Efficacy of antibodies, antivirals, and vaccination on SARS-CoV-2 Omicron Variant

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Abstract

The Omicron variation (B.1.1.529) is a variation of SARS-CoV-2 (the infection that causes COVID-19) that was first countered to the World Health Organization (WHO) from South Africa on 24 November 2021.
The omicron variation has transformations in both the RNA-subordinate RNA polymerase (RdRp), and the principle protease of SARS-CoV-2. Which focuses for antiviral medications like RdRp inhibitors (remdesivir and molnupiravir) and the primary protease inhibitor PF- 07304814,5 which enlivens concern in regards to the diminished viability of these medications against omicron.
WHO considers this variant as "Variant of Concern".
This is due to the 33 mutations this variant has, and the fact that it was believed to spread more rapidly than previous variants as the number of cases were increasing.
The antibodies, vaccines, and anti-virals that were previously used were proven to be effective towards the previous variants, but with the surprising number of mutations, how effective will it be towards the Omicron Variant? Our aim is to assess the efficacy of the Omicron Variant towards the antibodies, anti-virals, and vaccine.
And to our surprise, while some of the well-known interventions were found to be effective towards the omicron variant, other studies proved otherwise.
The fortunate thing is, despite its rapid mode of spread and diversities when it comes to intervention towards the well-known medications previously used, it is associated with a speedy recovery rate. This study would like to clearly state that previous medications will likely work on the Omicron variant although not as effectively as it does on previous variants, while a few maintain high efficacy rates.

List of abbreviations: SARS-CoV: Severe acute respiratory syndrome coronavirus ACE2, Angiotensin-converting enzyme 2, RBD: Receptor-binding domain, WHO: World Health Organization, BLI: Biolayer interferometry, VSVG: Vesicular Stomatitis Virus Glycoprotein, NPIs: Non-drug intercessions.

Keywords: SARS-Cov2, COVID-19 , Efficacy, anti-viral, antibodies, efficacy , vaccine, kidney transplant, ACE2.

Introduction

Our battle with COVID-19 is yet to reach an end, first emerging in 2019 as the SARS- CoV-2 virus in South-Eastern Asia, to eventually spread to all the continents becoming a global pandemic. (1) This has led to the death of 5.1 people worldwide (2).

More variants have been observed but managed to wane with time, not in 2020 though, as the alpha variant which first surfaced in the United Kingdom led to a winter wave of infection which extended to numerous countries. After the winter wave, when people anticipated that this would all be over, a delta variant took over during the spring/summer season starting in India in the late 2020. (1)

These variants had a rapid transmission rate; multiple variants afterwards were identified like the beta variant which was first detected in autumn 2020, lambda in august 2020, and Mu in January 2021. These mutations were localized to the epitopes which were recognized by the neutralizing antibodies and all were transitory. (1)

The world was taken by disbelief when another variant was introduced, the Omicron variant also known as B.1.1.529 of SARS- CoV-2 which was first discovered in November 2021, it is believed that it levitated from South Africa and has managed to spread very hurriedly around the world. It is also important to state that In South Africa only 24% of the population are fully vaccinated which increases the transmissibility of the virus. (31)

The omicron variant has managed to expand to over a 110 countries as stated by the WHO, this was mentioned in January 2022, (https://www.who.int/publications/m/item/e nhancing-readiness-for-omicron-(b.1.1.529)- technical-brief-and-priority-actions-for- member-states), this variant has been associated with an amplified rate of cases and hospitalizations. (3) And 2 days after the recognition of omicron variant as a variant under monitoring the WHO reclassified it as a variant of concern because of its high transmissibility. (31)

A tremendously concerning and distinguishing feature of this variant is that it has more than 30 amino acid substitutions in spike S protein which prompts the immune responses of the host, specifically in the production of neutralizing antibodies. A prominent feature is that 15 of these substitutions are in the receptor binding domain (RBD) of the S protein, this could possibly increase immune evasion/transmission as a study has already proposed that the Omicron variant is more proficient at infecting convalescent individuals in comparison with earlier circulating variants (3) as in Hong Kong it was thought that , a patient with Omicon variant has been infected via the airborne route within a designated quarantine hotel (4) and it is also believed that it carries a higher risk of re-infection. (4)

The substitutions in the receptor binding domain (RBD) of the S protein which is the dominant target for monoclonal antibody (mAb)- based therapy , has led to apprehensions all over the world in regards to the effectiveness of the current therapeutic mAbs for COVID-19 against this variant. (2) It also carries a disturbing number of mutations like those which are well-known to cause escape from the neutralizing antibodies and increasing binding to the host cell receptor angiotensin- converting enzyme-2 (ACE2). (4)

Mutations in the ACE2 receptor binding domain, viral spike protein and the N- terminal domain. These mutations allowed the virus to avoid antibodies produced by immune system and vaccination. Thus make it harder for medications to work effectively (3).

There are four main mutations highlighted by the CDC that could possibly help in transmission, which are: N501Y, H655Y, N679K, and P681H, similar to what has been found in the alpha variant, but not similar to delta, as a dissimilar mutation in position P681R has been found. [5]

A study stated that the Omicron variant is linked with a more rapid recovery, and a lower rate of viral replication in comparison to the other variants. [20], but the omicron variant as stated earlier is also associated more risk for re-infection and higher doubling time. [4]

It was also found that is has less severe respiratory symptoms, less pro- inflammatory cytokines and lower dys- regulated immune cells. The variant has many mutations that affect the binding affinity, transmissibility and makes it more susceptible to avoid immune response and neutralization by monoclonal antibodies. [30]

A study observed a noticeable deterioration in body mass in saline-control animals infested with both the Delta and Omicron variants, the omicron variant infected groups though is associated with speedy recovery of body weight in comparison with Delta-infected mice. [21] As well as, mice infested with the Omicron variant had lesser sub-genomic viral RNA than Delta variant-infected mice, which supports studies that indicated inferior viral replication of Omicron in both the upper and lower respiratory tract. Preceding data from searches have shown a positive correlation between viral RNA and disease severity are, and this finding is constant with reduced clinical severity for the Omicron variant when compared with the Delta variant. [22]

Regarding percentage of infections, Delta and Beta variants reached 80% and 50% respectively in 100 days from their outbreak. In contrast omicron variant reached 90% in only 25 days from the outbreak. [31]

ACE2 and Omicron Variant

The spike of the Omicron variant is found to connect competently to human ACE2 and manages its vigorous host-cell entry through ACE2-positive cell lines; this denotes that any mutation in the RBD does not compromise ACE2 interactions. [3]

The Omicron variation has 15 amino corrosive transformations in the RBD, three of which (K417N, T478K, and N501Y) have likewise been seen in past VoCs. To comprehend the effect of these alternates on receptor arrangement, the kinetics and kinship of monomeric human ACE2 restricting to immobilized Omicron, Wuhan- Hu-1 and Alpha RBDs utilizing biolayer interferometry (BLI) has been studied. [25]

It was observed that the Omicron RBD has a 2-2.5-overlap upgraded restricting fondness for ACE2 comparative with the Wuhan-Hu-1 RBD, in accordance with later surface plasmon reverberation findings. [25]

A study has hinted towards a high zoonotic potential due to the fact that Murine ACE2 was more proficient by the Delta Spike in contrast with B.1 spike, it also has a steadied entry driven by the Omicron spike with the extreme efficiency. [3]

Moreover, it was found that the ACE2 from Pearson's horseshoe bat (Rhinolophus pearsonii) was not proven to be efficient to the B.1 spike for entry. This opposes in particular the Omicron spike as well as the Delta since it used this receptor with extreme efficiency indicating that the Omicron spike uses ACE2 for host-cell entry. [3]

It was recently noticed for the Alpha RBD, which just harbors the N501Y mutation [25], the alteration of restricting is interceded by changes in ACE2 restricting off rates. Albeit the K417N transformation is known to hose ACE2 engagement[26,27], as of late resolved construction of ACE2-bound Omicron RBD uncovered that Q493R and Q498R present extra electrostatic associations with ACE2 deposits E35 and D38, respectively[27] , while S477N empowers hydrogen-holding with ACE2 S19. All in all, these transformations reinforce ACE2 restricting, comparative with the tribal detach .The study overextended restricting investigation to a cell based model utilizing cells transfected with full- length spike, trailed by ACE2 counter acting agent titration; we noticed fundamentally higher ACE2 restrictions for Omicron spike when contrasted with both Wuhan-1 and Delta variation spikes. This upgraded constraint could be a component in the improved contagiousness of Omicron in comparison with past variations. [25]

Lastly, according to a study in 2020 by Hofmann et. Al despite the mutations in the Receptor binding domain (RBD) the omicron variant was still capable of using ACE2 to invade positive ACE2 cells, moreover it was found to use different orthologous ACE2 for cell invasion [3].

Efficacy towards antibodies and antivirals

It has been shown that soluble ACE2 can be inhibiting the Omicron spike, soluble ACE2 did not modulate entry driven by VSVG, but has vigorously and comparably inhibited entry driven by not only the Omicron spike, but B.1., and delta making it a possible treatment for patients with the Omicron variant. [3]

This possibility was proven to be a reality when full resistance from the Omicron variant was found against mostly against casirivimab, as well as bamlanivimab, etesevimab, and imdevimab. [3], despite people anticipating a sprawling protection from killing antibodies in light of transformations in class I-IV antigenic areas in the RBD [28].

Supporting this finding was that a combination of bamlanivimab, and etesevimab did not succeed to inhibit access reconciled by the Omicron spike, whereas inhibition by a mixture of casirivimab and imdevimab was ineffective. On the contrary, sotrovimab has confirmed to be active against the spike, despite it being less effective that the spike of B.1. [3]

A combination of two mAbs, COV2- 2196/COV2-2130, was studied to test its efficiency towards Omicron spike, and it has been found that it suppressed the replication process in the lungs, when it is given one day post infection. [2]

Treatment one day post infection has been a common finding in current in-vitro studies being made. [17, 18]

In-vitro data has shown that sotrovimab with its parental form (S309) is also proficient in neutralizing this variant, and when IgG2a S309 is administered prophylactically it is shown to diminish and even prevent the replication of SARS-CoV-2 in hamsters. [19].

On the contrary, a study found that therapeutic administration of this mAb had no effect on the virus titers in the respiratory tracts of hamsters infected with Omicron (NC928), but could possibly be due to the antibody-binding activities detected in animals at the time of virus titration which was three days after antibody administration were inferior with S309-treated animals likened to those perceived with COV2- 2196/COV2-2130-treated animals. [2]

For the D614G (HP095) infected category, treatment with REGN10987/REGN10933 or COV2-2196/COV2-2130 brought about a huge decrease in infection titers in both the nasal turbinate's and lungs contrasted with control mAb-treated creatures. These outcomes were predictable with those of past examinations in which the blends of REGN10987/REGN10933 or COV2-2196/COV2-2130 were displayed to have restorative action against disease with ahead of schedule (USA-WA1/2020) or variation (USA-WA1/2020 N501Y/D614G) SARS-CoV-2 strains in rhesus macaques, hamsters, and mice15-17. Infection titers in the lungs of the creatures that were treated with S309 were essentially lower than those in the organs of the creatures treated with the control mAb. Furthermore, dissimilarities in viral titers in the nasal turbinate's were seen between the creatures that were treated with this mAb and the creatures treated with the control mAb. Accordingly, S309 showed less remedial impact against disease with D614G (HP095) contrasted and the other mAbs. For the Omicron (NC928)- contaminated gatherings, neither S309 nor REGN10987/REGN10933 had an impact on the infection titers in the nasal turbinate's or the lungs of the creatures. Notwithstanding, COV2- 2196/COV2-2130 essentially decreased the infection titers in the lungs of the creatures, while the infection titers in their nasal turbinate's were not impacted by this treatment. All together, these outcomes reveal that the COV2-2196/COV2-2130 blend can confine viral replication in the lungs of creatures tainted with Omicron regardless of whether the mAbs are administrated after the disease taken place. [2]

Ronapreve (REGN-COV2), made up of two such monoclonal antibodies (casirivumab and imdevimab), has proven its efficacy against preceding variants of SARS-CoV-2 in post-exposure prophylaxis, initial management and in sero-negative patients with severe COVID-196. [20] Therefore, the WHO as of now has a fragile or uncertain recommendation for groups with utmost risk of hospital admission. [23] Each antibody in Ronapreve displays molar effectiveness in contradiction of earlier SARS-CoV-2 variants which are orders of magnitude greater than existing repurposed minor molecule drugs such as molnupiravir and nirmatrelvir [20] but they are administered together in order to lessen the likelihood of emergence of resistance which has been recognized before for former monoclonal antibodies that were administered in the form of monotherapy.[24]

Ronapreve has manifested decreased effectivity against the variant [20], but multiple studies were able to confirm bargained activity of the Ronapreve combination. On the contrary, numerous studies have described the activity as "remaining activity" of the separate antibodies when they were considered in seclusion, nonetheless with a markedly inferior level of activity. [20] Data shows that the variant is sensitive to molnupiravir and nirmatrelvir. [34]

In conclusion, it is safe to say that the spike has proven to be resilient against several antibodies that are used for COVID-19, while maintaining efficacy in some. [3]

Current standard of care antiviral treatment for moderate to serious COVID-19 incorporates utilization of the monoclonal immunizer mix REGN 10933 and 10897. Without any clinical information for adequacy of these medicines against Omicron, their study originally demonstrated the association surface between every neutralizer and Omicron spike utilizing distributed structures. The E484A and Q493R changes were anticipated to influence aid's with casivirimab and S375F with imdevimab. Their study next tried sequential deterioration's of part mAbs, both independently and in mix, against Delta and Omicron live infections in tissue culture. While the Delta variation was successfully killed by casivirimab, imdevimab was somewhat successful, predictable with past data [29]. The blend was profoundly intense against Delta. Nonetheless, there was complete misfortune of killing movement against Omicron by either mAb alone or in mix. Given these outcomes, it was next tried directing acting antivirals remdesivir and the dynamic metabolite of molnupiravir against live infection. It was noticed that comparable antiviral movement against Delta and Omicron utilizing sequential titrations of the two mixtures. [25]

Many studies have been made to assess the efficacy, starting with testing the efficacy towards anti-virals to the Omicron variant (NC928) to antivirals in hamsters was assessed, and the dose of compounds for hamsters was decided based on preceding studies to assess the effect of molnupiravir and S-217622 against SARS-CoV-2 in the mouse model18,19. Hamsters intranasally contaminated with 103 PFU of infection were treated by oral gavage two times day to day (at 12-h spans) for 3 days with 1,000 mg/kg/day or with 120 mg/kg/day of molnupiravir and S-217622, separately, starting 24 h post-infection. On Day 4 post-disease, the creatures were forfeited and nasal turbinates and lungs were gathered for infection titration. Treatment with molnupiravir meaningfully affected the infection titers in the nasal turbinate's of the creatures tainted with the Omicron variation (NC928). In stamped contrast, both intensify decisively diminished lung infection titers; no infection was recuperated from the lungs of every one of the four creatures treated with molnupiravir or from the lungs of three of the four creatures treated with S-217622. Treatment with S-217622 additionally brought about a critical 9.9-crease decrease of infection titers in the nasal turbinate's. To assess whether treatment with these mixtures could bring about the development of safe variations, hamsters contaminated with 103 PFU of infection were dealt with, starting 24 h post-disease, for 5 days with by the same token molnupiravir or S-217622. No infection was recuperated from the lungs of every one of the four creatures that were treated with either molnupiravir or S-217622 on Day 7 post-disease, albeit low titers of infection were recognized in the nasal turbinates of three of the four molnupiravir- treated creatures (2.3, 1.7, and 2.4 log10 PFU/g) and in the nasal turbinates of one of the four S-217622-treated creatures (3.0 log10 PFU/g.) These outcomes recommend that the chance of the rise of safe variations in hamsters treated with molnupiravir or S- 217622 might be restricted under the circumstances tried. [(2)].

All things considered, these perceptions propose that the two antiviral mixtures tried here proficiently confine viral replication upon disease with the Omicron variation in the lower respiratory plot, yet entirely not in the upper respiratory lot, in spite of the fact that we saw a 9.9-crease decrease of infection titers in the nasal turbinate's of creatures treated with S-217622. [(2)]

An important finding stated by a study is that the antiviral drugs remdesevir and molnupiravir have managed to maintain efficacy against Omicron BA.1. Their study found analogous replication rates in the nasal epithelial 3D cultures in the Omicron and Delta variants. Interestingly, a noticeably significant lower rate of replication was found in the lower airway organoids, and cell lines of adenocarinomia as well as Calu-3 lung cells in the Omicron variant in comparison to the delta variant. This study also perceived that in spite of the mutations that were assumed to service spike S1/S2 cleavage, the cleavage is less proficient in the Omicron variant. [(25)],

A study in Hong Kong by Hanjun Zhao was conducted to compare the viral replication of Delta and omicron variants also to test the efficacy of camostat against those variants. The results showed less viral replication of omicron variant compared to delta variant in Calu3 cells or VeroE6/TMPRSS2. Regarding Camostat, it was found to be more potent against delta variant most likely because the omicron variant was less replicated in Calu3 cells or VeroE6/TMPRSS2 but more using the endocytic pathway. [(32)]

Three anti-virals had similar findings, paxlovid, molnupiravir, acriflavine and remdesivir the observed inhibition and IC50 maintained efficacy for all the variants, including the omicron variant. [(1)]

This has been supported again as data is indicative of the antivirals molnupiravir and S-217622 being effective in combatting the COVID-19 Omicron variant. [(33)]

Dabrowska studied the efficacy of anti-viral agents against covid19 variants. They isolated the delta and omicron variants in Czech Republic and the reference sample was isolated in Poland. According to the study

acriflavine, molnupiravir, paxlovid and remdisiver were all efficient in managing the different covid19 variants. (1)

In conclusion, the obtained information mentioned directs that the drugs that are under production against the SARS-CoV-2 are expected to preserve its efficacy also for the omicron variant. (1)

Do vaccines work against omicron variant?

With the speedy roll out of immunization programs and unparalleled non-drug intercessions (NPIs) by the public authority, during the past 2 years China has held in reserve a "dynamic zero-COVID-19" policy.(10)

Nonetheless, the "unique zero-COVID- 19" plan is now confronting enormous difficulties because of the worldwide pandemic brought about by the Omicron variation. At present-day, around 87.69% of the Chinese public has been immunized, generally with inactivated immunizations (https://ourworldindata.org/Covid). BNT vaccine, which is mRNA-based vaccine that has been proven effective against COVID- 19, and is currently being used in both the United States and Europe the Sera was collected from a duration of one to three months after they have received their second dose of BNT inhibited entry by the Omicron spike with a lower efficiency of 34-fold in comparison to the B.1. Spike, with the delta spike the efficiency was inferior by a 12- fold. All this indicates that two immunizations will noticeably be less effective against the omicron variant despite it providing more than 90% protection from severity linked with the Delta Variant. (3)

Breakthrough infections with the Omicron variation have moreover been found in people who received a homologous booster with a mRNA immunization (11). A disturbing concern is whether the killing antibodies prompted by inactivated immunizations can give adequate reassurance against the Omicron variation since nearby transmission of the Omicron variation is currently happening in China. (12)

A trivial report including simply 12 individuals in South Africa, which have been delivered through a preprint, demonstrated the findings that the viability of the Pfizer-BioNTech antibody could be altogether decreased against omicron, with a 41-fold lower level of counterbalancing antibodies when set side by side and a variation of the infection that was prevalent in the early phases of the pandemic (described by spike protein substitution D614G). (6) Jonathan Ball, teacher of sub- atomic virology at the College of Nottingham, said “Whilst the amount of virus killing observed in the lab is reduced markedly—up to 40-times reduction—there is still measurable virus neutralisation, especially in those who were vaccinated and previously infected. This group effectively mimics what we would expect in people who have had two doses of vaccine plus a boost . . . That’s why we still need to get the message across: get vaccinated, get boosted, even if you have been infected before.” Pfizer said its research showed that a third portion of immunization gave comparative degrees of killing antibodies against omicron as seen after two dosages against the first infection (wild type).(7)

In its proclamation the organization said that individuals who had two antibody portions showed "more than a 25-overlap decrease in balance titers" against omicron when contrasted and wild type, (7) recommending that two dosages of the Pfizer immunization "may not be adequate to safeguard against contamination with the omicron variation." The organization said "extra investigations demonstrate that a promoter with the current Coronavirus antibody increments the counter acting agent titers by 25-overlap." (5)

An in-vitro study conducted using steadfast SARS-CoV-2 variants highlighted that in contrast to the presently circulating Delta variant, the neutralization efficacy of vaccine-elicited sera against Omicron was rigorously reduced indicating T-cell mediated immunity as one of the crucial means in preventing severe COVID-19. (8) Another study, made to assess the SARS- CoV-2 Omicron Variant Neutralization after mRNA-1273 Booster

Vaccination was made by to evaluate the possible susceptibility of this variant to the mRNA-1273 vaccine, neutralization of the omicron variant by serum samples that were attained from recipients that were vaccinated were differentiated with neutralization of the following variants, the prototypical D614G variant and the beta (B.1.351) and delta (B.1.617.2) variants. A pilot study was made and, neutralization of the omicron variant after the chief two-dose regimen of the mRNA-1273 vaccine were found to be lesser than that of the D614G and beta variants but this finding has changed as increased substantially has been established in the participants that had a booster dose of the mRNA-1273 vaccine. (9)

It is worth bringing up patients that have undergone kidney transplant, since they are a high-risk group of mortality following SARS-CoV-2 infection (13), in which a cohort study was done for 51 participants with kidney transplants who received 3 doses of BNT162b2 vaccine to study the spike antibodies response after the third dose. Regarding wild-type variant, delta, alpha, beta and gamma variants, high number of Kidney transplants patients developed antibodies response after the third vaccine dose(67% KTRs, 25%KTRs, 51%, 53%,39% KTRs respectively). (16)

In contrast only 12% KTRs developed neutralizing antibodies response to the omicron variant after third dose and they also advance blunted antiviral responses following SARS-CoV-2 vaccination parallel to non-transplant patients.(14)

Moreover, the Delta and Omicron variants are less subtle in neutralizing antibodies from sera of vaccinated immune-competent persons. (15)
A study stated that "In KTRs, a third dose of mRNA vaccines increases antibody responses against wild-type and variants of SARS-CoV-2, while neutralizing responses to the Omicron variant remain markedly reduced."(16)

A study also suggested that heterologous AZ/BNT as well as homologous BNT/BNT/BNT immunization can possibly be able to give out better protection against the Omicron variant in comparison to receiving a BNT/BNT immunization. (3) Since SARS-CoV-2 Omicron was unaffected by casirivimab and imdevimab, genotyping of SARS-CoV-2 should be measured before mAb treatment being given to patients, Variant-specific vaccines and mAb agents may be essential to treat COVID-19 due to Omicron. (8)

Some findings were the opposite, as a study claimed that Monoclonal antibodies were found to be effectively used as a treatment for Covid-19. Antibodies were casirivimab, imdevimab, etesevimab and bamlanivimab. (3)

A study conducted in Japan stated that every one of the groupings of monoclonal antibodies that were tested (i.e., etesevimab in addition to bamlanivimab, imdevimab and casirivimab, and tixagevimab with cilgavimab) destroyed the early strain and the alpha and delta variations. The mix of etesevimab in addition to bamlanivimab showed surprisingly decreased killing movement against gamma and lost killing action against omicron and beta. The imdevimab-casirivimab combination held movement against beta and gamma yet lost inhibitory ability against omicron. (35)

In contrast the omicron variant was resistant to all previously mentioned antibodies most probably because of mutations K417N, N440K, G446S and more mutations in epitopes bound by these antibodies. Only sotrovimab was effective but still less efficient in treating omicron than B1 variant (3).

Exactly as expected, inoculation sera had out and out obstructed activity against Omicron when diverged from Delta. An mRNA 1273 inoculation roused sera showed near cross-over balance setback to BNT162b2. Coronavac sera showed almost no balance against Delta and 0/9 individuals had recognizable balance against

Omicron. Unusually sera from Delta defilements appeared to have lower cross balance when diverged from those from the early pandemic time period when Wuhan-1 D614G was winning. [25]

Conclusions

It is safe to say that all these results indicate different findings meaning some of these medications will be effective to some, while not being effective to others. This can clearly be observed by the versatile findings on multiple studies, but the fact that some maintained efficiency is relieving, especially when put into consideration that this variant is considered less effective. That being said, this variant is not a variant to ignore or take lightly as the rising number of mutations observed is extremely worrisome and concerning when considering the future COVID-19 generally holds in the world.

Recommendations

It is recommended that more studies should be made in a worldwide aspect to understand this in a broader aspect and to consider new treatments to decrease the complications associated with this condition. It is also recommended that the general guidelines should be followed to sufficiently prevent this virus. That being said the future that the Omicron variant is yet to be known. And there's always the uneasiness of new variants possibly rising with even more troubling mutations.

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