Review article

CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

The influence of Omicron on vaccine efficacy and durability: a neurology perspective

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Omicron variants present new challenges when it comes to understanding their impact on vaccines, antiviral strategies, and possible neurological consequences. This article describes the characteristics of the Omicron variant, its epidemiology, the efficacy of vaccines and monoclonal antibodies, and its association with lymphoid depletion. We also explore the neurological implications of Omicron, focusing on its association with encephalopathy and encephalitis. There are unique challenges associated with the Omicron variant, which is characterized by distinct mutations and increased transmissibility. For a better understanding of the effects of this disease and developing strategies to combat its spread, especially concerning neurological complications, ongoing research is necessary.

Keywords: SARS-CoV-2, Omicron, Monoclonal antibodies, Vaccines, Neurology

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a type of RNA virus that belongs to the β-coronavirus genus. The angiotensin-converting enzyme-2 (ACE2) receptor is the attaching site for the spike protein used by SARS-CoV-2 to infect humans, resulting in a wide spectrum of consequences ranging from mild to severe and sometimes even fatal [1]. Even though certain infected individuals are asymptomatic or have slight upper airway symptoms, others may have symptomatic pneumonia that can advance to acute respiratory distress syndrome, requiring intubation in the intensive care unit (ICU) and potentially resulting in fatal consequences [2]. Early signs and symptoms are restricted to the upper respiratory tract (sore throat, cough), and illness, exhaustion, and muscle aches are also present. Diarrhea and nausea are less common early in the disease [3]. Stage two is characterized by dyspnea and pneumonia [4]. Other common third-phase consequences were significant cardiac and renal injury, sepsis, and subsequent infections [5]. Advanced age, the presence of comorbidities, increased disease severity, deteriorating breathing problems, elevated concentrations of D-Dimer and C-reactive protein, reduced lymphocyte counts, and illnesses are all related to mortality [6]. The 2019 Novel Coronavirus Resource at the China National Center for Bioinformation conducted an alignment of 77,801 global SARS-CoV-2 genome sequences. This analysis revealed over 15,018 mutations, of which 14,824 were single-nucleotide polymorphisms. The aim was to evaluate the genetic diversity among various SARS-CoV-2 strains [7].

Variants of concern (VOC) are more infectious strains of SARS-CoV-2 that are more likely to reinfect previously vaccinated or sick persons. The SARS-CoV-2 VOCs include the following: the α-variant discovered in the United Kingdom, the β-variant reported in South Africa, the γ-variant reported in Brazil, and the δ-variant reported in India [8]. The emergence of a new variant of SARS-CoV-2 called Omicron has been linked to several changes in the virus, including deletion mutations in the spike protein. This new variant is more transmissible and infectious than previous variations but also appears to cause milder symptoms [9]. Omicron usually causes upper respiratory symptoms such as sinus congestion, runny noses, sore throats, headaches, fatigue (mild to severe), and sneezing. Its symptoms are similar to those of a common cold and are indistinguishable from those of that illness [10].

A total of 39 mutations were found in the BA.1, BA.1.1, BA.2, and BA.3 lineages. BA.1 had 39 mutations, BA.1.1 had 40 mutations (including spike R346K), BA.2 had 31 mutations, and BA.3 had 34 mutations [11]. Around 60 mutations in the BA.1 lineage have been found; 38 of them are in the spike protein, one is in the envelope protein, two are in the membrane protein, and six are in the nucleocapsid protein [12]. The spike protein's receptor-binding domain oversees binding to the host receptor ACE2 and can improve infection and promote evade from vaccine-induced neutralizing antibodies [13]. Through the critical infection phase, the spike protein binds the primary receptor ACE2 on the exterior of the host cell and penetrates it through membrane fusion facilitated by furin and type II transmembrane serine protease or cathepsin L [14]. Antigen-presenting cells (APC) function is suppressed by lymphoid depletion, and this contributes to the lethality of coronavirus disease 2019 (COVID-19) in mice. Moreover, immunocompromised individuals accounted for 22% of COVID-19 hospitalizations, 28% of ICU admissions, and 33% of deaths during the Omicron era. In the spleens of Omicron-infected mice with brain infection, lymphoid loss and apoptosis were detected [15].

There are distinct mutation patterns in the Omicron variant; the strain is highly transmissible, and the disease is often milder than in previous strains. This may harm antigen-presenting cells and worsen the severity of a disease. As a result of the Omicron era, individuals with compromised immune systems are at a greater risk.

Epidemiology

Global public health faced a substantial threat from the emergence of SARS-CoV-2, which gave rise to COVID-19 in December 2019, originating in Wuhan, China. Approximately 23 months after the initial informed case of COVID-19, a new VOC named Omicron, associated with SARS-CoV-2, was first reported on November 24, 2021, in South Africa. The B.1.1.529 variant was first recognized on 11th and 14th November 2021 in samples collected in Botswana and South Africa [16]. As of December 16, 2021, this variant had been detected in 89 countries spanning each of the six World Health Organization (WHO) regions. By January 10, 2021, the B.1.1.529 variant had reached 105 countries. On November 28, 2021, the WHO reported that other variants of Omicron do not exhibit symptoms that are distinguishable from those of Omicron [17]. As of March 31, 2022, this variant had been recognized in 188 countries and had become the prevailing strain globally, accounting for 99.7% of recorded sequences between February 23 and March 24, 2022 [18]. Between February 6 and March 6, 2023, a total of 59,294 classifications were updated to the Global Initiative on Sharing Avian Influenza Data for sharing. Out of these, 59,083 sequences, constituting 99.6% of the total, belonged to the Omicron VOC. According to the most recent information provided by the WHO, India has documented approximately 30 cases of COVID-19 linked to this variant as of March 2023 [19]. This particular strain could potentially be more lethal than the Delta variant, which, in 2021, led to numerous deaths, particularly in India, where the toll was significant [20]. While no new precautionary measures are being recommended, it is advised that the current health protocols and communal health measures be enhanced to comprise the dispersal of the virus.

Vaccine Efficacy

The vaccines currently available have shown reduced neutralizing antibody titers (NAT), effectiveness, and efficacy when confronted with variants of the virus assessed to the original strain. In comparison to the genome of the Wuhan variant, the Omicron variant's genome contains six mutations that have led to increased transmissibility and a degree of resistance to vaccination [21]. The NAT induced by the Pfizer (BNT 162b2) vaccine was 4 to 6 times lesser for the δ-variant when compared to the earliest or the α-variant [22]. While the Omicron variant reduces the effectiveness of the Pfizer-BioNTech

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vaccine, it is important to note that vaccination can still significantly decrease the risk of hospitalization [23]. Conversely, information from the United Kingdom revealed that though two doses of the AZD1222 or BNT162b2 vaccine did not protect against characteristic Omicron infection, they did lead to a reduction in hospitalization cases attributed to the Omicron variant [24]. In a different study conducted in Hong Kong, it was found that three and four doses of the BNT162b2 or CoronaVac vaccines showed initial effectiveness against Omicron infection within 7 days of vaccination. However, the protective effect diminished rapidly, especially in the case of CoronaVac [25]. Research conducted in Australia revealed that vaccines targeting the original spike protein were approximately 80% effective in preventing severe outcomes resulting from Omicron variant infection [26].

Role of vaccines

Diminished levels of neutralizing antibodies might still offer protection against severe COVID-19 cases. This is because the Omicron variant's spike protein, which has altered surface features, is a target for T cells. T cells, typically developed after immunization, may be less influenced by the Omicron mutations compared to antibody responses [27]. The primary and most significant concern regarding the Omicron variant is its remarkable ability to evade the immune response. Omicron can evade the immunity engendered through vaccination or former infection with other variants, potentially leading to increased transmissibility [28]. Several mutations in the spike protein of this variant collectively enable it to evade antibody nullification. However, elements of the cellular immune retort, like T-cells, remain capable of recognizing and targeting the Omicron variant, offering protection against severe outcomes. Research has demonstrated that the cellular immunity generated through vaccination or prior infection remains largely effective against the Omicron spike [29].

Booster dose

In general, standard vaccination doses often do not offer sufficient protection against the Omicron variant. This underscores the need for homologous (same vaccine) or heterologous (different vaccine) booster vaccinations. It also emphasizes the importance of ensuring an adequate stock and fair delivery of vaccines. Furthermore, the plasma from entities that have recovered from the virus has a limited ability to deactivate the Omicron variant, even though some cross-counteractions have been detected besides previous variants [30,31]. Overall, COVID-19 booster vaccines that cover both the original strain and the Omicron variant are demonstrating increased effectiveness against Omicron-related COVID-19 compared to earlier, single-target vaccines. The efficacy of the Omicron booster shot, in comparison to the original vaccine, relies on the vaccine type and the duration since the initial vaccination [32] (Fig. 1).

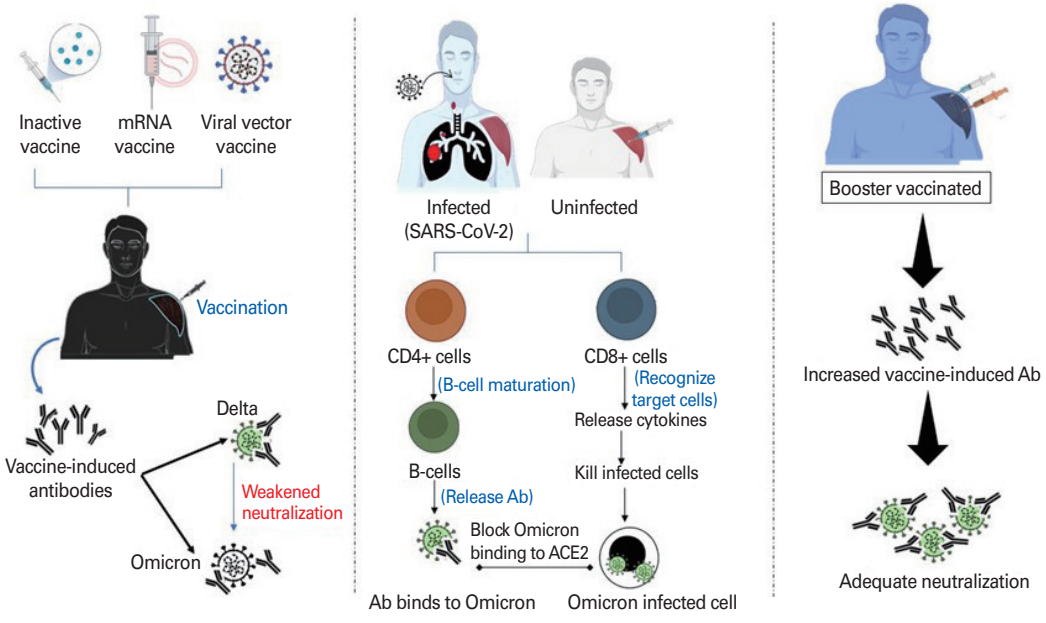

Fig. 1. Role of vaccines and booster doses in neutralizing of Omicron virus. mRNA, messenger RNA; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Ab, antibody; ACE2, angiotensin converting enzyme-2.

Monoclonal Antibodies

From the very beginning of the pandemic, a substantial amount of study has been dedicated to rapidly discovering pharmaceutical agents that can either hinder the intracellular entry of SARS-CoV-2 or hinder its viral replication. Monoclonal antibodies designed to combat SARS-CoV-2 have made a substantial contribution to these endeavors [33]. The U.S. Food and Drug Administration has accepted the use of certain monoclonal antibodies to treat COVID-19, and these antibodies have maintained their effectiveness against the Omicron variant [34]. Monoclonal antibodies are engineered to target and adhere to specific viral surface structures, known as antigens. In the case of SARS-CoV-2, monoclonal antibodies target the spike protein [35].

These antibodies work by impeding viral entry into human cells when they bind to the spike protein. This mechanism is shared by several authorized monoclonal antibodies, including Xevudy (sotrovimab), Evusheld (tixagevimab/cilgavimab), Regkirona (regdanvimab), and Ronapreve (casirivimab/imdevimab) [34,36] (Table 1). Furthermore, monoclonal antibodies can neutralize viral activity by attaching to the spike

Table 1. The effectiveness of monoclonal antibodies and antiviral medications against the Omicron variant

	Mechanism	Effectiveness
Monoclonal antibodies		
Etesevimab	Bind to the overlapping epitopes in RBD.	Distinct reduction
Tixagevimab	Blocks the interaction between the RBD of the S1 subunit and ACE2 inhibits viral host cell entry.	Efficacious
Casirivimab	Bind to the non-overlapping epitopes in RBD.	Efficacious
Bamlanivimab	Bind to the overlapping epitopes in RBD.	Distinct reduction
Imdevimab	Bind to the non-overlapping epitopes in RBD.	Distinct reduction
Cilgavimab	Bind to RBD of the spike protein.	Efficacious
Sotrovimab	Virus internalization inhibitor.	Efficacious
Antiviral drugs		
Remdesivir	Inhibits viral replication by terminating RNA transcription prematurely.	Efficacious
Molnupiravir	Increases the frequency of viral RNA mutations and impairs replication.	Efficacious
Nilmetravir	Binds to the protease active site and inhibits the activity of the enzyme.	Efficacious

The effectiveness of monoclonal antibodies and antiviral drugs in neutralizing the Omicron variant is diminished [36].
RBD, receptor binding domain; ACE2, angiotensin-converting enzyme-2.

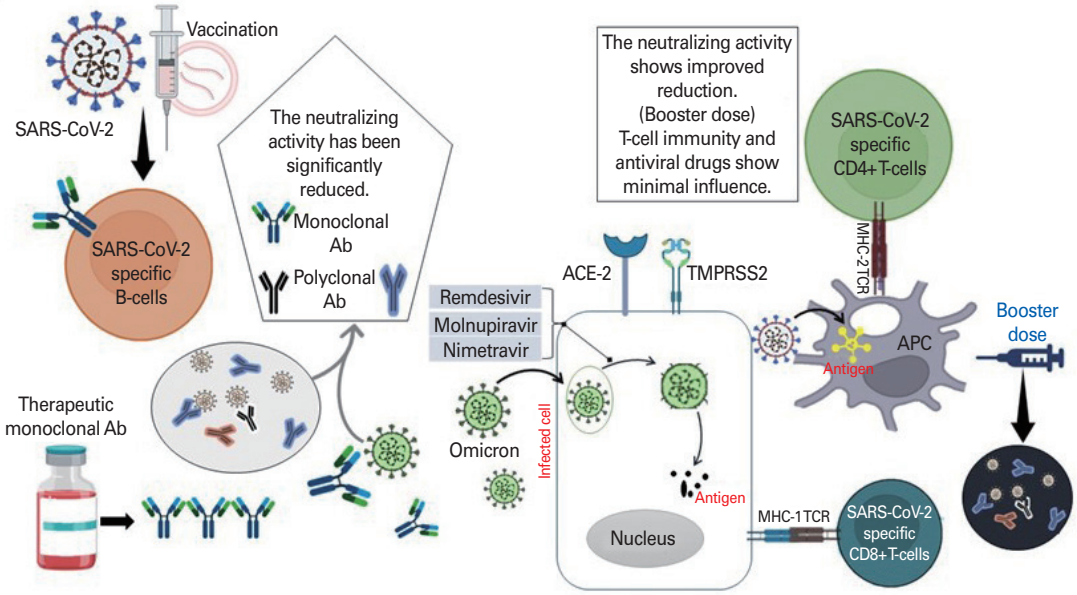

Fig. 2. Therapeutic role of monoclonal antibodies in neutralizing of Omicron virus. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Ab, antibody; ACE2, angiotensin-converting enzyme-2; TMPRSS2, transmembrane protease serine 2; APC, antigen-presenting cell; TCR, T cell antigen receptor; MHC-1, major histocompatibility complex class I.

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protein, inhibiting the virus from causing additional infection and replication within the body. It is important to note that the effectiveness of monoclonal antibodies may change based on the particular antibody and the subvariant of the Omicron variant. Some monoclonal antibodies may not retain their effectiveness against particular Omicron subvariants [32]. Monoclonal antibodies like the casirivimab/imdevimab combination bind to distinct epitopes within the spike protein receptor domain. This binding interferes with the virus's ability to interact with ACE2, thereby inhibiting the virus's intracellular penetration [37].

The Omicron variant, specifically its subvariant BA.2.75.2, has shown resistance to monoclonal antibodies and antiviral drugs [38] (Fig. 2). A study has indicated that the BA.2.75.2 subvariant displayed significant resistance to 17 out of 19 tested neutralizing monoclonal antibodies, including S309 (sotrovimab), which had maintained its effectiveness against other Omicron subvariants. This implies that the subvariant might have a higher capacity to evade the immune response compared to earlier Omicron subvariants [39]. Initial findings indicate that the BA.2.75.2 subvariant of the Omicron variant may have a greater affinity for the ACE-2 cell entry receptor, which could potentially lead to faster transmission. It is crucial to continue research to comprehend Omicron's characteristics fully [40].

Lymphoid Depletion

Lymphoid organs, including lymph nodes, the spleen, and tonsils, have a crucial role in the immune system's defense against infections. They serve as sites for the production and storage of immune cells that play a key role in combating various pathogens, including viruses [41]. It is worth noting that in certain instances of viral infections, such as with previous variants of SARS-CoV-2, there have been observations of lymphoid depletion or dysfunction [42]. For SARS-CoV-2 to enter cells, the human angiotensin-converting enzyme 2 (hACE2) protein must be present. In a study carried out on K18-hACE2 mice, which are vulnerable to this disease, it was exposed that the Omicron variant can lead to brain infection along with lymphoid depletion. This study observed instances of lymphoid depletion and apoptosis in the spleen of mice affected with Omicron, particularly in cases where brain infection occurred [15]. The findings indicate that the presence of lymphoid depletion lesions in the spleen is a significant aspect that correlates with mortality rates. Lymphoid depletion, along with a decline in APC function, was a distinct characteristic observed in infections caused by the Wuhan and δ-types of SARS-CoV-2 but not in other infections like Omicron and influenza-A. This lymphoid depletion, particularly in mice infected with the Wuhan and δ-variants, had the most significant predictive value for the severity of the disease [43].

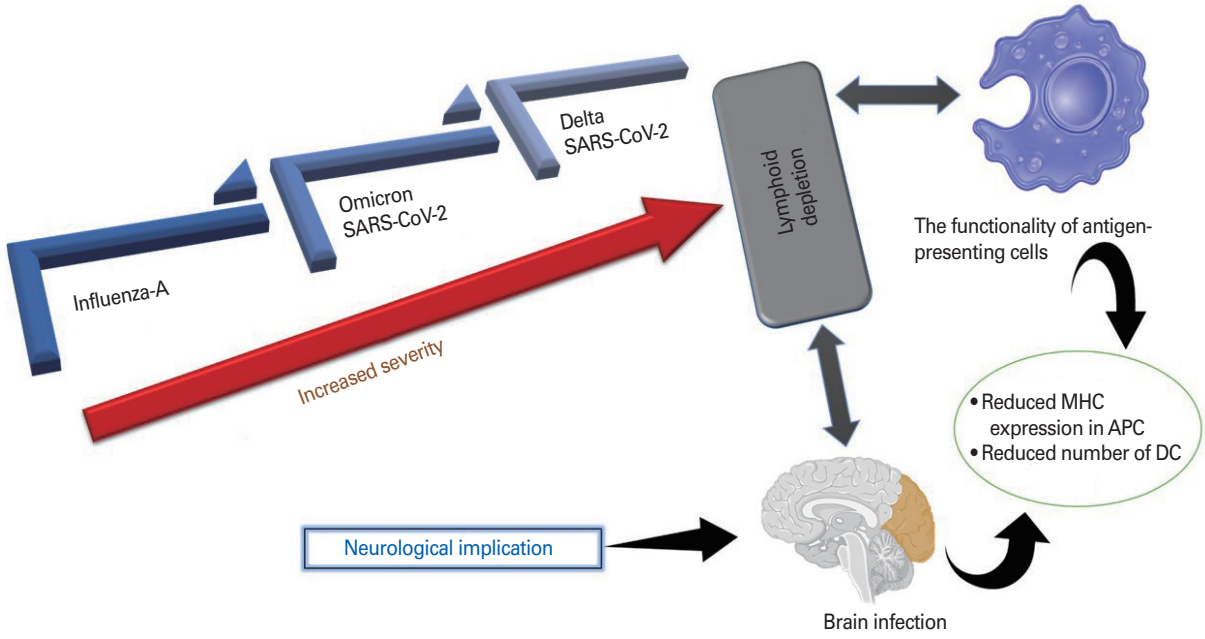

Fig. 3. Suppressed antigen-presenting cell (APC) function is linked to the depletion of lymphoid cells. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MHC, major histocompatibility complex; DC, dendritic cells.

Omicron has been detected in the platelets of severe patients, and it triggers a process known as selective autophagy within these platelets. However, the mechanisms involved in the intraplatelet processing of Omicron cargo, as part of the innate immune response, differ from that of the Delta variant (Fig. 3). This suggests that the mutations present on the spike protein of Omicron may modify the communications between the virus and platelets [44].

It is crucial to emphasize that these findings are derived from animal models, and more extensive research is required to ascertain the extent of the connection between Omicron and lymphoid depletion in human cases. Further investigations and studies in human subjects are necessary to understand the implications of these observations for human health fully.

Neurological Implication

Neurological complications associated with COVID-19 can manifest in diverse ways, and brain imaging studies have revealed a range of abnormal findings. Several conditions can lead to brain damage, including infarction, vasculitis, acute necrotizing encephalopathy, acute disseminated encephalomyelitis, posterior reversible encephalopathy syndrome, and severe encephalitis, which can sometimes result in cytotoxic lesions of the callosal splenium. COVID-19 can lead to various neurological issues, and the extent and nature of these complications can vary among individuals [45]. Recent studies have indicated a probable link between the Omicron variant and neurological complications, including conditions like encephalitis and encephalopathy [46]. A cohort study in China observed a significant increase in new-onset neurological issues, particularly encephalitis and encephalopathy, during the Omicron COVID-19 wave. Additionally, a case was reported involving a 28-day-old baby who developed serious encephalopathy linked to the Omicron variant [47]. Fever and respiratory symptoms were the main symptoms in children with COVID-19. However, the Omicron variant period showed an increase in severe neurological manifestations. During the Omicron variant period, an increase in severe neurological manifestations was observed in children with COVID-19. Altered mental status and seizures were more common with the Omicron variant compared to previous variants [48].

The devastating effect of COVID-19 on the central nervous system (CNS) is well-documented. Recent research suggests three key mechanisms that contribute to this damage. Firstly, the virus can penetrate the CNS through the olfactory tract or by attaching to the ACE2 receptor. This triggers a discharge of pro-inflammatory cytokines by astrocytes and microglia in the brain, exacerbating the CNS dysfunction. Secondly, COVID-19 can break down the blood-brain barrier, allowing peripheral cytokines to enter the CNS and contribute to the inflammatory response in the brain. Finally, COVID-19 infection in brain cells can cause oxidative stress and mitochondrial malfunction, which further worsens CNS dysfunction and results in the neurological symptoms perceived in many COVID-19 patients. It is crucial to understand these mechanisms to develop effective treatments and prevent long-term CNS damage caused by COVID-19 [49]. The conventional belief that SARS-CoV-2 is only an airborne virus that targets the respiratory system may hinder neurologists from considering it as a cause of encephalopathy [50]. It is important to note that Omicron can lead to the development or worsening of neurological diseases. In some cases, it can even result in life-threatening conditions like encephalitis/encephalopathy. Therefore, it is recommended that pathogen studies in the cerebrospinal fluid (CSF) be conducted early in the therapy process to guide treatment. Additionally, the COVID-19 booster has been proven to reduce mortality. To protect vulnerable individuals, it is advisable to consider a wider immunization program [47].

Conclusion

With the advent of the Omicron variety, new dynamics in the fight against COVID-19 have emerged. With its distinct mutation patterns and increased transmissibility, the Omicron has generated serious concerns about vaccination efficacy, the need for booster injections, and the potency of monoclonal antibodies. The probable link between Omicron and lymphoid depletion raises concerns about the immunological response to this variation. More studies are needed to determine the breadth of this relationship, particularly in human situations. Furthermore, the neurological consequences of Omicron, such as its link to encephalitis and encephalopathy, demand continuing research and monitoring from the medical community.

Omicron can worsen neurological conditions and even lead to life-threatening illness. Early pathogen studies in the CSF can guide treatment. To effectively resist the Omicron variety, researchers, healthcare providers, and policymakers must collaborate and adapt to the ever-changing COVID-19 scenario. This means that in addition to fine-tuning immuni-

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zation protocols and booster doses, research into Omicron's distinct characteristics and possible long-term effects must continue. The COVID-19 booster reduces mortality, and wider immunization is recommended to protect vulnerable individuals. To effectively handle the changing issues presented by this variation, we must continue to be knowledgeable and adaptable in our response to Omicron. A large-scale therapy study of persons with COVID-19 infection who have neurological symptoms is still required.

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