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SARS-CoV-2 emerging Omicron subvariants with a special focus on BF.7 and XBB.1.5 recently posing fears of rising cases amid ongoing COVID-19 pandemic

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron versions have been the sole one circulating for quite some time. Subvariants BA.1, BA.2, BA.3, BA.4, and BA.5 of the Omicron emerged over time and through mutation, with BA.1 responsible for the most severe global pandemic between December 2021 and January 2022. Other Omicron subvariants such as BQ.1, BQ.1.1, BA.4.6, BF.7, BA.2.75.2, XBB.1 appeared recently and could cause a new wave of increased cases amid the ongoing COVID-19 pandemic. There is evidence that certain Omicron subvariants have increased transmissibility, extra spike mutations, and ability to overcome protective effects of COVID-19

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neutralizing antibodies through immunological evasion. In recent months, the Omicron BF.7 subvariant has been in the news due to its spread in China and a small number of other countries, raising concerns about a possible rebound in COVID-19 cases. More recently, the Omicron XBB.1.5 subvariant has captured international attention due to an increase in cases in the United States. As a highly transmissible sublineage of Omicron BA.5, as well as having a shorter incubation time and the potential to reinfect or infect immune population, BF.7 has stronger infection ability. It appears that the regional immunological landscape is affected by the amount and timing of previous Omicron waves, as well as the COVID-19 vaccination coverage, which in turn determines whether the increased immune escape of BF.7 and XBB.1.5 subvariants is sufficient to drive new infection waves. Expanding our understanding of the transmission and efficacy of vaccines, immunotherapeutics, and antiviral drugs against newly emerging Omicron subvariants and lineages, as well as bolstering genomic facilities for tracking their spread and maintaining a constant vigilance, and shedding more light on their evolution and mutational events, would help in the development of effective mitigation strategies. Importantly, reducing the occurrence of mutations and recombination in the virus can be aided by bolstering One health approach and emphasizing its significance in combating zoonosis and reversal zoonosis linked with COVID-19. This article provides a brief overview on Omicron variant, its recently emerging lineages and subvairants with a special focus on BF.7 and XBB.1.5 as much more infectious and highly transmissible variations that may once again threaten a sharp increase in COVID-19 cases globally amid the currently ongoing pandemic, along with presenting salient mitigation measures.

1 Introduction

Coronavirus disease 2019 (COVID-19) pandemic, caused by Severe Acute Respiratory Syndrome Coronavirus - 2 (SARS-CoV-2), has now entered into its fourth year, with over 655 million confirmed cases and 6.6 million deaths recorded globally as of January 6, 2022, overall leading to devastating adverse health consequences and socio-economic impacts on mankind globally (Dhama et al. 2020; WHO 2023a). This pandemic is not seeming to an end owing to continuous evolution and emergence of several variants, strains, subvariants and lineages of SARS-CoV-2 despite developing vaccines, progressive massive vaccination drives, booster shots and finding out drugs and therapies for treating COVID-19 patients (Kopsidas et al. 2022; Wong 2022; Dhama et al. 2023). This urges for developing better diagnostics and more efficacious and newer vaccines, drugs and therapeutics to combat COVID-19 pandemic (Fernandes et al. 2022; WHO 2022). SARS-CoV-2 variants have been classified into variants of concern (VOCs), variants of interest (VOIs), and variants under monitoring (VUMs) (Reynolds et al. 2022; WHO 2023b). The SARS-CoV-2 Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) variants (VOCs) have now been designated as previously circulating VOCs, and its Omicron (B.1.1.529) variant that emerged in the late 2021, is now considered as the only circulating VOC along with its subvariants BA.1, BA.2, BA.3, BA.4, BA.5, and descendent lineages (Kopsidas et al. 2022; Dhama et al. 2023; WHO 2023b). Additionally, co-infections with different SARS-CoV-2 variants may pave ways to genetic recombination that may produce newer chimeric, recombinant and hybrid variants (such as XD, XF, and XE) with unpredictable pathogenic properties, which could feasibly pose a new alarm (Dhama et al. 2023; WHO 2023b).

2 Omicron variant, its emerging lineages and subvariants

Omicron variant (Pango lineage B.1.1.529) has produced different sub-lineages BA.2, BA.3, BA.1, BA.1.1, BA.2.12.1, BA.2.75, BA.2.75.2, BA.4, BA.5 (BA.4/5), BA.4.6, BA.5.1, and one after another these became dominant and predominant strains from time to time by displaying additional immunological escape mechanisms posing significant global health hazards (Ai et al. 2022; Aleem et al. 2022; Ferré et al. 2022; Farahat et al. 2022; Graham 2022; Tian et al. 2022; Elliot et al. 2022; Kurhade et al. 2022; Planas et al. 2022; Qu et al. 2022; Mohapatra et al. 2022a; Dhama et al. 2023). Omicron variant and subvariants have been implicated to compromise vaccine and infection-induced immunity and modify virus biology eventually to a higher extent (Evans et al. 2022; Cui et al. 2022; Qu et al. 2022). Additionally, newer Omicron subvariants, such as BA.4.6, BF.7, BQ.1, and BQ.1.1 (descended from BA.4/5), and BA.2.75.2, have emerged as a result of the spread of the BA.4/5 and BA.2.75 subvariants (derived from BA.2.75) (Hachmann et al. 2022). These new variants have been on rise and could replace as most common subtype in the future (Saito et al. 2022; Uraki et al. 2022; Wang et al. 2022).

Multiple sublineages of Omicron variant and its lineages revealed dynamic molecular phylogenetics and mutational landscape analysis, which demands approriate prepredeness planes to be excecuted (Chakraborty et al. 2022; WHO 2022). Some of these

variants gained higher mutations, are more contagious with higher transmissibility than the original Wuhan SARS-CoV-2 strain, can evade protective immunity, decreases antibody neutralization in vaccinated individuals and adversely affects therapeutic potential of monoclonal antibodies (mAbs) , and lead to reinfection, notably Delta variant has additional ability to cause severe COVID-19 disease too (Arora et al. 2022; Du et al. 2022; Chen et al. 2022; Tian et al. 2022; Hanai 2022; Kurhade et al. 2022; Mohapatra et al. 2022a, Mohapatra et al. 2022b; Uraki et al. 2022; Qu et al. 2022; Zhou et al. 2022).

Omicron has a much higher mutation rate than any other previously circulating VOCs and became the worldwide dominant variety after acquiring new mutations and splitting into several subvariants, each with its own unique epidemiological, clinical, and viral signature as it expanded over the world (Aleem et al. 2022; Dhama et al. 2023). Omicron variant shares at least 50 alterations/mutations with the reference strain, and about 30 of these alterations were detected in the viral S protein, that may lead to receptor binding domain (RBD) motif accumulations. Mutations in the Omicron S protein RBD increase its affinity for the human ACE2 receptor, allowing efficient virus entrance into human cells (Chen et al. 2022). Remarkably, Delta variant lead to a rapid surge in COVID-19 cases and higher deaths during 2021 due to being causing more serious COVID-19 disease, and thereafter Omicron variant that emerged in November 2021 from South Africa caused a very huge massive surge in COVIID-19 cases during early 2022, though not causing severe disease but cumulative number of deaths increased highly owing to very high surge in cases globally (Kannan et al. 2021; Balint et al. 2022; Khandia et al. 2022; Kurhade et al. 2022; Mohapatra et al. 2022b).

Of late, emergence of Omicron subvariants and sublineages such as BQ.1, BQ.1.1, BA.4.6, BF.7, BA.2.75.2, XBB.1 (a BA.2 subvariant) and BF.7 may pose an alarming global health situation and might lead to a new wave of surge in cases amid the ongoing COVID-19 as reflected by the most recent start of rise in cases being observed presently in few countries particularly in China and others (Graham 2022; Wong 2022; News 18, 2022; Sagar 2022; Ai et al. 2022; Aleem et al. 2022; Wang et al. 2022). Some of these Omicron subvariants have been implicated to possess additional spike (S) mutations, higher transmissibility, and immune evasion properties to escape protection rendered by neutralization antibodies of COVID-19 vaccines and boosters, and mAbs as therapeutics (Hanai 2022; Fernandes et al. 2022; Kurhade et al. 2022; Uraki et al. 2023; Qu et al. 2022). Notably, the RBD of the spike (S) protein, the primary target of COVID-19 vaccines and therapeutic mAbs, is more heavily modified in BQ.1.1 and XBB than in BA.5 and BA.2. These versions may, therefore, be more difficult for the immune system to combat than BA.5 and BA.2 (Imai et al. 2022). According to a recently amended FDA information sheet, bebtelovimab will not neutralize Omicron subvariant BQ.1 or BQ.1.1, while Paxlovid should “retain activity” against the new subvariants (Thakur and Ratho 2022).

Since Omicron BA.1 was supplanted by BA.2, the latter has diverged into the sublineages BA.2.12.1, BA.2.75, BA.2.75.2, BA.4, and BA5, with the latter now predominating in many countries. Both BA.4 and BA.5 share the same spike sequence (henceforth BA.4/5), and their progeny, BA.4.6, BF.7, and BQ.1.1, are on the rise. Vaccine efficacy may be compromised by the accumulation of spike mutations in the recently revealed SARS-CoV-2 Omicron sublineages, such as BA.2-derived BA.2.75.2 and BA.5-derived BQ.1.1 and XBB.1 (Kurhade et al. 2022; Qu et al. 2022). Omicron subvariant BQ.1 (a subvariant of BA.5), its sublineage BQ.1.1, and XBB (a recombinant of two separate BA.2 subvariants) have shown rise in many countries, including the United States, France, Singapore, and India. The RBD of S protein is the primary target for vaccinations and therapeutic mAbs against COVID-19. BQ.1.1 and XBB have substitutions in this region compared to BA.5 and BA.2, respectively. As both BQ.1.1 and XBB include the substitution R346T, which gives resistance to certain therapeutic antibodies, there is cause for worry that mAbs or vaccinations may be less successful against these strains than they are against other omicron strains (Uraki et al. 2022).

2.1 BF.7

Recently, BF.7 subvariant of omicron has been in the news owing to its spread in China and other few countries, posing worrisome situation of rise in COVID-19 cases again, and more recently, XBB.1.5, a more contagious and highly transmissible Omicron variant to date has attracted global attention due to rise in cases in the USA. BF.7 is a sublineage of Omicron variation BA.5, has stronger infection potential since it is highly transmissible with a shorter incubation time, and can also reinfect or infect the immunized population (Sagar 2022). Of note, Chinese cities have been afflicted by the highly transmissible Omicron strain, especially BF.7 that is spreading in Beijing and leading to a COVID outbreak after a long time since the first deadly disease outbreak started as a pandemic during early 2020 (Graham 2022; Wang et al. 2022). The BF.7’s high transmissibility in China may be due to inadequate immunity from past SARS-CoV infections and less potentially vaccination. It has also been found in few countries including such as the USA, Brazil, UK, Belgium, Germany, France, China, Denmark and India (Sagar 2022; WHO 2022). The basic reproductive number R0 of Omicron was noted to be an average of R0 of 5.08, while BF.7 is implicitated to presumably have an R0 of 10 to 18.6, which might be potentiating its ability of higher transmission and infectivity.

2.2 XBB and XBB.1.5

To be specific, XBB is a hybrid of the BA.2.10.1 and BA.2.75 variants. However, preliminary research suggests that XBB has a greater reinfection risk than other circulating Omicron sublineages. Only those who contracted XBB before the introduction of the Omicron variant were at risk of reinfection. There is currently no evidence suggesting additional Omicron lineages can evade the recent immunological responses they have elicited. The magnitude and timing of prior Omicron waves, as well as the COVID-19 vaccination coverage, appear to impact the regional immunological landscape, which in turn affects if the increased immune escape of XBB is adequate to drive fresh infection waves (Wang et al. 2022; WHO 2023b).

The rapidity of the XBB.1.5 Omicron subvariant's spread in the northeastern United States has raised concerns among health agencies including the World Health Organization (WHO). Until now, this subvariant had the highest transmission rate. While the WHO still lacks data on XBB.1.5's severity, there is currently no evidence to suggest that it is more dangerous than earlier subvariants. This is due to the fact that mutations in this particular omicron subvariant make the virus particularly well-suited to adhering to cells and replicating within them (CNBC 2023a; CNBC 2023b). No statistics on the severity of XBB.1.5 have been collected by the WHO just yet, although there is currently no evidence to suggest that it is more dangerous than prior Omicron strains. Researchers have shown that XBB.1.5 shares similar abilities to its related XBB and XBB.1 in avoiding the immunological responses prompted by vaccinations and infections. However, XBB.1.5 possesses a mutation that increases its ability to connect to cells, which provides a growth advantage (CNN 2023; Forbes 2023). The ability of a virus to infect people who have been exposed to it before, either by infection or immunization, is known as immune evasiveness. XBB.1.5 achieved this by developing an uncommon form of mutation termed F486P, found in its RBD. Whether or if it contributes to more severe disorders is unknown. This is deemed highly implausible by experts (Livemint 2023; WFLA 2023).

Despite a lower risk of severe COVID-19 and death than the previous SARS-CoV-2 variants comparatively, the high transmission levels and more contagious nature of Omicron and it's different subvariants and sublineages could lead to a significant increase in the COVID-19 cases and hospitalization rates, continue to overwhelm healthcare systems in many countries, and may lead to a considerably higher morbidity rate, especially in vulnerable populations (Kandeel et al. 2022; Dhama et al. 2023).

3 Mitigation strategies

Vaccination is the most effective method for conferring anti-COVID-19 protective immunity and avoiding infections of SARS-CoV-2 and its emerging variants, initial immunizations and recommended vaccine boosters need to be administered to cover up larger population. Vaccines and booster shots can reduce Omicron-related hospitalizations, ameliorate disease severity, deaths, and significant complications (Björk et al. 2022; Mohapatra et al. 2022c; Zhou et al. 2022). Vaccination boosters protect against both SARS-CoV-2 and its Omicron variant and subvariants, though to a different protective level, and despite administering three doses of COVID-19 vaccines only partial protection can be conferred against infection with Omicron variant and subvariants, therefore better and newer vaccines and vaccination strategies are the need of the current times (Wong 2022; Björk et al. 2022; Dhama et al. 2023).

New vaccinations and mAbs are urgently needed since the number of Omicron subvariants keeps growing (Fernandes et al. 2022; Hossain et al. 2022), halting resurgences of resistant strains by designing vaccines targeting Omicron subvariant(s). A variety of vaccination platforms, including those based on mRNA and viruses, as well as protein-based adjuvanted vaccines, which widen present immune responses have been explored. Moreover, RBD-dimeric vaccines, mosaic RBD nanoparticle vaccines, conservative S2-targeting vaccines have demonstrated their potential for countering pan-beta-CoVs (SARS-CoV-2, SARS-like sarbecoviruses), and human endemic CoVs protections by inducing broad-spectrum neutralizing antibodies (nAbs). Together, these active as well as passive vaccination strategies advance us further along the road to pan-beta-CoV, or pan-CoV immunity (Akkız 2022; Ke et al. 2022; Xia et al. 2022). Nasal vaccines generating both humoral and respiratory mucosal immunity could be beneficial in limiting transmission and spread of SARS-CoV-2 and its variants and subvariants.

Recent surge in COVID-19 cases in China and USA and other countries should be kept in mind, and optimal infection prevention and control methods should be closely followed until this pandemic comes to an end. Much is to be known about Omicron and its continuously emerging newer subvariants and lineages. Explorative research and deeper investigations are required for studying transmissibility, effectiveness of vaccines, immunotherapeutics and antiviral drugs against recently emerging Omicron subvariants and lineages as well as enhance surveillance and monitoring, strengthening genomic facilities for tracking their spread, tight vigilance, and throwing more light on their evolution and mutational events which would aid in formulating appropriate mitigation strategies (Hanai 2022; Qu et al. 2022; Uraki et al. 2022). These Omicron subvariants could increase the risk of serious illness and hospitalization altogether under threats of cumulative rise in COVID-19 cases again, especially in vulnerable population and under vaccine breakthrough events and reinfection (Farahat et al. 2022; Tuekprakhon et al. 2022). Of note, circulation of SARS-CoV-

2 and its variants among animals including pet and wild animals also need to be checked by strengthening of one health approach and promoting its importance in tackling zoonosis and reverse zoonosis associated with COVID-19, which will also aid in limiting events of mutations and recombination to happen in the virus.

4 Conclusion and Future Directions

We need to now be prepared holistically and act proactively to avoid any new dangerous COVID-19 wave and adopt appropriate and recommended COVID-19 protective and control measures. COVID-19 appropriate behaviours and safety measures including wearing of face mask, regular hand washing and norms of social / physical distancing, hygiene and disinfection practices, avoiding crowded places and mass gathering events must be remembered to be followed strictly. Along with these, enhancing immunization rates / vaccination coverages, checking vaccine hesitancy and throwing up reluctance to promote booster shots, equal global access of vaccines at global level, generate adequate herd immunity, could save us from facing again a massive surge in COVID-19 cases in the form of a new pandemic wave by restricting circulation of the virus in unprotected people and rapidly accumulate mutations to boost viral transmissibility and infectivity and closely watching the emergence of newer strains. This will ultimately help to avoid increase in COVID-19 cases and associated deaths as well as countering incidences of newly emerging subvariants of Omicron.

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