# Emerging SARS-CoV-2 Variants and Subvariants: Challenges and Opportunities in the Context of COVID-19 Pandemic

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# Emerging SARS-CoV-2 Variants and Subvariants: Challenges and Opportunities in the Context of COVID-19 Pandemic

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**ABSTRACT:** The COVID-19 pandemic has become the most devastating pandemic of the 21st century since its appearance in December 2019. Like other RNA viruses, continuous mutation is common for coronavirus to create several variants and subvariants. The main reason behind this mutation and evolvement of SARS-CoV-2 was its structural spike (S) glycoprotein. Coronavirus has become a threat to global public health due to its high mutation capability and antibody neutralizing capacity. According to the World Health Organization (WHO), there are 5 major variants of concern (VOC) are Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529). Recently, different Omicron subvariants have gained worldwide dominance, such as BA.1, BA.2, BA.3, BA.4, and BA.5. However, there is a discernible drop in this symptomatic sickness globally due to the success of numerous monoclonal antibodies and vaccinations. Here we also discussed the currently dominant Omicron subvariants and the effectiveness of antiviral agents and vaccines. Based on the available data and our knowledge, we can suggest that the global healthcare organizations can decide on the declaration of the end of the pandemic phase of COVID-19 soon; however, the covid-19 will continue.

**KEYWORDS:** SARS-CoV-2, SARS-CoV-2 subvariants, COVID-19, public health

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## Background

Coronaviruses belong to a class of encapsulated positive single-stranded RNA viruses that have a diverse spectrum of natural hosts. They can infect a wide range of animals and humans.[1,2] Tyrrell and Bynoe isolated the viruses from the common-cold patients and later gave them the name coronavirus in 1966 for their crown-like appearance.[3] The first SARS-CoV virus emerged suddenly in China in 2002 to 2003 that killed 813 of 8,809 affected people in 29 countries or regions.[4] After that, in 2012, the MERS-CoV emerged as a human disease with a high case-fatality rate.[5] The ongoing COVID-19 is the largest zoonotic pandemic after the Spanish influenza pandemic.[6] It was initially called Wuhan pneumonia due to the location and pneumonia symptoms. The World Health Organization (WHO) renamed this viral infection "COVID-19" on February 12, 2020.[7] The International Committee on Taxonomy of Viruses (ICTV) proposed this virus as SARS-CoV-2 since it belongs to the severe acute respiratory syndrome-associated coronavirus category.[8] The SARS-CoV-2 virus has been evolving since its discovery in December 2019. As several variants are developing around the world, the WHO classified those variants as variants of concern (VOC), variants under monitoring (VUM), and variants of interest (VOI).[9]

## SARS-CoV-2 Variants and Subvariants

RNA viruses are more likely than DNA viruses to develop variants. COVID-19 replication is widespread since it is an RNA virus.[10] In this case, the structural spike (S) glycoprotein plays the most important role, and mutations in this S-glycoprotein led to the emergence of VOC by increasing angiotensin-converting enzyme-2 (ACE-2) receptor affinity, resistance to neutralizing antibodies, viral replication, infectivity, higher transmissibility, and immune escape, resulting in increased reinfection risk and severity of reinfection.[11] Five reported VOCs are: Alpha (B.1.1.7; UK, Sep-2020); Beta (B.1.351; South Africa, May-2020); Gamma (P.1; Brazil, November 2020); Delta (B.1.617.2; India, October 2020); and Omicron (B.1.1.529; several countries, November 2021).[9,12,13]

Among the 5 VOCs, the Omicron has a unique feature with a total of 30 signature mutations.[13] Among them, 23 are bold-faced mutations.[13] These mutations are different from others variants.[13] The percentage of Omicron infection in Africa reached ~90% within the first 25 days after the first identification in November 2021. However, we have seen the Beta variant responsible for ~50% infection rate within roughly 100 days, and the Delta variant contributed ~80% infection within approximately 100 days.[14] According to an artificial intelligence (AI) model, the Omicron variant was

thought to be 2.8 times more transmissible than the Delta, eluding current immunizations by nearly 90% and drastically reducing monoclonal antibody efficacy (mAbs).[15] Until January 8, 2022, it was distributed in 150 countries or territories, resulting in 552,191 confirmed cases and 115 deaths [18].[16] Omicron has 5 sublineages such as BA.1, BA.2, BA.3, BA.4, and BA.5.[9] The ancestral lineage of the Omicron variant appears to be B.1.1.529, followed by the BA.1 sublineage, which looks to be the most similar to B.1.1.529 and BA.3 is the combined form of BA.1 and BA.2 sublineages.[16,17] A study revealed that BA.1 has 37 mutations in the spike protein, BA.2 has 31 mutations, BA.3 has 33 mutations with 21 common mutations in all 3 lineages.[16] The receptor-binding domain (RBD) interacts with host ACE-2 to induce infection. Also, it is a prominent target for vaccines and antiviral drug development.[18] There are 15 mutations in RBD of Omicron BA.1 subvariants, whereas we observed 12 mutations in RBD of Omicron BA.2 and BA.3 variants. Also, there are some common mutations among the sub-variants of Omicron.[19] According to a study by Chen and Wei, the BA.2 subvariant of Omicron is 1.5 and 4.2 times more infectious than BA.1 subvariants and Delta variants, respectively.[19] It also revealed that it has a 30% higher chance of eluding current vaccinations than BA.1 and the reinfection capacity of the patients who had recovered from BA.1.19.[19] BA.2 Omicron is also known as the stealth Omicron because its genetic alterations make it difficult to distinguish from Delta using PCR testing.[20] According to the WHO, it is now the most prevalent strain of COVID-19 worldwide and the virus's most transmissible version to date.[20,21] According to the Centers for Disease Control and Prevention (CDC), it is the most common form of COVID-19 in the USA, accounting for 74.4% of all COVID-19 occurrences till April 16, 2022.[22]

The WHO categorized BA.4, BA.5 (BA.1 and BA.2 sister lineages), and a few other BA.2 sublineages as VOC sublineages under monitoring (VOC-LUM). BA.2.12.1, BA.4 and BA.5 subvariants appear to escape antibody responses among fully vaccinated and boosted individuals and those who had previous Covid-19 infection.[23] The WHO will review the global epidemiology of VOC-LUM, monitor and track global spread, assist more laboratory investigations, review characteristics of the VOC-LUM and provide a separate label in case those are substantially different.[9] Moreover, the member states are asked to perform more investigations and research to unveil the viral characteristics of these VOC-LUM. A table of WHO-labeled Omicron subvariants is demonstrated in Table 1.

## Hybrid or Recombinant Forms of SARS-CoV-2 Subvariants

People are now concerned about several other hybrid or recombinant forms. Omicron's XE subvariant has now surpassed this.[37] According to Consumer News and Business Channel (CNBC), the first case of XE was discovered in the UK on January 19, 2022, and as of April 12, 2022, 1,125 cases of XE have been discovered in the UK.[24] Cases have also been reported in Thailand, India, China, Japan, and Israel, but no cases have been detected in the United States as of April 12, 2022.[38] XE is a recombinant virus that contains parts of Omicron strains, BA.1, as well as the more infectious BA.2 subvariant, popularly known as "Stealth Omicron," and is effectively a mixture of genetic material from 2 viruses.[39] According to United Kingdom Health Security Agency (UKHSA) data, XE has a growth rate of 9.8% higher than BA.2, whereas the WHO has put the figure at 10% so far.[38] Professor Susan Hopkins, UKHSA's main medical advisor, stated that "at this time, there is insufficient evidence to form conclusions concerning transmissibility, severity or vaccine effectiveness."[40] Rather than XE, there are several other BA.1 and BA.2 recombinants, including XQ in the UK, XG in Denmark, XJ in Finland, and XK in Belgium.[41] Furthermore, another controversial recombinant known as "Deltacron" (formally referred to as XD and XF) is usually the recombination variations of Delta and Omicron and appears to have a genetic sequence mostly identical to Delta, but with features of the spike protein from Omicron BA.1.[41] It was originally discovered in France in mid-February, and according to the UKHSA, fewer than 40 instances of XF have been discovered, all in the UK. Although no cases of XD have been documented in the UK, 49 cases, predominantly in France, have been reported to global databases.[42]

## Effectiveness of Potential Therapeutic Agents Against Omicron Subvariants

Recently, Omicron BA.2 has become the most common subvariant worldwide, with recombinant subvariants; for example, XE was a dominating variant in several countries, particularly the UK. A recent study found that boosting with Pfizer or Moderna, rather than 2 doses of Pfizer or AstraZeneca, offered a significant increase in protection.[43] On the contrary, the subvariants BA.1 and BA.2 didn't show much effectiveness against mAbs from Eli Lilly, Regeneron, AstraZeneca, Celltrion, Rockefeller University except sotrovimab developed by GlaxoSmithKline.[19]

According to WHO, a new variety known as the XE subvariant has evolved and is now classified as a new VOC.[9] Although more research and data are needed before drawing any conclusions regarding the efficacy of the current COVID-19 therapy option, there is still hope that the new recombinant versions are not as dangerous as previously thought.[44] There were XA, XB, XC, and XD subvariants before XE, but none of them constituted a threat to global health.[30] Furthermore, following the identification of the XE subvariant on January 19, 2022, the number of hospitalizations due to this variety did not increase significantly; however, the Delta and Omicron variants caused a catastrophic pandemic within the first 2 weeks.[45] Moreover, according to recent data, vaccine effectiveness against symptomatic infection was 9% and 13% for BA.1 and

**Table 1.** Currently identified Omicron subvariants.

| OMICRON SUBVARIANTS | SPIKE PROTEIN MUTATIONS[9,24] | UNIQUE MUTATIONS[24,25] | COUNTRY AND YEAR OF DETECTION[9,26] | TRANSMISSIBILITY[24,25,27,28] | DISEASE SEVERITY[28] | HOSPITALIZATION[28] | EFFECTIVENESS OF CURRENT VACCINES AND THERAPEUTICS[26,29-36] |
|---|---|---|---|---|---|---|---|
| BA.1 | 142D, G339D, S373P, S375F, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K, H69del, V70del, T95I, V143del, Y144del, Y145del, N211I, L212V, V213R, G446S, A67V, ins214EP, R216E, S371L, G496S, T547K, N856K, L981F | A67V, ins214EP, R216E, S371L, G496S, T547K, N856K, L981F | South Africa, November-2021 | Increased than delta variants | Reduced than delta variants | About 73% reduced hospitalization rate than delta variants | • Reduced vaccine effectiveness generated by infections or vaccination.<br>• After either a second or third vaccination, there is increased neutralization activity and maturation of cross-reactive antibodies against the Omicron BA.1.<br>• Resistant to the majority of antibodies. |
| BA.2 | 142D, G339D, S373P, S375F, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K, S371F, D405N, T19I, L24del, P25del, P26del, A27S, V213G, T376A, R408S | T19I, L24del, P25del, P26del, A27S, V213G, T376A, R408S | South Africa, November-2021 | Increased transmission rate than BA.1 | Sufficient information is not available. | Sufficient information is not available. | • After either a second or third vaccination, there is increased neutralization activity and maturation of cross-reactive antibodies against the Omicron BA.2.<br>• Among all clinically authorized monoclonal antibodies (mAbs) only bebtelovimab still effectively combats BA.2. |
| BA.3 | 142D, G339D, S373P, S375F, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K, H69del, V70del, T95I, V143del, Y144del, Y145del, N211I, L212V, V213R, G446S, S371F, D405N, R214del[24] | R214del | South Africa, November-2021 | Increased transmission rate than BA.1 | Sufficient information is not available. | Sufficient information is not available. | • Resist vaccine immunity more effectively than BA.1 and BA.2.<br>• The majority of mAbs totally or substantially lost their ability to neutralize BA.3. |

*(Continued)*

**Table 1.** (Continued)

| OMICRON SUBVARIANTS | SPIKE PROTEIN MUTATIONS[9,24] | UNIQUE MUTATIONS[24,25] | COUNTRY AND YEAR OF DETECTION[9,26] | TRANSMISSIBILITY[24,25,27,28] | DISEASE SEVERITY[28] | HOSPITALIZATION[28] | EFFECTIVENESS OF CURRENT VACCINES AND THERAPEUTICS[26,29-36] |
|---|---|---|---|---|---|---|---|
| BA.4 (BA.1 and BA.2 sister lineage) | BA.2-like constellation in the spike protein + S:del69/70, S:L452R, S:F486V, S:Q493R reversion | Beyond the spike protein: (NSP4: L438F reverted to wild type, ORF 6: D61 (wild type), ORF 7b: L11F, N: P151S | South Africa, January-2022 | Increased transmission rate than BA.1 and BA.2 | Sufficient information is not available. | Sufficient information is not available. | • BA.4 is much (4.2-fold) more resistant, which increases the likelihood that it will result in infections that are resistant to vaccination.<br>• Among all clinically authorized monoclonal antibodies (mAbs) only bebtelovimab still effectively combats BA.4. |
| BA.5 (BA.1 and BA.2 sister lineage) | BA.2-like constellation in the spike protein + S:del69/70, S:L452R, S:F486V, S:Q493R reversion | Beyond the spike protein: (M: D3N, ORF 7b: L11 (wild type), N: P151 (wild type), synonymous SNPs: A27038G, C27889T) | South Africa, January-2022 | Increased transmission rate than BA.1 and BA.2 | Sufficient information is not available. | Sufficient information is not available. | • Shows about 4.2-fold more resistant, which increases the likelihood that it will result in infections that are resistant to vaccination.<br>• Among all clinically authorized monoclonal antibodies (mAbs) only bebtelovimab still effectively combats BA.4. |
| BA.2.12.1 (BA.2 sublineage) | BA.2 + S:L452Q, S:S704F | Sufficient information is not available. | United States of America, December-2021 | Sufficient information is not available. | Sufficient information is not available. | Sufficient information is not available. | • Reduced effectiveness of most of the monoclonal antibodies except bebtelovimab. |
| BA.2.75 (BA.2 sublineage) | BA.2 + S:K147E, S:W152R, S:F157L, S:I210V, S:G257S, S:D339H, S:G446S, S:N460K, S:Q493R reversion | Sufficient information is not available. | India, May-2022 | Sufficient information is not available. | Sufficient information is not available. | Sufficient information is not available. | • Sufficient information is not available. |

**Table 2.** Effectiveness of potential therapeutic monoclonal antibodies (mAbs), antiviral agents, vaccines and combinations of some monoclonal antibodies.

| ANTIVIRAL AGENTS | ORIGINATOR | EFFECTIVENESS AGAINST CURRENT MAJOR SUBVARIANTS |
|---|---|---|
| Imdevimab (REGN10987) | Regeneron | Effectively neutralized the subvariants BA.1, BA.2, BA.4 and BA.5, but reduced neutralization capacity against BA.3.[46-48] |
| Casirivimab (REGN10933) | Regeneron | Reduced neutralization capacity against BA.2.[35,45,49] |
| Bamlanivimab (LY-CoV555) | Eli Lilly | Reduced neutralization capacity against BA.2.[35,45,49] |
| Etesevimab (CB6/LY-CoV016) | Eli Lilly | Reduced neutralization capacity against BA.2.[35,45,49] |
| Sotrovimab (S309) | GSK and Vir Biotechnology | Enable potential neutralization of BA.1 and BA.2 subvariants, but showed decreased activity against BA.4 and BA.5 subvariants.[46,49] |
| Cilgavimab (COV2-2130) | AstraZeneca | Effectively neutralized the subvariants BA.2, BA.4, and BA.5 but showed complete loss of effectiveness against BA.1.[46-48] |
| Tixagevimab (COV2-2196) | AstraZeneca | Reduced neutralizing activity against BA.4 and BA.5 subvariants.[47] |
| Regdanvimab (CT-P59) | Celltrion | Reduced neutralization capacity against BA.2.[35] |
| Amubarvimab (BRII-196) | Brii Biosciences | Reduced neutralization capacity against BA.2.[35] |
| Bebtelovimab (LY-CoV1404) | AbCellera and Eli Lilly | Effectively neutralized the subvariants BA.2, BA.2.12.1, BA.4, and BA.5.[46,47,49] |
| Adintrevimab (ADG-2) | Adagio Therapeutics | Enable potential neutralization of BA.1 and BA.2 subvariants, but showed decreased activity against BA.3, BA.4, and BA.5 subvariants.[46,48] |
| Remdesivir (GS-5734) | Gilead Sciences | Improved efficacy as early treatment against these new circulating variants, but with 3 days of intravenous administration.[45]<br>Reduced efficacy against BA.4 and BA.5 subvariants.[47] |
| Molnupiravir | Merk and co. | Because of its efficacy and safety issues, it is only recommended as an emergency treatment option.[45]<br>Reduced efficacy against BA.4 and BA.5 subvariants.[47] |
| Nirmatrelvir | | Reduced efficacy against BA.4 and BA.5 subvariants.[47] |
| BNT162b2 mRNA vaccine | Pfizer–BioNTech | Significant increase in effectiveness against BA.1 and BA.2 subvariants after third booster dose.[35,50,51] |
| CoronaVac (RBD protein (ZF2001)) | Sinovac Biotech | BA.1 and BA.2 showed no significant difference in resistance to neutralization by plasma after 6 months of second dose, whereas BA.4 and BA.5 exhibited increased immune-evasion capability. Moreover, vaccinated people previously infected with COVID-19 showed a marked decrease in neutralization of BA.2, BA.3, BA.4, and BA.5.[46] |
| ChAdOx1 | AstraZeneca | Significant effectiveness against omicron variants after second dose but the effectiveness is short-lived which require booster dose.[51] |
| mRNA-1273 | Moderna | Significant effectiveness against omicron variants after second dose but the effectiveness is short-lived which require booster dose.[51] |
| JNJ-78436735 | Johnson & Johnson | Significant effectiveness against omicron variants after second dose but the effectiveness is short-lived which require booster dose.[51] |
| Evusheld (cilgavimab and tixagevimab) | AstraZeneca | Improved efficacy against BA.2, but BA.4 and BA.5 showed about 20-fold resistance to Evusheld especially to cilgavimab.[47,49] |
| BRII-196 and BRII-198 cocktail (amubarvimab plus romlusevimab) | Brii Biosciences | Effectively neutralized the subvariants BA.3, BA.4, and BA.5.[46] |
| Casirivimab and imdevimab | Regeneron | Increased neutralizing activity against BA.4 and BA.5 subvariants.[47] |

BA.2 subvariants, respectively.[45] However, the rates can be improved to 63% for BA.1 and 70% for BA.2 at 2 weeks after a third booster dose.[45] The recombination of either Omicron sublineages or Omicron and Delta sublineages is one of the new developing variations. Therefore, their effectiveness against vaccines is assumed to be the same. The effectiveness of potential therapeutic monoclonal antibodies (mAbs), antiviral agents, vaccines, and combinations of some monoclonal antibodies against recent WHO-labeled COVID-19 Omicron subvariants is shown in Table 2.

## Ending of Pandemic Phase and Moving Back to Regular Life

Healthcare systems, educational institutions and communities, and the global economy have faced a devastating situation since the introduction of the ongoing COVID-19 pandemic.[52-57] The world has been dealing with the devastating pandemic crisis created by the 5 most hazardous VOCs by expanding vaccination facilities and raising public awareness about health safety guidelines.[58] Year 2020 was challenging to approach therapeutic options and develop vaccines against COVID-19. In 2021, the world has got several effective vaccines and anti-viral drugs to fight coronavirus.[59] Countries across the world are giving third or booster doses of vaccines, and the Omicron variant have infected a huge population worldwide.[60] In earlier, we assumed that the pandemic phase of COVID-19 will end after the massive wave due to the Omicron variant.[61] The present global SARS-CoV-2 immunity is at a high level than ever by the combined effect of natural immunity and vaccination efforts. However, there might have chances to evolve some deadly new variants of SARS-CoV-2 in the close future. Some countries might face rising peaks of SARS-CoV-2 transmission during their winter months. Moreover, we have some lessons from the earlier influenza pandemics and we know how the earlier deadly pandemics were brought under control. Therefore, healthcare authorities across the world need to revise and update their responses to the COVID-19 pandemic. They can emphasize new molecular, phylogenetic, and pathogenetic insights to explain and understand the efficacy of current vaccines and the potential risk of new variants.[62] Also, they should consider the declaration of the end of the pandemic phase of COVID-19 based on the previous experiences, present lessons, and nature of the coronavirus variants.

However, the future SARS-CoV-2 variants and subvariants might have less impact on humans. The healthcare authorities and people will face future waves with updated vaccines, improved antivirals, and well-adopted preventive techniques. Special countermeasures need to take for the vulnerable populations during the COVID-19 waves. Therefore, we can expect that the COVID-19 pandemic will be ended soon to turn back to regular life. Our healthcare systems will develop and adopt effective policies to manage future COVID-19 waves. The extra precautionary period of COVID-19 will be over soon. Therefore, the international healthcare authorities should prepare an integrated action plan to end the pandemic phase of COVID-19. They should take more initiatives to engage the general population in vaccination programs and health safety measures. Also, they should take an activity plan for research and closely observe the viral mutations to assess the impact of new variants on human health. Moreover, they should support fragile healthcare systems to protect the health of every people from any future pandemics across the world.

## Author Contributions

Smaranika Rahman, Md. Jamal Hossain, and Zabun Nahar reviewed articles, collected information and wrote the first draft. Mohammad Shahriar and Mohiuddin Ahmed Bhuiyan edited the manuscript, gave intellectual inputs in the revised manuscript. Md. Rabiul Islam supervised the whole work and revised the manuscript. All the authors reviewed and approved the final submission.

## Disclosures and Ethics

Not applicable to this article.

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