oJN.1: A New Threat to Global Health

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Abstract

A new coronavirus variation known as JN.1 first appeared in Luxembourg in August 2023 and has since spread to a number of nations. It is distinguished by a high transmissibility, and it may outpace earlier Omicron waves in terms of infections, hospitalizations, ICU admissions, and fatalities. More research is required to establish the projected continued efficacy of current vaccinations, treatments, and testing. An outline of JN.1's epidemiological, clinical, and virological characteristics as well as its effects on world health are given in this brief communication.

Keywords: JN.1, coronavirus, variant, outbreak, global health

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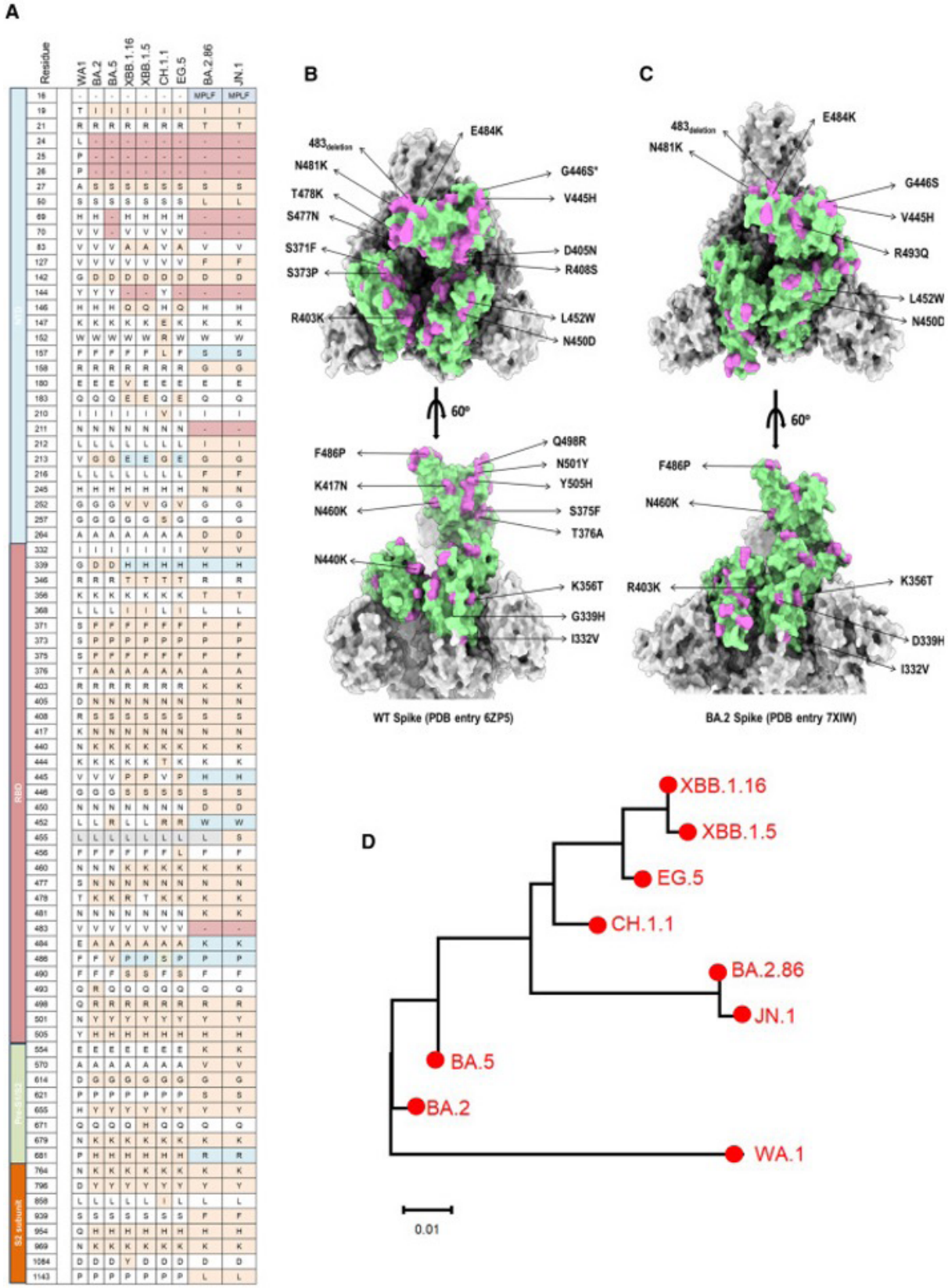
The JN.1 variant of COVID-19 is a new sub-variant that has emerged in late 2023 and has become the dominant and most transmissible strain of the virus in the world. It has currently affected more than 41 countries, and is expected to cause a bigger wave of infections and deaths than the previous ones, according to global experts. The World Health Organisation (WHO) has classified JN.1 as a variant of interest (VOI) because of its rapid spread and its ability to evade the immune system, which is causing a global surge of infections, hospitalisations, and ICU admissions (1). JN.1 was first detected in Luxembourg in August 2023 and is now present in many countries. It is derived from another VOI, BA.2.86, which was first identified in the same month. BA.2.86 is a lineage of SARS-CoV-2 that is phylogenetically distinct from the Omicron XBB variant lineages that were circulating before, such as EG.5.1 and HK.3. The genomic sequence of SARS-CoV-2 is known to code for a total of 29 distinct proteins. This set of proteins is categorized into three groups: 16 non-structural proteins that are crucial for the viral replication cycle, 4 structural proteins that form the virus particle, and 9 accessory proteins that modulate the host's cellular environment. As part of the global scientific community's response to the pandemic, researchers have determined the three-dimensional structures of these viral proteins (2). So far, over 1,228 SARS-CoV-2 experimental structures have been added to the Protein Data Bank (PDB). These entries include two different functional domain structures of the nucleocapsid (N) protein and the structures for all 16 of the non-structural proteins. Additionally, numerous structures of various protein complexes have been deposited. When these structures are compared to those of the closely related SARS-CoV, which caused the SARS outbreak in 2003, a high degree of structural similarity is observed. (2)

BA.2.86 has more than 30 mutations in the spike (S) protein, which is the part of the virus that attaches to human cells and is targeted by vaccines and antibodies. These mutations indicate that BA.2.86 has a high potential to escape the immune response and infect new hosts (3). JN.1 is similar to BA.2.86, but has one additional mutation in the spike protein, L455S, and three other mutations in non-S proteins. The Leu455Ser (L455S) mutation is a hallmark of JN.1 and is also found in HK.3 and other variants that are called "FLip" variants (3). These variants have the Leu455Phe (L455F) mutation, which is similar to L455S, but with a different amino acid change. An infection assay was conducted by Tamura er al. (4) using HIV-1-based pseudoviruses to evaluate the infectivity of different spike (S) protein mutations. The findings indicated that pseudoviruses carrying the S proteins from the B.1.1 or EG.5.1 variants demonstrated a marked increase in infectivity compared to those with the BA.2 S protein (Figure 1). However, the infectivity of pseudoviruses with the BA.2.86 S protein was found to be on par with those bearing the BA.2 S protein (4).

In order to analyse the effects of individual mutations on infectivity in more detail, Tamura er al. (4) created 33 different BA.2 derivatives, each of which included a different set of mutations identified in the BA.2.86 variant. The infectivity of the BA.2 S pseudoviruses was not significantly affected by the bulk of these alterations. However, it was shown that two mutations in the receptor-binding domain (RBD), N460K and F486P, increased infectivity. Notably, infectivity was significantly boosted by three unique mutations—F157S, N211del, and A264D—that were found in the N-terminal region of the BA.2.86 S protein. Six mutations specific to BA.2.86 increased the infectivity of BA.2, whereas sixteen mutations had the reverse impact, according to the mutagenesis assays, which revealed a complex interaction of mutations influencing infectivity. In spite of this, BA.2.86's overall infectivity was comparable to that of BA.2. This points to a possible evolutionary path for BA.2.86, in which the S gene may have mutated to avoid the humoral immunological response of the host, then acquired enhancing mutations to compensate for any infectivity lost as a result of immune evasion.

In addition to infectivity assays, the cleavage efficiency of the S protein was assessed through

Figure 1



Comparative analysis reveals mutations in the spike (S) proteins of Omicron subvariants BA.2, BA.5, XBB.1.5, XBB.1.16, CH.1.1, EG.5, BA.2.86, and JN.1, with reference to the ancestral SARS-CoV-2

Caption continues on page 8

Caption continued from page 7

strain WA1. The RBD of BA.2.86 exhibits specific amino acid changes when compared to both the original SARS-CoV-2 and BA.2. These mutations are highlighted in structural models with PDB IDs 7XIW (BA.2) and 6ZP5 (wild type). A phylogenetic tree of RBD sequences illustrates the evolutionary relationships and genetic divergence among SARS-CoV-2 WA1, its variants, and subvariants, including BA.2.86 and JN.1, with corresponding GeneBank accession numbers provided for their S protein sequences. Image credit to Liu et al. (5)

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western blot analysis of cells used for pseudovirus production (4). The results revealed that cells expressing the BA.2.86 S protein exhibited a higher band intensity for the S2 subunit compared to those expressing the BA.2 S protein. Analysis of point mutants based on the BA.2 S protein indicated that several mutations contributed to an increased cleavage efficiency of the S protein. Moreover, the level of the S2 subunit within virions pseudotyped with the BA.2.86 S protein was greater than that in virions with the BA.2 S protein. Among the BA.2-based point mutants, the three mutants—F157S, A264D, and N460K—showed not only increased cleavage efficiency in cells but also a higher incorporation of S2 protein into the viral particles released, suggesting a correlation between cellular cleavage efficiency and virion incorporation levels.

The presence of a four amino acids insertion (17MPLF) in the spike protein of JN.1 was reported by Chakraborty, (6). This insertion might enhance the transmissibility of JN.1 by compensating for the loss of eight amino acids (24LPP, 69HV, 145Y, 211N and 483V) in the spike. JN.1 was first detected in South India in December, 2023, and it was warned by scientists that it could become the dominant variant with 20–30% of all omicron infections worldwide in 2024. Lower affinity for the ACE-2 receptor but higher immune evasion than BA.2.86.1, was shown by JN.1 (6). A driving force for the higher transmission, compensating for the eight amino acids deletions, was JN1 17MPLF spike insertion. A more compact spike was predicted by SWISS-Model by Chakraborty, (6), although the surface amino acids for interaction with ACE-2 receptor were changed. The side chains of basic amino acid might interact with viral RNA for quick complete inclusion of virus into lung cells and thus might be involved in rapid spread among the people whose immunity to COVID-19 vaccines was lost considerably. More mutations and deletions and less protection to COVAXIN and COVISHILD vaccines were shown by spike protein of JN.1 along with more resistance to antibody of previously coronavirus-infected individual (6). Involvement in interaction with the ACE-2 receptor was indicated by the data for amino acids Glu484, Phe486, Gln474, Lys417, Tyr453 and Asn501 in the RBD of spike. But amino acids His442, Pro482, Lys480, Lys478 might be important in this aspect, as suggested by Chakraborty, (6) with JN.1 spike model. The first to interact were Arg346, Phe486, Lys444, Gly446, Val445 and Tyr449 (Figure 2).

A role for M-protein 3-D structure in the higher transmission of BA.2.86 and JN.1 subvariants was speculated by the finding of conserved M-protein mutations (6). A high degree of structural rigidity in a simple lipid bilayer was shown by molecular dynamics simulations and a role for M homodimers in scaffolding viral assembly was supported. An important electropositive cytosolic surface that might be important for interactions with N, S, and viral RNA was displayed by M. The charges in its surface should be changed by the D3H, A63T, A104V mutations in the M protein. NTD, TMI, TMII, TMIII and CTD were designated as the M protein domains AA 1–19, AAs 20–40, AAs 51–71 and AAs 80–100 and AAs 101–222 respectively. C-terminal Phe103, Arg107, Met109, Trp110, Arg131, and Glu135 were suggested as the common interacting residues of the M-protein with S and N proteins. However, an interacting role with Ser186 of N protein changing M-N interaction in JN.1 and BA.2.86 variants was found for Ala104 of M-protein (6).

JN.1 is believed to be associated with the second-biggest wave of infections in the US and unprecedented levels of wastewater viral load in several European countries (8). Global experts predict that JN.1 may result in a bigger wave than the previous ones, possibly exceeding the Omicron waves in 2022. Professor Christina Pagel of University College London (UCL) stated that the JN.1 wave has not yet reached its peak and may do so in mid-January, either next week or the week after. She expressed her certainty that this wave will rival or surpass the first two Omicron waves in 2022 (9). Professor Eric J. Topol of Scripps Research wrote in an opinion piece in the Los Angeles Times that JN.1 is now the main cause of infections in the US, based on the wastewater levels of the virus (8). He explained that the actual number of infections is difficult to track since most people either test at home or do not test at all, but he estimated that about 2 million Americans are getting infected each day. It was noted that several countries in Europe have reached unprecedented levels of wastewater viral load, exceeding Omicron. This allowed him to conclude that this virus variant, with its plethora of new mutations, has continued its evolution with mutations adapted for infecting or reinfecting us (10). Professor Peter Openshaw, a virus expert at Imperial College London, was quoted as saying to The Sun Health that the coming weeks could see a major surge in infections and that the wave could be bigger than anything we have seen before. A recent study by Qu et al. showed that BA.2.86 can infect cells in the lower lung and can enter cell membranes more efficiently than other versions of Omicron, raising the concern that JN.1 may have a similar or higher tendency to infect human lung epithelial cells, which could pose a serious threat to public health (11). The current vaccines, treatments and testing are expected to remain effective

Figure 2

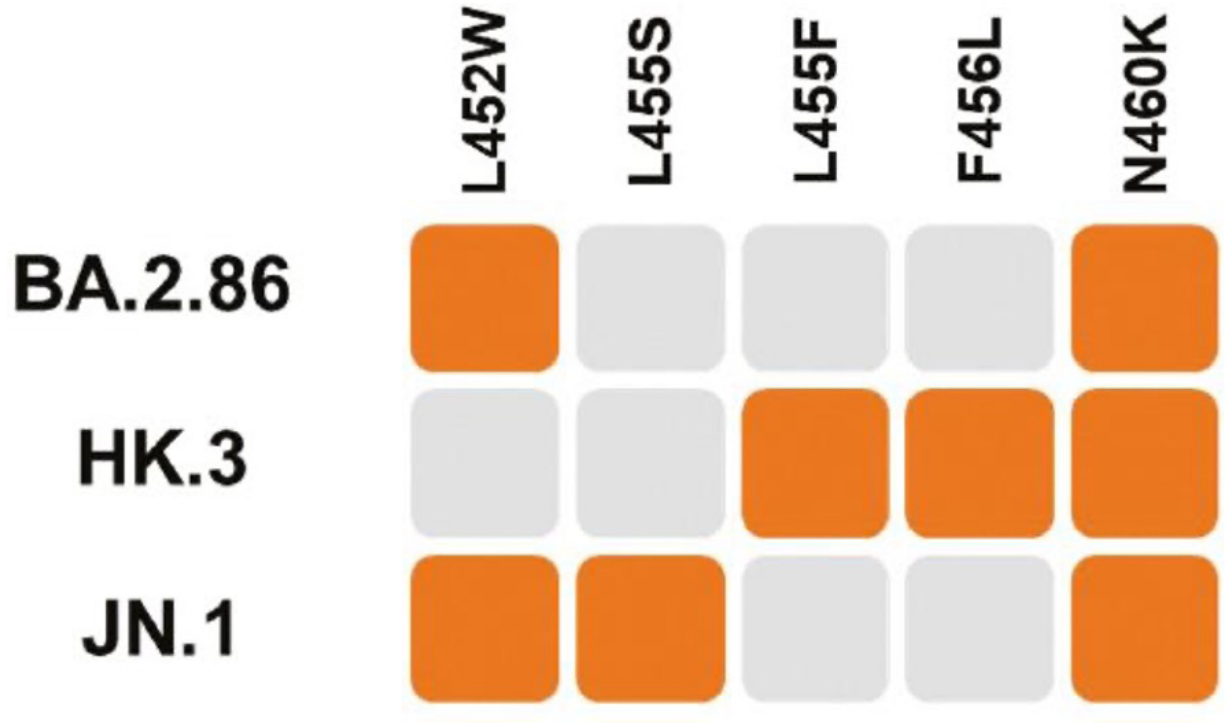

Figure 2 shows the various muations in variants of SARS-CoV-2. The orange cube shows the amino acid difference at the site between each variant and the reference strain Wuhan-Hu-1 (GenBank accession No. NC_045512.2) for the key mutations in the spike protein of BA.2.86, HK.3 and JN.1 variants, which are marked on the top. Image credit to Hang *et al.* (7)

against JN.1, but more rigorous and comprehensive studies are needed to confirm this (12). The experts advised people to take COVID-19 booster and wear masks in public again to help curb the spread of JN.1. The US Centre for Disease Control and Prevention (CDC) stated that there was only a single change between JN.1 and BA.2.86 in the spike protein, which is the part that existing vaccines target.

Another recent study by Jeworowski et al. investigated the immune escape potential of the two SARS-CoV-2 variants, BA.2.86 and JN.1 that have emerged and become dominant in different regions of the world (13). The study revealed that both variants can evade the neutralizing antibodies generated by prior infection or vaccination with earlier variants of SARS-CoV-2, such as XBB.1.5 and EG.5.1. The immune escape ability of BA.2.86 and JN.1 is comparable and significantly higher than that of the previous variants which could account for the rapid spread and prevalence of these variants in the global population. However, the study also suggested that immune escape alone may not be sufficient to explain the recent surge in JN.1 cases, as this variant does not exhibit any enhanced immune escape relative to BA.2.86 (13). Therefore, other factors, such as viral fitness, host susceptibility, and environmental conditions, may also contribute to the increased transmissibility and infectivity of JN.1.The study also compares its results with two other studies that used a different cohort of participants, who had a higher exposure to XBB variants through infection or vaccination (13). It was found that the results were not consistent with those studies, as it observes a lower level of neutralizing activity against the newer variants, including XBB.1.5, EG.5.1, BA.2.86, and JN.1, in its cohort. This discrepancy may indicate a decline in vaccine- or infection-induced immunity over time, which could pose a risk of re-infection in the coming winter months in the northern hemisphere. The study's implications are relevant for the public health response to the COVID-19 pandemic, as the emergence and spread of new variants pose a challenge for the effectiveness of vaccines, treatments, and testing (13).

Because the JN.1 variation may avoid the immune system, non-immunologic preventive measures may be the best way to stop its spread. This implies that in addition to making sure that public spaces are properly ventilated and sanitized, individuals should also practice excellent personal hygiene, which includes often washing their hands, using masks, and maintaining a safe distance from others (7). To combat the spread of the JN.1 strain, viral testing and self-isolation protocols should be reinforced in order to promptly identify and contain affected persons. Developing vaccinations or booster tactics tailored to the JN.1 strain and its distinct features will strengthen immunity against this new danger. According to the CDC, the new COVID-19 vaccinations for 2023–2024 can help the immune system block BA.2.86 and that they expect JN.1 to have a similar response and that the current treatments and testing methods remain effective against these variants. This is based on the analysis conducted by the SARS-CoV-2 Interagency Group (14)

The World Health Organization (WHO) has emphasized that the current immunizations continue to protect against serious illness and death from JN.1 and other circulating variations. The WHO has also recommended individuals to maintain current vaccination records, particularly those who are at high risk of illness. In order to lessen the spread of the virus and its variations, the WHO has also advised individuals to keep up with preventative practices including mask use, social distance, and hand cleanliness. Preliminary tests on a revised monovalent vaccination targeting XBB.1.5, subvariant, provide cross-protection against JN.1 (12). Targeting the XBB.1.5 spike protein, a novel COVID-19 vaccine has been created (12). The vaccine's ability to protect people against other newly developing viruses is presently being tested and reported. Interestingly, the vaccine can also generate strong immune responses against JN.1. A preprint study by Wang et al. shows that the vaccine can produce high levels of antibodies that can neutralize JN.1, which may help prevent serious complications of COVID-19, such as hospitalizations and deaths (15).Since SARS-CoV-2 continues to mutate and transmit, it

is critical that worldwide communities collaborate in sharing data, exchanging experiences, and undertaking scientific study to acquire a more thorough knowledge of the emerging forms. This collaborative approach will allow for faster and better judgments in implementing effective public health initiatives.

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