Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Omicron (B.1.1.529) variant and its subvariants and lineages may lead to another COVID-19 wave in the world? -An overview of current evidence and counteracting strategies

A B S T R A C T

The highly contagious Omicron variant of SARS-CoV-2 is a recent cause of concern during the COVID-19 pandemic. The World Health Organization (WHO) has classified SARS-CoV-2 variants into variants of concern (VOCs), variants of interest (VOIs), and variants under monitoring (VUMs). VOCs were categorized as Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2). Omicron (B.1.1.529) was a further modified strain that has a short incubation period; it was called VOC by the WHO, and it became fifth on the list of variants. Omicron has spread faster than any other variant since its emergence in late 2021. Omicron is currently the only circulating VOC. The various subvariants of Omicron are BA.1 (B.1.1.529.1), BA.2 (B.1.1.529.2), BA.3 (B.1.1.529.3), BA.4, BA.5, and descendent lineages. More recently, identified Omicron subvariants and sublineages BQ.1, BQ.1.1, BA.4.6, BF.7, BA.2.75.2, XBB.1, and BF.7 have also attracted global attention. The BA.5 strain of Omicron is the most contagious and dominant subvariant globally. Recent spikes in cases in China are due to the BF.7 subvariant. With the large increase in the number of cases, there has been an increase in hospitalisations in countries worldwide. In many countries, the lifting of infection prevention protocols, such as the use of masks and physical distancing, contributes to the spread of the virus. This article highlights the potential impacts of SARS-CoV-2 variants and subvariants, which have made the pandemic far from over. Effective vaccination remains the safest option to kerb transmission of these variants. Therefore, people must be vaccinated, wear masks, perform regular hand hygiene, and observe social distancing. Additionally, genome sequencing of positive samples can help detect various virus variants; thus, mapping cases in a particular area can be performed.

As of the date of writing (21 December 2022), Coronavirus disease 2019 (COVID-19), a highly contagious infectious disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has had a severe adverse impact on humanity in terms of health and socioeconomically, resulting in more than 650 million confirmed cases and more than 6.6 million deaths worldwide [1,2]. Due to this concern, the World Health Organization (WHO) declared COVID-19 a global pandemic on 11 March 2020, and is currently active. The clinical manifestations of COVID-19 vary from asymptomatic to critically ill (i.e., severe acute respiratory distress, pneumonia, multiorgan damage, and even death). Approximately 15% of confirmed cases develop the severe form of COVID-19, with the elderly group, immunosuppressed, and those with comorbidities being the most affected [3]. Several variants of SARS-CoV-2 are continuously emerging with different transmissibility, contagiousness, and mortality rates, and their rapid and evolving emergence has led to a change in the form of newer and more adaptive diagnostic methods for the detection of SARS-CoV-2 infections, as well as the development of more effective vaccines, administration of booster doses, and discovery of better drugs and therapeutics [4]. In this context, the WHO has classified SARS-CoV-2 variants into three categories to assess and monitor SARS-CoV-2 evolution and prioritise global research, monitoring, and measures. They include variants of concern (VOCs), variants of interest (VOIs), and variants under monitoring (VUMs). The VOCs were previously identified as Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) until late October 2021 [5]. These variants are more transmissible than the original Wuhan SARS-CoV-2 strain, induce relatively severe disease, have evasive immunologic characteristics, decrease antibody neutralisation in vaccinated individuals, are more susceptible to reinfection, and are under increased global surveillance because they are more contagious and associated with an increased risk of serious illness and hospitalisation [3].

The Gauteng province of South Africa saw a dramatic increase in COVID-19 cases in November 2021. With this increase, researchers have noticed an increase in the occurrence of S-gene target failure in TaqPath-based RT-PCR tests. Consequently, this unexpected discovery indicates that a variant of SARS-CoV-2, genetically unique to the rest of the strain, has spread throughout the population. At the same time, unusual viral sequences were found in samples collected from a tourist group in Gaborone, Botswana. The South African and Botswanan SARS-CoV-2 genomes were assigned to a new PANGO lineage (B.1.1.529) on 24 November 2021 [6,7]. Omicron is a highly modified strain that has spread rapidly worldwide, requiring the WHO to announce it as a VOC and make it the fifth on the variants list on 26 November 2021, subsequently leading to a massive surge in COVID-19 cases worldwide, leading to a new pandemic wave [5,8].

The Omicron (B.1.1.529) is currently designated as the only circulating VOC, including its subvariants BA.1 (B.1.1.529.1), BA.2 (B.1.1.529.2), BA.3 (B.1.1.529.3), BA.4, BA.5, and descendent lineages [9,10]. More recently, the identified Omicron subvariants and sublineages BQ.1, BQ.1.1, BA.4.6, BF.7, BA.2.75.2, XBB.1, and BF.7 have also attracted global attention, and investigations are being carried out on their transmissibility, effectiveness of vaccines, immunotherapeutics, and antiviral drugs, tackling their emergence and shed light on the evolution of these newly emerging subvariants and formulating adequate counteracting strategies [11–16].

Compared to the reference strain of SARS-CoV-2, the Omicron variant shares at least 50 alterations/mutations (A67V, del69–70, T95I, G142D, del143–145, T547K, D614G, H655Y, N679K, P681H, D796Y, N856K, Q954H, N969K, L981F, T478K, G339D, R346K, S371L, S373P, S375F, L452R, S477 N, E484A, Q493R, G496S, Q498R, N501Y, Y505H,

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N679K, N856K, H655Y, and A701V), including 43 substitutions, six deletions, and one insertion of the nucleotide. Approximately 27 of these changes were located in the S protein and are believed to lead to accumulation near the receptor-binding (RBD) motif. In addition to the 50 unique mutations, there were 10 highly mutated regions, seven non-synonymous and three synonymous. The spike (S) gene of Omicron consists of 49 representative haplotypes (each occurring in more than 50 sequences) [17]. This large number of mutations is because viral genomes acquire mutations over time, and RNA virus genomes are highly susceptible to mutations [17]. The Omicron variant may be more transmissible if it contains alterations in H655Y, N679K, or P681H at its S1–S2 furin cleavage site. Mutations were much lower for the remaining four VOCs, with 22, 18, 23, and 29 for Alpha, Beta, Gamma, and Delta, respectively [18]. As observed for Delta, the binding affinity to ACE2 was enhanced by mutations in Q498R and N501Y [19]. Omicron BA.1 has created great health concerns, especially among the scientific community, due to the substantial number of mutations, especially mutations in the S protein RBD, leading to atypical high infectivity and the ability to evade antibody protection enhanced by viral infection and vaccination [20]. The speed at which the Omicron variant spread to all continents and replaced the previous variants, Delta, Alpha, Beta, and Gamma, has raised concerns about its pathogenicity and fatality, but observations in several countries suggested that infections were less severe and that its pathogenicity was lower than that of the Delta variant; however, studies suggest that both Delta and Omicron variants are highly transmissible by contact transmission [21,22]. In non-contact transmission studies, the Omicron variant showed similar or higher transmissibility than the Delta variant [17,20]. Although vaccination against SARS-CoV-2 is based primarily on vaccines that induce immunity to spike glycoproteins, several studies have shown that the administration of booster shots and three doses of spike-based vaccines may provide only partial protection against infection with this variant, and co-infection between different SARS-CoV-2 variants can lead to genetic recombination that can create new chimeric variants with unpredictable pathogenic properties that could represent a serious health threat and cause a new alarm status [23].

The CDC warns that anyone infected with Omicron, regardless of vaccination status or the presence of symptoms, poses an increased risk of spreading the virus to others. Mutations in the RBD of the S protein of the Omicron variety boost its affinity for the human ACE2 receptor, facilitating the effective entry of the virus into human cells [24]. The effective number of reproductions increased approximately 3.19 times (95% CI, 2.82−3.61) compared to the Delta variant. As a result, Omicron cases skyrocketed quickly after its introduction due to a dramatic increase in transmissibility and infectivity. Several symptoms of Omicron, usually minor, are categorized as flu-like manifestations, aches, pains, fever, sore throat, or cough. Muscle or joint pain, loss of taste (anosmia) or smell (ageusia), and a runny nose are also common in the earliest forms.

Infection with heterologous variation to the most recent wave of infection by the Omicron/PANGO lineage B.1.1.529 had some unanticipated immune-damaging consequences, as discovered by Reynolds et al. [25]. Scientists have discovered that infection with the Omicron variant has increased immune responses to all variants of SARS-CoV-2, except the Omicron variant itself. However, Omicron-specific responses were only marginally bolstered by infection with the Alpha variant. The Omicron variant infection following the Wuhan Hu-1 infection did not enhance neutralising antibody and T cell responses against Omicron, showing a significant impact and explaining repeated reinfections [25].

Based on existing studies, the risk of the Omicron variant (B. 1.1.529) remains high. Omicron has a strong growth advantage over Delta, leading to faster propagation and increased incidence during the ongoing COVID-19 pandemic, and its subvariants and lineages could pose imminent risks ahead [8,10]. Despite a lower risk of severe forms of COVID-19 and death than that of previous SARS-CoV-2 variants, the high transmission levels of Omicron have led to a significant increase in hospitalisation rate, continuing to overwhelm healthcare systems in many countries and may lead to significant morbidity rates, especially in vulnerable populations [26].

It is well accepted that vaccination is the most effective public health intervention to prevent SARS-CoV-2 infection and its variants, including Omicron [27,28]. People who are not immune should have an initial series of vaccinations and subsequent boosters that may be necessary [8,29]. Currently available vaccines on the market can reduce the likelihood of serious problems, hospitalisations, and fatalities caused by Omicron variants [8,30]. A mix-and-match approach using heterologous prime-boost doses of COVID-19 vaccines has also been used to develop artificially acquired active immunity [31]. Booster doses of Pfizer and BioNTech's Moderna's bivalent COVID-19 vaccines have been approved by the U.S. Food and Drug Administration (FDA) for use in children and adults. These COVID-19 vaccine boosters aimed to protect against the original Wuhan SARS-CoV-2 strain and its Omicron variant, making them bivalent. It can be administered to patients for a 2-month period after finishing the initial series of two doses or after a previous booster dose [32].

Similarly, Novavax provides a COVID-19 vaccine booster dose injection; however, it may not be effective against the more recent Omicron subvariants of SARS-CoV-2 because it only protects against the original SARS-CoV-2 strain [33]. At the beginning of 2022, specialists observed that the BA.4 and BA.5 subvariants appeared to be able to evade some of the antibodies created following immunisation and disease, including those triggered by some Omicron subvariants. Neither the Omicron subvariant BQ.1 nor BQ.1.1 is expected to be neutralised by bebtelovimab, according to a recently revised FDA information sheet [34]. However, in the same revision, the FDA mentioned that other treatments, such as paxlovid, are expected to "retain activity" against the new subvariants.

Several studies have proven that current COVID-19 vaccines offer less protection against infection and mild disease caused by the Omicron subvariant BA.2; there is an urgent need to find and develop new vaccines with a certain effectiveness rate against this subvariant [34]. However, available vaccines continue to offer considerable protection against hospitalisation risk and severe COVID-19 infection with Omicron, especially after a booster dose [8,17,29]. Therefore, the WHO and other health authorities have urged and agreed that the COVID-19 booster dose has become indispensable to avoid a new dangerous COVID-19 wave [34]. It is also clear that the development of a global discussion and strategy plan is mandatory, which will require the intervention and reciprocal exchange of public health organisations and policy makers. Moreover, global regulators should encourage international and local scientific communities and vaccine developers to consider alternative approaches to monovalent vaccines [33,35]. In addition, countries must continue to implement tailored and effective public health measures and surveillance to reduce the circulation of SARS-CoV-2 variants among people, based on risk analysis, as the severity of SARS-CoV-2 infection has been found to increase significantly with comorbidities, such as heart disease, hypertension, and diabetes, as well as with a scientific approach [36]. Additionally, it is essential to emphasise vaccination compliance in all age groups and to combat vaccination hesitancy on a global scale to achieve herd immunity and, ultimately, to control and kerb or even stop the ongoing spread of COVID-19 [33,35].

There is a need for urgent research into the Omicron variants because little is currently known about them. Based on what we learned from Alpha and Delta, we expect that only time and surveillance will reveal more information on the new variant's transmissibility, vaccination efficacy, and severity of sickness. Protective measures and vaccination will continue to be the cornerstones in preventing waves of severe COVID-19 cases and deaths, as we have already confirmed. In other words, it is not a coincidence that Omicron first appeared in a country with a low immunisation rate. Indeed, the emergence of this new variant highlights

the critical need to expand access to vaccination worldwide, since unrestricted virus circulation in unvaccinated populations increases the risk of severe COVID-19 cases and deaths in these populations. Second, it allows the virus to rapidly accumulate mutations that can enhance viral transmissibility and infectivity or cause new deadly waves worldwide.

Furthermore, to combat the re-emergence of any known variant or emergence of new variants, adequate COVID-19 preparedness, proven and established control measures, and surveillance of any new COVID-19 variant mutations should be prioritised in addition to monitoring and sequencing the recent spread of different SARS-CoV-2 variant mutations and avoiding introduction into animal populations. To enhance global accessibility, the resulting genome sequences and associated metadata can be deposited in freely accessible databases and resources such as Global Initiative on Sharing All Influenza Data. In this regard, different governments worldwide should conduct field investigations and laboratory assessments to determine the potential impact of the Omicron variant on COVID-19 severity, epidemiology, different and specific diagnostic techniques, antibody neutralisation, immune system responses, and the efficacy and validity of public health and social measures [5]. Geographical information system (GIS)-based maps can be used to analyse changes in the epidemiological situation in a specific region [37].

Regarding personal measures, the most effective measures to kerb SARS-CoV-2 and its variant's infection and transmission rate adopted by each person are as follows: (1) maintaining a physical distance of at least 1 m from others; (2) continuing to wear a bib; (3) avoiding poorly ventilated or crowded spaces, using adequate ventilation, and limiting the time spent in crowded or enclosed spaces; (4) washing hands regularly; (5) coughing or sneezing in their elbow or handkerchief; (6) vaccinated with the COVID-19 vaccine and booster shots, three doses as soon as possible; (7) using a face mask, and (8) being isolated in case of suspicion of infection [5,38].

In conclusion, the SARS-CoV-2 Omicron variants and subvariants are continuously emerging, and their evolution dominates the current late 2022 COVID-19 waves. The recent increase in COVID-19 in China should be kept in mind, and therefore, optimal infection prevention and control measures must be strictly followed unless and until the world is free from the ongoing COVID-19 pandemic. To develop a more effective vaccination strategy, strict vigilance and adoption of appropriate, and adequate preventive measures are the critical needs of the present time to counter Omicron and other SARS-CoV-2 variants and lineages in the age of COVID-19 vaccines being administered to combat the COVID-19 pandemic and avoid any new surge of pandemic waves ahead [39–41]. The COVID-19 pandemic has introduced the "new normal" lifestyle into our daily lives. Therefore, surveillance and vaccination campaigns should be prioritised. Public health and safety measures should continue to be followed so that humanity can survive the pandemic with minimal possible side effects.

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