Research Article

Omicron Variant Could be an Antigenic Shift of SARS-CoV-2

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The COVID-19 pandemic has led to the emergence of various variants and recombinants since the arrival of the D614G recombinant in 2020. Alpha, Beta, Gamma, Delta, and Omicron variants of concern are ascribed to predominate, increasing the cases and hospitalizations. VOCs have already created a significant impact on people's lives, livelihoods, mental health, businesses, economies, etc., all around the world. The prime boosting concept emerged after observing the lowered vaccine efficacy due to the occurrence of antibody-resistant RBD mutations. Omicron has evolved separately from subvariant BA.1 and continues to provide antibody resistance due to heavy mutations in RBD, NTD, and S1/S2 regions of the virus, especially in the case of vaccination and breakthrough infections. The overall mutational landscape of Omicron shows a drift from other variants, lowering potency. The collective information, in this short review, focuses on the mutations affecting antibody efficacy, while also explaining some limitations that prompt further research studies.

Introduction

This is the fourth year since the COVID-19 pandemic erupted, which continues to be fueled by the emergence of many variants and recombinants around different geographies of the world. Pandemic fatigue has created sociological, economic, and psychological repercussions. Mutants and recombinants of the virus are more transmissible and virulent, posing a challenge to existing treatment modalities. Vaccines are indeed important prophylactic tools to control the spread of the virus in the population. The Delta variant was reported to be 97-100% more virulent than the original Wuhan strain due to mutations in the RBD region, which lowered the immune response produced through vaccination in a short time. Therefore, the concept of a prime-boosting vaccine strategy for COVID-19 has been applied to achieve an adequate immune response (Chakarabaraty et al. 2022, Planas et al. 2021, and Sasishekharan et al. 2021).

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Vaccine efficacy of Adenovirus-vectored vaccines (Oxford, AstraZeneca, and Serum Institute), inactivated vaccines, and mRNA vaccines showed a 1.4 to 9-fold decline in the case of the delta variant compared to alpha and WT/D614G. Furthermore, the Coronavac (Sinovac) vaccine also decreased antibody titers by 17-22 times (Chavda et al. 2022). Limited protection was achieved with primary vaccination (two doses) of ChAdOx1 nCoV-19 or BNT162b2 vaccines, which improved neutralization activity by administering the third dose as a booster with BNT162b2 or mRNA-1273, discovered to overcome waning immunity over time. The increasing dominance of the Omicron variant and its frequent subvariants allowed for alleviated full protection against symptomatic infection, hence shortening the time interval for booster doses by 3 months, yielding satisfactory results. A higher level of variant detection, testing, and sequencing activity has truly enabled rapid response vaccination efforts, increasing effectiveness against the emerging Omicron and even its predecessor variants. It is imperative to find the right combination of sequenced inducible variants that can provide sustainable and long-lasting immunity, at least for one year (Ochoa-Azze et al. 2022, Andrew et al. 2022).

The variants of concern are depicted in the figure. The subvariants of Omicron emerged from subvariant BA.1 and were classified into BA.1.1 (less transmissible than processor BA.1), BA.2 (with 9 spike mutations and more contagious – subdivided into BA.2.74, BA.2.75, and BA.2.76), BA.3 (less transmissible), BA.4 (evolved from BA.2 and less transmissible than BA.2), and BA.5 (evolved from BA.2 and more transmissible than BA.2 and BA.4). Currently, BF.7 is prevalent (Chavda et al. 2023, Dhawan et al. 2022). Risks of reinfection with BA.2 are far greater than BA.1 (https://www.who.int/news/item/22-02-2022-statement-on-omicron-sublineage-ba.2). BA5 and BA 2.75 further diversified into several other variants: BA.4.6, BF.7, BQ.1, and BQ 1.1 (originated from BA 5) and BA 2.75.2 (originated from BA.2.75) (Lacobucci G 2022, Qu et al., 2022).

XBB* recombinant, derived from BA.2.10.1 and BA.2.75, is capable of infecting individuals. BQ.1* sub-lineage of BA5 (Mutations K444T, and N460K). BQ1.1 sub-lineage has an antigenic site with an additional mutation (R 346 T). Their transmissibility pattern, immune escape status, and impact of vaccination are yet to be revealed (https://www.who.int/news/item/27-10-2022-tag-ve-statement-on-omicron-sublineages-bq.1-and-xbb).

XBB.1.5 is the descendant of the XBB offshoot from BA.2 and is nicknamed ‘Kraken,’ described as more transmissible and contagious (Katella K 2023). The main concern is for the older and immunocompromised, who can get infected and become resistant to drugs, which could lead to not only long COVID or post-acute COVID syndrome but also the birth of more contagious variants. The Omicron

variant appears to have evolved separately from all the previous mutational variants. Therefore, Omicron may have the potential to lead the pandemic by generating more and more resistant strains/variants against vaccine-driven immunity. Variants' emergence resulted from the possible antigenic drift of the early strain to help adapt them for more transmission during the evolutionary process (Dhawan et al. 2022).

Theories to support Omicron's birth are explained as follows: Intra-host environment in the immunocompromised host and a group of the population, or it has evolved from mice and jumped back to humans, conferring reverse zoonosis (Dhawan et al. 2022).

Neutralization Resistant Mutations

Despite the availability of advanced and next-generation vaccines, therapeutics, and diagnostics, the new variants easily sneaked their way to spread in the population more vigorously than ever. It has rendered debilitating effects on a) vaccine efficacy with a less protective immunogenic response, b) controlled transmissibility, and c) diagnostic accuracy (failure to detect the S-antigen) during the arrival of a new variant after Alpha (Dubey et al., 2022). Therefore, the most significant features of Omicron were immune escape to vaccine-generated nAbs (evolutionary process), enhanced binding of S-protein to ACE-2, and effective proteolytic priming via TMPRSS2 (Dhawan et al., 2022).

Most of the mutations in the RBD region are reported to increase transmissibility and infection rate. The NTD region is also linked to increased transmissibility and virus binding affinity, S1/S2 increase infectiousness and transmissibility, and S2 has immunogenic response development significance (Dhawan et al., 2022). Some known mutations, such as D614G (B.1), N501Y, E484K (Eek), K 417, and L452R, allow the virus to bind more tightly to human cells and help spread the virus faster than ever. Kumar et al. 2022 predicted mutations such as Y505H, N786K, T95I, N211I, N856K, and V213R through computational analysis could increase pathogenicity by imposing enhanced positive electrostatic effects to increase the interactions between RBD and hACE-2 for further transmission as compared to the wild type.

The eight significant mutations D614G, E484A, N501Y, Q493K, K417N, S477N, Y505H, and G496S were involved in antibody escape, infectivity quotient, stabilizing (increased), and destabilizing (decreased) molecular flexibility of the S-glycoprotein to interact with ACE-2. These mutations in the RBD region were investigated via $\Delta\Delta G$ score for their stability potential. D614G, Q493K, and S477N mutations are stable with molecular flexibility with S-glycoprotein to interact with ACE-2, enhancing the virulent nature of the variant (Chakraborty et al. 2022). The new evidence has shown that substitutions of R346K

(BA.1.1), L452, and F486V mutations exert more immunological pressure, bringing about immune evasion (Dhawan et al. 2022). A mutation like T478K is close to the mutation E484K involved in antibody escape in the epitope region. This variant is resistant to bamlanivimab, anti-RBD, and anti-NTD monoclonal antibodies (Planas et al. 2022). D614G is the first noticed mutation reported during SARS-CoV-1 and SARS-CoV-2, which is the selection for fitness that assists in transmission. Where S-glycoprotein clearly affects the cleavage pattern of its protein responsible for causing infection and reinfection (Kaushal et al. 2020, Qu et al. 2022).

The important mutations of the Omicron subvariant, such as R436S, K444T, F486S, and D1199N (HR2 region of S2), are involved in antibody recognition with altered spike position on the cellular membrane (Structural Modeling Study). Mutations like N460K, N658S, F486S, and D1199N determine the fusogenicity and S processing of Omicron subvariants. While R346T, K444T, N460K, and F486S mutations represent key neutralization escape positions (Qu et al. 2022). The emerging Omicron subvariants were tested against the sera obtained from vaccinated (three doses) healthcare workers, hospitalized BA.1-wave patients, and BA.5-wave patients. The subvariants BQ.1 and BQ.1.1, harboring N460K, R346T, and K444T mutations, and BA.2.75.2 with F486S mutations showed enhanced neutralization resistance. The N460K mutation in BQ.1 and BQ.1.1 exhibited enhanced fusogenicity and S-processing. On the other hand, the F486S mutation may enhance the fusogenicity and S processing, while the D1199N mutation interestingly reduced the pattern (Qu et al. 2022). Numerous sublineages of the Omicron variant of SARS-CoV-2 have been reported to be resistant to vaccination or infection-induced immunity and evading specific antibody reactions since November 2021. The immune evasion was recovered by the booster dose in six months (Evans et al. 2022, Kurhade et al. 2022, Qu et al. 2022, Qu et al. 2022, Gruell et al. 2022, Xia H. et al. 2022). Omicron BA.1 has been experimented in K18-hACE-2 mice and discovered to be less controlled by mRNA vaccination (Barut et al. 2022).

All the sub-lineages of Omicron have significantly challenged the efficacies of vaccines and shown a substantial decline in neutralizing antibodies against both BA.1, R346K, and BA.2. BA.2 also exhibited marked resistance against most monoclonals, including sotrovimab (Iketani et al., 2022).

Omicron variants have shown reduced infection efficiency in lung-derived CaLu-3 cells. Lung tropism was established as less likely by Omicron, due to the shift of TMPRSS2-mediated plasma membrane towards cathepsin B/L-mediated endosomal entry (Qu P et al., 2022, Barut et al., 2022, Meng B et al., 2022, Shuai H. et al., 2022). Vaccine boosters or breakthrough infections can produce a potent neutralizing response to combat Omicron infection. Moreover, the breakthrough infection elicits a better response

locally in the nasal cavity to control virus transmission. S2X324, a potent neutralizing antibody, provides effectiveness against all the variants of SARS-CoV-2 and is recommended for pan-variant potency (Park et al. 2022).

Polyclonal sera tested for serum neutralization were obtained from 5 cohorts of people vaccinated with 3 shots of WT (wild type) or 4 shots of WT bivalent vaccine (WT and BA.5), 3 shots of COVID-19 vaccine plus bivalent vaccine, and in people who had BA.2 & BA.4 or BA.5 breakthrough infection after vaccination. BA.2 and BA.4/5 revealed high resistance to serum neutralization compared to D614G against all the polyclonals. However, the neutralization titer decreased in the case of BQ.1, BQ.1.1, XBB, and XBB.1 compared to D614G. Polyclonals from BA.2 and BA.4/5 breakthrough cohorts responded well against the new emerging variants in terms of antibody induction. One limitation of the study is that the T-cell response hasn't been considered to understand the better immune response. The variants BQ.1 and BQ 1.1 were also resistant to class I and class IV epitope-mapped monoclonal antibodies like tixagevimab, bebtelovimab, sotrovimab, cilgavimab, nonRBD mapped, and NTD-SD2 monoclonal antibodies. The loss of neutralization in RBD class I and NTDs was due to the N460K mutation, and RBD class II monoclonal efficacy was reduced due to mutations R346T and K444T. Evidently, there was no greater affinity detected towards ACE-2 (Wang et al. 2023). Since these variants are predominantly present around the world and are distantly placed in the phylogenetic tree, as shown in the figure of sarbeco viruses, revealing an antigenic drift would be alarming to evade immunity frequently, despite having low hospitalization and reducing the risk of post-acute sequelae of COVID-19 or long COVID (Wang et al. 2023).

The neutralizing antibody level was reported as weakest in unvaccinated, convalescent, and naïve individuals who have received two doses of mRNA vaccine. Therefore, two doses of the vaccine were not sufficient to build the effective humoral response that was regained during reinfection or with a booster dose, still providing short-term protection. Interestingly, higher titers in convalescent vaccinated individuals were noticed when having mRNA-1273 compared to the BNT-162b2 vaccine. However, it was not clear which antigenic epitope the subjects' antibodies were involved in for the residual neutralization of Omicron (Correnol et al. 2022).

The vaccine efficacy to prevent symptomatic infection of Omicron by 73% for vaccinated and boosted individuals and 35% only for vaccinated individuals was suggestive of the vaccine compromise to provide enough protection against the highly transmissible Omicron (Cele 2022). Breakthrough infection, in vaccinated and convalescent individuals, has shown the pre-existing cellular and innate immunity, and non-neutralizing antibodies described to protect from severe disease. ChAdOx1 nCoV-19 (AZ) vaccine

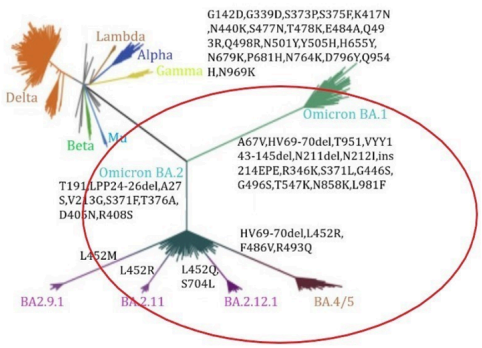
efficacy remained at 66.5% after two doses. However, the prospects of primary immunization against the symptomatic disease of COVID-19 Omicron remain limited (Chavda et al., 2022). This can be defined as antigenic drift.

Anti-RBD IgM (297 mAbs) protects against pseudovirus beta and Omicron BA.1. It was also effective against SARS-CoV-2 WA 1 when the infection was given to epithelial cells in vitro (Hale M. et al., 2022). A cocktail of monoclonal antibodies (297) used with Regeneron REGN 10987/10933 mAbs didn't neutralize Omicron. However, mAbs 297 possess neutralizing activity against Omicron BA.1 and BA.2 but is eventually reduced in the case of BA.4 and BA.5. Monoclonal antibodies are effective only if the prevalence of the respective variant is active (Huo et al. 2023). Therefore, it gives clues to develop pan-variant monoclonal antibodies that can be potent against RBD, NTD, and S2 conserved regions to boost immunity in the human body. There are 11 relevant mutations: 6 deletions and 1 insertion with N211∆, ins 214 EPE are unique in the NTD region. 15 mutations G339D, S371C, S373P & S375F are unique mutations responsible for antibody evasion in the RBD region. Mutations T547K and P681H modulate the cleavage S1/S2 in the RBD-S1/S2 site. Omicron robustly binds to orthologous ACE-2 from different animals for efficient entry into cells. Therefore, effective cell invasion is indicative of its zoonotic potential. Interestingly, the spike was inhibited by soluble ACE-2 but resistant against monoclonal antibodies bamlanivimab, etesevimab, imdevimab, and casirivimab (selective against RBD and NTD regions) that inhibit the spike entry in a concentration-dependent manner. A cocktail of bamlanivimab & etesevimab was inefficient to stop pseudovirus replication (Omicron B.1.1.529). Similarly, casirivimab and imdevimab were also inefficient. But sotrovimab was less inhibitory (Hoffmann et al. 2022).

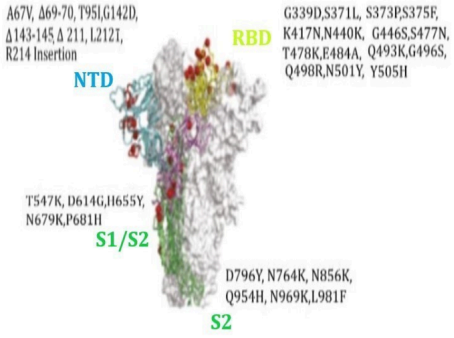
1. Most Prevalent VOCs Of SARSCoV-2

Name of VOC	Lineage Status	Average Number of Spike Mutations	First Identified
Alpha	B.1.1.7	29.7	UK in late 2020
Beta	B.1.351	28.4	South Africa in late 2020
Gamma	P.1	29.1	Brazil in late 2020
Delta	B.1.617.2	35.4	India in late 2020 became dominant worldwide
Omicron	B.1.1529	>50	South Africa in late 2021 rapidly disseminated worldwide

2. Evolutionaly landscape for SARSCoV-2 VOCs and Divergence of Omicron VOC



3.Notable Mutations on the Omicron Spike Region



4. Ab-resitant Mutations

Neutralization Resistant Mutations of Omicron	References
D614G, E484A, N501Y, Q493K, K417N, S477N, Y505H, G496S	Chakaraborty et al., 2022
D614G, T478K, E484K, E484A, N501Y, Q493K, K417N, S477N, Y505H, G496S	Planas et al., 2021
R346T, K444T, N460K, and F486S	Qu et al., 2022
S371F, S373P, S375F, and D614G	Park et al., 2022
Q183E, K444T, V445P, F490S, R346T, N460K, and F486S	Wang et al., 2023
K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, and Y505H	Hoffmann et al., 2022
R346K, S371L, N440K, G446S and Q493R	Liu et al.,2022
Y505H, N786K, T95I, N211I, N856K, and V213R	Kumar S et al., 2022
Q493R, N501Y, S371L, S373P, S375F, Q498R, and T478K	Dhawan M et al 2022

Figure 1. 1. Origin of the most prevalent VOCs (Alpha, Beta, Gamma, Delta, and Omicron) in different countries. Average number of mutations (Sun et al. 2021) and greater transmissibility (Chavda et al. 2023). 2. Omicron and its sublineages clearly diverged from their predecessors. Caption (https://doi.org/10.1016/j.cell.2022.09.018). 3. The most notable mutations on the Omicron spike. Caption (https://www.nature.com/articles/s41586-022-04411-y). 4. The reported mutations being resistant to neutralization by antibodies (Monoclonal antibodies, Convalescent Sera, and Sera from vaccinated individuals).

Mutations H655Y and N679K near the furin cleavage site can make it more contagious, blocking the T-cell response and increasing the chances of re-infection in the case of BA.5. Tomato Flu or HFMD (Hand, and Foot-Mouth Disease) outbreak caused by coxsackievirus A-16 virus spread frequently in COVID-19 and monkeypox patients, producing more complications in human health during 2021-2022 in India (Chavda et al., 2022).

Liu et al. revealed that the combination of all four monoclonals used for clinical use has lost their potency. Omicron might be a couple of mutations away from becoming pan-resistant to all currently available

antibodies (Liu et al. 2022).

New approaches

Nanobodies are under clinical investigation in medicine for cancer and various infectious diseases. Caplacizumab (bivalent nanobodies) is the first authorized treatment by the EU and FDA for patients with thrombotic thrombocytopenic purpura and thrombosis. Often, biparatropic nanobodies offer the best alternative to current monoclonals. Nanobodies can be nebulized to achieve better potency in the lungs than intravenous administrations. Specific neutralizing nanobodies bind to the RBD of the virus. At approximately 22 dissociation constants, these nanomolecules can neutralize the virus in plaque reduction assays. The biparatropic nanobodies were more efficient and effective against SARS-CoV-2, irrespective of known virulent mutations. They induce the premature transition of flexible spike conformation to irreversible post-fusion conformation, inhibiting the attachment to ACE-2 (Sasishekharan 2021). The next-generation vaccines introduced orally or intranasally in hamsters have shown a robust mucosal antibody response against SARS-CoV-2. This strategy will be applied to reduce the transmission of the virus during outbreaks (Mao et al. 2022, Langel et al. 2022).

The spike of the Omicron variant harnesses the richness in mutations, giving a direct indication of immune evasion, monoclonal antibody resistance, and higher transmissibility (Hoffmann et al. 2022). This variant showed the ability to reinfect convalescent and vaccinated individuals, evidently associated with waning immunity. However, beta and delta variants rarely cause reinfection, given the fact that Omicron's emergence indicated the need for significant upgrades in vaccine and monoclonal antibody developments. A large body of evidence revealed that Omicron harbors the capacity for immune evasion on a population-wide scale, unlike beta and delta variants.

A stable nanoparticle-based platform encapsulating monomeric forms of RBD amino acids was developed for future vaccines. mRBD is encapsulated with Myxomonas Xanthus displaying the receptor-binding derivatives (Khaleeq et al. 2023), providing long-term thermostability. It elicited ~100-fold immune response after one shot of immunization, which was increased approximately 42 times after a booster against the pseudovirus challenges of all variants. These types of nano-based platforms could considerably reduce viral loads and associated lung pathologies (Khaleeq et al., 2023).

The FINLAY-FR-1A vaccine, a recombinant protein and dimer of RBD (with Cys5p8 to Cys 538 disulfide bridge) 319-541 sequence obtained from CHO cells, produced >31 times anti-RBD antibodies against alpha, beta, and delta VOCs in clinical trials (Chavda VP et al. 2022). In recent studies, the monoclonal antibodies

appeared to bind against the antigenic determinants outside of the RBD motif – site IV-V, and the rare antibodies sites I-II partially overlap the RNB also involved to some extent (Liu L. et al., 2022, and Cameron E et al., 2021).

There is an utmost need for the development of new methods for virus detection, including regular surveillance linked to the waning immunity phenomenon, to measure vaccine-driven immunity and increasing risks of re-infections. These are important tools to work on pandemic preparedness (Pulliam et al. 2021).

Discussion and Conclusion

The protection in boosted individuals increased by 75%, but the long-lasting protection was not verified at that time. NAb binding was preserved in vaccinated, convalescent vaccinated, and boosted individuals against NTD, RBD, and other spike-specific regions. Most of the antibodies cross-reacted with the other specific spike regions, considered as the conserved region reacting to the S2 subunit of Omicron (Correnol et al. 2022). The non-neutralizing Abs have attained the binding capacity in cell culture that may contribute to establishing protection against viral infections. In connection with T-cell-based immunity, the non-neutralizing Abs can target the S2 domain along with RBD and NTD. The cross-reactivity of Abs can attach to S2 or any conserved region. mRNA induces a permanent B-cell germinal cell response. In boosted individuals, the germinal B-cell response and plasmablast activity that induced S-binding were sustained for 12 weeks (Turner et al. 2021). The cognate function of Abs through B-cells is still present even if it provides lower activity to RBD and NTD mutations. B-cell activity is also recognized during original or variant infection or vaccinations, producing a strong plasmablast response leading to control virus spread. Generally, the antigenic proteins can enter lymph nodes to engage the germinal cells producing Abs via affinity maturation. Moreover, Abs can also protect Fc-mediated effector function even if the actual neutralization activity is reduced, as reported in influenza. Broadly neutralizing MAbs against the stalk region of hemagglutinin interact through Fc (FcγRs), conferring protection against the lethal challenge of the H1N1 strain of influenza (DiLillo et al. 2014). However, in normal practice, the actual titre of Ab reactivity directly correlates with the conferred protection against virus infection.

Silent polymorphism and synonymous mutations don't affect the amino acid change but can contribute to the transmissibility and infectivity of the phenotype. Low 5' stability in synonymous changes may cause instability in mRNA, therefore affecting the translation mechanism and resulting in lowering or increasing severity risks during infection. tRNA in low abundance can enhance translation in rich

conditions. Any process involved in a change in translational capacity leads to the formation of a changed protein, translational accuracy, and changes in co-translational protein folding (Dhawan et al. 2022).

Regular environmental surveillance is needed to avoid the emergence of new variants and recombinants from unknown origins to stop their propagation in populations, creating havoc. Therefore, it warrants more research to map the trajectories of virus resurgence and monitor their biological functionality, which could help guide the preparation of effective medicines. Hence, the new challenge could be controlled easily to become a pandemic.

Sarbecovirus monoclonal antibodies (including sotrovimab 2, S2X2593, and S2H974) and broadly neutralizing antibodies are capable of recognizing the antigenic sites outside the receptor-binding motif. They play a key role in neutralizing omicron, despite the observation of antigenic shift in this particular strain, which may pave the way for dealing with the ongoing pandemic and future zoonotic spillovers (Cameroni E et al. 2021). Various recombinants can be formed during infection, especially in immunocompromised hosts, which can become a threat to the resurgence of virulent strains. Continuous environmental surveillance of emerging variants from unknown origins and growing trends of Nab evasion and their biological activities for vaccine candidate preparation (pan-variant vaccine) (Dhawan et al. 2022), alongside the preparation of its evolutionary trajectory (Sun et al. 2022), pandemic preparedness programs, and associated policies, education for the general population to avoid complacency in following containment measures, are significant parameters to cease the transmission and emergence of new outbreaks on time.

Reassortment in the virus can bring about drastic changes in the virus that confer the phenotype change and is often denoted as antigenic shift. A typical example is the influenza H1N1 outbreak in 2009, which was a result of antigenic shift and reassortment of antigens among avian, human, and swine viruses (Smith et al. 2009).

Most of the studies were conducted using pseudovirus instead of the original omicron strain, and the absence of an analysis of the actual T-cell response could be considered a limitation. Furthermore, heterologous immunity with AZ/BNT might provide a better response, along with the implementation of public health measures like face masks and social distancing, etc. (Hoffmann et al. 2022).

The booster dose had significantly improved the humoral response against omicron, which was necessary to counteract virus transmission. An update of pharmacopeia regarding monoclonal and vaccine effects is also required. The reduced and impaired activity of serum against omicron requires

boosters in a short period to maintain the protective level of neutralizing antibodies (Edara VV et al., 2022).

Smallpox is the only example of vaccine-mediated eradication of the disease in humans, achieved through massive global initiatives and efforts with high immunization coverage. It can be expected to establish sustained containment measures that are required for effective vaccine and infection control surveillance, as well as rapid molecular diagnostics (using the current version of the isolated variant through active surveillance). It is worth noting that virus elimination strategies are designed, taking into account the example of polio control failure, even due to the lack of an animal reservoir (Telenti et al. 2021).

GISAID data showed that Omicron is different from other VOCs. This makes the monophyletic group of Omicron might be aligned with the gamma variant. This divergence of omicron supports the hypothesis that it could have evolved from animals, after attaining a high number of mutations in the spike, it has drifted back to humans from animals (reverse zoonosis) (Sun Y. et al., 2021).

In conclusion, it is fair to say that the emergence of Omicron has significantly reduced hospitalizations with less severe clinical presentations compared to other VOCs, despite increasing the inefficiency of therapeutics for clinical use. Gene sequencing and genomics platforms are still under standardization to bring robust outcomes for many diagnostic and therapeutic platforms, which may warrant further research in these portfolios.

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