*Investment Insight June 2021*

## VACCINES, VARIANTS, BOOSTERS AND THE OUTLOOK FOR OVERCOMING COVID-19

The Covid-19 pandemic has affected every corner of the planet, and the outlook for overcoming it now depends upon the efficacy and availability of vaccines.

It has been more than a year since the World Health Organization declared Covid-19 a pandemic. Looking back, it has been an extraordinary period in all our lives. Hundreds of millions of people have been infected by the SARS-CoV-2 virus, and almost four million have succumbed to the disease. Our world has changed. But the devastation of the pandemic has also given rise to unprecedented scientific advancement, and we have risen to the challenge. In less than a year, several highly effective Covid-19 vaccines have been developed, approved and delivered. Mass vaccination is well advanced in many parts of the US and Europe, and concerted efforts from rich countries to help vaccinate the rest of the world are crucial in the race to bring the pandemic and variant epidemic outbreaks to an end.

The pandemic is as fast moving as the response. The first vaccines have succeeded in halting its progress, but we now face rapidly emerging variants and the likelihood that boosters will be needed to maintain protection.

Yet whilst populations are being vaccinated as quickly as vaccines can be produced, the virus is also adapting and mutating. Many variants have been detected, although thankfully most are inconsequential. However, some mutations are causing more concern. They are more infectious or more harmful, or both. Some have been shown to reduce the effectiveness of the current cohort of vaccines and treatment, and they could potentially derail the trajectory for returning to normality.

Although some recent Covid-19 variants can reduce vaccine effectiveness against infection, the current cohort of vaccines by and large still offers protection against severe illness and hospitalisation. Encouraging results from booster vaccine studies show that these vaccines raise the level of neutralising antibodies and could provide a broad spectrum of protection against several variants and any waning of immunity. Booster vaccines can also be developed relatively quickly, and more research has started on predicting and combatting the emergence of future variants. Potentially variant-agnostic oral antiviral drugs could also add another weapon to the antiviral arsenal.

This Insight attempts to provide a comprehensive review of current known Variants of Concern, booster vaccines and the future outlook for the pandemic.

*Classification of variants*

The Centers for Disease Control and Prevention in the US has classified SARS-CoV-2 variants according to their risk profile and ability to escape any immunity caused by either prior infection or vaccination. They are Variants of Interest (VOI), Variants of Concern (VOC) and Variants of High Consequences (VOHC), in order of increasing level of risk. The table below outlines the risk profile for each class of variant.

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| Variant | Immunity from Prior Infection or Vaccination | Transmissibility | Disease Severity | Susceptibility to Treatment | Diagnostic Detection |
|---|---|---|---|---|---|
| **VOI** | Some decrease | Increase predicted | Increase predicted | Decrease predicted | Decrease predicted |
| **VOC** | Significant decrease | Increase observed | Increase observed | Decrease observed | Decrease observed |
| **VOHC** | Significant decrease | Increase observed | Increased hospitalisation | Significantly reduced | Demonstrated failure |

The World Health Organization also has similar classifications, although different authorities may classify each variant differently.

*Effectiveness of current vaccines against known variants*

Covid-19 is manifested by the SARS-CoV-2 virus that binds to and subsequently enters our cells. Once inside, it replicates rapidly and causes the disease. Vaccines work by generating antibodies that slot into the virus' binding site and thus block it from invading our cells. Put simply, it is like a key (the antibody) fitting into a lock (the virus), and therefore preventing the virus from doing harm.

There are now six main VOC. The latest of these is the Delta (Indian) variant. These variants all have some changes in their structure that interfere with the ability of the antibody generated by the vaccine to work properly. Continuing the lock-and-key analogy, it is as if the lock has been modified and the key no longer fits perfectly. In an extreme case, if the mutation of the virus is dramatic it may completely nullify the effect of the vaccine, i.e. so that the lock has been replaced and the key no longer works. However, so far no VOHC has been identified which might cause this to happen.

| **Summary of Variants of Concern** | | | | | | |
|---|---|---|---|---|---|---|
| **Variant** | **B.1.1.7** | **B.1.351** | **P.1** | **B.1.617.2** | **B.1.427** | **B.1.429** |
| **First Identified** | **UK (Kent)** | **South Africa** | **Brazil** | **India (Delta)** | **US (California)** | **US (California)** |
| **Transmissibility** | 50% higher | 50% higher | May be higher | 60% higher than the UK variant | 20% higher | 20% higher |
| **Lethality** | Potential increase | ? | ? | ? | ? | ? |
| **Impact on effectiveness of monoclonal antibody treatment** | Minimal | Significant reduction | Significant reduction | Potential reduction | Modest reduction | Modest reduction |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Impact on neutralisation by convalescent and post-vaccination sera** | Minimal | Reduction | Reduction | Reduction | Reduction | Reduction |

*Sources: CDC, PHE*

All of the current cohort of vaccines were developed based on the structure of the ancestral strain of virus first discovered in Wuhan, China. Although these vaccines are highly effective against the Wuhan strain, the VOC have so far been shown to reduce the effectiveness of the vaccines in preventing infection.

*Trials of vaccine effectiveness against variants*

Clinical trials have been conducted in South Africa and the UK where variants have been widely circulating or dominant. In South Africa it was observed that the overall efficacy of the Novavax vaccine (NVX-CoV2373) was reduced to 49.4% in all trial participants, but that the efficacy was shown to be better (at 60.1%) in HIV-negative populations who were not immunocompromised. In the UK the Kent variant caused a minor reduction in the vaccine's efficacy, bringing it down to 86%. This compares to the Novavax vaccine's 96% efficacy against the ancestral strain from Wuhan.

Furthermore, the impact of variants on vaccine effectiveness is not uniform across the cohort of vaccines, with some vaccines faring better than others (although we caution that data are not directly comparable across all studies). For example, AstraZeneca conducted a trial of its vaccine ChAdOx1 nCoV-19 in South Africa, and in people under the age of 31 this showed that the vaccine's efficacy was as low as 10% in preventing mild and moderate disease, meaning that it was largely ineffective. This shocking news prompted the South African government to suspend the roll-out of the vaccine from AstraZeneca. Separate laboratory tests of Pfizer/BioNTech (BNT162b) and Moderna (mRNA-1273) vaccines showed a several-fold reduction in neutralising antibodies in convalescent and post-vaccination sera for both the South African and Brazilian variants, also suggesting a reduction in vaccine efficacy.

*Vaccine effectiveness in real-world settings*

Since the roll-out of the vaccines, several countries have conducted real-life studies to evaluate the effectiveness of vaccination. In Qatar, a study published in *The New England Journal of Medicine,* which centred on people who had been given two doses of the Pfizer/BioNTech vaccine, showed that the vaccine is 75% effective against the South African variant and 90% effective against the UK variant (compared with being 95% effective against the ancestral strain from Wuhan published in the original clinical trial). Several real-life studies conducted by public health authorities in the UK confirmed there was high efficacy against the UK's dominant B.1.1.7 (Kent) variant after two doses of either the Pfizer/BioNTech or AstraZeneca vaccine.

With the recent surge of the Delta (Indian) variant in the UK, Public Health England published real-life data for the efficacy of the Pfizer/BioNTech and AstraZeneca vaccines against the Delta variant. The study found that after a single dose of either vaccine the effectiveness was only 33.5%, compared to 51.1% against the UK (Kent) variant. The efficacy improved significantly after the second dose, though: to 87.9% for the Pfizer/BioNTech vaccine, but only to 59.8% for the AstraZeneca one. This prompted the

UK government to change its policy for the timing of the second dose from 12 weeks after the first dose to eight weeks for those aged over 50, in order to boost immunity.

*Vaccines are mostly effective against severe disease caused by variants*

However, all is not lost. Whilst our humoral (i.e. antibody-induced) immunity to infection can be reduced by different variants, our next line of defence at the cellular level – the T-cell response induced by the vaccine – is by and large intact. T cells kill viruses on their arrival inside cells even though they have escaped the antibody line of defence.

This is illustrated by a large-scale clinical trial conducted by Johnson & Johnson across several countries. A single dose of the company's vaccine JNJ-78436735 demonstrated an overall efficacy of 66% for preventing moderate to severe infections, with an efficacy of 72% in the United States, 66% in South America and 57% in South Africa. These numerical differences highlight the negative effect of variants on efficacy in each geographical area. Notwithstanding the reduced efficacy for preventing infection, the vaccine was shown to be 85% effective against severe disease and 100% effective against hospitalisation or death across all three regions.

Similar findings on the prevention of hospitalisation and death were also observed for Pfizer/BioNTech and Novavax vaccines against the South African variant, and for Pfizer/BioNTech, Novavax and AstraZeneca vaccines against the UK variant.

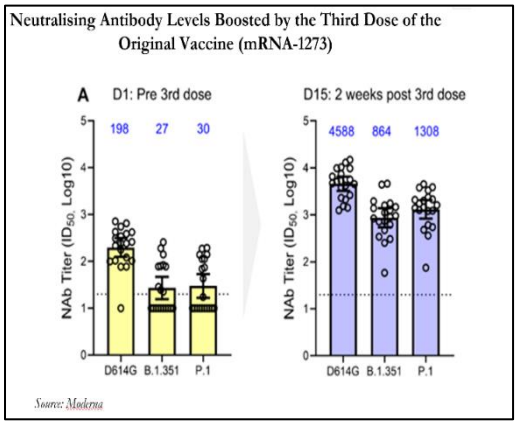
It is good news that the current cohort of vaccines appears to be largely effective in preventing severe disease against these known variants.

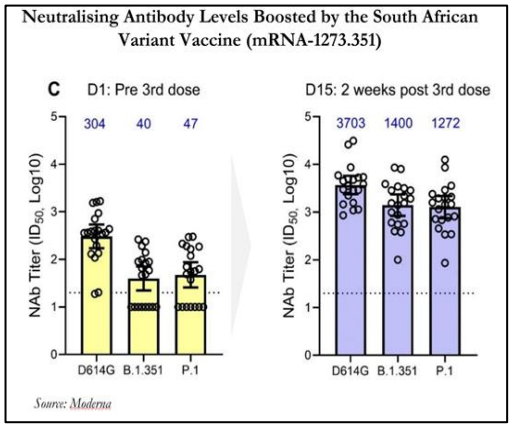
*Booster vaccine protection against variants*

The reduction in vaccine effectiveness against variants has brought about the development of booster vaccines. Although different vaccine manufacturers vary in their approach to this, it generally involves a third dose of the current vaccine (ancestral strain), a new booster dose of vaccine specifically against the South African strain and a multivariant booster containing both.

A third dose of the original vaccine (Wuhan strain) can boost the level of neutralising antibodies higher and therefore reduce the chance of mutants escaping. Amongst all the known variants to date, the South African strain is deemed most capable of evading immunity, and so a separate booster for this specific strain is being pursued to cover the gaps in immunity.

Moderna was the first to report its booster results. These showed that both a single dose of mRNA-1273 (Wuhan strain, the graphs on the left) and a single dose of mRNA-1273.351 (South African strain, the graphs on the right) can substantially increase the neutralising antibody level two weeks after the third dose is given to previously vaccinated clinical trial participants (as shown in the purple bars).




The yellow bars on the left show the antibody levels before the third dose, and the purple bars on the right show the antibody levels two weeks after the third dose. Variants tested were the Wuhan (D614G), South African (B.1.351) and Brazilian (P.1) strains. It is expected that these increases in neutralising antibody levels will provide a better protection against variants.

It was also observed that the mRNA-1273.351 South African variant booster enhanced neutralisation against not only the South African strain but also the Wuhan and Brazilian strains. This finding suggests that a strategy of combining the South African variant and Wuhan variant into a single booster dose should in principle be effective against a spectrum of emerging variants, and Moderna is pursuing this multivariant strategy with a clinical trial.

Other vaccine manufacturers like Pfizer/BioNTech, AstraZeneca, Novavax and Johnson & Johnson, amongst others, are also carrying out booster vaccine development.

*Booster vaccines for the waning of immunity*

There is now some evidence that over time the neutralising antibody levels will wane in people who have been either previously infected by the virus or vaccinated. In a laboratory study conducted by Moderna it was found that six to eight months after two doses of the original vaccination had been administered (shown in yellow bars on the left of both sets of graphs above), the neutralising antibody level was reduced against the Wuhan (D614G) strain, and it became almost undetectable (see the yellow bars at or below the dotted lines in these graphs) against the South African (B.1.351) and Brazilian (P.1) variants. The study demonstrated not only that vaccine effectiveness wanes over time but that its deterioration is also accelerated by the presence of variants.

We still do not know whether the memory B cells and T cells can be reactivated quickly when faced with a variant attack in real life. Out of an abundance of caution scientists believe that it would be most sensible to give a booster vaccine periodically to those most at risk of severe disease.

Fortunately, the efforts of the major vaccine providers have shown that booster vaccines can be developed relatively quickly.

*Identification of Variants of Concern*

To establish whether a variant is a VOC, scientists need to obtain and analyse its genomic sequence. GISAID is by far the most complete of the several online databases for SARS-CoV-2.

More than 1.5 million SARS-CoV-2 sequences from over 170 countries have been deposited in the GISAID data-sharing platform since January 2020. These genomic sequences, together with almost 400 high-resolution structures of spike protein from the Protein Data Bank, enable scientists to carry out bioinformatic analysis to identify VOC that pose the most risk of escaping immunity in order to help them design future vaccines.

Instead of handling live viruses, pseudoviruses that have the key genetic information of the VOC are constructed by scientists. These are then used in virus-neutralisation assays to evaluate the effectiveness of the current vaccine against the new variant. If a variant escapes the immunity, scientists can then design a new vaccine and carry out safety and efficacy studies in the laboratory and in preclinical settings before moving to human trials.

It could take two to three months from the detection of a VOC to a preclinical readout, but scientists are currently working to narrow this timescale. Our recent discussion with Moderna revealed that it took the company only 30 days from the sequencing of the South African variant to clinical trials.

*Conducting clinical trials*

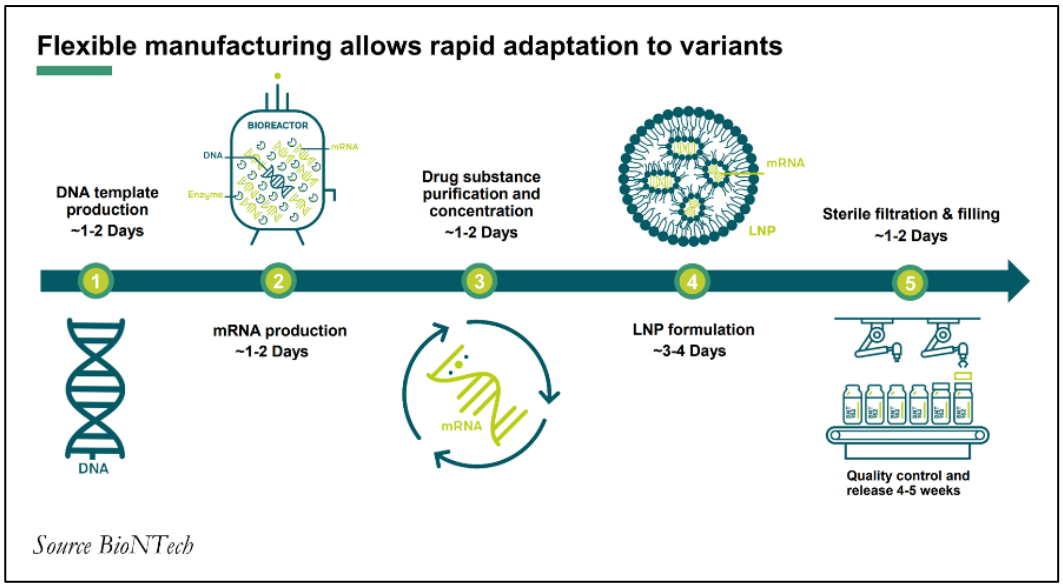
Whilst the development of a new vaccine requires large phase III trials including tens of thousands of volunteers to prove its safety and efficacy, the development of a variant vaccine requires much smaller trials and follows an established regulatory pathway which is similar to that used for other infectious diseases like seasonal flu. This reduces the clinical development timeline considerably. Typically, reactogenicity (side effects) and immunogenicity (efficacy) data are collected in these studies. If trials are successful, data will then be filed with regulators for approval.

*Vaccine manufacturing*

For vaccine manufacturing, the mRNA vaccine platform is the most flexible in dealing with the emergence of new variants and can rapidly adapt vaccines to variants. Unlike traditional vaccine production, mRNA technology simply requires a DNA template to be encoded with the genetic sequence of the new variant. Then the overall manufacturing process, from the DNA template to fill and finish, can be completed in less than two weeks without the need for new scale-ups of the overall process or having to wait for pending regulatory approval.

Following the production stage, quality control and release can take another four to five weeks. Yet within six to seven weeks, the vaccine for a new variant can be produced and ready for delivery. However, our discussion with a manufacturing expert suggests that other vaccine technologies may take up to an additional four weeks in the production process.

If everything goes well, a new variant booster vaccine could be available within as little as 100 days. Given the technology advantage, mRNA booster vaccines are likely to be the first available this autumn.




*How are we going to stay ahead of new Variants of Concern?*

So far, our way of dealing with virus mutation has been by identifying VOC once they have emerged, and yet this means we will always be one step behind the virus mutation. But can we do better? Can we identify and evaluate potential harmful mutations even before they emerge and get ahead of the game?

To stay ahead, we need to be able to predict mutations before they occur. Deep mutational scanning, a high throughput technology which analyses the biophysical properties of protein domains, showed encouraging results. Researchers at the Fred Hutchinson Cancer Research Center in Seattle built a comprehensive mutant library for the receptor-binding domain (RBD) of the spike protein. With this technique, scientists can sort through thousands of mutations according to their binding affinity for the ACE2 receptor (the site where the virus binds to our cells). This allows them to identify potential mutants that enhance ACE2 affinity but are not yet in existence naturally, and this provides crucial insights for the design of future vaccines.

*Predicting vaccine effectiveness against mutations*

Some interesting approaches have been explored by scientists in order to predict whether a mutation will escape vaccine immunity: for example, by analysing a subset of structures of the spike protein in the antibody footprint model. Through this method researchers at Moderna were able to create a contact map showing which positions on the spike protein are most important for neutralising antibody recognition. Mutations at these positions are thus more likely to evade antibody recognition and vaccine protection. This information can then be used to predict vaccine escape potential by looking at how many mutations occurred within the neutralising antibody contact surface in a new variant.

Another approach is a random forest model using a decision-tree-based machine learning method, which was revealed by Moderna at its Science Day this May. This trains the system using reliable data from antibody neutralisation experiments with the presence or absence of a single mutation. The outcome of the training allows the system to predict whether a

mutation can escape from antibody binding and hence from vaccine protection. Early results showed a good correlation of the level of neutralising antibodies between what was observed in the experiment and what was predicted by the system.

These initiatives are just the beginning of our understanding of this complex science. An enormous amount of work still needs to be done to enable us to get ahead of virus mutations.

*Effect of antiviral drugs on variants*

Much of the current effort in fighting the pandemic has been focusing on immunotherapy, including vaccines and antibody cocktails. However, the efficacy of both could be reduced by the emergence of new variants. Another therapy, antiviral drugs, appears underappreciated in our view in terms of its potential use against variants. Given the mechanism of action of this class of drugs, they could be variant agnostic.

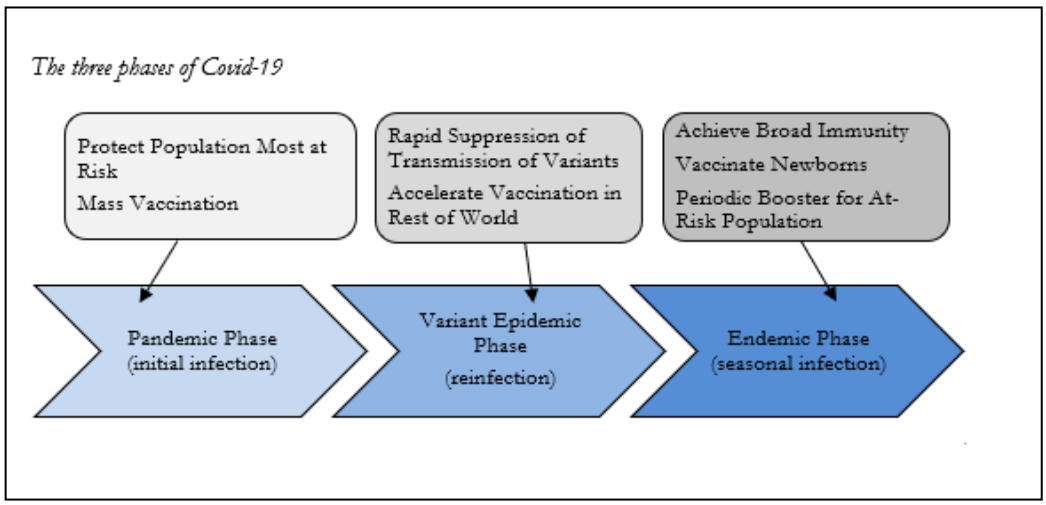
Remdesivir, the first antiviral drug for treating Covid, received an Emergency Use Authorization (EUA) from the FDA and other regulators last year. It works by interfering with the virus replication process and is variant agnostic. The biggest drawback of this drug is that it requires infusion and so needs to be administered at hospitals, which limits its usefulness in the early prevention of disease manifestation. However, other antiviral drugs in development are oral and can be self-administered. The convenience of an oral drug is particularly appealing, especially in countries/areas where access to hospitals is problematic.

The most advanced oral antiviral drug in development is Merck's molnupiravir, currently in phase III clinical trials in outpatient settings. The drug is given twice a day for five days to those who tested positive with Covid within seven days of symptom onset. Again, it works by interfering with viral replication by the introduction of errors into the virus' RNA, which then replicate until it is defunct. The interim analysis of phase II/III showed a good safety profile and an indication of efficacy for preventing severe illness. If the phase III trial is successful, Merck anticipates filing with regulators as early as the second half of 2021.

*Historical precedents*

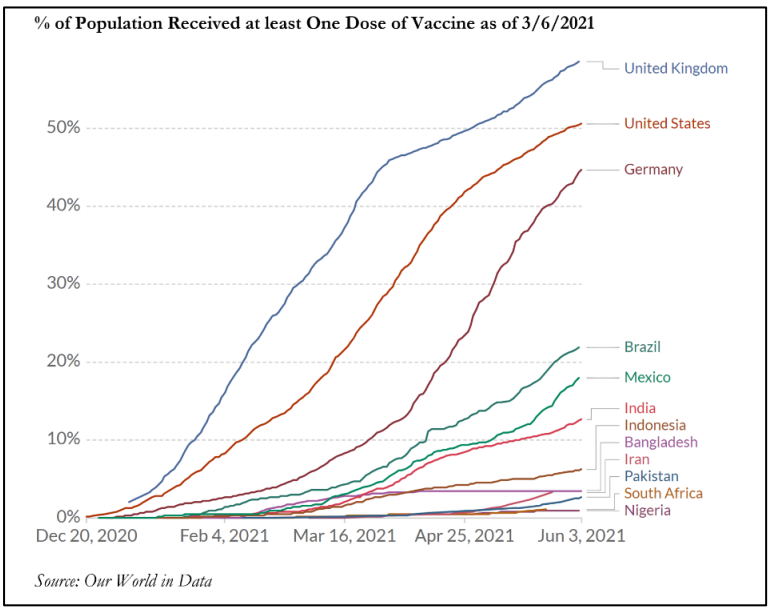
The Spanish Flu of 1918–1920 is often cited as a historical precedent to the current pandemic, although another past pandemic arguably shares more similarities with today's. In the winter of 1889–1890, a pandemic known as the Asiatic or Russian flu killed about one million people worldwide. It was later discovered that it was caused by a coronavirus (OC43) which jumped from bovine to human hosts. Even today, some 130 years later, 3–5% of acute respiratory infections are identified as OC43 every year.

Fast-forward to the present day, and SARS-CoV-2 may follow a similar evolutionary trend. Like OC43, Covid-19 could eventually evolve from pandemic to seasonal endemic with an intermediate phase of epidemic outbreaks caused by VOC.




*Epidemic outbreaks and reinfection*

Whilst rich countries like the US and the UK and those of the European Union are vaccinating their own citizens at full speed and achieving a high vaccination rate well before the end of 2021, the picture in the rest of world, especially in developing nations, is startlingly different (see graph).




Access to vaccines is not equal. While COVAX and other similar initiatives are working to close this gap, the lack of availability of vaccines and resources, or the inability to strike vaccine deals directly with manufacturers, means many low- to mid-income nations will not have enough doses to vaccinate all adults until well into 2022 and beyond.

This is an issue for nations in advanced stages of vaccination as a wide spread of infections in some of these countries could become a breeding ground for new VOC. We have already seen some variants, such as the South African variant, spreading across continents and reducing the effectiveness of vaccines. This means that in our connected world, nobody is safe until everybody is safe. We expect more VOC to develop, followed by epidemic outbreaks, for as long as the vaccination or natural infection rate remains low in these countries.

Some epidemiologists believe it is not a matter of if, but when, reinfection will occur in fully vaccinated people. Indeed, we have seen more pronounced resistance to vaccines from the South African and Brazilian variants, and more recently from the Delta (Indian) variant. If immunity starts waning after six to eight months of natural infection or post-vaccination, this also presents problems. VOC accelerate this deterioration.

During the variant epidemic phase, the focus for governments has to be to suppress the transmission of variants and to apply local restrictive measures like border controls and intensified testing, and in some cases even local lockdowns cannot be ruled out. Therefore the speed of response is key to breaking the chain of transmission.

Although broad immunity helps to ensure that outbreaks of the epidemic happen less regularly across the globe, a seasonal outbreak can nevertheless still flare up. This is still happening with OC43 today, although the number of people being affected will be much smaller in seasonal outbreaks. Nonetheless, severe disease can still occur in high-risk and immunocompromised populations during this phase as immunity wanes, and a booster vaccine is likely to be needed periodically, just as the annual flu jab is needed for at-risk populations today. Newborn babies will also need to be vaccinated, whilst the rest of the population can by and large enjoy a normal life.

*Global vaccination*

We expect the US, UK, Europe and other developed nations to achieve a high vaccination rate before or by the end of 2021, when life here should start to go back to normal (albeit with potential episodic disruptions from VOC outbreaks). However, the biggest challenge facing us today is how quickly we can vaccinate the rest of the world, as the timing of this will determine the duration of the variant epidemic phase.

One of the most important emerging lessons is that a nation vaccinating its own population alone will not bring the outbreak of variants to an end. Even from a self-interest perspective, developed nations need to do much, much more to help speed up the roll-out of vaccines in the rest of the world because only when everyone is safe can the developed world finally free itself from SARS-CoV-2.

Covid-19 is the first global pandemic of our time and it requires a global response. We welcome the G7 leaders' pledge of one billion doses of vaccines for poorer countries. However, many billion doses more are needed to vaccinate the world. Science offers the solution but the global community has to step up to provide the resources to produce the vaccines and boosters needed to overcome the pandemic.

Last year was the year of both the emergence of the pandemic and the development of vaccines, this year is the year of both the roll-out of the vaccines in parts of the world and the development of boosters, and next year will be the year of mass production of vaccines and boosters, and of their global roll-out, 2023 will be the year in which we should overcome the pandemic so that our lives can return to true normality.

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