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Review

Spotlights on the latest opinions on identification, prevention, and management of newer CoV-2 variants: A roundup appraisal on innovative ideas and designer vaccines for Omicron

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ABSTRACT

Although mass vaccination combined with some other preventative strategies and lockdown was associated with some early signs that COVID-19 infection might be fading away, the over 35 sites mutated new South African variant, "Omicron", emerged almost globally. Certain predisposed hosts may develop severe inflammatory thrombotic or mild long-Covid conditions due to this variant, which depletes T-cells, neutralizes antibodies circulating in the body, and coincidentally induces hypercoagulability. The surge of Omicron combined with Delta variants may confer unresponsiveness to the currently available vaccines even when the second dose is given up to 90 days. A drop in the antibody levels by 30 % has been identified in omicron-infected individuals, and one in five people is resistant to antibody treatment. This poses major concerns in the transmissibility rate of this new variant, even in a heavy mass vaccinated environment. This heavily mutated Omicron with other spike sites facilitates viral entry into the cells through conformational changes, irrespective of circulating neutralising antibody. Based on this consideration, we believe that speeding up mixed-matched vaccines with higher T-cell stimulation ability may improve the current situation.

Moreover, large orders for antiviral drugs and monoclonal antibodies that could tackle Omicron combined with other variants may be valuable. The use of free polyclonal antibody donations and, hopefully, T-cell immunotherapy, may represent further breakthrough therapeutic interventions. However, Omicron infection is relatively milder than the ongoing Delta variant but is extremely contagious, and therefore the development of novel interventions is highly demanding.

1. Introduction

It has been two years since the CoV-2 viral strain appeared on the scene as a pandemic [1]. More recently, some imported newer variants are lingering around globally, killing millions of individuals most at risk and winning the race against vaccine deployments. In some European countries, despite the most successful mass vaccination, mass testing, and tracing, overall, a significant number of individuals still tested positive.

Omicron infection, at large scale, originated in the young population of South African. Then came its subvariants (BA.1, BA.2, and BA.3), each with a distinct sublineage of the omicron that makes them somewhat different in their genetic sequence and transmissibility. In fact 28 distinct genetic differences in BA.2 identified, making it even more transmissible than BA, and according to latest WHO' epidemiological update BA.2 has become the most dominant type in 68 countries for which genetic sequencing data is available, while BA.3 subvariant never spread extensively, and the BA.4 and BA.5 that were also characterized by South African investigators.

Over the last few weeks, COVID-19 virus continues to spread and mutate globally, including the XE recombinant of BA.1 and BA.2 that was first seen in the U.K. in January 2022, and proved to be a milder type and led to drop the restriction. Since after some weeks of increase in the weekly surveillance data of this infection, the rate of spread is coming down again while keeping the fourth booster vaccination programs for high risks groups ongoing and introducing smaller dose for

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school children. Nevertheless, the 3 biggest challenging unresolved questions are: firstly how to predict SARS-CoV-2 will evolve next, in terms of transmissibility and side stepping immune responses induced by either natural infection or vaccination; secondly, would a potentially newly emerging form be able to overtake the currently circulating forms globally ?; and thirdly whether the SARS-CoV-2 will continue to evolve to escape immunity with its unpredictable evolution consequences of many others respiratory pathogens.

The SARS-CoV-2 has a pretty incredible ability to escape immunity. Most of the immunity that is critical for protection against infection comes from antibodies, but the heavy mutated virus omicrons can easily escape antibodies and to replicate in humans and to transmit from person-to-person. But not the entire COVID-19 vaccines induce long-lived immune memory, thus explaining the fact that people can have residual levels of antibodies against SARS-CoV-2 still be prone to get reinfected. This raises a fundamental kinetic constraints—SARS-CoV-2 gets in and establishes an infection more quickly than memory responses can activate, as could be exemplified in the cases of people who have been double vaccinated, boosted, and infected more than once with COVID-19.

These findings highlight the importance of how we define infection. Symptomatic infections are a clinical issue, but what about asymptomatic infections identified only through tests? Another consideration is whether people who are infected despite vaccination and prior infection are still able to transmit the virus to others. If they can't, and if their symptoms are quite mild, then these infections may not be important to track or control.

The challenge is how to predict what COVID-19 strains should be included in vaccine boosters that are going to need soon or later on this year and also we need to have a better understanding of how different kinds of past exposures will shape responses to these vaccines and to identify the causes of protection. We really need to be able to explore further how someone's antibody, T-cell, and other immune markers that vary in host depending ways influences their risk of infection and to build accurate quantitative scenarios about different vaccination strategies.

Clearly we need to invest much more in mathematical modelling of reinfection probabilities to understand how susceptibility is changing over time, and varies with age and past exposures by tracking how well vaccines are doing against different variants, among different age groups, and among people with different exposure histories to other respiratory viruses such as with influenza because our original CoV-2 strain vaccines' effectiveness estimates varies substantially between people according to their vaccination status.

The main objective of this roundup appraisal is, therefore, to provide an update on the progression of COVID-19 variants and to explore various innovative control measures. Such a newer antiviral/anti-inflammatory drug pharmacotherapy [2] and the use of some purer antibodies neutralising hyperconcentrate, which may be of help in non-responders subjects to the vaccine. The plausible use of Plasma Exchange Therapy [PET] to rescue patients with severe infection or the rare cases of Vaccine-induced Immune Thrombotic Thrombocytopenia [VITT] by removing various toxic elements of convalescent plasma is another one. Such as the critical use of the vaccine in pregnancy and school children and the impacts of the much earlier use of the third booster[3,4].

In this manuscript, we want to highlight the importance of creating vaccines that also stimulate more durable functional T-cells and explore the application of modern cellular therapy in terms of the latest development and research interventions on Coronavirus diseases[5,6]. Furthermore, free polyclonal antibody donations and T-cell immunotherapy may offer another breakthrough therapeutic intervention, which will also be discussed in this spotlight.

2. Current position on Omicron and need for timely multivariants vaccines

Viral genome sequencing of the SARS-CoV-2 virus, providing variant detection, enables surveillance of global transmission and leads to insights into viral evolution and pathology. The Coronavirus infection has created some extraordinary challenges to global health systems and led to the initiation of some multilayer Diagnostic, Development, and Research(DDR) projects to understand better the dynamics of its ever-increasing variants' interaction with our highly variable physiological defence system. Some persisting fast-spreading Delta variants combined with the newly Omicron, potentially acting through households or communities transmission, have emerged from South Africa. The capability index of our current vaccines in use to slow down the spread rate also remains yet established. Many countries put several emergency action plans in place to create a barrier to the rapid spread of this new variant. In fact, all CoV-2 viral strains have extraordinary capabilities to consume neutralising antibodies and deplete T-cells functionality, and coincidently induce hyper-coagulability and severe inflammatory thrombotic conditions in some predisposed hosts, which should be taken into consideration to control better the associated viral or vaccine-induced organ injury and death or mild Long Covid. Various restrictions are currently introduced to slow down Omicron spread in multiple countries. Recent data indicate that the two doses of vaccines appear to be insufficient, and only the third booster will achieve over 75 % neutralising activity.

Some novel therapeutic interventions, toxic-free plasma-derived neutralising antibodies concentrate, newer antiviral/ anti-inflammatory, and other innovative technologies such as cellular therapy have been proposed for clinical trials. Moreover, the introduction of high-affinity booster vaccines that are moving fast forward, but results are still preliminary. The use of free polyclonal antibody donations and, hopefully, T-cell immunotherapy, may represent further novel therapeutic interventions.

3. Current status of the CoV-2 progression and need for multivariants vaccines

Although the Coronavirus pandemic was starting to fade away, with the current vaccination strategy combined with other clinical and non-clinical interventions, unfortunately, there are plenty of unknowns in the pathogenesis of newly contagious variants, such as the unexpected appearance of Delta plus and the recently imported Omicron from South Africa, with huge 35 mutations in some doubled jabs mass vaccinated countries.

Omicron BA2 is now replacing Omicron BA1,which peaked at the end of January, and now it represents about 5–6 % of the population in most European countries. The children are getting the vaccine at a 1:3 dose. Over 55 getting fourth vaccine and hospitalisation rate increasing too and the oldies like me at risk of mortality, despite eastern countries were targeting herd immunity and dropping testing and restriction.

This clearly raises an essential question of how mass vaccinated countries can stand up to this most virulent and contagious variant in differing ages. In fact, Omicron spreads exponentially two to three folds every two days after its discovery and elicited plenty of global concerns among scientists, drug companies, vaccine developers, and the general public population. It looks like we must learn to coexist with this viral infection that can quickly mutate and undergo shape, size, and charge to beat the human biological defence systems of some vulnerable hosts. No wonder many vaccine companies urgently tested the effectiveness of their vaccines against this imported variant that was discovered by fingerprinting analyses in South Africa and promptly alerted most countries concerned and the World Health Organisation (WHO), a very noble jester.

Early observational data indicate that the Pfizer(Pfizer Inc., New York City, New York, United States) vaccine is about 20–40 % less

effective than it was previously indicated for other variants. Nevertheless, some antibody surveillance must be put in place [7]before following up on the third booster vaccine that appears to be 90 % effective.

Regarding types and the nature of the existing variants, for practical reasons, the WHO earlier has designated some variants as "Variants of Concerns (VOCs)" or "Variants of Interests (VOIs)", according to significant changes in their viral properties [8]. Initially, the most fearful fast-spreading circulating variants by Greek alphabets were known to be Alpha for B.1.1.7 (UK variant), imported from Spain; Beta for B.1.351 (South Africa); Gamma for P.1 (Brazil); and now the Delta for B.1.617.2 (India) that appears to be most contagious and had a devastating number of mortality in Indian communities, that were poorly vaccinated [< 2 %] and still spreading rapidly all over the world simultaneously, sometimes in parallel with other variants but often displacing the gravity of Alpha variant that believe to be the most prevalent earlier. Another new variant so-called "Lambda variant", sparked headlines this summer after the WHO noted its rapid spread in the South American countries.

In fact, the UK genetic fingerprinting analyses have been instrumental in the identification and characterisation of the most contagious circulating variants of concerns so far, including The United Kingdom B.1.1.7, "Alpha"; The United States B.1.429, "Epsilon" and B.1.526," Iota"; and India B.1.617.1, "Kappa", and the new CoV-2 VOI the Mu (PANGO lineage: B.1.621), that sparked a wave of attention for its potential risk as a highly virulent and immune-resistant strain and since its first identification in January 2021 in Columbia, this variant has been responsible for most COVID-19 cases circulating in neighbouring countries.

Interestingly, on the other side of the globe, a C.1.2 strain with an unprecedented set of complex mutations on the spike protein emerged in South Africa. It remains to be fully established that Omicron with more than 35 mutations in the spike protein is equitant to the previous strain. Needless to highlight that these variants are easily characterised by mutations and/or deletions within the Spike coding region, and many are showing either increased transmissibility by augmenting binding to the host receptor ACE2 (e.g., D614G and N501Y) or helping in immune evasion by altering epitopes of neutralising antibodies (e.g., K417N/T, L452R, and E484K/Q).

Since many of these mutations are observed within the S protein's receptor-binding domain (RBD), it is therefore expected that the major activity of serum antibodies is targeting the RBD region of the spike protein as identified by serological analyses of individuals infected with CoV-2 strains. Hence, the currently approved vaccines are expected to be sufficiently effective against the emerging variants. Still, their efficacy might vary depending on the types of variant, the vaccine efficacy in the individual recipient receiving only the first dose or fully vaccinated with the 2-shot regimens, and the time intervals between the two shots to enhance the durability of vaccines efficacy.

Moreover, since vaccine-induced antibody efficacy wanes about 3–6 months, the third dose of booster vaccines, even in a shorter time lag, is believed to be needed to enhance the protection, possibly after estimating the serological antibody prevalence to stop the potential overproduction of neutralising antibody or autoantibodies [9]. It should be noted that the latter strategy might also overcome the major unresolved challenges in the timely distribution of vaccines by manufacturers in the right place and at the right time, as many witnessed during earlier South African outbreaks. A lesson to be learnt by those in urgent need is vaccines to stop further the spread of some new variants as vaccines are becoming a rare commodity and not equally distributed.

In the meantime, it is worth highlighting that the complete vaccination with either ChAdOx1 or BNT162b2, mRNA-1273, on evidence-based vaccines provided a significant level of protection against both symptomatic infections and hospitalisations, at least up to 3 months. But we still need continuously to monitor the effectiveness of the existing vaccines and decide whether additional doses or even produce newer vaccines based on adaptations with the mutated Spike or using a mixed matched vaccination strategy to combat the related emerging variants. This is particularly relevant when the viral loads of the newer variants of CoV2 infective agents are very high, which might lead to rapid antibody consumption.

In this context, the mixed matched vaccination strategy is a preferred option for clinical trial as it does not only do enhance the level of circulating antibodies to fight the virus but also the levels of the functional T-cells protection shied that do matter, and perhaps Oxford AstraZeneca vaccine[OAZ](Oxford, England, United Kingdom) provides a higher degree of durable T-cells stimulated protection, and that is why we do not see a higher rate of hospitalisation in England than some European countries, during the recent third wave of infections by the fast-spreading Delta variants, as the OAZ vaccine for over 65 ages was rejected by some European countries.

In this context, there is some supportive evidence that the mixed matched booster vaccine has proven to be highly effective even when vaccines efficiency after a double dose is fading off [10]. After in-depth clinical trials, this approach provides a more durable T-cell protection that is considered a breakthrough in future vaccination programs. Moreover, a recent study in Israel has shown that individuals over 60 who were given a booster shot of the Pfizer/BioNTech mRNA vaccine had an 11-fold lower risk of being infected with COVID and a 20-fold decrease in their risk of developing severe illness than those who did not receive a booster dose. Strong priming of memory B-cell responses occurred in both CoV-2-infected and mRNA-vaccinated individuals; in parallel, the neutralisation potency against CoV-2 variants was stronger in infected individuals than those vaccinated, suggesting boosting may be of utility in this setting.

Moderna (Moderna, Inc., Cambridge, Massachusetts, United States) had already been working "nonstop" on it, while researchers at BioNTech (BioNTech SE, Mainz, Germany) are using a pseudo virus engineered to look like the new strain to discover if their vaccines will be less effective against the strain within the next two weeks. Moreover, Johnson & Johnson groups (Johnson & Johnson, New Brunswick, New Jersey, United States) are testing its vaccine against the new strain, while University of Oxford scientists are expecting a delivery of the virus imminently as they were already researching in Botswana and Eswatini, where the variant is present, to assess how its vaccine stood up to this new variant of concern.

Needless to highlight, those mRNA vaccines should be easier to adapt because they simply deliver genetic codes in tiny bubbles of fat, then use the body as a factory to make the protein the immune system needs to recognise. These codes can be quickly swapped out, and there is no need for the enormously time-consuming process of growing cells in tanks required for other types of vaccines. We need some new mRNA cassettes and put them in if one needs to produce a new vaccine. Hence creating a new plant locally in Africa is the best option for such a new vaccine production locally to the benefit of all, a real breakthrough in countries with poor infrastructure where most needed [11].

BioNTech Pfizer took action "months ago" to adapt the mRNA vaccine they developed together within six weeks and to ship initial batches within 100 days, in case there was an "escape variant", cutting the time from the start of the process to putting vaccines into vials from 110 d to 31 days. Similarly, adenovirus vector vaccines such as the OAZ and Johnson & Johnson jabs are also reasonably easy to adapt to their systems. One vaccine that could benefit enormously and timely too is Valneva's (Valneva SE, Saint-Herblain, France)whole inactivated vaccine that teaches the immune system how to recognise other key proteins as well as the Spike. The EU recently agreed to buy up to 60 m Valneva doses. Still, the UK, which had helped fund the expansion of Valneva's Scottish factory, backed out of its agreement with the company in September. If the world needs a vaccine tailored to this new variant, or another future strain, governments, regulators, and the WHO will have to decide when to make the switch hence keeping a close eye on how severe the disease becomes for vaccinated people.

Meanwhile, we must also be pursuing other critical alternative interventional therapy such as:

a) Planned antibody therapy if vaccines become less effective and so if the drug therapy to treat Covid becomes even more important to treat such a variant. However, the immune protection from vaccines could work against the whole spike protein. Antibody treatments focused entirely on the receptor-binding domain where the virus is bound to cells. The Omicron, B.1.1.529 strain has 15 mutations in this area. The variant could dent the effectiveness of vaccines but not completely undermine them, but we could make some antibody treatments completely non-functional. In fact, early analysis in Seattle forecast that antibody treatments from AstraZeneca and GlaxoSmithKline are more likely to tackle the new strain. It consists of treating with two antibodies that act in different ways. One of the major treatments, Ronapreve (F. Hoffmann-La Roche AG, Basel, Switzerland), made by Regeneron, is current antibodies and next-generation candidates, one combination of which is already in clinical trials;
b) Antiviral therapy is good news: the antivirals used to treat Covid worked differently from vaccines. Hence, they were less likely to be affected by mutations in the spike protein. The new variant highlighted the need for this type of treatment as a second line of the defence system. In fact, Pfizer and Merck (Merck & Co., Inc., Kenilworth, New Jersey, United States) recently reported positive late-stage trial results for their antivirals. The latter has received approval in the UK. Recently, Merck revised its efficacy data to analyze the full results, showing that its treatment reduced the risk of hospitalisation and death by 30 % instead of 50 %. However, pharma companies have not scaled up the production of antivirals to the level that might be required if the new variant does take off.

4. Therapeutic scope of polyclonal COVID antibodies donation and the use of immunoadsorption tools for safer CoV2 neutralising antibody purification

The prevention of CoV-2 infection remains a worldwide challenge. In fact, the vaccine alone is not sufficient to arrest COVID infection even in mass-vaccination countries. One promising therapeutic option is based on the administration of some polyclonal antibodies hyper concentrate, easily obtainable from online immunoadsorption from either convalescing donor volunteers or other sources, including from doubled dose vaccinated donors having optimal protection against Cov2 strains. The online processing of circulating plasma should be in the range of 200–1200 mL [11,12]. The mobile therapeutic apheresis process may partially remove the neutralising CoV2 antibodies as a new therapeutic product and be used in-patient suffering from autoimmune diseases immunocompromised and for the poor or non-responders to vaccines [11,13,14]. Moreover, such plasma donations could be pooled under GMP regulatory conditions for standardisation of the antibodies contents and after immunoadsorption resuspended in the cryosupernatant co-administrated during transfusion, providing not only the standardised dose of neutralising antibody free from the potentially toxic elements of the source products and resuspended, in SD plasma or cryosupernatant to compensate for the content of Albumin and Antithrombin that are low in severe cases on COVID patients.

Recently a group of investigators in Germany applied this proposal and reported the success of the first two antibody donations performed at the University Hospital Dusseldorf. In both cases, immunoadsorption was well tolerated, with no side effects observed. Neutralised elates are concentrated using tangential flow filtration, increasing the concentration of immunoglobulin by tenfold compared with peripheral blood leading to 8 fold concentration in the plasma unit [16].

Today several countries, including the UK, are collecting a considerable amount of convalescent plasma. Clearly, such a procedure has an enormous future for countries with poorer infrastructure. It could also be used in poor responders and non-responders to any vaccines, where no remedial action exists, except newer drug therapy with an enormous cost. Moreover, such a product could be obtained on a large scale even from cadaveric serum under the auspices of some interested manufacturers under GMP regulatory conditions [11,16].

Considering commercial aspects at this stage is challenging to determine a price for one unit of such a most useful neutralising polyclonal neutralising antibodies. Prices can vary, being an innovative breakthrough procedure. The source material comes from dedicated volunteers donors and or cadaveric serum upon permission and will be priced much less than current monoclonal antibodies concentrate.

5. Antiviral/anti-inflammatory and monoclonal antibodies therapy

The use of antiviral and anti-inflammatory drug therapy is considered amongst the broad intervention armatures to stop the progression of COVID infection. But often with partial success, where like in all innovative interventions, the risks benefit stratification had to be taken into consideration for their usages for all ages, and where artificial intelligence in big data and pattern analysis were instrumental in the identification of the best products and the best practices [11].

The recent good news is that the Merck Company has developed a new antiviral drug that works by incorporating some errors into the virus's genetic code to make the virus less able to replicate and spread through the body. In fact, based on a successful clinical trial, in 775 patients, in the outpatient setting, with mild to moderate Covid who were at risk of more severe illness, it appeared that just 7 % of those given the antiviral drug "moinupiravil" were hospitalised or died as compared to with 14 % of patients given a dummy pill. Moreover, no death occurred in the group on the antiviral therapy.

Merck Company has submitted its trial data for emergency approval to relevant regulatory authorities, including the FDA, for approval. Hopefully, if authorised by the end of the year, COVID infection will be treated like a flue pill or injection as the best fit. The USA has already placed already two million doses of this product, with an approximate cost of £ 520 for the course of treatment. The UK Antiviral Taskforce looks closely at all results and opinions to ensure that UK patients access the best treatments alongside the current successful mass vaccination programme for all ages.

Moreover, another antiviral drug, favipiravir, licensed to treat flu in Japan, is being tested in the UK for differing age groups or patients with underlying health conditions.

Moreover, Pfizer is also testing another antiviral drug in 2660 healthy adults somehow infected with COVID-19asa real game-changer. Nevertheless, all such drug therapies proposals need to be fully authorised. Once satisfactory quality, safety, and efficacy standards are met with reliability and consistency. Such a product could be used as an essential added value of the COVID infection drug therapy.

Another targeted mode of drug therapy is the use of Dapsone (Rivopharm SA, Manno, Switzerland) which exerts its therapeutic effect by specifically inhibiting the neutrophil adherence to IgA, hence providing another tool to inhibit the initiation of the destructive process by neutrophils, that believed to be a life-saving mode for the treatment of moderate to severe COVID infection and to help in reducing mortality when the patients are admitted to hospitals. In fact, the lack of cellular functionality in cellular remains a crucial issue: Firstly, given the involvement of dysfunctional neutrophils and immunoglobulin, an association with a cytokine storm that leads to overreacted neutrophils that destroy the respiratory tract, including the epithelial-endothelial barrier, and leads to the failure of respiratory function and ultimately death and Secondly the destruction of tissues caused by neutrophils that are activated when it adheres to IgA resembling neutrophil/IgA mediated autoimmune diseases, which are best treated with Dapsone.

Another ground-breaking new treatment to be rolled out to vulnerable hospital patients from next week is that thousands of vulnerable

NHS patients in hospital due to COVID-19 are set to benefit from a new antibody treatment. On September 17, 2021, the government announced using a combination of two monoclonal antibodies, the so-called Ronapreve, initially in the hospital that has not mounted an antibody response against COVID-19. These include immunocompromised people, for example, those with certain cancers or autoimmune diseases, and therefore have difficulty building up an antibody response to the virus, either through being exposed to COVID-19 or through vaccination.

From an operational standpoint, Ronapreve will be used to treat patients lacking antibodies to CoV-2 who are either aged 50 and over or are aged 12–49 and considered immunocompromised. Therefore, antibody testing will first be used to determine whether patients do not have an adequate existing antibody response for receiving such a treatment. Such combined antibodies therapy- casirivimab and imdevimab - will then be administered to patients through a drip. The antibodies work by binding to the virus' spike protein, stopping it from infecting the body's cells.

Following clinical trial results from the government-funded REMAP-CAP trial, the NHS has also rolled out monoclonal immunomodulatory antibody treatments tocilizumab and sarilumab. The treatments were found to reduce the relative risk of death by 24 % when administered to patients within 24 h of entering intensive care. Earlier this year, the government also brought together a new Antivirals Taskforce to supercharge the search for new treatments for patients exposed to COVID-19 to stop the infection from spreading and speed up recovery time.

Ronapreve is just another step in our journey to overcome COVID-19. The goal is to continue collaborating with partners to identify and investigate multiple options that may help different groups of patients. This essential antibody cocktail to treat and prevent acute COVID-19 across the UK is another step to drug therapy as the follow up to the Dexamethasone that has saved at least 22,000 lives in the UK and a million worldwide since being rolled out to COVID-19 patients last year [16], tocilizumab and sarilumab [14] and some other innovative moves by the Antivirals Taskforce [15,16].

The key considerations in the greater access are to have a wider range available of antibodies enabling some greater flexibility of experimental design and the overall quality of the final antibodies in terms of the effectiveness, reliability, and sensitivity of the reagents used at each stage. In fact, following a thorough review of all available data carried out by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and recommendation by the Commission on Human Medicines, the UK government's independent expert scientific advisory body, the first monoclonal antibody combination so-called" Ronapreve" for use in the prevention and treatment of acute Covid-19 infection is approved for the UK. It is noteworthy to mention that this drug acts at the lining of the respiratory system, where it binds tightly to the Coronavirus and prevents it from gaining access to the cells of the respiratory system can also be administered either by injection or infusion. Based on recent clinical trial data assessed by MHRA scientists and clinicians, this new drug could also be used to prevent infection, promote the resolution of symptoms of acute Covid-19 disease, and reduce the likelihood of being admitted to Covid patients admitted to hospitals. Accordingly, another useful new drug of choice is added to our list of the armoury of drugs therapy to tackle Covid-19, such as using the Dexamethasone and Tocilizumab to save lives.

The MHRA has authorised Merck and Ridgeback Biotherapeutics' molnupiravir pill to treat at-risk Covid-19 patients, following positive clinical trial results. Molnupiravir is the first oral antiviral medicine licensed to treat mild-to-moderate Covid-19 in adults with a positive CoV-2 diagnostic test and who have at least one risk factor for developing severe illness. In the UK, Lagevrio is the planned trademark for molnupiravir, while the trademark for use in other countries has not yet been approved.

It appears that its application with the US Food and Drug Administration (FDA) for Emergency Use Authorization (EUA) of molnupiravir is under review, and recently announced that the European Medicines Agency (EMA) has initiated a rolling review of the company's Marketing Authorization Application. Merck is submitting applications to other global regulatory agencies.

Molnupiravir offers an essential addition to the vaccines and alternative clinical interventions against the Covid pandemic. The authorisation is based on positive results from a planned interim analysis from the Phase III clinical trial, which evaluated molnupiravir 800 mg twice-daily in non-hospitalised, unvaccinated adult patients with laboratory-confirmed mild-to-moderate Covid-19, symptom onset within five days of study randomisation and at least one risk factor associated with poor disease outcomes (e.g., heart disease, or diabetes).

Pfizer's Paxlovidis an investigational oral antiviral candidate that reduces COVID risks by 89 % in phase II/III study and can be commercially used as a nasal spray.

Birmingham Biotech and the University of Birmingham, UK, have signed a licensing agreement for an antiviral spray against COVID − 19. Monoclonal antibodies for Prophylaxis for COVID-19 patients and beyond come of age.

6. The UK approach to vaccination and timely booster jab deployment

With either Pfizer/BioNTech or OAZ, the mass vaccination proved to be highly effective in reducing hospitalisation, but there are considerable numbers of poor responders to current vaccines. Moreover, Omicron-infected individuals can even reinfect some individuals after the second dose is given up to 90 days, and one in five people are resistant to antibody treatment. Furthermore, evidence shows that Omicron infection can drop the neutralising antibody levels by 30 %.

Currently, almost 22 vaccine candidates from different platforms are approved at least by one country. It is noteworthy to highlight that these vaccines were designed based on the original CoV-2 strain, circulating earlier in the pandemic. Today, several other imported variants have emerged, and logically, it is difficult to estimate to what degree these variants could jeopardise the efficacy of the approved vaccines for all ages. That remains an open question. Needless to highlight, even with the complete vaccination with either ChAdOx1 or BNT162b2, mRNA-1273 that provides a significant level of protection against both symptomatic infections and hospitalisations. We still need continuously to monitor the effectiveness of the existing vaccines and decide whether additional doses or even produce newer vaccines based on adaptations with the mutated Spike or using a mixed matched vaccination strategy to combat this and related emerging variants.

In this context, the mixed matched vaccination strategy is a preferred option for clinical trial as it is not only the level of circulating antibody to fight the virus but also the levels of the functional T-cells protection shied does matter and Oxford Astra Zeneca vaccine provides the higher degree of durable T-cells stimulated protection. This is perhaps why we do not see a higher hospitalisation rate in England during the recent third wave of infections by the Delta variants that spread fast in some European countries that rejected OAZ vaccine for those over 65 ages. This means that we need to change and redirect our effort on the mixed matched strategy and focus on developing some vaccines to enhance improved T-cell functionality stimulation, combined with neutralising antibodies generation for optimised and clinical outcomes.

In this context, there is some supportive evidence that the mixed matched booster vaccine has proven to be highly effective even when vaccines efficiency after a double dose is fading off, and 93 % efficacy is achievable using Pfizer booster vaccine in patients who had double dose Astra Zeneca vaccine. This approach to providing more durable T- cell protection is considered a breakthrough in vaccination programs. On the other hand, some supportive evidence for booster vaccine comes from a study in Israel indicating that individuals over 60 who were given a booster shot of the Pfizer/BioNTech mRNA vaccine had an 11-fold lower risk of being infected with COVID and a 20-fold decrease in their risk of

developing severe illness than those who did not receive a booster dose. Moreover, strong priming of memory B-cell responses occurred in both CoV-2-infected and mRNA-vaccinated individuals. The neutralisation potency against CoV-2 variants was stronger in infected individuals than those vaccinated, suggesting boosting may offer some additional information advantages. Finally, in the Washington-1 strain infection, some investigators indicated that while four antibodies were identified to have potent neutralising activity against 23 existing CoV2 variants, only two antibodies showed some ultra-potent ability to mitigate against the Delta variant effectively [17,18].

Nevertheless, in some cases, 'Spike-driven syncytia' exist where besides its ability to drive fusion of viral and cellular membranes, the spike protein can drive the fusion of neighbouring cells, resulting in the formation of multinucleated giant T-cells, so-called syncytia have been identified. This phenomenon has been well known to be associated with chronic tissue damage and has been frequently observed in the autopsies of individuals with severe COVID, and is believed to contribute to COVID severity. Hence, some comprehensive research is still needed to understand the various variants' pathogenesis fully [8,19].

The good news is that in August 2021, the first COVID-19 vaccine received full approval from the US Food and Drug Administration (FDA). Numerous studies focused on the durability of immunity induced by COVID vaccines and the need for booster doses because of expected waning immunity induced by all mRNA vaccines.

In fact, approximately 16 million have already opted to have booster jabs in the UK. However, we still have an enormous number of fully unvaccinated individuals and a new South African variant that is even more contagious than the Delta variant appearing on the scene in Europe that might bypass our current vaccine and given the opportunity of introducing some travelling restrictions immediately to slow down the potential for this imported variant.

Having roughly 20–30 % of the population unvaccinated and an approximately 20 % that absolutely will not get vaccinated, as compared to other adult vaccination schemes, where should you put your effort and your skilled personnel focus on primary vaccination or moving them to tertiary boosters, what is going to happen to the whole attempt to deal with the fully unvaccinated around the world, only assure other variants will be emerging sooner or later. This means that eradication will be challenging, and we must learn how to coexist to survive with variants of this nasty viral infection.

7. Benefits of vaccinating during pregnancy and fetal-newborn immunity

It is well established that antibodies get transferred from the mother to the baby. But there is much more than antibodies that are transferred from mother to fetus. Mothers' colostrum contains several active molecules, such as the S100 molecule at a very high concentration associated with much less downstream inflammatory responses in newborns. Several other bi-directional exchanges of cells across the placenta (microchimerism) exist, which is still a vastly underappreciated phenomenon. The microbiome's role and its impact on pregnancy need to be considered. Looking at the complexes intimately immune system of the mother and fetus, the mother drives adverse pregnancy outcomes, including neonatal sepsis, which appear to have a common pathway centred around the vascular endothelium.

Regarding COVID-19 vaccines in pregnant women and to improve maternally-severe outcomes from SARS-CoV-2 infection that excluded pregnant women from vaccine trials is still the default. Yet, there is hardly any data that shows that they cause harm to pregnant women except the evidence that in midterms and post-delivery, the pregnant women are in hypercoagulable states. Both infection and the spike Protein used in all vaccines might lead to a higher host prethrombotic state.

Needless to say that some vaccine, such as the smallpox vaccine, is the only vaccine for which we have reliable data that show that if you take it while pregnant, there is a significant chance that the baby suffers harm. In contrast, the yellow fever vaccines one of the most widely used reactogenic vaccines, and millions of pregnant women have received it. The BCG vaccine for tuberculosis and the measles, mumps, rubella, and polio vaccines are all live vaccines that millions of pregnant and lactating women have received. There isn't a concern that they cause harm. While this doesn't mean that any future vaccine couldn't harm pregnant women, observational trials through AI would justify the inclusion of pregnant women in vaccine clinical trials. If that were the case, we'd be miles ahead by now.

In fact, some observational data revealed that immunising the mother either before or during pregnancy can improve newborn outcomes. One study reviewed vaccination safety during pregnancy and found that women who received either pertussis or influenza vaccines during pregnancy had reduced preterm birth or stillbirth risk by 50–80 %. This wasn't likely due to a pathogen-specific response but rather a non-specific response. Other observational, population-based studies had shown that women who received the BCG vaccine before pregnancy also had a lower risk of neonatal mortality. Now, there is a trial in Melbourne looking at this prospectively. Other vaccine-intervention trials focused on the mother-infant dyad are also underway.

Finally, evidence is accumulating that there are differences in the transfer ratio of antibodies from mother to fetus induced by COVID vaccination compared to those induced by COVID infection. This possibly relates to the glycosylation patterns of the antibodies. The question now is how we could use this information to mould this interaction not just for antibodies but also for T-cells and other molecules to improve neonatal/newborn immunity. Does vaccination improve pregnancy outcomes and protect newborns. Moreover, the immunization of parents, mother, and father impacts immune development in the offspring. Given the immune system's complexity, the added layer of complexity of a mother and her baby and their shared immunity.

Vaccination of pregnant women is now on the agenda in the UK and approved by the vaccination authority. Immunity to viral infection and vaccines and a better understanding of immunity of the mother/ infant, in both health and disease and upon vaccination, are the essential part of current personal precision therapy in this century.

8. The scope of the T-cell therapy and the use of antigen-specific T-cells

Another area of major interest is exploring the impact of T-cell therapy as the second pillar of passive immunotherapy. In fact, in Germany, some investigators used a sensitive technology to characterise antigen-reactive T-cells directly in combination with closed-system cell sorting to enrich and purify antigen-reactive T-cells. These groups characterised CoV-2 and pre-existing T-cell memory generated by frequent infections with the related "common cold" Coronavirus-specific T-cells from both healthy donors and COVID-19 patients. Using single-cell gene expression profiling, the analysis of antigen-specific T-cell responses contributed to a better understanding of the induced immune reaction and characterising and potentially predicting the success of vaccination and their clinical outcome [20].

In this context, multiparameter flow cytometry, T-cell receptor (TCR) avidity, and cross-reactivity measurements were used to deepen the characterisation of these cells and assess the pre-existing CoV-2–specific memory. It is believed that these cells are protective and may contribute to the development of severe COVID-19. Therefore, the analysis of these cell subsets is essential to reveal whether or not long-term protection is gained after infection or vaccination and is necessary for understanding fundamental immunological processes in immune tolerance [21]. Working with antigen-specific T-cells can help in challenging areas of the critically low cell frequencies, inflammatory environments, unspecific labelling, and high background that often hamper reliable analysis.

The experience gained by the above procedures can be applied to manufacturing newer bioproducts and safer therapy based on hyper-immune globulins against other emerging variants and viruses. This may be a helpful approach in poorer infrastructures that most need vaccines and others. There are always some poor responders and even non-responders even to mixed matched vaccines, requiring alternative therapy and or the use of costly designer monoclonal antibodies.

Interestingly, some newer automated manufacturing units for chimeric antigen receptor (CAR) T-cell therapies, using allogeneic, off-the-shelf CD45RA-memory T-cells obtained from a convalescent donor for passive adoptive cell therapy CoV2 is in the development stage. German scientists in oncology are working with Optima Pharma (OPTIMA packaging group GmbH, Schwäbisch Hall, Germany) to create an automated manufacturing unit for the decentralised production of CAR T-cell therapies. Moreover, a dose-escalation clinical trial was conducted in patients in Spain to assess the safety and feasibility of using allogeneic memory T-cells obtained from convalescent donors. It shows a clinical improvement six days after infusion without serious adverse effects, with lymphocyte recovery two weeks after the procedure and donor microchimerism at least three weeks after infusion. The long-term effects of such an approach are under evaluation.

While antiviral treatments and administration of convalescent plasma have not shown the expected impact on mortality, only treatment with steroids has been reported to decrease mortality in specific memory T-cells. However, no clinical trial was performed using SARS-CoV-2 specific memory T-cells despite the procedure for obtaining these cells being feasible, easy to implement for small-scale manufacture, quick and cost-effective, involves minimal manipulation, and has no GMP requirements.

The importance of robust and durable T-cell memory for CoV-2 for the management of the current pandemic is now confirmed by the outcomes of the first report of human passive adoptive cell therapy for COVID-19 using allogeneic, off-the-shelf CD45RA− memory T-cells obtained from a convalescent COVID-19 donor is workable with no serious adverse effects as the most inflammatory parameters were stabilised post-infusion. At the same time, the implications of all the available evidence so far, effective treatments are still needed to reduce the severity of symptoms, time of hospitalisation, and mortality of COVID-19. But the hypothesis that CoV-2 specific memory T-lymphocytes obtained from convalescent donors recovered from COVID-19 can be used as passive cell immunotherapy to treat pneumonia and lymphopenia in moderate/severe patients is great news showing the treatment efficacy progression in a biphasic way, initially viral and afterward inflammatory. Since the COVID-19-induced lymphopenia constitutes a therapeutic window that may facilitate donor engraftment and viral protection until recovery, it can be used as passive cell immunotherapy to treat pneumonia and lymphopenia in moderate/severe patients.

In addition, the broad donor memory T-cell repertoire may protect these vulnerable patients from other common viral co-infections, as has been previously reported in hematopoietic stem cell transplants [12, 22–26].

The existence of a CoV-2 specific T-cell population within the CD45RA−memory T-cells from the blood of convalescent donors with a vast number of doses can be easily manufactured using CliniMACSMiltenyi®(MiltenyiBiotec, BergischGladbach, Germany)device without the need of a Good Manufacturing Practice (GMP) facility. These cells can be stored and be immediately available as an "off-the-shelf" COVID-19 convalescent donor-derived biobank.

In the dose-escalation study, participants were sequentially enrolled to receive a single infusion in a dose-escalating manner. The first cohort of patients received a single dose of 1×10^5 cells/kg (low dose), the second cohort received a single dose of 5×10^5 cells/kg (intermediate dose), and the third cohort of patients received a single dose of 1×10^6 cells/kg (high dose). The participants were infused with CD45RA−T-cells at their respective doses through a standard blood filter in a gravity-driven system previously medicated with intravenous diphenhydramine 5 mg and acetaminophen 1 gm.

In brief, donor selection and procedure for memory T-cells selection and preservation were based on the presence of SARS-CoV-2 specific memory T-cells. The percentage of CD45RA−CD3 + cells was 99.8 % post depletion, and the total cell number was 1.44×10^9. A Spanish Regional Blood Transfusion Centre [27] performed blood donor selection according to the following criteria: ≤ 65 years old, positive SARS-CoV-2 tested by RT(real-time)-PCR (polymerase chain reaction) during the disease, and complete resolution of symptoms for at least 14 days before donation. We note that the performance of this type of screening test should be evaluated to ensure testing with an insignificant risk of false results, i.e., clinical sensitivity/clinical specificity trade-off favouring 100 % sensitivity of true positives [28–30]. The donor had to have at least one SARS-CoV-2 negative test by PCR from a nasopharyngeal swab or, if available, a negative SARS-CoV-2 viremia tested by quantitative PCR in blood before the blood donation. The donor blood was HLA typed. Clinical history and physical examination, including venous access, blood count, biochemistry, and serological studies, were performed within seven days before the apheresis.

From an operational standpoint, the non-mobilised apheresis was obtained from the convalescent donor using Spectra-Optia. CD45RA+ cells were depleted by immunomagnetic separation using CliniMACS CD45RA Reagent from MiltenyiBiotec, following the manufacturer's instructions. CD45RA- cells were aliquoted for cryopreservation in doses adjusted to 100 kg of weight and the three planned doses. Aliquots were cryopreserved in a double bag using autologous donor plasma with a final concentration of 5 % dimethyl sulfoxide (DMSO). CD45RA- aliquots were removed from liquid nitrogen storage and thawed in a dry defroster. Infusion of cryopreserved CD45RA− lymphocytes was performed 15 min after thawing. Cell count, viability, and microbiological studies were performed after each aliquot was thawed. CD45RA-fraction viability and purity were analysed by flow cytometry (FCM).

From an operational point of view, subjects were screened within two days before inclusion and dosing to determine their eligibility to participate in the study. Inclusion criteria and dosing occurred on the same day. Participants must have completed the following assessments before administration of the study drug: Physical examination, documentation of respiratory status, blood samples collections (only before day one, for haematological, chemical, immunological function markers, and donor chimerism analysis), and a record of any adverse events. These assessments and studies of donor chimerism and SARS-CoV-2 PCR were repeated on the study visits. Additional inspections were performed when possible, considering the increased workload. Patients will be followed until day 90, discharge or death.

In respect to outcome, the primary outcome was to determine the safety of a single infusion of memory T-cells from a healthy donor recovered from COVID-19 to determine the dose-limiting toxicity (DLT) and higher adverse event (AE) directly or as a direct result of the cell infusion.

Secondary outcomes were to evaluate time to lymphopenia recovery and immune dysregulation, the time needed for a negative SARS-CoV-2 result by PCR, clinical improvement through the NEWS, and a 7-category point ordinal scale and length of stay. The NEWS consists of six parameters (respiratory rate, oxygen saturation, temperature, systolic blood pressure, heart rate, level of consciousness) to improve the early detection and response to clinical deterioration. Each parameter is assigned a score of 0–3 points. NEWS is stratified into three categories: low risk (0−4), medium risk (5−6), and high risk (≥ 7). Besides, we monitored the patient´s clinical index using a 7-category point ordinal scale. Scores on the scale were defined as follows: a score. Replication of some proteins as a new target for COVID vaccine appears to have enormous prospects for the future vaccine should activate T-cells to attack infected cells expressing replication protein.

Curiously based on analysis of published data, we observed [31] that the inverted CD4/CD8 ratio < 1.0 appears to be associated with the severity of disease, and the progressively rising CD4/CD8 ratio > 1.0

towards death that are the same SARS CoV-2 virus and comparing T-cell subset counts for influenza and Coronavirus. Hence, cellular immunosuppression follows hyper inflammation of the severe disease even though the impact of different viruses on the T-cell immunosuppression appears to be coincident. Pfizer has announced results from an analysis of 2246 adults enrolled in its Phase II/III EPIC-HR (Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients) trial of its novel Covid-19 oral antiviral candidate Paxlovid (nirmatrelvir [PF-07321332] tablets and ritonavir tablets).

9. Future perspective and newer developments

Omicron variant may increase its transmissibility and make it more resistant to current vaccines in use. This variant gives an S-gene dropout in the standard tests, which can be used to track the variant without doing complete genetic analysis. Accordingly, the S-Gene Sequencing is Key for SARS-CoV-2 surveillance as:

i. The S-gene encodes a surface protein, which is a homotrimeric glycoprotein complex essential for infectivity;
ii. The complex is made up of two subdomains; S1 contains a receptor-binding domain (RBD) with a high affinity for mammalian angiotensin-converting enzyme (ACE2) that modulates the activity of angiotensin II, a vasoactive polypeptide hormone active throughout the body;
iii. When the S1 subdomain binds to ACE2, cleavage at the S1-S2 site facilitates SARS-CoV-2 entry to infect the host T-cell. Since the spike protein is on the virus surface, it plays a major role in the host immune response. Also, it makes an excellent target for novel therapeutic strategies and vaccine development.

Therefore, while South Africa's S-gene dropout suggests that 90 % of cases in Gauteng may already be this variant but does not tell us whether it spreads faster than the current circulating Delta globally or any more severe or to what extent it can evade the immune protection that comes from the current vaccines in use. Moreover, it does not tell us how well the variant will spread in countries with much higher vaccination rates, such as the UK, than the 24 % of South Africa that is fully vaccinated. However, many people in the country have had Covid before due to the earlier South African Beta variant. In many western countries, highly vaccinated countries, the Delta variants, the most predominant infection still flying high and staying in peak regions for a very long time. There was an unusual constellation of mutations, and it was very different from other variants that have circulated. Urgent research is underway to learn more about its transmissibility, severity, and vaccine-susceptibility. What we do know is there's a significant number of mutations, perhaps double the number of mutations that we have seen in the Delta variant, and that would suggest that it may well be more transmissible. The current vaccines that we have may well be less effective to the original that emerged in Wuhan, China.

In fact, the 32 mutations in the spike protein, the part of the virus that most vaccines use to prime the immune system against Covid, is about double the number associated with the Delta variant. Mutations in the spike protein can affect the virus's ability to infect T-cells faster and spread and make it harder for immune cells to attack the pathogen.

There is some good news in the pipeline as the Novavax vaccine demonstrate 89.3 efficacy, and Moderna is further pursuing their vaccination strategies against this and other variants of concerns; the Oxford nasal spray that targets the nasal and lung cells at the point of entry of this infection appeared to be highly effective and applicable for use in schoolchildren and younger ages. Magnetic beads with high-affinity binding to pre-coupled various proteins is another area of recent development with a promising DDR perspective. In fact, a team from Peking University developed a screening of the neutralising antibodies against CoV-2 early this year, using RBD and S protein pre-coupled magnetic beads to enrich the RBD binding B cells. Compared to the traditional cell isolation method, the pre-coupling beads help to increase the efficiency to 20-fold. Moreover, predominantly used for extraction, purification, and enrichment of desired antibodies as a simple, accurate, reliable, and safe strategy, as newly emerging tools of choice to streamline the immunocapture process as the future perspective [30].

Bispecific antibodies are becoming a key arsenal against malignancies in the last decade. They will herald a new era of targeted, potent therapeutics strategy despite the complexity of diseases and engineering challenges to develop a full and selective format that needs to continue to be fully realised.

Endoplasmic reticulum stress signalling has been identified as one of the avenues leading to the inflammatory response. The integration of this stress, oxidative stress, and the inflammatory response is critical to the pathogenesis of various diseases. Therefore, cytokine profiling provides a valuable tool for examining the relationship between cytokine expression and ER stress response, and attempts are already made either by inhibiting or removing IL-6 harmful effects as an essential mode of therapy by using newer tools.

10. Conclusion

Many factors have contributed to the fast-spreading of Omicron infection in western countries, such as a delay in childhood vaccination, avoidance of timely vaccine passports, mask-wearing and distancing while attending big events, and the significant number of no-vax individuals. Added to these is the combination of emerging Omicron with Delta plus variant, with 10–15 % transmissibility, with a more severe outcome lingering around in the plateau region for an extended period.

The focus remains on persuading and encouraging non-vaccinating people, who constitute about 30 % of the population locally, on board to be vaccinated. However, it should be remembered that a vaccine is only a part of the whole jigsaws for optimisation and should always be combined with other rapid, progressive interventions or barriers to becoming a breakthrough clinical intervention.

In this context, novel agents such as Opaganib, the first oral pill-based therapy, and Sanofi's (Sanofi S.A., Paris, France) Fluzone® influenza vaccine with Moderna's COVID-19 mRNA investigational booster dose may be of enormous clinical utility. Moreover, for the long-term plans, many researchers are taking the challenges of pursuing strategies to develop universal vaccines through a better understanding of the pathogenesis of various contagious infections.

Recently, some investigators generated two replication-competent vesicular stomatitis viruses (VSVs), rVSV-CoV-2 and rVSV-CoV, expressing the Spike (S) envelope proteins of CoV-2 and CoV, respectively, demonstrating to elicit much more robust immune responses compared to rVSV-CoV-2. Additionally, a VSV-based chimeric vaccine candidate, rVSVCoV/2-RBD, with enhanced efficacy, was developed by the transplantation of the receptor-binding domain of the CoV-2 S protein into CoV S in an animal model treated with a single dose rVSVCoV/2-RBD demonstrated significantly higher neutralising antibody responses than those treated with rVSV-CoV-2. This highlights the potential of transplanting CoV S with the RBD of CoV-2 S as a promising approach for developing novel COVID-19 vaccines [32].

With half of the world's population yet to receive a single dose of the COVID-19 vaccine, SARS-CoV-2 continues to spread across the globe.

New variants will likely emerge sooner or later, as evolutionary or revolutionary changes are the only constant in life. Many of the viral variants to emerge so far are more transmissible than the original CoV-2 strain [32,33]. The virus has evolved to some degree to escape our individual physiological defence immune pressure, and the future variants that entirely evade vaccine-induced immunity remain unknown. Vaccine companies are preparing for that, as we witness the South African variant today. Some mutations expectedly would make it fitter, either by increasing its ability to infect by entering cells or to evade antibodies, and we've seen both of those types of mutations occurring as CoV-2 has

been evolving. In the early course of CoV-2 evolution, we may see more replication- or transmission-enhancing mutations that plateau, and then the selective pressure exerted by population immunity may become such that antibody escape becomes the primary driving force of CoV-2 evolution. The variant with the most mutations that allow it to escape antibodies is the Beta variant. But this variant has essentially been displaced by other variants and isn't circulating anymore, so antibody escape alone is not the whole story. Viral genome sequencing, we can understand, has become critical in controlling the evolution of pandemics, allowing the identification of viral multivariate.

The big six Ps in 2022 for enhancing the safer practices on COVID variant patients' outcomes either in endemic and even pandemic that we cannot do without at any price to be taken into consideration are: our "Preparedness, Partnerships, Platforms, practical Policy, Process, Products" much in line with our mission statement. Undoubtedly, there will be some challenging issues of Compliance, Conflict of interest, Complacency, and crisis in confidence, making somewalk away from necessary action taken. Clearly, we must rise above the national projects and go for international goals by intervening and helping countries in need with vaccines and all our tools and know-how in the spirit of international collaborations.

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