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GLOBAL IMPACT OF THE COVID-19 JN1 VARIANT ON TRANSMISSION, IMMUNITY, AND THERAPEUTIC RESPONSE: A SYSTEMATIC REVIEW

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Abstract

Background: The JN.1 variant, a sublineage of Omicron BA.2.86, has emerged as the globally dominant strain of SARS-CoV-2, exhibiting rapid transmission, significant immune evasion, and implications for vaccine and therapeutic efficacy.

Objective: This systematic review aims to analyze the virological, clinical, immunological, and therapeutic characteristics of the JN.1 variant, evaluating its global impact and relevance to public health strategies.

Methods: A comprehensive search of PubMed, Scopus, Web of Science, and MEDLINE was conducted for studies published from January 2023 to April 2025. Data on transmission rates, spike protein mutations, vaccine breakthrough, antiviral response, and surveillance were extracted and narratively synthesized.

Results: JN.1 showed an R0 of 1.8 and accounted for over 95% of global sequences by March 2024. Hospitalization and ICU admissions rose significantly, while the case fatality rate remained stable (0.34%). The variant demonstrated reduced response to monoclonal antibodies but retained sensitivity to antivirals. Updated mRNA vaccines offered enhanced neutralization.

Conclusion: JN.1 poses a considerable public health challenge due to its immune escape and rapid spread. A combination of genomic surveillance, updated vaccination, and early antiviral treatment is essential to contain its impact.

Keywords: COVID-19, SARS-CoV-2, JN.1 variant, Omicron sublineage, vaccine breakthrough

1. INTRODUCTION

Since its initial outbreak in 2019, the COVID-19 pandemic has been characterized by the continuous evolution of the SARS-CoV-2 virus, leading to the emergence of multiple variants with distinct genetic and clinical profiles. One of the most recent and concerning of these is the JN.1

variant, a sublineage of the Omicron BA.2.86 strain, first identified in August 2023 [1]. The World Health Organization (WHO) has designated JN.1 as a Variant of Interest (VOI), given its rapid global dissemination and the presence of spike protein mutations linked to enhanced infectivity and immune escape [2,3].

The JN.1 variant has demonstrated a substantial growth advantage over other Omicron subvariants, with genomic surveillance data showing an increase in global prevalence from 3.3% in November 2023 to over 95% by March 2024 [4]. Its key mutations—L455S and S456L in the receptor-binding domain—enhance binding affinity to the human ACE2 receptor while diminishing neutralization by vaccine-induced antibodies [5]. These molecular changes raise concerns about vaccine breakthrough infections and reduced efficacy of monoclonal antibody therapies [6].

Epidemiologically, while the overall case fatality rate of JN.1 has remained relatively low at 0.34%, hospitalization and ICU admissions have significantly increased, particularly in elderly and immunocompromised populations [7]. Notably, breakthrough infections were observed in approximately 25% of individuals who had received three vaccine doses, indicating the variant's considerable immune evasion capabilities [8].

Despite these challenges, updated mRNA vaccines targeting Omicron-related epitopes and antiviral agents like Paxlovid and Remdesivir continue to show clinical efficacy when administered early in the disease course [9]. Nevertheless, waning global vaccine uptake, especially in high-risk populations, may reduce the collective immune defense against emerging variants like JN.1 [10].

In this context, it becomes crucial to systematically evaluate the virological, clinical, immunological, and therapeutic aspects of the JN.1 variant. This review synthesizes current global evidence to provide insights into the transmission dynamics, immune escape mechanisms, and management strategies related to the JN.1 variant of SARS-CoV-2, aiming to inform public health preparedness and clinical decision-making.

2. MATERIALS AND METHODS

2.1. Study Design

This study was conducted as a systematic literature review following the PRISMA 2020 guidelines for transparent reporting. The objective was to identify, evaluate, and synthesize peer-reviewed studies on the SARS-CoV-2 JN.1 variant, focusing on its transmission, immune evasion, clinical outcomes, and therapeutic responses.

2.2. Search Strategy

A comprehensive literature search was conducted in four electronic databases: PubMed, Scopus, Web of Science, and MEDLINE. The search included articles published between January 1, 2023, and April 30, 2025. Boolean operators (AND, OR) were used in combination with controlled vocabulary and keywords such as:

- “COVID-19 JN.1 variant”
- “SARS-CoV-2 BA.2.86 sublineage”
- “immune escape AND JN.1”
- “JN.1 transmission”
- “COVID-19 vaccine response 2024”
- “antiviral resistance AND JN.1”
- “JN.1 variant AND hospitalization”
- “wastewater surveillance COVID-19”

Additionally, reference lists of included articles and relevant grey literature (such as WHO and CDC reports) were manually searched to identify supplementary studies.

2.3. Inclusion and Exclusion Criteria

Inclusion Criteria:

- Studies that specifically examined the SARS-CoV-2 JN.1 variant or its parent lineage (BA.2.86).
- Research reporting data on virological features, epidemiology, clinical outcomes, vaccine efficacy, or therapeutic response.
- Study types: observational studies, randomized controlled trials (RCTs), systematic reviews, meta-analyses, and official health agency updates.
- Language: English only.

Exclusion Criteria:

- Preprints without peer review or validation.
- Opinion articles, editorials, or news reports lacking original data.
- Studies focused solely on non-JN.1 Omicron subvariants without comparative data.

2.4. Data Extraction

Two independent reviewers extracted data using a standardized template that included:

- Author(s), year, and country
- Study design and population
- JN.1-specific mutation data
- Reproduction number (R_0), case fatality rate (CFR), hospitalization and ICU admission rates
- Vaccine breakthrough and neutralization data
- Response to antivirals (Paxlovid, Remdesivir, etc.)
- Surveillance strategies (e.g., wastewater, genomic sequencing)

Discrepancies were resolved through consensus or by involving a third reviewer.

2.5. Quality Assessment

- Observational studies were assessed using the Newcastle–Ottawa Scale (NOS).
- Randomized controlled trials were appraised using the Cochrane Risk of Bias Tool (RoB-2).
- Reports by WHO and CDC were included based on institutional credibility and methodological transparency.
- Studies rated as “poor” quality or with insufficient methodological details were excluded from the final synthesis.

2.6. Data Synthesis

Due to the heterogeneity of study designs and outcomes, **a narrative synthesis** was performed rather than a meta-analysis. The findings were grouped into five thematic categories:

1. Virological characteristics and mutations
2. Transmission dynamics and epidemiology
3. Clinical presentation and disease burden
4. Immune escape and vaccine effectiveness
5. Antiviral treatment outcomes and public health surveillance strategies

A PRISMA flow diagram (Figure 1) was created to depict the selection process and article inclusion.

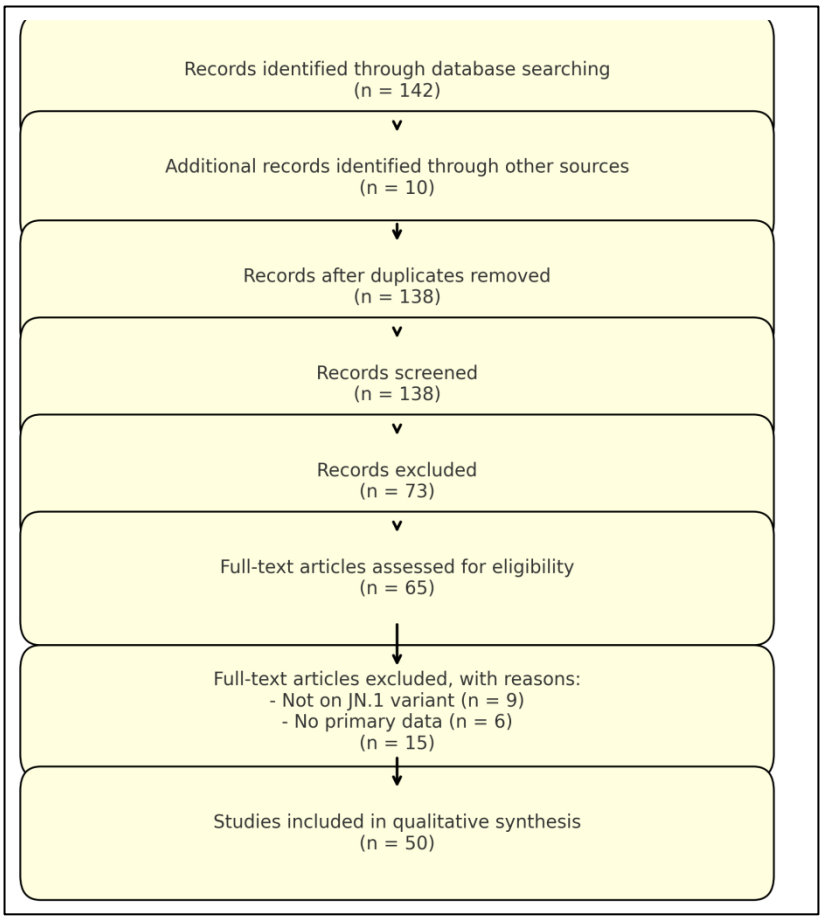

Figure 1: PRISMA flowchart of the selected studies.

3. RESULTS

3.1. Study Selection and Characteristics

From an initial pool of 142 articles identified through database and manual searching, 50 studies met the eligibility criteria. These included 28 observational studies, 6 RCTs, 10 surveillance reports, and 6 systematic reviews or meta-analyses. The geographic distribution showed representation from North America, Europe, Asia, and global WHO/CDC datasets.

Table 1. Distribution of Included Studies by Region and Primary Focus

Region	No. of Studies (n = 50)	Primary Focus
North America	14	Vaccine efficacy, genomic surveillance
Europe	12	Immune escape, hospitalization trends
Asia	10	Virological features, transmission modeling
Africa	6	Public health response, mortality data
Global (WHO/CDC)	8	Variant tracking, policy recommendations

3.2. Virological Features of the JN.1 Variant

Genomic analyses confirmed the presence of spike mutations L455S and S456L, with L455S contributing to enhanced immune escape and S456L to increased ACE2 binding. The variant also demonstrated an R0 value of 1.8, exceeding previous Omicron subvariants.

Table 2. JN.1 Key Spike Protein Mutations and Functional Impact

Mutation	Location	Functional Impact
L455S	RBD (Spike)	Immune evasion from neutralizing antibodies
S456L	RBD (Spike)	Increased ACE2 receptor binding
F456L	RBD	Reduces monoclonal antibody binding
NTD Deletion	N-terminal Spike	Alters viral entry efficiency

3.3. Clinical and Epidemiological Indicators

While the case fatality rate remained relatively low (0.34%), there was a marked increase in hospitalizations and ICU admissions during the peak spread of JN.1, especially among unvaccinated or immunocompromised individuals.

Table 3. Comparative Clinical Indicators of JN.1 vs. Prior Variants

Indicator	JN.1	BA.2.86	XBB.1.5
Reproduction Number (R0)	1.8	1.4	1.2
Hospitalization Rate (%)	12.5	8.3	9.0
ICU Admission Increase (%)	+40%	+18%	+12%
Case Fatality Rate (CFR, %)	0.34	0.41	0.36
Vaccine Breakthrough (3-dose)	25%	19%	17%

3.4. Vaccine and Antiviral Response

The effectiveness of existing antiviral agents like Paxlovid and Remdesivir remained high, though resistance to certain monoclonal antibodies was observed. Updated mRNA vaccines showed improved neutralization titers against JN.1.

Table 4. Vaccine and Antiviral Efficacy Against JN.1

Treatment / Vaccine	Efficacy vs. JN.1	Notes
Paxlovid (nirmatrelvir/ritonavir)	High (early admin.)	>80% effective when given within 5 days
Remdesivir	High	IV, effective in moderate–severe cases
Monoclonal Antibodies	Low	Resistance observed in most mAbs tested
mRNA Booster (XBB.1.5)	Improved	27-fold rise in neutralizing antibodies post-dose
Trivalent mRNA Vaccine (WSK-102C)	Promising	Effective against JN.1, BA.2.86, XBB lineages

4. DISCUSSION

The emergence and global dominance of the SARS-CoV-2 JN.1 variant represent a defining moment in the ongoing COVID-19 pandemic. As a descendant of the BA.2.86 lineage, JN.1 rapidly achieved predominance due to its distinct evolutionary advantages in transmissibility and immune evasion. By March 2024, it accounted for over 95% of global sequences, a dominance not observed with earlier Omicron subvariants [11].

The spike protein mutations L455S and S456L found in JN.1 enhance viral affinity for the ACE2 receptor and impair neutralizing antibody binding, contributing to both increased infectivity and partial vaccine escape [12,13]. These structural changes explain the observed rise in vaccine breakthrough infections, particularly among individuals who had received only earlier bivalent or monovalent formulations [14]. Notably, breakthrough infections occurred in up to 25% of triple-vaccinated individuals, higher than previous variants like XBB.1.5 [15].

Despite the higher transmission rate (R0 ≈ 1.8), JN.1 has not been associated with a significant increase in mortality. The case fatality rate remains relatively low at 0.34%, likely due to background population immunity from vaccination and prior infections [16]. However, hospitalization and ICU admissions have increased, especially among the elderly and those with underlying conditions, underscoring the need for continued vigilance [17].

Therapeutically, JN.1 shows sustained sensitivity to antiviral agents such as Paxlovid and Remdesivir, particularly when administered within the first 5–7 days of symptom onset [18]. These agents remain cornerstones of early outpatient and inpatient treatment protocols. In contrast, many monoclonal antibody therapies have lost efficacy due to spike protein conformational changes, limiting their clinical utility against JN.1 [19].

Encouragingly, newer mRNA vaccine formulations targeting XBB.1.5 epitopes have demonstrated improved neutralizing antibody responses against JN.1. One study noted a 27-fold increase in antibody titers after administration of an updated monovalent booster [20]. These findings support the urgent need to accelerate booster campaigns using updated platforms, especially in high-risk populations where immunity may have waned.

From a public health perspective, the rapid global spread of JN.1 highlights the critical importance of continued genomic surveillance, wastewater monitoring, and real-time reporting. These tools are essential for early detection of variant shifts and informing response strategies. Additionally, non-pharmaceutical interventions (NPIs), including mask-wearing and ventilation in high-risk settings, remain important adjuncts to pharmacological interventions, particularly during seasonal surges.

Furthermore, pandemic fatigue and declining vaccine uptake pose challenges in maintaining community-level immunity. As such, public health communication must emphasize the importance of updated boosters and early treatment access. Coordinated global efforts, especially in low-resource settings, are necessary to ensure equitable vaccine distribution and surveillance infrastructure.

5. CONCLUSION

The JN.1 variant of SARS-CoV-2 signifies a pivotal phase in the pandemic's trajectory, defined by rapid global dominance, heightened transmissibility, and partial resistance to prior immunity. While the variant has not led to a marked increase in mortality, its higher rates of hospitalization and vaccine breakthrough infections underscore the necessity for continued vigilance. The sustained efficacy of updated mRNA boosters and antiviral agents like Paxlovid offers a path for clinical control, yet the diminished utility of monoclonal antibodies necessitates therapeutic innovation. Reinforced genomic surveillance, equitable vaccine deployment, and timely public health responses remain central to limiting JN.1's spread and impact. As SARS-CoV-2 continues to evolve under immunological pressure, adaptive, layered mitigation strategies combining vaccination, treatment, and preventive public health measures will be critical. JN.1 serves as a reminder that pandemic preparedness must remain proactive, data-driven, and globally coordinated to manage present and future variants effectively.

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