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Short Commentary

Artificial Intelligence Tools in the Global Deployment of Vaccines and Alternatives Modes of Immunotherapy for the Evolving SARS-CoV-2 Variants, From the UK Perspectives

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Short Commentary

This commentary is focused 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, where the use of newer artificial intelligence tools become extremely useful in the procedurals, patterns and big data analyses of the "new generation of vaccines and convalescent plasma therapy for management of CoV-2". The goal is to highlights the current status of deployment of vaccines, from the UK perspectives, in two specific areas.

Firstly reflecting on the factual increase in demands for approved vaccines and on their questionable efficacy in long terms immunity, in particular on the most fearful Kent-UK, South African and Brazilian variants strains of CoV-2 variants

In this context demands for vaccines is continuously increasing and understandably the manufactures are committed to complying with several big international demands such as:

- Firstly the President Biden's promise to distribute 100 million doses of vaccine, in a centralized way, within the first hundred days of his presidency. In fact 30 million doses already delivered but only 12 million are used before his presidency and;

- Secondly the recently agreed portfolio the new EU president by ordering 2.3 billion doses of vaccines, enough to vaccinate the whole EU populations 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 and these constitute an enormous additional demand on the timely supply of vaccine.

- Thirdly, increasing demand from the UK side, being the first big country that launched the largest massive vaccination programme to achieve herd immunity globally, by pre-ordering large amount of all types of vaccine candidates and even creating a ministry of vaccine to closely monitor the vaccination programme. The great news is so far up to15 million of the 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 vaccine for the planned mass deployment of vaccines, without any bottlenecks. 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 of such live biological material 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. Nevertheless to overcome the shortcoming in the supply and to safeguard public health a decision is made, following the scientific advice, to delay the second dose of inoculation from 3 weeks to 3 months in order to speedily vaccinate the four high priority groups in most need as soon as possible to time and save lives.

However 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 are safe" and many countries in the world are attempting to narrow down the windows of viral infection, but the stability and the security of the supply chain, must be surely 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.

- Fourthly there are several other important factors that might influence the emergency demands for vaccines: a) First there is no clinical evidence that vaccines can block transmission of the mutated strains in all cases. This is of particular relevant to the fast spreading 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; b) 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 and in particular to those have already being exposed some how to this infection asymptomatically and developed already antibody. In this context it is noteworthy to mention that in the UK the second dose, acceding to recommended protocols by the relevant manufacturers has been already changed, [from the 3 weeks

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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, has not been approved by many, 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 establishments some patients who received vaccine 3 weeks before are developing infection. Moreover evidence is accumulating that the current vaccines in use might not be as effective against some newer variants, requiring almost 10 times more antibodies to be approach t a balanced dose; c) Thirdly there are some issues around how to priorities the use of vaccines, such as which occupations should be vaccinated first. i.e. extending the high priority list to cover the severely disable groups that are 6 time more in risks urgently, and some frontline social workers embodying: health workers; teachers; police officers; main store keepers , requiring the use of computerized tools so called artificial intelligence for modelling to establish the best fit groups.

- In regard the UK- Kent variant that vaccination appeared to some degree of effectiveness in bringing down hospitalization to a manageable levels, only one study in the US comes up with promising positive results, looking at the neutralizing of spike proteins and the results of this in vitro study conducted by the University of Texas and Pfizer 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 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 ACE-2 (angiotensin converting enzyme 2 receptors). 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.

- 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, South African and the Brazil fast spreading variants. In fact these vaccine were not been either designed or validated for such a variants, though might have to have some non-specific effectiveness that remains to be fully investigated by genetic finger printing analysis. Therefore a fine-tuning in vaccine should be made urgently to improve their efficacy. This will not be an enormous task.

- In fact apart from the two most fearful mutated of South African origins, with the ever increasing numbers of 157 and there are some other variants such as: Nigerian, Malian, Japanese the most fearful Brasilia 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 even if the majority people affected by these variants are developing some degree of immunity by developing balanced levels antibody against these strains of virus but the effective protective against viral infection can only achieved be stopping the transmitting the virus and they can still get re-infected again as the natural immunity, through vaccination, does persist for long period possibly 5 months and the safest strategy, requiring frequent revaccination even after mass vaccination 6 monthly to newly regenerate neutralizing antibody or using alternative ways to deliver timely neutralizing antibodies timely. Noteworthy are that highly specific monoclonal antibody could be produced by available technology for these variants and the current highly expensive existing monoclonal antibodies will become irrelevant to be used . Nevertheless the use pool convalescent plasma - derived polyclonal neutralizing 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 14-21 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 in combination with the vaccinotherapy to induced passive immunity.

It should be noted that, apart from the SARS-CoV-2-specific antibodies to the spike protein the specific memory B cells also increases in number over time, therefore as a precautionary note in considering to use the infusion of some other bioproduct concentrates one need to consider the role played by T-cells for taming these variants. One possibility is by introducing newer trial clinical trial protocols adding some newer branches using the pooled buffy coat residues that have become the norm against various infections as a new proposal and compared it with the proposed CCP protocol or the cadaveric serum strategy in collaboration with the relevant manufactures for affinity column purification for the large scale source production of the neutralizing antibody purification under GMP regulatory manufacturing conditions.

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 90,000 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, do not travel, 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 6 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 we are still in the peak of infection.

Needless to highlight that the UK Government, after the surge of newer variants, with 1600 daily death, 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. Interestingly the government in Israel, where almost quarter of population are already vaccinated is also to stop all the incoming and outgoing flight until the end of this month from the fear of new deadly variants.

Secondly reflecting on the current supply of the approved vaccines and the alternative polyclonal neutralizing antibodies

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 2021 and 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 mobilization programme has faced criticism, for falling behind the UK and USA, taking much longer to approve the Pfizer/BioNTech jab that received authorization 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:

- Swissmedic, the Swiss Agency for Therapeutic Products, has authorized the COVID-19 Moderna Vaccine in Switzerland. The authorization 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.

- 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.

- India has launch mass immunization 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.

- 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 characterizations 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 neutralizing 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 re-suspended 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.

Future Perspectives

The Coronavirus virus has challenged human ingenuity, as the infection- associated deaths being not only over millions but 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 the dropping our guard too early recently. However with the on-going 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 and to halt the spread by imposed ban on travel from Britain, being one of the 5 countries with highest infection rates, though 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 and South Africa and other hot spots so be it even late as many variants are already establishing firmly locally in the UK. It is noteworthy to highlight 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 the enhanced degree of transmission of these newer mutational strains, remains as a matter of concerns in view of mutation - induced the shape as well of 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 so far, except a clear shift toward younger hospitalized populations and no wonder that children and school staff are becoming amongst the next high priority list for mass vaccination as children are now more prone to be infected by these new variants and transmitting infection more easily like the adult. Moreover it must be 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 backup alternative tools in place to boost he levels of neutralizing 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 leading countries with the highest cases of recorded death whilst almost two 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 in over 60 age will invited 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 and reportedly 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. However, even if a new variant is able to get around, the current position is that it is quite easy to target them 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 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 survive CoV-2 variants too and to save lives. Nevertheless some others unfortunate bad news are appearing that may lead to rethinking our approaches in real time:

a) The further shortage in vaccines supply is expected, as AstraZenika is dropping the earlier 80 million doses to UK to almost 40 million, in view of increasing demands for vaccinating all over 60 groups in addition to those populations that just received only the first dose and the second jab is still in waiting . Fortunately the good news is that we could introduce some other validated available vaccine ,such as Moderna vaccine as appeared to have a better efficacy of over the 90% as single dose for at least 2 months, hence based on earlier the prediction we might be able to achieve the proposed deadline to give the first dose to new nine priority groups the end of April 2021 as the government achievable-targeted deadline; b) We need continuously monitor the rate of hospitalization and the rate of infection, as compared to rate of vaccination, in the race between vaccination and the infection, as so far COVID is winning the race; c) put in place more restriction and adhere to more severe restriction and imposed rules and regulations; d] 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 that it is believe are achievable in the sprit of oneness to save lives, as we are experiencing so far.

These remind us again to recalibrate our thinking about how to approach the pandemic virus and shift the focus from the goal of herd immunity against transmission to the protection of all at risk individuals in population against severe disease. Hence full adherence to all restriction and not dropping our guard remains essential, as this virus is here to stay and mutate if is given some chance without challenging its fast growth.

Special Note: As this commentary was heading to press, it is reported that in the UK we are confronted with a more serious catastrophic crises, with ever increasing spread of newer fast spreading variants, being highly contagious and transmissible and clinically more virulent and causing enormous challenges in hospitalization. Moreover the current validated and approved vaccines in use appears not to be effective, as once expected as were not designed to have a high specificity and efficacy for such variants, Hence required some fine- tuning making them most effective with the high affinity binding to the spike proteins in order to reducing transmission rates via vaccination.