Since its emersion, coronavirus disease 2019 (COVID-19) has been a significant global dilemma. Several mutations in the severe acute respiratory virus (SARS-Co-2) genome has given rise to different variants with various levels of transmissibility, severity and mortality. Up until November 2021, the variants of concern declared by the World Health Organization were Alpha, Beta, Delta and Gamma. Since then, a novel variant named Omicron (B.1.1.529) has been developed. BA.1, BA.1.1, BA.2 and BA.3 are four known subvariants of Omicron. The Omicron variant involves new mutations in its spike protein, most of which are in its receptor binding site, and increase its transmissibility and decrease its antibody and vaccine response. Understanding the virology and mutations of Omicron is necessary for developing diagnostic and therapeutic methods. Moreover, important issues, such as the risk of re-infection, the response to different kinds of vaccines, the need for a booster vaccine dose and the increased risk of Omicron infection in pediatrics, need to be addressed. In this article, we provide an overview of the biological and immunopathological properties of Omicron and its subvariants, its clinical signs and symptoms, Omicron and pediatrics, vaccines against Omicron, re-infection with Omicron, diagnostic approaches and specific challenges of Omicron in the successful control and management of the rapid global spread of this variant.

KEYWORDS
biology, coronavirus disease 2019 (COVID-19), genetic, Omicron, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), virology

INTRODUCTION
Two years ago, a novel coronavirus disease 2019 (COVID-19) started in Wuhan, China. Caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it has created a problematic and dangerous scenario worldwide.\textsuperscript{1–3} As this pathogen swiftly spread around the globe, COVID-19 was declared a global pandemic and a public health emergency of worldwide importance in early 2020. COVID-19 infection manifestations can range from asymptomatic (no symptoms) to acute pneumonia and even multiple organ failure, and the severity of the disease varies from mild to deadly.\textsuperscript{4,5} COVID-19 has infected and killed over 406 and 5.8 million individuals, respectively, in the last two years. Based on the available data, 52.7% of the global population has received at least one dose of a SARS-CoV-2 vaccine to help eliminate this infection (COVID-19 Map, Johns Hopkins Coronavirus Resource Center, https://coronavirus.jhu.edu/map.html, accessed 31 January 2022).

SARS-CoV-2 contains the capacity to undergo mutations and antigenic change over time. This incredibly infectious epidemic is

List of abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; CRS, cytokine release syndrome; IL-6, interleukin-6; IVIG, intravenous immunoglobulin; NAAT, nucleic acid amplification testing; NGS, next-generation sequencing; RBD, receptor binding domain; RDT, rapid diagnostic test; RNA, ribonucleic acid; RT-PCR, reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VOC, variants of concern; WHO, World Health Organization.
being fought by scientists, academics and medical professionals, but the announcement of the new coronavirus variety has caused a shock recently. Based on the Centers for Disease Control and Prevention, variation between SARS-CoV-2 subtypes contributes to disease progression, increased transmissibility, decreased treatment efficacy and other worrying aspects (‘What you need to know about variants’, https://www.cdc.gov/coronavirus/2019-ncov/variants/about-variants.html?c_id = 11720:covid-variant:sem.ga:RG:GM:gen:PTN:FY22, accessed 7 February 2022). Particular strains of SARS-CoV-2, known as variants of concern (VOC), are more infectious and are more likely to re-infect previously vaccinated or infected individuals. The VOCs of SARS-CoV-2 include the following: the Alpha (B.1.1.7) variation which was first detected in the UK, the Beta variation (B.1.351) which was found in South Africa, the Gamma (P.1/B.1.1.28) variation which was first seen in Brazil, and the Delta (B.1.617.2) variant which was found in India. The features of Delta and Omicron have been listed in Table 1.

On 24 November 2021, a novel coronavirus variant, Omicron (B.1.1.529) was detected in a patient’s test sample in South Africa. The number of mutations in this strain was greater than in any prior strain of the virus, nearly 50, of which more than 26 are in its spike protein region. On 26 November, this novel variant was announced as a variant of concern (VOC) by the World Health Organization (WHO). Soon after this announcement, Omicron was reported in many other countries. Omicron is the most altered of the VOC variants, leading to expanded transmissibility. There are several mutations in this new “Omicron variant” that might significantly impact its behavior. It may resist vaccine-induced immunity and pose an expanded chance of re-infection. Moreover, alterations in the spike protein cause the virus to show unique traits, such as increased transmissibility and severity, which can lead to more severe infection as well as higher morbidity and mortality rates. The rapid spread of Omicron is an important matter of concern since the infection rate has been reported to be 7 times higher after only 2 weeks.

The increased pathogenicity of the Omicron variety has made it a public health concern. Notably, Omicron appeared when humanity was on the verge of achieving worldwide immunity with global vaccination against SARS-CoV-2. The emergence of recent SARS-CoV-2 variations, such as Omicron, serves as a reminder that this disease pandemic is still far from over. Individuals must obtain the vaccine as soon as possible and keep following existing measures to reduce virus transmission, including physical separation, mask use, frequent hand-washing and ventilation of interior spaces. In this literature review, we aim to review the virological, biological and diagnostic implications of Omicron and discuss the specific challenges confronted in fighting this novel variant of SARS-CoV-2.

### 1.1 Immunopathogenesis of Omicron

SARS-CoV-2 contaminates many respiratory system cell types by attaching to the ACE2 receptor, including vascular endothelial cells, airway and alveolar epithelial cells, and macrophages. Innate immune cells, mainly macrophages and neutrophils, identify the pathogen-associated molecular patterns through their Toll-like receptors and activate the host immune system. Interleukin-6 (IL-6), IFN-γ and monocyte chemoattractant protein-1 are secreted by innate and adaptive immune cells. These cytokines and chemokines help monocytes, macrophages and neutrophils shift the infection. These cells release cytotoxic chemicals to eradicate the virus. Immune homeostasis may be altered owing to an imbalance in the immune system’s ability to respond to a viral infection. An essential part of innate immunity is the production of inflammatory mediators and the recruitment of other immune cells into the lungs by alveolar macrophages.

| Variant features | Delta      | Omicron    | Reference |
|------------------|------------|------------|-----------|
| Lineage          | B.1.617.2  | B.1.1.529  | [8]       |
| Origin           | India      | South Africa | [8,9]  |
| Subvariants      | AY.4.2     | BA.1/BA.1.1/BA.2/BA.3 | [10] |
| Total mutations  | More than 13 | More than 50 | [11,12] |
| Spike mutations  | 9          | 36         | [13]      |
| Transmissibility | ↑          | ↑↑↑↑↑↑↑↑↑↑↑↑ | [12,14,15] |
| Infectiousness   | ↑          | ↑↑         | [15-17]   |
| Re-infection     | ?/?/↑      | ↑↑↑↑↑↑↑↑↑↑↑↑ | [17,18]   |
| Mortality        | ↑↑         | ↑↑↑↑↑↑↑↑↑↑↑↑ | [19]      |
| Pediatric infection | ↑↑         | ↑↑↑↑↑↑↑↑↑↑↑↑ | [16,20]   |
| Vaccine efficacy | ↑↑         | ↑↑↑↑↑↑↑↑↑↑↑↑ | [21-24]   |

**Table 1** Comparison of Delta and Omicron variants of concern
Cytokine release
The capacity of SARS-CoV-2 has been revealed to disrupt normal immunological responses in severe COVID-19 patients by draining the immune system and producing uncontrolled inflammatory reactions. Severe COVID-19 manifests itself through raised cytokines, organ failure, lymphocyte hyperactivity and malfunction, lymphopenia, and granulocyte and monocyte irregularities. Studies have also demonstrated that the IL-6 signaling pathway has a particular role in CRS pathogenesis.

There are two primary methods through which SARS-CoV-2 is transmitted, including direct virus spread through droplets/airborne from infected patients. In the pathophysiology of COVID-19, the immune system plays a critical function, and an uncontrolled innate immune response and problems with adaptive immunity are two ways in which SARS-CoV-2 can induce overall tissue damage. SARS-CoV-2 has been revealed to disrupt normal immune responses in severe COVID-19 patients by draining the immune procedure and producing uncontrolled inflammatory reactions. There is mounting evidence that the immunological characteristics of SARS-CoV-2 patients are inextricably connected to the disease progression. Leukocytosis, lymphopenia and a high ratio of neutrophils to lymphocytes are the first changes in blood cells. SARS-CoV-2 has been revealed to disrupt normal immune responses in severe COVID-19 patients by draining the immune procedure and producing uncontrolled inflammatory reactions. Severe COVID-19 manifests itself through raised cytokines, organ failure, lymphocyte hyperactivity and malfunction, lymphopenia, and granulocyte and monocyte irregularities. Studies have also demonstrated that the IL-6 signaling pathway has a particular role in CRS pathogenesis.

According to investigations, tissue damage in COVID-19 appears to be caused chiefly by immune system disturbances and not direct viral damage. The host’s immunological response to COVID-19 appears to be crucial in the development of clinical symptoms and the pathogenesis of this disease. There is an excessive expansion of monocytes, macrophages and neutrophils near the site of infection because of the presence of proinflammatory cytokines. Cytotoxic substances like reactive oxygen species, which are constructed by these cells, can cause cell death and tissue damage. Understanding the immunopathogenesis of COVID-19 has helped in developing efficacious immunological therapies for COVID-19; however, the exact mechanisms of the immunopathogenesis of Omicron are unclear.

Previous research uncovered that the Omicron variation might be 10 times more transmissible than the wild type. The capacity of Omicron to escape the vaccination may be two times greater than that of the Delta version, according to 132 3D structures of antibody receptor binding domains (RBDs). Omicron possesses a novel mode of entry into cells, making it more effective than Delta at entering cells and less efficient at causing lung illness. It is capable of causing upper respiratory infection but not lung disease, which makes Omicron’s activity more similar to that of prior human coronaviruses clinically. There is still the possibility of severe illness; therefore, it is not identical to them, but it functions pretty similarly. Omicron virus replication is diminished in cells overexpressing TMPRSS2 but boosted in cells that only allow endosomal entrance. Additionally, by inhibiting cell-surface fusion mediated by TMPRSS2 and endosomal fusion mediated by cathepsin, Omicron can enter via either pathway but prefers endosomal fusion over cell-surface fusion. The capability of Omicron to infect cells via both routes significantly expands the number of cell types that it can infect. Finally, research indicates that Omicron may utilize ACE2 receptors from a wider variety of host species than previous variations, particularly mice and domestic fowl. This raises the chance that SARS-CoV-2 might establish a long-term reservoir in a new animal host, facilitating the virus’s spread in future human epidemics. However, while the full efficacy of vaccinations vs. Omicron has not been proved, it may give some protection and decrease the spread of COVID-19.

1.2 Clinical signs and symptoms of Omicron

COVID-19 prevention and control efforts depend heavily on SARS-CoV-2 diagnosis. SARS-CoV-2 diagnosis is based chiefly on epidemiological data, clinical symptoms and adjuvant technologies like nucleic acid detection and immunological testing. Omicron clinical signs and symptoms are divided into the most common, the less common and
the severe. Fever, cough, tiredness and a loss of taste or smell are the most common complaints of patients. It is not uncommon for the Omicron to cause other symptoms, such as pharyngitis, headaches, skin rashes, discolored fingers and toes, red or itchy eyes, stomach cramps and diarrhea. Furthermore, it can cause severe symptoms such as chest discomfort, shortness of breath, difficulty moving, trouble breathing and disorientation. In case of respiratory involvement, pulmonary characteristics, such as cough, scratchy throat, shortness of breath and pneumonia, may also be observed. Studies have reported that, compared with the Delta variant, Omicron is associated with a 50–70% reduced risk of hospitalization.

1.3 Laboratory diagnosis of Omicron

COVID-19 assays, both PCR and rapid test, can detect all Omicron subvariants as COVID-19, but additional testing is required to differentiate the subvariants from one another and other COVID-19 variants. The use of swift and accurate diagnostic technologies to detect the virus and then pick appropriate and effective therapies is significant for epidemic control. Reverse transcriptase-polymerase chain reaction (RT-PCR), the gold-standard test for laboratory diagnosis of SARS-CoV-2, remains the best method for determining if a patient has Omicron. The S gene has been most frequently affected by Omicron mutations. SARS-CoV-2 may also be identified by searching for the S genes that encode the spike glycoprotein. The E, Rd, Rp and N genes are the primary focus of the RT-PCR diagnostic kits that have been approved for usage. Using the most commonly used RT-PCR kits makes it possible to identify the RT-PCR test result as either positive or negative. The S gene mutation may or may not cause a positive result, depending on the test. Patients may be recommended to get their DNA sequenced to discover the new mutation.

Laboratory diagnosis of Omicron can be divided into two parts: first molecular diagnosis and then immunological diagnosis. Molecular diagnosis has two main sections: real-time PCR and next-generation sequencing (NGS). Immunological diagnosis entails looking for antigens and antibodies. Viral RNA may be amplified via molecular assays, allowing for the detection of viral infection. The term “nucleic acid amplification testing” also describes these tests (NAATs). The first step is to collect a sample from the nose or mouth of a potentially infected individual, where the virus could be present. A molecular diagnostic technique can identify millions of copies of viral genomic material if SARS-CoV-2 is present in the sample. To conduct molecular testing, secretions of nasopharyngeal surfaces, which are most likely to carry the virus, must be collected. Most tests now available or in development for COVID-19 use nasopharyngeal or oral specimens to make testing easy. If someone is infected, viral RNA will be detected. Several molecular diagnostics are available, and some produce findings faster than traditional PCR-based techniques. Rapid molecular diagnostics, such as LAMP, are specific but exceedingly sensitive since they intensify genetic material in the patient sample. All of these approaches follow the same basic procedure: identify DNA or RNA pathogens and amplify a region of the pathogen’s genome discovered. Then, if any amplified genetic material is present in the sample, provide an output measurement showing its amount. In BA.1, there is a small deletion mutation in the form of deletion 69–70, which changes the structure of the spike protein and allows it to be hidden from the PCR test. Thus the test result is doubtful for Omicron. Other specialized tests can identify the strain, but in the BA.2 sub-variant, this omission mutation does not exist, and despite being Omicron, the test result will be erroneous with other strains, especially the Delta variant in routine PCRs. Type BA.2 is known in the USA as the Stealth Omicron because it spreads faster and carries mutations that make it difficult to quickly differentiate this subtype from the Delta type by routine PCR tests.

NGS sequencing methods have quickly established themselves as the technique of choice for various virological applications, including the discovery of new viruses. This method is critical in determining the origin of SARS-CoV-2. Most coronavirus and SARS-CoV-2 genomes found using NGS are currently publicly available for academics to use in their investigations on the origins of SARS-CoV-2. SARS-CoV-2 has benefited from the use of both second- and third-generation NGS technology and a variety of proprietary library preparation techniques created by various companies. When using NGS-based techniques, whole-length viral genomes may be rebuilt, even for viruses that have not been previously defined, which is one of the most critical advantages of NGS. NGS can also be useful to detect probable novel variations of SARS-CoV-2 and Omicron subvariants. Therefore, sequencing of further specimens is necessary.

Antigen-detecting diagnostic testing identifies viral proteins in upper respiratory samples or saliva to screen for SARS-CoV-2 infection. The use of antigen-detecting rapid diagnostic tests (Ag-RDTs), rather than NAATs, may be a more practical method of screening for SARS-CoV-2. Ag-RDTs work best in those with a high viral load early in their illness and would be most accurate in areas where the SARS-CoV-2 prevalence is less than 5%. Ag-RDTs have a low positive predictive value when there is a low transmission. Hence, NAATs are recommended for first-line testing or the confirmation of Ag-RDT positive results in these situations. Ag-RDTs are less accurate than NAAT, especially in asymptomatic individuals. However, this can be mitigated by carefully selecting cohorts for testing. The WHO recommends Ag-RDTs that meet 80% sensitivity and 97% specificity minimum performance parameters (‘Antigen-detection in the diagnosis of SARS-CoV-2 infection’, https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov2-infection-using-rapid-immunoassays, accessed 5 February 2022).

Sequencing is now the most frequently used approach for identifying, classifying, and tracking SARS-CoV-2 variations. Compared with other genotyping procedures like PCR, sequencing is slow and needs specialist mechanisms and interpretation. Although PCR techniques target preselected mutations, they are less expensive and more convenient than sequencing for SARS-CoV-2 genotyping, producing more rapid results. Because variations propagate throughout populations over time, these techniques may allow for an improved search of variants, particularly in resource-limited contexts. Genome sequencing is the gold standard for tracking the virus’s genesis and
evolution, but it is expensive, time-consuming and challenging to get. Using single-nucleotide discriminating molecular beacons, multiplex quantitative RT-PCR assays for SARS-CoV-2 have been created that identify all VOCs and additional variants of interest in the viral genome, for a total of nine mutations. Several significant mutations in the spike protein-coding sequence have been identified using quantitative RT-PCR experiments. Using readily accessible five-color thermal cyclers, these tests may be quickly and inexpensively put into practice to monitor the spread of these variations.54

SARS-CoV-2 antigens emanating from a spike glycoprotein or nucleocapsid will elicit one of three reactions: a robust, weak or difficult-to-detect reaction. Individuals with lesser antibody responses to infection had better viral clearance rates and prognoses, whereas patients with robust responses had more severe clinical outcomes. Therefore, the human antibody response to viral infection can be an independent prognostic indicator. Likewise, antibodies cannot shed viral particles from the body soon after release since a patient might even have extended virus shedding after seroconversion.65

Serum and other body fluids can be tested for antibodies using serological tests. Immune reactions to microbes and foreign or one’s own proteins contain antibodies, which may be discovered by serological testing. A lack of commercially available reagents for serological tests mean that they are not routinely used to detect coronavirus infections.55 When a virus enters the body and releases viral antigens into circulation, the human immune system produces IgA, IgM and IgG antibodies that are more effective and long-lasting than the antigenic proteins. As a result, scientists are switching their attention to serological antibodies as a diagnostic option rather than focusing on viral antigens to create faster, more straightforward and more sensitive serological tests.66 To identify SARS-CoV-2, many studies have employed S or N protein-specific antibodies. It was demonstrated that testing for virus-specific antibodies was more accurate than testing for total immunoglobulin.67

The intensity of a patient’s symptoms can be reflected in serological detection results, but RT-PCR results can only provide a limited view. Compared with mild-to-moderate COVID-19 patients, severe COVID-19 patients had considerably higher levels of IgM and IgG antibodies. Most serological test kits presently utilize particular IgM and IgG for detection. Changes in a virus’s genome can change its proteins, making an antigen or serology test less effective.68

1.4 | Structure, mutations and biology of Omicron

SARS-CoV-2, a novel Beta coronavirus, is an enveloped virus with a single-stranded RNA genome and a helical symmetry nucleocapsid. The host cell receptor for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2).69,70 SARS-CoV-2 contains three main proteins. The envelope (E) protein is a tiny protein complex that helps to construct pentameric ion channels in the body. The M protein is the principal structural protein. The head S1 and stem S2 subunits make up the spike (S) protein. The S protein promotes the binding of the virus to ACE2 receptors on host cell surfaces.3 It is usual for the S1 heterotrimer’s N terminus to attach to carbohydrate molecules on the cell surface. However, the C terminal domain only targets angiotensin II and aminopeptidase N.71 The primary target tissue for SARS-CoV-2 is the respiratory epithelium. As the virus replicates and releases from the lungs, it causes non-specific symptoms, including headache, muscle aches, fever and respiratory problems.72 The location of ACE2 receptors in various organs may help clarify where infections occur. For instance, ACE2 receptors are also expressed by the intestinal epithelium and blood vessel endothelial cells, reflecting gastrointestinal complaints and cardiovascular issues.73,74

It is important to remember that structural proteins, including those found in the spike, envelope, membrane and nucleocapsid, play an essential part in the virulence, pathogenicity and virion assembly processes.75 The S protein binds to cell surface receptors, cleaving the receptor-attached S protein by a host cell protease, which causes the host cell and virus membranes to merge. Virus RNA uses host facilities to induce specialized RNA polymerase and viral genomes and proteins. The viral M protein combines into the endoplasmic reticulum and promotes the creation of viral particles, which are subsequently created, exocytosed and released as new virions.76 The spike of SARS-CoV-2 is a critical predictor of viral infectivity and mediates cell entrance via interactions with ACE2 and TMPRSS2 at the cathepsins in endosomes or the plasma membrane.77

Since the beginning of 2020, there have been three significant COVID-19 outbreaks in South Africa. The Beta and Delta variations, respectively, are responsible for two of them. Within roughly 100 days of the epidemic, the rate of infections linked to the Beta variation grew to 50% of all daily infections. The infection rate for the Delta version, on the other hand, increased to 80% within the same time frame. The Delta variety is more capable of spreading than the Beta variant.16 In less than a month, Omicron had spread to 90% of the population in South Africa. Doubling times for Beta, Delta and Omicron types were estimated to be 1.7, 1.5 and 1.2 days.78 Based on studies, Omicron is more efficiently transmitted than Beta or Delta. In addition, a recent study from South Africa suggests that Omicron may enhance the chance of SARS-CoV-2 re-infection.79

Various sequences studies have indicated that just a few mutations successfully induce a more severe illness with high disease transmission and pathogenicity.79 COVID-19 spread through the population was associated with several gene mutations in SARS-CoV-2, similar to other RNA viruses. According to phylogenetic analysis, the Omicron variation is intimately bonded to the Gamma (P.1) variant.80 Compared with the previous variants, at least 50 mutations have been found in the Omicron genome, 32 impacting the spike protein.81 Beta contained six and Delta had 10 variant-specific mutations, while Omicron has 26. Omicron has 23 of the 30 signature mutations, and none of these mutations has ever been found in any other variant. Altogether, 46 distinct mutations in the S, ORF1a and ORF1b genes of the Omicron variant were identified, with over 50% frequency.82

As mentioned earlier, numerous non-synonymous mutations in the Omicron variants have been discovered through genomic sequence analysis. Most of these mutations are in spike proteins and are correlated to disease severity, transmission and immune evasion.
Furthermore, more than 60 insertions, substitutions and deletions have been discovered in Omicron, creating the variant with the most mutation area of all SARS-CoV-2 variants reported to date. The RBD of Omicron contains numerous threatening mutations. One of Omicron’s pathogenic properties appears to be its ability to connect to ACE2, which is a particular source of concern when virus mutations improve their capacity to connect to cell surface receptors. Two mutations in the Omicron may significantly boost the S protein’s affinity to ACE2. Moreover, three mutations located near the cleavage site of Omicron have a potential chance of improving transmissibility, whereas other mutations may lead to immune system evasion. Changing a hydrophilic amino acid to a hydrophobic amino acid in the most recent SARS-CoV-2 variant would affect the hACE2 and RBD connection. Omicron has an approximately 6–10 times extended mutation rate in the receptor-binding motif compared with other VOC variants. As a result, the virulence aspects of the Omicron variation may be superior to those of the other variants. It is crucial to mention that many of the “concerns” with the mutations stated above are theoretical.

1.5 Subvariants of omicron

The WHO classifies Omicron into four different substrains: BA.1, BA.1.1, BA.2 and BA.3 (Table 2). BA.1 and BA.2 differ significantly in their mutations in the most critical places that are often associated with higher transmissibility. When compared with Omicron subvariants, BA.2 is 1.5 times more transmissible. On the other hand, in comparison with BA.1, BA.2 has a significant growth advantage. When identifying the BA.2 variation, there are five distinct mutations on the spike (RBD) that are frequently related to increased transmissibility. According to studies, the BA.2 subvariant infects individuals at a 33% higher rate than BA.1. Researchers at Statens Serum Institute have demonstrated that if you have been exposed to Omicron BA.2 in your family, you have a 39% chance of contracting the infection within 7 days. In contrast, if you have been exposed to BA.1, your risk is only 29%. According to a Danish study, BA.2 or Omicron spreads about 1.5 times faster than Omicron itself, and researchers did not find any evidence that the disease was more severe than BA.1, but they said that it could cause a wave of infection. Furthermore, laboratory results indicate an increase in the pathogenicity of BA.2 compared with BA.1. The new SARS-CoV-2 subvariants emerged concurrently from the same source with an equal probability of global spread. However, it is unclear why just BA.1 dominated the global expansion. This is most likely due to spike protein variations, which are critical for viral propagation and host cell entrance.

According to the UK Health Security Agency, there have been over 1000 instances of BA.2. Compared with the original Omicron form (BA.1), BA.2 has an expanded growth rate in all regions of England. Moreover, there is more evidence that people with BA.2 were more likely to spread the disease to their families. It has been shown that 13.4% of BA.2-infected individuals spread the virus, while this is only 10.3% in BA.1-infected patients. The agency also stated that early research revealed no indication of BA.2 vaccination efficacy against symptomatic illness compared with BA.1. At least 25 weeks after two doses, vaccination efficacy against symptomatic infection was reported to be 9% for BA.1 and 13% for BA.2, which climbed to 63% for BA.1 and 70% for BA.2 2 weeks after a third booster dose.

Moreover, two novel subvariants of the BA.2 have emerged, recognized as BA.2.12 and BA.2.12.1. Already, these two sublineages of BA.2 encompass an estimated 80.6% of all COVID-19 infections in New York. Even if the original BA.2 Omicron subvariant looks to be 23–27% more transmissible, the new BA.2.12.1 subvariant appears to be a significant time rush for the virus. The COVID-19 vaccinations are as effective against BA.2.12 and BA.2.12.1 as BA.2.

New cases of SARS-CoV-2 Omicron strain subvariants are now being tracked by the WHO to determine whether they are more infectious or destructive. The WHO have announced that BA.4 and BA.5 have been added to its list of Omicron variations to track. This will shed light on their immunological resilience. BA.1 and BA.2 are the subvariants that are presently prominent worldwide. BA.1.1 and BA.3 are already under the watchful eye of the WHO. Scientists are

| Subvariant features | BA.1 and BA.1.1 | Ba.2 | Ba.3 | Reference |
|---------------------|-----------------|------|------|-----------|
| Transmissibility    |                 | ![Increase] | ![Decrease] or ![Increase] | ![Increase] | 46,87 |
| Global dominance    |                 | ![Increase] | ![Increase] | Ongoing | 88 |
| Number of additional mutations | 20 | 27 | 13 | Ongoing | 89 |
| Deletions in S proteins | ![Increase] | ![Decrease] | Ongoing | ![Increase] | 46 |
| Re-infections       |                 | ![Increase] | ![Increase] | Ongoing | 90 |
| Severity            | Ongoing         | Ongoing | Ongoing | Ongoing | 9 |
| Contagious          |                 | ![Increase] | ![Increase] | Ongoing | 9 |
| Hospitalization     |                 | ![Increase] | Ongoing | Ongoing | 46 |

TABLE 2 Characteristics of Omicron subvariants
still studying the novel Omicron variety. As of right now, BA.5, found in South Africa, is spreading at an 84% faster rate than BA.2. The BA.4 strain found in South Africa is now growing 63% faster than the BA.2 strain. In the Delta form, the L452R harmful mutation is present in both BA.4 and BA.5. (What do we know about Omicron BA.4 and BA.5?, Medriva, https://medriva.com/what-do-we-know-about-Omicron-ba-4-and-ba-5/).

### 1.6 | Transmission of Omicron

The Omicron variation spread over the world in days and the number of cases rose rapidly. There is not enough information available on infection rates to determine how contagious the newly discovered, highly altered Omicron strain is. Studies have shown that the Gamma variation had similar infection rates to the wild type. In contrast, the Beta variant had fewer infections, and Delta was approximately two-fold more efficient in disease spread than the wild type. The Omicron variation has an infection rate four times greater than the wild type, while the Delta variant had an infection rate that was twice as high. Various circumstances can influence the Omicron variant’s increased transmission capacity. The most important one is that over 30 mutations changed the S protein of SARS-CoV-2 in Omicron. Furthermore, the rate of re-infection is significantly increased in the Omicron variation. It has been reported that, in South Africa, the re-infection rate of formerly COVID-19-infected individuals is significantly higher with Omicron. This is attributed to the mutations of the spike protein in Omicron’s structure. According to further computational analysis, Omicron has been shown to have a greater affinity for ACE2 than Delta. Q498R, S371L and T478K are mutations in the RBD of Omicron’s S protein accountable to this enhanced affinity to ACE2. Also, Omicron is not as good at causing cell fusion inside cells as Delta, and this is because of the imperfect cell-to-cell transmission capability of Omicron. Fusion cells are prevalent in tissues taken from the lungs after a destructive infection. To support the findings of the decreased cell entrance, an infection experiment utilizing lung cells used a live Omicron variation which showed that Omicron’s entrance into the target cell was significantly lower than that of the Delta variant.

An early clinical investigation in South Africa found that the Omicron variation might evade the immune system and spread more quickly, both of which could have serious repercussions. Investigators gathered evidence of Omicron immune escape potential, discovering that alterations at the T478, N440K, and N501Y locations increase the infectivity of OMICRON ten times more than the original SARS-CoV-2 variant and two times more than Delta variant, respectively. When neutralized with pseudo-type Omicron virus, antibody titers were 36 times lower for convalescent serum from patients infected with early strains and 39 times lower for convalescent serum from patients infected with the Delta strain, indicating natural immune escape by Omicron.

Coronavirus vaccinations do not protect against the Omicron form, which can elude the immune system’s defenses. Thorough preventative measures, including immunization, will be critical for eradicating the Omicron strain. The mutation rate and consequences on viral dynamics between individual hosts alter the host’s response to transmission and infection. All of these elements affect the genesis of viral variations and the expansion of pandemics.

To neutralize SARS-CoV2, the human immune system produces a wide range of antibody categories: class 1, class 2 and class 3. Each of these classes targets a distinct part of the spike protein. The spike proteins that include the full-length trimer, the S1 subunit, the NTD and the RBD are the principal targets of immune responses to Omicron. The absence of one of the three target genes responsible for spike protein production is called S gene dropout or S gene target failure, and it can be detected utilizing the RT-PCR technique.

### 1.7 | Severity of Omicron

Omicron-infected individuals have been demonstrated to have a broad spectrum of disease, from moderate disease to organ failure and death. The severity of COVID-19 is determined by the need for hospitalization, the length of hospital stay, the use of ventilators, the time necessary to recover and mortality. The most prevailing type of infection is asymptomatic. An increase in hospitalizations is expected as the Omicron variety spreads rapidly. People who have not been immunized, the elderly and those with preexisting medical conditions are at a higher risk of developing a severe infection.

A study in South Africa was designed to compare the severity of BA.1 and BA.2 using logistic regression models. This study revealed that the hospitalization rate and disease severity did not differ between the two groups and concluded that the clinical settings of BA.1 and BA.2 are similar, despite the possible growth advantage of BA.2. The previous immunization rate against SARS-CoV-2, economic status, healthcare system quality and the existence of comorbidities are among the most important determinants of the Omicron outcome. The severity of Omicron will have to be investigated in more depth in a much larger group of people before a conclusive illustration can be produced.

### 1.8 | Vaccine immune protection against omicron

Numerous vaccines against SARS-CoV-2 have been produced and given for therapeutic and preventive purposes (Figure 1). Current vaccinations continue to be effective against severe disease and mortality, including the Delta variant, and boosters provide additional protection. Vaccinated individuals are highly protected against hospitalization owing to Delta or Alpha. Although the Omicron version diminishes the efficacy of Pfizer-BioNTech’s SARS-CoV-2 vaccine, the vaccination can still minimize the risk of hospitalization. Compared with the Wuhan variant’s genome, six mutations in Omicron’s genome have expanded transmissibility and vaccination resistance.

Low levels of neutralizing antibodies may protect against severe COVID-19 infections. Since the surface features of the Omicron’s
spike protein are targeted by T cells, which generally arise after immunization. T cells may be less affected than antibody responses by the Omicron mutations. BioNTech and Pfizer stated that two doses of the vaccine should still protect against severe illness. On the other hand, according to computer modeling, Omicron appears to escape immunity consulted by T cells. Most patients evaluated who had received two doses of an mRNA vaccine or had recovered from COVID-19 infection demonstrated that the poly mutant spike was resistant to neutralizing antibodies.

Omicron may bypass immunity induced by vaccinations or past infections and significantly reduce the efficacy of neutralizing antibodies, making current vaccines less effective against the Omicron. According to research conducted by Discovery Ltd in South Africa, Omicron diminished vaccination efficacy against infection to 33%, down from 80% for Delta. Moreover, the effectiveness of the Pfizer-BioNTech vaccine against severe disease and hospitalization has reduced from 93% to 70%. Individuals infected with the Delta variation have a 40% relative risk of getting the Omicron form. In contrast, those infected with the Beta variant had a 60% likelihood of reinfection with Omicron at the start of 2020. Since the Omicron infection has been recorded in people administered with the Johnson & Johnson, Pfizer–BioNTech and Oxford–AstraZeneca vaccines in South Africa, it can be concluded that Omicron infection cannot be prevented using the standard two-dose mRNA vaccine. However, the Pfizer vaccine was reported to improve SARS-CoV-2 neutralization.

Approximately 120 days after vaccination, the immune system’s response to SARS-CoV-2 declines. As a result, irrespective of VOC, a booster dose can prevent the transmission of this virus. Omicron may also be diminished by applying heterogeneous vaccinations; however, this assumption needs additional exploration. Booster dosages have been advised to compensate for immunological evasion. Pfizer and BioNTech commented that booster dosage generates virus neutralization equivalent to the protection conferred by two doses against the prototype virus.

The frequency of mutations on the spike protein of Omicron variation predicts that the efficiency of antibodies generated by immunizations will be reduced. Despite contradictory reports on the efficiency of the current vaccinations against the four SARS-CoV-2 mutations that preceded Omicron, their efficacy is acceptable. Vaccines have so far assisted in reducing the numbers of severe COVID-19 infection, hospitalization and death, and the transmission of earlier mutations. The fact that vaccination effectiveness is dependent on T cell immune responses rather than antibodies might explain this hopeful outcome. While CD4+ T cells do not prevent infection, they are essential for developing protective antibody responses and the maturation of CD8+ T cells. As a result, given the capacity of pathogenic variants to evade neutralization, the establishment and maintenance
of strong SARS-CoV-2-specific T cell responses may contribute to long-term vaccination effectiveness against severe disease. Owing to the inability of HCoV-specific antibodies and cellular responses to produce sterilizing immunity, there is a fear that protective immunity against SARS-CoV-2 will be similarly temporary. The information available at the moment paints a slightly contradictory picture. It is possible to be re-infected with SARS-CoV-2; however, prior infection provides approximately 87% protection for 6 months with a stable profile for at least 10 months.\(^\text{127}\)

The sequencing of the seed strain should be modified during clinical trials according to the Omicron variation for the SARS-CoV-2 vaccine design and mixed vaccination to avoid immunological escape.\(^\text{127}\) Broad vaccination in conjunction with highly efficient oral anti-COVID-19 medicines targeting conservative areas, such as RdRp, will significantly contribute to the epidemic's abolition.\(^\text{128}\)

The immune protection of vaccines is being investigated in clinical trials. NCT05249829 is evaluating the immunogenicity of the mRNA-1273.529 (Moderna) vaccine against B.1.1.529. A phase II study (NCT05238441) is designed to investigate the immune protection of SCTV01E against different SARS-CoV-2 variants. Two phase III trials, NCT05230953 and NCT05231005, are designed to evaluate the immunity given by the fourth dose of Moderna and Pfizer vaccines against Omicron.

### 1.9 Re-infection with Omicron

Natural infection with the Alpha, Beta and Delta forms of the SARS-CoV-2 results in considerable protection against re-infection. On the other hand, as discussed earlier, the Omicron carries several mutations that might facilitate immune evasion. This is associated with a higher potential for re-infection and poor early estimates of vaccination efficacy against symptomatic infection.\(^\text{129}\) Since SARS-CoV-2 re-infection has been linked with negative S gene target failure data, most likely owing to random PCR target failure induced by the lower virus loads during re-infection, scientists utilized genotype data to examine the influence of Omicron on re-infection rates. Omicron was related to a 5.40-fold increased risk of re-infection compared with Delta after controlling vaccination status, age, sex, ethnicity, asymptomatic status, area and specimen data. To put this in context, the UK “SIREN” research on COVID infection in healthcare professionals in the pre-Omicron period found that past infection provided 85% protection against a second COVID infection over 6 months. According to the present study’s anticipated re-infection risk, this protection against an Omicron infection has dropped to 19%.\(^\text{130}\) The previous infection was assessed to be 90.2% successful in avoiding re-infection against the Alpha version, 85.7% effective against the Beta variation, 92.0% effective against the Delta variant and 56.0% effective against the Omicron form.\(^\text{117}\) To conclude, current data have demonstrated that, owing to the mutations in the viral genome, immunity from previous COVID-19 infection is less effective against re-infection with Omicron. However, further studies are still required to evaluate the exact re-infection probability and the risk of re-infection associated with each variant.

### 1.10 Omicron and pediatrics

Despite the lower number of pediatric infections with previous forms of COVID-19, Omicron has been shown to infect young individuals more often. During the Omicron outbreak, the number of new COVID-19 hospitalizations in children exceeded an all-time high.\(^\text{131}\) Parents might take solace from knowing that Omicron does not appear to be associated with more severe disease in children than previous variations. Children, on average, continue to be at a lower risk of severe disease from COVID-19 than adults.\(^\text{132}\) On the other hand, children with particular health problems still have an elevated chance of severe disease.\(^\text{20}\) The main theories suggested for the higher infection rate of Omicron in pediatrics are the late vaccination of children, the existence of naive B and T cells without prior immunity to Omicron antigens and a lack of cross-immunity between prior immune responses to the Omicron spike protein.\(^\text{133}\)

Countries with substantial exposure to the Omicron form are reporting record numbers of child coronavirus hospitalizations, putting further strain on healthcare systems, even though the great majority of cases are mild, according to health specialists. Data from Europe and the USA suggest that there have been more child admissions recently than at any other time throughout the pandemic. However, severe cases are uncommon in the lowest age groups, and Omicron infections appear comparable with those of other typical respiratory illnesses.\(^\text{132}\) It is crucial to keep an eye out for any signs of COVID-19 infection as the disease progresses. Typically, manifestations of Omicron in children continue to be comparable with those produced by earlier variations. Among the symptoms of COVID-19 in children are fever (a minimum temperature of 100°F), chills, cough, breathing difficulties, diarrhea, shortness of breath, fatigue, vomiting, etc.\(^\text{134}\)

According to research, pediatric SARS-CoV-2 infections and hospitalizations are on the rise in South Africa and the USA. One study found that the risk of hospitalization with Omicron variant among unvaccinated children under the age of 5 was one-third that of the Delta variant, while the risk of an Emergency Department visit was less than one-fifth, both of which were statistically significant.\(^\text{132}\) Similar hospitalization and emergency visit patterns were detected in children aged 5–11 and 12–17.\(^\text{135}\) This is especially alarming considering that in the USA, children under the age of 5 are ineligible for COVID-19 immunization, and children aged 5–11 do not qualify for boosters.\(^\text{131}\) These findings imply that, although the numbers of pediatric SARS-CoV-2 infections and hospitalizations are increasing, the outcomes are milder following the introduction of the Omicron variation compared with the preceding dominant Delta variant period. One Swedish study confirmed previous findings that the SARS-CoV-2 virus is linked to neurological results in children.\(^\text{136}\)

Based on research, although children have the same symptoms and quantities of virus in their systems, their involvement with SARS-CoV-2 is more likely to induce antibodies against the virus than adults. In comparison with adults, children appear to have a more potent first immune response to COVID-19 and can eliminate the infection quickly.\(^\text{137}\) However, since antibodies are expected to play a role in preventing re-infection, the findings raise concerns about how
effectively protected infants are against subsequent diseases. Researchers collected nasal and throat swabs to determine patients’ viral RNA levels and blood samples to determine if they had IgG antibodies against the Omicron. They discovered that, while children and adults had comparable virus loads, only 37% of children developed antibodies, compared with 76% of adults. Adults produce a more extensive range of antibodies than children, including a more significant number of virus-blocking antibodies. Children may produce fewer antibodies than adults owing to a potent innate immune response. This is the initial defense against infections, and it is non-specific. Additionally, children may be more adept at reacting to illnesses that enter the body by the throat or nose. This subject implies that the virus is cleared swiftly by the body and does not persist to induce the adaptive response that creates antibodies.

1.11 Challenges and alternative approaches

The new Omicron variant has shown partial resistance to natural immune antibodies, monoclonal antibodies and vaccine-induced antibodies, and is also associated with new challenges compared with previous variants, including higher transmissibility, infectious rate and immune evasion. These challenges necessitate the development of novel technology-based methods to tackle and neutralize the virus. In the case of diagnosis, nanofiber swabs are an example of more rapid tests that can be used to detect SARS-CoV-2.

Nanosystems can be used as carriers of the drugs for efficient delivery of the drugs to a specific organ. To achieve this aim, drugs are nano-encapsulated (using different nanocarriers such as nanosomes, nanoemulsions, etc.). Nanosystems can be used as a therapeutic option for the successful delivery of drugs for Omicron. Nano- neutratecticals, in the shape of nanosystem-based masks, gloves and disinfectants, are another example of using nanotechnology for overcoming the higher transmissibility of Omicron. Nanotechnology can also be used to improve therapeutic methods and develop vaccines with a higher efficacy (lipid nanoparticles). Nanosystems can be used for the delivery of vaccines to the target site of the virus using smart nanocarriers. Moreover, bioinformatics and artificial intelligence can be used to improve the computer simulation and evaluate the efficacy of novel drugs against SARS-CoV-2. According to the several mutations of the Omicron variant, novel antiviral drugs should be developed for successfully tackling the virus. Paxlovid and Mulnopiviral are two examples of these specific drugs that have recently shown potent efficacy against Omicron.

In this context, specialists have studied the opto-electro-magnetic nanosystem using biosensing to diagnose the SARS-CoV-2 virus. These efficient-miniaturized biosensors may be managed with a smartphone and advocate for early-stage COVID-19 infection diagnosis in clinical settings. Researchers have created stimuli-responsive nanotechnology that can capture aerosols of viral size and eliminate viruses upon external stimulation, such as nano-enable phosh-sensitive virus destruction, to avoid the spread of SARS-CoV-2 virus infection. In terms of studying innovative therapeutic compounds with more efficacy and fewer and more tolerable adverse effects, the participation of biotech-pharma companies seems to be of great importance. Although the SARS-CoV-2 virus is novel, it has shown variant variation, making therapy optimization difficult. However, biotechnology specialists examine all facets of bioinformatics to create and develop a successful cure based on innovative antiviral drugs, antibodies, CRISPR-Cas and vaccines.

Orienting or boosting immunity through diet is another method for managing COVID-19 infection. For instance, nutraceuticals have served as inhibitors to disrupt the interaction between the COVID-19 virus and ACE2. Investigating features of nanomedicine might be a potential strategy for developing innovative therapeutics to treat COVID-19 infection and strengthen the immune system and organs impacted by the SARS-CoV-2 virus.

Because of the multiple mutations outlined in Omicron, this variety has developed more elevated immune evasion than the previous ones, meaning that it is partially resistant to monoclonal antibodies, vaccination neutralizing antibodies and those constructed from natural immunity. Current results also imply that natural and vaccine-induced immunity would act differently in the case of Omicron infection. To successfully treat Omicron patients, the first phase is to diagnose Omicron patients correctly. As an important topic, the most reliable diagnostic techniques efficient in detecting Omicron variants related to S-protein include PCR and antigen COVID-19 testing. However, intense efforts are necessary for Omicron-specific fast testing kits because these tests are time-consuming and costly.

The literature contains proposals that can be adjusted to the variety and may be commercially available shortly. The use of nanoparticles to separate RNA or DNA from biological materials through a magnetic field can be an alternative means of immediate diagnosis. These nano-enable SARS-CoV-2 sensors effectively identified a low level of specific viral concentration. In addition to the intelligent nanosystem, various efficient biomarkers, including antibodies, CRISPR/Cas, and segment-specific DNA/RNA, have been studied to detect SARS-CoV-2 in actual samples. Regardless, before they can be recommended for clinical and point-of-care testing, these nanotechnology-supported biosensing devices must undergo comprehensive validation and population-based confirmation. In addition, these nanobiosensors have not been evaluated against the Omicron, which must be the top priority. Modern SARS-CoV-2 biosensors target the spike protein; therefore, they should theoretically function. Because Omicron includes more mutations at the spike protein than other variations, a reasonably designed and high-throughput validation of existing diagnostic tools must be performed to diagnose a large population and establish whether COVID-19 infection is due to Omicron.

2 CONCLUSION

The Omicron variant has thus far received less awareness, and further research is urgently needed to understand its threat correctly. Previous experiences with other variants, especially Delta strains, have
shown that we can only better understand the transmission potential, vaccination effectiveness and severity of infection through continued compliance. Undoubtedly, it is not by chance that Omicron has developed in a country where vaccination rates are low. As this new variant emerges, it becomes even more critical to provide universal access to vaccination because allowing the virus to circulate freely in non-vaccinated populations threatens them with severe COVID-19 cases and deaths. Moreover, this will provide the virus with more opportunities to undergo mutations that can boost viral transmissibility and infectivity or conduct new harmful waves around the world. Vaccination and other preventative measures will continue to be crucial in halting the spread of COVID-19 and preventing further outbreaks of severe illness and death.

3 | FUTURE PERSPECTIVES

According to the research, Omicron infection is distinct from the COVID-19 infection induced by other variations. Even if it is less severe than Delta, it has substantial health consequences. Furthermore, Omicron can re-infect the COVID-19-infected population or those who have received both vaccine doses. A thorough investigation of how Omicron may escape vaccine-induced immune protection and how it could reduce immunity to infection is urgently needed, notwithstanding the possibility that the variant can evade immunity resulting from previous infections. Nevertheless, comprehensive vaccination is suggested to reduce hospitalization and fatality rates; however, it is uncertain how successfully the antibodies generated by current vaccinations can neutralize Omicron variants, and this should be explored thoroughly. With early access to anti-inflammatory, antiviral and immunotherapies, like MAbs, to treat Omicron infection, hospitalizations and deaths in high-risk infected and exposed patients could be cut by 70%.

Pfizer and Moderna came up with the idea of a fourth booster dose, which could be followed by other doses. The health agencies agree with this claim because they want to develop timely and effective treatments. The appearance of the Omicron variant, with its high-level transmission and quick expansion worldwide and its significant danger to several authorized COVID-19 vaccines and therapies, highlights the need for the creation and development of innovative treatments and techniques that can forecast the evolutionary path of SARS-CoV-2 and its severity in the event of the appearance of a deadlier coronavirus in the future. Many studies must be conducted in corporate and academic settings to prevent such contagious infections.

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CONFLICT OF INTEREST

The authors declare having no financial or scientific conflicts of interest.

AUTHOR CONTRIBUTION

M.B. contributed to data gathering, writing the primary manuscript, and designing tables and Figures. R.E. contributed to revising the manuscript and editing figures and Tables. A.E. contributed to the hypothesis, correspondence, and editing manuscript before submission.

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