



Review

The humoral and cellular immune evasion of SARS-CoV-2 Omicron and sub-lineages

Tiandan Xiang^{a,b}, Junzhong Wang^{a,b}, Xin Zheng^{a,b,*}^a Department of Infectious Diseases, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China^b Joint International Laboratory of Infection and Immunity, Huazhong University of Science and Technology, Wuhan 430022, China

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ABSTRACT

The recently discovered SARS-CoV-2 variant Omicron (B.1.1.529) has rapidly become a global public health issue. The substantial mutations in the spike protein in this new variant have raised concerns about its ability to escape from pre-existing immunity established by natural infection or vaccination. In this review, we give a summary of current knowledge concerning the antibody evasion properties of Omicron and its subvariants (BA.2, BA.2.12.1, BA.4/5, and BA.2.75) from therapeutic monoclonal antibodies and the sera of SARS-CoV-2 vaccine recipients or convalescent patients. We also summarize whether vaccine-induced cellular immunity (memory B cell and T cell response) can recognize Omicron specifically. In brief, the Omicron variants demonstrated remarkable antibody evasion, with even more striking antibody escape seen in the Omicron BA.4 and BA.5 sub-lineages. Luckily, the third booster vaccine dose significantly increased the neutralizing antibodies titers, and the vaccine-induced cellular response remains conserved and provides second-line defense against the Omicron.

1. Introduction

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been a pandemic worldwide since 2019 (Zhou et al., 2020). After that, a variety of SARS-CoV-2 variants such as Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) emerged with varying transmissibility and disease severity (Harvey et al., 2021; Tao et al., 2021; Tegally et al., 2021). On November 24, 2021, World Health Organization (WHO) announced the sequence of a novel SARS-CoV-2 variant Omicron (B.1.1.529) (Callaway, 2021) and rapidly classified it as the fifth variant of concerns (VOCs) (Viana et al., 2022). The Omicron variant hosts 34 mutations in the spike protein and showed unprecedented transmissibility and striking immune evasion. Within a few months, the Omicron variant (mainly BA.1 subvariants) rapidly replaced Delta VOC and became the dominant strain (Lambrou et al., 2022). Subsequently, a series of Omicron sub-lineages continuously emerged: mainly including BA.2, BA.2.12.1, BA.4, and BA.5, which exhibit different characteristics of transmission and immune evasion capacity (Cao et al., 2022c; Desingu et al., 2022; Iketani et al., 2022). More recently, a new prevalent Omicron subvariant, BA.2.75, was discovered in India and Japan, and reported in multiple other countries (Tan et al., 2022). This new BA.2.75 variants

harbored nine additional mutations in the spike protein compared to BA.2, including G446S, R493Q, and N460K (Shaheen et al., 2022) (Fig. 1). These mutations significantly increased BA.2.75's affinity to ACE2 and enhanced cell-cell fusion, which may set off a new wave of epidemic peak (Zappa et al., 2022; Qu et al., 2022).

In this review, we first describe the epidemic properties of SARS-CoV-2 Omicron and its subvariants by analyzing its transmissibility and pathogenicity. We then focus on evaluating the antibody evasion ability of Omicron sub-lineages by convalescent sera, vaccine recipients' sera, and therapeutic monoclonal antibodies, and exploring the underlying mechanism behind immune evasion. Lastly, we describe Omicron-reactive B cell and T cell responses in COVID-19 vaccine recipients and propose potential strategies for the SARS-CoV-2 Omicron variants' threat.

2. The SARS-CoV-2 Omicron

2.1. The SARS-CoV-2 Omicron transmission

Epidemiological evidence from different countries suggests that the Omicron variant is substantially more transmissible than prior VOCs (Kumar et al., 2022; Ren et al., 2022). According to previous studies, the original Omicron variant has an average basic reproduction number and

* Corresponding author.

E-mail address: xinz@hust.edu.cn (X. Zheng).<https://doi.org/10.1016/j.virs.2022.11.007>

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The SARS-CoV-2 Omicron variant of concern

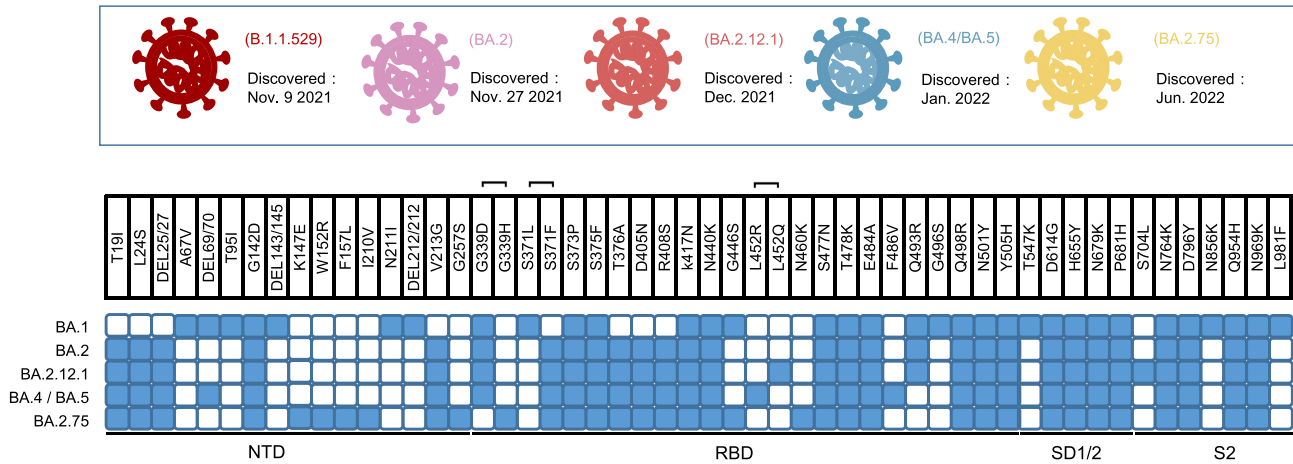


Fig. 1. The spike mutations within the Omicron sub-lineages. The mutated residues in the spike protein among Omicron sub-lineages are colored blue.

effective reproduction number of 8.2 and 3.6, respectively (Liu et al., 2022), and triggered 3.8 and 2.5 times higher transmissibility than the Delta variant (Nishiura et al., 2022; Liu and Rocklöv, 2022). The doubling time is also very short among populations that have achieved herd immunity, ranging from 3.2 days to 3.6 days (Grabowski et al., 2022). These data validated Omicron's high transmission rate.

Although the original Omicron variant has shown unprecedented transmissibility, the subsequent Omicron sublineages seem to be much more transmissible. It was reported that the BA.2 strain is spreading about 1.5 times faster than the Omicron BA.1 strain (Rahimi et al., 2022). The BA.2.12.1 lineage, branched off from BA.2, was reported to have 25% higher transmissibility than BA.2 (Beheshti et al., 2022). The BA.4 and BA.5

(BA.4/5), which are sister variants, harboring L452R, F486V, and R493Q mutations in the spike RBD, show even greater growth potential (Cao et al., 2022c). After a large wave of infections dominated by BA.1 and BA.2 (Rahimi et al., 2022), BA.4/5 has swept the globe and surpassed BA.1 and BA.2 as the most prevalent subtype in the world. Currently, data are limited for the transmissibility of the Omicron BA.2.75 variant. The preliminary study showed that the effective reproduction number of BA.2.75 is greater than that of BA.5 (Saito et al., 2022), which was expected to be more transmissible over other Omicron sub-lineages (Sugano et al., 2022).

A study revealed that the largely increased infectivity of original Omicron could be attributed to the accumulated mutations that created new salt bridges and hydrogen between Omicron and ACE2 receptors,

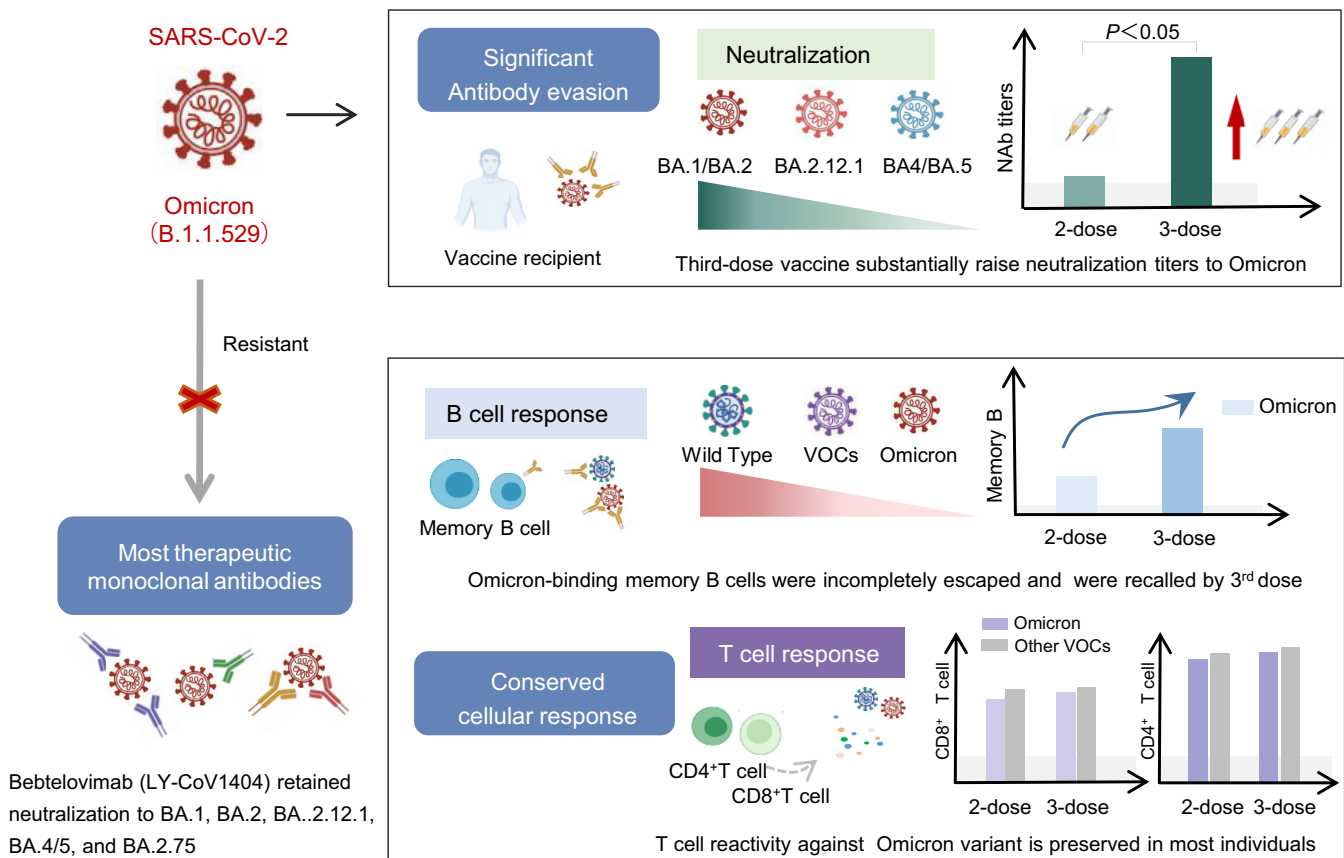


Fig. 2. The humoral and cellular immune evasion of Omicron. VOCs, variant of concerns.

enhancing the binding of Omicron spikes protein with human ACE2 (Mannar et al., 2022). Besides, the lower thermal stability of Omicron RBD and the altered lower dependence on transmembrane serine protease 2 (TMPRSS2) utilization also accounted for Omicron's increased transmission (Yin et al., 2022).

2.2. The SARS-CoV-2 Omicron pathogenicity

In contrast to the high transmissibility, the SARS-CoV-2 Omicron appears to have attenuated disease severity and mortality compared with previous VOCs. Most cases diagnosed with original Omicron manifested asymptomatic or mild disease, with more pronounced upper respiratory symptoms but rarely pneumonia (Meo et al., 2021). One significant real-world study reveals that the hospitalization and death rates of Omicron patients were reduced by 41% and 79% respectively when compared to Delta patients (Lewnard et al., 2022). In a large national cohort containing 1.5 million cases, the risk of severe outcomes is also substantially lower for Omicron infection than for Delta infection, suggesting that Omicron variants had a significantly reduced clinical severity (Nyberg et al., 2022). This observed milder clinical severity may be related to the immune barrier formed by vaccination. However, even in patients who had not been vaccinated, the Omicron infection group had substantially lower rates of emergency department visits, hospitalizations, ICU admissions, and the need for mechanical ventilation than the Delta group, confirming Omicron's attenuated pathogenicity (Wang L et al., 2022).

A series of studies shed light on the reason why the original Omicron infection showed attenuated pathogenicity. One of the most important reasons was that the Omicron variant exhibited much less damage to the lungs compared with other VOCs (Halfmann et al., 2022). Firstly, the replication ability of the Omicron variant in human lung and intestinal epithelial cells is significantly reduced (Shuai et al., 2022). Secondly, the lung pathological lesions and mortality rate of Omicron-infected mice models were lower than those of other VOCs infections (Uraki et al., 2022). Furthermore, although the TMPRSS2 protein is extensively expressed on the surface of lung cells, the Omicron reduced efficiency in utilizing the host TMPRSS2 to help the virus enter into cells (Shuai et al., 2022). These findings may explain why the Omicron infection was associated with reduced hospitalizations and deaths.

Several studies evaluated the pathogenicity between different Omicron sub-lineages. Despite BA.2 having higher transmissibility and fitness than BA.1, the risk of severe outcomes was comparable to BA.1/BA.1.1 (Wolter et al., 2022; Obermeyer et al., 2022). Similarly, there is no evidence suggesting that BA.2.12.1 causes more severe disease than the Omicron BA.1 strain. Although the BA.4/5 variants exhibit more pathogenic in hamster models infected with Omicron sublineages (Kimura et al., 2022), they did not increase the risk of critical illness in the real-world investigation (Davies et al., 2022). To date, it remains unclear whether novel BA.2.75 causes more severe clinical disease. In the lungs of infected hamsters, BA.2.75 showed a stronger replication capacity than BA.5 and caused the most severe focal viral pneumonia (Uraki et al., 2022). However, further large clinical studies are required to corroborate the disease severity of BA.2.75 infection.

3. The significant antibody evasion of SARS-CoV-2 Omicron

SARS-CoV-2 Omicron and its subvariants contain a large number of mutations in its spike protein and have occurred antigenic shift (McCallum et al., 2022). Since most SARS-CoV-2 vaccines and monoclonal antibodies are designed to target the wild-type (WT) spike protein, it's quite probable that the Omicron variant will drastically reduce the efficiency of pre-existing immunity induced by previously natural infection or current vaccines. Hence, it is necessary to investigate the antibody evasion potential of the original Omicron and its subvariants (BA.2, BA.2.12.1, BA.4/5, and BA.2.75) against convalescent COVID-19 individuals, vaccine recipients, and therapeutic monoclonal antibodies (Fig. 2).

3.1. Neutralization of Omicron by convalescent sera

Multiple studies suggested that there was a significant difference in neutralizing activity to Omicron between vaccinated and unvaccinated COVID-19 convalescent patients.

Serum obtained from most unvaccinated convalescent participants could not neutralize the original Omicron. In the early convalescent phase (less than three months) of WT SARS-CoV-2 infection, the majority of serum samples exhibited undetectable neutralizing activity against the original Omicron, with the seropositivity ranging from 20% to 26.7% (Carreño et al., 2022; Liu et al., 2022). The serum neutralizing titers against Omicron were significantly lower (8–80 fold) when compared with WT (Hoffmann et al., 2022; Lusvarghi et al., 2021; Zhang et al., 2022). Unsurprisingly, the neutralization titer exhibited a further substantial decline over time. Only 13%–39% of serum samples from COVID-19 convalescents had detectable neutralizing antibodies against the Omicron one year following recovery, whereas 71%–94% of serum still exhibited neutralizing antibody response against Delta (Planas et al., 2022; Ma et al., 2022). Of note, even convalescent individuals who have previously been infected with Alpha, Beta, or Delta variants can barely neutralize the Omicron (Dejnirattisai et al., 2022; Wrátil et al., 2022; Zhang et al., 2021). In brief, both WT and VOCs-infected COVID-19 patients had very little neutralization capacity against Omicron, indicating considerable antibody escape.

However, SARS-CoV-2 vaccination dramatically improved neutralizing antibodies against the original Omicron in convalescent individuals. Several studies showed that almost all convalescent individuals (90%–100%) were able to neutralize the Omicron after a single dose vaccine (Cheng et al., 2022; Rössler et al., 2022; Sheward et al., 2022). The serum antibody titers against Omicron increased by 63–154 fold on average after vaccination (Schmidt et al., 2022; Wrátil et al., 2022). Of note, compared to a single shot, vaccinated with a two-dose vaccine did not increase the neutralizing activity against Omicron in convalescent patients (Wrátil et al., 2022). However, prolonging the interval between the second and third doses induced greater neutralization capacity against all SARS-CoV-2 VOCs, including Omicron (Wrátil et al., 2022). The significant increase in neutralization capacity following convalescence-vaccination may be related to the consecutive antigen exposure rapidly induced broader neutralizing antibodies and affinity-matured memory B cell subsets (Wrátil et al., 2022; Goel et al., 2022). This “hybrid immunity” achieved by infection-plus-vaccination or vaccination-plus-breakthrough infection resulted in repeated exposure to the original SARS-CoV-2 spike proteins, inducing high-quality and high-avidity neutralizing antibodies against various VOCs, including Omicron (Wrátil et al., 2022). Supplementary Table S1 summarizes the neutralization of COVID-19 convalescent sera against Omicron variants before and after vaccination.

Several studies have described the antibody evasion capabilities among Omicron sub-lineages. Omicron BA.1 have a comparable antibody escape capacity to BA.2 (Ai et al., 2022; Yu et al., 2022), despite the BA.1 and BA.2 strain escaping neutralizing antibodies that target different epitopes (Cao et al., 2022b). However, those unvaccinated participants who had recovered from the Omicron BA.1 or BA.2 infection were unable to effectively cross-neutralize the Omicron BA.2.12.1, BA.4/5, and BA.2.75 sub-lineages (Khan et al., 2022; Cao et al., 2022a), suggesting the Omicron BA.2.12.1, BA.4/5, and BA.2.75 sub-lineages exhibit more striking antibody evasion over BA.1 or BA.2. The potential mechanism behind this phenomenon may be due to the humoral immune memory recalled by BA.1 breakthrough infections primarily target the SARS-CoV-2 wild type, and the neutralizing antibodies mainly enriched on spike epitopes that do not bind ACE2, thus were evaded by the BA.4/5 and BA.2.75 (Cao et al., 2022a). To date, BA.4/5 exhibited the greatest antibody resistance among known Omicron sub-lineages, followed by BA.2.75 (Wang Q et al., 2022b). In convalescents with BA.1 or BA.2 breakthrough infections, the neutralization titer against BA.2.75 was higher than that against BA.5 (Tan et al., 2022). Intriguingly, plasma from BA.5 breakthrough infection showed much lower neutralization against BA.2.75 than BA.5, this phenomenon may be accounted for

Table 1
Neutralization of Omicron by monoclonal antibodies.

Developer	Generic Name	Other name	BA.1.1.529	BA.2	BA.2.12.1	BA.4/BA.5	BA.2.75	BA.2.76
Eli Lilly	Bamlanivimab	LY-CoV555	Complete loss	Complete loss	Complete loss	Complete loss	Complete loss	Complete loss
	Etesevimab	LY-CoV016	Complete loss	Complete loss	Complete loss	Complete loss	Complete loss	Complete loss
	Bebtelovimab	LY-CoV1404	Retained	Retained	Retained	Retained	Retained	Retained
Regeneron	Casirivimab	REGN10933	Complete loss	Complete loss	Complete loss	Complete loss	Partially retained	Complete loss
	Imdevimab	REGN10987	Complete loss	Partially retained	Partially retained	Partially retained	Complete loss	Considerable loss
AstraZeneca	Cilgavimab	COV2-2130	Considerable loss	Retained	Retained	Retained	Partially retained	Complete loss
	Tixagevimab	COV2-2196	Considerable loss	Considerable loss	Considerable loss	Complete loss	Partially retained	Considerable loss
GSK and Vir	Sotrovimab	S309 / VIR7831	Partially retained	Partially retained	Partially retained	Partially retained	Partially retained	Complete loss
Adiagio	Adintrevimab	ADG20	Considerable loss	Complete loss	Complete loss	Complete loss	Complete loss	Complete loss
Brii Biosciences	Amubarvimab	BR11-196	Complete loss	Considerable loss	Considerable loss	Considerable loss	Considerable loss	Complete loss
	Romlusevimab	BR11-198	Retained	Considerable loss	Complete loss	Complete loss	Complete loss	Complete loss
Singlomics Biopharmaceuticals	DXP604	–	Retained	Partially retained	Partially retained	Considerable loss	Partially retained	Complete loss
Shanghai Jemincare Pharmaceuticals	JMB2002	–	Retained	Retained	–	–	–	–
Celltrion	Regdanvimab	CT-P59	Complete loss	–	–	–	–	–

Retained, $IC_{50} < 100$ (ng/mL); Partially retained, $100 < IC_{50} < 1000$ (ng/mL); Considerable loss, $1000 < IC_{50} < 5000$ (ng/mL); Complete loss, > 5000 (ng/mL).

BA.2.75's unique RBD and NTD-targeting antibody escape pattern (Cao et al., 2022a).

To sum up, those unvaccinated COVID-19 convalescent individuals showed an almost complete loss of neutralization to Omicron, requiring SARS-CoV-2 vaccination to boost their immunity against re-infection. The serum from Omicron BA.1 or BA.2 infection showed significant neutralization resistance to Omicron BA.4/5 sub-lineages, suggesting that Omicron natural infection will not be enough to protect us against emerging mutant strains.

3.2. Neutralization of Omicron by SARS-CoV-2 vaccines

Most primary SARS-CoV-2 vaccine regimens consisted of two doses. The new emergence of Omicron variants poses a huge challenge to the effectiveness of two-dose vaccine-induced immunity. Increasing evidence demonstrates that Omicron and its sub-lineages greatly evade two-dose vaccine-induced antibodies in healthy individuals. For the mRNA vaccines, two-dose vaccination induced poor neutralization against Omicron (Dejnirattisai et al., 2022; Liu et al., 2022; Planas et al., 2022). The seropositivity of neutralizing antibodies ranges between 12.8% and 85% (Cheng et al., 2022; Lusvarghi et al., 2021; Muik et al., 2022) and the titer against Omicron dramatically decreased 43–122 fold when compared with WT (Garcia-Beltran et al., 2022). At 5–7 months after two-dose vaccination, neutralizing antibodies waned or were completely absent (Planas et al., 2022). Other primary vaccination regimens, such as an adenoviral-vectored vaccine or inactivated vaccines, displayed similar poor neutralization against Omicron (Cameroni et al., 2022; Lu et al., 2021; Meng et al., 2022). The above studies indicated that the immune barrier established by the primary vaccine regimen is too vulnerable to neutralize the Omicron.

Fortunately, the third booster dose significantly increased the neutralizing antibody against Omicron and its sub-lineages regardless of what vaccine platform was considered (Qu et al., 2022). Compared to the second dose, a third homologous mRNA-boosting vaccine substantially increased neutralization titers against the original Omicron by 23.4–34.2 fold, reaching approximately 100% seropositivity (Lusvarghi et al., 2021; Nemet et al., 2022; Planas et al., 2022). Compared to homologous boosting, a heterologous booster vaccination regimen can produce higher Omicron immunogenicity (Costa Clemens et al., 2022; GeurtsvanKessel

et al., 2022). More importantly, the third-dose mRNA vaccine was efficient in neutralizing most Omicron sublineages, including BA.2, BA.3, BA.4, and BA.5 subtypes (Qu et al., 2022), despite some studies reporting that BA.4/5 show significant antibody escape to the sera from three-dose vaccine recipients, and was more prone to occur breakthrough infections (Tuekprakhon et al., 2022). In addition to substantially increasing the neutralizing antibodies, the third dose vaccine is effective in protecting individuals from serious COVID-19-related outcomes (Barda et al., 2021; Tseng et al., 2022). Some studies assessed the durability of neutralizing antibody responses against Omicron and its subvariants (BA.2.12.1 and BA.4/5) after the third booster dose (Qu et al., 2022; Lyke et al., 2022). It seems that the boosted peak titers decline rapidly within two months, but the effective antibody titer against Omicron is persistent for a long time (at least nine months) in the majority of the individuals (Qu et al., 2022; Lyke et al., 2022). The rate of decay of antibody titers was comparable between the Omicron sub-lineages (Qu et al., 2022). Supplementary Table S2 summarizes vaccine recipients' neutralizing capacity against Omicron variants before and after the third booster vaccination.

The data presented above showed that the initial two-dose vaccination regimen resulted in a large reduction or complete loss of Omicron neutralization titers; however, the third booster vaccination substantially raised neutralization to Omicron and provided better protection. The third booster vaccine, regardless of homologous or heterologous regimen, should be extensively recommended for the general population, particularly high-risk groups.

Although the third booster dose has shown a satisfactory effect in increasing antibody titers and preventing hospitalization and death, the necessity for a fourth dose vaccine remains to be determined. The preliminary study in Israeli holds the opinion that the three-dose mRNA vaccines hit a “ceiling of immunity” (Regev-Yochay et al., 2022). Even though the fourth dose restores the maximal antibody titers that were achieved after three doses, it provides little additional protection against Omicron infection. The three-dose mRNA vaccines were efficient in preventing Omicron infection by 71.6% (Tseng et al., 2022), whereas the fourth dose was substantially less effective (11%–30%) (Regev-Yochay et al., 2022). Individuals who are young and healthy are unlikely to benefit significantly from a fourth dose, which mostly protects elderly high-risk groups (aged over 60 years) from COVID-19 hospitalization and death (Nordstrom et al., 2022; Arbel et al., 2022). Consistent with this

study, Wang et al. reported that the fourth dose of inactivated COVID-19 vaccination was capable of recalling waned antibody titers, however, the peak value was lower than the third dose (Wang J et al., 2022). Furthermore, the fourth dose facilitates the shift of immune reactions from RBD to nucleocapsid protein (NP) and N-terminal domain (NTD) (Wang J et al., 2022); the shifted response was unable to neutralize Omicron due to significantly altered conformation. These studies revealed that immune responses could not be elevated indefinitely. More large studies are required in the future to determine the necessity for a fourth dose.

In summary, the above data highlighted the importance of the third vaccine dose. Facing the ongoing challenge of Omicron, the third booster vaccination is the best strategy in the context of the existing vaccine.

3.3. Neutralization of Omicron by therapeutic monoclonal antibodies

In addition to having a major impact on vaccines, Omicron created a great challenge to the therapy. Many studies estimated the neutralization efficacy of approved or developing antibodies against divergent Omicron sub-lineages, and the results were presented in Table 1. Overall, Omicron variants exhibit significant resistance to most of these monoclonal antibodies, including bamlanivimab (LY-CoV555), etesevimab (LY-CoV016), casirivimab (REGN10933), tixagevimab (COV2-2196/AZD8895), adintrevimab (ADG20), and amubarvimab (BRII-196). Among them, bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016) completely lost their neutralizing capacity to all major Omicron sub-lineages (BA.1, BA.2, BA.2.12.1, BA.4/5, BA.2.75, and BA.2.76) (Cameroni et al., 2022; Dejnirattisai et al., 2022; Planas et al., 2022; Schulz et al., 2022). Fortunately, a part of the antibodies retained their neutralizing activity. For the BA.1 sub-lineages, sotrovimab (S309), romlusevimab (BRII-198), DXP604, and JMB2002 remained superior neutralizing activity (Cao et al., 2022b; Schulz et al., 2022; Yin et al., 2022). For the BA.2, BA.2.12.1, and BA.4/5 sub-lineages, bebtelovimab (LY-CoV1404), cilgavimab (COV2-2130/AZD1061), imdevimab (REGN10987), and sotrovimab (S309) retained or partially retained their neutralization (Wang Q et al., 2022a; Cao et al., 2022c). Despite the casirivimab (REGN10933) and tixagevimab (COV2-2196/AZD8895) showed a considerable or complete loss of neutralization to BA.1, BA.2, BA.2.12.1, BA.4/5, their neutralizing activities against BA.2.75 is partially restored due to R493Q reversion (Cao et al., 2022a; Qu et al., 2022). Of note, bebtelovimab (LY-CoV1404) was reported to potently neutralize major Omicron sub-lineages (BA.1, BA.2, BA.2.12.1, BA.4 and BA.5) (Ai et al., 2022; Iketani et al., 2022; Westendorf et al., 2022), including recently emerged BA.2.75 and BA.2.76 (Cao et al., 2022a).

Omicron's considerable antibody escape can be attributed to the numerous mutations accumulating on the spike epitopes targeted by these antibodies (Cao et al., 2022b). Compared to BA.2 variants, BA.4/5 and BA.2.75 bear four and nine additional mutations in their spike proteins respectively (Tan et al., 2022). The genetic and antigenic distance of Omicron sublineages is far away from the previous SARS-CoV-2 VOCs, especially WT strains, facilitating the Omicron's remarkable antibody evasion (Wang J et al., 2022). Due to crucial mutation sites like L452R and F486V being far from the bebtelovimab-RBD interface, LY-CoV1404 maintains potent neutralizing activity against all known Omicron sub-lineages (Zhou et al., 2022). Only K444Q, V445A, or P499 R/S mutation in spike protein will significantly decrease the activity of bebtelovimab (Westendorf et al., 2022). Apart from that, the alterations in local conformation and hydrophobic micro-environments drive epitope modification, leading to Omicron is not recognized by most RBD- and NTD-antibodies (Cui et al., 2022). Together, the antigenic shift in Omicron mediated considerable evasion to the majority of therapeutic monoclonal antibodies, emphasizing the importance of developing broadly neutralizing antibodies to combat the ongoing COVID-19 pandemic.

4. The conserved cellular immunity to Omicron

Given Omicron variants' striking antibody evasion, whether infection or vaccine-induced memory B cells or T cells may recognize Omicron is a major concern.

4.1. The Omicron RBD specific memory B cell response

Memory B cells constitute an important part of long-term immunity because memory B cells can rapidly differentiate and produce numerous new antibodies with higher affinity when exposed to a similar antigen. Several recent studies investigated whether memory B cells induced by two-dose mRNA vaccination can recognize Omicron. They found that only 40%–50% of memory B cells retained recognition of the original Omicron, which was substantially reduced compared with other variants (71% on average) (Goel et al., 2022; Sokal et al., 2022; Tarke et al., 2022). This is consistent with the findings that the neutralizing activity elicited by two-dose vaccination against Omicron is low. Nevertheless, the third booster dose significantly increased the Omicron neutralizing antibody titers, which is possible because the frequency of Omicron RBD-binding memory B cells significantly increased after the third dose (Goel et al., 2022; Muecksch et al., 2022). This increase was related to the continued expansion of existing memory B cell clones that were present after the second dose, as well as the appearance of new clones induced by the third dose. The existing resting RBD-binding IgG + memory B cells are steadily increasing the B cell receptor (BCR) breadth over time, which may enable the production of more broadly neutralizing antibodies (Kotaki et al., 2022). The newly produced memory B cell clones after the third dose targeted more conserved epitopes on Omicron spike protein, promoting the neutralizing antibodies encoded by these cells exhibited significantly increased breadth and potency (Garcia-Beltran et al., 2022; Muecksch et al., 2022). In addition to memory B cells, the long-lived plasma cells in the bone marrow also accumulated a high amount of somatic hypermutations, contributing to enhanced antibody affinity against Omicron (Kim et al., 2022).

Therefore, the immune evasion of Omicron to memory B cells is incomplete. Despite the Omicron variant exhibiting remarkable antibody escape, the memory B cell repertoire continues to evolve and can provide some protection in vaccinated individuals.

4.2. The preserved Omicron spike-specific T cell response

T cell response, particularly CD8⁺ T cell responses, is critical in preventing severe COVID-19 outcomes (Gao et al., 2021; Chandrashekar et al., 2022). Studies have shown that the case fatality ratio of Omicron infected patients with two-dose full vaccination was far lower than those with partial vaccination (Tan et al., 2020; He et al., 2022). Considering the neutralizing antibodies induced by two-dose vaccination having poor activity against Omicron, this protection against severe disease may be provided by T cells.

Many studies have shown that CD4⁺ and CD8⁺ T cell immunity induced by current vaccines is highly conserved to the original Omicron variants (Naranbhai et al., 2022; Liu et al., 2022; Mazzoni et al., 2022). No significant differences were found between the frequency of Omicron- and WT-specific polyfunctional CD4⁺/CD8⁺ T cells in two-dose vaccinated subjects (GeurtsvanKessel et al., 2022; Keeton et al., 2022). Even in six months post-vaccination, 84% (CD4⁺) and 85% (CD8⁺) of memory T cell responses preserved recognition of Omicron, demonstrating the long-term persistence of cross-reactive T cells (Tarke et al., 2022). Not only that, T cell repertoire analysis revealed that CD4⁺ and CD8⁺ T cells can recognize the majority of Omicron spike epitopes, with an average epitope preservation rate of 80%–85% (Tarke et al., 2022). After the third booster dose, the frequency of Omicron-specific CD4⁺ and CD8⁺ T cell responses

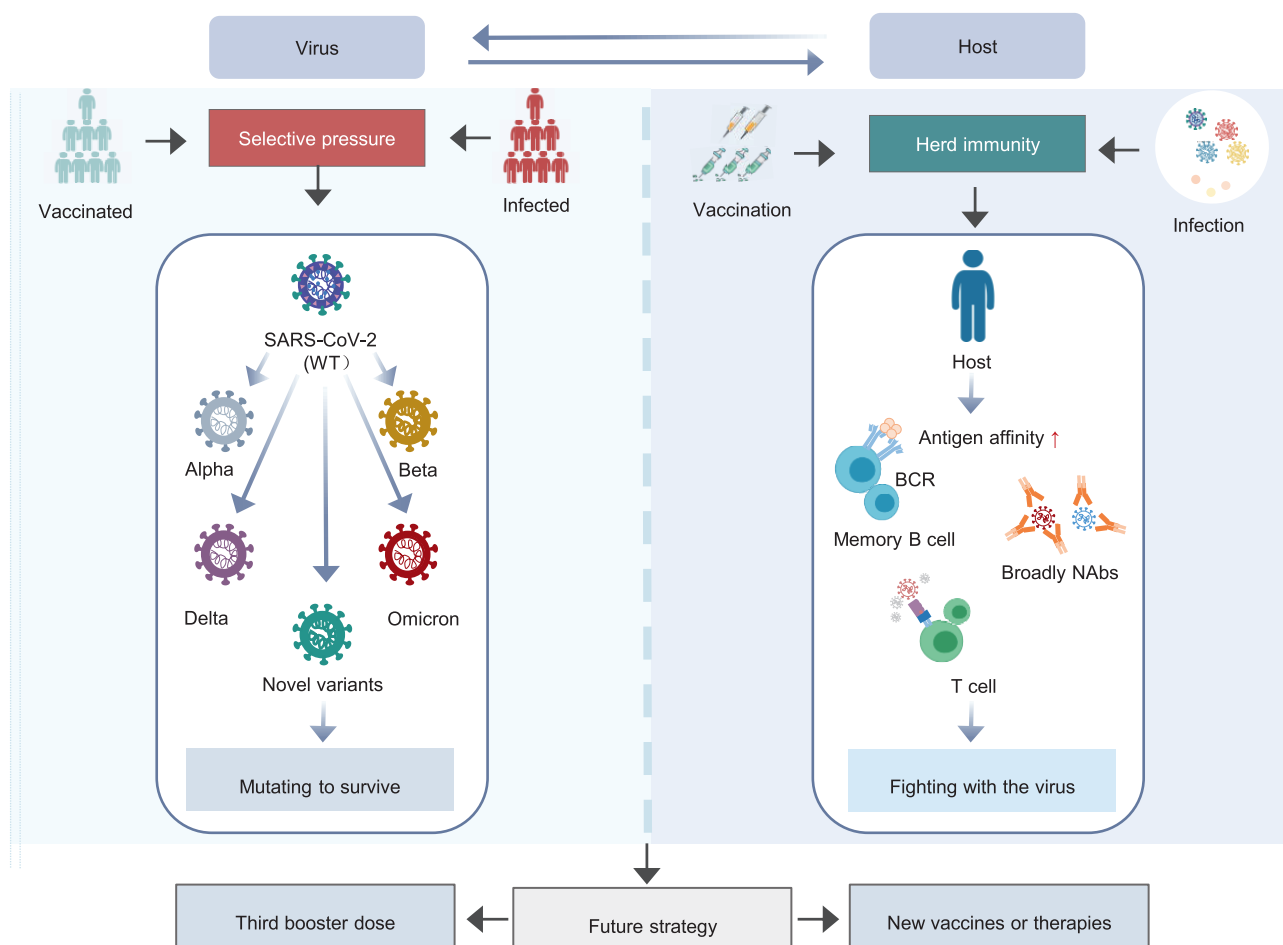


Fig. 3. The interrelation between SARS-CoV-2 virus and host immunity. WT, wild-type; NABs, neutralizing antibodies.

remained stable or further increased in both healthy vaccinees and convalescents (Keeton et al., 2022; GeurtsvanKessel et al., 2022).

In contrast to antibody response, Omicron can hardly escape from T cell responses. One possible explanation is that T cells in each individual recognize a different fragment of the virus, moreover, T cell epitopes are distributed among structural and nonstructural proteins (Choi et al., 2022). These findings suggested that SARS-CoV-2 spike-specific T cell responses against Omicron were largely preserved, which could provide robust second-level protection against severe disease under the circumstances of substantially reduced neutralizing antibodies. The development of second-generation SARS-CoV-2 vaccines can fully utilize the role of T cells, including adding other immunogens such as SARS-CoV-2 nucleocapsid proteins, membrane proteins, or antigens in conserved regions to help develop pan-beta coronavirus vaccines.

5. Conclusions

Over the past few months, the original Omicron variants have further evolved into multiple sub-lineages. Compared with previous VOCs, SARS-CoV-2 Omicron and its sub-lineages significantly enhanced their transmissibility and immune evasion. This may be a consequence of selective pressures arising from herd immunity due to mass vaccination and Omicron infection. The virus constantly evolves and mutates to survive, creating strains with higher affinity and stronger evasion capacity. Under the circumstances, being vaccinated with a third booster dose is extremely important. In addition to increasing the neutralizing antibody titers against various Omicron sub-lineages, the booster vaccine dose also improved the function of B cells and T cells to reduce the clinical severity of Omicron infection. Hence, active vaccination is essential regardless of a history of

SARS-CoV-2 infection. With Omicron dominating COVID-19, strategies for developing Omicron-specific vaccines and novel therapeutics are still worth exploring (Fig. 3).

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.virs.2022.11.007>.

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