TONY BLAIR INSTITUTE FOR GLOBAL CHANGE

Understanding the Covid-19 Variants of Concern

EVA THORNE

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Published at https://institute.global/policy/understanding-covid-19-variants-concern on June 18 2021

Introduction

There is renewed urgency in rolling out mass-vaccination programmes due to the rise of variants of SARS-CoV-2. Mass death in India and Brazil along with collapsing public-health systems have caused alarm among public-health officials and governments desperate to access vaccines to halt the spread of these variants, some of which are highly transmissible. For example, the UK reported 9,055 new Covid-19 cases on 16 June; based on government data, between 10 June and 16 June, 55,216 people had a confirmed positive test, which represents a 31.8 per cent increase. [1] Public Health England (PHE) reports that the Delta variant is now the dominant strain in circulation. The rise in new infections is prevalent among younger people and the unvaccinated. Alarmingly, there is preliminary evidence that suggests the Delta variant is at least 40 per cent more transmissible than the Alpha variant and is associated with two times the risk of hospitalisation.

Countries with high vaccination rates, such as Bahrain and the Seychelles, have reported infections in people who are fully vaccinated, likely from the Delta variant. While death rates and hospitalisation rates remain quite low among vaccinated populations that become infected, the rapid spread of Delta and other variants is concerning. Santiago, Chile went back into lockdown on 10 June amid a 17 per cent increase in cases in the country over the preceding two weeks, and a 25 per cent rise in Santiago, despite the fact that more than 50 per cent of Chileans are fully vaccinated. [2] Some countries have gone back to reimposing restrictions and lockdown measures as Delta variant cases surge. In some instances, these countries have lower vaccination rates. For example, residents of Victoria, Australia are being forced into an extension of a lockdown triggered by the rise in infections from the Kappa variant (a sub-type of B.1.617). A few cities in India are just emerging from lockdown. The Portuguese government will see its economy affected by the UK government's decision to move the country from "green" to "amber", which went into effect on 8 June. The classification means that travel is allowed when necessary – subject to testing and quarantine – but is discouraged. The proliferation of variants is generating illness and undercutting efforts to open economies.

There are some variations in how variants are classified, but there are at least four variants of concern (VOCs) in circulation that have emerged since the onset of the pandemic. It is clear that until the world is fully vaccinated, these VOCs will continue to develop. Identifying them early through genomic surveillance mechanisms is absolutely vital. However, the current system for undertaking this critical work is inadequate to meet the challenge.

It is important to distinguish between and among variants – their origins, their degree of transmissibility and whether they lead to worse health outcomes. The crucial question is whether the current Covid-19 vaccines are effective against them, particularly the VOCs, and if drug companies need to make updated

versions that can respond to them. This could be in the form of a booster shot, which many experts expect to be necessary, although the timeframe is not clear and will require serological testing to make such a determination. Vaccine makers are already testing different possibilities, ranging from adding additional doses of the original vaccine in order to increase protection against variants, to adding a dose of vaccine designed to protect against specific variants, to a booster that has doses of both existing vaccine and doses developed to protect against new variants. [3] Ultimately, the way to arrest variants is to ensure that all countries have access to vaccines as well as sufficient absorptive capacity. [4] Otherwise, variants will proliferate, more people will become infected and die, and economic recovery will remain elusive.

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What Is a Variant?

SARS-CoV-2, like all viruses, evolves over time. Changes occur when a virus makes copies of itself. When the replication process involves a change – even a small one – it means that a mutation has occurred. When a virus has at least one new mutation, then it becomes known as a "variant" of the original virus that is already in circulation among the general population. Most viruses that mutate do not change in terms of their ability to generate infection and disease. What matters for a virus's properties is where in the virus's genetic material the changes are located.

Not all variants are the same. An interagency group in the US government created a three-class variant-classification system for SARS-CoV-2: Variants of Interest; Variants of Concern; and Variants of High Consequence. Variants of interest are those that are *suspected* to evade the protection conferred by vaccines, cause more severe disease or be more contagious than the original strain. [5] They become variants of concern when data emerge to suggest that they cause one or more of the outcomes listed above. Variants of high consequence are the third class and are defined as follows by the US Centres for Disease Control and Prevention (CDC) : "A variant of high consequence has clear evidence that prevention measures or medical countermeasures (MCMs) have significantly reduced effectiveness relative to previously circulating variants." [6] Despite concerns about the range of variants currently in circulation, no variants of SARS-CoV-2 have yet been classified as variants of high consequence. Such a designation would trigger reporting to the World Health Organisation (WHO) and the CDC as well as recommendations for updating vaccines and treatments, in addition to announcing how to achieve transmission containment and prevention. [7] Understanding the evolution of variants is the domain of epidemiology and involves testing to confirm Covid-19 cases, identifying which variant caused the infection, and cross-referencing that information with a person's clinical symptoms and vaccination status. [8] Central to this work is genomic sequencing data, which allows scientists to detect and sequence variants. This paper focuses on VOCs.

What We Know About Each Variant of Concern

Alpha/B.1.1.1.7/UK

This variant (also known as 201/501Y.V1) was initially detected in the UK sometime in late summer/early autumn 2020 and was designated as a VOC in early December 2020. Research in the UK indicates that the B.1.1.1.7 variant is somewhere between 30 per cent and 50 per cent more transmissible than the original strain of SARS-CoV-2. [9] Alarmingly, UK studies show that it is also more likely to lead to hospitalisations and deaths. [10] One particular study by the University of Exeter and the University of Bristol found that the Alpha variant could be 64 per cent deadlier. The study looked at those who tested positive for Covid-19 but were not hospitalised, so it is not fully representative since hospitalised people who are diagnosed with Covid-19 are more likely to be sicker and more likely to die than those who are not hospitalised. [11]

On the positive side, evidence has emerged that current vaccines maintain their effectiveness against this variant. For example, data from Israel – where the Pfizer-BioNTech vaccine was used – showed that just 254 out of 416,900 became infected with Covid-19 a week after second dose, all mild cases; [12] this is reassuring given that up to 80 per cent of Covid-19 samples tested in Israel at the time of the study were the B1.1.1.7 variant. Johnson & Johnson's Janssen (J&J) single-dose vaccine provides comparable levels of protection against the Alpha variants as it does against the original strain. Results from phase II/phase III study of the two-dose, viral-vector Oxford/AstraZeneca vaccine showed that it provided good protection against the Alpha variant: 75 per cent, as compared to 84 per cent against the original SARS-CoV-2. [13] More data from PHE and Public Health Scotland (PHS) from the UK vaccination rollout confirm the effectiveness of the vaccine in the context where Alpha is the dominant variant in circulation. Death rates, hospitalisation rates and cases have plummeted among those vaccinated with both the Astra Zeneca and Pfizer vaccines.

Novavax performs well against the Alpha variant as well (it has not yet received emergency use authorisation); results from phase III trials showed that it was 86.3 per cent effective. [14] Moderna maintains its effectiveness against the Alpha variant, with early lab data showing "no significant impact on neutralizing titers against the B.1.1.7 variant relative to prior variants." [15] In a letter to the editors of the *New England Journal of Medicine*, Chinese researchers reported results from what they said was an analysis of "the neutralizing activity of convalescent serum and vaccinee serum against D614G, B.1.1.7, and B.1.351 variants as compared with wild-type pseudovirus," with results showing that the vaccines

performed well against the UK variant but less so against the South African one. Bharat Biotech's Covaxin vaccine also performs well. Finally, the Russian-made viral vector vaccine, Sputnik V, was shown to effectively protect against viruses with spike from the Alpha variant. [16]

Beta/B.1.3.5.1/South Africa

The B.1.3.5.1 variant was detected by South African scientists during the course of routine sequencing in November 2020. The variant has mutations in common with the Alpha and Gamma (first identified in Brazil, see below) strains. In total, it has eight distinctive mutations in the virus's spike protein. Of particular concern to scientists is the E484K mutation, which affects the spike protein that is located on the virus's outer surface. The spike protein is needed for the virus to link to and enter human cells, causing infection. Some studies have found that that the Beta variant is 50 per cent more transmissible than previous strains. [17] At issue is the role of the E474 mutation in reducing the potency of neutralising antibodies and the duration of the body's immune response; reinfection is possible for those infected with the original strain of SARS-CoV-2. [18] Although the variant is more transmissible, it does not appear to be deadlier. The Beta variant is present in the UK, although in low numbers.

Data on the ability of vaccines to protect against B.1.3.5.1 are emerging and point in the same direction: lower levels of protection. However, this does not mean that there is no protection conferred by the vaccines. Evidence from Israel's use of the Pfizer vaccine shows that the prevalence of the Beta variant in vaccinated people is eight times higher than in the unvaccinated group, indicating that the vaccine worked well against the original virus but less well against the variant. [19] It should be noted that the prevalence of the South African variant in Israel remains low, that its numbers were low in the unvaccinated group and that the size of the study was small. In April, Pfizer/BioNTech released data from phase III trials of people living in South Africa. The vaccine was shown to be 100 per cent effective in preventing severe disease (as defined by the CDC) and 100 per cent effective in preventing Covid-19 cases, where the Beta variant is prevalent. [20] The company announced that it is working on a booster, which specifically targets the Beta variant.

The J&J vaccine went through clinical trials in the US, Brazil and South Africa, which generated data on performance against the Beta variant. Even at that time, the variant was in widespread circulation and constituted about 95 per cent of the virus type that was circulating. While the clinical trial sample size was small, the data did show that the J&J vaccine was less effective against mild and moderate Covid-19 but was still highly effective against severe Covid-19 (82 per cent effective). The vaccine's overall efficacy rate was 57 per cent in South Africa. [21] A study of 2,026 healthy, HIV-negative people showed that Astra Zeneca's vaccine exhibited vaccine efficacy against mild to moderate Covid-19 of 21.9 per cent. [22] Among participants with Covid-19, 95.1 per cent were infected by the Beta variant and efficacy

against it was 10.4 per cent. [23] It should be noted, however, that there is indirect evidence that the vaccine is likely to be effective against severe disease in the case of the Beta variant, as a result of a very strong T-cell response. [24] The University of Oxford is adapting the vaccine to work against Beta, as well as other variants, with a booster expected to be available by the autumn of this year.

At the end of January, Novavax released early results from its clinical trials, which showed that its two-shot protein-subunit vaccine was just 50 per cent effective at preventing infection with the Beta variant; results were based on a trial in South Africa that enrolled more than 4,400 people. [25] On the positive side, there were no cases of severe Covid-19 in the vaccinated group. Also in late January, Moderna released a carefully crafted statement that reported on results from blood samples of vaccinated people: "A six-fold reduction in neutralizing titers was observed with the B.1.351 variant relative to prior variants. Despite this reduction, neutralizing titer levels with B.1.351 remain above levels that are expected to be protective." [26] Specific numbers were not available in the statement and the company stated that it would work on developing a booster – as a third shot – that specifically targeted the Beta variant. It is in phase I clinical trials in the US.

China released data from a small-N study in early February that showed that Sinopharm's vaccine (which uses inactivated virus) did trigger an immune response against the Beta variant, although it was weaker than the response against the original strain of SARS-CoV-2. [27] Chinese scientists published data that indicated that the Sinovac-CoronaVac vaccine was 70 per cent less effective against the Beta variant. [28] Finally, Sputnik V also was less effective against Beta. Researchers at the Icahn School of Medicine at Mount Sinai in New York analysed samples from antibody-rich blood serum from 12 people who had received the Sputnik V vaccine. Results from tests of the serum against benign viruses engineered to make versions of spike found in variants of SARS-CoV-2 showed that eight out of 12 failed to stop the Beta variant. [29]

Gamma/ B.1.1.28.1/Brazil/Japan

Japanese health officials and Brazilian scientists first reported that they had detected the B.1.1.28.1 variant, also known as P1. The Gamma variant's mutations make it easier for it to escape antibodies from vaccinations or prior infections, which means that it is possible for people to be reinfected with Covid-19. The Gamma variant contains a number of mutations as compared to the original Sars-CoV-2 virus, including the mutation found in the B.1.351 (Beta) variant as well as the N501Y mutation that is also found in the B.1.1.7 (Alpha) variant. [30] It could be more infectious because the N501Y mutation makes it easier for the virus's spike proteins to bind with human cells. The Gamma variant's E484K mutation is also concerning; lab testing indicates that it helps the virus evade antibodies produced by earlier infections, making it more resistant to antibody drugs. [31] Studies indicate that antibodies made in

response to the Pfizer vaccine are still active, but are slightly less effective against mutations found in the Gamma variant. [32] The same pattern of interaction with the variant holds true for the AstraZeneca and Moderna vaccines. The Sinovac vaccine has been shown to be about 50 per cent effective against symptomatic Covid-19 in a Brazilian city where more than 75 per cent of the cases were caused by the variant at the time of study. [33] Real-world data about the Sinovac vaccine are more encouraging. Nearly all adults in Serrana, a town in the state of São Paulo, Brazil, received both doses of the vaccine between February and April, during the time when the prevalence of the variant was at its highest. Cases of symptomatic Covid-19 fell by 80 per cent, hospitalisations by 86 per cent, and deaths by 95 per cent – all since the beginning of the mass-vaccination campaign. [34]

It is too early to determine whether the Novavax vaccine will provide protection against this variant. Brazil has blocked the use of Sputnik V, and data from elsewhere are not yet available. The Indian Council of Medical Research (ICMR) in association with the National Institute of Virology released data from a study that reports the Covaxin vaccine shows effectiveness against Gamma. [35] The J&J vaccine is slightly less effective at preventing mild and moderate cases but still prevents hospitalisations and death, while the data show that the two mRNA vaccines – made by Pfizer and Moderna – provide full protection against this variant. [36]

Delta/B.1.6.1.7/India

Over the past few months, India has experienced a surge in new infections and high rates of hospitalisations and death, many as a result of what has been termed a "double mutation" variant. This name has been given to a variant that was first detected and reported last year by a scientist in India. This B.1.617 variant, also known as Delta, has three mutations that may make the variant both more transmissible and less responsive to existing vaccines. The British Heart Foundation summarises these three mutations as follows:

1. "The L452R mutation, which may help the virus escape the immune response, including antibodies (which attach to the virus to help neutralise it) and immune cells (which help to directly attack the virus and infected cells). There is also some evidence it can affect how well the virus binds to ACE2 receptors on the surface of our cells. As this is a vital step in the virus getting into our cells, this mutation could potentially make it more infectious."
2. "The P681R mutation – which is also present in other variants, including the Kent strain. It's thought that this mutation may make it easier for the virus to spread."
3. "The B.1.617.1 and B.1.617.3 sub-lineages also carry the E484Q mutation, which is similar to the E484K mutation first identified in the South African strain. There is evidence that this mutation may help the virus escape the immune response. This does not mean vaccines won't offer any protection against this variant, it may just be reduced." [37]

One epidemiologist estimates that the variant may be responsible for about 60 per cent of cases in India's most populated area, suggesting transmissibility of between 20 per cent and 30 per cent. [38] The virus seems to be behaving differently in that it is affecting younger people, including babies. Population density, multigenerational living groups and poorly ventilated spaces also fuel the spread of the virus. The variant has moved out of India and is now in widespread circulation. It was initially detected in India sometime in October 2020 and is now the dominant variant in the UK, representing 90 per cent of all infections. [39] Moreover, the Delta variant is associated with a 60 per cent increased risk of household transmission as compared to the Alpha variant; cases are doubling rapidly from between 4.5 to 11.5 days. [40] The British government is studying the variant to understand whether it is more deadly than previous variants of SARS-CoV-2. Evidence indicates that Delta is behaving differently, with people presenting with what appear to be seasonal cold symptoms such as runny nose, sore throat, fever and headaches. [41] Limited evidence suggests that it may lead to worse disease. Those who are being hospitalised in Bolton, England – an area heavily affected by the variant – are younger, but very few were fully vaccinated. [42] This suggests that vaccinations are having the intended effect. Moreover, the rise is hospitalisations has been low.

There is preliminary evidence that indicates that vaccines maintain their effectiveness against Delta, albeit at a slightly lower level. [43] India is currently using three vaccines. First is the domestically manufactured vaccine Covaxin, which is made by Indian company Bharat Biotech in partnership with Pennsylvania's Ocugen. biRxiv, the preprint server, published a study that shows that Covaxin neutralises the Delta variant. The non-peer-reviewed study showed that the neutralisation capacity against the variant in people vaccinated with Covaxin was similar to those who had recovered from Covid-19. [44] Two studies carried out in India about the effectiveness of Covaxin and Covishield – another name for the AstraZeneca vaccine – showed similar results, and also that when breakthrough infections occurred, they were mild. [45] In the UK, public-health officials have stated that there is no evidence to date that the Delta variant can evade vaccine immunity. [46] There is not published data on the effectiveness of the Pfizer/BioNTech vaccine's effectiveness against the Delta variant, but the BioNTech CEO has said the company did testing on other double mutants and that they are "confident" based on the results that the vaccine will work well. [47] PHS gathered data between 1 April and 6 June on the effectiveness of the AstraZeneca and Pfizer vaccines against the Delta variant that were published in the *Lancet*. These data showed a decline in protection as compared with the Alpha variant after the second dose of both vaccines. For the Pfizer vaccine, protection against infection declined from 92 per cent for the Alpha variant to 79 per cent against the Delta variant two weeks after the second dose; the AstraZeneca vaccine level of protection fell from 73 per cent to 60 per cent. [48] Both vaccines are highly effective against hospitalisation, with the Pfizer vaccine registering a 94 per cent rate of effectiveness against hospitalisation after one dose and 96 per cent after two doses; AstraZeneca posted figures of 71 per cent and 92 per cent respectively. [49] An expert with China's Centre for Disease Control and Prevention

asserted that the country's vaccines provide protection against the Delta variant "to a certain extent" but no data have been publicly released. [50]

The European Medicines Agency expressed confidence that the J&J vaccine would provide protection against the variant. [51] A preliminary lab-based study conducted by the NYU Grossman School of Medicine and NYU Langone Center found that the Moderna vaccine should remain "highly effective" against the Indian variants. [52] Sinovac will work against the variant but more data are needed. [53] Information on Sputnik V comes from the Russian Direct Investment Fund, which claimed that its vaccine is more effective against the Delta variant than other vaccines and that results will be published in a peer-reviewed journal. [54] Specific data are not available. A few days after the statement was made on Twitter, Gamaleya Institute, the maker of the Sputnik V vaccine, announced that it would make available to vaccine manufacturers a booster shot specifically designed to work against the Delta variant; it will be available "soon." [55] Data for Sinopharm and Sinovac are not available. However, in a recent development, more than 350 Indonesian doctors became infected despite being fully vaccinated with Sinovac; most were asymptomatic. Worryingly, dozens were sick enough to be hospitalised. [56] The data indicate that the Delta variant was responsible.

Detecting Variants: The Importance of Genomic Surveillance

Because of the scale of the pandemic, scientists are tracking changes to the virus at pace and at scale. While their efforts have been unprecedented, there are still gaps that affect the ability of scientists to quickly detect mutations and adapt vaccines accordingly. Genomic surveillance is now as critical as vaccine and treatment development. To maximise the value of this evolving sphere of scientific inquiry, it needs to be global in its activity, "standardized and embedded in national pandemic-prevention programmes." [57] GISAID is a non-profit online database that uploads and makes available information on viral genomes. More than 140 countries are covered (although most upload only a small number of sequences) and more than 360,000 SAR-CoV-2 genomes have been sequenced and put in the database. [58] Denmark has uploaded 7 per cent of genomes on the database while the UK has contributed 45 per cent. [59] Despite the enormous value of this online database, there are significant gaps that keep it from serving as a comprehensive repository. For example, as a paper on genomic sequencing and surveillance by the Global Health Security Consortium – a partnership between the Tony Blair Institute, the Ellison Institute for Transformative Medicine and scientists at the University of Oxford – points out, technology limitations must be addressed to ensure that leaders have real-time information on emerging variants.

Progress is being made to address gaps. For example, the University of Oxford and Oracle have collaborated to create a Global Pathogen Analysis System (GPAS), which combines Oxford's Scalable Pathogen Platform Pipeline (SP3) with the capabilities of Oracle Cloud Infrastructure (OCI). The SARS-CoV-2 is the first pathogen being used in GPAS. According to a press release from Oracle, the tool will allow collaborating scientists, researchers, and governments worldwide to "process, analyze, visualize, and act on a wide collection of COVID-19 pathogen data for the first time. This includes identifying variants of interest and their potential impact on vaccine and treatment effectiveness. For example, analytics dashboards in the system will show which specific strains are spreading more quickly than others and whether genetic features contribute to increased transmissibility and vaccine escape. Already, Oxford has processed half the world's SARS-CoV-2 sequences, more than 500,000 in total." [60]

The partnership benefits from work already underway in the UK, which leads tracking mutations of SARS-CoV-2 through a scientific consortium that provides the UK's hospitals with procedures for sending samples to specialised labs that will conduct genomic sequencing on those samples. Scientists use cloud computing to analyse any mutations found to understand how they differ from the original strain. The Covid-19 Genomics UK Consortium has, to date, sequenced 452,045 viruses; it was created

with UK government funding [61] and is responsible for the majority of coronavirus genomes sequenced to date.

Making More Effective Vaccines

As of 8 June, there are 331 Covid-19 vaccine candidates under development. [62] The breakdown is as follows:

- Pre-clinical (pre-human work): 225
- Phase I (small-N safety trial): 28
- Phase I/II: 31
- Phase II (larger-N safety trial): 8
- Phase III (assessing efficacy with large N): 23
- Authorised (vaccines in limited or early use): 16 [63]
- Abandoned (vaccines abandoned after trials): 4

Fifteen months into the pandemic, drug companies are already developing second-generation Covid-19 vaccines. The slow pace of global vaccination campaigns allows new variants to emerge, giving urgency to the drive to either develop new vaccines or retrofit current ones. Two-thirds of epidemiologists, virologists and infectious-disease specialists surveyed by People's Vaccine Alliance believe that it may only be a year or less before existing Covid-19 vaccines are rendered ineffective; 88 per cent of them indicated that low vaccination rates in many countries increase the likelihood of the development of mutations that are vaccine-resistant. [64]

One area of research involves multivalent vaccines, which remain effective against emerging mutations. Such an approach is currently used in the annual flu vaccine, which combines several strains of influenza virus. GlaxoSmithKline (GSK) is collaborating with CureVac through a €150 million partnership with the goal of developing a multivalent candidate vaccine to address emerging variants for both endemic and pandemic use, using the mRNA platform. [65] Both companies will contribute research and development, as well as manufacturing capabilities. Both GSK and CureVac will pay half the cost if regulatory requirements are fulfilled; the companies are aiming to have the vaccine candidate ready some time in 2022. [66] Monovalent approaches will also be included. "These next generation COVID-19 vaccines may either be used to protect people who have not been vaccinated before, or to serve as boosters in the event that COVID-19 immunity gained from an initial vaccination reduces over time. In addition, the collaboration will assess the development of novel mRNA vaccines to protect against multiple respiratory viruses, including COVID-19." [67] Also in the race is J&J, which is focused on developing a new vaccine that can be effective against the Beta variant that has caused such concern. [68] London's Imperial College abandoned its research on an mRNA Covid-19 vaccine for two reasons. First, a number

of vaccines have received emergency use authorisation in the UK. Second, researchers wanted to redeploy the mRNA technology platform that they were using to develop the initial vaccine to address emerging mutations. [69]

BioNTech, which is Pfizer's partner, is trialling a third dose to determine whether it would increase protection against variants; it is also weighing the development of a variant-specific vaccine that could replace the existing one, or be used alongside the existing one, which may be more effective. [70] At issue is how quickly such a vaccine could be ready for use. Moderna is exploring including protection against the variants directly in its main candidate, with positive results from an initial trial reported. These potential doses could not be administered – at least early on – to those who are already vaccinated; and they would be slightly more expensive for Moderna to make. [71] Such a vaccine would be of greater relevance to countries where the variants are spreading quickly, such as South Africa and Brazil. J&J is developing a second-generation vaccine that targets the Beta variant; it is also exploring a two-dose version. [72]

A novel approach is being used by German company Prime Vector Technologies (PVT), which has received €5 million from the German Economics Ministry. First-generation Covid-19 vaccines target the spike protein. In contrast, PVT is exploring targeting the immune response at antigens other than the spike protein in an effort to follow the virus's evolution. [73] In a similar vein, a team of virologists at Nottingham University are experimenting with a next-generation Covid-19 vaccine that targets the spike protein that sits on the virus's surface as well as the N protein. [74]

Conclusion

The proliferation of variants presents several challenges. First, they must be quickly detected, which requires ongoing surveillance programmes, and some countries have more capacity than others. Second, the information must be shared and made available on a global basis for it to be used effectively. To date, efforts have been piecemeal. Third, in some instances vaccine makers must quickly adapt their vaccines to address emerging variants. Scientists are working on all fronts, and efforts are bearing fruit. For countries that are unlikely to reimpose restrictions and that have pockets of unvaccinated people, it is very likely that we will see an uptick in hospitalisations and death. Robust initiatives to address vaccine hesitancy will be critical in both rich and poorer countries. And for poorer countries vaccine access, absorptive capacity and vaccine hesitancy all need to be addressed. All of these challenges underscore the need for global vaccination programmes executed at pace, as this is ultimately the only way to address the evolution and spread of variants.

Appendix: Notable SARS-CoV-2 Variants of Concern So Far

WHO Name	Scientific Name (Pango lineage and/or Nextstrain)	Where It Was First Detected	Mutations	Attributes
Alpha	B.1.1.7	Kent, UK	N501Y (increases transmissibility) P681H 69/70 deletion	~50 per cent increased transmissibility Potential increased severity based on hospitalisations and case fatality rates No impact on susceptibility to monoclonal antibody treatments that have received emergency use authorisation Minimal impact on neutralisation by convalescent and post-vaccination sera
Beta	501Y.V2 or B.1.351	South Africa	N501Y (increases transmissibility)	~50 per cent increased transmission Significantly reduced susceptibility to the

WHO Name	Scientific Name (Pango lineage and/ or Nextstrain)	Where It Was First Detected	Mutations	Attributes
			E484K (reduces antibody recognition) K4 17N (reduces antibody recognition)	combination of bamlanivimab and etesevimab monoclonal antibody treatment, but other monoclonal antibody treatments are available under emergency use authorisation Reduced neutralisation by convalescent and post-vaccination sera
Gamma	P1	Brazil	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I	Significantly reduced susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment',[7] but other monoclonal antibody treatments are available under emergency use authorisation [14] Reduced neutralisation by convalescent and post-vaccination sera

WHO Name	Scientific Name (Pango lineage and/or Nextstrain)	Where It Was First Detected	Mutations	Attributes
Delta	B.1.617	India	Carries the L452R spike mutation, among others.	Potential reduction in neutralisation by some monoclonal antibody treatments available under emergency use authorisation Reduced neutralisation by post-vaccination sera

Note: This table is an updated version of one that appears in TBI's earlier paper "The New Necessary: How We Future-Proof for the Next Pandemic"

Charts created with Highcharts unless otherwise credited.

Footnotes

1. ^ "Coronavirus in the UK: Simple Summary for United Kingdom," 16 June 2021, available online at https://coronavirus.data.gov.uk/easy_read#cases
2. ^ Anne Gulland, "China Producing Millions of Doses but Questions Over Vaccine Efficacy Remain," The Telegraph, 12 June 2021, available online at https://www.telegraph.co.uk/global-health/science-and-disease/china-producing-millions-doses-questions-vaccine-efficacy-remain/
3. ^ Alice Park, "Moderna Reports That Booster Doses of Its COVID-19 Vaccine Appear to Be Effective Against Virus Variants," Time 5 May 2021, available online at https://time.com/6046405/moderna-covid-19-vaccine-booster-study/
4. ^ Peter Mwai, "Covid-19 vaccines: Why some African states can't use their vaccines," BBC News, 8 June 2021, available online at https://www.bbc.co.uk/news/56940657. Many governments are struggling with vaccine hesitancy, and the inability to administer vaccination programmes before the vaccines are past their expiration date.
5. ^ Melissa Couto Zuber, "COVID-19 Variant of Interest vs. Variant of Concern: What Does It Mean?," CTV News, 22 April 2021, available online at https://www.ctvnews.ca/health/coronavirus/covid-19-variant-of-interest-vs-variant-of-concern-what-does-it-mean-1.5398083. A more scientific definition is presented on the US CDC website: "A variant with specific genetic markers that have been associated with changes to receptor binding, reduced neutralization by antibodies generated against previous infection or vaccination, reduced efficacy of treatments, potential diagnostic impact, or predicted increase in transmissibility or disease severity." See "SARS-CoV-2 Variant Classifications and Definitions," CDC, 27 April 2021, available online at https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html#Interest
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7. ^ Ibid.
8. ^ David Adam, "What Scientists Know About New, Fast-Spreading Coronavirus Variants," Nature, 24 May 2021, available online at https://www.nature.com/articles/d41586-021-01390-4
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