

SARS-CoV-2 JN.1 variant: a short review

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-stranded, positive-sense RNA virus. The SARS-CoV-2 virus is evolving continuously, and many variants have been detected over the last few years. SARS-CoV-2, as an RNA virus, is more prone to mutating. The continuous evolution of the SARS-CoV-2 virus is due to genetic mutation and recombination during

the genomic replication process. Recombination is a naturally occurring phenomenon in which two distinct viral lineages simultaneously infect the same cellular entity in an individual. The evolution rate depends on the rate of mutation. The rate of mutation is variable among the RNA viruses, with the SARS-CoV-2 virus exhibiting a lower rate of mutation than other RNA viruses. The novel 3'-to-5' exonuclease proofreading machinery is responsible for a lower rate of mutation. Infections due to SARS-CoV-2, influenza, and respiratory syncytial virus have been reported from around the world during the same period of fall and winter, resulting in a "triple-demic". The JN.1 variant, which evolved from the predecessor, the Omicron variant BA.2.86, is currently the most dominant globally. The impact of the JN.1 variant on transmissibility, disease severity, immune evasion, and diagnostic and therapeutic escape will be discussed.

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Introduction

The Centers for Disease Control and Prevention (CDC) define a variant as a viral genome (genetic code) that may contain one or more mutations [1]. Normally, RNA viruses mutate more frequently than DNA viruses. In addition, single-stranded viruses mutate more quickly than double-stranded viruses [2]. The rate of mutations among the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) varies from 1×10^{-6} to 2×10^{-6} mutations per nucleotide per replication cycle [3]. Under pressure due to vaccines and herd immunity, the SARS-CoV-2 Omicron variant produced numerous subvariants, including BA.2, BA.5, BA.2.75, XBB, and JN.1 [4]. The XBB.1.5 subvariant or "Kraken" developed from the predecessor XBB.1 by acquiring the S486P spike mutation [5]. The S486P spike mutation was uncommon throughout the pandemic because it takes two nucleotide substitutions in the same codon to shift the amino acid from serine to proline [6]. SARS-CoV-2 is a single-stranded positive-sense RNA virus (ssRNA+). The two untranslated regions (UTRs) in the genome are located at the 3'-poly-A tail and the 5'-cap structure, respectively. The genome is 29.8 kb in size with approximately 30,000 nucleotides. Other structures include the open reading frame (ORF), spike, envelope, membrane, and nucleocapsid. The ORF 1a and 1b (ORF1a and ORF1b) encode a non-structural polyprotein where spike, envelope, membrane, and nucleocapsid encode structural proteins [7]. ORF1a and ORF1b are located at the 5' end of the genome and occupy about two-thirds of the genome. They also overlap each other. The nonstructural polyproteins play a role in viral replication, transcription, and assembly processes [8]. Figure 1 shows the genomic structure of the SARS-CoV-2 gene.

The evolution of the virus may affect its transmissibility, severity of disease, and immune evasion properties. This review will describe the BA.2.86 and JN.1 variants in detail.

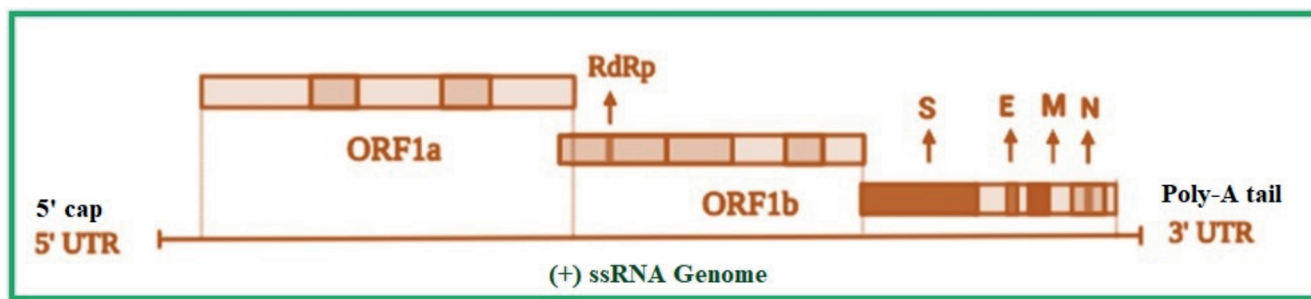


Figure 1. Genomic structure of the SARS-CoV-2 gene. Spi5' untranslated region (UTR) means 5' UTR. ORF1a means open reading frame (ORF) 1a and ORF1b means ORF 1b. 3' UTR means 3' UTR. Spike (S), envelope (E), membrane (M), nucleocapsid (N) are structural proteins.

The BA.2.86 variant

The BA.2.86 variant of Omicron was first detected in Denmark and Israel in late July 2023 [9]. It was nicknamed “pirola” for better communication on social media. The World Health Organization (WHO) designated BA.2.86 as a variant under monitoring (VUM) on August 17, 2023 [10]. The BA.2.86 carries more than 30 mutations in the spike protein compared with the BA.2 and 35 mutations distinct from XBB.1.5 [11]. The BA.2.86 variant exhibited a significant antigenic drift, increased receptor binding affinity, and less immune evasion in the sera of individuals upon XBB breakthrough infection or reinfection. This variant also showed a significantly reduced intrinsic pathogenicity in the hamsters model [12,13]. Two distinct cell lines have been employed to assess viral infectivity. The human lung epithelia type II pneumocytes are the source of the caLu-3 cell, which expresses human angiotensin-converting enzyme 2 (ACE2) receptor and the host co-factor transmembrane protease serine 2 (TMPRSS2). TMPRSS2 aids in the fusion of the virus-host membrane and subsequent infection of the airways [14]. The endolysosomal system is another mechanism of virus entry into cells. The 293T-ACE2 cells are used to assess this pathway, and they lack TMPRSS2. Zhang *et al.* found that BA.2.86 enters the caLu-3 cell lung cells efficiently in a serine- but not cysteine-protease-dependent manner [15]. This is mostly due to the presence of mutations S50L and K356T. BA.2.86 exhibited a high level of resistance against all tested therapeutic antibodies induced by non-adapted vaccines. However, when the XBB.1.5-adapted vaccine was used, antibodies considerably neutralized BA.2.86. In addition, BA.2.86 exhibits low specific infectivity, which might limit transmissibility. Specific infectivity is defined by the phenomenon of restricted virus-cell interaction [16]. According to Qu *et al.* [17], BA.2.86 had lesser immune evasive capabilities compared to XBB.1.5, EG.5.1, and Flip subvariants. Additional characteristics include the monoclonal antibody S309’s inability to neutralize BA.2.86, which is possibly caused by the D339H mutation. BA.2.86 showed a 1.9-2.8-fold higher infectivity compared to XBB.1.5, EG.5.1, and FLip ($p < 0.0001$). Since BA.2.86 is less immune-evasive compared to EG.5.1 and Flip, it failed to become the predominant variant. A few notable spike mutations detected in the pirola subvariant are I332V, R403K, D339H, V445H, G446S, N481K, N450D, L452W, 483del, E484K, and F486P. The effective reproduction number of BA.2.86 was 1.29-fold greater than that of XBB.1.5 and comparable to or even greater than that of EG.5.1 [18]. Females are more likely than males to contract the BA.2.86

infection, with a higher prevalence among those over the age of 60 [19]. Another subvariant, EG.5 (Eris), was originally reported by the WHO on February 17, 2023, and was later designated as VUM. EG.5 is a descendant of the XBB.1.9.2 variant. EG.5 differs from the parent variant in that it has an additional F456L mutation on the spike protein, whereas EG.5.1 has an additional Q52H mutation [20]. The F456L mutation helps with immune evasion. Subsequently, EG.5.1 has evolved and acquired the S:L455F mutation. The EG.5.1+S:L455F subvariant has been designated as HK.3 (XBB.1.9.2.5.1.1.3). XBB subvariants with L455F and F456L spike mutations are known as Flip variants. This is due to the switch of the two amino acids labeled F and L on the spike protein [21]. The FLippeR variants carry the K478R spike mutation, which can occur before the FLip (as in JF.1), concurrently with the FLip (as in GW.5) or acquired after the FLip (as in GK.1.4 and JR.1.1) [22]. The Flip mutation confers a growth advantage to these subvariants. The BA.2.86 variant showed considerable antigenic drift and enhanced ACE2 binding affinity. However, BA.2.86 exhibited moderate immune evasion compared to EG.5 and HK.3 [23]. Compared to the EG.5.1 variant, the L455S mutation enhanced the transmissibility and immune evasion capabilities of HK.3 and other “Flip” variants [24]. As a result, it can evade immunity more effectively than the other contemporary variants.

The JN.1 variant

The WHO identified the JN.1 (BA.2.86.1.1) subvariant in August 2023. It is a descendant of BA.2.86 [25,26]. By December 16, 2023, 7344 JN.1 sequences had been submitted to the Global Initiative on Sharing All Influenza Data (GISAID) from 41 countries, accounting for 27.1% of all globally available sequences for epidemiological week 48 (November 27 to December 3, 2023). The following countries had the highest percentage of JN.1 sequences: France (20.1%, 1552 sequences), USA (14.2%, 1072 sequences), Singapore (12.4%, 934 sequences), Canada (6.8%, 512 sequences), United Kingdom (5.6%, 422 sequences), and Sweden (5.0%, 381 sequences) [27]. On December 20, 2023, the WHO designated the JN.1 variant as a variant of interest due to its enhanced transmissibility and immune evasion capabilities [28]. The JN.1 became the most predominant variant worldwide and was the main contributor to the epidemic surge in December 2023-January 2024 [29]. Wastewater surveillance provides a cost-effective and rapid assessment of the population spread of the variants. A German study from Berlin detected SARS-CoV-2 RNA fragments in wastewater, indi-

cating the emergence of JN.1 lineages [30]. As of March 1, 2024, the JN.1 variant was projected to contribute to more than 95% of COVID-19 infections in the USA [31].

As per the GISAID report, the following mutations have been detected in JN.1 variants as of February 23, 2024. These are located in various genes. The ORF1a gene mutations include the following: S135R, A211D, T842I, P3395H, V1056L, G1307S, K1973R, N2526S, A2710T, L3027F, T3090I, T3255I, V3593F, del3675/3677, R3821K, F499L, and T4175I [32]. The ORF1b mutations are the following: P314L, R1315C, I1566V, and T2163I. ORF1a and 1b are required for the primary protease and replicase involved in the digestion of polyproteins and regulation of viral replication; mutations in these genes may affect the virus's effectiveness of replication [6].

The hallmark mutation of the JN.1 subvariant is the L455S mutation, located within the receptor-binding domain (RBD) of the spike protein [23]. The L455S is detected in JN.1 and JN.2, but not in BA.2.86 and JN.3 subvariants [33]. Other spike protein mutations include T191 I, R21T, L24S, S50L, del25/27, del69/70, V127F, G142D, del144/144, F157S, R158G, N211I, del212/212, V213G, L216F, H245N, A264D, I332V, G339H, K356T, S371F, S373P, S375F, T376A, R403K, D405N, R408S, K417N, N440K, V445H, G446S, N450D, L452W, L455S, N460K, S477N, T478K, N481K, del483/483, E484K, F486P, Q498R, N501Y, Y505H, E554K, A570V, D614G, P621S, H655Y, N679K, P681R, N764K, D796Y, S939F, Q954H, N969K, and P1143L. Besides these, there are other mutations as well. The rapid global spread and the fact that it is becoming the dominant variant indicate that JN.1 is more transmissible than the prior variants [34]. *In vitro* data clearly indicate that increased transmissibility is mainly driven by the evasion of neutralizing antibodies rather than changes in viral fitness. The L455S spike protein mutation is responsible for the JN.1 variant's high immune evasion capabilities. Kaku *et al.* assessed the reproductive number of JN.1 using genomic surveillance data from France, the United Kingdom, and Spain [24]. They reported a greater reproductive number for JN.1 compared to the BA.2.86.1 and HK.3 lineages. The JN.1 variant had shown very high growth rates at the end of November 2023. Further *in vitro* human ACE2 receptor binding assays revealed that the JN.1 variant had a considerably greater dissociation constant from the RBD than the BA.2.86 RBD lineages, indicating a lower ACE2 receptor binding affinity [24]. The L455S mutation causes a reduced binding affinity to the human ACE2 receptor. Surprisingly, the pseudovirus assay showed that JN.1 has significantly higher infectivity than BA.2.86. The authors proposed that spike stability, trimer packing, and spike dynamics contribute to the observed phenomenon. On the neutralization assay, the 50% neutralization assay (NT_{50}) value against JN.1 was similar to that against BA.2.86, and the L455S mutation had no effect on the antigenicity of BA.2.86. In addition, JN.1 demonstrated more robust resistance to monovalent XBB.1.5 vaccine sera than BA.2.86. Thus, the L455S mutation exhibits immune evasion features. This explains JN.1's increased reproductive number. Yang *et al.* from China demonstrated that the L455S mutation significantly increases immune evasion properties at the cost of reduced ACE2 binding affinity [19]. They also demonstrated that the L455S mutation contributes to immune evasion against class 1 neutralizing antibodies [23]. It outperforms not only BA.2.86, but also HV.1 (XBB.1.5+L452R+F456L) and JD.1.1 (XBB.1.5+L455F+F456L+A475V). The pseudovirus-based neutralization assay was used to assess the ability of antibodies or medications to neutralize the virus's infectiousness. They used plasma from convalescent XBB-infected patients who acquired breakthrough infection with XBB

subvariants with the S486P mutation after receiving three doses of inactivated vaccines. JN.1 demonstrated substantial immune evasion compared to BA.2.86, HV.1, and JD.1.1, as there was a 2.1-fold decrease in NT_{50} titers in individuals who were re-infected with XBB after BA.5 or BF.7 infection and a 1.1-fold decrease in NT_{50} titers in those recovering from XBB breakthrough infections. Class 1 is the most immunodominant against the RBD-targeting antibodies [35]. JN.1 has better humoral immune evasion properties than those of the competitive variants HV.1 (EG.5+L452R) and JD.1.1 (FLip+A475V). They also reported a lower ACE2 binding affinity. Immune evasion against class 1 neutralizing antibodies occurs because the Leu455Ser mutation is typically located at the epitope of the RBD of class 1 antibodies. This contrasts with BA.2.86's increased susceptibility to class 1 antibody. Based on the available literature, the WHO classified JN.1 as having a high risk of growth advantage since the variant is fast growing throughout all WHO regions. However, the levels of risk for severity and antibody escape are low and moderate, respectively [36]. The immune evasive capabilities of JN.1 due to the presence of the L455S mutation may explain the rapid global spread of this variant. This mutation significantly reduced the ACE2 binding affinity of the JN.1's RBD, explaining the immune evasion properties [37]. The L455S mutation also causes JN.1's resistance to classes 2 and 3. According to data from the CDC, there is currently no evidence that JN.1 produces a more severe disease than the past Omicron subvariant infections [25]. Neither is there any evidence to suggest that the JN.1 variant produces different symptoms from the pre-existing COVID-19 symptoms. The lack of severity could be attributed to the development of herd immunity through vaccination and natural infections. People with comorbidities would be at a higher risk of severity, as was seen earlier. Usually, all the variants show similar symptoms. In addition, the type of symptoms rather depends on the immune status of the host and the presence of comorbidities [26]. The high-risk group for JN.1 infection would be the same as before, such as elderly people, the unvaccinated, those with multiple medical conditions, and those who are immunocompromised [38]. Despite an increase in COVID-19 cases in the USA, hospitalizations and mortality rates remain considerably lower than a year before [39]. The typical symptoms of COVID-19 are fever, chills, coughing, muscle aches, shortness of breath, sore throat, congestion, headaches, fatigue, and loss of taste or smell. It is often difficult to differentiate it from other respiratory viral illnesses. Prompt testing is therefore required. The odds of hospitalization in a Danish study involving patients ≥ 65 years old showed no difference between JN.1 and the non-BA.2.86 variant [40]. The infectious phase of JN.1 is comparable to other Omicron variants that have been circulating over the past year. The period of infectiousness varies from 1 to 2 days before the onset of symptoms to at least 2 to 3 days after the symptoms appear [41].

Reverse transcription-polymerase chain reactions in real-time also revealed S-gene target failure [SGTF] in the JN.1 lineages. It is caused by a deletion in the spike protein at positions 69 and 70, and SGTF can act as a surrogate for JN.1 infection [42].

The National Institutes of Health, USA, updated the COVID-19 treatment guidelines in February 2024, recommending ritonavir-boosted nirmatrelvir (paxlovid) therapy in non-hospitalized adults with mild-to-moderate COVID-19 infection who are at high risk of progression to severe COVID-19 disease [43]. Even though the JN.1 variant has many mutations, the Infectious Disease Society of America suggests that paxlovid is still expected to offer protection by reducing the severity of infection in high-risk groups. However, real-world data is required to evaluate the impact of therapeutics on

JN.1 infection outcomes [38]. Paxlovid must be taken as soon as possible after symptom onset, preferably within 5 days of symptom onset. Vaccines are designed to replicate the spike protein component. Spike protein mutations may reduce the efficacy of vaccines. Link-Gelles *et al.* reported that the overall vaccine effectiveness (VE) among adults aged ≥ 18 years was 54% [95% confidence interval (CI)=46-60%] at a median of 52 days after vaccination [42]. The VE 60-119 days after vaccination in the SGTF and non-SGTF groups were 49% (95% CI=19-68%) and 60% (95% CI=35-75%), respectively. Therefore, the VE is lower against the non-JN.1 variants. A non-peer-reviewed study by Wang *et al.* showed VE of the XBB.1.5 monovalent mRNA vaccine in uninfected individuals by boosting the serum virus-neutralization antibodies against the XBB.1.5 (27.0-fold), EG.5.1 (27.6-fold), and HV.1, HK.3, JD.1.1, and JN.1 (13.3-to-27.4-fold) subvariant [44]. Werkhoven *et al.* from the Netherlands, had shown a VE of 70.7% (95% CI=66.6-74.3) against hospitalization and 73.3% (95% CI=42.2-87.6) against intensive care unit admission in high-risk populations during a period of BA.2.86 and JN.1 circulation [45]. Chalkias *et al.* published the reactogenicity and immunogenicity of SARS-CoV-2 XBB-containing vaccines mRNA-1273.815-monovalent (50- μ g Omicron XBB.1.5-spike mRNA) and mRNA-1273.231-bivalent (25- μ g each Omicron XBB.1.5- and BA.4/BA.5-spike mRNAs) vaccines [46]. They measured the immunogenicity results 29 days post-vaccination and found robust, diverse antibody responses against more recent JN.1 variants with XBB.1.5-containing mRNA-1273 vaccines. Huijberts *et al.*, in a pre-print data of a prospective cohort study conducted in the Netherlands from October 2023 to January

2024, assessed the VE of the XBB.1.5-containing vaccine against Omicron XBB and JN.1 infection [47]. They reported a VE of 41% (95%CI=23-55) in 18-59-year-olds and 50% (95% CI=44-56) in 60-85-year-olds, respectively. On September 12, 2023, the CDC Advisory Committee on Immunization Practices recommended COVID-19 vaccination with a monovalent XBB.1.5-derived vaccine for all individuals aged ≥ 6 months to prevent severe disease [43]. Tables 1 and 2 show the characteristics of the BA.2.86 and JN.1 subvariant.

Conclusions

The SARS-CoV-2 variants have been undergoing continuous evolution. Detecting new variants is not a surprising phenomenon. However, new variants may pose a constant threat to public health. It requires continuous vigilance and surveillance, including molecular surveillance. At present, there is no evidence of a severe disease caused by the JN.1 variant. The severity of infection due to the new variant is likely to be low due to the acquisition of herd immunity in many geographical areas and good vaccine coverage. There is a need to emphasize COVID-appropriate behaviors time and again. Prompt triaging and respiratory isolation, coupled with rapid detection of the variant, are equally important. International co-operation regarding the exchange of genomic data, proper vaccine distribution, and updating management protocols is equally important. An attempt should be made to predict the development of a new variant at the earliest. In addition, evaluations of existing drugs and vac-

Table 1. Characteristics of the BA.2.86 subvariant.

Characteristics	The BA.2.86 variant or "pirola" first identified in July 2023 It carries more than 30 mutations in the spike protein compared to BA.2 Variants under monitoring Significant antigenic drift
Key mutations	I332V, R403K, D339H, V445H, G446S, N481K, N450D, L452W, 483del, E484K, and F486P
Reproductive number	Reproductive number of BA.2.86 1.29-fold greater than that of XBB.1.5 and EG.5.1
Receptor binding affinity	Increased receptor binding affinity
Transmissibility	Somewhat transmissible
Infectivity	Higher fusogenicity and infectivity compared to XBB variants in CaLu-3 cells Low specific infectivity Exhibits 1.9-2.8-fold higher infectivity compare to XBB.1.5, EG.5.1 and Flip ($p < 0.0001$)
Immune evasion	Less immune evasive compared to FLip and other XBB variants

Table 2. Characteristics of JN.1 subvariant.

Characteristics	The JN.1 subvariant identified in August 2023 World Health Organization designated JN.1 variant as a variant of interest
Key mutation	Leu455ser mutation on spike protein
Receptor binding affinity	Lower receptor binding affinity
Transmissibility	More transmissible than the prior variants
Infectivity	Significantly higher infectivity than BA.2.86
Reproductive number	Higher reproductive number compared to BA.2.86.1 and HK.3 lineages
Immune evasion	High immune evasion capabilities compared to BA.2.86
S-gene target failure (SGTF)	Has been detected in JN.1 subvariant. It occurs due to a deletion in the spike protein at position 69 and 70 ³⁷
Therapeutic and vaccine efficacy	Ritonavir-boosted nirmatrelvir (paxlovid) are expective to be effective Overall vaccine effectiveness among adults aged ≥ 18 years 60-119 days post-vaccination in the \geq SGTF group was 49% (95% confidence interval=19-68%)

cines against the new variants should be done. Vaccine adaptation should also be called for if required in the future. The updated vaccine booster dose should be administered, particularly in the high-risk group. Continuous effort should be made to increase vaccination coverage, particularly among the high-risk group. Vaccine hesitancy should be reduced by continuous public awareness. Proper information, education, and communication should be provided when required in order to reduce panic among the public. We have to remember that the SARS-CoV-2 virus is going to stay for a longer period. In the future, we will get many more variants.

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