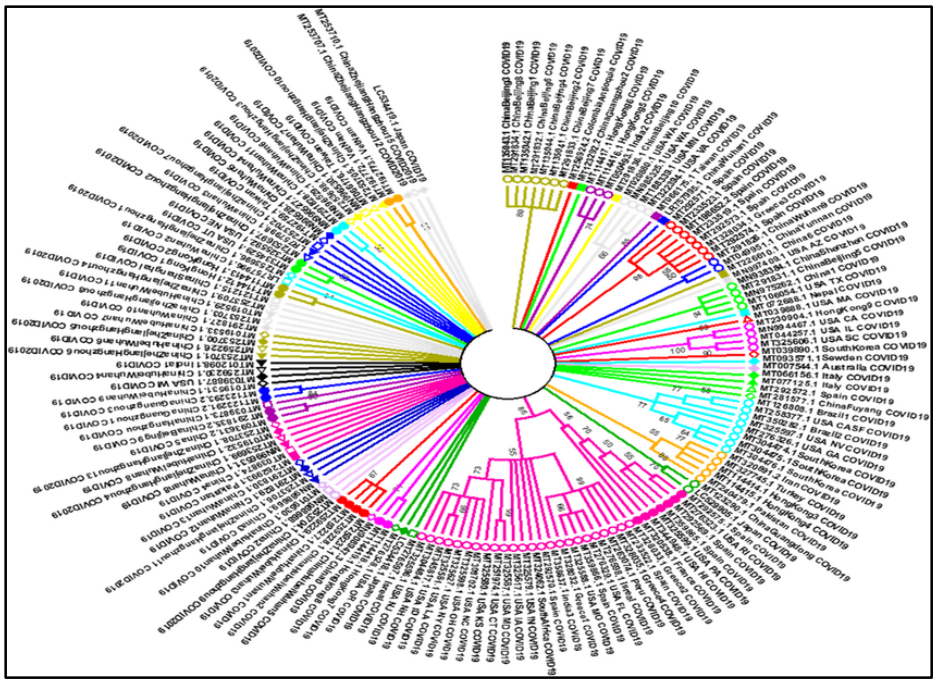
The mutations seen in JN.1 and NB.1.8.1 appear to have three primary outcomes:

A.Enhanced ACE2 Receptor Affinity: L455S (JN.1) [Fig.no.2] and S486P (NB.1.8.1) enhance spike-receptor interaction, facilitating viral entry even at lower viral loads [8,10]. This parallels earlier enhancements seen in N501Y (Alpha) and P681R (Delta) but now occur in a context of stronger immune pressure.

B.Robust Immune Evasion: Both sub-variants contain multiple substitutions at antigenic sites in the RBD (e.g., G446S, F486P, R346T) that reduce neutralization by vaccine-induced or convalescent sera[8,10]. This resembles previous patterns seen in BA.1 and XBB.1.5 but adds novel mutations that bypass memory responses formed during earlier waves.

Stability of Viral Fitness: Unlike earlier heavily mutated variants that sometimes sacrificed viral fitness, JN.1 and NB.1.8.1 appear to maintain replication efficiency while accumulating immune escape features, representing an evolutionary refinement rather than radical change.

Figure. No.3: Phylogenetic-tree-of-Covid-19 sequences from different countries



Epidemiological Patterns and Clinical Outcomes

Compared to Delta, which was associated with higher severity and hospitalization, JN.1 and NB.1.8.1—like most Omicron sub-variants—are associated with mild to moderate symptoms, particularly in vaccinated individuals or those with prior infection[12]. The current variants outpace previous ones in transmission, yet do not significantly alter hospitalization or ICU admission rates, likely due to the pre-existing hybrid immunity in the global population[13].

Additionally, the shorter incubation period and rapid community spread observed with JN.1 mirror patterns seen with XBB sub-lineages, underscoring their epidemiological advantage over earlier variants [Fig.no.3][14].

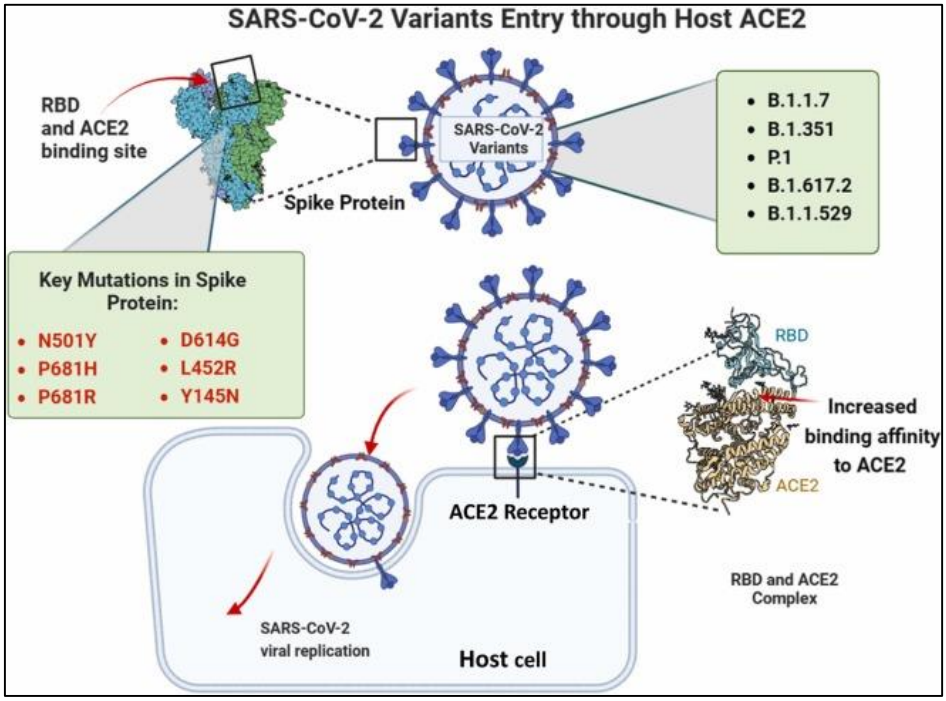
Broader Implications for Vaccines and Surveillance

The increasing antigenic distance between current sub-variants and the original Wuhan strain highlights the need for updated vaccine formulations, including monovalent Omicron-

specific and possibly pan-sarbecovirus vaccines[15]. Monoclonal antibodies that were once effective (e.g., bamlanivimab, casirivimab) now show reduced or no activity against JN.1 and NB.1.8.1, necessitating the development of next-generation therapeutics[16].

Furthermore, the rising recombination frequency (e.g., in XBB and NB lineages) suggests that future variants may emerge not just via point mutations but also through inter-lineage genetic reshuffling, complicating evolutionary forecasting and surveillance strategies.

Figure no. 4: Emerging variants to vaccines



Spike Protein Mutations in SARS-CoV-2 Variants and Their Role in Host Cell Entry: SARS-CoV-2 gains entry into host cells primarily through the interaction of its spike (S) protein with the human angiotensin-converting enzyme 2 (ACE2) receptor [Fig.no.4]. This binding process is largely mediated by the receptor-binding domain (RBD) of the spike protein. As depicted in the diagram, several variants of concern—including B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta), and B.1.1.529 (Omicron)—harbour key spike mutations such as N501Y, P681H/R, L452R, and D614G, which have been shown to enhance viral transmissibility and increase ACE2-binding affinity. These structural changes facilitate more efficient viral entry and replication within host cells. During the second wave in India, such mutations were associated with altered clinical manifestations and more severe disease progression[17]. Furthermore, emerging subvariants like JN.1 raise new concerns regarding immune evasion and reduced efficacy of previously effective monoclonal antibodies, highlighting the evolving threat posed by spike protein mutations[18].

Molecular Evolution of SARS-CoV-2 Variants: From Alpha to JN.1

The SARS-CoV-2 virus, responsible for the COVID-19 pandemic, utilizes its spike (S) protein to bind to the host ACE2 receptor, facilitating viral entry. Over the course of the pandemic, several variants of concern (VOCs), including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2 and AY lineages), and Omicron (B.1.1.529), have emerged with distinct spike protein mutations, many of which cluster around the receptor-binding domain (RBD) and are associated with increased transmissibility and immune evasion[19–21]. As illustrated in the diagram, mutations such as N501Y, E484K, K417N/T, L452R, and P681R/H are common among these variants and impact the

virus's ability to evade immune responses[22-24]. During the second wave of COVID-19 in India, a marked shift in symptomatology and severity was observed, which correlated with the rise of these mutated strains [17]. More recently, the JN.1 variant, a descendant of Omicron, has attracted attention due to additional spike protein mutations that may enhance viral fitness and reduce the efficacy of existing monoclonal antibody therapies, prompting a re-evaluation of its classification as a variant of interest (VoI) or concern (VoC)[18,25-26].

Conclusion:

The JN.1 and NB.1.8.1 sub-variants of SARS-CoV-2 illustrate the ongoing evolutionary arms race between the virus and host immune systems. While these sub-variants have achieved higher transmissibility and immune evasion, their clinical severity remains low—largely due to widespread population immunity. Continuous genomic monitoring, adaptive vaccine strategies, and a deeper understanding of host-virus interactions are essential to contain future surges and minimize public health impact. A proactive, evidence-based, and collaborative response remains the cornerstone of global COVID-19 preparedness.

The emergence of JN.1 and NB.1.8.1 as highly transmissible and immune elusive SARS-CoV-2 Omicron sub-variants underscores the virus's ongoing adaptive evolution in response to global immune pressures. While current clinical presentations remain predominantly mild—likely due to widespread hybrid immunity—their unique constellation of RBD mutations highlights potential challenges for existing therapeutic antibodies and future vaccine effectiveness. These findings reinforce the critical need for sustained genomic surveillance, iterative vaccine updates, and the development of broad-spectrum antiviral strategies. Embracing a comprehensive One Health framework that integrates genomic, immunological, and epidemiological data will be essential for timely risk assessment and responsive public health action. JN.1 and NB.1.8.1 serve as poignant reminders that SARS-CoV-2 remains a dynamic threat requiring vigilant scientific and public health engagement.

Conflict of Interest Statement:

None.

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