THERAPEUTIC ADVANCES in
Infectious Disease

Review

The JN.1 variant of COVID-19: immune evasion, transmissibility, and implications for global health

Ther Adv Infect Dis

2025, Vol. 12: 1–13

DOI: 10.1177/20499361251314763

Araj Naveed Siddiqui, Imshaal Musharaf and Bashar Haruna Gulumbe

***Abstract*:** The emergence of the COVID-19 JN.1 variant has raised global health concerns as it gains prevalence in several regions worldwide. First identified in August 2023, JN.1 evolved from the Omicron lineage's BA.2.86 subvariant. Patients infected with JN.1 commonly exhibit symptoms such as sore throat, fever, dry cough, nausea, and vomiting. While the World Health Organization has labeled JN.1 a Variant of Interest, it currently presents a low global health risk. However, its increased transmissibility, particularly in cold, dry climates, is concerning. This review provides a comprehensive overview of JN.1's biological characteristics, epidemiology, transmissibility, immune evasion, and the efficacy of existing antiviral treatments and vaccination strategies. A literature search across key databases targeted studies from January 2023 to August 2024, emphasizing recent insights into JN.1's spread and clinical impact. Findings reveal that JN.1 exhibits higher infectivity and immune evasion than previous variants, largely due to the L4555 mutation. From November 2023 to March 2024, JN.1 showed an increasing trend in transmission. Previously approved antivirals, including Paxlovid, Veklury, and Lagevrio, demonstrate effectiveness against JN.1, and current vaccines still protect against severe illness from this variant. However, vaccination rates remain low. Monitoring efforts include genomic assessments, wastewater surveillance, and digital tracking to contain the variant's spread. It is essential to encourage the public to maintain vaccination and preventive measures to reduce JN.1's impact. Continued research is critical for understanding and managing the evolving landscape of COVID-19 and its emerging variants.

Plain language summary

The COVID-19 JN.1 variant: How it spreads, escapes immunity, and what it means for global health

The COVID-19 JN.1 variant has raised global health concerns as it spreads in many regions. First identified in August 2023, JN.1 developed from the Omicron variant's BA.2.86 subvariant. People infected with JN.1 often experience symptoms like sore throat, fever, dry cough, nausea, and vomiting. While the World Health Organization considers JN.1 a Variant of Interest, it currently poses a low risk to global health. However, its ability to spread more easily, especially in colder and drier climates, remains a concern. This review provides a detailed overview of JN.1's characteristics, including how it spreads, its ability to evade immunity, and the effectiveness of current treatments and vaccines. We examined studies from January 2023 to August 2024 to gather the latest insights on JN.1. Findings show that JN.1 is more infectious and better at evading immune defenses than previous variants, largely due to a specific mutation known as L4555. The spread of JN.1 increased between November 2023 and March

Correspondence to:
Bashar Haruna Gulumbe
Department of Microbiology, Faculty of Science, Federal University Birnin-Kebbi, PMB, 1157, Birnin Kebbi, Kebbi State, Nigeria
bashar.haruna@fubk.edu.ng

Araj Naveed Siddiqui
Imshaal Musharaf
Jinnah Sindh Medical University, Karachi, Sindh, Pakistan

2024. Current antiviral medications, such as Paxlovid, Veklury, and Lagevrio, remain effective against JN.1, and existing vaccines still protect against severe illness. However, vaccination rates remain low, which makes the spread of JN.1 harder to control. Efforts to monitor the variant include genomic analysis, wastewater testing, and digital tracking. Encouraging the public to stay updated with vaccinations and preventive practices is essential in controlling JN.1. Continued research is also crucial to better understand and manage COVID-19 and its evolving variants.

Keywords: COVID-19, COVID-19 variants, Global health, infectious disease, JN.1, pandemic, vaccination

Received: 29 June 2024; revised manuscript accepted: 2 January 2025.

Introduction

The first case of SARS-CoV-2 was documented in December 2019 in Wuhan, China.[1] Subsequently, virus transmission quickly escalated, leading to the COVID-19 pandemic. Viruses such as SARS-CoV-2 evolve over time due to changes in their genetic code brought about by viral recombination or mutations during genome replication. This evolution has resulted in novel variants that differ significantly from the original strain.[2] The World Health Organization (WHO) categorizes COVID-19 variants under three classifications: Variants under Monitoring (VUM), Variants of Interest (VOI), and Variants of Concern (VOC). The term VUM describes a variant that requires vigilant surveillance, as it poses a greater threat to global health compared to other circulating variants. A VOI refers to a variant with acquired changes that impact its behavior or influence on public health, specifically one with increased infectivity compared to other circulating variants, indicating a potential emerging threat. On the other hand, a VOC, in addition to meeting the definition of a VOI, satisfies at least one of the following criteria: it may negatively impact illness severity, significantly affect healthcare system capacity to treat COVID-19 or other diseases—necessitating major public health measures—or reduce the effectiveness of current vaccines in preventing serious illness caused by the variant.[3] The SARS-CoV-2 variants are classified into alpha, beta, gamma, and delta based on their time of emergence, with newer additions including Omicron parent lineages like BA.1 and various other strains with the F456L mutation.[3,4]

A novel COVID-19 variant, JN.1, emerged in August 2023 and quickly dominated other strains. This variant represents a new chapter in the COVID-19 pandemic, raising concerns about the current state of COVID-19 management.[5,6] The advent of the winter season has been accompanied by the co-circulation of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and similar pathogens, potentially increasing the burden of respiratory illnesses. The rapid spread of the JN.1 variant and its parent strain, BA.2.86, suggests a potential for heightened transmissibility, which could overburden healthcare systems and lead to economic challenges.[7,8] A rise in mortality of 10.5% was observed, while the United States saw an 8.7% increase in hospital admissions in the week ending September 2, 2023.[5] This situation further emphasizes the need to assess JN.1's impact on global health.[5]

The WHO labeled JN.1 as a VOI on December 19, 2023, though it is considered to pose a minimal risk to global public health.[9] A study in Belgium involving patients aged 65 and over found that hospitalization rates were similar for JN.1 and non-BA.2.86 variants.[10] Nevertheless, transmissibility remains a concern, as preliminary data suggest increased spread compared to earlier strains, especially in cold, dry conditions. The holiday season, with increased international travel, further complicates containment efforts.[9]

With the persistent evolution of SARS-CoV-2, each emerging variant brings new challenges to global health, requiring an adaptive response to

mitigate risks effectively. This review examines the JN.1 variant, a recent and increasingly prevalent strain, detailing its unique biological attributes, transmissibility, immune evasion capabilities, and current management strategies. Through the synthesis of recent insights into JN.1's epidemiology, vaccine response, and antiviral efficacy, this review aims to deepen understanding of the COVID-19 variant landscape and inform targeted surveillance and proactive global health strategies essential to minimizing potential impacts

Methodology

Literature search strategy

We conducted a focused search of peer-reviewed literature on the JN.1 variant of COVID-19 using Scopus, PubMed, and MEDLINE, targeting studies published between January 2023 and August 2024. Our search aimed to capture the most current insights on the JN.1 variant's emergence, biological characteristics, transmissibility, immune evasion potential, and clinical impact. We included studies and reviews specific to the JN.1 variant or those discussing COVID-19 variants within the Omicron lineage (BA.2.86 and related sublineages) to establish a well-rounded perspective on JN.1's context and implications. To maintain focus, our selection criteria prioritized studies with robust data and relevance to the objectives of this review. Our search strategy used keywords such as "JN.1 COVID-19 variant," "BA.2.86," "SARS-CoV-2 Omicron variants," "COVID-19 transmissibility," "immune evasion mutations," "antiviral efficacy," and "vaccination response," employing Boolean operators (AND, OR) to ensure comprehensive yet relevant coverage.

Data extraction and synthesis

We extracted key data from selected studies, including mutation profiles, epidemiological data, clinical characteristics, and outcomes related to antiviral and vaccine effectiveness against JN.1. To ensure coherence with the discussion, we synthesized these findings to provide a comprehensive view of JN.1's implications for global health, integrating them directly into the manuscript. Additionally, a summary list of included studies has been added in the appendix to enhance transparency.

Distinct viral characteristics: Increased infectivity and immune evasion

JN.1 continues the progeny of the BA.2.86 variant, categorizing within the Omicron lineage as illustrated in Figure 1.[11] The spike protein of JN.1 has accumulated over 30 mutations, a surface protein of SARS-CoV-2 that facilitates attachment, with the addition of a novel mutation, L455S.[12] The mutation is based on the receptor-binding motif (RBM) within the receptor-binding domain of the S protein, which is deemed essential for the viral spike to bind effectively to human ACE2 located on the epithelial cell of the host.[13] Therefore, it has been indicated that JN.1 demonstrates consequential decreased RBD-binding affinity to human ACE2 in contrast to BA.2.86, while it exhibits considerably greater infectivity.[14] This hinders the competence of antibodies to effectively attach to the virus and thwart infection. In addition, the mechanism of the arrival and replication of JN.1 in our cells differ as well. Recent laboratory research conducted in Europe and the States established that BA.2.86 invades lung cells analogous to pre-Omicron variants like delta, showcasing its ability to evade the immune system while evolving to find different ways to infect cells and transmit effectively.[12] Hence, it is evident that the newly added L455S mutation has made JN.1 one of the most immunologically evasive variants, facilitating its rapid spread globally. Chronic infections are one of the potential causes of these mutations as they remain unresolved in the body for a long duration, facilitating the emergence of these transformative variants. In persistently inflicted people, the virus quietly undergoes testing and acquires mutations that aid its evasion from the immune system, ensuring its survival in that person.[12] Transmission of the virus occurs through inhalation of air-borne droplets or by touching contaminated surfaces.[15] Even though it is less likely to cause severe disease, certain groups such as the elderly, obese, and those with comorbidity are more vulnerable to JN.1.[9] In the elderly population, immunosenescence and comorbidities can weaken the efficacy of the immune response.[16]

Mechanism of action of the JN.1 variant

The mechanism of action for the SARS-CoV-2 JN.1 variant largely mirrors that of other COVID-19 variants, with evolved features enhancing infectivity and immune evasion. Viral entry is

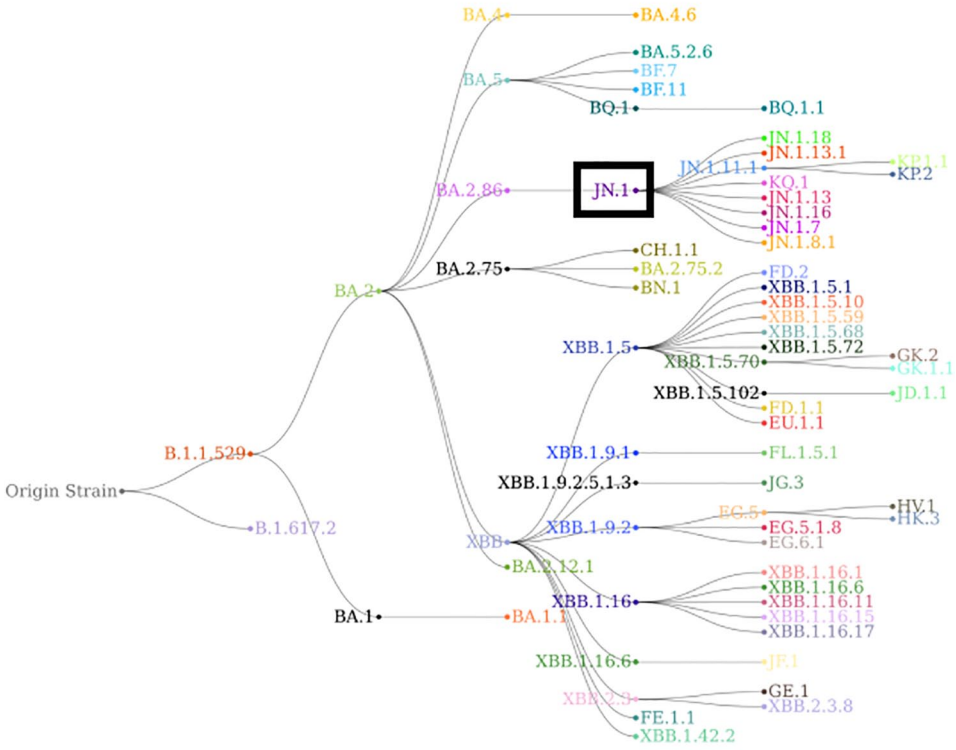

Figure 1. The illustration depicts the relationships among the lineages of SARS-CoV-2 as tracked by the CDC's COVID Data Tracker. The box in the image highlights the evolution of the JN.1 variant from the BA.2.86 variant, which itself evolved from BA.2, categorizing it within the Omicron lineage. This visual representation emphasizes the ongoing changes in the genetic makeup of SARS-CoV-2. Materials developed by CDC.[11]

facilitated by the trimeric spike (S) protein, specifically through its S1 and S2 subunits. The S1 subunit contains the receptor-binding domain (RBD), which binds to the ACE2 receptor on host cells. Initially in an "all-down" conformation, the RBD must transition to an "up" state to effectively bind ACE2.[17]

Upon ACE2 binding, the spike protein undergoes a conformational shift, moving progressively from one RBD-up to two and then three RBD-up states. This activation triggers the host protease furin to cleave the spike protein into its S1 and S2 subunits during viral entry. Subsequently, a second cleavage at the S2' site—mediated by host proteases like TMPRSS2 or cathepsin—activates the fusion capacity of the spike protein. This fusion allows the viral envelope to merge with the host cell membrane, permitting the viral genome to enter the cytoplasm and hijack the host's machinery to replicate.[17–19]

In addition to enhanced binding affinity, JN.1 exhibits advanced immune evasion mechanisms, likely contributing to its increased transmissibility and rapid spread. These adaptations highlight the potential of JN.1 to evade immune responses, expediting infection propagation. Figure 2 summarizes the mechanism of action of JN.1.

Global impact of JN.1 and COVID-19

Since the beginning of the COVID-19 pandemic in 2019, the WHO has recorded over 775 million cases of COVID-19 globally.[20] Most cases were reported from the United States (103.4 million), China (99.3 million), India (45 million), France (39 million), and Germany (38.4 million).[20] To date, COVID-19 has caused over 7 million deaths worldwide.[20] According to the WHO, the first COVID-19 vaccine was introduced on July 22, 2020.[20] Currently, 67% of the global population has received a full primary course of COVID-19

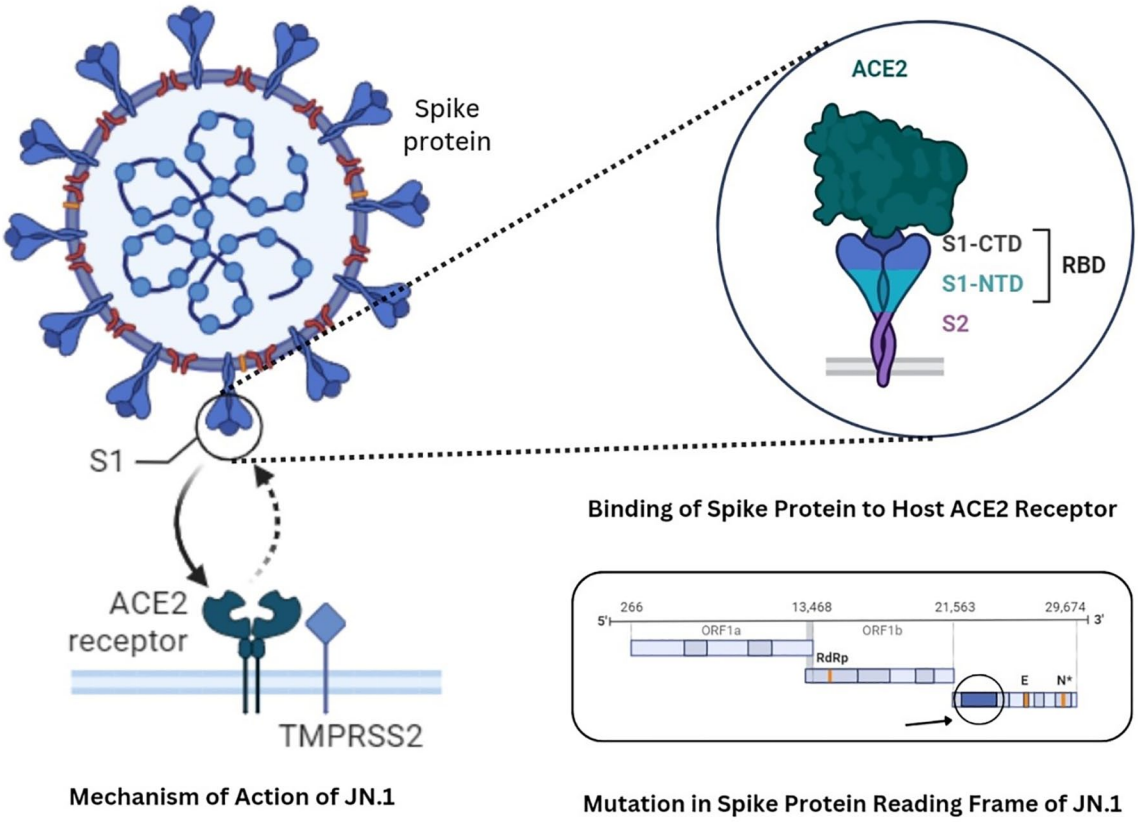

Figure 2. The figure illustrates the mechanism of action of JN.1, focusing on the critical interaction between the viral spike protein and the host ACE2 receptor. It depicts the mutated spike protein responsible for enhanced infectivity of JN.1.
Source: Created in https://www.biorender.com.

vaccination, and 32% have further enhanced their immunity with at least one booster dose, totaling 13.5 billion doses distributed.[20]

The currently circulating VOIs include JN.1, BA.2.86, EG.5, XBB.1.16, AD XBB.1.5, XBB.1.16, and EG.5.[5] Among these, JN.1 has established itself as the dominant strain worldwide.[21] The earliest samples of JN.1 were documented on August 25, 2023.[20,22] JN.1 appeared on the CDC's COVID Tracker as a distinct variant from its parent lineage on December 8, 2023.[11,23] Variants with a weighted estimate of <1% are combined with their parent lineage on the CDC's Nowcast.[23] This indicates that the proportion of JN.1 variants based on genomic sequencing results was significant enough for it to be identified separately from its parent lineage.[11,23]

Here, we present statistics related to COVID-19 and the JN.1 variant, as documented by the Weekly Epidemiological Record (WER) published by the WHO, covering data from November 2023 onward. This resource tracks epidemiological data on outbreaks, communicable diseases, and emerging or re-emerging diseases of global health significance.[24] The WER primarily monitors disease trends using a system known as epidemiological weeks, a standardized week-counting approach that enables data comparisons across years.[25]

According to the data shared by the Weekly Epidemiological Record (WER) from November 20, 2023, to December 17, 2023, indicated a 52% increase in new COVID-19 cases (>850,000 new cases), while COVID-19-related deaths decreased by 8% (>3000 new deaths) compared

to the previous month.[26] During this period, COVID-19 hospitalizations rose by 23% (>118,000 new hospitalizations), and ICU admissions increased by 51% (>1600 new ICU admissions).[26] JN.1 accounted for 27.1% of SARS-CoV-2 genomic sequences in epidemiological week 48, compared to 3.3% in week 44.[26] The highest numbers of JN.1 sequences in week 48 were reported from France (20.1%, 1552 sequences), the United States (14.2%, 1072 sequences), Singapore (12.4%, 934 sequences), Canada (6.8%, 512 sequences), the United Kingdom (5.6%, 422 sequences), and Sweden (5.0%, 381 sequences).[27]

From December 11, 2023, to January 7, 2024, the WHO reported a 4% increase in new cases (>1 million) and a 28% decrease in new deaths (>8,700).[28] Hospitalizations and ICU admissions rose by 40% (>173,000) and 13% (>1,900), respectively, and JN.1 sequences further increased to 65.5% in week 52.[28] By week 2 of 2024, JN.1 constituted 77.1% of sequences, which increased to 88.2% by week 5.[29] JN.1 was detected in 99 countries, making it the most prevalent VOI to date, while its parent strain, BA.2.86, declined to 3.7% from 5.4% in week 2 of 2024.[29] Between January 8 and February 4, 2024, new cases and deaths decreased by 58% (>503,000 new cases) and 31% (>10,000 new deaths).[29] Additionally, new hospitalizations and ICU admissions fell by 32% (>119,000) and 38% (>1500), respectively.[29] By week 4, JN.1 was the dominant VOI in all four WHO regions, with a prevalence of 91.7% in the European region, 86.0% in the Americas, 83.3% in South-East Asia, and 71.1% in the Western Pacific.[30]

From February 5 to March 3, 2024, WHO reported further decreases in new cases (44%, >292,000), deaths (51%, >6200), hospitalizations (34%, >78,000), and ICU admissions (61%, >500).[31] In week 9, JN.1 constituted 90.3% of total sequences, up from 89.4% in week 6, with reports from over 115 countries.[31] Between March 4 and March 31, 2024, there were additional declines in new cases (11%, >275,000), deaths (41%, >4200), hospitalizations (44%, >49,000), and ICU admissions (46%, >1200), though clinical detection and wastewater surveillance indicated an underestimation of COVID-19 burden by 2 to 19-fold.[32] By week 13, JN.1 was reported in 121 countries, making up 95.1% of total SARS-CoV-2 sequences, a rise from 93.0% in week 10.[32]

In the United States, JN.1 quickly became the most widespread variant, accounting for 83.7% of all circulating variants according to the latest CDC estimates.[17,21] Wastewater surveillance and test positivity—measures of asymptomatic and symptomatic COVID-19 infections—were approximately 27% and 17% higher, respectively, than the previous year.[21] Hospitalizations, emergency visits, and COVID-19-related mortalities increased, though these were 22%, 21%, and 38% lower, respectively, than the corresponding period last year.[21] These findings suggest that, despite JN.1's increased infectivity and rapid spread, illness severity has decreased, likely due to improved immunity from prior infections, vaccinations, or both.[21]

Clinical presentation

At present, it is uncertain how symptoms may vary specifically with JN.1.[23,33] However, COVID-19 symptoms are generally consistent across diverse variants.[33] The virus exhibits symptoms similar to most respiratory diseases, which complicates diagnosis.[33] The incubation period ranges from 2 to 14 days.[34,35] Patients infected with JN.1 may experience symptoms such as pharyngitis, fever, rhinorrhea or nasal congestion, persistent dry cough, fatigue, headache, loss of taste, loss of smell, muscle pain, conjunctivitis, diarrhea, and vomiting.[35] A more serious respiratory symptom to monitor is shortness of breath, which warrants prompt medical attention.[33] Patients infected with the JN.1 variant may experience more severe muscle fatigue and exhaustion compared to typical COVID-19 cases.[36,37]

Mild symptoms can often be managed with symptomatic care and do not require immediate medical attention.[2] The severity of symptoms depends more on the patient's health status and immunity than on the specific variant causing the infection.[23] Due to increased immunity from vaccinations and prior infections, the JN.1 variant is less likely to cause severe manifestations compared to previous strains.[21,38]

Table 1. Common antiviral medications effective against JN.1 and their characteristics.[43,44–46]

Brand name	Generic name	Route of administration	Mechanism of action	Age	Golden time
Paxlovid	Nirmatrelvir and Ritonavir	Oral	3Cl protease inhibitor	Adults and children (⩾12 years old)	Promptly; within 5 days after the onset of symptoms
Veklury	Remdesivir	Intravenous (IV)	RNA-dependent RNA polymerase (RdRp) inhibitor	Adults and children	Promptly; within 7 days after the onset of symptoms
Lagevrio	Molnupiravir	Oral	RNA-dependent RNA polymerase (RdRp) inhibitor	Adults	Promptly; within 5 days after the onset of symptoms

Management of the JN.1 variant: Diagnosis, treatment, and sensitivity to monoclonal antibodies

COVID-19 diagnostic tests can detect an infection by SARS-CoV-2; however, these tests cannot specify the causative variant.[39] The polymerase chain reaction (PCR) test, a type of nucleic acid amplification test (NAAT), is considered the gold standard for COVID-19 diagnosis.[40] In addition, antigen tests can be used; while they provide quick results, they are generally less reliable than PCR tests.[34] Patients may visit a nearby testing center or use self-testing kits.[40]

Treatment strategies for JN.1 align with established COVID-19 protocols, including antiviral medications, conservative management, and oxygen therapy for severe cases.[41] Approved oral antivirals for COVID-19 (Table 1), such as Paxlovid, Remdesivir, and Molnupiravir, have demonstrated efficacy against JN.1 and BA.2.86 strains.[42] It is recommended that these medications be initiated within five to seven days after symptom onset.[43]

Paxlovid, a novel oral antiviral medication, is used as a first-line treatment for new COVID-19 strains, including JN.1.[47,48] It combines two medications, nirmatrelvir and ritonavir, and has shown promising efficacy and safety against SARS-CoV-2.[49,50] It is particularly beneficial for patients with immunocompromised conditions and neurological or cardiovascular comorbidities.[44] Given the novelty of the drug, there is limited data on its potential adverse effects and long-term efficacy.[49] However, a few studies have reported typical side effects, such as diarrhea, nausea, headache, altered taste, muscle pain, and increased blood pressure.[46,49] Other frontline antivirals for treating JN.1 include Remdesivir (Veklury), administered intravenously over three consecutive days in a healthcare setting, and Molnupiravir (Lagevrio), which is taken orally.[39,42] Table 1 provides an overview of common antiviral drugs effective against JN.1 and their characteristics.

Apart from antiviral drugs, JN.1 has shown resistance to neutralization by most monoclonal antibodies (mAbs). Monoclonal antibodies targeting the spike protein are categorized into four distinct groups (I, II, III, and IV) based on their receptor-binding configurations. Li et al. conducted a study on the neutralization of JN.1 using two specific neutralizing antibodies: class I mAb 2B04 and class III mAb S309. Although S309, which targets epitopes on non-RBD spikes, has proven effective against many Omicron strains, it showed reduced neutralization activity against BA.2.86 and was entirely ineffective against JN.1. Furthermore, the RBM-epitope-targeting class I mAb 2B04 also proved ineffective against JN.1.[51]

Vaccination

The JN.1 variant's reputation for immune evasion has raised legitimate concerns regarding its potential to bypass immunity provided by existing COVID-19 vaccines. In an initial study, Chalkias et al. found that JN.1 demonstrates resistance to

sera from monovalent XBB.15 vaccinations, revealing its ability to evade immune detection.[52] However, Wang et al. showed that mRNA vaccines utilizing the XBB.15 spike sequence can elicit potent, albeit varied, immune responses, suggesting that updated vaccine formulations targeting this sequence could enhance protection.[53]

Currently, a combination of monovalent and bivalent vaccines is in use. A study conducted on individuals who first received three doses of the original wild-type vaccine, followed by a bivalent BA.5 booster and eventually a monovalent XBB.1.5 vaccine, revealed notable findings. Neutralizing antibody levels were assessed, and results indicated that both the XBB.1.5 monovalent vaccine and breakthrough infections with XBB contributed to increased neutralizing antibody levels against multiple variants, including JN.1.[53] This study demonstrated that the neutralizing efficacy from the vaccine was comparable to that obtained through breakthrough infection, emphasizing the role of the XBB.1.5 monovalent booster as an effective means of cross-protection against the JN.1 variant. Another promising protective agent is the trivalent mRNA vaccine (WSK-102C), which incorporates the XBB.1.5 spike protein and has shown substantial efficacy against multiple variants, including JN.1. After a fifth dose, it achieved geometric mean titers of 2567, reflecting its robust neutralizing capability.[54]

Despite these promising findings, concerns remain regarding the original Pfizer vaccine series' ability to neutralize JN.1. Studies indicate that individuals who received three doses of the original Pfizer vaccine exhibited a significantly reduced neutralization capacity against JN.1 compared to newer variants.[42] WHO emphasizes that current vaccines remain effective against severe illness and mortality caused by JN.1.[55] Administering updated monovalent mRNA vaccines, such as Moderna's, induces a substantial increase in virus-neutralizing antibodies in the serum. These vaccines effectively target XBB.1.5 (27.0-fold), EG.5.1 (27.6-fold), and variants HV.I, HK.3, JD.1.1, and JN.1, with neutralization titers increasing from 13.3- to 27.4-fold.[53]

However, following the decline in COVID-19 cases, vaccination uptake has dropped, contributing to decreased population immunity and a subsequent increase in vulnerability to disease, hospitalization, and mortality from infections preventable through vaccination.[56] According to a recent report by the US CDC, only 8% of children and 19% of adults in the United States have been vaccinated with the updated formula. Among older US adults (65 years or older), only 38% have received this vaccination, which is concerning given that JN.1 poses a higher risk for older adults with weakened immune systems.[11] In response, WHO encourages individuals, particularly those in high-risk groups, to stay current with vaccinations.

Monitoring and surveillance

The CDC recognizes that employing diverse surveillance techniques is essential for the timely identification of new SARS-CoV-2 variants, which can aid in risk assessment, public health outreach, and effective communication. To monitor the JN.1 variant's global presence, the CDC has adopted a comprehensive approach that includes genomic assessment, wastewater surveillance, traveler monitoring, and digital public health monitoring.

For the National SARS-CoV-2 Genomic Surveillance program, three independent sequence sources are used to generate variant proportions, weighted appropriately and systematically analyzed over two-week intervals. Sequences from around the world are shared with the Global Initiative on Sharing All Influenza Data (GISAID) and the National Center for Biotechnology Information Sequence Read Archive (NCBI SRA). These weighted estimates are crucial for understanding the dynamics and prevalence of variants. The Traveler-Based Genomic Surveillance (TGS) program collects genetic information from travelers to track the potential spread of variants across international borders and monitor their distribution. The National Wastewater Surveillance System (NWSS) helps identify variant hotspots and provides insights into the widespread distribution of viral variants across various populations.[5,57]

Additionally, the WHO's monthly epidemiological reports offer a global overview of COVID-19, including the prevalence and spread of its variants, such as JN.1.[26–32] The WHO has also initiated studies using blood samples from infected individuals to conduct neutralization assays with live JN.1 virus specimens, collected over two- to four-week intervals. This comparative analysis

aims to detect any immediate or ongoing indicators of severity over a 4- to 12-week period. Furthermore, WHO and its Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) continuously assess how these emerging variants impact COVID-19 vaccine efficacy to inform decisions on vaccine updates.[27]

Discussion

The emergence of the JN.1 variant has reignited concerns within the global health community, largely due to its heightened transmissibility and potential to evade immune responses. JN.1 has quickly established dominance, accounting for 95.1% of SARS-CoV-2 genomic sequences across 121 countries, indicating its rapid adaptation and transmission advantages over other circulating strains.[32] Despite its spread, JN.1 is currently assessed as posing a low to moderate risk to global health, with existing vaccines continuing to provide effective protection against severe disease and hospitalization.[5,6] However, the capacity of JN.1 to partially evade immunity highlights the persistent need for a comprehensive, layered approach to managing COVID-19, especially as new mutations continue to arise in global circulation.

A key feature of JN.1 is its enhanced immune escape potential, which may compromise the durability of immunity derived from both natural infection and vaccination. Studies have shown that while some vaccines, especially updated mRNA vaccines targeting Omicron-related lineages, provide neutralizing activity against JN.1, the overall efficacy varies, especially among populations with waning immunity or in individuals with compromised immune systems. This has brought renewed attention to non-immunologic preventive measures. Reinforcing strategies like mask-wearing in crowded settings, regular handwashing, maintaining social distancing, and improving ventilation in public spaces can offer significant protection. In particular, prompt testing at the onset of symptoms and self-isolation in cases of confirmed infection is crucial to minimizing JN.1's spread. Wastewater surveillance, along with individual testing, can also play a role in identifying community-level outbreaks early, providing a valuable tool for tracking variant prevalence.[58]

While non-pharmaceutical interventions are critical, it is also essential to consider the socio-behavioral aspects of pandemic fatigue, which have led to diminished compliance with these preventive measures. Public health messaging must therefore balance the necessity of continued vigilance with an understanding of public weariness. Targeted communication strategies that emphasize the effectiveness of combining vaccinations with non-pharmaceutical measures could bolster compliance, particularly in high-risk environments.

On a positive note, society has adapted considerably to the ongoing presence of COVID-19, demonstrating a level of resilience and preparedness that was lacking at the pandemic's outset. This adaptation is due in large part to the cumulative immunity within the global population, bolstered by previous infections, widespread vaccine campaigns, and continued advances in antiviral therapies.[38] Yet, JN.1's emergence is a reminder that SARS-CoV-2 has not been eradicated and retains the potential for mutation-driven evolution. Unlike the early days of the pandemic, the virus has evolved under immunological pressure, creating variants with complex mutations such as S456L and L455S on the spike protein. These mutations, which affect the virus's binding affinity and immune evasion capacity, may impact the effectiveness of vaccines and monoclonal antibody therapies. Notably, mutations in the spike protein can reduce the efficacy of certain monoclonal antibodies by altering epitope accessibility, thus limiting treatment options for severe cases in high-risk populations.[2]

The addition of spike mutations in JN.1 suggests an evolutionary trend toward further immune escape, which has implications for vaccine design and efficacy. The adaptation of vaccines to target specific mutations, such as those seen in JN.1 and other recent variants, is vital. Without such updates, immunity may wane more rapidly, especially in vulnerable populations, and the risk of breakthrough infections may increase. Continued investment in mRNA technology has enabled the relatively rapid adaptation of vaccines to evolving strains, although logistical and distributional challenges remain, particularly in low-resource settings. The potential for JN.1 to evolve further highlights the importance of global coordination in vaccine updates, distribution, and public health response.

Another aspect that warrants attention is the role of surveillance in detecting and responding to

variant emergence. The WHO, in conjunction with the Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC), is actively monitoring JN.1 and other variants to assess their impact on vaccine effectiveness. Studies involving live virus neutralization assays and continuous monitoring of clinical severity indicators are critical to understanding the real-world impact of these variants. Genomic surveillance through organizations like GISAID has been pivotal in identifying mutations in near real-time, allowing researchers and public health officials to adjust response strategies accordingly. Yet, disparities in surveillance capabilities across regions highlight the need for a globally coordinated response to variant monitoring.

The continued evolution of SARS-CoV-2 and the rise of variants like JN.1 highlight the importance of sustained vigilance. In addition to enhancing public health systems' adaptability, there is a growing need to address structural and systemic challenges that may hinder rapid responses to new variants. These challenges include logistical barriers to vaccine deployment, disparities in healthcare infrastructure, and public resistance to vaccination and preventive measures. Addressing these issues is vital to ensuring that global health systems remain resilient in the face of ongoing COVID-19 evolution.

Conclusion

The emergence and rapid spread of the JN.1 variant, with its enhanced transmissibility and immune escape capabilities, highlights the ongoing evolutionary dynamics of SARS-CoV-2 and its persistent threat to global health stability. This variant exemplifies how SARS-CoV-2 continues to challenge our current prevention and control measures, highlighting the need for vigilant, real-time genomic surveillance and swift, data-driven public health responses. The adaptability of JN.1, including mutations that may attenuate vaccine and therapeutic efficacy, signals an urgent need for sustained innovation in vaccine formulations and antiviral strategies to maintain effective population immunity. Ongoing research into JN.1's clinical impact, coupled with robust global surveillance, will be critical in understanding and mitigating its potential consequences. As we adapt to living alongside SARS-CoV-2, integrating vaccine updates and reinforcing non-pharmaceutical interventions remain essential in our collective response. The JN.1 variant serves as a reminder of the virus's capacity for adaptation and persistence, underling the importance of a dynamic, multifaceted approach in combating COVID-19's evolving landscape.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Araj Naveed Siddiqui: Conceptualization; Writing – original draft; Writing – review & editing.

Imshaal Musharaf: Conceptualization; Writing – original draft; Writing – review & editing.

Bashar Haruna Gulumbe: Conceptualization; Writing – original draft; Writing – review & editing.

Acknowledgements

None.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

All the data are available on the paper and listed references.

ORCID iDs

Araj Naveed Siddiqui https://orcid.org/0009-0000-4966-0411

Bashar Haruna Gulumbe https://orcid.org/0000-0003-0642-6902

References

1. Bogoch II, Watts A, Thomas-Bachli A, et al. Pneumonia of unknown aetiology in Wuhan, China: potential for international spread via commercial air travel. *J Travel Med* 202; 27: taaa008.

2. Quarleri J, Delpino MV and Galvan V. Anticipating the future of the COVID-19 pandemic: insights into the emergence of SARS-CoV-2 variant JN.1 and its projected impact on older adults. *GeroScience* 2024; 46: 2879–2883.
3. Coronavirus disease (COVID-19): Variants of SARS-COV-2. Who.int, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-%28covid-19%29-variants-of-sars-cov-2?gad_source=1&gclid=Cj0KCQjwj9-zBhDyARIsAERjds2HUTUzIVpYFj37AxB9WMKr0qftAyhJ6SdLv4QXco0-pYUHyiVmJkMaApigEALw_wcB (2023, accessed 24 April 2024).
4. Who.int. https://www.who.int/activities/tracking-SARS-CoV-2-variants (2024, accessed 24 April 2024).
5. Hemo MK and Islam MA. JN.1 as a new variant of COVID-19 – editorial. *Ann Med Surg (Lond)* 2024; 86: 1833–1835.
6. Eshraghi R, Bahrami A, Karimi Houyeh M, et al. JN.1 and the ongoing battle: unpacking the characteristics of a new dominant COVID-19 variant. *Pathogens Global Health* 2024; 118(6): 453–458.
7. Satapathy P, Kumar P, Gupta JK, et al. The emergence and implications of SARS-CoV-2 omicron subvariant BA.2.86 on global health. *Int J Surg* 2024; 110(4): 2498–2501.
8. Srivastava S, Kumar S, Ashique S, et al. Fast-spreading jn.1: what you need to know about the latest COVID-19 Subvariant. *J Infect Public Health* 2024; 17(7): 102451.
9. Rijhwani P. JN1 Variant: navigating the next phase of the COVID-19 challenge. *Daily Guardian*, https://thedailyguardian.com/jn1-variant-navigating-the-next-phase-of-the-covid-19-challenge/ (2024, accessed 24 April 2024).
10. Statens Serum Institut, Denmark. Presentation at the WHO Technical Advisory Group (TAG-VE meeting on 11 December 2023).
11. CDC. COVID-19 data tracker. https://covid.cdc.gov/covid-data-tracker/ (accessed 24 April 2024).
12. Crabb B, Pakula E, Turville S, et al. The emergence of JN.1 is an evolutionary 'step change' in the COVID pandemic. Why is this significant? *The Conversation*, http://theconversation.com/the-emergence-of-jn-1-is-an-evolutionary-step-change-in-the-covid-pandemic-why-is-this-significant-220285 (2024, accessed 24 April 2024).
13. Wang X, Lu L and Jiang S. SARS-CoV-2 evolution from the BA.2.86 to JN.1 variants: unexpected consequences. *Trends Immunol* 2024; 45: 81–84.
14. Yang S, Yu Y, Xu Y, et al. Fast evolution of SARS-CoV-2 BA.2.86 to JN.1 under heavy immune pressure. *Lancet Infect Dis* 2024; 24: e70–e72.
15. CDC. COVID-19 and your health. *Centers for Disease Control and Prevention*, https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/how-covid-spreads.html (2024, accessed 24 June 2024).
16. Pawelec G (n.d.) The conundrum of human immune system "senescence". *Mech Ageing Dev* 2020; 192: 111357.
17. Yajima H, Anraku Y, Kaku Y, et al. Genotype to phenotype Japan (G2P-Japan) consortium; Ito J, Maenaka K, Sato K, Hashiguchi T. Structural basis for receptor-binding domain mobility of the spike in SARS-CoV-2 BA.2.86 and JN.1. *Nat Commun* 2024; 15(1): 8574.
18. Johnson BA, Xie X, Kalveram, et al. Furin cleavage site is key to SARS-CoV-2 pathogenesis. *Nature* 2020; 591: 293–299.
19. Jackson CB, Farzan M, Chen B, et al. Mechanisms of SARS-CoV-2 entry into cells. *Nat Rev Mol Cell Biol* 2022; 23: 3–20.
20. WHO. Why is COVID-19 data being presented as weekly statistics? https://data.who.int/dashboards/covid19/cases?n=c (2024, accessed 24 April 2024).
21. CDC. COVID-19 activity increases as prevalence of JN.1 variant continues to rise, https://www.cdc.gov/ncird/whats-new/JN.1-update-2024-01-05.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Frespiratory-viruses%2Fwhats-new%2FJN.1-update-2024-01-05.html (accessed 24 April 2024).
22. GISAID – hCov19 variants. Gisaid.org, https://gisaid.org/hcov19-variants/ (2024, accessed 24 April 2024).
23. CDC. Update on SARS-CoV-2 variant JN.1 being tracked by CDC, https://www.cdc.gov/ncird/whats-new/SARS-CoV-2-variant-JN.1.html (accessed 24 April 2024).
24. Who.int (n.d.) Weekly Epidemiological Record (WER). Available at: https://www.who.int/publications/journals/weekly-epidemiological-record (accessed 26 October 2024).
25. CDC.gov (2022) Check code: Customizing the data entry process. Available at: https://www.cdc.gov/epiinfo/user-guide/check-code/epiweekfunctions.html (accessed 26 October 2024).

26. WHO. COVID-19 epidemiological update – 22 December 2023, https://www.who.int/publications/m/item/covid-19-epidemiological-update—22-december-2023 (accessed 24 April 2024).

27. WHO. https://www.who.int/docs/default-source/coronaviruse/18122023_jn.1_ire_clean.pdf?sfvrsn=6103754a_3 (accessed 24 April 2024).

28. WHO. COVID-19 epidemiological update – 19 January 2024, https://www.who.int/publications/m/item/covid-19-epidemiological-update—19-january-2024. (2024, accessed 24 April 2024).

29. WHO. COVID-19 epidemiological update – 16 February 2024, https://www.who.int/publications/m/item/covid-19-epidemiological-update-16-february-2024. (2024, accessed 24 April 2024).

30. WHO. Updated Risk Evaluation of JN.1, https://cdn.who.int/media/docs/default-source/documents/health-topics/sars/jn.1-9-february-2024.pdf?sfvrsn=9a39d825_3 (2024, accessed 24 April 2024).

31. WHO. COVID-19 epidemiological update – 15 March 2024, https://www.who.int/publications/m/item/covid-19-epidemiological-update-15-march-2024 (accessed 24 April 2024).

32. WHO. COVID-19 epidemiological update – 12 April 2024. https://www.who.int/publications/m/item/covid-19-epidemiological-update-edition-166 (accessed 24 April 2024).

33. Satapathy P, Kumar P, Mehta V, et al. Global spread of COVID-19's JN.1 variant: implications and public health responses. *New Microbes New Infect* 2024; 57: 101225.

34. Khan SA, Bhuiyan MA and Dewan SMR. JN.1: The present public health concern pertains to the emergence of a novel variant of COVID-19. *Environ Health Insights* 2024; 18: 11786302241228958.

35. CDC. Symptoms of COVID-19, https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html (accessed 24 April 2024).

36. Yamasoba D, Kimura I, Nasser H, et al. Virological characteristics of the SARS-CoV-2 Omicron BA.2 spike. *Cell* 2022; 185: 2103–15.e19.

37. Kamble P, Daulatabad V, Singhal A, et al. (2024) JN.1 variant in enduring COVID-19 pandemic: is it a variety of interest (VoI) or variety of concern (VoC)?. *Hormone Mol Biol Clin Investig* 2024; 45(2): 49–53.

38. Lewnard JA, Mahale P, Malden D, et al. (2024) Immune escape and attenuated severity associated with the SARS-CoV-2 BA.2.86/JN.1 lineage. *Nat Commun* 2024; 15(1): 8550.

39. American Medical Association. JN.1 Omicron subvariant: Questions patients may have. https://www.ama-assn.org/delivering-care/public-health/jn1-omicron-subvariant-questions-patients-may-have (2023, accessed 24 April 2024).

40. CDC. COVID-19 testing: What you need to know, https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/testing.html (2024, accessed 24 April 2024).

41. Times of India. COVID JN.1 variant: How timely identification and intervention can help, https://timesofindia.indiatimes.com/life-style/health-fitness/health-news/covid-jn-1-variant-how-timely-identification-and-intervention-can-help/articleshow/106954260.cms (accessed 24 April 2024).

42. Planas D, Staropoli I, Michel V, et al. Distinct evolution of SARS-CoV-2 Omicron XBB and BA.2.86/JN.1 lineages combining increased fitness and antibody evasion. *bioRxiv* 2023; 2023.11.20.567873.

43. CDC. COVID-19 treatment and preventive medication, https://www.cdc.gov/coronavirus/2019-ncov/your-health/treatments-for-severe-illness.html (2024, accessed 24 April 2024).

44. Marzi M, Vakil MK, Bahmanyar M, et al. Paxlovid: mechanism of action, synthesis, and in silico study. *Biomed Res Int* 2022; 2022: 1–16.

45. Gordon CJ, Tchesnokov EP, Feng JY, et al. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. *J Biol Chem* 2020; 295: 4773–4779.

46. Kabinger F, Stiller C, Schmitzová J, et al. Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. *Nat Struct Mol Biol* 2021; 28: 740–746.

47. Hashemian SMR, Sheida A, Taghizadieh M, et al. Paxlovid (Nirmatrelvir/Ritonavir): a new approach to Covid-19 therapy? *Biomed Pharmacother* 2023; 162: 114367.

48. Amani B and Amani B. Efficacy and safety of nirmatrelvir/ritonavir (Paxlovid) for COVID-19: a rapid review and meta-analysis. *J Med Virol* 2023; 95: e28441.

49. Najjar-Debbiny R, Gronich N, Weber G, et al. Effectiveness of Paxlovid in reducing severe Coronavirus disease 2019 and mortality in high-Risk Patients. *Clin Infect Dis* 2023; 76: e342–e349.

50. Mayoclinic. Nirmatrelvir and ritonavir (oral route). https://www.mayoclinic.org/drugs-supplements/nirmatrelvir-and-ritonavir-oral-route/side-effects/drg-20528231?p=1 (accessed 24 April 2024).

51. Li P, Liu Y, Faraone JN, et al. Distinct patterns of SARS-CoV-2 BA.2.87.1 and JN.1 variants in immune evasion, antigenicity, and cell-cell fusion. *mBio* 2024; 15(5): e0075124.

52. Chalkias S, McGhee N, Whatley JL, et al. Interim report of the reactogenicity and immunogenicity of severe acute respiratory syndrome coronavirus 2 XBB–Containing vaccines. *J Infect Dis* 2024; 230(2): e279–e286.

53. Wang Q, Guo Y, Bowen A, et al. XBB.1.5 monovalent mRNA vaccine booster elicits robust neutralizing antibodies against XBB subvariants and JN.1. *Cell Host Microbe* 2024; 32(3): 315–321.

54. Xun W, Shujun J, Wentai M, et al. Robust neutralization of SARS-CoV-2 variants including JN.1 and BA.2.87.1 by trivalent XBB vaccine-induced antibodies. *bioRxiv* 2024. 2024.02.16.580615.

55. WHO. Statement on the antigen composition of COVID-19 vaccines. https://www.who.int/news/item/13-12-2023-statement-on-the-antigen-composition-of-covid-19-vaccines (accessed 24 April 2024).

56. Marks P and Califf R. Is vaccination approaching a dangerous tipping point? *JAMA* 2024; 331: 283.

57. Coutinho. UNICEF. COVID-19: WHO designates JN.1 'variant of interest' amid sharp rise in global spread. *UN News*, https://news.un.org/en/story/2023/12/1145012 (accessed 24 April 2024).

58. Fan H, Qin S and Cui Y. Emergence and characterization of the SARS-CoV-2 JN.1 variant: Global prevalence and implications for public health. *Zoonoses (Burlingt)*. Epub ahead of print 10 January 2024. DOI: 10.15212/zoonoses-2023-0061.