Title

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Journal

Yonsei Medical Journal, 63(11)

ISSN

0513-5796

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Publication Date

2022

DOI

10.3349/ymj.2022.0383

Peer reviewed

Review Article

Yonsei Med J 2022 Nov;63(11):977-983
https://doi.org/10.3349/ymj.2022.0383

Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

SARS-CoV-2 Omicron Variant of Concern: Everything You Wanted to Know about Omicron but Were Afraid to Ask

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As soon as the first case of the omicron variant of severe acute respiratory syndrome coronavirus 2 was reported in November 2021, it quickly spread worldwide with the emergence of several subvariants. Compared to previous variants, omicron was heavily mutated, especially for those in the Spike (S) protein and its receptor-binding domain. These mutations allowed the viruses to evade immune responses (i.e., previous infections and vaccine-elicited) and increase in transmissibility. Although vaccine effectiveness is decreased for omicron, boosters remain effective for protecting against severe diseases. Also, bivalent vaccines have been developed to increase vaccine effectiveness. Interestingly, although omicron is highly infectious, it has less morbidity and mortality compared to previously identified variants, such as delta. Additionally, the mutations that allow the virus to evade immune responses also allow it to evade many of the monoclonal antibodies developed at the beginning of the pandemic for treatment. Here, we reviewed the omicron variant's epidemiology, genetics, transmissibility, disease severity, and responsiveness to vaccine and treatments.

Key Words: SARS-CoV-2, COVID-19, variant, variant of concern, omicron variant, omicron

INTRODUCTION

After the first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China in December 2019, it has spread worldwide, causing significant morbidity and mortality. Unlike other RNA viruses, coronaviruses have a proofreading mechanism leading to fewer mutations than other RNA viruses, but the SARS-CoV-2 virus has mutated to form a number of variants. These variants have evolved to escape from neutralizing antibodies by changing the Spike (S) protein sequence and structure. The emergence of these variants has led to repeated waves worldwide, and changed the pathogenesis of the infection and the efficacy of vaccines.

The WHO Virus Evolution Working Group suggested using letters of the Greek alphabet for naming each major variant of SARS-CoV-2, classified as a variant of concern (VOC). As of November 2021, there have been four VOCs (alpha, beta, gamma, and delta), which was reviewed in our previous study.[1] In late 2021, a new VOC was identified and named "omicron." In the present study, we discuss this new VOC, which has now replaced all other variants worldwide.

EMERGENCE OF OMICRON

On November 24, 2021, South Africa reported the first case of B.1.1.529 variant from a specimen collected on November 9,

Received: August 31, 2022 **Accepted:** October 5, 2022
Published online: October 18, 2022
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•Shin DH and Choi JY have no potential conflict of interests. Smith DM has served as a consultant for Evidera, Bayer Healthcare, FluxErgy, Pharma Holdings, Kiadis, Linear Therapies, and Model Medicines.

2021. After the week of the first detection, cases with this new variant increased dramatically. Given the spike in cases, the WHO designated the B.1.1.529 variant as a VOC.[2] By December 15, 2021, the variant had spread to 80 countries. Then, by January 6, 2022, the number of countries reporting the presence of this VOC had increased to 149, and the variant soon became the predominant cause of COVID-19 worldwide.[3]

Since the original identification of the omicron variant, several subvariants have emerged. The first reported subvariants were BA.1 and BA.1.1, and then BA.2 and BA.3 were also reported in South Africa around the same period (Fig. 1). Additionally, BA.4 and BA.5. subvariants were identified on April 4, 2022; and on May 22, 2022, BA.2.75 was also designated by the WHO.[3]

MUTATIONAL PATTERNS

Genetic analysis of the omicron VOC has suggested that omicron evolved either from the alpha VOC or a new monophyletic clade, depending on the evolutionary substitution model method.[4] However, more than 50 mutations were found to be different between omicron and its ancestral strain. Thirty of these mutations were in the S protein and 15 were mutated sites in the receptor-binding domain (RBD). Such extensive mutation in the S protein pointed to likely immune evasion, likely antibody, which explains its increased infectiousness and breakthrough infections compared to other SARS-CoV-2 variants.[5] Table 1 presents the summary of mutational differences across VOC and sublineages of omicron. Interestingly, a 69–70 deletion in the S gene of omicron caused a "S gene target failure (SGTF)," which was only present in the alpha variants previously. This meant that the virus was not detectable by standard PCR test in one of the three target genes of the S protein, leading to a false negative molecular test.[8,9] Thus, when two out of three target genes were positive on a qRT-PCR test, it was a way to identify that the person was likely infected with the omicron variant rather than the delta variant, which was also circulating at the time.

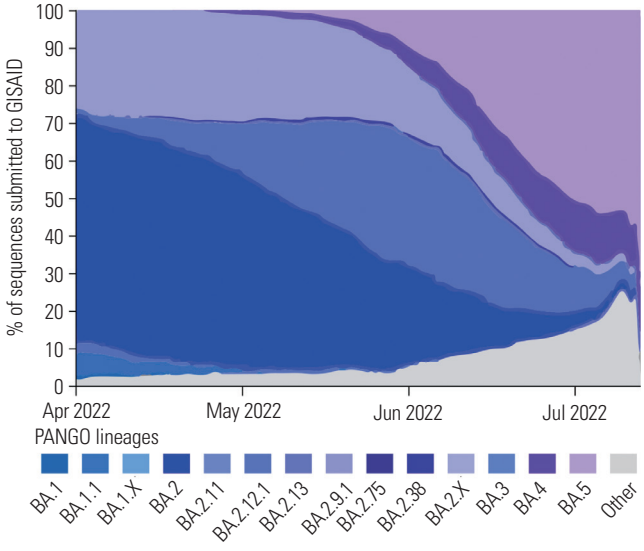

Fig. 1. The proportion of all circulating variants among SARS-SoV-2 sequence data and metadata from the Global Initiative on Sharing Avian Influenza Data (GISAID) since April 1, 2022 (as of July 18, 2022).[3] Omicron sister-lineages and sublineages under further monitoring are shown. BA.1.X and BA.2.X include all BA.1 and BA.2-pooled descendent lineages.[3] PANGO, Phylogenetic Assignment of Named Global Outbreak.

As omicron has continued to spread around the world, its sublineages have been identified. Comparing BA.1, BA.1.1, BA.2, and BA.3 mutations, there are 21 mutations that are commonly shared. BA.1.1 and BA.3 each have one unique mutation. BA.2 has eight unique mutations.[10] BA.4, BA.5, and BA.2.75 are close to BA.2, and compared to BA.2, BA.4, and BA.5 have deletions of residues 69 and 70 in the N-terminal domain and lack the Q493R and additional mutations at L452R, and F486V in the RBD.[11] BA.2.75 has nine more mutations compared to BA.2.[12] This progressive evolution likely points to further immune evasion from pre-existing immune responses in populations, likely also impacting infectiousness of the virus. Table 1 shows the estimated reproductive numbers for each VOC and subvariant of omicron.

PATHOGENICITY

Interestingly, shortly after omicron was first identified, it was found that people infected with it seemed to have less severe symptoms compared to people infected with previous VOC.[13] A multicenter, nationwide retrospective cohort study based on the US Electronic Health Record data from December 2021 until January 2022 showed significantly less severe outcomes with omicron infection than with the delta variant. The study matched the omicron cohort with the delta cohort for demographics that included the socioeconomic determinants of health, comorbidities, COVID-19-related medications, and vaccination status. The data showed that the omicron cohort's 3-day risk of hospitalization from SARS-CoV-2 infection, emergency room visit, intensive care unit admission, and use of mechanical ventilation were significantly lower than those of previous variants.[14] A national cohort from Scotland also showed that COVID-19 hospitalization decreased in the S-gene-negative group (compared to the S-gene-positive group) after adjusting confounders.[15]

Although the reason for this decreased pathogenicity of omicron is not fully clear, a number of studies have offered some clues. One in vitro study from Hong Kong found that the omicron variant replication was lower and had weak fusion activity in VeroE6/TMPRSS2 cells compared to delta variants, indicating that the omicron variant is less dependent on the TMPRSS2 pathway.[16] Furthermore, Hui, et al.[17] compared the replication competency and tropism of original strain with delta and

https://doi.org/10.3349/ymj.2022.0383

Table 1. Main Mutational Differences Across VOC and Reproductive Number

Variant	Mutations in S protein			R_0	R_e
	N-terminal domain	Receptor binding domain	Others		
Original					Reference
Alpha	Δ69-70, Δ144	N501Y	A570D, D614G P681H, T716I, S982A, D1118H	4.56[6]	29% (95% CI: 24–33)[7]
Beta	L18F, D80A, D215G, Δ242-244, R246I	K417N, E484K, N501Y	D614G, and A701V		25% (95% CI: 20–30)[7]
Gamma	L18F, T20N, P26S, D138Y, R190S	K417T, E484K, N501Y	D614G, H655Y, T1027I V1176		38% (95% CI: 29–48)[7]
Delta	T19R Δ157-158	L452R T478K	D614G P681R D950N	5.94 (95% CI: 5.19–6.68)[22]	97% (95% CI: 76–117)[7]
Omicron					
Common Shared mutation	G142D	G339D S373P S375F K417N N440K S477N T478K E484A Q498R N501Y Y505H	D614G H655Y N679K P681H N764K D796Y Q954H N969K	9.5[22]	3.4[22]
BA.1	A67V Δ69-70 T95I Δ143-145 N211I Δ212 ins214EPE	S371L G446S Q493R G496S	T547K N679K N856K L981F		
BA.1.1	A67V Δ69-70 T95I Δ143-145, N211I Δ212 ins214EPE	R346K S371L G446S Q493R G496S	T547K N679K N856K L981F		
BA.2*	T19I Δ24-26 A27S V213G	T376A R408S **Q493R**			
BA.3	Δ69-70 T95I Δ143-145 N211I Δ212 Δ214	S371F D405N G446S Q493R			
BA.4*	T19I Δ24-26 **Δ69-70** A27S V213G	T376A R408S **L452R F486V**			
BA.5*	T19I Δ24-26 **Δ69-70** A27S V213G	T376A R408S **L452R F486V**			
BA.2.75*	T19I Δ24-26 A27S V213G **K147E W152R F157L I210V G257S**	**D339H** T376A R408S **G446S N460K**, **R493Q**			

R_0, basic reproduction number; R_e, effective reproduction number; VOC, variant of concern; CI, confidence interval; S, spike.
*BA.4/5, BA.2.75 share common mutations with BA.2, and the mutations marked in bold indicate differences between each subvariant.

B.1.1.529/omicron variants in ex vivo explant cultures of the human bronchi and lung parenchyma, and found that the omicron variant showed higher replication competence in the human bronchi explant cultures ex vivo, but had lower human lung explant cultures ex vivo compared to the delta variant and original strain. Another study showed that the replication capacity of omicron variant was similar with delta isolates in human nasal epithelial cultures; however, in lung cells and gut cells, omicron showed lower replication.[18] Omicron S protein was less efficiently cleaved compared to the delta variant. Also, the entry of omicron variant to specific cell types was affected by the cellular RNA expression of TMPRSS2. The less formation of multinuclear syncytia in cell lines demonstrated another reason for less virulence of omicron variant.[19] Additionally, while multiple mutations on the S protein of omicron enable escape from antibodies, T-cell immune responses are still present and likely to lessen disease severity.[20]

Studies comparing the pathogenicity of subvariants have been enlightening. One study compared the omicron subvariants BA.5, BA.1, BA.2, and original B.1.1 in vitro and in vivo. In the airway-on-a-chip study, BA.5 showed more destruction and higher viral load in the blood compared to the other subvariants. Also, BA.5 that infected the hamsters' lung tissues had a higher histopathological score, larger area of type II pneumocytes, and increased inflammatory responses (i.e., CXCL10, IL-6, ISG15, and MX-1) compared to infection by other subvariants. Taken together, these data suggest that BA.5 subvariant is likely more pathogenic than other omicron subvariants.[21]

TRANSMISSIBILITY

Increased transmissibility is a main characteristic of the omicron variant, and is also the reason why it is the predominant variant present around the world. During the last week of December 2021, the total number of new SARS-CoV-2 cases reported worldwide was 9.5 million, which was 71% more than the previous week, and the omicron subvariant accounted for the largest proportion of cases by the first week of January 2022 in many countries.[22] The doubling times were estimated as 3.3 days in the South African province of Gauteng, and even shorter doubling times were reported in many countries such as Australia (3.0 days), New York State (2.5 days), the UK (2.4 days), and Denmark (2.0 days).[23] The meta-analysis of effective and basic reproduction numbers (Re and R0) for omicron showed that the average effective reproduction number (Re) was 3.4 (a range from

0.88 to 9.4, IQR: 2.03, 3.85), and the basic reproduction number was 9.5 (a range from 5.5 to 24, IQR: 7.25, 11.88) (Table 1).[24]

There are several mutations known to contribute to an increase in transmissibility of SARS-CoV-2, including the combination of N501Y, Q493R, Q498R, T478K, and Y505H mutations at receptor binding motif, which increases the binding affinity with the ACE2 receptor, enabling the virus to easily infect target cells. Interestingly, the G496S mutation of BA.1 is known to have the highest affinity.[10] Additionally, Hui, et al.[17] also found that the omicron replicated significantly faster than the original strain or delta variant in the human bronchi, which may suggest higher infectious virus load in the airways. Of course, being able to infect people who were previously infected or have been vaccinated, or both would also likely increase the transmissibility of omicron compared to other variants.

PRE-EXISTING IMMUNE RESPONSE FROM PRIOR INFECTIONS AND VACCINATION

Currently, most people around the world have pre-existing immune responses to SARS-CoV-2 either from vaccination or prior infection, or both.[25,26] This level of pre-existing immune responses impacts the overall spread of SARS-CoV-2, and the evolution of the virus to produce variants is based on the evasion of these immune responses. Since the RBD is most targeted for the immune system, mutations in these sites are considered to influence the ability of antibodies to neutralize the virus. One study found that convalescent patients' serum and vaccine serum neutralization activities against omicron were lowered compared to the original strain and other variants.[27] In addition, a study compared each omicron subvariants' neutralizing antibody titers in people who had been boosted with an mRNA vaccine, and found that titers of neutralizing antibody were different for each subvariant. Specifically, compared to the BA.1 subvariant, BA.2.12.1 and BA.4 or BA.5 were lower by the factor of 1.5 and 2.9, respectively.[28] Another study showed that BA.4 and BA.5 were more resistant to neutralization by boosted vaccine than BA.1, and BA.2.[11]

One meta-analysis study showed that after stratification by predominant strain, an increased reinfection rate of omicron variant was observed. During the first 3 months of the omicron wave, the reinfection rate was 3.31% [95% confidence interval (CI): 1.15–6.53] compared to 0.57% (95% CI: 0.28–0.94) on the alpha wave and 1.25% (95% CI: 0.97–1.55) on the delta wave.[29] These results showed that the pre-existing immunity from prior infection might have less protective effect on the omicron variant.

Data on vaccine effectiveness against omicron showed benefits of a booster vaccination. A large, matched case-control study was conducted during the BA.1.1.59 omicron surge in Israel comparing individuals who took the booster shot of BNT152b2 mRNA vaccine with controls who had not. Vaccine effectiveness was estimated to be 93% (95% CI: 88–97) for admission to hospital, 92% (95% CI: 82–97) for severe disease, and 81% (95% CI: 59–97) for COVID-19-related death.[30] Another study from Qatar evaluated the effectiveness for each vaccination, previous Infection, and hybrid immunity against BA.1 and BA.2. It found that previous infection, booster of vaccination, and hybrid immunity offered protection from both BA.1 and BA.2 subvariants in terms of severe, critical, or fatal COVID-19.[31] Now, more countries are offering second booster vaccines for higher risk populations. For example, in Israel, a fourth dose of BNT162b2 vaccine began in January 2022 when the B.1.1.529 variant was predominant. During this period, the team compared people who received four doses of vaccine with people who had received only three doses, and found that the people who received four doses had greater protection against severe illness. They also observed a decrease in confirmed SARS-CoV-2 infection in the short term, but the effectiveness on infection itself waned after 4 weeks.[32]

For this reason, the U.S. CDC recommends getting booster vaccinations.[33] For certain adults and adolescents (aged ≥12 years and weighing ≥40 kg) who are moderate to severely immunocompromised and may have an inadequate immune response or unable to take COVID-19 vaccine, it is recommended to administer the vaccines as two consecutive intramuscular of tixagevimab 300 mg plus cilgavimab 300 mg injections for 6 months.[34] In June 2022, Pfizer and Moderna each developed an omicron-adapted bivalent vaccine. The Pfizer vaccine (BNT162b2 OMI Combination BNT162b2) consisted of ancestral SARS-CoV-2 and BA.1 subvariant spike mRNA, and the Moderna vaccine (mRNA-1273.214) consisted of ancestral SARS-CoV-2 and B.1.1.529 omicron spike mRNA. Interim results showed that the bivalent vaccines were well-tolerated, and their neutralizing capacity against omicron was superior to the previously authorized mRNA vaccines.[35,36]

TREATMENT

Since the evolution of variants resulted from immune evasion, many antibody-based therapies that were developed early in the pandemic have been thwarted by omicron. A modeling study of monotherapy or combination therapy, which proved to be effective in previous variants, showed that omicron subvariants can escape the antibodies (Table 2).[37] Casirivimab, imdevimab cocktail and bamlanivimab, etesevimab cocktail both failed to neutralize omicron subvariants.[11] Several studies were conducted to compare each antibody's efficacy between each subvariants including BA.2.75. Interestingly, the tendency of potency against each subvariant was different according to the monoclonal antibody. Sotrovimab was active against B.1 and B1.1 but substantially decreased against the BA.2, BA.4/5, and BA.2.75. subvariants. Bebtelovimab retained neu-

https://doi.org/10.3349/ymj.2022.0383

Table 2. Monoclonal Antibodies for Treatment or Prophylaxis of COVID-19[32]

	Date of first EUA or approval	Most recent authorization and usage	Efficacy of monoclonal antibodies (Omicron/B.1.1.529) Neutralization activity of monoclonal antibody (ng/mL)*
Bebtelovimab	02/11/2022	Mild-to-moderate COVID-19 in adults and pediatric patients with positive results who are at high risk for progressing to severe COVID-19 and for whom alternative COVID-19 treatment options are not accessible or clinically appropriate	2[36]
Evusheld (tixagevimab co-packaged with cilgavimab)	12/08/2021	For emergency use as pre-exposure prophylaxis in adults and pediatric individuals for those who have moderate to severe immune compromise For whom vaccination is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine(s)	255.86±45.31[37]
Sotrovimab	05/26/2021	Currently not authorized in any U.S. region (05/12/2022)	373.47±159.49[37]
Bamlanivimab and etesevimab	02/09/2021	Currently not authorized in any U.S. region (05/04/2022)	>10000[37]
REGEN-COV (Casirivimab and Imdevimab)	11/21/2020	Currently not authorized in any U.S. region (06/27/2022)	>10000[37]

EUA, emergency use authorization.
*The individual monoclonal antibodies were tested at a starting concentration of 50000 ng per milliliter/combinations of 10000 ng per milliliter for each antibody.

tralization activity against all circulating omicron subvariants, which is why it became the only monoclonal antibody that can be used as an alternative therapy for non-hospitalized adults with omicron.[38,39] For cilgavimab, potency against BA.5 and BA.2.75 reduced by approximately 13-fold compared to BA.2. On the other hand, tixagevimab had enough potency against BA.2.75, but it failed to neutralize BA.2 and BA.5.[40,41] Based on these data, among five of the monoclonal antibody agents that were first approved or issued emergency use authorization (EUA), three of them withdrew authorization.[37] Fortunately, non-antibody-based antiviral therapies for COVID-19 in non-hospitalized patients using direct-acting antiviral inhibitors that target viral proteins, such as the RNA-dependent RNA polymerase or proteases, are still effective against omicron subvariants. In particular, one study that assessed the in vitro antiviral effect of remdesivir, molnupiravir, and nirmatrelvir showed that the EC50 (50% effective concentration) was not significantly decreased compared to other variants.[42]

SUMMARY

Despite the widespread containment efforts and strategies, SARS-CoV-2 has evolved to become more infectious, leading experts to become skeptical about the end of the pandemic. Among all VOCs, omicron is the most mutated type of variant and has unfortunately made the virus more infectious, though less pathogenic. However, who knows what the next variant will bring? We assume that the next VOC will be more infectious than the current one, only because that is how variants become VOC. However, as pathogenicity is more difficult to predict, persistent monitoring and early detection will be required.

ACKNOWLEDGEMENTS

This work was supported by the Korea National Institute of Infectious Diseases, Korea National Institute of Health, Korea Disease Control and Prevention Agency (#2021-ER1902–00 and #2021-ER2601-0), the 2020 Joint Research Project of Institutes of Science and Technology (grant no. HI14C1324), National Institute of Health (AI036214), John and Mary Tu Foundation, and Pendelton Foundation.

AUTHOR CONTRIBUTIONS

Conceptualization: all authors. Data curation: all authors. Formal analysis: all authors. Funding acquisition: Davey M. Smith and Jun Yong Choi. Investigation: all authors. Methodology: all authors. Project administration: all authors. Resources: all authors. Software: all authors. Supervision: Jun Yong Choi and Davey M. Smith. Validation: all authors. Visualization: all authors. Writing—original draft: Dong Hoon Shin. Writing—review & editing: all authors. Approval of final manuscript: all authors.

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