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Evolving immune evasion and transmissibility of SARS-CoV-2: The emergence of JN.1 variant and its global impact

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SUMMARY The continuous evolution of SARS-CoV-2 variants constitutes a significant impediment to the public health. The World Health Organization (WHO) has designated the SARS-CoV-2 variant JN.1, which has evolved from its progenitor BA.2.86, as a Variant of Interest (VOI) in light of its enhanced immune evasion and transmissibility. The proliferating dissemination of JN.1 globally accentuates its competitive superiority and the potential to instigate fresh surges of infection, notably among cohorts previously infected by antecedent variants. Notably, prevailing evidence does not corroborate an increase in pathogenicity associated with JN.1, and antiviral agents retain their antiviral activity against both BA.2.86 and JN.1. The sustained effectiveness of antiviral agents offers a beacon of hope. Nonetheless, the variant's adeptness at eluding the immunoprotective effects conferred by extant vaccines highlights the imperative for the development of more effective vaccines and therapeutic approaches. Overall, the distinct evolutionary trajectories of BA.2.86 and JN.1 underscore the necessity for ongoing surveillance and scholarly inquiry to elucidate their implications for the pandemic's evolution, which requires the international communities to foster collaboration through the sharing of data, exchange of insights, and collective scientific endeavors.

Keywords SARS-CoV-2 variants, JN.1, immune evasion, vaccine refinement, global public health

Since the emergence in late 2021, SARS-CoV-2 Omicron variant (Pango lineage designation B.1.1.529) has perpetuated successive waves of incidence on a global scale, attributable to their evolving immune evasion (*1*). Of particular concern, BA.2.86 subvariant of Omicron emerged in 2023, characterized by a markedly increased number of mutations in the spike protein when compared with its BA.2 predecessor (*2*). Moreover, JN.1 subvariant (also referred to as BA.2.86.1.1) evolving from BA.2.86 has escalated internationally since its emergence in late 2023 with notable increases in Europe and the United States (*3*).

The BA.2.86 variant, delineated as the "second generation of BA.2", is characterized by the possession of another 34 mutations in the spike protein, distinguishing significantly from both BA.2 and XBB.1.5 variants (Figure 1). These mutations are predominantly located within the N-terminal domain (NTD) and the receptor-binding domain (RBD), impacting the variant's receptor binding and immune evasion capabilities (*4*). Emerging from BA.2.86, JN.1 is characterized by an additional mutation, L455S, within the RBD of the spike protein (*5*). This mutation endows JN.1 with enhanced transmissibility and immune evasion, setting it apart from its antecedent, BA.2.86.1, as well as other variants within the XBB lineage (*6*). The *in vitro* analyses reveal that JN.1 exhibits diminished binding affinity for the human angiotensin-converting enzyme 2 (ACE2) receptor, a pivotal mechanism facilitating viral ingress into host cells (*6*). Nevertheless, JN.1 is associated with elevated infectivity relative to the BA.2.86 variant (*5*), and epidemiological modeling has elucidated that the JN.1 variant is characterized by advantageous growth and spread dynamics with a growth rate approximately 2.3 times superior to that of the EG.5.1.1 variant (*5*). Furthermore, JN.1 displayed significantly enhanced immune evasion against previous infection induced neutralization and extensive resistance against class 1, and 3 monoclonal antibodies targeting the RBD (*5*). This phenomenon underscores a sophisticated interplay between the variant's immune evasion strategies and its efficiency in receptor binding.

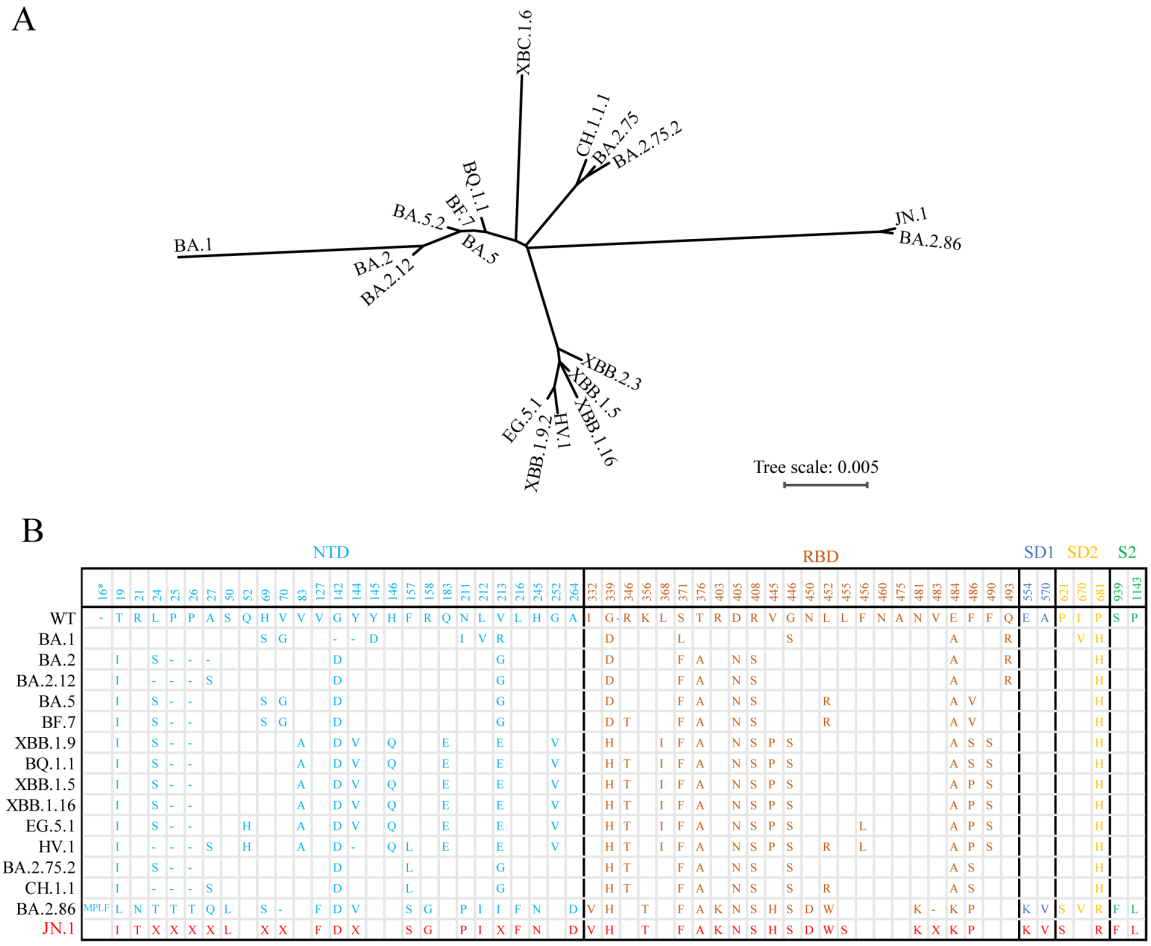

Figure 1. The phylogenetic evolution and key amino acids mutations of Omicron sub-variants. A: Phylogenetic tree of Omicron sub-variants based on spike sequences. **B:** Key amino acid mutations in the spike protein of the Omicron sub-variants.

The World Health Organization (WHO) has subsequently classified JN.1 as a Variant of Interest (VOI), positioning it within the second-tier category of its variant monitoring framework (*7*). The ascendancy of JN.1 correlates with increased detections in wastewater surveillance and a surge in hospital admissions within regions such as the Netherlands and Singapore (*8*). Numerous studies have been conducted to track the proliferation of SARS-CoV-2 through the analysis of regional wastewater samples (*9-11*). A report published by the Centers for Disease Control and Prevention (CDC) on January 5 highlighted a notable intensification in viral activity, particularly evidenced by a 27% augmentation in wastewater viral loads compared to the preceding year (*10*). Furthermore, subsequent to its initial identification in wastewater samples in Germany, JN.1 has rapidly ascended to a position of major endemic prevalence (*11*). As of January 20, 2024, a total of 78,178 JN.1 and 95,183 BA.2.86 related sequences were detected globally (Figure 2A and 2B), according to the data sourced from the cov-spectrum database (*https://cov-spectrum.org*) (*12*). Notably, JN.1 accounted for 88.6% of these sequences, and demonstrated a persistent upward trajectory with rapid spread to multiple regions around the world (Figure 2C). To date, there is no empirical evidence to suggest that the JN.1 variant is implicated in exacerbating clinical symptoms or augmenting pathogenicity (*13*). The clinical manifestations associated with JN.1 infection align closely with those observed in preceding Omicron variants, predominantly presenting as fever, cough, headache, and in many instances, asymptomatic or mild conditions (*14*). Moreover, one recent study has elucidated that antiviral agents, including paxlovid, remdesivir, and molnupiravir, retain their antiviral activity against both BA.2.86 and JN.1 (*15*).

In light of this waning SARS-CoV-2 specific immunity from infection and vaccination, particularly pronounced among the elderly demographic, the evaluation of booster vaccination strategies has been undertaken (*2,8*). Bivalent booster vaccinations have been shown to transiently augment neutralization titers, while their immunogenic potency also diminishes within a six-month timeframe (*8*). Moreover, with the rapid evolution of SARS-CoV-2 during the continuous spread, researches highlight the urgent need to update vaccine formulations in response to emerging SARS-

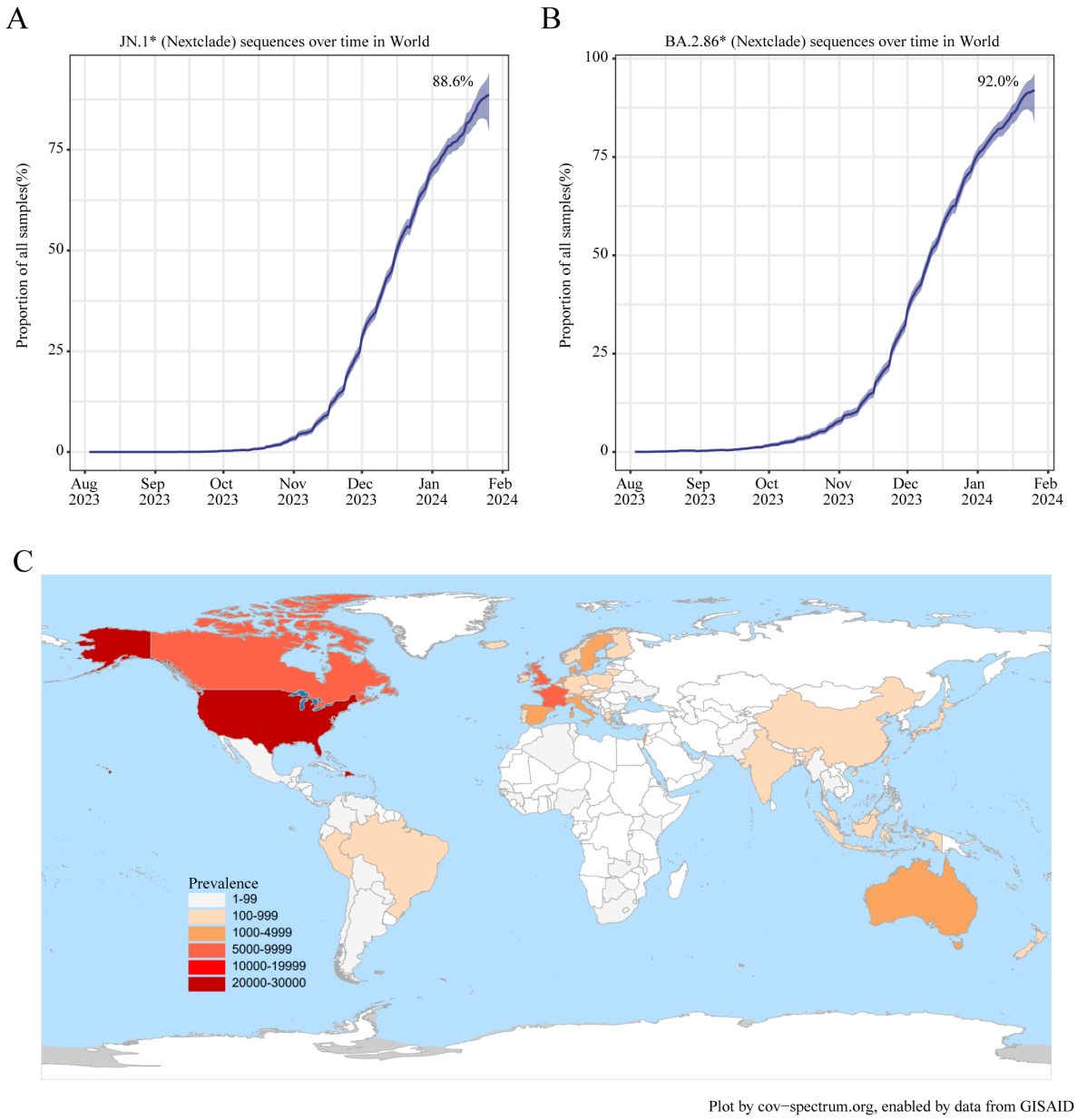

Figure 2. The global spread and prevalence of JN.1 or BA.2.86 related variants. The proportion of emerging SARS-CoV-2 variants JN.1* **(A)** and BA.2.86* **(B)**. The global geographical distribution of JN.1* prevalence **(C)**. The figure was generated by *https://cov-spectrum.org/*. *, including all the JN.1 or BA.2.86 related variants.

CoV-2 variants (*16*). The immune responses initially shaped by vaccines based on the ancestral strain are less effective against Omicron-based boosters due to immune imprinting (*17,18*). Studies in both mice and humans have shown that the efficacy of a single Omicron booster is compromised by immune imprinting, a challenge that can be addressed with a second Omicron booster (*16*). This approach not only mitigates the imprinting effect but also induces a broad neutralizing response. Further analysis revealed that individuals with repeated Omicron exposures develop mature, Omicron-specific antibodies, markedly different from those triggered by the ancestral strain, effectively reducing immune imprinting (*16*). Thus, removal of the ancestral strain component from future vaccine updates should be advocated, and it is recommended that individuals lacking prior Omicron exposure should receive two updated booster doses to enhance protection. Vaccines recently updated to target variants such as XBB.1.5 have demonstrated cross-reactivity with JN.1, intimating their prospective efficacy against emerging variants (*8*).

The distinct evolutionary trajectories of BA.2.86 and JN.1 underscore the necessity for ongoing surveillance and scholarly inquiry to elucidate their implications for the pandemic's evolution. The propensity of JN.1 to evade immune responses presents formidable challenges to extant vaccines and therapeutic antibodies, highlighting the imperative for the development of more

effective vaccines and therapeutic approaches. Moreover, the escalating prevalence of JN.1 may be attributable to factors beyond mere escape from neutralization, which merits comprehensive investigation. Therefore, in the face of persistent mutations and the proliferation of SARS-CoV-2, it is imperative for international communities to foster collaboration through the sharing of data, exchange of insights, and collective scientific endeavors.

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