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A Variant of Concern (VOC) Omicron: Characteristics, Transmissibility, and Impact on Vaccine Effectiveness

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Abstract: Almost three years have passed since the start of the COVID-19 pandemic. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has constantly been mutating, producing variants with evolutionary advantages. A total of 5 variants of concern (VOCs) have emerged since the start of the COVID-19 pandemic, including Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), Gamma (P.1), and Omicron (B.1.1.529). However, as of October 2022, only the Omicron variant remains a VOC. As compared to the previous variants, although Omicron has the most extensive mutations but it appears to have lower severity and risk of hospitalization. Symptoms of Omicron infection seem to also differ from previous variants. Omicron is highly transmissible and infectious and seems to have immune evasion capability. This is worrying as even after COVID-19 vaccination has been implemented globally, there are findings that COVID-19 vaccines may not be able to provide complete protection against Omicron. This review aims to provide insight into the characteristics of Omicron, including its symptoms, severity, risk of hospitalization, transmissibility and infectivity, immune evasion, and impact on the effectiveness of COVID-19 vaccines.

Keywords: COVID-19; SARS-CoV-2; Omicron; severity; transmissibility

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused a severe pneumonia outbreak in China in late December 2019 [1]. Then in early March 2020, it was declared a global pandemic known as COVID-19 [2, 3]. Since the emergence of SARS-CoV-2 from Wuhan, Hubei province of China, in December 2019 [2, 4], this viral strain has spread like wildfire across the globe. It has undergone multiple mutations resulting in the emergence of variants of concern (VOCs), which are variants with evolutionary advantages [5]. This is alarming and led to global havoc as many lives were lost upon infection, and neither was

there a cure nor had the global vaccination program been initiated [5]. During the peak of the pandemic, mounting research was being conducted towards developing vaccines effective against SARS-CoV-2. There was indeed a rapid development of COVID-19 vaccines to put a halt to the spread and severity of COVID-19 infection. Some vaccines that were developed include CoronaVac (SinoVac Biotech), BBIBP-CorV (Beijing Institute of Biological Products/Sinopharm), Comirnaty (BNT162b2) (Pfizer), mRNA-1273 (Moderna), ChAdOx1 nCoV-19/CoviShield (AstraZeneca/University of Oxford), NVX-CoV2373 (Novavax), Covaxin (BBV152B)(Bharat Biotech International Limited), Ad5-nCo (CanSino Biologics), Sputnik V (Gamaleya Research Institute), Ad26.COV2.S (Janssen Pharmaceutical Companies) [6]. As soon as some COVID-19 vaccines were approved by the World Health Organization (WHO) under the emergency use listing, many countries implemented a National Vaccination Program, encouraging people to be vaccinated [7, 8]. However, factors such as waning immunity, reduction in the protective effect of COVID-19 vaccines against VOC, or some risk groups having inadequate protection from the primary vaccination led to the development of COVID-19 booster vaccine that targets improved and prolonged protection against COVID-19 [8].

Up until October 2022, there have been a total of 5 variants of concern (VOCs), namely B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.2 (Delta), P.1 (Gamma) [5, 9, 10], and B.1.1.529 (Omicron) [11-13]. However, as of October 2022, the only circulating variant listed as a VOC by the World Health Organization (WHO) is Omicron [14]. When this review went to press, 629,740,541 confirmed infections and 6,587,818 deaths were recorded worldwide (as of 29th October 2022) [15]. This review aims to provide some background information on Omicron, and discuss its characteristics in terms of symptoms, severity and hospitalization, transmissibility and infectivity, immune evasion and the impact on vaccine effectiveness.

2. Background of Omicron

B.1.1.529, or Omicron, is the fifth VOC and the only mutant of SARS-CoV-2 that remains a VOC as of October 2022 [14]. The first sequenced omicron case was reported on the 11th of November 2021 from Botswana, and a couple of days later, another sequenced case from Hong Kong in a traveler from South Africa [16]. Although the first Omicron case in South Africa was in a COVID-19 patient diagnosed on the 9th of November 2021 [16], on the 24th of November, only the Omicron variant was reported to the WHO in South Africa [17]. Later on the 26th of November 2021, only B.1.1.529 was designated as a VOC, named Omicron by the WHO [18]. Three theories have been proposed with regard to the origin of Omicron. This includes the possibility of Omicron being circulated and evolving from a hidden population; Omicron might have evolved from a cat-and-mouse game between virus and host in some immunocompromised patients; and Omicron may have originated from animal reservoirs and transmitted back to humans. The possibility of these theories with

current evidence has been analyzed by Du et al [19]. This agrees with Sun et al.'s findings, which revealed Omicron has five mouse-adapted mutation sites, suggesting this variant might have evolved in a mouse host [20].

The Omicron variant has five lineages: BA.1, BA.2, BA.3, BA.4, and BA.5 [14]. It possesses numerous mutations, a significant concern implicating the COVID-19 pandemic. Compared to the original wild-type strain, Omicron contains more than fifty mutations [20]. Furthermore, Omicron's spike protein has 26-35 amino acids that differ from the original SARS-CoV-2 and the Delta variant [21]. Omicron has some deletions and more than thirty mutations in the spike protein, with a few overlapping with those in Alpha, Beta, Gamma, or Delta VOCs [16, 22]. The list of spike mutations present on previous and current VOCs will be listed in Table 1 [23]. Surprisingly, compared to Omicron, the previous VOCs only have nine to twelve mutations on their spike protein region. This finding is in agreement with another study [22]. Additionally, fifteen out of the thirty-plus mutations happen on the receptor-binding domain (RBD). This has significant implications as the RBD is the binding site to the host angiotensin-converting enzyme 2 (ACE-2) receptors which allows SARS-CoV-2 to enter the body, but also the key target of neutralizing antibodies produced by immune response and therapeutic antibodies [20, 22].

Table 1. Spike mutations of SARS-CoV-2 Variants: Alpha, Beta, Gamma, Delta, and Omicron.

SARS-CoV-2 Variants of Concern	**Spike mutations**	**Reference**	**Total mutations**
Alpha	69–70HV and 144Y deletions, N501Y, D614G, A570D, P681H, T716I, S982A, D1118H,*E484K, *S494P, *K1191N (*Found only in some sequences)	[5, 24]	12
Beta	L242–244 deletions, A701V, D215G, D80A, D614G, E484K, K417N, N501Y, R246I, L18F	[5]	10
Gamma	K417T, E484K, N501Y, L18F, T20N, P26S, D138Y, R190S, D614G, H655Y, V1176F, T1027I	[5, 25]	12
Delta	156–157 deletions, D614G, D950N, L452R, T19R, T478K, P681R, R158G, *G142D (*Found only in some)	[5, 9]	9
Omicron	A67V, Δ69-70, T95I, G142D/Δ143-145, Δ211/L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969 K, L981F	[23]	32

3. Characteristics of Omicron

3.1. Symptoms, Severity, and Risk of Hospitalization of Omicron

Besides the extent of mutations, other critical differences between the Omicron variant and previous VOCs are the symptoms, severity, and risk of hospitalization after infection. Reports suggest Omicron infection is less severe than previous variants [26, 27]. In a South Korean study that involved only 40 Omicron-infected patients, some were asymptomatic (47.5%), while some had mild symptoms (52.5%) that resolved within a few days. The initial presenting symptoms include sore throat (25%), fever (20%), headache (15%), cough (12.5%), sputum (12.5%), runny nose (10%), myalgia (5%), fatigue/weakness (2.5%), and loss of taste or smell (2.5%) [27]. Additionally, a United Kingdom (UK)-based study involving symptomatic COVID-19-positive patients who had received at least two doses of the COVID-19 vaccine found that sore throat was more common during Omicron prevalence. At the same time, loss of smell was less common, and there was a 25% lower hospital admission rate than Delta [28]. On a side note, findings of a lower hospital admission rate were consistent with the South African private health insurer Discovery Health in Johannesburg, which found a 29% lower risk of hospital admission among Omicron-infected individuals compared to those infected with Delta [29]. A study from France and Denmark also found a lower hospitalization rate (2% vs. 1.2%) in Omicron-infected patients [26, 30]. Furthermore, both France study and the South Korean study found that the loss of taste (9%; 2.5%) and smell (8.3%; 2.5%) were less common in Omicron-infected patients, which were somewhat consistent with the UK study that found loss of smell to be less common [26-28]. Although the France study found symptomatic cases presents mostly with mild symptoms of asthenia/fatigue, cough, fever, headache, myalgia, sore throat or runny nose but the symptomatic cases makes up 89%, which differs from the South Korean study with only 52.5% [26, 27]. The Omicron symptoms mentioned in the UK study suggest less respiratory tract involvement in Omicron infections. Moreover, their findings indicate a shorter period of illness and potential infectiousness [28]. This might be due to Omicron having a lower replication competence in the human lungs, which is compatible with the lower disease severity as presented by Hui et al [31].

3.2. Transmissibility and Infectivity of Omicron

Omicron is found to be highly transmissible. For instance, in South Africa, the mean number of 280 COVID-19 cases per day in the week before the detection of Omicron rose to 800 cases per day in the following week. Furthermore, there is a higher early doubling time in the fourth wave (Omicron) compared to previous waves in the Gauteng province of South

Africa [16]. Based on the increase of Omicron cases and sequencing data in Gauteng, Omicron is estimated to have the ability to infect three to six times as many individuals as Delta over the same period [32]. Within months, Omicron has become the dominant variant in many countries and has spread rapidly across the globe. In the UK, 1,239 Omicron cases were found on the 12th of December 2021, bringing the total cases to 3,137. On the 15th of December 2021, within days, the confirmed cases increased to a total of 4,671 in Britain, the most significant daily increase [21]. In the United States (US), the first Omicron case was detected in San Francisco, California, and was identified on the 1st of December 2021. As of 15th of December 2021, Omicron cases have been detected in at least 31 states in the US and Washington DC [21].

The enhanced SARS-CoV-2 transmission [21], and infectivity [33] are associated with Omicron mutations. Karim et al. suggest that if the overlapping omicron mutations maintain their known effects, increased transmissibility is expected, mainly due to mutations near the furin cleavage site [16]. This somewhat agrees with Thakur et al., that state mutations at H655Y, N679K, and P681H in the S1-S2 furin cleavage site of the Omicron may be associated with enhanced transmissibility [34]. On the other hand, Hui et al. suggest that Omicron has an intrinsic capacity for increased transmission due to its quick and increased viral replication efficiency in the human bronchi compared with earlier lineages [31]. With regards to an increased infectivity, Lupala et al. found that the binding energies for ACE2-RBD structures for Omicron is lower than the SARS-CoV-2 wild type, indicating stronger binding interactions and hence enhanced infectivity [33]. Besides that, as a consequence of the extensive mutations in Omicron, the surface of the spike protein is highly positively charged. Based on the molecular dynamic simulation, Nie et al., that compared to the wild type, the Omicron spike has a much stronger interaction with polysulfates. This consequently favors Omicron binding, leading to cell entry and infection. Furthermore, the P681H mutation located next to the -RRAR- furin cleavage site indicates an increased infectivity potential [23]. Additionally, using an artificial intelligence model (TopNetmAb), Chen et al. demonstrated that Omicron might be more than 10 times more contagious than the original SARS-CoV-2. It is more infectious than other variants, roughly 2.8 times as infectious as Delta, primarily due to Omicron's RBD mutations N501Y, N440K, and T478K [35].

3.3. Immune evasion and Impact on the Effectiveness of COVID-19 Vaccines against Omicron

Omicron seems to have an enhanced immune escape capability. Due to Omicron's extensive mutations, there have been serious concerns regarding the neutralization antibodies and reduced efficacy of COVID-19 vaccines. In South Africa, it is found that individuals who have received any vaccines from Pfizer-BioNTech, Oxford-AstraZeneca, and Johnson and Johnson reported breakthrough infections [36]. Additionally, 83% of Omicron cases in Denmark involved fully or booster-vaccinated individuals [30]. Furthermore, a study conducted by the South African Centre of Excellence in Epidemiological Modelling and Analysis through late November 2021 that analyzed 35,670 reinfections among close to 2.8 million positive tests found the proportion of reinfections increased greatly as Omicron spreads. This suggests earlier infection only provides half as much protection against the Omicron variant compared to the Delta variant [37]. This is concerning, as it seems that Omicron has a more remarkable immune evasion ability and more extensive mutations on the spike protein than previous VOCs. Moreover, we know that SARS-CoV-2 enters the human host via the spike protein, and COVID-19 vaccines are targeted at the spike protein. So, the one important question is whether the currently available COVID-19 vaccines effective against this new VOC.

Preliminary results from teams in South Africa, Germany, Sweden, and the Pfizer-BioNTech collaboration suggest that protection provided by current COVID-19 vaccines will not be lost entirely and booster vaccines should strengthen immunity against Omicron [21, 38]. A study conducted at the Africa Health Research Institute in Durban, South Africa, involving 12 individuals who received Pfizer-BioNTech vaccines, showed a 40 times less potent serum against Omicron than previous SARS-CoV-2 strains. This finding is consistent with results reported by Pfizer-BioNTech in a press release dated 8th of December 2021 [38]. Hoffmann et al. also found that compared to B.1, the antibodies induced upon BNT/BNT immunization neutralized the Omicron spike with 34-fold reduced efficiency, indicating that two doses of BNT may not provide enough protection against Omicron infection [39]. A study by Chen et al. used structures of 185 known antibody-RBD complexes and detected that the vaccine escape capability of Omicron is almost 14 times as high as that of Delta.

On the other hand, based on an artificial intelligence model, Chen et al. also found Omicron's RBD mutations E484A, K417N, and Q493R might decrease the efficacy of Eli Lilly monoclonal antibody cocktail. In contrast, the RBD mutation Q498R may moderately reduce the effectiveness of AstraZeneca monoclonal antibody cocktail tixagevimab and cilgavimab [35]. Furthermore, according to Cao et al., numerous single mutations of Omicron

can impair neutralizing antibodies of different epitope groups. In particular, neutralizing antibodies in group A-D, the epitopes that overlap with the ACE-2 binding motif, are largely escaped by G446S, E484A, Q493R, and K417N. Interestingly, their study found more than 85% of the tested neutralizing antibodies were escaped by Omicron, suggesting this new variant could result in substantial humoral immune evasion and potential antigenic shifting [40].

Although Omicron is likely to affect vaccine effectiveness but based on a Pfizer BioNTech study, booster vaccines may still be able to provide protection against Omicron as results showed individuals who received a booster dose had neutralizing antibody levels against Omicron comparable to those against SARS-CoV-2 variants that were triggered by two vaccine doses [38]. Furthermore, A UK study found that patients infected during Omicron prevalence receiving the third dose of vaccine presented with higher symptom duration reduction than patients infected during Delta prevalence [28], suggesting a decrease in severity. These findings indicate that a booster dose can still provide some protection against Omicron.

4. Conclusions

Omicron is the most mutated variant of the SARS-CoV-2 VOCs to date. Despite the rapid development of COVID-19 vaccines and the worldwide implementation of the National Vaccination Program, Omicron still spreads across the globe and remains a VOC. Compared to the Delta prevalence, there is a difference in symptom, severity, and hospital admission upon Omicron infection. Both severity and hospital admission decreased during Omicron prevalence, and symptoms tend to affect the respiratory tract less. After an Omicron infection, sore throat appears to be one of the most prevalent symptoms, while the loss of taste and smell is significantly less prevalent than during the Delta. Despite the lower severity and hospital admission, Omicron appears more transmissible, infectious, and likely capable of immune evasion. The current COVID-19 vaccines seem to have lower effectiveness against Omicron, but boosters still provide some protection. Furthermore, existing public health prevention measures implemented towards SARS-CoV-2 strains and their VOCs should be continued to protect and prevent one against Omicron infection [41, 42]. These measures include wearing a face mask, proper hand hygiene, social distancing, and avoiding crowded places or poorly ventilated areas. In conclusion, combining vaccination and public health measures is crucial in preventing and decreasing the severity of SARS-CoV-2 infection.

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