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A review on SARS-CoV-2 Omicron (B.1.1.529) variant

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ABSTRACT
SARS-CoV-2 has been quickly developing and changing since its discovery in late December 2019, giving rise to a variety of variants with varying degrees of infectivity and fatality. During the continuing COVID-19 pandemic, the virus that first arrived in China mutated multiple times, causing havoc and killing countless people throughout the world. After the Alpha, Beta, Gamma, and Delta variants, the Omicron (B.1.1.529) is the most recently emerged variant of concern (VOC), which has evolved as a result of the accumulation of large numbers of mutations, particularly in the spike protein, raising concerns about its ability to evade pre-existing immunity acquired through vaccination or natural infection, as well as overpowering antibodies-based therapies. On the surface, several ideas exist to explain how the Omicron accumulated so many mutations in such a short period of time. Higher mutation rates within a subgroup of the population and then introduction to a larger population, long-term persistence and evolution of the virus in immune-compromised patients, and epizootic infection in animals from humans, where the virus mutated and was reintroduced to humans under different immune pressures. A multifaceted approach that includes rapid diagnosis, genome analysis of emerging variants, ramping up vaccination drives and receiving booster doses, efficacy testing of vaccines and immunotherapies against newly emerged variants, updating available vaccines, designing multivalent vaccines capable of generating hybrid immunity, upgrading medical facilities, and strict implementation of adequate prevention and control measures must be given high priority to handle.

Keywords
Omicron, Immune escape, Variant of concern, Vaccine failure, Omicron origin, Prevention and control

I. INTRODUCTION

As of January 21, 2022, it has been almost two years since the start of the coronavirus disease (COVID-19) pandemic, which was caused by the severe acute respiratory syndrome coronavirus – 2 (SARS-CoV-2), which has resulted in over 5.5 million deaths out of over 340 million confirmed cases worldwide (WHO, 2022). The virus has wreaked havoc on the global economy, limiting free travel, impacting millions of people, and placing a strain on medical personnel, leaving them exhausted both mentally and physically, as well as emotionally vulnerable (Kutscher, 2021). Since January 2020, the World Health Organization (WHO) has been actively monitoring the genesis and appearance of SARS-CoV-2 in collaboration with public health organisations and scientists (WHO 2021a; WHO 2021b). In May 2021, WHO recommended terminology for categorization of SARS-CoV-2 emerging variations as variants of concern (VOC) and variants of interest (VOI) for easy-to-pronounce and non-stigmatizing labels, as well as the scientific nomenclature used by researchers and academics (WHO 2021b) [1]. The periodic appearance of numerous SARS-CoV-2 variations and mutations has resulted in increasing morbidity and death amongst successive waves of pandemic within the continuing epidemic, causing widespread worldwide health concerns and alarm (Boehm et al., 2021; Thakur et al., 2021) [2]. Following the Alpha, Beta, Gamma, and Delta SARS-CoV-2 variations, the Omicron (B.1.1.529) variety appeared in November 2021 as a highly mutated viral variant, designated as VOC by WHO on November 26th, and is currently a dominant strain in multiple countries because to its extremely high transmissibility (NewsNodes, 2022; WHO, 2021a; WHO, 2021c). The pattern of infection rate, greater transmissibility, and cases of immune evasion against acquired immunity with breakthrough infections in vaccinated persons is so impulsive that Omicron spread quickly over the world in a matter of weeks (Rahmani and Rezaei, 2021).

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According to the WHO, the VOI is a genetic change that has been linked to increased transmissibility, immune or diagnostic evasion, disease severity, and has been identified as a source of significant community transmission and increased prevalence, as well as having epidemiological implications. A SARS-CoV-2 VOC, on the other hand, is a variant that meets all of the VOI requirements, but when compared to other variants, it poses a threat of increased transmissibility, negative epidemiological effects, increased virulence or variability in clinical presentation, and decreased diagnostic, therapeutic, and vaccine interventions (WHO 2021a) [3]. The WHO formed the Technical Advisory Group on SARS-CoV-2 Virus Evolution (TAG-EV) to track, monitor, and evaluate the pandemic virus's evolving situation, as well as the WHO COVID-19 reference laboratory network, members of GISAID, Nextstrain, Pango, and scientific representatives from a variety of countries and institutions. One of the responsibilities assigned to this group is to offer non-stigmatizing and simpler VOI and VOC labels to the general population. The inclusion of Greek Alphabet letters in the SARS-CoV-2 nomenclature, such as Alpha, Beta, Gamma, Delta, and now Omicron, has been advocated by this expert panel to mediate non-scientific public conversations in order to promote public health awareness (WHO, 2021b) [4] .

The current article discusses the advent of the SARS-CoV-2 Omicron variant, its key characteristics and significant global health concerns, as well as tactics for dealing with it in the context of the continuing COVID-19 pandemic. Various mutations in Omicron have been discussed that contribute to increased transmissibility and immune evasion from vaccine-induced or natural immunity acquired after infection. In order to understand the similarities and differences between different VOCs and Omicron, we conducted a comparison investigation. Several computer models have been created to anticipate mutants that may be immune to the immune system and have been proven to be effective (Greaney et al., 2021; Miller et al., 2021) [5, 6]. Escape mutants pose a risk of rendering convalescent serum, vaccines, and monoclonal antibodies (mAbs) ineffective (Planas et al., 2021; Dejnirattisai et al., 2021; Taylor et al., 2021); this is also true in the case of Omicron, where it has been discovered that after two doses of SARS-CoV-2 vaccine, Omicron neutralisation is far less than Delta or (Garcia-Beltran et al., 2021; Natario, 2021; Barda et al., 2021) [7,8,9]. Experiments by several groups of scientists and commercial firms indicated that the third dosage of the vaccine (booster) greatly improves Omicron neutralisation (Nemet et al., 2021; Garcia-Beltran et al., 2021) [10, 11]. Experimental data suggests that Omicron replicates 70 times quicker in human bronchus than it does in human lung tissue (Chi-wai, 2021; Dyer, 2021), resulting in low disease severity. Despite the modest severity of the condition, its increased transmissibility may pose a risk to co-morbid patients (WHO, 2021a). Various strategies to combat the rising Omicron pandemic are discussed, including government involvement to ensure effective implementation of prevention, control, and preparedness interventions (Luo et al., 2021), partnerships with both the public and private sectors to increase the number of testings (CDC, 2021b), and government implementation of strict measures and decisions based on scientific facts (Queen, 2022) [12].

II. EMERGENCE OF OMICRON

The most recent new SARS-CoV-2 variation was originally reported from a specimen collected on November 9, 2021, and was previously termed B.1.1.529, until WHO recognised the variant B.1.1.529 as a VOC dubbed "Omicron" on November 26, 2021. (WHO 2021c) [13]. With over 50 mutations in its genome, Omicron is the most mutated SARS-CoV-2 variation. It is of special interest and concern since 26–32 mutations are found in the viral spike (S) protein region (WHO 2021c), 15 of which are in the receptor-binding domain (RBD) (ECDC, 2021a) [14]. On November 29, 2021, only three days after the Omicron was declared a VOC, it was discovered in Austria, Australia, Belgium, Canada, Czech Republic, Denmark, France, Germany, Italy, the Netherlands, and the United Kingdom, with the majority of the cases being travel-related (Petersen et al., 2022; Maxmen, 2021) [15,16]. Omicron has recently been found in two overseas travellers who visited Omicron undetectable regions in Japan (Maruki et al., 2022) [17]. As a result, this newer version quickly spread to numerous nations, with Omicron being recorded from 150 countries and territories as of January 22, 2022, with approximately 0.5 million confirmed cases and 115 deaths (ECDC, 2021b; Mohapatra et al., 2021; NewsNodes, 2022) [18,19,20] . Because the Omicron variant's effective (instantaneous) reproduction number is 3.19 (95 percent CI 2.82–3.61) times greater than the Delta variant's, a substantial increase in Omicron instances is likely

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in the near future due to its significant advantage of increased transmissibility (Ito et al., 2021) [21].

Omicron also has a shorter incubation period and clinical symptoms that are similar to or less severe than the prior variations (Jansen et al., 2021) [22]. According to preliminary data from the National Institute of Infectious Diseases' illness monitoring programme in Japan, the viral RNA level peaks three to six days after the beginning of symptoms (NIID, 2022). When the isolation time in various nations, such as England, is decreased from 10 to 7 days, this issue becomes even more pressing (Torjesen, 2022) [23].

Though it appears that this variety has displaced previous forms in South Africa, such results may be skewed due to the fact that viral characterisation rose in tandem with the number of cases and remained mostly restricted to Omicron-infected regions. Furthermore, a study of multiple Omicron strains indicated that it emerged in late September or early October, suggesting that it is spreading more slowly than currently thought (Kupferschmidt, 2021a; Quarleri et al., 2021). Children aged 10–19 years have accounted for 9.2% of all COVID-19 cases in South Africa since the commencement of the SARS-CoV-2 pandemic, and this cohort is also prone to Omicron risk (Lima et al., 2021) [24].

Preliminary findings from a clinical investigation in South Africa revealed that the Omicron version would be able to evade immune responses and have a greater transmissibility, which might have serious repercussions (Cele et al., 2021; Vaughan, 2021) [25,26]. The possibility of immune evasion by the Omicron variant is supported by in vitro data obtained by Chinese scientists, who found that mutations at the N440K, T478K, and N501Y sites confer tenfold and twofold higher infectivity to Omicron, respectively, when compared to the initial SARS-CoV-2 variant and Delta variant (Chen et al., 2021a) [27]. In the absence of an Omicron-specific vaccine, existing vaccines licenced by competent authorities might be employed as a countermeasure to minimise the number of Omicron infections in circulation (Thakur and Kanta Ratho, 2021) [28, 29]. Due to its extensive mutations, some researchers have shown that the Omicron variant may reduce the efficacy of COVID-19 vaccines and neutralisation antibodies (antibodies-based immunotherapies) (Callaway, 2021a; Cele et al., 2021; Chen et al., 2021a; Kozlov, 2021; Lu et al., 2021; Torjesen, 2021; Dejnirattisai et al., 2021; Kannan et al., 2022; X. Zhang et al., 2021, L. Zhang et al., 2021) [30].

The Omicron version might be ten times more contagious and twice as infectious than the Delta variant, according to an artificial intelligence (AI) model that was developed and verified with a large number of experimental data points (Chen et al., 2021a) [31]. It's too early to say whether Omicron is more benign than its prior forms because it's a frequent biological phenomena for viruses to undergo mutations and have several variants with the potential to evade immune responses. In reality, early signs exist, with less severe symptoms than the last wave, and doctors attending a higher number of minor patients than in past waves [32]. Furthermore, as of December 6, 2021, recent data suggested a lower number of people seeking medical attention with substantial lung damage and requiring oxygen assistance than in past COVID-19 pandemic waves (Vogel and Kupferscgmidt, 2021) [33]. However, as of December 20, 132 hospitalised patients had been diagnosed with proven Omicron; 17 had received a booster vaccine (a total of three doses), 74 had received two doses, eight had only had one dose, 27 had not been vaccinated, and the immunisation status of six people was unclear. In addition, 14 individuals aged 52 to 96 died within 28 days after receiving an omicron diagnosis (Mahase, 2021a) [34].

III. WHERE OMICRON FITS IN CLASSICAL VIROLOGY?

Coronaviruses (CoVs) are not like other RNA viruses in that they are extremely adaptive to shifting ecological niches due to high mutation rates caused by a variety of reasons. SARS-CoV-2 has a low-fidelity RNA-dependent RNA polymerase enzyme that accumulates mutations in the RNA genome (about 10-4 nucleotide substitution/site/year) and even greater mutation rates, permitting the virus to adapt to even more harsh settings and perhaps persist in the human host (Banoun, 2021). The unique technique of viral replication, which is handled by the "copy-choice" approach and viral recombination, adds to the genome's variety (Terada et al., 2014) [35]. In the copy-choice model, RNA-dependent RNA polymerase generates nascent cRNA and nascent RNA [36, 37, 38]. Then it dissociates from the original template and attaches to another RNA template in the same or nearly similar place, resuming RNA synthesis and causing recombination (Herrewegh et al., 1998). At

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numerous locations, template switching may occur. As in the instance of Feline Coronavirus Type II Strains (viruses 79–1683 and 79–1146), which resulted from a dual recombination between Feline Coronavirus Type I and Canine Coronavirus, this template swapping leads in the synthesis of new viruses (Herrewegh et al., 1998) [40-45]. Recombination between two genetically diverse parent viruses is clearly feasible in CoVs, and child viruses may differ in cell culture and receptor utilisation (Terada et al., 2014) [46-50]. The spread of diverse strains is most likely to blame for the establishment of VOC. This Omicron variety picked up at least one mutation from another virus, most likely one that causes the common cold, that enables it elude the human immune system and spread more easily while generating a mild version of the disease [51-55].

In general, fitness and virulence traits are thought to be linked, however major discrepancies have been documented. Most RNA viruses, including as vesicular stomatitis virus (VSV), have compact genomes and are sensitive to point mutations and adaptive changes caused by only a few substitutions (Holmes, 2008; Domingo and Perales, 2018) [55-60]. Viral fitness and virulence, on the other hand, are influenced by complicated cell specificities, viral-host interactions, and virus-virus interactions. In a research by Furio et al. (2012), the fitness and virulence of 21 single- or double-nucleotide mutants of the VSV were quantified, and a positive association between virulence and fitness was found, while both properties are independent in a few mutants [60,61]. These researchers discovered mutants with reduced fitness but unchanged virulence (single mutant) as well as mutants with high within-host fitness but poor virulence (dual mutant) (double mutant) [62]. Viral quasispecies, which are well-defined mutants originating from the complicated mutation-selection process, are constantly present in a host cell niche due to mutations resulting from immunological pressures, changing environment, or simple error-prone replicating machinery. VOC, which is high in both fitness and pathogenicity, is likely to emerge from among them. Increased fitness is documented in the case of Omicron, as shown by high transmissibility (WHO, 2021a); nevertheless, data on increased virulence is not readily available in the current context, which is somewhat reassuring [63-65].

IV. THEORIES ON OMICRON EMERGENCE

Pulliam et al. (2021) found significant immune evasion by the Omicron variation in a preliminary population-level unpublished research. However, the variation had a lower hazard coefficient for first infection and a higher hazard coefficient for reinfection. Mutations are typical in viruses, and SARS-CoV-2 is no exception; nonetheless, the scientific community's primary worry stems from the high number of mutations found in the Omicron variant's genome [65-70].

Sequence alignment, pair-wise comparison, and generation of an identity matrix were used to perform phylogenetic analysis on the Omicron variation. When compared to other SARS-CoV-2 variations, the Kimura model was shown to form a whole separate monophyletic clade, while the Jukes-Cantor model indicated a close link between alpha and Omicron, suggesting that Omicron has been between us for longer than we think [70-75].

The Omicron variant's sequence study found that mutagenic pressure is higher on S1 than on S2, and the backbone hydrogen bonds are absent, increasing mutability [76]. This information might be used to forecast future mutation locations and aid vaccine development (Penner et al., 2021). Omicron has recently been divided into two lineages, BA.1 and BA.2, with a few differences that are unique to each lineage and some that are shared by both [77]. There are 51 mutations in the BA.1 and BA.2 lineages, 32 of which are common to both, and 19 hallmark mutations in each branch. BA.1 has 13 of the 19 distinct mutations found in the S glycoprotein region, whereas BA.2 has seven (Majumdar and Sarkar, 2021) [78-81]. Another BA.3 lineage has been discovered [82-85].

The origin of Omicron, such as VOC, might be explained by one of four explanations or hypotheses [86-90]. The first is that the virus began circulating and changing in a small group of people, where it significantly changed to become extremely distinct from versions outside of that group, and then it spread to the rest of the population [91-95]. Alternatively, as in the case described by Karim et al., (2021), where SARS-CoV-2 infection persisted for more than six months in a patient with advanced Human Immunodeficiency Virus (HIV) who presented with antiretroviral therapy failure. The development of the E484K alteration associated with immunological escape and the N501Y substitution associated with most VOC were both

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documented in the same patient, bolstering the idea of VOC evolution inside the host (Kupferschmidt, 2021c) [96,97]. In a persistently infected COVID-19 patient, mRNA- and non-mRNA-based vaccinations may play a role in creating Omicron variations, allowing the virus to develop and mutate while gaining the capacity to evade the body's immune response (breakthrough vaccine-induced immunity) (Li, 2021)[98-100].

Another method for generating mutations so quickly is back spilling of the virus from the human host, as described by Oreshkova et al. (2020), who found that mink were infected by humans and that the viral sequences from both the mink and human isolates were closely related [101]. SARS-CoV-2 zoonotic transmission and consequences of reintroduction into human populations, as well as zoonotic problems, require more research. The virus has already been transmitted from mink to humans, and studies are underway to establish the virus's origin (Banerjee et al., 2021; Holmes et al., 2021; Korath et al., 2021; Sharun et al., 2021a, 2021b) [102-105]. Immune pressure may differ between species, which might contribute to the increased mutation rate. It should be emphasised that animals have been infected with SARS-CoV-2 developing variations, including the delta form (Bonilla-Aldana and Rodriguez-Morales, 2021; Karikalan et al., 2021)[106-110]. SARS-CoV-2 vaccinations for animals have recently been produced, which might help combat the pandemic virus at the human-animal interface by limiting its circulation in the animal population and using holistic health initiatives (Chavda et al., 2021; Sharun et al., 2021c; Vandeputte et al., 2021)[111]. Another argument is that if a person is infected with two coronaviruses, recombination is possible, and Omicron may have acquired so many mutations. Recombination events between SARS-CoV-2 types are visible, despite the theory's scepticism (Le Page, 2021)[112]. Only Omicron has the insertional mutation ins214EPE, which was not discovered in any of the prior SARS-CoV-2 lineages. This insertion may have occurred as a result of template swapping during co-infection with other or SARS-CoV-2 viruses in the same host cell (Venkatakrishnan et al., 2021)[113]. Wei et al. (2021) has offered a notion of Omicron genesis in mice [114]. The researchers described the molecular spectra of mutations as well as the relative frequency of 12 different types of base substitutions. The process may be further understood by looking at the G > U transversion that happens in reactive oxygen species, as well as the C > U transitions that occur when cytidine is deaminated. If mutations occur in the same host species, poliovirus, Ebola virus, and SARS-CoV-2 have similar molecular spectra, while if the host species changes, various molecular spectra are displayed (Shan et al., 2021) [115]. The host for the Omicron virus may be discovered by analysing the spectrum of mutations in Omicron since the molecular spectrum of mutations is extremely host-specific. When scientists looked into whether Omicron's mutational spectra were consistent with the human cellular environment, they discovered a difference between Omicron's molecular mutation spectra and mutational molecular spectra in human-evolved viruses [116]. Further investigation based on a comparison of molecular mutation spectra of various host species and then molecular docking revealed that pre-epidemic Omicron mutations in the Spike protein significantly match the mutations present in mouse-adapted SARS-CoV-2, potentially promoting adaptation to mouse as a host, particularly via increased S protein binding affinity for the mouse cell entry receptor (Wei et al., 2021) [117]. The findings of this study suggest that the progenitor of Omicron may have jumped from humans to mice, gained mutations quickly that made it easier for the virus to infect mice, and then jumped back into humans, indicating an inter-species (human-mice-human) evolutionary trajectory that may be responsible for the current Omicron variant outbreak.

V. MUTATIONS IN OMICRON AND THEIR BIOLOGICAL CONSEQUENCES

Previously, it was discovered that the fatal combination of K417N + E484K + N501Y mutations observed in beta and gamma increased transmissibility by 50%, resulting in greater hospitalisation rates, ICU hospitalizations, and deaths (Wahid et al., 2021) [118-120]. These alterations may have an impact on Omicron's transmissibility. Asn501Tyr increases ACE2 receptor binding, which may aid transmission (Ali et al., 2021). The Omicron will most certainly become more infectious as a result of D614G, N501Y, and K417 (Poudel et al., 2022)[121]. The D614G mutation is found in all VOCs, while the N501Y mutation is found in all VOCs except the Delta version (Shanmugaraj et al., 2021; Corum and Zimmer, 2021)[122]. Omicron has a number of deletions and mutations that coincide with those found in other VOCs (Dhawan et al., 2022)[123].

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While the N501Y mutation is linked to greater transmissibility, other changes, such as the L452R in the B.1.429 lineage, have been linked to increased ACE2 interaction (Gong et al., 2021) [124,125]. Signaling in SARS-CoV-2 entry is dependent on kinases like PI3K/AKT. In mutants with N501Y, structure-prediction-based molecular docking research suggested that epidermal growth factor receptor might be another possible acceptor. Because numerous kinases are increased in cancer patients, lineages with the N501Y mutation may be more harmful [126-130].

Additionally, His655Tyr is close to the furin cleavage site, which can speed up spike cleavage and aid transmission (Chen et al., 2021b) [131]. The changes at positions N679K and P681H, which are also seen in Alpha and Delta versions, may improve the virus's capacity to transmit (CDC, 2021a, Poudel et al., 2022, Thakur and Kanta Ratho, 2021)[132]. The presence of Asn679Lys near the furin cleavage site increases the polybasic character of the protein, which may aid in cleavage and transmission (Tao et al., 2021)[133]. Electrogenic mutations that induce alterations in the electrostatic force between the RBD of spike protein and ACE2 may be employed by the virus as a tactic, according to Pawowski (2021), and the ensuing Coulomb attraction is greater and stronger in Omicron than in the original SARS-CoV-2 virus. Because ACE2 has patches of negative electrostatic surface potential, it is obvious that a higher positive potential of RBD will enhance virus tropism, and indeed, multiple replacements of neutral or negatively charged amino acids with positively charged amino acids have demonstrated the relationship between positive electrostatic potential and Delta variant affinity for ACE2 (Pascarella et al., 2021a)[134]. Omicron is expected to be more transmissible and interact with other molecules such as antibodies if any direct association between electrostatic potential and receptor affinity and infectivity survives (Pascarella et al., 2021b). Because the interaction between ACE2 and RBD is a complicated process impacted by the presence of numerous additional mutations in the spike protein, including a unique insertion at position 214 that might drastically change the structure and function, in-vivo research must back up this in-vitro results (Venkatakrishnan et al., 2021)[135]. The changes at R493, S496 and R498 in RBD resulted in the development of novel salt bridges and hydrogen bonds in the Omicron variant spike protein complexed with human ACE2[136]. These changes may compensate for other Omicron mutations, such as K417N, which are known to lower ACE2 and S protein affinity (Mannar et al., 2022)[137].

All of the evidence suggests that the Omicron form has a higher transmissibility potential. The proteins RNA-dependent RNA polymerase (Nsp12) and nonstructural protein 14 (Nsp14) are required for viral replication, although it is unclear whether mutations in these areas result in greater Omicron mutation rates (Gao et al., 2021)[138-140]. Omicron also have mutations in the nucleocapsid protein (R203K and G204R), which are not unique to Omicron but have been associated to increased subgenomic RNA production (Leary et al., 2021) and viral replication [141-145]. The R0 of the original SARS-CoV-2 is 2.5, while the R0 of the Delta version is below 7. The Omicron version is thought to have a high R0 value of 10 (Burki, 2021), as well as a fast doubling time of 2–3 days, making contact tracing problematic [146]. The CHARMM36 force fields were used to describe the interaction between wild type ACE2-RBD and ACE-2-Omicron RBD. Mutations on the RBD Omicron variant have been observed to result in higher binding to the human ACE2 receptor than wild type virus, according to atomistic molecular dynamics modelling simulations using the GROMACS 5.1.2 package [147,148]. A computational comparison of the Omicron and Delta versions revealed that the Omicron variant had a greater affinity for ACE2 receptors than the Delta variant. Q493R, N501Y, S371L, S373P, S375F, Q498R, and T478K are the mutations that contribute to greater affinity for ACE2 receptors, according to docking studies. Many hydrophobic amino acids, such as leucine and phenylalanine, are found in the RBD region of the Omicron version, which are necessary for structural stability [149-153]. Viral pathogenicity and infectivity are connected to disordered areas of viral proteins. Values of higher than 0.5 indicate that there is an underlying abnormality, but scores of 0.2 to 0.5 are deemed flexible. The Omicron variation has less disordered area than other variants, according to the intrinsic disorder score predicted by PONDR® VLXT, and displays the disorder-to-order transition. This disorder-order transition region of Omicron's spike protein is located between 468 and 473 amino acids (Kumar et al., 2021) [154]. Wang and Cheng's (2021) sequencing study found that the variation contains two subclades, and that it may have evolved from clade 20B rather than the currently circulating delta form, and that changes in the sequence might influence ACE2 receptor and/or antibody binds.

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Omicron is closely connected to the Gamma variation, according to a new phylogenetic study based on the relative number of hallmark mutations [155]. The MAFFT programme was employed in the study, and 10 sequences for each of the alpha, beta, gamma, delta, and mu variants were obtained (Kannan et al., 2022)[156].

VI. MAJOR PUBLIC HEALTH CONCERNS RELATED TO OMICRON

Since the first emergence of SARS-CoV-2, several mutations have been discovered in various SARS-CoV-2 variants reported across the world. The Omicron VOC would become the majority variety (>50 percent) of SARS-CoV-2 infections in the European Union and European Economic Area (EU/EEA) nations by March 1, 2022, according to (ECDC 2021d) modelling data. Initial modelling estimates put the Re for Omicron at 1.5 in the Kingston, Frontenac, Lennox, and Addington (KFL&A) area of Canada (A. Li et al., 2021). The development of the Omicron variation has sparked widespread alarm since it is the most mutated SARS-CoV-2 variant, with approximately 50 mutations in its genome and at least 30 alterations in the viral spike (S) region, notably in the receptor binding domain (RBD). This raises the risk of neutralising antibodies produced by past SARS-CoV-2 infection, variations, or immunisation losing their potency (Callaway, 2021b) [157-160]. The early data suggests that the rate of reinfection in South Africa has increased. In contrast to the Beta and Delta forms of SARS-CoV-2, there is emerging evidence of diminished neutralisation of some SARS-CoV-2 variants by post-vaccination serum and evasion of immunity from a prior infection [161-165]. Out of 51 contacts, 88 percent were boosted (3 doses) with BNT162b2 vaccine and 92 percent were masked, according to contact tracing studies for Omicron conducted in Israel among multiple patients and healthcare workers exposed to a pre-symptomatic physician who was triple vaccinated with BNT162b2 vaccine. Only one enhanced main contact was infected with Omicron out of the 51 contacts. This demonstrates the effectiveness of vaccines and the relevance of infection-prevention measures such as masks [166]. Immunological escape from natural infection-induced immunity, vaccine-induced immunity, mAbs, and immune escape in the face of selection pressure are described in the sections below.

6.1 Natural immunity escape

When convalescent sera from early strains infected subjects and Delta strain-infected patients were neutralised with pseudotyped Omicron S protein-expressing virus, the neutralising antibody titre was 36 times lower for convalescent sera from early strain patients and 39 times lower for convalescent sera from Delta strain patients, implying natural immune escape by Omicron (X. Zhang et al., 2021)[167-170]. Omicron partly or totally evades neutralisation in 115 sera from vaccination recipients or convalescent patients, according to tests [171-175].

6.2 Evasion against vaccine-induced immunity

Omicron variant can even defy vaccine-induced immunity, resulting in breakthrough infections in COVID-19 immunised persons who are mostly asymptomatic or have minor symptoms. In South Africa, for example, epidemiological surveillance indicated that two vaccination doses still protected people from severe illness three weeks after the Omicron-emerged wave (SAMRC, 2021)[176-177]. Two doses of the AstraZeneca or Pfizer-BioNTech vaccines, however, provided some protection against infection with the Omicron strain (Dejnirattisai et al., 2021) [178-180]. Patients infected with several spike variants generate a broader range of protection in cross-neutralizing Omicron, which contributes to booster techniques (Laurie et al., 2021)[181-185]. Omicron variant strains HKU691 and HKU344-R346K were evaluated with sera from 25 BNT162b2 and 25 Coronavac vaccination patients in a live virus microneutralization experiment. Detectable neutralising antibodies against HKU691 and HKU344-R346K were found in 20% and 24% of BNT162b2 recipients, respectively, but none of the Coronavac patients had detectable neutralising antibodies against either of these Omicron variant strains (Lu et al., 2021) [186-190]. According to the UK Health Security Agency, 25 weeks after receiving two SARS-CoV-2 vaccine injections, the protection against symptomatic illness is just 10%, compared to 40% protection against the Delta form (Burki, 2021). More information may be found in the review's "SARS-Cov-2 vaccination effectiveness against Omicron" section [191-195].

6.3 Immune escape against monoclonal antibodies

The binding of neutralising antibodies (NAbs) is hampered by insertions and deletions in the N3 and N5 domains of spike protein, according

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to a computational investigation (Andreano et al., 2021b) [196-200]. Andreano et al. (2021b) tested serum from ten donors who had received the BNT162b2 mRNA vaccination. Scientists aimed to assess viral neutralisation by B cells against various VOC and antibody response elicited against vaccinations at the individual cell level in this experiment [201]. A total of 6000 cells were sorted, with around 3000 cells capable of producing monoclonal antibodies (MAbs) against S protein. The wild-type SARS-CoV-2 virus, which originated in Wuhan, was neutralised by antibodies from more than 400 cells. Variants, on the other hand, displayed varying degrees of neutralisation and were able to escape neutralisation. When compared, the beta and gamma variants avoided 70% of antibodies, whereas Alpha and Delta versions escaped a lesser percentage of antibodies (Andreano et al., 2021b) [202-205]. Omicron was totally neutralised by nine mAbs that are either clinically authorised or in development for therapy [206]. Many commercial mAb preparations are ineffective against the mutations at E484A and K417N, and increased resistance is observed (Ai et al., 2021) [207-210]. Because some of the Omicron mutations are found in the area likely to bind neutralising antibodies and weaken the immune defence against Omicron, the decreased degree of protection might be due to immunological escape (Callaway and Ledford, 2021)[211-215]. When tested utilising a peusotyped SARS-CoV-2 virus-like particles with mutations in all four structural proteins, Casirivimab and Imdevimab mAbs showed significant neutralisation against Delta variant but were ineffective against Omicron (Syed et al., 2022). S309 (parent mAb of sotrovimab), COV2-2196, COV2-2130 (parent mAbs of AZD8895, AZD1061), REGN10933, REGN10987, and LY-CoV555 are among the anti-RBD mAbs in this panel. Omicron neutralisation was evaluated on LY-CoV016 and Celltrion (CT-P59), both of which are intended for clinical usage. In both Vero-TMPRSS2 and Vero-hACE2-TMPRSS2 cells, LY-CoV555, LY-CoV016, REGN10933, REGN10987, and CT-P59 mAbs were entirely ineffective against Omicron, but a combination of COV2-2196 and COV2-2130 or S309 was slightly effective (VanBlargan et al., 2022) [216-220].

More information on the efficacy of various mAbs may be found in the review's "Therapeutic Advances Against Omicron" section.

6.4 Immune escape in presence of selective pressure of antibodies

How might the selective pressure of polyclonal immunity, which is responsible for the generation of VOC variations in convalescent or vaccinated patients, be tested? Natural disaster immunity Andreano et al. (2021a) conducted an experiment to quantify the escape of viral particles from herd immunity and antibody therapy in order to determine whether presently existing vaccinations will be effective against developing VOCs. Plasma from 20 convalescent patients was collected and cultured with the Wuhan virus for three months in the experiment. The serum was able to neutralise the virus for up to seven passages; however, the deletion of F140 in the spike protein resulted in a partial reduction in neutralisation after 45 days. E484K change in the RBD on day 73, and an insertion on day 80 resulted in the formation of a novel glycosylation site, resulting in a wholly new variation that was completely resistant to plasma neutralisation (Andreano et al., 2021a). Omicron contains the E484K substitution (Kupferschmidt, 2021c) [221-223].

VII. PREDICTION OF ESCAPE MUTANTS THROUGH BIOINFORMATICS ANALYSIS

Deep mutational scanning tests make it easier to see how viral changes affect antibody binding and neutralisation. To examine the antigenic consequences of different mutations in the RBD region of SARS-CoV-2, Greaney et al. (2021) created an escape calculator based on experimental data gathered for 33 monoclonal antibodies [224]. The calculator may be used interactively at https://jbloomlab.github.io/SARS2 RBD Ab escape maps/escape-calc/, and it implies that the new omicron form has a lot of alterations. Furthermore, the results of the escape calculator are closely associated with human polyclonal sera neutralisation testing (Greaney et al., 2021) [225]. Miller et al. (2021) used amino acid interaction (AAI) networks to describe the mutational landscape of the Omicron variant, revealing that antibody escape breadth is increased in the Omicron due to mutations in class 3 and 4 antibody epitopes, while escape depth is also increased due to mutations in class 1 antibody epitopes [226]. Subclades with R346 S/K mutations, in particular, should be monitored for possible escape [227-230].

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VIII. IS NATURAL INFECTION FOLLOWED BY VACCINATION PROVIDES SUPERIOR PROTECTION AGAINST OMICRON?

There have been reports that vaccination after natural infection (hybrid immunity) results in higher NAbs against Omicron variant in vaccinated patients with no previous infection history (Callaway, 2021a; Schmidt et al., 2021a) [231]. Cele et al. (2021) observed similar results using plasma from BNT162b2 vaccinated and both BNT162b2 vaccinated and previously infected patients with Delta variant or ancestral strains in a focus reduction neutralisation test (FRNT50) [232]. For vaccinated and previously infected patients, the Omicron live virus neutralisation was 22 times lower than the original D614G strain. BNT162b2 vaccine efficacy in preventing Omicron symptomatic infection was estimated using the same FRNT50 assay, and the vaccine efficacy was 73 percent (95 percent CI 58–83 percent) for vaccinated and prior infected individuals and 35 percent (95 percent CI 20–50 percent) for vaccinated only participants [233].

IX. BOOSTER SHOTS OF VACCINES

The importance of a third vaccination with BNT162b2 is emphasised, due to a 100-fold increase in neutralisation efficacy after a third shot against the omicron variant (Nemet et al., 2021); and other researchers have also obtained similar results (Garcia-Beltran et al., 2021), who revealed that the vaccine's ability to protect against infection is compromised (Cele et al., 2021) [234]. Schmidt et al. (2021b) found that sera from people who had received two mRNA vaccine doses were 30- to 180-fold less effective in neutralising Omicron, whereas sera from patients who had previously been infected or patients who had received three doses of mRNA vaccine showed a 38–154-fold increase in neutralisation of Omicron. All of the findings point to the need of increasing dosages to increase Omicron neutralisation (Garcia-Beltran et al., 2021; Natario, 2021; Barda et al., 2021) [235]. The vaccine maker must be vigilant in order to modify the vaccine to meet the needs of extensively altered coronavirus strains. Such plans will aid in limiting the significant repercussions that may arise as a result of the introduction of new mutant varieties. Following the appropriate laboratory testing, both Pfizer and BioNTech believe that the three doses of their mRNA vaccine can successfully combat the Omicron form (Sohan et al., 2022) [236]. Binding free energy variations for 15 RBD mutations on these complexes were examined using a data-driven technique employing a library of 132 known antibody and S protein complexes to identify the likely influence of Omicron mutations on vaccination efficacy. The study discovered that Omicron RBD mutations might drastically alter the binding patterns of known antibodies, with overall analysis revealing that modifications that reduced antibody-RBD complex binding were more prominent than those that increased binding, indicating serious disruption. It's also possible that the alterations in Omicron are encouraging vaccination evasion. K417N (a mutation frequent in beta variants) and E484A are two of the 15 RDB mutations that have extremely disruptive effects on many known antibodies (Chen et al., 2021a) [237]. Individuals who received two doses of inactivated whole-virion vaccinations (BBIBP-CorV) had lower Omicron neutralisation, but homologous or heterologous vaccination with protein subunit vaccine (ZF 2001) increased Omicron neutralisation (Wang et al., 2022)[238]. In a cohort of 292 patients, homologous boosting with BBIBP-CorV vaccine 9 months after a two-dose immunisation regimen demonstrated that Omicron was neutralised in 78.08 percent of the subjects (Yu et al., 2022) [239]. However, this enhanced protection against Omicron may wane faster than it did against Delta, with a 15–25% loss in protection after ten weeks following the booster (Mahase, 2021a). The amplitude and breadth of neutralising antibodies in infected and vaccinated people with mRNA-vaccine were assessed using vesicular stomatitis virus (VSV) pseudoparticles encoding a spike of SARS-CoV-2. Although boosting with a third dosage increased neutralisation capability, Omicron is the most resistant to neutralisation of all the VOCs studied, and boosting was unable to elicit a strong reaction in pregnant vaccinated women. The data point to significant variation in the amplitude and breadth of Omicron neutralisation reactions among populations (Sievers et al., 2022) [240]. There was no discernible Omicron neutralisation after two doses of Heterologous immunisation with CoronaVac vaccine, but when supplemented with BNT162b2, it demonstrated 1.4 fold greater neutralisation than two doses of mRNA vaccine (Pérez-Then et al., 2022) [241].

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X. WHAT IF NEUTRALIZING ANTIBODIES ARE PARTIALLY EFFECTIVE AGAINST OMICRON

Multiple evidences suggest that the Omicron form is immune to neutralising antibodies, resulting in reduced neutralising powers of convalescent serum. Due to the opsonizing action of non-neutralizing antibodies and cell mediated immunity, the immune system may still combat Omicron.

10.1Efficacy of non-neutralizing antibodies

On the one hand, neutralising antibodies target a particular portion of the viral spike implicated in attachment and/or fusion, whereas antibodies regulating Fc activity may bind over the whole antigenic area. The antigen-antibody complex must be configured in such a way that the Fc region of antibodies is accessible to immune cells for Fc activity to occur. Non-neutralizing antibodies may thus continue to opsonize Omicron and Omicron infected cells even in the absence of neutralising antibodies [242]. Even in the absence of antibody-mediated neutralising activity, the three vaccinations, BNT162b2 and mRNA-1273 mRNA vaccines, and CoronaVac, showed persistently increased opsonophagocytic FcR2a and cytotoxic FcR3a receptor binding activity that persisted to detect, bind, and remove the virus (Bartsch et al., 2021) [243].

10.2 T cell immunity obtained from natural infection and vaccination

While knowing the extent to which the humoral response will be successful against Omicron is crucial, the virus is often difficult to evade T cell response due to the wide response induced and the presence of a range of HLA haplotypes. T cells have a longer response time following infection or vaccination than antibodies, and they identify more S protein sites than antibodies, giving them a better capacity to detect changed variations (Ledford, 2022) [244]. Over two-thirds of the immune response was unaffected by Omicron mutations in an investigation of the influence of Omicron mutations on the binding of CD4+ and CD8+ T to epitopes present on S protein. Because Omicron mutations are mostly found in the Spike protein, over 95% of T cell epitopes found in other genes were unaffected (May et al., 2021) [245]. Only one putative epitope specific against CD8+ T cell responses exhibited cross over in one of the trials done by Redd et al. (2021) in the direction of assessing T cell immune response escape, and only 2/30 people carried the alteration in amino acid present in Omicron. It showed that Omicron was identified by anti-SARS-CoV-2 CD8+ T-cell responses in almost all of the subjects, ruling out the possibility of T cell immunity escape during the development of the SARS-CoV-2 virus [246]. SARS-CoV-2 spike-specific CD4+ and CD8+ T lymphocytes were shown to be evoked after spontaneous infection or vaccination with BNT162b2, and cross identified Omicron at 84 percent and 91 percent in infected and vaccinated SARS-CoV-2 patients, respectively [247]. 96.7 percent of MHC class I-restricted CD8+ T cell epitopes found by activation-induced marker tests were entirely preserved in the Omicron variation, according to an analysis of 454 MHC class I-restricted CD8+ T cell epitopes (Tarke et al., 2021). 90.0 percent of MHC class II-restricted CD4+ T cell epitopes were found to be conserved in a study of 280 MHC class II-restricted CD4+ T cell epitopes (Choi et al., 2022). Overall, T cell epitopes of SARS-CoV-2 proteins are largely conserved in Omicron, suggesting that T cell memory might provide protection during reinfection or breakthrough infection with Omicron (Gao et al., 2022; Faraz Ahmed et al., 2022) [248].

XI. IS THE SEVERITY FOR OMICRON IS LESS THAN ITS OTHER VOC COUSINS?

Omicron is less severe than other variations, according to early research, with a risk of hospitalisation ranging from 15% to 80% lower than the Delta form (Christie, 2021; Wolter et al., 2021). Omicron may not cause serious disease, especially in those who have been vaccinated and who have received a booster injection (Burki, 2021; Garcia-Beltran et al., 2021; Khan et al., 2022; Mahase, 2021d ; Tanne, 2021b). The majority of reported cases fall into the category of clinically asymptomatic or moderate instances (ECDC, 2021b; NewsNodes, 2022). Runny nose, headache, weariness (moderate or severe), sneezing, and sore throat are among symptoms of the Omicron variety (Iacobucci, 2021a; Mohiuddin and Kasahara, 2021). The children, on the other hand, were participating in the Omicron-led fourth wave in South Africa, where early data revealed that the risk of hospital admission for children was 20% greater than in the D614G-led first wave (SAMRC, 2021). In ex vivo culture investigations, Hong Kong University researchers discovered that Omicron multiplies 70 times faster than Delta in human bronchus but ten times slower in human lung tissue, which might explain why Omicron

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infected individuals had a milder illness (Chi-wai, 2021; Dyer, 2021) [249].

In Calu3 and Caco2 cell lines, the Omicron variant replicates at lower levels. In compared to other VOCs, Omicron is poor at utilising transmembrane serine protease 2 (TMPRSS2). Virus replication is minimal in the upper and lower respiratory tracts of Omicron-infected K18-hACE2 mice, resulting in improved lung pathology (Shuai et al., 2022). In compared to Delta virus, Omicron virus seemed to reproduce at a lower level in lung cells (expressing TMPRSS2) and lung organoids (Meng et al., 2021; Kozlov, 2022). In comparison to Beta and Delta versions, experimental infection with Omicron live virus in C57BL/6 mice, BALB/c mice, K18-hACE2 transgenic mice (producing hACE2 under an epithelial cytokeratin promoter) and Syrian hamsters exhibited clinically less severe morbidity (Diamond et al., 2021). Similarly, hamsters infected with wild type SARS-CoV-2, Alpha, Beta, or Delta strains lost up to 10%–17% of their body weight by day 6 of infection, but hamsters infected with Omicron did not lose any weight despite receiving greater challenge doses (McMahan et al., 2022). Lower entry efficacy and fewer proteases cleavage have been reported in pseudotyped Omicron particles containing all S mutations with HIV viral backbone, suggesting reduced replicative efficacy in HEK293T cells or ACE2 receptor expressing A549 cells (Hu et al., 2022). When utilising SARS-CoV-2 virus-like particles (VLPs) with all four Omicron structural gene alterations, the infectivity of the virus increased (Syed et al., 2022). The difference in results between pseudotyped Omicron particles (Hu et al., 2022), which have a lower entry efficacy, and SARS-CoV-2-like VLPs with Omicron-like mutations, which have a higher infectivity, could be due to the types of mutations incorporated in the viruses and the cell line used for the assay. In Beta and Gamma versions (Kannan et al., 2022), the E484K mutation is present, however in Omicron, it has been altered to E484A. The E484K mutation in the Gamma variety has been linked to the ability to produce reinfection (Resende et al., 2021). The shift from a negatively charged, hydrophilic residue (glutamic acid) to a positively charged, relatively high hydrophilic amino acid may be responsible for the Gamma variant's improved potential to cause reinfection (lysine). The Omicron has a different capacity to reinfect due to a shift in amino acid from glutamic acid to alanine, which may affect the interacting forces between ACE2 receptors and may play a role in changing the interaction between ACE2 receptor and RBD. Because Omicron's RBD domain has a larger electrostatic potential than Delta's, it has a lower affinity for the ACE2 receptor. The N terminal domain of Omicron has a low affinity for lipid rafts, making it less fusogenic and harmful (Fantini et al., 2022). In compared to the wild type virus, Omicron has 5 more positively charged amino acids in its spike protein, which improves the virus's binding to cellular targeted drug development (Nie et al., 2022).

So far, the clinical features of Omicron reinfection cases have been minor (Vogel and Kupferscgmidt, 2021). The South African commercial health insurer Discovery Health in Johannesburg said on December 14 that the probability of hospitalisation in Omicron infection is 29 percent lower than in earlier strains (Ledford, 2021), which is a ray of optimism.

XII. DIAGNOSIS OF OMICRON

Antigen-based tests are less sensitive than RT-PCR-based tests, but they swiftly discover positive persons when the viral load is high, making them useful in clinical situations and approved for self-testing in many countries. Deerain et al. (2021) tested the diagnostic capacity of 10 commercial kits and discovered that all of them could identify both the Delta and Omicron variants. For Delta and Omicron, the detection limits were 6.50 log10 copies per mL and 6.39 log10 copies per mL, respectively (Deerain et al., 2021). Since its discovery, SARS-CoV-2 has gone through a long process of recombination and mutation, resulting in a wide range of VOIs and VOCs. S gene dropouts have been recorded as a result of differences in the targeted region, calling into doubt the trustworthiness of currently deployed detection techniques. Immunoassays based on prototype SARS-CoV-2 virus coated antigens may not necessarily detect antibodies against presently circulating variations, necessitating constant re-evaluation and revalidation of live viral neutralisation tests based on evolving VOIs and VOCs (Lippi et al., 2021).

The current RT-PCR assay can identify the Omicron (ThermoFisher TaqPathTm kit available by Applied Biosystems). Yet, there have been cases of S gene target failure (SGTF) resulting in a false negative result; however, a rapid increase in the SGTF (S gene dropout) might be interpreted as a signal of the development of Omicron with a decrease in the circulation of other variations. Switzerland and Liechtenstein have

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provided us with field evidence. Metzger et al. gathered data from the most commonly used SARS-CoV-2 PCR assays targeting several areas (including the ORF1ab region (N = 16), the RdRp gene (N = 13), the S gene (N = 8), the E gene (N = 11), the N gene (N = 32), and the M gene (1)). (2021). When S gene dropouts were investigated, only two of the eight tests provided indicated S gene dropout for Omicron, implying that S gene dropout cannot be used as a marker for the presence of Omicron, and that confirmation of the existence of Omicron should be based on gene sequencing data analysis (Metzger et al., 2021; Torjesen, 2021).

Neopane et al. (2021) developed a TaqMan SARS-CoV-2 mutation panel molecular genotyping test that could distinguish between variants B.1.617.2 (Delta), B.1.1.7 (Alpha), B.1.526 (Iota), B.1.351 (Beta), P.1 (Gamma), P.2 (Zeta), B.1.617.1 (Kappa), B.1.427/B.1.429 (Epsilon). In the current situation, the assay is quite beneficial and may be utilised for monitoring and epidemic control. The speedy creation of a testing kit to meet the pandemic's rigorous requirements, however, remains a hurdle. The emergency use authorisation (EUA) has simplified the approval procedure in the United States, allowing for faster assay development and clearance. Governments have been able to greatly expand the number of tests in the emergence of novel varieties as a result of these efforts (Thomas et al., 2021). Despite its time and cost, next-generation sequencing (NGS) of Omicron's whole genome may serve as the gold standard for diagnosis and variation discovery. When the results from the Allplex SARS-CoV-2 Master Assay and Variants I Assay were compared to NGS as a reference for 115 samples, the sensitivity for detecting spike mutations was 98.7% and 100% for the Allplex Master Assay and Variants I Assay, respectively (Fu et al., 2022). Multiplex RT-PCR to identify SARS-CoV-2 VOCs and spike variant PCR techniques can be useful in resource-constrained situations for swiftly monitoring chosen VOCs, although they may require updates when new variants appear (Fu et al., 2022). During the SARS-CoV-2 genomic surveillance in Georgia, Omicron was diagnosed on time using a combination of the Spike SNP PCR test (which took only 2 hours and 12 minutes to run) and genome sequencing and lineage classification (which took 72 hours). Furthermore, the SNP analysis allowed the assay to discriminate between the other VOCs and Omicron, and the assay could be tweaked to identify additional mutations if necessary (Sexton et al., 2022). According to WHO guidelines, Omicron was found in an aeroplane wastewater sample using the CDC N1, CDC N2, and del (69–70) RT-qPCR tests, and sequencing verified the presence of Omicron belonging to the BA.1 sub-lineage (Ahmed et al., 2022).

Changes in the epidemiological situation, local epidemiology, demographic dynamics, and resource availability should all be factored into testing techniques. Furthermore, proper sample and technique selection is critical to the testing strategy's effectiveness, and it is highly dependent on the testing strategy's specific public health objectives, such as assessing different variant circulation and outbreaks, selecting representative samples for sequencing, monitoring virus evolution, and determining vaccine efficacy. As a result, the European Center for Disease Prevention and Control (ECDC) and the WHO Regional Office for Europe published the first update for methodologies and strategies for identifying and characterising SARS-CoV-2 variants on December 20, 2021. (ECDC, 2021c).

XIII. IS PREVIOUS SARS-COV-2 INFECTION INCREASE SUSCEPTIBILITY TO OMICRON?

People who had previously been infected with SARS-CoV-2 were more likely to get infected with omicron than earlier forms, according to a UK study released on December 23, 2021, with 9.5 percent of those afflicted having a history of illness (Mahase, 2021a). Furthermore, Mahase (2021a) argued that this figure is likely understated since some patients are unaware of previous silent illnesses. As a result, they are excluded from the total. When researchers looked at the transmission dynamics of Omicron in immunocompetent and immunosuppressed people, they discovered that, in comparison to other VOCs, asymptomatic carriage increased to 16 percent in both HIV and HIV/AIDS patients, compared to 2.6 percent during the Beta and Delta outbreaks (Garrett et al., 2022).

XIV. SARS-COV-2 VACCINE EFFICACY AGAINST OMICRON

The effectiveness of the Pfizer-BioNTech vaccine against classical SARS-CoV-2 is 41 times lower for Omicron, according to a trial involving a small sample of participants (n = 12). (Cele et al., 2021). Pfizer reported similar results, stating that the third dosage of vaccination might demonstrate the same level of neutralising antibodies as the

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previous two doses against the classical virus (Mahase, 2021b).

Omicron produced an epidemic in Norway in late November 2021, indicating strong transmissibility despite full immunisation. Omicron caused a 74 percent attack rate in a party of 117 persons, with all of them developing symptoms. None of them, however, required hospitalisation. Despite being properly vaccinated, 96% of the participants got the symptoms (Brandal et al., 2021) that are evidence of immunisation failure on Omicron infection. In Denmark, 785 Omicron cases have been documented as of December 9, 2021. The third dosage was given to 7.1 percent of those who were fully immunised. Symptoms were noted in 76% of cases, with 9 patients requiring hospitalisation, and no deaths were documented (Espenhain et al., 2021). Omicron produced an epidemic in Norway in late November 2021, indicating strong transmissibility despite full immunisation. Omicron caused a 74 percent attack rate in a party of 117 persons, with all of them developing symptoms. None of them, however, required hospitalisation. Despite being properly vaccinated, 96% of the participants got the symptoms (Brandal et al., 2021) that are evidence of immunisation failure on Omicron infection. In Denmark, 785 Omicron cases have been documented as of December 9, 2021. The third dosage was given to 7.1 percent of those who were fully immunised. Symptoms were noted in 76% of cases, with 9 patients requiring hospitalisation, and no deaths were documented (Espenhain et al., 2021). According to Singhal (2022), previous viral infection or vaccination does protect against hospitalisation and severe outcomes during Omicron infection, yet vaccinations have no effect on Omicron spread. Neutralizing antibodies were examined in serum samples from people who had been infected and then vaccinated (convalescent–vaccinated) or who had been vaccinated and then became sick (vaccinated–convalescent). Omicron neutralisation was shown in both the convalescent–vaccinated and vaccinated–convalescent samples, but to a smaller level than Delta; nonetheless, in the aforesaid example, Omicron neutralisation was somewhat greater in the convalescent–vaccinated serum (Rössler et al., 2022). Six months after the second vaccination dosage and before the third boosting dose, antibody fading has been seen, particularly in individuals who received two doses of AstraZeneca ChAdOx1 nCoV-19 vaccine (Faustini et al., 2022). Furthermore, when produced using the highly attenuated, replication-competent vaccinia virus vector NYVAC-KC, a mouse-adapted strain having all five mutations seen in Omicron (K417, E484, Q493, Q498, N501) in the spike region gave 100 percent protection against mortality but not from symptoms (Kibler et al., 2021). With previous infection, a single dosage of the ChAdOx1 nCoV-19 vaccine was able to elicit a higher degree of antibody response, which was similar to two vaccination doses (Gelanew et al., 2022). This information is critical in lowering the number of vaccination doses required in resource-constrained areas. mRNA vaccines had a 4.2-fold and 21.3-fold poorer effectiveness against Delta and Omicron variants in cancer patients, respectively, and a 3.6-fold and 5.1-fold worse efficacy after boosting. It demonstrated the efficacy of boosting techniques in immunocompromised individuals, such as cancer patients (Zeng et al., 2021). In a multivariate Cox proportional hazards regression analysis, a substantial decreased risk of infection with Omicron was not established in previously infected participants, but it was found in vaccinated people (Shrestha et al., 2022).

XV. READINESS FOR OMICRON SPECIFIC VACCINE

The developers of the two mRNA vaccines, Pfizer-BioNTech and Moderna, stated that they could build an mRNA-based vaccination against Omicron in 100 days due to the inefficacy of the previously established vaccines (Burki, 2021). Pfizer and BioNTech, as well as Moderna, have provided encouraging updates on the development of an Omicron-specific vaccine (Mahase, 2021c), which might lead to a bright future in the fight against the Omicron version of SARS-CoV-2. The COVID-19 pandemic is being prolonged due to the ongoing evolution of SARS-CoV-2 and the out-of-control scenario, placing the entire globe at risk of COVID-19 and its devastating effects on global health and severe economic implications (Petersen et al., 2022). However, evolutionary researcher Jesse Bloom's perspective is somewhat reassuring, as he claims that Omicron will not be destroyed, but will instead permanently establish itself in humans, similar to other seasonal CoVs that have been circulating in humans for decades (Callaway, 2021c).

XVI. THERAPEUTIC ADVANCES AGAINST OMICRON

Several repurposed drugs, including antivirals and immunotherapies (based on antibodies), have been suggested for use in

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emergency situations to reduce disease severity in COVID-19 patients, while many drugs and therapies are still being investigated and tested. However, the most appropriate choices for COVID-19 treatment are still being determined (Bae et al., 2021; Rabaan et al., 2021; Zou et al., 2021; NIH, 2022). In this part, we'll go over some recent developments in medications and therapies that may be useful for Omicron.

16.1Ribonucleoside analog

SARS-CoV-2 is now being treated with a ribonucleoside analogue and a protease inhibitor. Because these two antivirals target the NSP14 and NSP5 genes, and Omicron exhibited only one mutation in each of these genes, the method of action of these two antivirals appears to be unaffected. However, even for Delta variants, the effectiveness of these antivirals has yet to be proved (Ferré et al., 2022). In addition, ResCovidinTM, a potential medication that inhibits all SARS-CoV-2 entrance ports and may prevent Omicron infectivity, was recently developed (Fang and Shi, 2021).

16.2 Antivirals

Molnupiravir (Lagevrio®), an oral antiviral medicine with anti-RNA polymerase action, was recently authorised by the FDA's Antimicrobial Drugs Advisory Committee as the first oral antiviral treatment for COVID-19, and others are expected to follow soon (Fan et al., 2021; Lee et al., 2021; Persad et al., 2021; Pourkarim et al., 2022). Apart from Molnupiravir, another antiviral drug, nirmatrelvir/ritonavir [PaxlovidTM (PF-07321332 + ritonavir), Pfizer], has shown promising results in clinical trials to protect against serious COVID-19 illness, and the FDA has recently granted this oral antiviral drug emergency use authorization (EUA) (Graham, 2021; Mahase, 2021e; Wang and Yang, 2021). In the face of threats from Omicron and other variations like Delta, such antiviral oral medications and tablets have sparked fresh expectations for COVID-19 therapy and reducing hospitalisation, and might be useful in modifying the pandemic's trajectory (Fan et al., 2021; Couzin-Frankel, 2021; Graham, 2021; Parums, 2022).

16.3 Monoclonal antibodies

Currently, there are eight authorised or approved mAbs for therapy; seven of these (bamlanivimab, etesevimab, casirivimab, imdevimab, cilgavimab, tixagevimab, and regdanvimab) inhibit viral S protein binding to ACE2. Omicron variations revealed that viral changes altered the antibody binding of approved therapeutic antibodies, such as Casirivimab + imdevimab and Bamlanivimab + etesevimab (Falcone et al., 2021). Early simulations suggest that the REGN-COV2 (Casirivimab and Imdevimab) antibodies, as well as the Rockefeller University antibody C135, are still effective against the omicron (Chen et al., 2021a; Aleem et al., 2022). The preventative and therapeutic antibodies NA8 and NE12 were produced utilising combinatorial antibody phage-display library technology, and they are effective against Omicron at picomolar doses (Chen et al., 2022). To tackle Omicron in the future, high-potency medications are needed that can inhibit viral replication and spread while still being effective against all circulating versions, as well as any future variants that may appear (Fang and Shi, 2021; Mohiuddin and Kasahara, 2021). Sotrovimab (S309) or Tixagevimab + Cilgavimab combo binding was unaffected by Omicron mutations (Miller et al., 2021). Hoffmann et al. (2021) published similar results, stating that Omicron spike is resistant to numerous marketed therapeutic antibodies but susceptible to suppression by sotrovimab. In vitro studies have shown that sotrovimab, an MAb antibody developed by GSK, is effective against the Omicron spike protein (Mahase, 2021b). Sarbecovirus mAbs that neutralise the virus broadly identify the region outside of the receptor-binding motif. Three mAbs, sotrovimab, S2X259, and S2H97, fit into this category, finding conserved epitopes and neutralising Omicron (Cameroni et al., 2021). When a panel of 44 mAbs was tested for neutralising Omicron belonging to cognate RBD binding sites (I, I, IV, and V), only a few of the antibodies targeting conserved epitopes were found to be broadly neutralising; these will be useful in targeting Omicron, which is resistant to antigenic shift due to virus evolution (Cameroni et al., 2021), and may help control the ongoing pandemic. The connecting B cell receptor to antigen specificity through sequencing (LIBRA-seq) method, which permits simultaneous reporting of B cell receptor and antigen reactivity at the single-cell level, was used to recover a panel of neutralising antibodies. Only SARS-CoV-2 neutralising antibodies were tested, and no additional coronaviruses were found. Among these, the RBD region 54042-4 was the most powerful and targeted. The neutralisation of presently circulating VOCs is unaffected by using the 54042-4 antibody, according to shotgun

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alanine-scanning mutagenesis of the SARS-CoV-2 RBD. 54042-4 distinguishes itself from other SARS-CoV-2 neutralising antibodies by using a unique S protein recognition mode and having a unique genetic signature. Its capacity to neutralise Alpha, Beta, Gamma, and Delta VOCs, as well as the fact that its epitope is conserved across presently circulating strains, making it a promising therapeutic and diagnostic target (Kramer et al., 2021).

XVII. STRATEGIES TO TACKLE EMERGING SARS-COV-2 VARIANTS

The pandemic virus is quickly mutating, posing a serious health hazard to humans. While we've made progress against covid-19 in the previous two years, the development of the omicron version serves as a stark reminder that there's still a lot more work to be done (Rae, 2021). The developing SARS-CoV-2 mutations necessitate timely diagnosis, thorough surveillance, and monitoring (Rahimi et al., 2021; Raman et al., 2021; Khan et al., 2022). There is a pressing need to lessen vaccination apprehension while also developing even more effective vaccines (Blasi et al., 2021; Fiolet et al., 2021). To reach the whole world's population, such an effective vaccination is necessary. The safety precautions implemented during the early waves of SARS-CoV-2, such as quarantine, masks, and other sophisticated protective equipment, as well as appropriate hygiene practises, must be maintained (Dhama et al., 2021; Zhou et al., 2021). One of the primary tasks in any Omicron-stricken country should be to enhance medical facilities and make these upgraded facilities available and accessible to virus-infected patients, particularly those who live in the most impacted areas. Apart from creating therapies against new variations, most of the research should focus on drug repurposing, which involves using medications that have previously been created, tested for safety and efficacy, and are currently being used to treat another disease to treat SARS-CoV-2 (Dhama et al., 2020).

Currently, only a small percentage of persons in low-income countries have been vaccinated against COVID-19 (Anonymous, 2021; Tareq et al., 2021). The issue with the vaccination push is that ethnic minorities are less likely to get vaccinated, and financially disadvantaged people are less likely to be vaccinated (Rae, 2021). People living in low-income and less-developed nations should be a primary priority for mass immunisation since vaccination has been shown to be beneficial in managing COVID-19 and preventing high burdens of disease severity (Nainu et al., 2020; Liu et al., 2021). (He et al., 2021). During a pandemic, when multiple varieties develop one after another, each with varying illness severity and transmissibility, it is critical to have clear signals, which have been shifted from "stay home" to "remain alert," which many people may find perplexing and might be interpreted as "Alert Fatigue" (McKee, 2021). Furthermore, when government individuals in charge of setting regulations break the rules, there is a reduction in adherence to guidelines and faith in government, which is known as the Cummings effect when we look at all the scenarios from a behavioural standpoint (McKee, 2021). Moreover, despite widespread vaccination, the emergence of the Omicron variety is causing public concern and dread, fueled by disinformation propagated on social media channels. Medical personnel are also anxious as a result of the challenges they experience in dealing with anti-vaxxers, and the situation intensifies when dealing with violent mental patients (Jain and Jolly, 2021). Following the development of SARS-CoV-2, China changed a number of policies to guarantee that preventative and control actions are implemented effectively, and the public health concept is integrated (Luo et al., 2021). As part of the readiness programme, the government plans to build Nightingale centres in the first week of 2022, where patients who are not suitable for release but require minimum nursing assistance, are not a source of infection, and do not require oxygen support would be housed (Mahase, 2021f).

High-income and developed countries can handle a fully organised and focused mass vaccination assistance operation. Vaccines must be supplied to individuals living in low-income nations in order to promote vaccination equity and worldwide access, since the longer vaccine inequality exists, the more opportunities the virus will have to reproduce, mutate, and adapt (Vaughan, 2021). As a result, more than 100 nations and hundreds of organisations have banded together to support a campaign to temporarily waive intellectual-property (IP) rights to COVID-19 vaccines and treatments, which was launched and spearheaded by India and South Africa (Wouters et al., 2021) and supported up by the WHO (Anonymous, 2021). Better tactics for developing improved vaccine candidates with a longer shelf life, higher stability, and ease of

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vaccination, such as an oral or nasal vaccine, should be pursued (Snehota et al., 2021). Many mRNA-based vaccines may be efficiently designed to meet the pace of emerging SARS-CoVB-2 VOCs and VOIs at this time, when there is a high demand for protecting the population from emerging SARS-CoVB-2 VOCs and VOIs; however, there is a quest to develop a much more experimental one-shot universal vaccine that can protect individuals for the rest of their lives (Li, 2021).

Based on existing hospital occupancy monitoring data and the weekly rate of new hospitalisation, Yaesoubi et al. (2021) proposed decision guidelines. This might aid policymakers in keeping a close watch on current and developing events and formulating decision-making guidelines (Yaesoubi et al., 2021). Thermal screening for infection, as well as social distancing, are recommended as safety precautions upon arriving at the airport. Passengers from high-risk nations should also be tested using RT-PCR, and standard safety protocols should be followed. If these tests come out positive, the material should be submitted to be sequenced (Thakur and Kanta Ratho, 2021).

To increase the number of tests and tracking of SARS-CoV-2 and its developing variations, government entities may collaborate with business organisations (CDC, 2021b). Genome sequencing technologies must be improved to track the development of novel variations in real time so that timely tactics may be developed to address the pandemic's looming problems. Much is still unknown and unknown about the most recently emerged Omicron SARS-CoV-2 variant, its threat assessment, and as a result, high vigilance, necessary public health alerts, collaborative efforts, action plans, and preparedness plans in advance, while translating the entire knowledge gained on COVID-19 into prevention and control of emerging variants to be best feasible ways, are the utmost need of the present time to tackle this VOC, which appears to pose a high threat (Anonymous, 2021; Choudhary et al., 2021; Daria et al., 2021; Gao et al., 2021; Karim and Karim, 2021; Wang et al., 2021; Ingraham and Ingbar, 2021).

XVIII. WHAT CAN BE DONE IN THE PRESENT SCENARIO?

As of January 22, 2022, Omicron VOC had knocked on the doors of 150 countries, with nearly 0.5 million confirmed cases and 115 deaths worldwide, and is spreading into the population of all affected countries due to its faster transmission rates (ECDC, 2021b; NewsNodes, 2022), so the number of cases is likely to rise rapidly as a massive surge in COVID-19 cases at the global level. Given the limited knowledge available on the Omicron type, a multi-layered strategy is essential, particularly when immunological escape and vaccine failure are a major issue (ECDC, 2021e). The spread of the Delta type among countries compelled authorities to make vaccinations a major priority, particularly for individuals who are unvaccinated or have not been completely vaccinated. In the United States, for example, the need of obtaining vaccinations is emphasised even for children over the age of five, as well as getting booster injections for those over the age of eighteen (Tanne, 2021b). Until the epidemiological situation is fully understood, certain travel restrictions may be enforced and prolonged. By December 2, 2021, more than 50 nations will have strengthened border restrictions to slow the spread of Omicron (Mallapaty, 2021). Despite the fact that travel restrictions have been introduced in reaction to the discovery of a novel coronavirus strain, experts believe we are too late and may even impair Omicron research. As a result, the WHO advised against travel bans and proposed quarantining new arrivals and testing passengers for SARS-CoV-2 before and after their journeys to avoid viral transmission (WHO 2021d). Furthermore, at a meeting of the Scientific Advisory Group for Emergencies (SAGE, 2021) in England on December 16, they advised the government of England to implement more stringent measures as soon as possible to reduce infection levels in the public and prevent the expected high levels of hospital admissions and deaths across the UK, similar to those in place after step 2 or step 1 of the government's roadmap. Government choices should be based on scientific facts rather than political considerations (Queen, 2022). Furthermore, they emphasised that postponing such programmes until 2022 would significantly reduce their efficacy and make it less likely that they would alleviate major pressure on health and care facilities.

Lubin et al. (2021) used computational analysis to create a structural model based on Omicron RBD binding to its matching ACE2 and neutralising and therapeutic antibodies. R493, S496, Y501, R498, and ACE2 residues formed a multi-residue interaction network. While the binding of Barnes Class 1 and Class 2 neutralising antibodies against Omicron RBD exhibited overall decreases in interfacial contacts, this interaction

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network demonstrated positive co-operation between residues to promote the binding of Omicron RBD and ACE2. Furthermore, only a handful of the Omicron changes are known to reduce antibody binding (e.g., K417N). The expanded WKDE model is an updated model that does retrospective analysis based on spatiotemporal data to infer the date of infection for individual patients and forecast the likelihood of illness development in the future (Tong et al., 2021). More data-driven spatial prediction models are needed to lessen the reliance on theoretical assumptions and reliably anticipate illness start in the future, especially when dealing with Omicron, which has extremely high infection rates.

According to Monte Carlo simulations, a bigger number of sick people are now behaving as super-emitters. The ratio was 1 in 1000 for wild type virus, but 1 in 20 or 10 for Omicron (Riediker et al., 2022). This research suggests that surgical masks alone are insufficient, and that well-fitting FFP2 respirators can give enough protection. Several non-pharmaceutical approaches have been shown to be effective in reducing delta variant VOC transmission. Social distance, ensuring proper ventilation, and maintaining excellent hand and respiratory hygiene are also important in reducing SARS-CoV-2-related morbidity and death. Wearing masks, even if fully vaccinated, is critical and must be combined with non-pharmaceutical actions to combat the pandemic. According to several mathematical models, the present vaccination rate is insufficient to entirely prevent viral propagation (Brüssow and Zuber, 2021). The Omicron variant (B.1.1.529) was discovered in an asymptomatic, fully vaccinated traveller in a quarantined hotel in Hong Kong, China, and was transmitted to another fully vaccinated traveller staying in a room across the corridor from the index patient, indicating that the virus variant was transmitted despite strict quarantine precautions (Gu et al., 2021). Aerosols may seep into guest rooms and corridors, and infectious aerosols may be breathed when room doors are opened, according to smoke studies conducted in designated quarantine hotels (Wong et al., 2021). The Wells-Riley model is a frequently used model for estimating the risk of airborne pathogen transmission in interior environments. Using computational fluid dynamics (CFD) simulations of airflow and aerosol transport, the spatiotemporal distribution of airborne pathogens was determined, and it was discovered that a combination of proper ventilation and personal protective equipment (PPE) is required for preventing transmission risk in hospital wards (X. Li et al., 2021). According to experts, governments should impose strong limitations based on modelling, which shows that without additional restrictions, hospital admissions might reach 3000 to 10000 per day, with a mortality toll of 600 to 6000 per day (Iacobucci, 2021b).

Early genomic detection, field investigation, and laboratory assessments will continue to be useful in understanding epidemiological trends, virus characteristics, disease severity, the effectiveness of public health and social interventions, diagnostic procedures, immunological responses, and vaccine effectiveness, as well as taking the necessary steps to prevent further dissemination (Wang and Powell, 2021).

XIX. CONCLUSIONS AND FUTURE PERSPECTIVE

Despite large vaccination campaigns throughout the world and significant efforts to contain the spread of SARS-CoV-2, the COVID-19 pandemic persists as the virus develops into various strains and mutations. The SARS-CoV-2 epidemic has struck the world, wreaking havoc on global health and wreaking havoc on the global economy. After nearly two years after the virus and its many forms first appeared, an unusual accumulation of high numbers of mutations has given rise to the most mutated SARS-CoV-2 Omicron variant. The emergence of the Omicron variant could be attributed to either the accumulation of mutations in a small group of people and then their spread to a larger group of people, or to long-term persistence in immune-compromised patients, which resulted in virus evolution and the emergence of a variant with more mutations. Alternatively, the theory of epizootic viral transmission from people to animals and then back to humans must be thoroughly explored before any conclusions can be drawn. Whatever the cause of Omicron's appearance, it has currently caused chaos and raised serious public health concerns on a worldwide scale. Safety measures such as quarantine, social distancing, wearing face masks, hand hygiene, respiratory hygiene, medical facility upliftment, development of highly efficacious vaccines and universal vaccine effective against all variants of SARS-CoV-2, and exploring drug repurposing should be given until its complete etiology regarding infectivity, neutralisation through immune sera, and effectiveness against

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currently available vaccines and immunotherapies is understood. Infectivity, the efficiency of therapies against the pathogen, the efficacy of pre-existing immunity established by natural infection or vaccination via vaccines against the new virus, and probable health risks associated with immunological escape are all major issues when a virus emerges. Strengthening research, improving genomic surveillance and tracking, developing highly effective vaccines and immunotherapies, designing appropriate strategies, action plans, and future preparedness plans must all be prioritised and implemented quickly at global levels to mitigate the high global health concerns associated with the emergence of this new Omicron variant well before it causes large-scale COVID-19 outbreaks.

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