Research Article

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

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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 big impact on people's lives, livelihoods, mental health, businesses & economies, etc. all around the world. The prime boosting concept emerged seeing the lowered vaccine efficacy due to the occurrence of Ab-resistant RBD mutations. Omicron has evolved separately from subvariant BA.1 continuing to provide antibody resistance due to heavy mutations in RBD, NTD, and S1 /S2 regions of the virus, especially in case of vaccination and breakthrough infections. The overall mutational landscape of Omicron showed a drift from other variants lowering potency. The collective information, in this short review, is on the mutations affecting antibody efficacy, besides explaining some limitations prompting further research studies.

Introduction

This is the fourth year going on since the COVID-19 pandemic erupted which is continued by the emergence of many variants and recombinants from time to time around the different geographies of the world. Pandemic fatigue has created sociological, economical, and psychological repercussions. Mutants and recombinants of the virus are more transmissible and virulent creating a challenge for existing treatment modalities. Vaccines are indeed important prophylactic tools to control the spread of the virus in the population. Delta variant was reported to be 97-100% more virulent than the original Wuhan strain due to the mutations in RBD-region lowered immune response produced through vaccination in a short time. Therefore, the concept of a prime-boosting vaccine strategy of COVID-19 has been applied to

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achieve an adequate immune response (Chakarabaraty et al. 2022, Planas et al. 2021, and Sasishekharan et al.2021).

Vaccine efficacy of Adenovirus vectored (Oxford, AstraZeneca, and Serum Institute), inactivated vaccines, and mRNA vaccines were shown 1.4 to 9-fold decline in the case of the delta as compared to alpha and WT/ D614G. Furthermore, the coronavac (Sinovac) also decreased the antibody titre by 17-22 times (Chavda et al. 2022). A limited protection was achieved with primary vaccination (two doses) of ChAdOx1 nCoV-19 or BNT162b2 vaccines. Which was improved on neutralization activity by administering the third dose as a booster with BNT162b2 or mRNA-1273 discovered to overcome the waning immunity over time. The increasing dominance of omicron variant and its frequent subvariants allowed alleviated full protection against the symptomatic infection, hence, shortening the time interval for booster dose by 3 months giving satisfactory results. A higher level of variants detection, testing, and sequencing activity had truly enabled the rapid response vaccination efforts, its effectiveness against the emerging omicron, and even its predecessor variants. It is imperative to find out the right combination of sequenced inducible variants which 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 to infect individuals. BQ.1* sub -lineage of BA5 (Mutations K444T, and N460K). BQ1.1 sublineage has an antigenic site with 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 descendent of the XBB. offshoot from BA.2 and nicknamed ‘Kraken’, which is 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 could develop not only long COVID or post-acute COVID syndrome, but may give birth to more contagious variants. Omicron variant appeared to be 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 the 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-Intra host environment in the immunocompromised host and a group of 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 & 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 the 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 an 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 RBD-region are reported to increase the transmissibility and infection rate. NTD- region is also linked to increased transmissibility and virus binding affinity, S1/S2 increase the infectiousness and transmissibility, S2 does have immunogenic response development significance (Dhawan et al. 2022). Some known mutations viz. D614G (B.1), N501Y, E484K (Eek), K 417, and L452R, are allowing the virus to bind more tightly to the 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 the pathogenicity by imposing the enhanced positive electrostatic effects to increase the interactions between RBD and hACE-2 for further transmission as compared to wild type.

The eight significant mutations D614G, E484A, N501Y, Q493K, K417N, S477N, Y505H, G496S were involved with Ab escape, infectivity quotient, stabilizing (increased) and destabilizing (decreased) molecular flexibility of 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 that brings out immune evasion (Dhawan et al. 2022). A mutation like T478K is close to the mutation E484K involved with antibody escape in the epitope region. This variant is resistant to bamlanivimab, anti-RBD, and anti-NTD monoclonal Abs (Planas et al. 2022). D614G is the first noticed mutation reported during SARSCoV-1 and SARSCoV-2, which is the selection for fitness assists in transmission. Where S- glycoprotein clearly affects the cleavage pattern of its protein responsible for causing infection and re-infection (Kaushal et al. 2020, Qu et al. 2022).

The important mutations of Omicron subvariant such as R436S, K444T, F486S, and D1199N (HR2 region of S2) mutation located in the HR2 region of S2--- are involved in Ab recognition with altered spike position on the cellular membrane (Structural Modelling 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 harbouring N460K, R346T, and K444T mutations and BA.2.75.2 with F486S mutations showing enhanced neutralization resistance. The N460K mutation in BQ.1 and BQ.1.1 exhibited enhanced fusogenicity and S-processing. On the other hand, F486S mutation may enhance the fusogenicity and S processing, while D1199N mutation interestingly reduced the pattern (Qu et al. 2022). Numerous sub lineages of Omicron variant of SARSCoV-2 have been reported to be resistant to vaccination or infection-induced immunity and evading the 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 etal. 2022, Gruell et al. 2022, Xia H. et al. 2022). Omicron BA.1. has been experimented in K18-hACE-2 mice 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 of 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 Ca Lu -3 cells. Lung tropism was established as less likely by Omicron, due to the shift of TMPRSS2 mediates 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 the virus transmission. S2X324 - a potent neutralizing antibody provides effectiveness against all the variants of SARSCoV-2 recommended for a pan variant potency (Park et al. 2022).

Polyclonal sera tested for serum neutralization, was obtained from 5 cohorts with people vaccinated with 3 shots of WT (wild type) / or 4 shots WT, bivalent vaccine (WT and BA.5), 3 shots of COVID-19 vaccine plus bivalent vaccine, in people had BA.2 & BA.4 or BA.5 breakthrough infection after vaccination. BA.2 and BA.4/5 revealed high resistance to serum neutralization in comparison with D614G against all the polyclonal. But the neutralization titer was decreased in the case of BQ.1, BQ.1.1, XBB, and XBB.1 in comparison to D614G. Polyclonal from BA.2 and BA.4/5 breakthrough cohorts responded well against the new emerging variants in terms of antibody induction. Limitations of the study is as the T-cell response hasn't been noticed to understand the better immune response. The variants BQ.1 and BQ 1.1 were also resistant against class I and class IV epitope-mapped monoclonal antibodies like tixagevimab, bebtelovimab, sotrovimab, cilgavimab, nonRBD mapped and NTD-SD2 monoclonals antibodies. The loss of neutralization in RBD class I and NTDs were due to N460K mutation and RBD class II monoclonal efficacy was reduced due to mutation 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 the 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 Ab level was reported weakest in unvaccinated, convalescent, and naïve individuals who have two doses of mRNA vaccine. Therefore 2 doses of vaccine were not sufficient to build the effective humoral response that was regained during reinfection or with a booster dose still providing the short time protection. Interestingly, the higher titres in convalescent vaccinated individuals were noticed having mRNA-1273 as compared to BNT-162b2 vaccine. However, It was not clear which antigenic epitope the subject's antibodies involved in the residual neutralization of omicron (Correnol et al.2022).

The vaccine efficacy to prevent the 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, have shown the pre-existing cellular and innate immunity, and non-neutralizing Abs described to protect from severe disease. ChAdOx1 nCoV-19 (AZ) vaccine efficacy

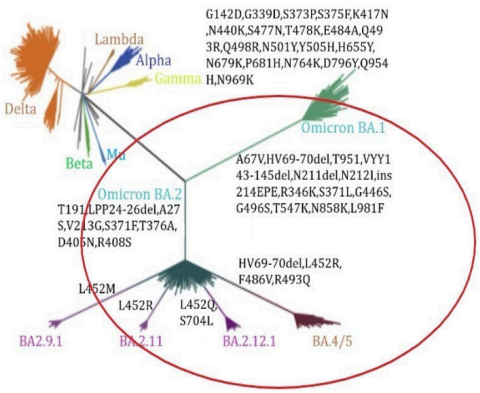
remained 66.5% after two doses. However, the prospects of primary immunization against the symptomatic disease of COVID-19 omicron remain limited (Chavda et al., 2022). This can be defined as antigenic drift.

Anti-RBD IgM (297 mAbs) protects against pseudovirus beta and Omicron BA.1. It was also effective against SARSCoV-2 WA 1 when the infection was given to epithelial cells *in-vitro* (Hale M. et al., 2022). A cocktail of monoclonal Abs 297 used with Regeneron REGN 10987/ 10933 mAbs didn't neutralize the omicron. However, MAbs 297 possesses neutralizing activity against Omicron BA.1 and BA.2, but eventually reduced in the case of BA.4 and BA.5. MAbs are effective only if the prevalence of the respective variant is active (Huo et al. 2023). Therefore, it gives the clues to develop pan variant MAbs that can be potent against RBD, NTD, and S2 conserved regions to boost immunity in the human body. 11 relevant mutations- 6 deletions and 1 insertion with N211Δ, ins 214 EPE are unique in NTD-region. 15 mutations G339D, S371C, S373P & S 375 F are unique mutations responsible for Ab evasion in RBD-region. Mutations T547 K, P681H modulate the cleavage S1/S2 in RBD-S1/S2 site. Omicron robustly bound to orthologues ACE-2 from different animals for efficient entry into cells. Therefore, the effective cell invasion is indicative of its zoonotic potential. Interestingly, the spike was inhibited by soluble ACE-2, but resistant against monoclonal Abs bamlanivimab, etesevimab, imdevimab, and casirivimab (selective against RBD and NTD regions) that inhibit the spike entry in a concentration-dependent manner. A cocktail bamlanivimab & etesevimab was inefficient to stop pseudovirus virus (Omicron B.1.1.529) replication. Similarly, casirivimab and imdevimab were inefficient too. But sotrovimab was less inhibitory (Hoffmann et al. 2022).

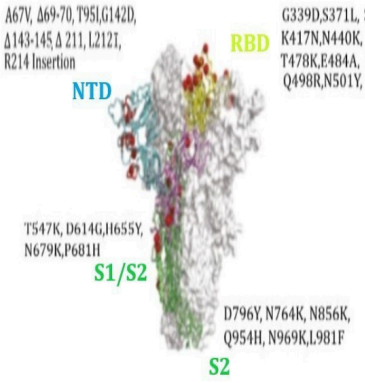
1. **Most Prevalent VOCs Of SARSCoV-2**

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) 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 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 to increasing the chances of re-infection in case of BA.5. Tomato Flue 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 to become pan resistant to all currently available antibodies (Liu et al. 2022).

New approaches

Nanobodies are under clinical medicine investigations against cancer and various infectious diseases. Caplacizumab (bivalent nanobodies) is first authorized by EU and FDA to treat patients with thrombic thrombocytopenic purpuria and thrombosis. Often biparatropic nanobodies offer the best alternative to current monoclonals. Nanobodies can be nebulized to attain the better potency in lungs than intravenous administrations. Specific neutralizing nanobodies bind to the RBD of the virus. At appx. 22 dissociation constants, these nano-molecules can neutralize the virus in plaque reduction assay. The biparatropic nanobodies were more efficient and effective against SARSCoV-2 irrespective of known virulent mutations. It induces 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 the 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).

Spike of Omicron variant harnesses the richness in mutations giving the direct indication of immune evasion, mAb resistance, and higher transmissibility (Hoffmann et al. 2022). This variant showed the ability to re-infect convalescent and vaccinated individuals, evidently associated with waning immunity. However, beta and delta variants rarely cause the re-infection given the fact that omicron emergence indicated the great antigenic shift does require upgradation in vaccine and monoclonal abs developments. A large piece of evidence revealed that omicron harbors the capacity for immune evasion population-wide, but beta and delta had not.

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) provided long-term thermostability, eliciting ~100-fold immune response after one shot of immunization that was increased approximately 42-times after 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).

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. The vaccine produced >31 times anti-RBD antibodies against alpha, beta and delta VOCs in clinical trial (Chavda VP et al. 2022). In recent studies the monoclonal antibodies were appeared to bind against the antigenic determinants outside of 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 to be linked to the waning immunity phenomenon to measure the vaccine-driven immunity and increasing risks of re-infections are the important tools to work on pandemic preparedness (Pulliam et al. 2021).

Discussion & Conclusion

The protection in boosted individuals was 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 to the other specific spike regions considered as the conserved region reacts to S2 subunit of Omicron (Correnol et al. 2022). The non-neutralizing Abs have attained the binding capacity in cell culture that may contribute towards establishing protection against viral infections. In connection with T-cell based immunity, the non-neutralizing Abs can target S2 domain along with RBD and NTD. The cross-reactivity of Abs can attach to S2 / or any conserved region. mRNA induces permanent B-cell germinal cell response. In boosted individuals, the germinal B-cell response and plasmablast activity that induced S-binding was 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 reported in influenza. Braodly neutralizing MAbs against the stalk region of hemagglutinin interacts through Fc (FcγRs) conferring protection against the lethal challenge of H1N1 strain of influenza (Dilillo et al. 2014). However, in normal practice the actual titre of Ab reactivity directly correlates to the conferred protection against the virus infection.

Silent polymorphism and synonymous mutations don't affect the amino acid change, but can contribute to the transmissibility and infectivity of 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 the translation in rich conditions. Any process involved in a change in translational capacity leads to the formation of 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 could help guide preparing 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 abs are capable to recognize 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 carve the way to dealing with ongoing pandemic and future zoonotic spillovers (Cameroni E et al. 2021). Various recombinants can be made during infection, especially in immunocompromised hosts that can become a threat to the resurgence of virulent strains. Continuous environmental surveillance of emerging variants from unknown origins & growing trends of Nabs 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 & associated policies, education to the normal population to avoid complacency in following the containment measures, are the significant parameters to cease the transmission and emergence of new outbreaks on time.

Reassortment in the virus can bring out drastic changes in the virus that confer the phenotype change is often denoted as antigenic shift. A typical example is influenza H1N1 outbreak in 2009 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 by using pseudovirus instead of the original omicron strain and the absence of analysis of actual T-cell response could be considered as the limitation. Furthermore, heterologous immunity AZ/ BNT might provide a better response along with the implementation of public health measures like face masks, social distancing, etc. (Hoffmann et al. 2022).

Booster dose had improved the humoral response against the omicron largely which was necessary to counteract the virus transmission. An update of pharmacopeia in regards to monoclonal and vaccine effects is also required. Reduced and impaired activity of serum against omicron requires boosters in a short period to maintain the protective level of Nabs (Edara VV et al., 2022).

Smallpox is the only example of vaccine mediated eradication of the disease in humans taken via massive global initiatives and efforts with high coverage of immunization in the mass. It can be expected to establish sustained containment measures that are required to be implemented for effective vaccine and infection control surveillance, and rapid molecular diagnostics (with the current version of the isolated variant through active surveillance). It is worthwhile to say that virus elimination strategies are designed considering the example of polio control failure even due to the lack of 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 gamma variant. This divergence of omicron supports the hypothesis that it could have evolved from animals, after attaining the high number of mutations in the spike it has drifted back to humans from animals (reverse zoonosis) (Sun Y. et al., 2021).

At last, it is fair to say that the emergence of Omicron has significantly reduced hospitalizations with less severe clinical presentations as compared to the 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 on these portfolios.

References

- Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, Gower C, Kall M, Groves N, O'Connell AM, Simons D, Blomquist PB et al. (2022) Covid-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant. N Engl J Med. 386:1532-1546 DOI: 10.1056/NEJMoa2119451
- Barut GT, Halwe NJ, Taddeo A, Kelly JN, Schon J, Ulrich L (2022) The spike gene is a major determinant for the SARS-CoV-2 Omicron-BA.1 phenotype. Nat Commun. 13(1):5929. doi: 10.1038/s41467-022-33632-y. https://pubmed.ncbi.nlm.nih.gov/36207334/
- Cameroni E, Bowen JE, Rosen LE, Saliba C, Zepeda SK, Culap K, Pinto D, VanBlargan LA, Marco AD, di Iulio J, Zatta F, et al. (2021) Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic

shift. Nature. 602(7898):664-670. doi: 10.1038/s41586-021-04386-2

- Cele S, Jackson L, Khoury DS, Khan K, Moyo-Gwete T, Tegally H, San JE et al. (2022) Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization. Nature. 602. https://doi.org/10.1038/s41586-021-04387-1
- Chakraborty C, Bhattacharya M, Sharma AR and Mallikd B (2022) Omicron (B.1.1.529) - A new heavily mutated variant: Mapped location and probable properties of its mutations with an emphasis on S-glycoprotein. Int J Biol Macromol. 219: 980–997. doi: 10.1016/j.ijbiomac.2022.07.254
- Chavda PV, Balar P, Vaghela D, Solanki HK, Vaishnav A, Hala V, and Vora A (2023) Omicron Variant of SARS-CoV-2: An Indian Perspective of Vaccination and Management. Vaccines 11(1):160 https://doi.org/10.3390/vaccines11010160
- Chavda VP, Bezbaruah R, Deka K, Nongrang L, and Kalita T (2022) The Delta and Omicron variants of SARS CoV-2: What we know so far. Vaccines 10:1926. https://doi.org/10.3390/vaccines10111926 https://www.mdpi.com/journal/vaccines
- Correnol JM, Alshammary H, Tcheou J, Singh G, Raskin AJ, Kawabata H, Sominsky LA, Clark JJ, Adelsberg DC, Bielak DA, Gonzalez-Reiche AS, Dambrauskas N, Vigdorovich V, RSP-Paris Study Group, Srivastava K, Sather DN, et al. (2022) Activity of convalescent and vaccine serum against SARS-CoV-2 Omicron. Nature 602. https://doi.org/10.1038/s41586-022-04399-5
- Dhawan M, Said ARA, Mitra S, Alhumaydhi FA, Emran TB, and Walairatana P (2022) Omicron variant (B.1.1.529) and its sublineages: What do we know so far amid the emergence of recombinant variants of SARS-CoV-2? Biomedicine & Pharmacotherapy 154: 113522 https://doi.org/10.1016/j.biopha.2022.113522
- Dilillo DJ, Tan GS, Palese P, and Ravetch JV (2014) Broadly neutralizing hemagglutinin stalk-specific antibodies require FcγR interactions for the protection against influenza virus in vivo. Nat. Med. 20: 143-151. doi: 10.1038/nm.3443
- Dubey A, Choudhary S, Kumar P, and Tomar S (2022) Emerging SARS-CoV-2 Variants: Genetic Variability and Clinical Implications. Current Microbiology 79: 20 https://link.springer.com/article/10.1007/s00284-021-02724-1
- Edara VV, Manning KE, Ellis M, Moore KM, Foster SL, Floyd K, Davis-Gardner ME, Mantus G, Nyhoff LE, Bechnak S, Alaaeddine G, Naji A, Samaha H, Lee M, Bristow L, Gagne M, Roberts-Torres J, Henry AR, Godbole S, Grakoui A, Saxton M, Piantadosi A, Waggorner JJ, Douek DC (2022) mRNA-1273 and BNT162b2 mRNA vaccines have reduced neutralizing activity against the SARS-CoV-2 omicron variant. Cell Reports Medicine 3

- Evans JP, Zeng C, Qu P, Faraone J, Zheng YM, Carlin C, Bednash JS, Zhou T et al. (2022). Neutralization of SARS-CoV-2 Omicron sub-lineages BA.1, BA.1.1, and BA.2. Cell Host Microbe. 30(8):1093-1102.e3. doi: 10.1016/j.chom.2022.04.014 https://pubmed.ncbi.nlm.nih.gov/35526534/
- Gruell H, Vanshylla K, Tober-Lau P, Hillus D, Schommers P, Lehmann C, Kurth F, Sander LE, Klein F (2022) mRNA booster immunization elicits potent neutralizing serum activity against the SARS-CoV-2 Omicron variant. Nat Med. 28(3): 477–480. doi: 10.1038/s41591-021-01676-0 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8767537/
- Hale M, Netland J, Chen Y, Thouvenel CD, Smith KN, Rich LM, Vanderwal ER et al. (2022) IgM antibodies derived from memory B cells are potent cross-variant neutralizers of SARS-CoV-2. J Exp Med. 219(9): e20220849. doi: 10.1084/jem.20220849 https://pubmed.ncbi.nlm.nih.gov/35104837/
- Hoffmann M, Kru ger N, Schulz S, Cossmann A, Rocha C, Kempf A, Nehlmeier I, Graichen L, Moldenhauer A-S, Winkler M, Lier M, Dopfer-Jablonka A, Ja-ck HM, Behrens GMN, and Po-hlmann S (2022) The Omicron variant is highly resistant against antibody-mediated neutralization: Implications for control of the COVID-19 pandemic. Cell 185:447–456
- Huo L, Hsiang T-Y, Dalmat RR, Ireton R, Morton JF, Stokes C, Netland J, Hale M, Thouvenel C et al. (2023) Dynamics of SARS-CoV-2 VOC Neutralization and Novel mAb Reveal Protection against Omicron. Viruses 15:530. https://doi.org/10.3390/v15020530
- Iketani S, Liu L, Guo Y, Liu L, Chan JFW, Huang Y, Wang M et al. (2022) Antibody evasion properties of SARS-CoV-2 Omicron sublineages. Nature 604(7906):553-556. doi: 10.1038/s41586-022-04594-4 https://pubmed.ncbi.nlm.nih.gov/35240676/
- Katella K (2023) Omicron XBB.1.5 'Kraken' Subvariant Is on the Rise: What To Know. Family Health. Yale Medicine. https://www.yalemedicine.org/
- Kaushal A (2020) mutants and Vriants of SARSCoV-2 across the globe-A comprehensive Review. Acta Scientific Microbiol 4(3):93-113.
- Khaleeq S, Sengupta N, Kumar S, Patel UR, Rajmani RS, Reddy P, Pandey S, Singh R, Dutta S, Ringe RP, Varadarajan R (2023) Neutralizing Efficacy of Encapsulin Nanoparticles against SARS-CoV2 Variants of Concern. Viruses 15(2):346; https://doi.org/10.3390/v15020346
- Kumar S., Karuppanan k., Subramaniam (2022) Omicron (BA.1) and Sub-Variants (BA.1, BA.2 and BA.3) of SARS-CoV-2 Spike Infectivity and Pathogenicity: A Comparative Sequence and Structural-based Computational Assessment. bioRxiv. doi: https://doi.org/10.1101/2022.02.11.480029
- Kurhade C, Zou J, Xia H, Cai H, Yang Q, Cutler M, Cooper D, Muik A et al. (2022) Neutralization of Omicron BA.1, BA.2, and BA.3 SARS-CoV-2 by 3 doses of BNT162b2 vaccine. Nat Commun.13: 3602. doi:

10.1038/s41467-022-30681-1 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9225806/

- Lacobucci G (2022) Covid-19: Hospital admissions rise in England as some trusts reinstate mask requirements. BMJ 379: o2440 doi: https://doi.org/10.1136/bmj.o2440 https://www.bmj.com/content/379/bmj.o2440.long
- Langel SN, Johnson S, Martinez C, Tedjakusuma SN, Peinovich N, Dora EG, Kuehl PJ, Irshad H, Barrett EG, Werts AD, Tucker SN (2022). Adenovirus type 5 SARS-CoV-2 vaccines delivered orally or intranasally reduced disease severity and transmission in a hamster model. Sci Transl Med. 14(658): eabn6868. doi: 10.1126/scitranslmed. abn6868. https://pubmed.ncbi.nlm.nih.gov/35511920/
- Liu L, Iketani S, Guo Y, Chan JFW, Wang M, Liu L, Luo Y, Chu H, Huang Y, Nair MS, Yu J, Chik KKH, Yuen TTT, To KKW, Chen H, Yin M, Sobieszczyk ME, Huang Y, Wang HH, Sheng Z, Yuen KY, Ho DD (2022) Striking antibody evasion manifested by the Omicron variant of SARS-CoV-2. Nature 602. https://doi.org/10.1038/s41586-021-04388-0
- Mao T, Israelow B, Suberi A, Zhou L, Reschke M, Pena-Hernandez MA, Dong H, Homer RJ, Saltzman WM (2022) Unadjuvanted intranasal spike vaccine booster elicits robust protective mucosal immunity against sarbecoviruses. BioRexiv Preprint: 2022. doi: https://doi.org/10.1101/2022.01.24.477597 https://www.biorxiv.org/content/10.1101/2022.01.24.477597v1
- Meng B, Abdullahi A, Ferreira IATM, Goonawardane N, Saito A, Kimura I et al. (2022) Altered TMPRSS2 usage by SARS-CoV-2 Omicron impacts infectivity and fusogenicity. Nature 603(7902):706-714. doi: 10.1038/s41586-022-04474-x
- Ochoa-Azze R, Chang-Monteagudo A, Climent-Ruiz Y, Macías-Abraham C, Valenzuela-Silva C, de los Ángeles GarcíaGarcía M, Jerez-Barceló Y, Triana-Marrero Y, Ruiz-Villegas L, Dairon Rodríguez-Prieto L et al. Safety and Immunogenicity of the FINLAY-FR-1A Vaccine in COVID-19 Convalescent Participants: An Open-Label Phase 2a and Double-Blind, Randomised, Placebo-Controlled, Phase 2b, Seamless, Clinical Trial. Lancet Respir. 10: 785–795
- Park YJ, Pinto D, Walls AC, Liu Z, Marco AD, Benigni F, Zatta F et al. (2022) Imprinted antibody responses against SARS-CoV-2 Omicron sublineages. SCIENCE 378 (6620) DOI: 10.1126/science.adc9127 https://www.science.org/doi/10.1126/science.adc9127
- Planas D, Saunders N, Maes P, Guivel-Benhassine F, Planchais C, Buchrieser J, Bolland WH, Porrot F, Staropoli I, Lemonine F, Pere H, Veyer D, Puech J, Rodary J, Baele G, et al. (2022) Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. Nature 602. https://doi.org/10.1038/s41586-021-04389-z

- Pulliam JRC, von Schalkwyk C, Govender N, von Gottberg A, Cohen C, Groome MJ, Dushoff J, Mlisana K, Moultrie H (2021) Increased risk of SARS-CoV-2 reinfection associated with emergence of Omicron in South Africa. Science 376: 6593. DOI: 10.1126/science.abn494 doi: https://doi.org/10.1101/2021.11.11.21266068
- Qu P, Evans JP, Faraone J, Zheng YM, Carlin C, Anghelina M, Stevens P et al. (2022) Distinct Neutralizing Antibody Escape of SARS-CoV-2 Omicron Subvariants BQ.1, BQ.1.1, BA.4.6, BF.7 and BA.2.75.2. Version 1. bioRxiv. Preprint. doi: 10.1101/2022.10.19.512891
- Qu P, Evans JP, Zheng YM, Carlin C, Saif LJ, Oltz EM, Xu K, Gumina RJ et al. (2022) Evasion of neutralizing antibody responses by the SARS-CoV-2 BA.2.75 variant. Cell Host Microbe. 30(11): 1518–1526.e4. doi: 10.1016/j.chom.2022.09.015
- Qu P, Faraone J, Evans J, Zou X, Zheng YM, Carlin C, Bednash JS, Lozanski G, Mallampalli RK, Saif LJ (2022) Neutralization of the SARS-CoV-2 Omicron BA.4/5 and BA.2.12.1 Subvariants. N Engl J Med. NEJMc2206725. doi: 10.1056/NEJMc2206725 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9258774/
- Sasishekharan R (2021) Preparing for future- Nanobodies for COVID-19? N Engl J Med. 384:1568-1571. DOI: 10.1056/NEJMcibr2101205 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9359758/
- Shuai H, Chan JFW, Hu B, Chai Y, Yuen TTT, Yin F, Huang X, Yoon C (2022). Attenuated replication and pathogenicity of SARS-CoV-2 B.1.1.529 Omicron. Nature 603(7902):693-699. doi: 10.1038/s41586-022-04442-5 https://pubmed.ncbi.nlm.nih.gov/35062016/
- Smith GJD, Vijaykrishna D, Bahl J, Lycett SJ, Worobey M, Pybus OG, Ma SK, Cheung CL, Raghwani J, Bhatt S, Peiris M, Guan Y, and Rambaut A (2009). Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. Nature 459:1122-1125.
- Statement of Omicron Sublineage BA.2. (https://www.who.int/news/item/22-02-2022-statement-on-omicron-sublineage-ba.2)
- Sun Y, Lin W, Dong W, and Xua J (2021) Origin and evolutionary analysis of the SARS-CoV-2 Omicron variant. J Biosaf Biosecur. 2022 Jun; 4(1): 33–37. doi: 10.1016/j.jobb.2021.12.001
- TAG-VE statement on Omicron sublineages BQ.1 and XBB (https://www.who.int/news/item/27-10-2022-tag-ve-statement-on-omicron-sublineages-bq.1-and-xbb)
- Telenti A, Arvin A, Corey L, Corti D, Diamond MS, Garcia-Sastre A, Garry RF, Holmes EC, Pang PS, and Virgin HW (2021) After the pandemic: perspectives on the future trajectory of COVID-19. Nature 596: 495–504. https://www.nature.com/articles/s41586-021-03792-w
- Turner JS et al (2021) SARSCoV-2 mRNA vaccines induce persistent human germinal centre responded. Nature 595: 109-113.

- Wang Q, Iketani S, Li Z, Liu L, Guo Y, Huang Y, Bowen AD, Wang M et al. (2023) Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants. Cell Volume 186(2): 279-286.e8 https://doi.org/10.1016/j.cell.2022.12.018 https://www.sciencedirect.com/science/article/pii/S0092867422015318
- Xia H, Zou J, Kurhade C, Cai H, Yang Q, Cutler M, Cooper D, Muik A, Jansen KU, Xie X, Swanson KA, Shi PY (2022). Neutralization and durability of 2 or 3 doses of the BNT162b2 vaccine against Omicron SARS-CoV-2. Cell Host Microbe.30(4):485-488.e3. doi: 10.1016/j.chom.2022.02.015. https://pubmed.ncbi.nlm.nih.gov/35245438/

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