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# Facts and challenges on global deployment of vaccines for the Immunotherapy of the evolving SARS Cov-2 variants, from the UK perspectives

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This editorial commentary is focussed on a working title: "The story of a different year, with enormous challenges imposed by CoV-2 strains and how we have responded to the way back to normality. The goal is to highlights the current status of deployment of vaccines, from the UK perspectives, in two specific areas:

## Firstly reflections on the factual increase in demands for approved vaccines and on their questionable efficacy in long terms immunity, in particular on the most fearful Brazilian variants strains

In this context demands for vaccines is continuously increasing and understandably the manufactures are committed to complying with several big international demands such as: a] Firstly the incoming President Biden's promise to distribute 100 million doses of vaccine, in a centralised way, within the first hundred days of his presidency. In fact 30 million doses already delivered but only 12 million are used and; b] Secondly the recently agreed portfolio the new EU president on 2.3 billion doses of vaccines, enough to vaccinate the whole population of the 27 European countries. In fact the EU' president just reached a deal with Pfizer, for 300 million additional doses, [increasing it to 600 million doses, as equivalent amount to USA], ready to be used and 75 million doses in addition to be delivered in the second quarter constitute an enormous additional demand; c] Thirdly, increasing demand from the UK side, being the first country that launched the largest massive vaccination programme to achieve herd immunity in the world, by pre-ordering large amount of all types of vaccine candidates and even creating a ministry of vaccine to closely monitor the vaccination programme. Nevertheless only up to 5 million doses of vaccines, have inoculated to four high priority groups, and we need more communication at community levels and we must secure appropriate links with the CEOs of the various manufacturers of the approved vaccines to ensure the timely production and distribution of mass deployment of vaccines, without bottle necks. In fact, there is already a shortage in supply and it will take almost a month from the planned production: putting in the vial; and quality control for the batch to batch variation and timely delivery and distribution to area to be used, All in all an enormous task requiring advanced strategic planning and teams working together on all levels. While it is great news that internationally we are all moving in the right direction for deployment of the mass vaccination, given that in pandemic no one is safe until all the countries in the world are able to narrow down the windows of viral infection, but the stability and the security of the supply chain, must be also maintained at all price. Understandably there is some doubt that some manufacturers can meet these committed demands in time alongside ever-increasing demands due to incoming fast moving variants spreading all over; d] There are several other important factors that might influence the emergency demands for vaccines: Firstly there is no clinical evidence that vaccines can block transmission of the mutated strains in all cases. This is of particular relevant to the South African and Brazil origins, having almost 12 mutations in the spike site, being almost 50-70% more effective in spreading the transmission and making the fight against these variants substantially harder with transmission being more spreadable and already moving extremely fast across the UK with differing rates and; Secondly it is unknown how effective the first dose of vaccine will be not only in the first 3 weeks after inoculation but for what duration of time, without monitoring the expected individual variability in the immune responses. In this context it is noteworthy to mention that in the UK the second dose, acceding to recommended protocols by the relevant manufacturers is going to be changed, [from the 3 weeks to 3 months], to make the first dose to be available to all 4 high priority groups more quickly. Such ad hoc decision making on the part of the Government to overcome shortages, is not warranted, as currently there is some disagreement in the efficacy of moving the second dose from 3 weeks to 12 weeks and in fact in some home care establishements some patients who received vaccine 3 weeks before are developing infection; Thirdly there are some issues around how to prioritise the use of vaccines, such as which occupations should be vaccinated first. i e. extending the high priority list to cover the frontline social workers embodying: health workers; teachers; police officers; shop keepers , using artificial intelligence tools for modelling to establish the best fit groups; e] Finally another intriguing challenge, that preoccupies many minds, is if the Pfizer vaccine that is currently in use internationally might not be as effective in neutralizing viruses with N 501Y mutation of the spike proteins, that include both the UK, South African and the Brazil fast spreading variants. In fact these vaccine were not been either designed or validated for such a variants, though appears to have some non-specific effectiveness that remains to be fully investigated by genetic finger printing analysis.

Currently one study in the US comes up with promising positive results, looking at the neutralising of spike proteins and the results of this in vitro study conducted by the University of Texas and Pfizer

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shows the antibodies from people who have received the Covid vaccine effectively neutralize the key mutation that is also found in two highly transmissible strains that have arisen in the United Kingdom and South Africa sharing the spike N501Y substitution. This is of particular relevance because the mutation is located in the viral receptor-binding site for cell entry and increases binding to the receptor (angiotensin converting enzyme 2). Nevertheless, this finding is of limited value because it does not reflect at the full set of mutated variants embodying more than 71 alterations and it remains to be seen the clinical outcome, in particular, in those already vaccinated with first dose only and after the second booster doses of various vaccines. There are some other variants such as Nigerian, Malian, Japanese variants that are in the pipelines that should be taken into account. Hence the race between speed of vaccination and the increasing rate of developing variant is still on and so far variant with fast transmission rate are the winners.

The unfortunate news is that the majority people affected by these variants while develop some degree of immunity and might develop antibody against these strains of virus but the protective effect against viral infection can only be transmit and can still get re-infected again as the natural immunity, through vaccination, does persist for long period of time [possibly 5 months] and the safest strategy, requiring frequent revaccination even after mass vaccination is to generate neutralising antibody or using alternative ways to deliver timely neutralsing antibodies timely. Nevertheless these variants will make the use highly specific monoclonal antibody irrelevant. Nevertheless the use pool convalescent plasma - derived polyclonal neutralising antibody hyperconcentrate [P –NAB-H] proposed by this author, will be the best shot available to provide antibody from the first day of infusion rather than to wait for being develop at measurable concentration up to 14 days by vaccination. Meanwhile adopting the recommended slogan of self-isolation, stay home and save your and community lives must be adhered to with rigors.

Moreover, apart from the SARS-CoV-2-specific antibodies that seems to remain stable up to five months the spike protein-specific memory B cells also increases in number over time, therefore as a precautionary note the infusion of some other bioproduct concentrates should be considered to become useful for taming these variants: a] a clinical trial in some additional branch using the pooled buffy coat residues that have become the norm against various infections as a personal proposal that we have planned to perform; b] the cadaveric serum strategy in collaboration with the relevant manufactures for affinity column purification for source neutralising antibody purification as proposed before by this author.

It is important to highlight that, it is not only vaccines and alternative therapy but also the behaviour and compliance to rules of individuals, are highly important in mass vaccination and other interventional therapy. In this context, despite all efforts to tame the spread of this pandemic virus the UK has now become amongst the 5 countries registered having over 80,000 deaths, almost approaching to USA and Mexico. Moreover the UK infection rate and death are still intensifying on the community basis and the UK government are pushing hard on compliance to the rule, with the slogan "Stay home, save life", but this might not be sufficient in this late stage, as new variants appear to have 75% higher transmission rate and, the R number remaining above one, suggesting that we are at the beginning of the third wave of infection, while over 30 million of most vulnerable population still need to be vaccinated to save their lives. Moreover, today more than 3 million people have tested positive and increasing numbers of doctors, nursing staff, and some of those giving vaccines are becoming exposed to infection. We need to urgently vaccinate the high priority group, as the peak of infection is still to come.

Needless to highlight that the UK Government, after the surge of newer variants, with 1600 daily death, possibly from new variants of CoV-2, finally announced today the belated launching of a comprehensive team effort to vaccinate all vulnerable high priority groups by mid-February and general population by the autumn. An enormous task that is achievable, where compliance is highly important without complaisance. Moreover, finally some lessons are now learned, by the UK, to close boarders temporary and require some documents for being vaccinated or tested to be free from CoV-2 variants, using PCR technologies as well as introducing the quarantine without exemption as long as the R number is reaching to a manageable levels allowing to remove some the severe restrictions.

## Secondly reflecting on the current supply of the global vaccines deployments of the approved vaccines

In this context the Moderna is the third vaccine that has been independently approved this week by the UK and European health and safety /efficacy authorities and a total 17 million doses of Moderna vaccine are secured by the UK government that will be available in spring 2021and the UK, by securing large doses of 3 types of vaccines, remains the front runner country compared to USA and Europe who are mainly using the two mRNA vaccines.

In fact, in the recent past, the European countries, were relatively slow and well behind with their vaccine orders, as compared to the US ordering 600 million doses of the Pfizer vaccine in July. It was not until November that the EU did a limited deal for 300 million doses. No wonder that the EU's vaccination mobilisation programme has faced criticism, for falling behind the UK and USA, taking much longer to approve the Pfizer/BioNTech jab that received authorisation by the UK first, then followed by USA.

One important factor is no individual country in European community is allowed to communicate directly with manufacturers about their individual order, which is arranged from the top down by the EU president. However, the infection rate in Europe is continuing to surge up, as mass vaccination rollouts stall. Germany, as a role model for Europe, has only inoculated 130,000 people and some of its vaccine centres have shut down due to supply shortages. Currently France is planning to scale up their mass vaccination to one million individuals, but only 352 people were vaccinated. Spain's authorities are provided only 1.3 million vaccines for their most urgent use and Italy was provided only 8,300 jabs, despite the fact that it is still unclear how long the protection by various vaccines might last. It is therefore highly important to secure well in advance firstly the supply through a better communication, then have a well-planned practical and effective delivery strategy, through a better coordination and to avoid unwanted waste. More importantly to educate people to take vaccines timely in line with the appearance of more transmissible viral mutation; our age- dependent immune system that might change making us more prone to infection; and with this new variants youngsters and children are now becoming the target of these new variants, and transmitting infection more readily.

While supply of approved vaccines would remains a rate limiting factors, meanwhile there are some good news in the pipeline that might overcome the shortage in vaccines to some degree, as newer vaccine candidates coming to the market, hence reducing the pressure on supply as where we stand now:

1. Swissmedic, the Swiss Agency for Therapeutic Products, has authorised the COVID-19 Moderna Vaccine in Switzerland. The authorisation is given according to the ordinary approvals procedure and is based on a rolling submission of data and the totality of scientific evidence shared by the company, including a data analysis from the pivotal Phase 3 clinical study announced on November 30. The Swiss Federal Government has secured 7.5 million doses of the vaccine. The first deliveries are expected to begin in Switzerland in the next week;
2. Novavax has executed an Advance Purchase Agreement with the Commonwealth of Australia for 51 million doses of NVX-CoV2373, Novavax' COVID-19 vaccine candidate, in November 2020. NVX-CoV2373 is a recombinant protein vaccine adjuvanted with Novavax' proprietary Matrix-M to enhance the immune response. Novavax is currently conducting late- stage clinical studies to demonstrate the efficacy, safety and immunogenicity of NVX-CoV2373 for the prevention of COVID-19. This includes two large pivotal Phase III clinical trials in the United States/Mexico (the PREVENT-19 trial) and in the United Kingdom, as well as a Phase IIb trial in South Africa. The opportunity of ensuring having access to a protein-based vaccine that can be distributed using existing distribution channels and should it receive regulatory approval is another breakthrough in developing various types of vaccine that we need right now. As part of the agreement, Australia will have the option to purchase up to an additional 10 million doses;
3. India has launch mass immunisation using the two types of nationally approved vaccines Bharta Biotech a viral-inactivated and the AstraZenika- based vaccine, made locally. While the Indian Government has approved their locally bioprocessed bioproduct but not enough information on the efficacy of the local products disclosed;
4. Sinovac Bioteck, a leading Chinese Covid 19vacine has developed and signed deals to provide 46 million doses of its Covid-19 vaccine to Brazil; 50 million doses to Turkey and 7.5 million doses to Hong Kong. It'll also supply 40 million doses of vaccine bulk — the vaccine concentrate before it is divided into vials — to Indonesia for local production. Intriguingly Sinovac's vaccine has had wildly different results from various countries: The Chinese Sinopharm's efficacy rate of 79%, is lower than the 86% announced by the United Arab Emirates for the same vaccine in December; Indonesian drug regulators say interim data from Phase 3 trials showed it is 65.3% effective and gave it the country's first emergency use approval; Turkey indicate it is 91.25% effective; new trials in Brazil indicate a significantly lower than earlier results for the efficacy rate of Sinovacs' Corona vaccine in Brazil , the lowest amongst its global competitors, but meeting WHO requirement of minimum standard [>50%]. Clearly, the use of any vaccine that meet WHO requirements >50% efficacy, as well as showing an efficacy rate of 78% for mild cases and 100% for moderate and severe cases of Covid-19, would relieve pressures on healthcare systems while reducing potential deaths, given its higher efficacy for moderate and severe cases that would require medical treatment. It is probable that the final efficacy rate of any vaccine might be related to differing populations under study, causing some problems for the national vaccine regulators.

Meanwhile the mass vaccination with the low first dose Oxford vaccine, that is now approved for all ages is already started, since the 4 Jan 2021, in view of the enormous demand for such a vaccine without the added operational difficulty, with the frozen vaccines. Britain has secured 100 million doses on this new vaccine and hospital begun giving the first 530,000 doses yesterday and now distribute to Scotland and Wales for massively planned programs. Time therefore to celebrate that UK being more reactive to survive virus with a cheaper vaccine, even though aiming to increase the long-term durability of this vaccine up to 3 months.

Clearly, newer research and development works, using newer tools are needed to investigate the processes that control the variabilities in T cell activation, killing power and the potential exhaustion, in Patient-to-Patient cases. The advanced flow cytometry platform, to provide a rapid, high throughput solution to the study or monitoring of T cell function and phenotype, plus helps to identify early biomarkers or perform serological characterisations that are highly relevant to the current states of newer generation of vaccines.

Moreover, some in- depth blood proteome profiling analysis of some infected cases revealed distinct functional characteristics of plasma proteins between severe and non-severe CoV-2 patients, indicate that almost a total of 76 unreported proteins, as novel prognostic biomarker candidates, have been identified as plasma proteome signatures. This supports the view that activation of neutrophil, complement, and platelet function, T cell suppression as well as, the activation of pro-inflammatory factors upstream and downstream of interleukin-6, interleukin-1B, and tumor necrosis factor might occurred. These events are amongst important issues to be borne in mind in any therapeutic modalities used for the immunotherapy, including the proposed alternative therapy, using a small pool of the neutralising antibodies as a hyperconcentrate [P-NAB-H]- derived from convalescent plasmas, or cadaveric serum, that conceptually would cover comprehensively all variants.

Interestingly AstraZenika is developing an antibody bioproduct, based on the same principle, to deliver directly antibody to those individual who fail to develop antibody through vaccination [poor responders], though this interventional modality does not overcome some of the toxic effects of viral infection- induced in severely infected individual, that is achievable by our proposed plasma exchange therapy by using our proposed protocol of P-NAB-H, obtainable by affinity adsorption column and then resuspended it in cryosupernatant or FFP to provide in addition to fixed amount of antibody, a balanced anti-inflammatory factors and albumin in view of deficiency that usually created by severe infection.

It is noteworthy to highlight that the combined with the newer ''Drug's-induced Instant Immunity or the pooled NAB- Concentrate" would be also more helpful to those who fail vaccination [non-responder] to survive Covid. The population –based variability in results nevertheless spark some intriguing questions if the reported variabilities in efficacy might be related to the population under investigation and presence of some new variants in real time.

To conclude, the Coronavirus virus has challenged human ingenuity, as the infection- associated deaths reaching now to millions and still rising with the appearance of newer fast transmissible variants on the scene, and this is supported by the colder months, traveling season and the participation in various social events as well as dropping our guard too early. However with the ongoing mass distribution of multiple vaccines and the targeted use of newly proven pharmaceuticals bioproducts and advanced technologies to mitigate infections and prevent deaths there is some hope we will survive this deadly infection.

Nevertheless the discovery of the new strains set off alarm bells worldwide and more countries began mass vaccination programme

campaigns to halt a pandemic that has claimed more than 2 million lives since it emerged. Many countries quickly imposed ban on travel from Britain, being one of the 5 countries with highest infection rates but EU Governments have since begun to relax the restrictions. Today the UK also finally imposed severe travel restriction to stop the spread of variants from Brazil.

As a precautionary note, it must be highlighted that the mechanisms of SARS CoV-2 infection that thought to be mediated by the virus's S-spike protein and CoV-2's high affinity binding to the angiotensin converting enzyme (ACE-2) and neuropilin-1 (NLP1) host cell receptors of the normal strain of virus, however it is a matter of concerns, about the enhanced degree of transmission of these newer mutational strains, in view of mutation - induced the shape and charge changes, that facilitate the direct viral entry into the cells and the greater speed of the proliferation. Therefore, it remains to be proven if the current mass vaccination immunotherapy is still effective on these new variants, though no additional clinical severity of these new variants is observed, except a clear shift toward younger hospitalized populations and moreover the children are now more prone to be infected by these new variants and transmitting infection more easily like the adult. Needless to reemphasize that the contagion, concomitant multiorgan dysfunction and deranged physiology that are responsible for the considerable increase in hospitalizations stretching that has stressed the healthcare system is still here and we should not drop our guard for long to come and everyone should be more vigilant at all levels in concert.

In this context it is only hoped the existing vaccines will remains effective in neutralizing the mutated South African virus and help the T- cell to clear it from the circulation that is remaining as a matter of wait and see soon and watch to space. Meanwhile we have already a back up alternative tools in place to boost he levels of neutralising antibodies of even the variants already in place and are still in validation stages for the clinical trials. Hence drug therapy is most likely direction to enhance the efforts against the mutated strain detected in Britain and other countries, as nobody is safe until everybody is safe and we need to incorporate more in depth research / development, for better understanding of the dynamics of the new strain of this virus and works on the application of the artificial intelligence and computerized tools for data, patterns and procedural analyses.

Today Britain is now one of the 5 countries with 80.000 cases of death recorded. During the past two weeks more than 1000 Covid-related deaths were recorded whilst one third of over 80s have been vaccinated, ensuring that by mid-February about 30 million people will be vaccinated helping to reduce hospitalization. However, everyone must take responsibility to make sure rules are followed rigorously. The UK Government today finally put together a comprehensive mass vaccination program making everyone involved in the rollout, taking the fight against these strains of virus seriously.

This is despite the bad news that the Brazilian 'super strain' is already in the UK, there are now fears that could make vaccines less effective, and once more the UK is too slow in putting lives at risk by being too slow to close the borders. It is worth noting that the COVID-19 Genomics UK Consortium (COG-UK) revealed the variant, known as P.2, had been picked up 11 times through routine testing in Britain.

It is noteworthy to report that at least two nurses in Brazil have been infected with P.2 despite having caught and beaten Covid in the spring, which has raised fears the new variant can slip past vaccines and any natural immunity. The variant is also thought to be more infectious than regular Covid after being linked to an explosion of cases this winter in Brazil. The variant, known as P.1, led to the banning of travellers from South America and Portugal from entering the UK from today. Both Brazilian variants share a mutation on their spike proteins, known as E484K, which is thought to play a role in making them more transmissible. Both variants might impact the way that antibodies work. However P.1 has two other problematic mutations — K417T and N501Y — which P.2 does not have, making it more infectious and more likely to slip past the immune system than the version found in Britain.

Nevertheless even if a new variant is able to get around, the current position is that it is quite easy to target it with some new versions of modified vaccines and to beat CoV-2 variants strains timely. Therefore the fight is still on now and it is not the time to be fearful of the new variants but having the joy of surviving infection and beating it by mas vaccination programs using the best-fit vaccines and other interventional clinical strategies such as anti-inflammatory drug and passive immunotherapy therapy. In fact a Nanobodies [12–15 kDa single-domain antibody fragments, that can be delivered by inhalation], has been isolated by NIH investigators that bind to the CoV-2 spike protein receptor binding domain and block spike protein interaction with the angiotensin converting enzyme 2 (ACE2), with 1–5 nM affinity and are amenable to relatively inexpensive large scale production compared to other bioproducts. Hence we must keep our faith to human ingenuity, while sticking to the rule of "staying home by reducing social contact", to beat CoV-2 variants too and to save lives.

Finaly as we head to press, in the UK we are confronted with a serious catastrophic crises, with ever increasing spread of newer fast spreading variants, while clinically not being more virulent but causing enormous challenges in hospitalisation and spreading fast. Moreover the current validated and approved vaccines in use were not designed to have high specificity and efficacy for such variants, despite being on evidence based so far being effective in reducing transmission rates via vaccination.

Nevertheless there is some bad news: a] Potential delay in vaccines supply in view of increasing demands; b] In order to achieved the February deadline to give the first dose to four top priority groups the UK government has postponed the time of vaccinating the second dose from 3 weeks to 3 month and tonight reportedly some individual in home care units after 3 weeks of vaccination become infected with some regret. What we need right now is a Living Systematic Review: We need to look the rate of hospitalisation continuously and the rate of infection as compared to rate of vaccination, in the race between vaccination and the infection, as COVID is winning so far. Hence requiring more restriction and adherance to more severe restriction and imposed rules and regulations. While 5 million individual in the UK has received the first Jap, it will be some doubt if 15 million jabs will be giving up to 15 February, the government achievable targeted deadline. Meanwhile vaccine supply is still the rate-limiting factor. The key question is if we are up to it? Even having obligatory "Mask Up" and not drop our guard after vaccination. I believe we are in sprit of oneness to save lives.