



Omicron variant of COVID-19: A focused review of biologic, clinical, and epidemiological changes

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Abstract

On 25 November 2021, the world health organization listed Omicron as a newly arisen and the fifth variant of concern (VoC) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The genome sequence of Omicron showed the utmost number of mutations compared to other known VoCs up to now, and it was regarded as the only SARS-CoV-2 variant with changes in the receptor-binding domain (RBD). However, the Omicron is still detectable via previous polymerase chain reaction (PCR) tests. Clinical presentation of the disease is identical to previous VoCs, however in vitro and in vivo studies revealed a higher transmission rate. The biggest obstacles posed by Omicron are the immune escape and reduction in vaccine effectiveness, as indicated by many simulations and real-world studies. Although the efficacy of the two-dose vaccinations is suboptimal for Omicron, preliminary studies have considered the injection of a booster shot is beneficial and can decrease the risk of severe disease. All these new features of Omicron warranted close investigation of this VoC as a new chapter in the pandemic, especially with emergence of subvariants BA.4 and BA.5. This review presents a conspectus of the current knowledge on the COVID-19 Omicron variant biological, clinical, and epidemiological changes.

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Introduction

The world has struggled to confront the burden of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) since its initial detection in November 2019. The official declaration of a pandemic occurred on 11 March 2020, as the number of affected cases had snowballed quickly (1). Coronavirus frequently mutates like other viruses, constantly challenging its appropriate management. The United States government-led SARS-CoV-2 Interagency Group classifies the different variants of SARS-CoV-2 into four types variant being monitored, variant of interest, variant of concern (VoC), and variant of high consequence (2). On 25 November 2021, a new novel coronavirus VoC was recognized by the World Health Organization (WHO) named Omicron (B.1.1.529) (3). Alpha, beta, gamma, and delta represent the other members of the VoC group (2). The primary SARS-CoV-2, beta, delta, and recently emerged Omicron strains have given rise to

Key point

- Although Omicron can challenge vaccine effectiveness against infection, still vaccines can effectively prevent severe disease and death.
- Higher receptor binding domain affinity with angiotensin-converting enzyme 2 (ACE2) was favored by several studies and pointed to a higher transmission. Additionally, real-world data support transmission even among fully vaccinated populations.
- Diagnosis and treatment of Omicron variant of COVID-19 is similar to previous variants.
- Giving a booster shot to the mass population is the current solution at hand to control new outbreaks.

the major waves of this disease, sabotaging the health care and economic aspects of the world.

Genome sequencing of the first Omicron cases from Southern Africa exhibited the highest number of mutations in comparison with all previous VoCs, raising concerns over its immune escape, transmission, and vaccine insufficiency towards this new VoC (3). Due



to its unexpected appearance, there is a lot of uncertainty and a lack of solid evidence of Omicron characteristics. This study presents a conspectus of the current knowledge on the COVID-19 Omicron variant to portray an organized picture of the different aspects of the variant with all of the currently available data.

Methods

Literature search

We performed a literature search on 21 January 2022 to investigate findings on the Omicron variant of COVID-19. The second search on 15 June 2022 aimed to update the evidence on Omicron sub-lineages. The electronic search included the WHO COVID-19 database, PubMed, Scopus, and Google Scholar databases. Our search terms encompassed: "Omicron," "B.1.1.529", and "Omicron variant." The inclusion criteria were articles on the Omicron variant of COVID-19 performed on either animals or humans. We included preprint articles after our team's review to assure a standard quality. Articles in languages other than English were excluded. We dismissed duplicates, studies with the same content, and grey literature. Next step, articles were screened regarding their title, abstract, and full-texts consequently to determine the eligible studies for the systematic search approach.

Discussion

Omicron mutations and VoCs history

RNA viruses have a high rate of genome mutations, some of which may lead to changes in the properties of the virus. Since late 2021, the WHO has monitored the characteristics of COVID-19 variants to detect those that may threaten public health through evolutions in transmissibility, virulence, clinical presentation, or vaccine effectiveness (4). Table 1 shows previous VOCs recognized by WHO (4,5).

The Omicron variant has the most significant number of mutations compared to other VoCs, representing the only one with the amino acid mutation within the receptor-binding domain (RBD) (6). The phylogenetic analysis demonstrated Omicron as a new emergent class

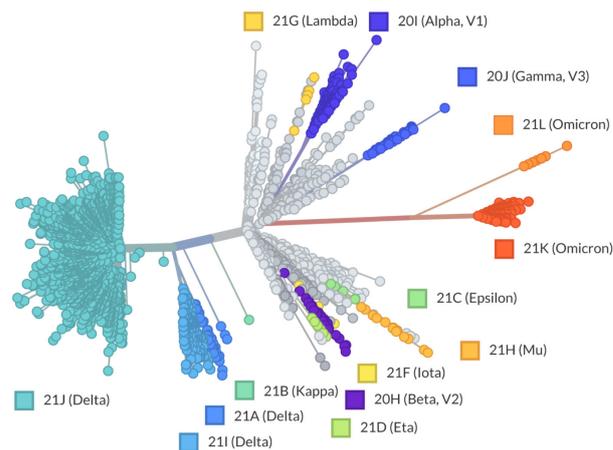


Figure 1. The genetic distance of Omicron and other COVID-19 clades is depicted in the radially rooted tree. Source: curated (labeled) image from NextStrain.org (Hadfield et al Bioinformatics) based on 3044 of 3044 genomes sampled between Dec 2019 and Jan 2022 GISAID data under CC-BY-4.0 license.

not originating from other variants. However, some similarities of Omicron with the alpha and gamma variants may elucidate the prolonged time of circulation and chance for the mutations (5). Moreover, some studies suggested Omicron might have undergone mutations in the mice, as a reservoir host (7, 8). Figure 1 shows the genetic distance of Omicron and other VoCs in the radially rooted tree. The Omicron had three sub-lineages BA.1, BA.2, BA.3, and recently sub-lineages BA.4 and BA.5 are acknowledged as new sub-variants under investigation (9).

The genome sequence of the first Botswana case revealed a total of 50 mutations with 32 changes in the spike (S) protein (10). Further cases revealed that the Omicron embodies 59 mutations, 36 of which belong to its spike protein (11). It is a highly concerning issue whether these changes bring on higher transmission or lower vaccine efficacy or not, which will be discussed in the following.

The human immune system creates diverse antibodies to neutralize SARS-CoV-2. The essential antibodies are divided into three classes and each target a slightly different place on the spike protein of SARS-CoV-2.

Table 1. Information on a variant of concerns (VOCs) is recognized by world health organizations

WHO label and date of VoC recognition	Pango lineage	GISAID* clade	Next strain Clade	Additional amino acid changes	Country and date first documented samples	Differences with Omicron in nucleotide composition
Alpha, 18 December 2020	B.1.1.7	GRY	20I (V1)	+S:484K +S:452R	The United Kingdom, Sep-2020	109
Beta, 18 December 2020	B.1.351	GH/501Y.V2	20H (V2)	+S: L18F	South Africa, May-2020	140
Gamma, 11 January 2021	P.1	GR/501Y.V3	20J (V3)	+S:681H	Brazil, Nov-2020	130
Delta, 11 May 2021	B.1.617.2	G/478K.V1	21A, 21I, 21J	+S:417N +S:484K	India, Oct-2020	138
Omicron, 26 November 2021	B.1.1.529	GRA	21K, 21L, 21M	+R346K	Multiple countries, Nov-2021	First COVID-19 case of US: 141

One of the Omicron's mutations, known as E484K, alters the recognizable regions by class 2 antibodies, making antibodies less effective but it does not change the binding affinity of antibodies classes 1 and 3 (12).

Receptor binding and transmission

Increased transmission rate for a variant, even with decreased severity, can lead to disastrous outcomes (Figure 2). Early studies of doubling time (the amount of time in which the cumulative incidence doubles) showed a doubling time of 3.1- 3.6 and 2 days in Gauteng province of South Africa and England, respectively (13). It implies that Omicron would have become the dominant strain worldwide due to this short doubling time.

Several studies have investigated and proposed mechanisms that how mutations affect the binding affinity. The S glycoprotein of the virus contains two functional subunits, S1 and S2, which mediate attachment to the angiotensin-converting enzyme 2 (ACE2) receptor of the host cell (14). The RBD is an integral part of the S1 subunit that attaches the host cell receptor (ACE2) (15). Therefore, assessing the mutations in these areas can lead us better to understand the VoC's infectivity (16). Omicron's S protein region has 25 unique mutations and 12 mutations shared with other four VoCs, which have previously been proved to enhance transmissibility (17).

The increased hydrophilicity of the amino acid residues, which is one of the results of Omicron mutations, is another justification for its increased affinity to the ACE receptor. Numerous unique mutations in the RBD and other regions of Omicron increased hydrophilicity. Therefore, the RBD of the Omicron variant and ACE2 would have a higher binding affinity (6). This hypothesis was confirmed by molecular dynamics trajectories that demonstrate the enhanced binding of Omicron compared to the wild-type SARS-CoV-2. In contrast to Omicron, wild-types have intermittent dissociation from ACE2. This could be due to π - π and salt-bridge interactions between Omicron's RBD and ACE2 (18). While most of the evidence (19, 20) favor higher binding affinity and higher transmission risk, some studies reported opposite findings (21, 22).

Of note, evaluation of proliferation phase, peak viral RNA, clearance phase, and clearance rate of Omicron via real-time polymerase chain reaction (RT-PCR), revealed similarities between Delta and Omicron; suggested that increased viral load cannot be associated with Omicron's higher infectivity (23).

The duration of infectious virus shedding in 21 Omicron cases showed that the levels of viral RNA in the respiratory samples were the highest 3-6 days following the diagnosis or symptom onset, and no infective virus was detectable in the samples after 10 days. Nevertheless, decreasing shortening the isolation period warrants more investigation by further studies (24).

Omicron has at least 60 mutations in coding and non-coding areas compared to the original Wuhan strain.

Many mutations are in common with previously known VoCs, whereas others are only exclusive for Omicron. In the Omicron variation, there are six deletions (in places 69, 70, 143, 144, 145, and 211), which only the deletion in position 211 is exclusive for Omicron and the rest have been reported in the other VoCs (25). Against all considerable mutations, the Omicron is structurally identical to other SARS-CoV-2 variants of concern. Interestingly, the S protein is still a trimer, with two subunits in each monomer (S1 and S2). The S1 subunit contains the RBD, which interacts with the ACE2 receptor (26).

Overall, some controversies were observed regarding the transmission and binding affinity of Omicron. However, higher RBD affinity with ACE2 was favored by many studies and pointed to a higher transmission. Furthermore, real-world data support transmission even among fully vaccinated young populations (27). During the same period, an increase of 3 to 6-fold in the number of Omicron infected cases seems to happen compared to Delta cases (28). Further real-world studies are needed to confirm the results of in vivo and simulation studies.

Diagnosis

Highly conserved regions are frequently used as targets of PCR; however, new variants of the disease may challenge the diagnosis. The Omicron is reported to be diagnosed by previous PCR tests. Moreover, Most Omicron strains influence the accuracy of conventional PCR detection. In RT-PCR, the BA.1 lineage showed S target gene failure (SGTF) due to multiple deletions of the S glycoprotein NTD, while the BA.2 lineage may skip SGTF due to NTD deletion (29). The Omicron variant has a specific genetic trait known as the S gene dropout. Since this feature is also seen in alpha variant, this dropout cannot confirm, but it increases the Omicron diagnosis. Hence, surveillance can use kits detecting S gene dropout to track the spread of Omicron by detecting potential cases (30).

A study on PCR efficacy in laboratories suggested that a targeted approach utilizing the existing tests and whole-genome sequencing is efficient for the surveillance program (6). Also, some attempts have been made to develop RT-PCR assays specific to Omicron (31). However, some Omicron "stealth versions" may be harder to trace (32). Conversely, mutations in the Omicron strain did not seem to impact the accuracy of the commonly used antigen-based rapid diagnostic test (33).

Clinical presentation

Among 66 confirmed and 15 probable cases of Omicron in Norway, the results showed that cough (83%), runny/stuffy nose (78%), fatigue/lethargy (74%), sore throat (72%), headache (68%), and fever (54%) were the most prevalent symptoms (27). Comparing the Omicron manifestations with other variants, the results of an investigation in the United Kingdom reported a rise in the upper respiratory symptoms such as sore throat, compared

to the lower respiratory symptoms (Figure 2B), alongside a marked decline in reported loss of taste/smell, which was common during the time delta was the dominant variant (34). Nevertheless, there is no evidence of Omicron VoC inflicting different symptoms from the previous variants (35).

Omicron severity

An early study on 161 328 COVID-19 patients in South Africa showed a lower probability of hospitalization and severe disease compared to October 2021 and Delta wave. The high population immunity in this area, either acquired by infection or vaccination, may explain the protection against severe disease (36). However, it seems the COVID-19 vaccines faced a challenge of infection breakthrough based on the current studies (37).

A Scottish cohort on the severity of SARS-CoV-2 Omicron VoC linked Omicron to a two-thirds lower risk of COVID-19 hospitalization than Delta (35). Another cohort of 40,538 healthcare workers with breakthrough infections concluded Omicron to be more infectious with less severity than Beta and Delta. The study suggested a combination of immune evasion, Omicron infectivity, and waning vaccine effectiveness as the explanation (38).

In contrast, a recent study found that the crude ratios of hospitalizations to cases could not be associated with severity since 18–29-year-olds had higher incidence rates

than previous cohorts. Consequently, hospitalization and asymptomatic infection rates were not significantly linked to Omicron infection, implying only minor differences in severity compared to Delta (39). It is crucial to remember that the severity of a viral illness in humans is dictated not only by the virus replication but also by the host's immunological response to the infection. So VoC's severity cannot be determined only by the current evidence and further clinical studies on inpatients are necessary.

Vaccine effectiveness and immunity

As it has already mentioned, notable mutations in RBD of S1 protein have made Omicron a potential threat to vaccine efficacy and a risk factor for reinfection (32,40, 41). Several studies evidenced attenuated vaccine-induced antibody response against Omicron variant, which has been accompanied by increased infection rate and hospital admissions even among vaccinated populations (42,43). Figure 2A is a graphical summary of the omicron immunologic response.

The serum antibody levels against SARS-CoV-2 decline over the months after the second dose which mandates booster shots (44). In addition, due to RBD mutations, Omicron can escape the existing circulating antibodies (especially neutralizing antibodies) in 2-dose-vaccinated individuals (32,37,45–49). To assess the vaccine efficacy against symptomatic infection and severe outcomes

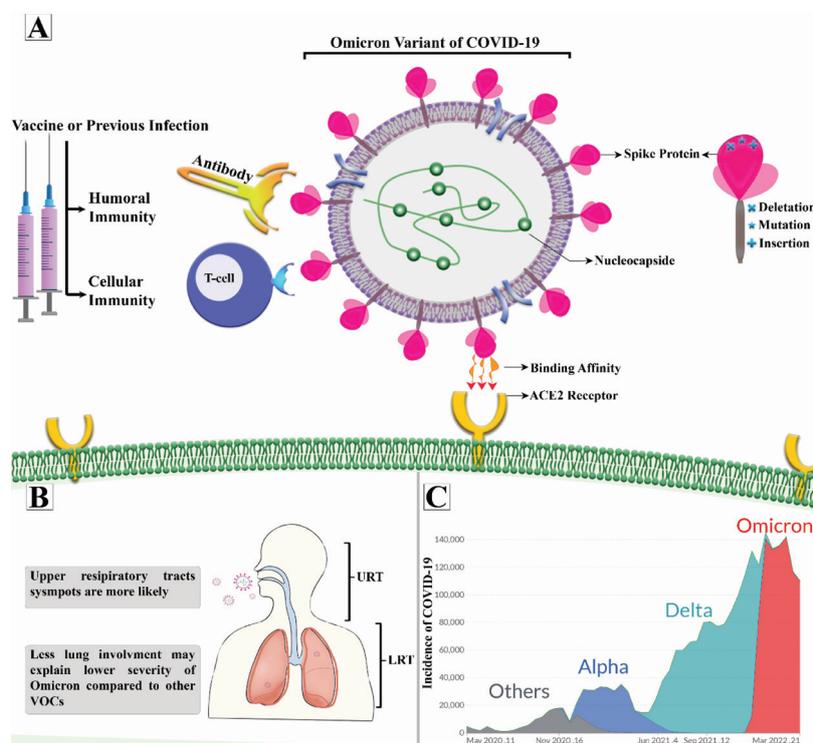


Figure 2. Its spike protein revealed 37 amino acid mutations. Its higher binding affinity to human ACE2 may stem from the 15 mutations in the receptor-binding domain. Regarding its immune escaping properties, both vaccine-induced and natural antibodies indicate diminished efficacy towards Omicron infection than other VOC. T cell immunity of vaccines is regarded to remain unattenuated towards different variants including the Omicron. Diagnosis is still attainable with former PCR kits, detecting its nucleocapsid. Studies suggest a decrease in lung-affected cases as well as an increase in cases with upper respiratory tract symptoms compared to other VOCs, which may be the reason behind its milder course of the disease. Moreover, this VoC has brought on a new COVID-19 wave with the biggest number of infected patients among all the previous SARS-CoV-2 waves.

(hospitalization or death), a study was conducted using the data of 16087 Omicron-positive cases, 4261 Delta-positive cases, and 114087 test-negative controls. Vaccine efficacy diminished remarkably after two doses against symptomatic infection for Omicron compared to Delta. Interestingly, the vaccine efficacy against severe outcomes after the third dose was high for both variants (50).

Furthermore, a meta-analysis showed a 9.7-fold drop in neutralization by antibodies, 40% symptom vaccine effectiveness, and 80% efficacy against severe disease for mRNA vaccines efficacy against omicron. They also noted receiving a booster dose will raise the efficacy against infection and severe illness up to 86.2% and 98.2%, respectively (51). Simulations and real-world observations are controversial, yet they growingly report that the booster shots would be potent enough to confront with omicron variant or at least prevent the severe disease (6,21, 49,52-54).

Although our knowledge with the Omicron is within preliminary stages, we can postulate that the efficacy of different vaccines after the booster shots are not the same; while AstraZeneca and Pfizer show notable effectiveness against Omicron after their booster shot, the Sinopharm demonstrates much lower neutralizing antibody production after the third shot. Even a specific type of vaccine (e.g., Moderna) produces different antibody responses when injected as the booster shot of other vaccines (either Pfizer or AstraZeneca versus Johnson and Johnson). Of note, the antibody titer should not be considered the only determinant of an individual's immunity (42,54-56).

As well as humoral immunity, cellular immunity is provoked by covid-19 vaccination. Based on the currently limited evidence, the vaccine-induced cellular immunity is effective against Omicron and is presumably not affected by its mutations (57). Concerning this matter, Naranbhai et al monitored the T cell immunity towards Omicron variant through the samples of 76 people taken before vaccination, after completing a series of receiving vaccines, and/or following the booster shot. They found out the T cell immunity against the Omicron was maintained, while in 21% of the observed individuals, the reactivity of T cells towards the virus declined above 50%. This reduction in T cell recognition of the S protein predominantly stems from the Omicron escaping from binding to HLA in the CD8+ section of T cells. The booster dose amplified responses of T cell immunity against Omicron S protein (11).

There are still some uncertainties to declare a definite statement about the Omicron variant, its immunogenicity, and its interaction with the immune system and vaccines. Nevertheless, the primary and limited available evidence dedicate the effectiveness of vaccines against severe diseases (58). Even preliminary reports roughly showed vaccine effectiveness against new Omicron sub-lineages BA.4 and BA.5 (59). However, there are reports of vaccine failure against contracting COVID-19 infection. Future

studies evaluating the efficacy of the existing vaccines and promoting more efficacious ones would be desired.

Reinfection

A significant proportion of the population who have been previously infected by other variants experienced reinfection in South Africa. It demonstrates that natural immunity is temporary and does not endure enough to defend people against the next wave of another variant. Immunity towards other COVID-19 variants cannot prevent attracting Omicron. Although natural infection-induced immunity forcefully defends against the Alpha, Beta, and Delta reinfections (60-62), this variant can bring much higher reinfections (63).

According to a database investigation in Qatar, a prior infection brought about potent prevention efficacy of virtually 90% towards reinfections with Alpha, Beta, and Delta VoCs, consistent with earlier observations. Omicron reinfection, however, is prevented by about 60% by similar natural immunity, reflecting diminished but still noticeable effects of innate immunity. Furthermore, Robust vaccination impacts decreasing hospital stays and mortality occurred for all variants (64).

Scientists hypothetically attribute the Omicron surge to its infectious ability to contaminate people with ready immunity against the Delta variant resultant from either natural infection or vaccination (28). The base titer of COVID-19 antibodies to counteract the disease seems to be obscure, hindering the establishment of the requisite levels of SARS-COV2 vaccine-associated antibodies for surmounting reoccurring infection burden concerning each individual (64).

Treatment

As discussed, Omicron holds about 36 mutations in the S protein and has undergone changes in the RBD, which may alter the efficiency of some treatments. A recent study was undertaken on the drug's affinity for the omicron variant's major protease. Nirmatrelvir, ritonavir, ivermectin, lopinavir, boceprevir, MPro 13b, MPro N3, GC-373, GC376, and PF-00835231 were among the medications investigated. The enhanced binding affinity of nirmatrelvir (Paxlovid), MPro 13b, and lopinavir may imply that these drugs are more effective against this Omicron variant than prior variations. Ivermectin, however, appeared the most effective (65). A study evaluated the neutralizing impacts of monoclonal antibodies (mAbs) on Omicron. The mAbs were as follows: casirivimab, bamlanivimab, tixagevimab, sotrovimab, imdevimab, and cilgavimab. The results demonstrated that although all of these mAbs have been efficient against previous VoCs, but against Omicron, only sotrovimab and tixagevimab have been efficient yet with decreased potency (66). Omotuyi et al study also revealed challenges for mAbs to treat Omicron (18). Surprisingly, the engineered ACE2 was applicable against Omicron, showing even better neutralizing effects

than the Wuhan variant (18). Further assessments suggest that the ACE2 decoy functions independently of viral mutation alterations and might be an alternative to the current COVID-19 treatment. Despite the lack of full assessment of other medications, early results imply the same therapeutic effect for corticosteroids (67).

Epidemiology

B.1.1.529 was initially discovered in specimens taken in Botswana on November 11, 2021, and in South Africa on November 14, 2021. The first incidence of Omicron in the United States was reported on December 1, 2021, in a traveler who had come back from South Africa (68). Since then, Omicron has been a global concern due to its high transmission rate; by December 21, 2021, 106 countries reported definite cases of Omicron (Figure 2C).

New Omicron subvariants, BA.4 and BA.5 acknowledges as VoC as of 12 May 2022 by ECDC. In May 2022, they took over as the prevalent variations in that South Africa and Portugal reported the first case of this new subvariant in March 2022. The sub-lineage BA.4 and BA.5 of Omicron have the potential to cause the next surge of the COVID-19 disease (69).

As estimated, the Omicron variant became the most prevalent variant of SARS-CoV-2, forming another surge of disease, with special transmission rate, morbidity, and hospitalization, especially among European countries with their high vaccine coverage and Asia with its vulnerable health care facilities (70,71). Different studies have reported a range of reproduction numbers (R) of the Omicron variant. A study from the United Kingdom estimates it from 1.0 to 1.2, with a growth rate of 0% to 2% per day. Other studies from Denmark and South Africa have stated 1.8-3.2 and 3.2-3.6 doubling days (13,68). Proper action plans against the emerged variant should be provided as soon as possible to decrease its burden.

Public health policy

Since the breakthrough of SARS-CoV-2 in late 2019, preventative actions were always of great significance; various measures, including locking down, quarantine, travel ban, contact tracking, social distancing, face masks, and recent mass vaccinations have all been applied to minimize the viral spread in communities. After identifying the B.1.1.529 variant, multiple pieces of evidence suggested its viral escape from circulating antibodies. Booster shots were thus widely encouraged to reinforce the immunity system (72).

While several countries have lifted their travel bans, detecting Omicron in full vaccinated, negative-PCR-tested passengers drastically challenged the current criterion for traveling, which mandates more strict considerations (73,74). Some experts believe that a travel ban would not be an effective strategy against the highly transmittable Omicron variant (74). Developing more complicated and effective vaccines based on early detection of new variants

and predicting the future mutations via simulation would be a more sustainable solution.

Additionally, the global policy-makers should be aware that resource-limited countries with low vaccine coverage are susceptible to develop new variants with unpredictable, challenging characteristics such as Omicron (3,75,76). However, Omicron peaks may increase the demand and reduce vaccine supplies (76). The public health sectors should actively monitor the incidence of COVID-19 cases and prepare for new possible outbreaks such as BA.4 and BA.5 (69). Wearing a mask, concise social distancing, and giving a booster shot to the mass population are the current solutions at hand.

Conclusion

Omicron possesses more notable mutations than other VoCs, which may be the rationale behind the difference in its disease characteristics from others. Although the clinical manifestations and treatment options are roughly the same, changes in transmission rate and vaccine efficacy may challenge a fragile healthcare system. All variants known to date can threaten the vulnerable groups, leading to mortality or severe symptoms. Hence, preventative approaches play the chief role in the fight against COVID-19. Based on the current evidence, injection of a booster dose of the COVID-19 vaccine may magnify both T and B cell immunity, alleviating the current challenges. Thus far, we lack controlled reliable findings to conclude this variant. The invention of new vaccines that prevent Omicron and future variants is demanded. Upcoming investigations of T-cell immunity against Omicron in addition to antibody levels, as well as different doses of vaccine effectual for each specific populations, including various types of individuals (e.g., different age groups, immunity capabilities, and disease exposures), are required to negotiate us towards a reliable comprehension of the disease, eventuating in the best preventative modality.

Limitations of the study

Although we have tried to make a full-aspect picture of Omicron VoC, our study has some limitations and we strongly suggest further studies to focus on and elucidate these points. There is inconsistency in the outcomes of different clinical studies, most of which were not fully controlled for bias. Due to asymptomatic states in a large number of cases, we cannot have an accurate estimation of the exact number of cases and the disease transmissibility. Further, we cannot distinguish Omicron cases from the patients of other COVID-19 variants or diseases of different etiologies without RT-PCR, which is not performed in most cases. Constantly evolving the SARS-CoV-2 virus impedes the invention of an effective vaccine. The diversity in individuals' response to both the disease and the preventative strategy poses another burden. The unavailability and unwillingness of vaccines in many countries may increase the risk of severe infection.

Additionally, the long-term vaccine impacts are not yet identified. Each vaccine variant may need a different variant-targeted vaccine in the future.

Acknowledgments

Figure 1 of this article is curated (by adding clade labels) using Nextstrain.org (Hadfield et al Bioinformatics) illustration. We want to thank Nextstrain.org team and GISAID initiative for making their work publicly available and also to permit distribution of their illustrations under CC-BY-4.0 license. We want to express our gratitude towards Mohamad Saeed Rezaii Zavare and Iran scientometrics (<https://t.me/scientometric>) for providing the most recent expert opinions and researches on COVID-19 since the beginning of the pandemic.

Authors' contribution

Conceptualization: SAASN.

Methodology: SAASN.

Validation: ENM, MJN, SAASN.

Investigation: HM, SS, YF, AT, SI, ZT, AN, NF.

Resources: SAASN.

Writing—original draft preparation: HM, SS, SAASN, YF, AN.

Writing—review and editing: HM, YF, SS, AT, SI, ZT.

Visualization: SAASN, NF.

Supervision: MJN, SAASN.

Project administration: SAASN.

All authors reviewed the manuscript and met the criteria of authorship.

Data availability statement

The data supporting the findings of this study are available within the article and its supplementary materials.

Conflicts of interest

The authors declare no financial, governmental, or any known conflict of interest related.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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