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Narrative Review

The incidence of COVID-19 is once again increasing

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Abstract

The ongoing evolution of the COVID-19 pandemic, characterized by the emergence of novel variants, diminishing vaccine-induced immunity, and the relaxation of public health measures, has heightened concerns regarding potential resurgences of infection. This review critically examines the interplay of seasonal fluctuations, the durability of vaccine effectiveness, and viral mutations in contributing to the recurrence of COVID-19. It further examines the implications for public health infrastructure, including the preparedness of healthcare systems, the risks associated with reinfection, and the effectiveness of current mitigation strategies. By synthesizing recent epidemiological data and contemporary research, the review highlights the importance of continuous surveillance, adaptable vaccination policies, and evidence-based interventions in effectively managing and mitigating the impact of future infection waves.

Keywords: COVID-19, SARS-CoV-2 variants, Vaccine Efficacy, Public health preparedness, Pandemic response.

1. Introduction

Coronavirus disease 2019, or COVID-19, is a virus that causes fever, coughing, and dyspnea [1]. Even though 80–85% of COVID-19 infections seem to be moderate, the virus can cause serious illness, including pneumonia, in those at greater risk, like the elderly and those with long-term medical issues [2]. Countless people across multiple continents have been affected by the swift global spread of COVID-19 [3]. On March 11, 2020, the World Health Organization (WHO) announced COVID-19 as a pandemic. Human sickness is known to be caused by various coronaviruses [4]. When a person with a respiratory infection cough, sneezes, or speaks, respiratory droplets can spread the virus from person to person [5]. Studies also indicate that the virus is transmitted from person to person before symptoms appear [6,7,8,9,10]. On frequently touched surfaces, the virus can live for a short period of time [11].

In 2025, COVID-19 transformed from an acute global health emergency to a chronic and adaptable public health challenge, and the world community is still navigating its complicated, long-term presence [12]. The SARS-CoV-2 virus has experienced substantial genetic evolution since it first appeared in late 2019, giving rise to several variants with differing levels of clinical severity, immunological escape abilities, and transmissibility [13].

Even though the burden of severe sickness and mortality has decreased due to widespread vaccination programs, natural immunity, and better treatment practices, the virus is still a persistent pathogen that can reappear [14].

In 2025, COVID-19 continues to cause pressure on healthcare systems, especially in areas with few resources and among vulnerable groups like the elderly, people with immunocompromised conditions, and people with long-term illnesses [15,16,17] as presented in Figure 1. Even though hospitalizations and fatalities are generally lower than during the pandemic's peak years, staff shortages and rising care demands continue to strain the healthcare system, making it vulnerable [18]. Additionally, the ongoing prevalence of prolonged COVID symptoms affects millions of people and carries significant social and financial costs [19].

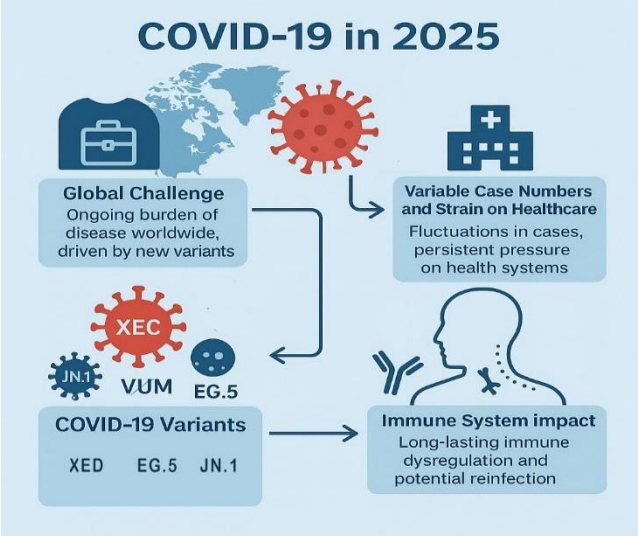

Figure 1 : Shows the COVID-19 development steps in 2025

Several governments have relaxed restrictions on preventive measures, including masking, testing, and isolation, to normalize social and economic life [20]. However, this relaxation and decreasing natural and vaccine-derived immunity have made it easier for outbreaks to occur locally and, in some areas, for waves of infection to recur [21,22].

The pandemic's current phase is characterized by variable case numbers, which are caused by both behavioral changes in society and novel variants that partially evade immunization, such as the recently discovered placeholder for the 2025 variant XEC [23].

After five years of the pandemic, the original COVID-19 strain had more than thirty identified variations [24]. The World Health Organization (WHO) divides them into three groups to facilitate monitoring and research [25].

Variants of Concern (VOC): These variants transmit rapidly and could influence immunity [26]. A SARS-CoV-2 variant causes significant changes in the severity of clinical disease, thereby substantially affecting the ability of health systems to care for COVID-19 patients or those with other conditions [27].

Variants of Interest (VOI): These are closely monitored for potential risks [28]. They have genetic alterations that are likely or have been shown to affect the virus's features, such as its virulence, transmissibility, susceptibility to treatment, antibody evasion, and detectability, such as XBB.1.16, XBB.1.5, and EG.5 [29].

Variants Under Monitoring (VUM): Variants that scientists monitor but are not yet considered a major threat. Compared to other circulating variants, this SARS-CoV-2 variant shows early signs of growth advantage and is suspected of having genetic alterations affecting virus properties. For instance, worldwide or within a particular WHO area, such as BA.2.86, CH.1.1, XBB.1.9.1, XBB.2.3.

As of early 2025, XEC is the most prevalent version globally, followed by JN.1 and other developing Omicron subvariants. This is displayed in Figure 2.

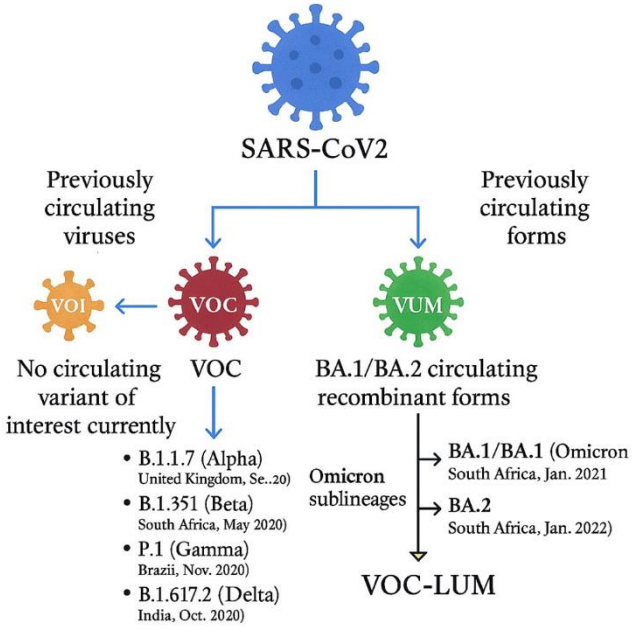

Figure 2: A schematic figure of SARS-CoV-2 description

What is the XEC variant?

As of April 2025, the dominant COVID-19 variant globally is XEC, which emerged as the

predominant strain worldwide. XEC, which was initially recognized in Germany in June 2024 and has since spread quickly, was created by merging two Omicron subvariants (KS.1.1 and KP.3.3) [8,9]. About 45% of COVID-19 infections in the US were caused by this variation by December 2024, and its frequency was also rising in Europe and Australia. This finding emphasizes the significance of continuous viral surveillance and the SARS-CoV-2 virus's continual evolution. Even among those who have received vaccinations, the variation has shown a moderate capacity to avoid protection, resulting in breakthrough infections [10].

What is the JN.1 variant ?

The JN.1 variant is a subline age of the Omicron variant of SARS-CoV-2. JN.1, a descendant of the BA.2.86 lineage, is distinguished by certain spike protein modifications, most notably the L455S mutation. These genetic alterations may be attributed to their increased capacity to proliferate and partially elude immune responses.

By the close of 2024, JN.1 became the leading strain of SARS-CoV-2 in the United States and globally. Its swift proliferation suggests it might be more transmissible or better at avoiding the immune response compared to other circulating variants. [11,12].

Because of its quick spread, JN.1 has been classified as a "variant of interest" by the World Health Organization (WHO) [13]. Nonetheless, the public health risk has been moderate [14]. The WHO recommends preventive measures, such as being vaccinated, using masks in crowded or poorly ventilated areas, and remaining at home while experiencing symptoms [13].

The World Health Organization monitors several SARS-CoV-2 variants, including one variant of interest (VOI) named JN.1 and seven variants under surveillance (VUMs) [13]. In the first week, JN.1, the VOI, represented 15.0% of the sequences 2025. As of week 1 in 2025, the VUM, XEC, and LP.8.1 variants continue to increase in prevalence, comprising 44.8% and 4.7% of the sequences, respectively. Currently, these are the only monitored variants still showing growth, while all other VUMs are decreasing in prevalence [8,10].

How COVID-19 Affects the Immune System Long-Term

- The immune system may remain overactive or dysregulated for weeks or months following an infection, particularly in moderate to severe infections. This may include [14]:
- • Elevated inflammatory indicators, such as cytokines.
- • Overactive T-cells and B-cells.
- • Chronic immune cell fatigue, a condition where immune cells lose effectiveness.

The immune system makes memories, antibodies, and memory T-cells after infection. Nevertheless, with new variants (JN.1 and XEC), immune leakage may happen, which means People can still become reinfected, and the body cannot respond as powerfully to new virus types [15] as shown in Figure 3.

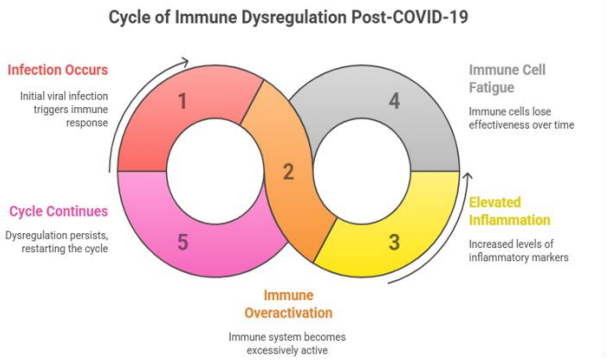

Figure 3: Cycle of immune dysregulation post-COVID-19

A recent study by Bernhard Kratzer and colleagues [12] investigated immune parameters in 133 COVID-19 survivors and 98 uninfected individuals. The analysis focused on the quantity and types of immune cells, cytokines, and growth factors present in the blood of recovered patients, assessed ten weeks and ten months following their initial infection. Notably, since there were no available COVID-19 vaccines during the 2020 observation period, all participants were unvaccinated. This allowed the study authors to investigate the long-term effects of SARS-CoV-2 infection without the influence of vaccines [16,17]. Moreover, the cytokines and growth factors present in the blood were clear indicators of an acute inflammatory response. When comparing samples from patients taken ten months after their COVID-19 infection, researchers found an unexpected result: even with mild disease progression, there was a notable reduction in immune cells in the blood [15]. Furthermore, a well-documented drop in SARS-CoV-2-specific antibodies and an unexpected shift in blood growth factor patterns were noted [17]. These findings suggest that for individuals recovering from COVID-19, their immune systems may be less capable of responding effectively to new challenges [12,13]. This could clarify specific lingering effects of COVID-19, including long COVID [18]. The findings indicate a potential connection between the prolonged impacts of COVID-19 and the harm inflicted on the cellular immune system by SARS-CoV-2, alongside the diminished maturation

and/or release of immune cells from the bone marrow [12,19].

COVID-19 threat in 2025

COVID-19 is still a complicated and persistent public health concern in 2025, mainly because of the virus's continual development and new variants like JN.1, Fornax, and Arcturus [20,22]. Due to their enhanced transmissibility and immune evasion, these variations make it simpler for the virus to infect individuals, even those who have already received a vaccination or been infected [15]. While most infections currently cause only mild to moderate symptoms, the virus continues to pose a substantial risk to vulnerable populations, including the elderly, those with underlying health issues, and individuals with weakened immune systems [23]. During variant outbreaks, hospitalizations can still increase, burdening healthcare systems and delaying treatment for patients who are not COVID-19 [15,16]. Furthermore, prolonged COVID is still a serious worry [24-28]. Even if their initial infection was mild, many people experience chronic symptoms for months afterward, including exhaustion, brain fog, breathing problems, and heart or neurological disorders [29]. Millions of people worldwide are impacted by these chronic issues, which have consequences for society and the economy, such as reduced employment opportunities and higher healthcare costs [30]. Inequality in access to vaccines and treatment worldwide also contributes to the virus's continued spread [17]. Hotspots for viral mutation and variant formation are created in some areas by low booster uptake or outdated vaccination formulations, which may result in the development of new strains with unexpected behavior [31]. Despite enormous improvements in therapies and vaccinations, COVID-19 in 2025 is far from finished; it is still a dynamic and unpredictable threat that requires constant monitoring, global collaboration, and public health preparedness [15,18]. COVID-19 remains a dynamic and unpredictable global threat in 2025, characterized by periodic resurgences, the perpetual emergence of new variants, and uneven vaccination coverage worldwide [32]. Despite substantial advances in antiviral therapies and widespread vaccine uptake, SARS-CoV-2 continues to circulate with localized spikes, such as recent upticks in Singapore and Hong Kong, underscoring the virus's ability to adapt and evade immunity [33]. Though significantly reduced from the pandemic's peak, global case counts and hospitalizations continue to vary [34]. In early 2025, the WHO observed a 10% rise in hospitalizations, along with ongoing results from sewage surveillance, indicating that community cases might be underreported [35]. Variants of concern keep appearing, creating challenges for current vaccines and requiring continuous genomic surveillance managed by WHO's global network [36]. As of May 2025, CDC Rt estimates indicate that SARS-CoV-2 transmission is "growing or likely growing" in several states, emphasizing that COVID-19 is still not classified as endemic control [37]. These epidemiological factors necessitate ongoing surveillance via case reporting, wastewater analysis, and seroprevalence studies to swiftly identify and address new outbreaks [38]. SARS-CoV-2's high mutation rate has led to successive waves driven by variants with enhanced transmissibility or partial immune escape [39]. Recent reports indicate that new sublineages are regularly detected in wastewater and clinical samples, frequently ahead of any clinical symptoms [40,41,42]. This highlights the importance of genomic surveillance systems at national and regional levels. Even highly vaccinated populations experience breakthrough infections, indicating that vaccine-induced protection against infection wanes over time, although vaccines effectively prevent severe disease and death [43-45].

Therapeutic options, including enhanced antiviral pills and monoclonal antibodies, have significantly lowered COVID-19 mortality and hospitalization rates since 2020 [46-48]. However, access remains inequitable: low- and middle-income countries have lower uptake of new treatments, perpetuating global health disparities. Booster programs have been implemented in many countries [49]. Yet, coverage varies, and periodic recommendations by bodies like the WHO and the U.S. CDC reflect evolving evidence on optimal dosing and target populations [50].

2. Conclusions:

In 2025, COVID-19 is far from over; it remains an evolving threat necessitating uninterrupted vigilance. Continuous genomic and epidemiological surveillance, agile vaccine and therapeutic strategies, and strengthened global partnerships are imperative to anticipate and counteract new variants. Moreover, sustained public health preparedness through resilient health systems and community engagement will be key to managing SARS-CoV-2 alongside other infectious diseases in the years ahead.

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