COVID-19 Global Trends and Analyses

Volume 2: Vaccines and Viral Variants Update

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CONTENTS

SUMMARY

Vaccines

- As of 30 May, **more than 1.84 billion vaccine doses** have been administered worldwide, equal to 24 doses for every 100 people.
- The global distribution of COVID-19 vaccines has been marked by inequality. More than 84 per cent of doses given worldwide have been administered in high- and upper-middle-income countries. Only **0.3 per cent of doses have been administered in low-income countries**.
- The countries with the highest rates of vaccination (per 100 people) are Seychelles, UAE, Israel, Bahrain, Malta, Chile, UK, Mongolia, Maldives and Hungary.
- In **Australia**, the seven-day moving average of daily vaccinations is 84,000. At the current pace of roughly 535,000 doses a week, the 40 million doses needed to fully vaccinate Australia's adult population will not be reached until late July 2022.
- **COVAX** has so far shipped over 69 million COVID-19 vaccines to 125 countries. This is far short of the goal of delivering two billion doses in 2021. The initiative has said it wanted to ship more than 250 million by the end of May. With the ban on exports of Indian manufactured vaccines, this goal is unlikely to be attained.
- The AstraZeneca-Oxford vaccine has been deployed against COVID-19 in **at least 115 countries**. Since early March 2021, reports have emerged in many countries of a rare but serious side effect involving thrombosis (clotting) with thrombocytopaenia (low blood platelet count), known as TSS, in young healthy people who had received the AstraZeneca-Oxford vaccine. Most cases involved clotting in a large vein such as in the brain, called cerebral venous sinus thrombosis.
- In **Australia**, the incidence of TSS has been around 1 in 87,000 doses, similar to Europe.
- Fewer cases have been associated with the Johnson and Johnson vaccine but American and European regulators have added a warning label to the vaccine.
- A Public Health England (PHE) study has found the Pfizer vaccine was 88 per cent effective against symptomatic disease from **the B.1.617.2 (Indian) variant** two weeks after a second dose, compared with 93 per cent against the B.1.1.7 (Kent) variant. The AstraZeneca vaccine was 60 per cent effective, compared with 66 per cent against the Kent variant over the same period.
- Two doses of the **AstraZeneca COVID-19** vaccine may be 85 to 90 per cent effective against symptomatic disease, PHE announced, while cautioning that it continued to monitor the data.
- The first modified vaccine against variants of concern that emerged in South Africa (B.1.351) and Brazil (P.1) has successfully neutralised them in laboratory trials, according to Moderna. The results suggest that **boosters against the variants** will be feasible and could be rolled out this year.
- In Qatar, the effectiveness of the **Pfizer vaccine** against any documented infection with the B.1.1.7 variant was 89.5 per cent at 14 or more days after the second dose. The effectiveness against any documented infection with the B.1.351 variant was 75 per cent.
- Spanish researchers have found that vaccinating people with both the AstraZeneca-Oxford and Pfizer-BioNTech COVID-19 vaccines produces a potent immune response against the virus SARS-CoV-2. Preliminary results are the first to show the **benefits of combining different coronavirus vaccines**.
- Adults infected with COVID-19 three weeks after receiving one dose of the Pfizer-BioNTech or AstraZeneca-Oxford vaccine were **38-49 per cent less likely to pass the virus on** to their household contacts than people who were unvaccinated, according to a preprint by PHE.
- On 10 May, the US FDA expanded the emergency use authorisation of the Pfizer-BioNTech vaccine for the prevention of COVID-19 to include adolescents 12 through 15 years of age. The European Medicines Agency followed suit on 28 May.

- The WHO announced on 7 May that it would list, for emergency use, a coronavirus vaccine made by Chinese firm **Sinopharm**. The step means that the vaccine can be used to bolster WHO-backed efforts such as the COVAX initiative.
- The authors of a Boston study concluded that receipt of a COVID-19 mRNA vaccine was **immunogenic in pregnant women**, and vaccine-elicited antibodies were transported to infant cord blood and breast milk. Pregnant and non-pregnant women who were vaccinated developed cross-reactive antibody responses and T-cell responses against SARS-CoV-2 variants of concern.

Variants of Concern

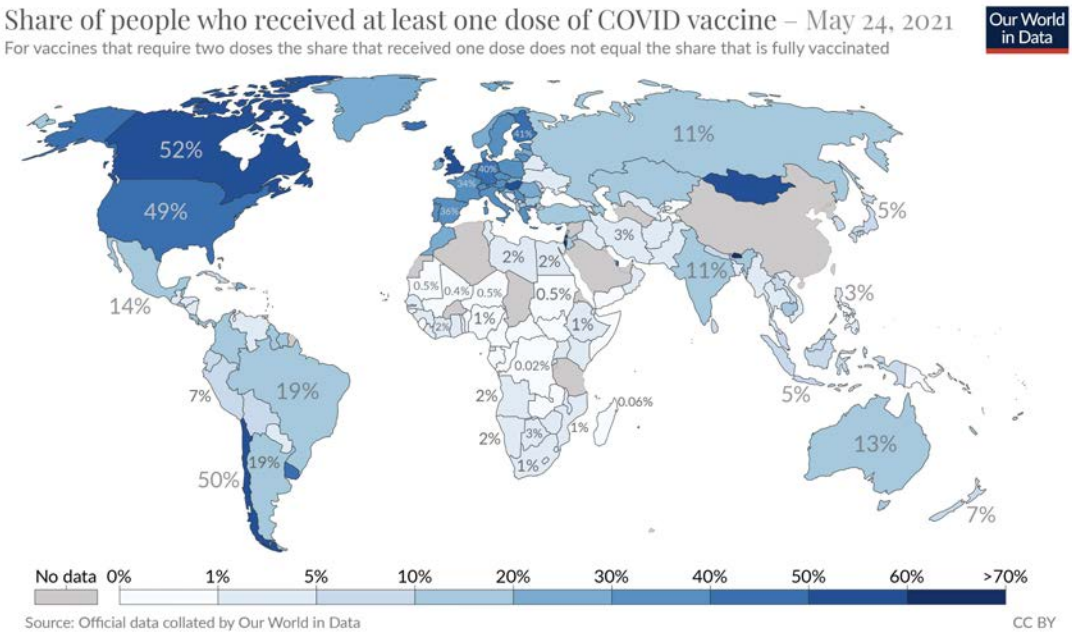
- The current SARS-CoV-2 variants of concern are B.1.1.7 (originally detected in the UK), B.1.351 (South Africa), P.1 (Brazil), B.1.617 (India), B.1.427 and B.1.429 (California) and B.1.526 (New York).
- First reported in December 2020, SARS-CoV-2 lineages **B.1.617.1, B.1.617.2 and B.1.617.3** have been increasingly detected in India and other countries. In just a few weeks, the B.1.617.2 variant has become the dominant sub-lineage across India and has spread to about 40 nations, including the United Kingdom, Fiji, Vietnam and Singapore.
- Lab scientists report that B.1.617 was resistant against an antibody agent used for COVID-19 treatment. Also, **B.1.617 evaded antibodies** induced by infection or vaccination. Collectively, the study reveals that antibody evasion of B.1.617 may contribute to the rapid spread of this variant.
- Another study found that the B.1.617.1 variant is **6.8-fold more resistant** to neutralisation by sera from COVID-19 convalescent and Moderna and Pfizer vaccinated individuals. Despite this, a majority of the sera from convalescent individuals and all sera from vaccinated individuals were still able to neutralise the B.1.617.1 variant.
- The PHE study, reported in the Vaccines section, indicates that the **B.1.617.2 variant does not evade the immune response** induced by the Pfizer and AstraZeneca vaccines.
- The rapid rise in reported cases of the B.1.617.2 variant in north-west England indicates increased transmissibility. On 19 May, PHE reported that there had been 3,424 cases in the country. Preliminary studies indicate that the variant may be **50 to 60 per cent more transmissible** than the B.1.1.7 variant.
- The **B.1.351 variant** has shown evidence of increased transmissibility, a considerable reduction in neutralisation by convalescent and post-vaccination serum, and significantly decreased neutralisation by monoclonal antibodies.
- Clinical trials of AstraZeneca, Johnson and Johnson, and Novavax vaccines showed **lower efficacies** in South Africa than in countries where the variant is not circulating. Currently there is no evidence to suggest that this variant has any impact on disease severity.
- Recent research suggests that the **P.1 variant** is 2.5 times as infectious as the Wuhan strain. The variant accounts for 47 per cent of cases in Brazil and has spread to 40 countries. It is thought to be contributing to current COVID-19 surges in Argentina, Uruguay, Paraguay, Peru, Bolivia and Colombia.
- Researchers **in Angola detected a new variant of interest** in three incoming travellers from Tanzania who were tested together at the airport in mid-February. The three genomes from these passengers were almost identical and presented highly divergent sequences within the A lineage. This new VOI, temporarily designated A.VOI.V2, has several mutations present in other VOCs/VOIs and are evolving under positive selection.
- Vietnam's Health Ministry announced on 29 May that it had detected a **highly transmissible new variant** of the coronavirus that has helped fuel a recent wave of infections in the country. Genetic sequencing found the variant in at least four COVID-19 patients in the country. It has the Y144 deletion on spike protein S of the B.1.617.2 variant. This mutation is similar to the one found on the B.1.1.7 variant.

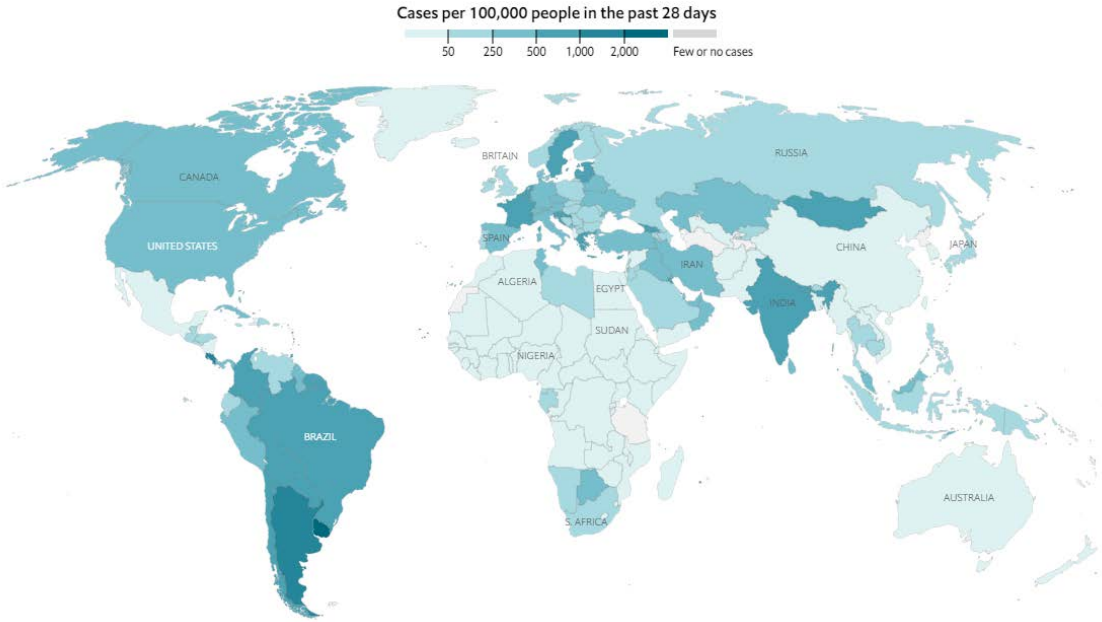
GLOBAL SCIENTIFIC UPDATES

SARS-CoV-2 Vaccines Update

Global Rollout of Vaccines

As of 30 May, more than 1.84 billion vaccine doses have been administered worldwide, equal to 24 doses for every 100 people. But the distribution across countries is highly uneven. **The map on the top shows** the per cent of people who have received at least one dose of vaccine. By contrast, **the map underneath** it shows the cases per 100,000 people in the past 28 days. If vaccines were distributed according to caseload, the greatest needs are in South and Central Asia and South America.





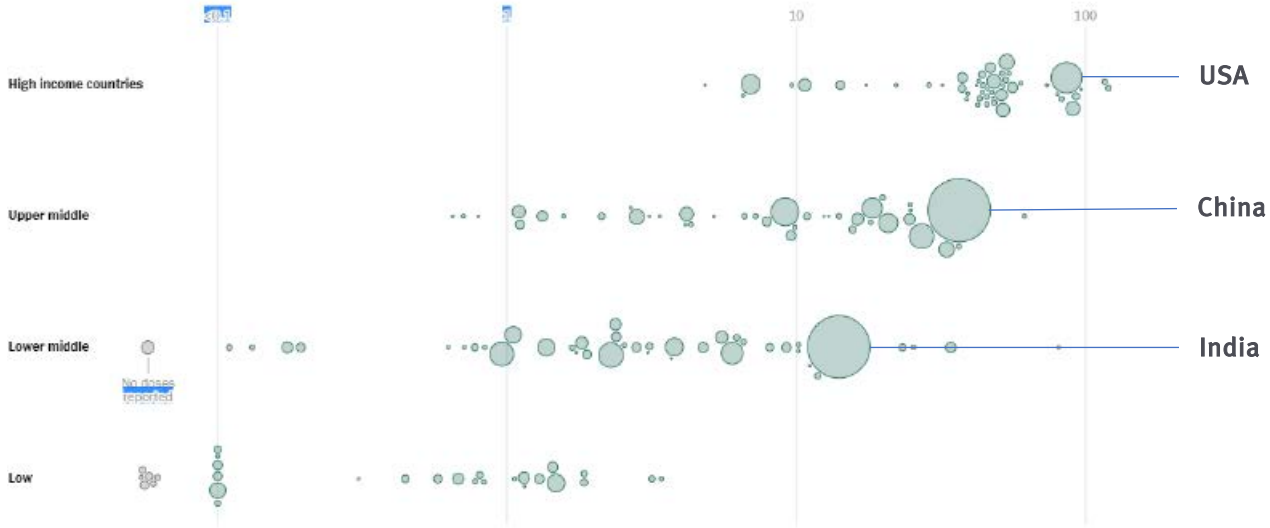
High performers

The threshold for COVID-19 vaccine coverage to achieve population (or 'herd') immunity is still unknown but expert estimates range between 70 and 90 per cent. **Seychelles** is vaccinating its people faster than any other nation. About 63 per cent of the population has received the two doses needed to be fully vaccinated. (Almost all the vaccines currently being used internationally require two doses several weeks apart. People are not fully vaccinated until they receive the second dose.) It is followed by **UAE**, where 61 per cent of people have been fully vaccinated, and **Israel**, which has fully vaccinated 59 per cent of its population.

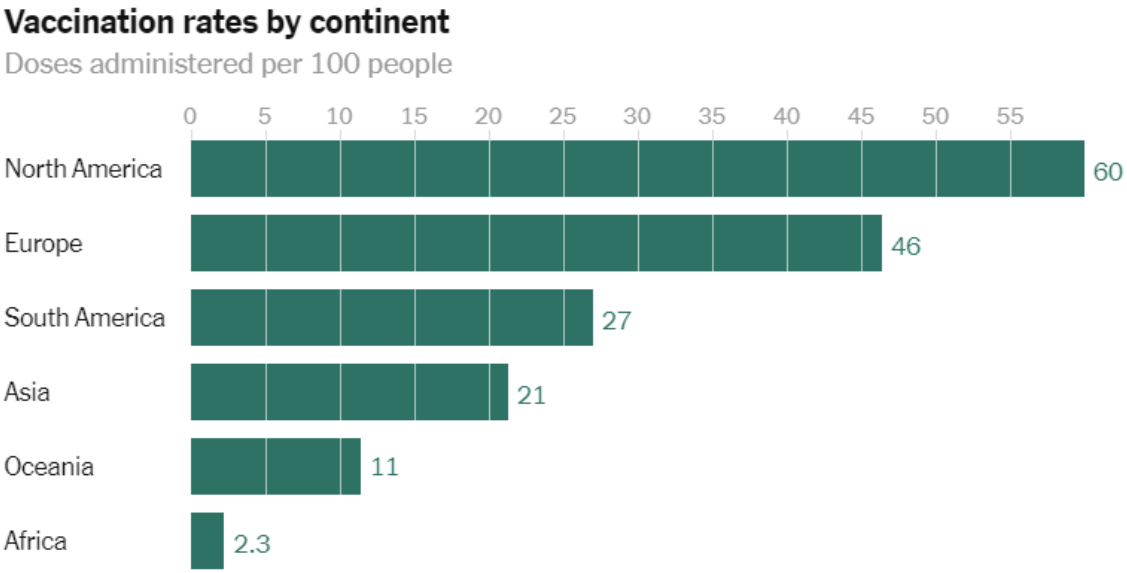
Nauru has the highest percentage of people — 68 per cent — partially inoculated against COVID-19, meaning they have received the first dose of a two-dose vaccine regime. It is closely followed by Bhutan, at 63 per cent.

Global Vaccine Inequity

The global distribution of COVID-19 vaccines has been marked by inequality. 84 per cent of doses given worldwide have been administered in high- and upper-middle-income countries. **Only 0.3 per cent of doses have been administered in low-income countries.** The following figure indicates the gap in coverage (doses per 100) by income levels.



There is also a striking divide between continents. Africa has the slowest vaccination rate of any continent, with some countries yet to start mass vaccination campaigns.

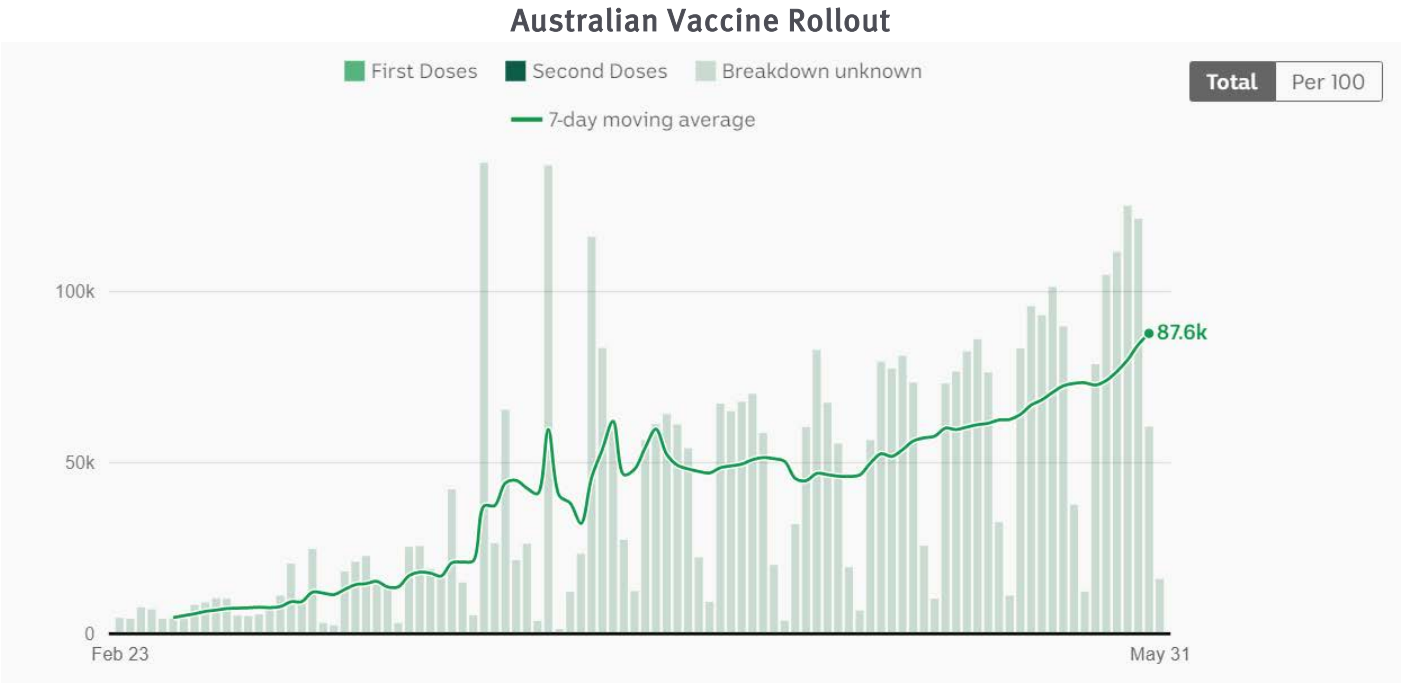


Australia | Vaccine Rollout and Trends

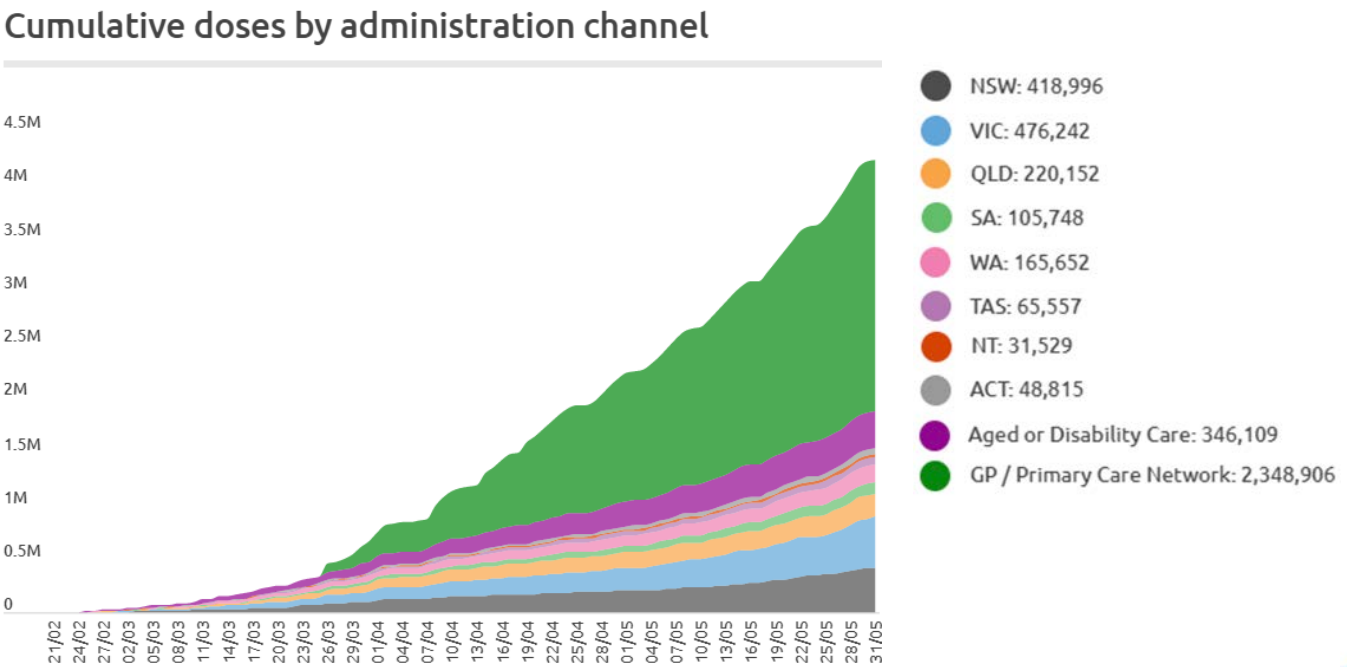
By 30 May, more than 4.15 million doses of COVID-19 vaccines had been administered, equivalent to 15 per 100 people. Mass COVID-19 immunisation hubs in Australia's two biggest states have pushed the nation's daily vaccination rate to new highs. Vaccinations have climbed to 84,000 doses a day, based on the seven-day moving average.

Victoria has led the way with the expansion of its mass vaccination hubs, fuelling a surge in its daily vaccination rate from 3,400 doses on 3 May to about 8,100 doses on 24 May. In NSW, daily vaccinations have more than doubled since the state opened its first mass vaccination hub on 10 May, from roughly 3,500 to 9,300 on 24 May, based on the seven-day moving average.

At the current pace of roughly 535,000 doses a week, Australia can expect to reach the 40 million doses needed to fully vaccinate the adult population in late July 2022.



As seen in the graph below, GP and primary care network vaccinations have increased and scaled up over time.



South Asia | Vaccine Rollout and Trends

India has been the powerhouse vaccine manufacturer for the world, notably through the Serum Institute of India (SSI) which is the largest single supplier to the COVAX (2 billion doses scheduled this year). India's export ban instituted in March continues to divert vaccines to the domestic response. However, vaccination remains slow with supply and distribution issues. So far, India has provided at least one dose to 15 per cent of the population. Just over 3 per cent have been fully vaccinated and distribution has not been equitable since eligibility criteria were loosened in late April.

A major bottleneck is the lack of a centralised procurement system with each state essentially competing to secure supply. New Delhi's chief minister said city authorities had been forced to halt vaccinations for those aged between 18 and 44 as supplies had run out. The chief minister of Andhra Pradesh urged the prime minister to help with supplies as the state had no stocks to vaccinate those aged below 45.

Of concern, vaccination is not free for all citizens – this is unparallel in other federal democracies. Some states, such as West Bengal and Delhi have re-defined priority group, but this is not uniform across the country.

In addition to the viral adenovirus vector vaccines, Covishield (SSI) amd Covaxin (Bharat Biotech), India has now approved Sputnik V, available from the second week of June.

In South Asia, **Maldives** has the highest rate of vaccinations having administered at least one dose to 87 per 100 people and fully vaccinated 29 per cent of the population. **Bhutan** ranks second, followed by much lower coverage in the other countries of the region.

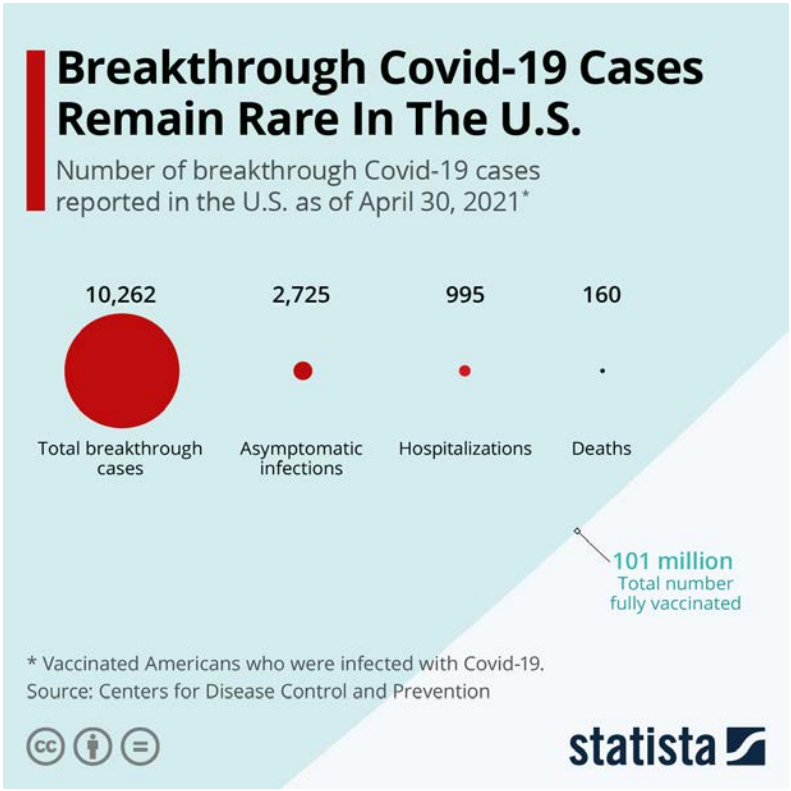
Country	At least one dose per 100	Per cent fully vaccinated
Maldives	87	29
Bhutan	63	-
India	14	3.1
Nepal	9.2	1.9
Sri Lanka	8	1.5
Bangladesh	6	2.4
Pakistan	1.8	0.6
Afghanistan	1.4	0.2

Countries in the region that rely on the COVAX facility are being affected by the ban on the export of vaccines manufactured in India. A number of countries, including Nepal and Bangladesh, are on the verge of running out of vaccines.

The United States | Vaccine Rollout and Trends

As of 27 May, the US had administered more than 287 million doses of vaccines, equivalent to 86 per cent of the population. 39 per cent have been fully vaccinated.

Data recently published by the US CDC show that vaccines have been highly effective at reducing infections, hospitalisations and deaths. As of late April, around 101 million Americans had been fully vaccinated and the CDC's data states that 10,262 cases of COVID-19 occurred among fully vaccinated people, 995 of whom required hospitalisation with 160 deaths recorded.



Africa | Vaccine Rollout and Trends

Across the 54 countries on the African continent, at least one dose of vaccine has been administered to 1.42 per cent of the population. Only 0.42 per cent has been fully vaccinated. The highest coverage rate is in **Seychelles** where 62 per cent of the population has been fully vaccinated, followed by **Morocco**, which has fully vaccinated 12.2 per cent of the population. The only other African countries that have fully vaccinated more than one per cent of their populations are **Tunisia** (1.6 per cent) and **Zimbabwe** (1.5 per cent). Not a single dose has been administered in Burundi, Central African Republic, Chad, Eritrea, Madagascar, Tanzania, Sahrawi Republic and Burkina Faso.

Most African countries have been using vaccines manufactured in India, such as CoviShield (AstraZeneca). More than 40 countries have already received shots from COVAX and are relying on further deliveries. However, the Serum Institute of India (SII) has announced that it would not be able to export the vaccine until the end of 2021. The delays raise the prospect of hundreds of millions of people across Africa waiting until 2022 or even 2023 for vaccination, which will lead to many more deaths and further damage to economies, and could allow new and potentially more harmful variants of the virus to emerge.

The WHO, a co-leader of COVAX, has called on vaccine makers outside India to advance supplies to the program to make up the shortfall. Gavi, a public-private global health partnership that aims to increase access to immunisation in poor countries and co-leads COVAX, has said at least 140m doses that it had expected from SII by the end of May will now remain in India.

Pacific Island Countries (PICs) | Vaccine Rollout and Trends

Up until now, most Pacific Island Countries (PICs) have done well controlling COVID-19. The highest numbers of COVID-19 cases in the Pacific have been in French and US territories, such as French Polynesia and Guam, and Papua New Guinea (PNG). Having had very few cases of COVID-19 over the last year, PNG is now battling with widespread community SARS-CoV-2 transmission highlighting the need for urgent mass vaccination.

For the smaller PICs, the importation of COVID-19 is a constant threat – as has been seen in Fiji where community transmission continues after a leak in quarantine. Although PICs have had very few community cases over the course of this pandemic, many people are now desperate for the relaxation of international border restrictions as they rely on tourism for their income. However, the PICs have some of the highest rates of risk factors for severe COVID-19 in the world. Obesity and diabetes are risk factors for severe COVID-19 and PICs have the highest burden of these co-morbidities in the world. So, in order to open their borders fully, these countries need high vaccination rates and a vaccine that protects against new variants.

The PICs have small but growing populations, from less than 2,000 in Niue and Tokelau, to 8.8 million in PNG. They are countries characterised by remoteness, susceptibility to natural disasters and vulnerability to external shocks, as well as limited resources, which means an increased dependence on international trade.

Growth and development are restricted by the high costs of communication, energy and transportation due to their smaller size. Their reliance on tourism led to huge social and economic changes in 2020. In Fiji, it's estimated that tourism contributes 38 per cent of the economy and almost totally ceased as the global pandemic took hold in March 2020.

Where are vaccines coming from?

The United States is supporting Guam, Palau, FSM, the Marshall Islands, American Samoa and Northern Marianas under Operation Warp Speed. The French territories of New Caledonia and French Polynesia along with Wallis and Futuna have commenced vaccination. New Zealand is assisting its associated states (the Cook Islands and Niue) and dependent territory (Tokelau), while Australia and New Zealand are providing support to PNG, Solomon Islands, Vanuatu, Fiji and others. India and China have also offered COVID-19 vaccines to PICs. Further support is being provided by the Asian Development Bank and the World Bank.

The COVID-19 Vaccines Global Access (COVAX) Facility plans to deliver COVID-19 vaccine to all PICs who sign up. COVAX allocates vaccines based on equity and per centage of population, although these allocations have been a higher per centage for smaller countries due to small freight volumes. Australia has also announced that it will export up to 10,000 doses weekly of the locally made AstraZeneca vaccine, prioritising Melanesian countries.

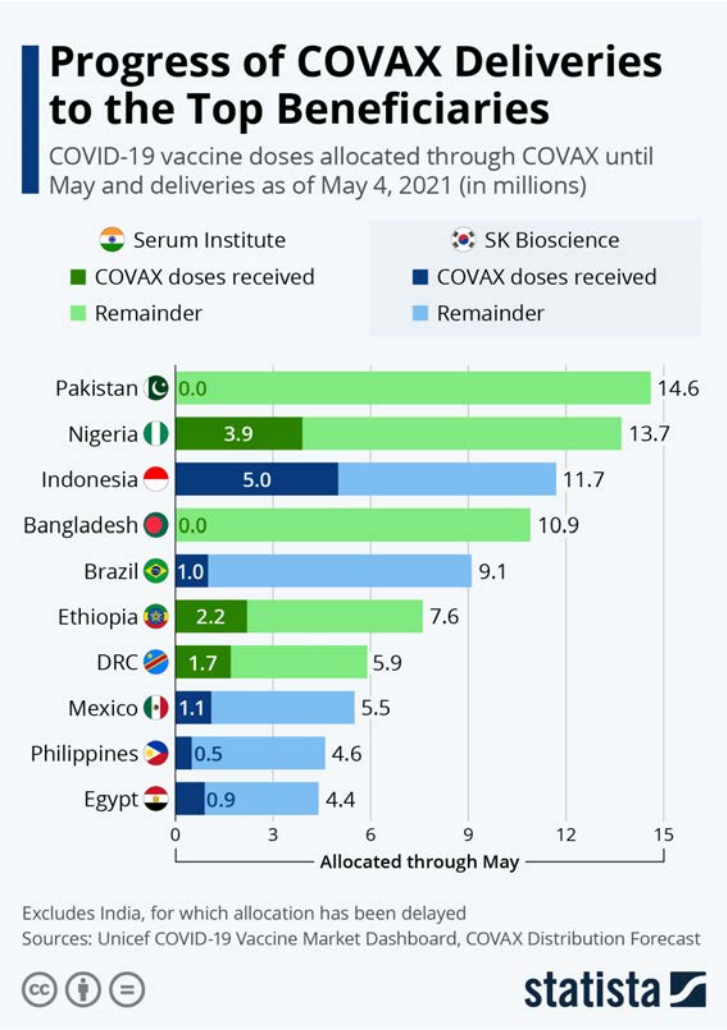
A vaccination schedule that only requires a single dose and a regular fridge would be ideal for PICs. Therefore, the Johnson and Johnson vaccine would appear best suited for the region, particularly for remote outer islands, due to its one-dose regimen, normal cold chain requirements, as well as its authorisation and availability through COVAX. The second preference would be the AstraZeneca vaccine. It's unlikely there would be any cases of the blood clotting disorder in most PICs because most countries have very small populations and this side effect is very rare. In PNG, there could be 15-30 cases if the whole adult population were vaccinated. But given the surge in COVID-19 cases, a delay in the vaccination would have much more severe consequences in terms of deaths from COVID-19.

As of the end of May, Palau and Nauru have effectively vaccinated their entire adult populations with one dose, while US-supported Guam (86 per cent have received one dose) and Marshall Islands (49 per cent) are not far behind. Of the independent PICs, Tonga leads (21 per cent), followed by Fiji and Samoa (both 10 per cent). PNG has provided at least one dose to less than 0.1 per cent of its population.

COVAX Progress | Vaccine Rollout and Trends

COVAX has so far shipped over 69 million COVID-19 vaccines to 125 countries. This is far short of the goal of delivering two billion doses in 2021. The initiative has said it wanted to ship more than 250 million by the end of May. With the ban on exports of Indian manufactured vaccines, this goal is unlikely to be attained. Much depends on when the Novavax vaccine, which is the second largest planned source of vaccines for COVAX, will become available. Novavax has announced a delay in seeking authorisation until the third quarter of the year.

As seen in the chart that shows shipments between 24 February and 4 May, COVAX deliveries that were made in India before the sudden halt in late March were more plentiful than those coming out of South Korea. The exception is deliveries to Indonesia. Here, around 5 million doses have already arrived from contractor SK Bioscience. Still, the number makes up less than half of the allotment through May.



Among the ten biggest beneficiaries of the initiative, Nigeria, Ethiopia and the Democratic Republic of the Congo - being supplied by India - have received around 30 per cent of their planned shipments. In comparison, Brazil and the Philippines only received around 11 per cent of the delivery pledge out of South Korea, while Egypt and Mexico received around 20 per cent.

Bangladesh and Pakistan have not received any of their COVAX allotments yet. While Bangladesh has purchased 7 million doses and has been given an additional 3.3 million by its ally India (6 per 100 of population), Pakistan is not cooperating with its larger neighbour on vaccines and has received 4 million doses - purchased and donated - from China (1.8 per 100 population). In the Pacific, Fiji, PNG, Solomon Islands, Samoa, Tonga and Tuvalu have received vaccines from COVAX.

Leading Vaccine Candidates Update

AstraZeneca

Two AstraZeneca doses could be 85-90 per cent effective

Two doses of the Oxford-AstraZeneca COVID-19 vaccine may be around 85 to 90 per cent effective against symptomatic disease, Public Health England (PHE) announced, while cautioning that it did not yet have enough data to be conclusive. In a weekly surveillance report, PHE said the estimated effectiveness of the AstraZeneca/Oxford vaccine, was 89 per cent compared to unvaccinated people. That compares to 90 per cent estimated effectiveness against symptomatic disease for the Pfizer/BioNTech vaccine, not a statistically significant difference. This was a routine announcement, not a peer-reviewed paper.

PHE said there was a small reduction in vaccine effectiveness from ten weeks after the first dose of the AstraZeneca shot before the second shot is given. Last week, the UK reduced the gap between doses down to eight weeks for over 50s, aiming to give maximum protection to more vulnerable people in light of concern about the B.1.617.2 variant first found in India.

Moderna

Tweaked Moderna vaccine neutralises SARS-CoV-2 variants in trials

The first modified vaccine against the coronavirus variants of concern that emerged in South Africa (B.1.351) and Brazil (P.1) has successfully neutralised them in laboratory trials, according to an announcement by Moderna. The results of the small trial suggest that boosters against the variants will be feasible and could be rolled out this year to counter the threat from variants that have appeared around the world and are in some cases more transmissible and/or partially vaccine-resistant.

The company has tested both a booster shot of its standard vaccine and a modified version of the vaccine in people who have previously had two doses. Twenty adults were recruited for each arm of the trial, or 40 in total. Two weeks after the new jab, both the booster shot and the tweaked vaccine increased the antibodies in the blood that can neutralise the two variants of concern. But the tweaked vaccine – called mRNA-1273.351 and designed specifically to combat the B.1.351 and P.1 variants, which have similar mutations to the spike protein – produced higher levels of neutralising antibodies than the standard booster shot, mRNA-1273.

Pfizer

Effectiveness of Pfizer-BioNTech vaccine against variants in Qatar

In a letter to the *New England Journal of Medicine (NEJM)*, real-world data on the effectiveness of the Pfizer/BioNTech vaccine in Qatar were shared. Qatar launched a mass immunisation campaign with this vaccine on 21 December 2020. As of 31 March 2021, a total of 385,853 persons had received at least one vaccine dose and 265,410 had completed the two doses.

Vaccination scale-up occurred as Qatar was undergoing its second and third waves of SARS-CoV-2 infection, which were triggered by expansion of the B.1.1.7 and B.1.351 variants. Viral genome sequencing conducted from 23 February through 18 March indicated that 50 per cent of cases of COVID-19 in Qatar were caused by B.1.351 and 44.5 per cent were caused by B.1.1.7. Nearly all cases in which virus was sequenced after 7 March were caused by either B.1.351 or B.1.1.7.

The estimated effectiveness of the vaccine against any documented infection with the B.1.1.7 variant was 89.5 per cent at 14 or more days after the second dose. The effectiveness against any documented infection with the B.1.351 variant was 75.0 per cent. Vaccine effectiveness against severe, critical, or fatal disease due to infection with any SARS-CoV-2 was very high, at 97.4 per cent.

Vaccine effectiveness was also assessed with the use of a cohort study design by comparing the incidence of infection among vaccinated persons with the incidence in the national cohort of persons who were antibody-negative. Effectiveness was estimated to be 87.0 per cent against the B.1.1.7 variant and 72.1 per cent against the B.1.351 variant, findings that confirm the results reported above.

In summary, the Pfizer/BioNTech vaccine is effective against infection by both variants, although protection against the B.1.351 variant is 15 per cent lower than against the B.1.1.7 variant. The vaccine is highly effective against severe disease caused by both variants.

Delay in giving second dose of Pfizer improves immune response

Published as a pre-print paper, a study led by the University of Birmingham in collaboration with PHE found that antibodies against the virus were three-and-a-half times higher in those who had the second Pfizer dose after 12 weeks compared with those who had it after a three-week interval. Most people who have both doses of the vaccine will be well protected regardless of the timing, but the stronger response from the extra delay might prolong protection because antibody levels naturally wane over time.

The researchers analysed blood samples from 175 over-80s after their first vaccine and again two to three weeks after the booster. Among the participants 99 had the second shot after three weeks, while 73 waited 12 weeks. After the second dose, all had antibodies against the virus's spike protein, but the level was 3.5 times higher in the 12-week group. They found that T cell responses were weaker when the booster was delayed but settled down to similar levels when people were tested more than three months after the first shot.

FDA grants emergency use authorisation to Pfizer-BioNTech vaccine for 12 to 15 year olds

On 10 May, the U.S. Food and Drug Administration expanded the emergency use authorisation (EUA) for the Pfizer-BioNTech COVID-19 vaccine for the prevention of COVID-19 caused by the SARS-CoV-2 virus to include adolescents 12 through 15 years of age.

The effectiveness data to support the EUA in adolescents down to 12 years of age is based on immunogenicity and an analysis of COVID-19 cases. The immune response to the vaccine in 190 participants, 12 through 15 years of age, was compared to the immune response of 170 participants, 16 through 25 years of age. In this analysis, the immune response of adolescents was non-inferior to (at least as good as) the immune response of the older participants.

An analysis of cases of COVID-19 occurring among participants, 12 through 15 years of age, seven days after the second dose was also conducted. In this analysis, among participants without evidence of prior infection with SARS-CoV-2, no cases of COVID-19 occurred among 1,005 vaccine recipients and 16 cases of COVID-19 occurred among 978 placebo recipients; the vaccine was 100 per cent effective in preventing COVID-19.

On 28 May, the EMA also extended EUA of the Pfizer-BioNTech vaccine to 12-15 year olds.

On 25 May, **Moderna** announced Tuesday that its two-dose coronavirus vaccine produced the same immune response in teenagers aged 12-15 years as adults, and it plans to submit the data to U.S. regulators in early June.

Novavax

Efficacy of Novavax vaccine against the B.1.351 variant

In this paper, published in the *NEJM*, the authors describe a Phase 2a-b trial of the NVX-CoV2373 nanoparticle vaccine. The 6,324 participants were either HIV-negative aged between 18 and 84 years or medically stable HIV-positive between 18 and 64 years. Among 2,684 baseline seronegative participants (94 per cent HIV-negative and 6 per cent HIV-positive), predominantly mild-to-moderate COVID-19 developed in 15 participants in the vaccine group and in 29 in the placebo group (vaccine efficacy, 49.4 per cent). Vaccine efficacy among HIV-negative participants was 60.1 per cent. Of 41 sequenced isolates, 38 (92.7 per cent) were the B.1.351 variant. Post hoc vaccine efficacy against B.1.351 was 51.0 per cent among the HIV-negative participants.

Novavax delays seeking authorisation in the US

On 11 May, Novavax announced that it would delay seeking authorisation of its vaccine (NVX-CoV2373) by the US FDA at least into the third quarter. The postponement is reported to be due to delays in completing the US and Mexican Phase 3 trials and "manufacturing regulatory issues".

The company's vaccine, shown to be about 90 per cent effective in a 15,000-person UK trial, could fill an urgent global need — an easy-to-store vaccine that could help bolster strained supplies as the pandemic rages. **Australia** has ordered 51 million doses of the Novavax vaccine. However, that depends on the company earning regulatory clearance and scaling up manufacturing.

Novavax, which didn't have its own manufacturing capacity at the beginning of the pandemic, has set an ambitious goal of producing 2 billion doses a year, relying on a global manufacturing network, including the Serum Institute of India (SII), which will produce one billion doses.

The company has a widely spread and complex supply chain. The antigen component of NVX-CoV2373 is being manufactured at Novavax CZ in the Czech Republic (formerly Praha Vaccines), as well as at the following partnered manufacturing sites: Biofabri in Spain; FUJIFILM Diosynth Biotechnologies in North Carolina and Texas; FDB in the UK, SII in India; SK Bioscience in South Korea; and Takeda Pharmaceutical Company in Japan. Novavax' Matrix-M adjuvant is now being manufactured at Novavax AB in Uppsala, Sweden.

Sinopharm

WHO grants emergency use authorisation to Sinopharm vaccine

The World Health Organization announced on 7 May that it would list for emergency use a coronavirus vaccine made by Chinese firm Sinopharm. The step means that the vaccine, developed by Sinopharm with the Beijing Institute of Biological Products, can be used to bolster WHO-backed efforts such as the COVAX initiative to share doses equitably around the world. It marks the first time that any Chinese-made vaccine received emergency authorization from the WHO.

Though the Sinopharm vaccine is already in widespread use around the world, with an estimated 65 million doses administered, its developers have released limited information about the vaccine's efficacy and side effects. A report by WHO's Strategic Advisory Group of Experts (SAGE) on Immunisation released the week of 3 May said it was "very confident" the Sinopharm vaccine protects people aged 18 to 59, citing evidence from clinical trials in China, Bahrain, Egypt, Jordan and the United Arab Emirates.

The inactivated virus vaccine had a 79 per cent efficacy rate in preventing symptomatic COVID-19 in adults between 18 and 59 years of age – lower than some high-performing vaccines, such as those produced by Pfizer-BioNTech and Moderna, but in the same range as AstraZeneca vaccine. However, the report's authors said they had a "low level of confidence" in the vaccine's efficacy in people 60 and older, and a "very low confidence" in the data about potential side effects in that age group.

Benefits of Vaccination

One dose of vaccine cuts risk of passing on infection by as much as 50 per cent in the UK

Adults infected with COVID-19 three weeks after receiving one dose of the Pfizer-BioNTech or Oxford-AstraZeneca vaccine were 38-49 per cent less likely to pass the virus on to their household contacts than people who were unvaccinated, according to a preprint by Public Health England.

The study compared household contacts of index cases receiving either the AstraZeneca or Pfizer vaccines with contacts of unvaccinated index cases and the proportion of contacts that tested positive within 2-14 days of the index case in each group.

The final cohort consisted of 365,447 households with a single index case and 1,018,842 contacts. There were 4,107 households where the index case was vaccinated 21 days or more before testing positive (1.12%), and 20,110 where the index case was vaccinated less than 21 days before testing positive (5.51%).

In households where the index case **was not vaccinated** before testing positive, there were 96,898 secondary cases out of 960,765 household contacts (10.1%). There were 196 secondary cases in 3,424 contacts (5.72%) where the **received the AstraZeneca** vaccine 21 days or more before testing positive, and 371 secondary cases in 5,939 contacts (6.25%) where the index case **received the Pfizer vaccine** 21 days or more before testing positive.

These results show that the likelihood of household transmission is 40-50 per cent lower for households in which the index cases are vaccinated 21 days or more prior to testing positive (compared to no vaccination), with similar effects for both Pfizer and AstraZeneca vaccines.

Pfizer and AstraZeneca vaccines highly effective against the B.1.617 variants in the UK

A Public Health England (PHE) study has revealed the vaccines are highly effective after a second dose. The analysis, carried out between 5 April and 16 May, found the Pfizer vaccine was 88 per cent effective against symptomatic disease from the B.1.617.2 (Indian) variant two weeks after a second dose, compared with 93 per cent effectiveness against the B.1.1.7 (Kent) variant. For its part, the AstraZeneca vaccine was 60 per cent effective, compared with 66 per cent against the Kent variant over the same period.

It was also found that both vaccines were 33 per cent effective against symptomatic disease caused by the B.1.617.2 variant, three weeks after the first dose. This compared with about 50 per cent effectiveness against the B.1.1.7 variant.

One dose of either AstraZeneca or Pfizer vaccine gives 80 per cent lower COVID-19 death risk in England

Data from the rollout of AstraZeneca's COVID-19 vaccine shows one dose results in 80 per cent lower risk of death from the disease. PHE also said protection against death from the Pfizer-BioNTech vaccine rises from approximately 80 per cent after one dose to 97 per cent after two doses in its new analysis.

In a pre-print paper, PHE says that 48,096 cases aged 70 years and above were included in the analysis, of which 79.1 per cent were unvaccinated; 12.7 per cent had been vaccinated with Pfizer/BioNTech (3,910 received their first dose within 20 days of their test date, 2,007 received their first dose ›=21 days before their test date and 191 received their 2nd dose ›=7 days before their test date); and 8.2 per cent had been vaccinated with AstraZeneca (2,686 received their first dose within 20 days of their test date, 1,258 received their first dose ›=21 days before their test date and 6 received their 2nd dose ›=7 days before their test date).

COVID-19 cases that had a single dose of AstraZeneca vaccine were 55 per cent protected against death, with a figure of 44 per cent protection for a single dose of Pfizer, compared to unvaccinated cases.

Protection against mortality from the Pfizer-BioNTech vaccine improved to 69 per cent for cases who had their second dose at least a week before they tested positive. Combined with the estimated protection from getting COVID-19 to start with, this is equivalent to an estimated 97 per cent protection.

In another dataset, PHE said it estimated that two doses of the Pfizer-BioNTech vaccine reduces the risk of hospitalisation by 93 per cent for the over 80s.

Mix-and-match COVID vaccines trigger potent immune response

Spanish researchers have found that vaccinating people with both the AstraZeneca-Oxford and Pfizer–BioNTech COVID-19 vaccines produces a potent immune response against the virus SARS-CoV-2. Preliminary results are the first to show the benefits of combining different coronavirus vaccines. A UK trial of a similar strategy reported safety data last week, and is expected to deliver further findings on immune responses soon.

Starting in April 2021, the Spanish trial enrolled 663 people who had already received a first dose of the Oxford–AstraZeneca vaccine, which uses a harmless chimpanzee adenovirus to deliver instructions for cells to make a SARS-CoV-2 protein. Two-thirds of participants were randomly picked to receive the mRNA-based vaccine made by Pfizer- BioNTech at least eight weeks after their first dose. A control group of 232 people has not yet received a booster.

After the second dose, participants began to produce much higher levels of antibodies than they did before, and these antibodies were able to recognise and inactivate SARS-CoV-2 in laboratory tests. Control participants who did not receive a booster vaccination experienced no change in antibody levels. The researchers found that the antibody response to the Pfizer-BioNTech booster seems to be even stronger than the one most people generate after receiving two doses of the AstraZeneca-Oxford vaccine, according to earlier trial data.

A UK study called Com-COV, which analysed combinations of the same two vaccines, found that people in the mix-and-match groups experienced higher rates of common vaccine-related side effects, such as fever, than did people who received two doses of the same vaccine. In the Spanish trial, however, mild side effects were common, and similar to those seen in standard COVID-19 vaccine regimens.

Technical Vaccine Update

Reported blood clotting with low platelet events associated with SARS-CoV-2 vaccines

Since early March 2021, reports have emerged in many countries of a rare but serious side effect involving thrombosis (clotting) with thrombocytopaenia (low blood platelet count) in young healthy people who had received the AstraZeneca-Oxford vaccine. Most cases involved clotting in a large vein such as in the brain, called cerebral venous sinus thrombosis (CVST).

This clotting syndrome has been called several names - thrombosis with thrombocytopenia syndrome (TTS), vaccine induced prothrombotic immune thrombocytopenia (VIPIT); vaccine associated thrombosis and thrombocytopenia (VATT) and vaccine induced immune thrombotic thrombocytopenia (VITT). It will be referred to as TTS in this report and has been attributed associated with only adenoviral vaccines (currently AstraZeneca and Johnson and Johnson).

A recent German study posted as a pre-print paper presents a possible mechanism of action. On one hand, thrombocytopaenia mechanism is based on the artificial activation of PF4 by adenoviral proteins or DNA molecules, which can similarly to heparin. The other side of the pathological disease mechanism is due to membrane-anchored and soluble Spike protein variants that are produced after vaccination

When the immune system now starts the production of anti-Spike antibodies (days 4–16), these antibodies will recognise the membrane-anchored as well as soluble Spike proteins. However, the soluble fraction of Spike protein variants is disseminated throughout the body and concentrates at various sites of those endothelial cells expressing the ACE2 surface protein. These ACE-bound Spike protein variants will become targets of the newly produced antibodies and will cause an immune mediated reaction which can induce thromboembolic events. In analogy to the thromboembolic events caused by Spike protein encoded by the SARS-CoV-2 virus, they termed the underlying disease mechanism the "Vaccine-Induced COVID-19 Mimicry" syndrome (VIC19M syndrome).

AstraZeneca-Oxford Vaccine (Vaxzevria)

The AstraZeneca-Oxford (ChAdOx1 nCoV-19) vaccine has been deployed against COVID-19 in **at least 115 countries**.

In **Australia**, there have been 27 confirmed and 6 probably cases of TTS judged by Therapeutic Goods Association as associated (using the UK case definition) with the 1.9 million doses of the AstraZeneca-Oxford vaccine administered. One of the patients died so the case fatality ratio of 4.2 per cent is lower than reported in Europe and the UK – experts have postulated that this is due to prompt diagnosis and management. The risk is estimated at 2.6 per 100,000 in those under 50 years and 1.6 per 100,000 in those over 50. The reporting rates of TTS in Australia remain consistent with what is being seen internationally, including in Europe, the UK, the Middle East and Canada.

A recent statement by the Australian Technical Advisory Group on Immunisation (ATAGI) and the Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ) details risk factors where Pfizer is the recommended vaccine and a clinical guideline.

In assessing the relative risks of the AstraZeneca vaccine and severe COVID-19 disease, it is important to realise that thrombotic events frequently occur with COVID-19 and are predominantly venous thromboemboli which are associated with increasing disease severity and worse clinical outcomes.

In its latest update on TTS, the European Medicines Agency (EMA) provided the additional guidance that leg pain, seizures and mental status change as possible signs and symptoms of TTS (in addition to the signs and symptoms already included in the product information: severe or persistent headache, blurred vision, skin bruising beyond the site of vaccination after a few days, shortness of breath, chest pain, leg swelling, or persistent abdominal pain).

In **Germany**, 77 cases of TTS have been reported after almost 7 million doses of Vaxzevria vaccine had been administered, equivalent to one in 88,000 doses.

- 30 reports concerned women aged between 20 and 59 years. In eleven cases the age was between 60 and 69 years. In three cases the age was between 70 and 80 years. In one case there was no information on age.
- 23 reports concerned men. In 18 cases the age was between 20 and 59 years. In four cases the age was between 60 and 69. In one case there was no information about the age.
- 14 persons died as a result of TTS: ten women (CFR 18.5%) and four men (CFR 17%).

In **Australia**, there have been 24 cases of TTS judged by the Advisory Committee on the Safety of Vaccines as associated with the AstraZeneca-Oxford vaccine which has been administered to 2.1 million Australians. One of the patients died so the case fatality ratio of 4.2 per cent is lower than reported in Europe and the UK. The overall incidence is one in 87,000 shots; in under 50s it is 2.8 per 100,000 and in over 50s 1.4 per 100,000. The reporting rates of TTS in Australia remain consistent with what is being seen internationally, including in Europe, the UK, the Middle East and Canada.

The most common types of clots were deep vein thrombosis (12 cases), pulmonary embolism (12 cases) and portal vein thrombosis (4 cases). There were also clots found in a variety of other locations in the body, including two cases with cerebral venous sinus thrombosis. Where the information was available, the most common time to onset or diagnosis was 14 days, with a range of 2–44 days after vaccination.

Johnson and Johnson/Janssen Vaccine

A case series of TTS associated with the Ad26.COV2.S vaccine in the US was recently published in *JAMA*. These cases were identified through the Vaccine Adverse Event Reporting System (VAERS), a national vaccine safety surveillance program of the US CDC and FDA. The 12 patients—all women aged 18 to 59 years—developed symptoms beginning 6 to 15 days after vaccination, along with declines in platelet counts and clinically severe clotting, including CVST (12 patients), and non-CVST thrombosis (8 patients). Of the 12 patients, ten required intensive care, seven also had intracerebral haemorrhage, and three have died. In addition to the 12 patients with CVST with thrombocytopenia described in this case series, at least three patients without CVST but meeting diagnostic criteria for TTS have been reported to VAERS (as of 21 April 2021), all in women aged 18 to 59 years (median age, 37 years). Of the 15 total patients, three have died.

The case for a causal relationship with vaccine administration includes a much higher reported rate of CVST with thrombocytopenia (approximately 5 per million women aged 18-50 years shortly after vaccination) than the background rate (approximately 0.05-0.13 per million per month, based on estimated annual US incidence of 0.7-1.6 per million per year). The current cases also include substantial similarities to the clinical syndrome of TTS associated with the ChAdOx1 nCov-19 vaccine manufactured by Oxford/AstraZeneca. The Ad26.COV2.S and ChAdOx1 nCov-19 vaccines use similar technology, namely modified adenovirus vectors.

Both the FDA and the EMA have added warning labels to the vaccines but advise that the benefits of the vaccine outweigh the very rare risk of severe adverse events. Only Denmark has stopped providing this vaccine to their people while Belgium has halted giving the vaccine to people under the age of 41.

Immunogenicity of mRNA vaccines in pregnant and lactating women in the US

Pregnant women and their babies are at increased risk of morbidity and mortality from COVID-19 but have been excluded from the phase 3 COVID-19 vaccine trials. Data on vaccine safety and immunogenicity in these populations are therefore limited. This study, conducted in a number of Boston hospitals and published in *JAMA* set out to evaluate the immunogenicity of COVID-19 messenger RNA (mRNA) vaccines in pregnant and lactating women, including against emerging SARS-CoV-2 variants of concern.

This exploratory, descriptive, prospective cohort study enrolled 103 women who received a COVID-19 vaccine from December 2020 through March 2021 and 28 women who had confirmed SARS-CoV-2 infection from April 2020 through March 2021. The study enrolled 30 pregnant, 16 lactating, and 57 neither pregnant nor lactating women who received either the mRNA-1273 (Moderna) or BNT162b2 (Pfizer-BioNTech) vaccines and 22 pregnant and 6 non-pregnant unvaccinated women with SARS-CoV-2 infection.

Binding, neutralising, and functional non-neutralising antibody responses as well as CD4 and CD8 T-cell responses were present in pregnant, lactating, and non-pregnant women following vaccination. Binding and neutralising antibodies were also observed in infant cord blood and breast milk. Binding and neutralising antibody titres against the SARS-CoV-2 B.1.1.7 and B.1.351 variants of concern were reduced, but T-cell responses were preserved against viral variants.

The authors conclude that in this exploratory analysis of a convenience sample, receipt of a COVID-19 mRNA vaccine was immunogenic in pregnant women, and vaccine-elicited antibodies were transported to infant cord blood and breast milk. Pregnant and non-pregnant women who were vaccinated developed cross-reactive antibody responses and T-cell responses against SARS-CoV-2 variants of concern.

Effectiveness of COVID-19 vaccines in immunocompromised individuals

There is reasonable concern that COVID-19 vaccines may not be as immunogenic or effective in people who are immunocompromised, either through a medical condition or medication. In the US, an estimated 3 to 4 per cent of the population is immunocompromised . There are surprisingly few studies on the immunogenicity of the vaccines in this sizeable population, who were largely excluded in the initial vaccine clinical trials. Several small studies are indicating that immunosuppression such as chemotherapy or for transplant recipients, may be associated with reduced antibody responses post vaccination, in particular therapies that target antibody producing B-cells. Early data suggest that the vaccines offer some protection, although perhaps to a lesser degree, for most patients with **HIV and autoimmune conditions** such as rheumatoid arthritis. Key knowledge gaps are the significance of these reduced antibody levels (including the role of testing post vaccination) and the need for booster vaccination. We do know that it is safe to vaccinate immunocompromised people with the AstraZeneca, Pfizer or Moderna vaccines and in fact, these people should be prioritised for vaccination.

Case studies have detailed how some immunocompromised patients can have active infections for many months — resulting in questions about whether they can act as incubators for mutations that lead to new variants and underscoring the need for an effective vaccine strategy not just for their sake, but for the greater good. CDC Director Rochelle Walensky and White House adviser Anthony S. Fauci highlighted the challenges of such patients in a recent news briefing in which they acknowledged that the first documented case of the so-called New York variant, B. 1.526, was found in a patient with advanced AIDS.

One study published as a pre-print measured SARS-CoV-2 IgG production in 67 patients with haematologic malignancies who received two mRNA vaccine doses. They found that 46 per cent of these patients did not produce antibodies and were therefore vaccine non-responders. Many of those were on B-cell-depleting medications, such as rituximab, used to treat certain autoimmune diseases and cancer, or ocrelizumab, a newer drug for multiple sclerosis. Patients with B-cell chronic lymphocytic leukaemia were at a particularly high risk, as only 23 per cent had detectable antibodies despite the fact that nearly 70 per cent of these patients were not undergoing cancer therapy.

As for transplant patients, the early data are also concerning: A May 5 study published in *JAMA* found that 46 per cent of 658 transplant patients did not mount an antibody response after two doses of the Pfizer-BioNTech or Moderna vaccines. After their first dose, only 15 per cent mounted an antibody response.

Another pre-print study found that patients with chronic inflammatory diseases on a common steroid, prednisone had greatly reduced antibody responses to vaccines. Compared to immunocompetent controls, a three-fold reduction in anti-S IgG titres and SARS-CoV-2 neutralisation were observed in these patients. B cell depletion and glucocorticoids exerted the strongest effect with a 36- and 10-fold reduction in humoral responses, respectively.

Numerous potential solutions for the immunocompromised are being debated and studied, such as booster shots or double doses, as is often done with other vaccines. Another possibility is to try preventive doses of lab-produced antibody proteins known as monoclonal antibodies that until now have been mostly used as treatments for those who are infected with the coronavirus.

Impact and effectiveness of nationwide vaccination campaign with Pfizer-BioNTech in over 70s in Israel

The US CDC reports that after Israel's national campaign vaccinated more than three-fourths of adults 70 years or older against SARS-CoV-2, the need for mechanical ventilation among patients with COVID-19 in that age group declined dramatically.

By February 2021, two-dose vaccination coverage among persons aged ≥70 years was 84 per cent. To assess the effect of COVID-19 vaccination on the occurrence of severe disease, an ecological study was conducted. Requiring mechanical ventilation was used as a proxy for severe COVID-19.

The number of COVID-19 patients aged ≥70 years (who had the highest two-dose vaccination coverage, 84.3 per cent) requiring mechanical ventilation was compared with that of patients aged <50 years, who had the lowest 2-dose vaccination coverage (9.9 per cent). Since implementation of the second dose of the vaccination campaign, the ratio of COVID-19 patients requiring mechanical ventilation aged ≥70 years to those aged <50 years has declined 67 per cent, from 5.8:1 during October–December 2020 to 1.9:1 in February 2021. These findings provide preliminary evidence of the effectiveness of vaccines in preventing severe cases of COVID-19 at the national level in Israel. Receipt of COVID-19 vaccines by eligible persons can help limit spread of disease and potentially reduce the occurrence of severe disease.

Impact of vaccination on SARS-CoV-2 cases in the UK

The UK Medicines and Healthcare products Regulatory Agency (MHRA) gave regulatory approval to the Pfizer–BioNTech vaccine on 2 December 2020. The initial approval was for a two-dose schedule, with the second dose administered after three weeks. On 30 December 2020, the MHRA approved the Oxford–AstraZeneca vaccine for use in a two-dose schedule. Given the rapid increase in confirmed COVID-19 infections in the UK in late 2020, the Joint Committee on Vaccination and Immunisation (JCVI) advised that there was a need for rapid, high levels of vaccine uptake among vulnerable persons.

Given that data for the AstraZeneca vaccine indicated that a longer interval between doses led to a stronger boost response and higher efficacy and that data from both vaccines indicated high vaccine efficacy from a single dose, the JCVI advised that the AstraZeneca-Oxford and Pfizer–BioNTech vaccines could be offered with an interval of up to 12 weeks. Prioritising delivery of the first vaccine dose was considered highly likely to have a greater public health impact in the short term and reduce the number of preventable deaths from COVID-19.

Primary care in the UK has been at the centre of the vaccine program and teams have worked tirelessly in delivering vaccines at speed. Local clinical commissioning groups have supported and coordinated the arrival of vaccines to practices. Primary care network leads and practice managers have organised and facilitated the administration of vaccines within the practices. Vaccinators include general practitioners, nurses, practice pharmacists, and recently retired doctors and nurses.

The UK Government has also developed mass vaccination centres, staffed by trained vaccinators, including health care professionals, paramedics, volunteers, and, in some centres, members of the armed forces. Vaccines are also being delivered in local hospitals, pharmacies and community centres.

The UK's vaccine program has been a huge success. Thirty-two million vulnerable individuals have been vaccinated with their first dose of either the Pfizer–BioNTech or the AstraZeneca-Oxford vaccines (10 April 2021). These vulnerable individuals include those over the age of 50 years and those with underlying health conditions. Coverage has been very high among older people, with a 90 per cent coverage in people aged over 70 years. However, there are some geographical and ethnic disparities: vaccine coverage is lower in London, among black and Asian minority groups, and among white Eastern European groups.

The key lesson is that the simple, predominantly age-based structure of the vaccination program has enabled a rapid delivery with high vaccine uptake. The aim of the program has been clear: to prevent deaths by vaccinating individuals most at risk first.

Global shortage of mRNA vaccine raw materials

Vaccine manufacturers are struggling to secure supplies of giant plastic bags used in bioreactors that mix pharmaceutical ingredients, creating a bottleneck that threatens the rollout of COVID-19 vaccines around the world. Some vaccine makers have been days away from stalling production because of the shortage of the bags, which can hold up to 2,000 litres of material. COVID-19 vaccines developed by companies including BioNTech/Pfizer, Moderna and Novavax are made in the bags — which are used as sterile liners in the tanks where the vaccines are produced — although they use differing sizes.

Novavax has reported that shortages of the plastic bags are hindering the manufacture of their new vaccine, which has not yet authorised for use in any country. MilliporeSigma, a main supplier of the bags worldwide, has said there had been "unprecedented demand" for COVID-19 related products, and that it had been working around the clock to expand facilities, prioritise customers working on pandemic products and find additional raw material suppliers. Thermo Fisher, which also makes the single use liners, said it had increased production capacity by 50 per cent in 2020 and anticipated expanding it by another 50 per cent in 2021.

The shortage of the bags follows other supply chain problems, such as a challenge obtaining enough lipid nanoparticles — which the mRNA vaccine makers need to deliver genetic code into the body — and securing the right kind of syringes to extract as many doses as possible from a vial. Germany's Merck, which is also one of the few lipid producers, recently expanded production to meet demand from Mainz-based BioNTech.

In March, India's largest vaccine producer the Serum Institute warned those restrictions meant it was struggling to find enough raw materials to make vaccines. But it took until late April - when India was breaking global records of new infections every day for the US to agree to lift them.

Vaccines require hundreds of products to make: Pfizer's has more than 280 ingredients, sourced from 86 sites in 19 countries. Vaccine manufacturers, including CSL, use the plastic bags to line the vessels in which they grow the vaccine's components. CSL has said that its existing supply chains had helped it largely avoid the supply crunch. The plastic bags have to be manufactured to an extremely high standard of sterility; only a few companies in the world make them. Vials, glass, plastic, bottle stoppers, chemicals and reagents also in short supply.

Vaccines in Development

What do we know about Bharat Biotech's Covaxin vaccine?

Covaxin was developed by Indian pharmaceutical company Bharat Biotech in collaboration with the Indian Council of Medical Research, a government funded biomedical research institute, and its subsidiary the National Institute of Virology. The vaccine is similar to CoronaVac (the Chinese vaccine developed by Sinovac) in that it uses a complete infective SARS-CoV-2 viral particle consisting of RNA surrounded by a protein shell but modified so that it cannot replicate. Covaxin comes as a two-dose regimen, recommended to be taken 28 days apart.

Covaxin's Phase I trial to assess safety and immunogenicity is published. All 375 subjects who received the vaccine had notably elevated antibody response. The phase II trial result has not yet been published in a peer reviewed journal, but a preprint has been posted on *MedRxiv*. The provisional data indicate enhanced immune response and tolerable safety outcomes. Since November, 25,800 participants have been enrolled in ongoing phase III trials. Bharat Biotech released interim efficacy data on 3 March 2021, which showed a clinical efficacy of 81 per cent.

Covaxin is available in multi-dose vials and is stable at the 2-8°C that ordinary refrigeration can achieve. Bharat Biotech says it has a stockpile of 20 million doses of Covaxin for India and is in the process of manufacturing 700 million doses at its four facilities in two cities by the end of the year. It says it can provide 300 million shots annually.

The Central Drugs and Standards Committee, India's top drug regulator, issued an emergency approval for Covaxin on 3 January 2021, even though phase III clinical trials are still ongoing and phase II studies are unpublished. The vaccine is currently being administered in India to people over 60 and those over 45 with comorbidities, as well as to health workers. So far, eight other countries have approved the vaccine. Bharat Biotech has signed deals with Ocugen, a US based biopharmaceutical company, to produce the vaccine for the US market, and Precisa Medicamentos to supply to Brazil, pending regulatory approval there.

Cuban vaccines in development

Cuba has invested heavily to produce local COVID-19 vaccines and this month began a mass rollout of its own vaccines: Abdala, named after Cuban revolutionary Jose Martí, and Soberana-2 (Sovereign-2). Cuban health officials began vaccinating 141,000 healthcare workers in March and last week expanded the program to its general population. This is in addition to an ongoing Phase 3 trial in Cuba (n = 44,000). Neither of the vaccine candidates is yet to be fully approved for emergency use by the country's regulatory authority, and no peer-reviewed studies have been published on their efficacy.

Soberana-2 contains a part of the coronavirus spike protein, fused to a standard tetanus vaccine to make it stable, with aluminium hydroxide as an adjuvant. On the basis of as-yet-unpublished results from early-stage clinical trials, the director-general of the Finlay Institute, which developed the Soberana-2 vaccine, expects it to show an efficacy in the region of 80–95 per cent. A second phase 3 trial of Soberana-2 is planned for Iran, as part of a partnership between the Finlay Institute and the Pasteur Institute of Iran. A phase 2/3 trial has been scheduled for Soberana-1, which was also developed by the Finlay Institute. The Centre for Genetic Engineering and Biotechnology (Havana, Cuba) is behind the other vaccine candidates. Abdala and Mambisa, a nasal spray, both entered phase 1/2 trials late last year.

Officials claim the country — well known for its free healthcare system and reputation for vaccine production — is on track to inoculate 70 per cent of its 11 million population as early as August. If it is successful, Cuba would become the first country in the world to immunise its entire population with its own vaccine. With production expected to reach 10 million doses a month, officials claim Cuba will have plenty of its vaccines to share with its neighbours.

GLOBAL SCIENTIFIC UPDATES

Variants of Concern Update

Naming of SARS-CoV-2 Variants

The established nomenclature for naming and tracking the genetic lineages such as B.1.1.7 or B.1.617 are currently used in public discussions of variants. To assist in discussions, agencies have considered easy-to pronounce and non-stigmatising labels for variants of interest (VOI) and concern (VOC). On 1 June, the expert group convened by the WHO has recommended using labelled letters of the Greek Alphabet as a more practical way to discuss variants with non-scientific audiences. More information is available here.

Variants of Concern (VOC)

WHO label	Pango Lineage	GISAID clade/lineage	Nextstrain clade	Earliest documented samples	Date of designation
Alpha	B.1.1.7	GRY (formerly GR/501Y.V1)	20I/S:501Y.V1	United Kingdom, Sep 2020	18 Dec 2020
Beta	B.1.351	GH/501Y.V2	20H/S:501Y.V2	South Africa, May 2020	18 Dec 2020
Gamma	P.1	GR/501Y.V3	20J/S:501Y.V3	Brazil, Nov 2020	11 Jan 2021
Delta	B.1.617.2	G/452R.V3	21A/S:478K	India, Oct 2020	VOI: 4 Apr 2021 VOC: 11 May 2021

Variants of Interest (VOI)

WHO label	Pango Lineage	GISAID clade/lineage	Nextstrain clade	Earliest documented samples	Date of designation
Epsilon	B.1.427/B.1.429	GH/452R.V1	20C/S.452R	USA, Mar 2020	5 Mar 2021
Zeta	P.2	GR	20B/S.484K	Brazil, Apr 2020	17 Mar 2021
Eta	B.1.525	G/484K.V3	20A/S484K	Multiple countries, Dec 2020	17 Mar 2021
Theta	P.3	GR	20B/S:265C	Philippines, Jan 2021	24 Mar 2021
Iota	B.1.526	GH	20C/S:484K	USA, Nov 2020	24 Mar 2021
Kappa	B.1.617.1	G/452R.V3	21A/S:154K	India, Oct 2020	2 April 2021

The current SARS-CoV-2 variants of concern are B.1.1.7 (originally detected in the UK), B.1.351 (South Africa), P.1 (Brazil), B.1.617 (India), B.1.427 and B.1.429 (California), and B.1.526 (New York).

Kappa (B.1.617.1), Delta (B.1.617.2) variants

First reported in December 2020, SARS-CoV-2 lineages kappa, delta and B.1.617.3 have been increasingly detected in India and other countries. In just a few weeks, the delta variant has become the dominant strain across India and has spread to about 40 nations, including the United Kingdom, Fiji, Vietnam and Singapore.

In March, India's National Centre for Disease Control, a division of the Ministry of Health and Family Welfare, announced that the new variants had been identified in samples of saliva taken from people in Maharashtra, Delhi and Punjab.

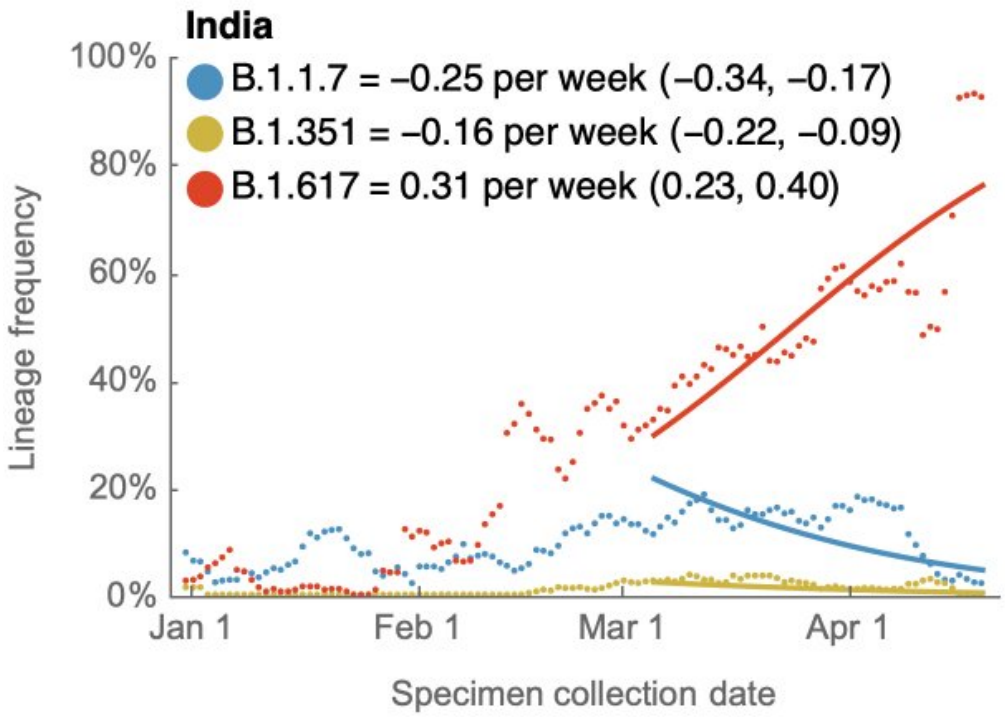
The Indian SARS-CoV-2 Consortium on Genomics has identified two important mutations in the kappa variant. First, the **E484Q** mutation, which is similar to the E484K mutation identified on the P.1 and beta variants, can change parts of the coronavirus spike protein. The second is the **L452R** mutation, which has also been found in a variant thought to be responsible for outbreaks in California. Scientists believe this mutation increases the spike protein's ability to bind to human host cells, thereby increasing its infectivity.

While B.1.617.3 shares the L452R and E484Q mutations found in kappa and delta variants do **not have the mutation E484Q**. Delta has the T478K mutation, not found in kappa and B.1.617.3.

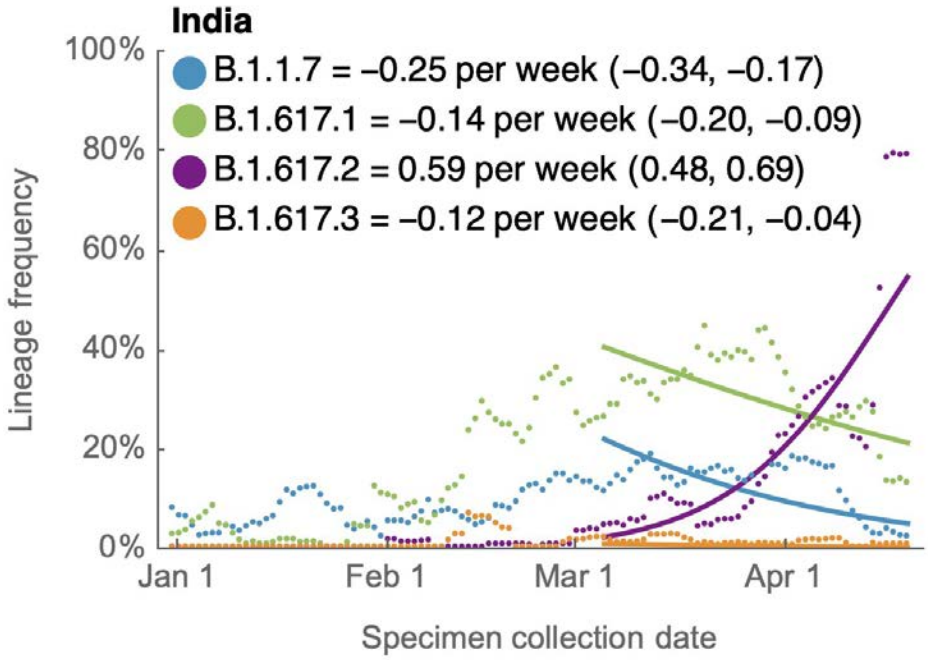
By late March, half of all reported sequences in India were kappa, but the proportion fell in April. It has been detected in many other countries, but only accounts for a very small proportion of cases. **B.1.617.3** has been detected in very few cases in India and the UK.

The variant of most concern is delta, which was first detected in India in December 2020. It remained rare until early March, when it became the dominant variant reported. It has spread to many other countries and is increasing rapidly in some. In the UK, it has become more common than alpha (B.1.1.7), although overall case numbers remain relatively low.

Tracking frequencies over time, in sequence data shared to GSAID, shows an increase in delta and kappa while alpha and beta (B.1.351) are in decline.



In the following figure, trends in frequencies of sub-lineages show that the overall increase is driven by delta.



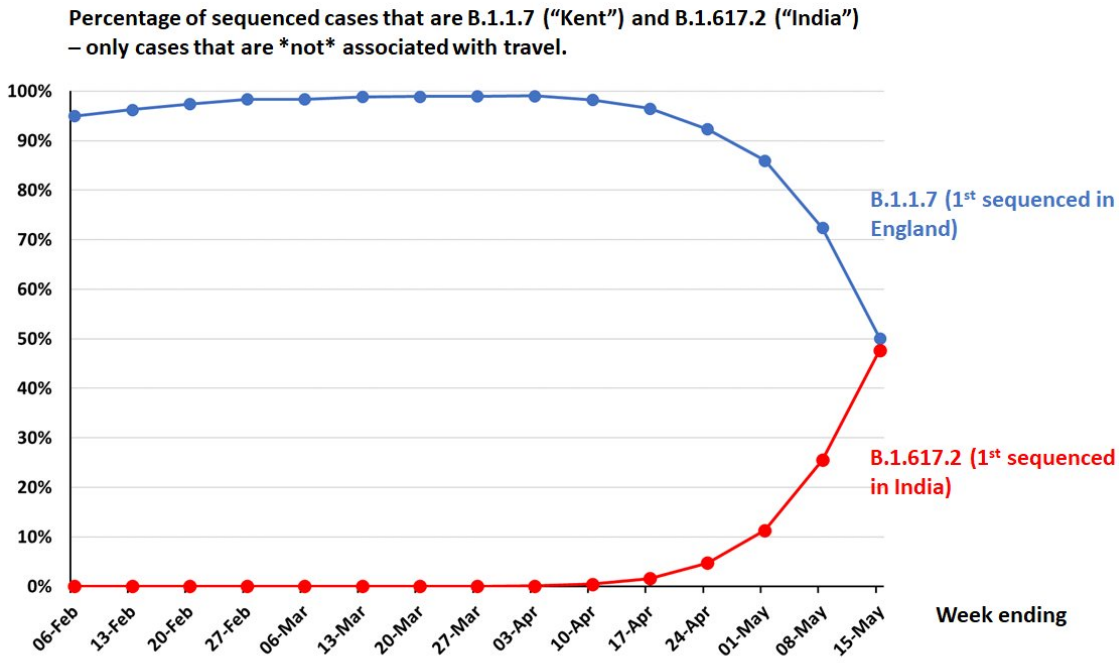
Transmissibility and evasion of antibodies

In a pre-print paper, lab scientists report that B.1.617 was resistant against Bamlanivimab, an antibody agent used for COVID-19 treatment. Also, B.1.617 evaded antibodies induced by infection or vaccination, although with moderate efficiency. Collectively, the study reveals that antibody evasion of B.1.617 may contribute to the rapid spread of this variant.

In another study published in pre-print, using a live virus assay, researchers described the neutralising antibody response to the kappa variant in serum from infected and vaccinated individuals. They found that the kappa variant is 6.8-fold more resistant to neutralisation by sera from COVID-19 convalescent and Moderna and Pfizer vaccinated individuals. Despite this, a majority of the sera from convalescent individuals and all sera from vaccinated individuals were still able to neutralise the kappa variant. This suggests that **protective immunity by the mRNA vaccines tested here is likely retained against the kappa variant.**

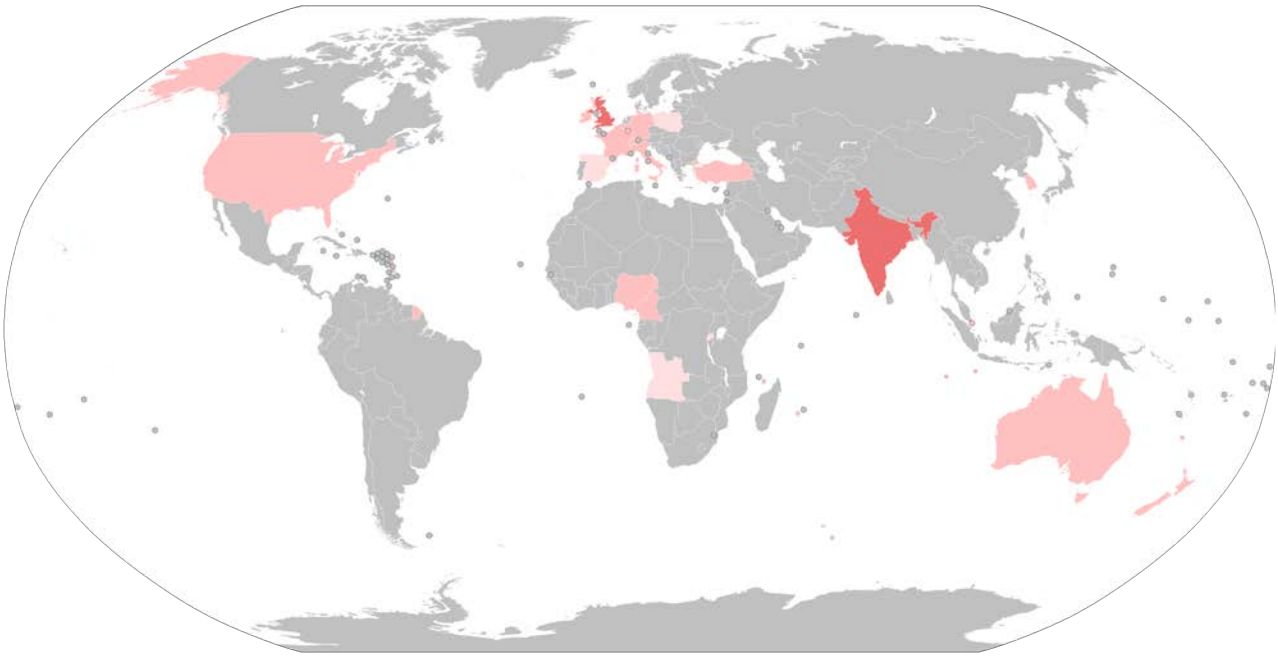
Positive news: The PHE study, reported in the Vaccines section, indicates that the delta variant does not evade the immune response induced by the Pfizer and AstraZeneca vaccines. In addition a lab study at Emory University found that antibodies generated by vaccination are seven times less effective at blocking entry of the kappa virus compared to the ancestral Wuhan strain that circulated early in the pandemic. Despite a reduction in neutralising potential, **immune serum from all 25 vaccinated people were able to neutralise kappa to some extent.**

The rapid rise in reported cases of the delta variant in north-west England indicates increased transmissibility. On 19 May, PHE reported that there had been 3,424 cases in the country. The city of Bolton has been most affected. Surge testing and vaccinations are being carried out in affected areas. Preliminary studies indicate that the variant may be 50 to 60 per cent more transmissible than the alpha variant. The following figure shows trends in the alpha and delta variants among sequenced cases in England.



Data from Fig 5, https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/988619/Variants_of_Concern_VOC_Technical_Briefing_12_England.pdf
Note: I give dates as "week ending" whereas PHE report uses week commencing

Global spread of the Delta (B.1.617.2) variant

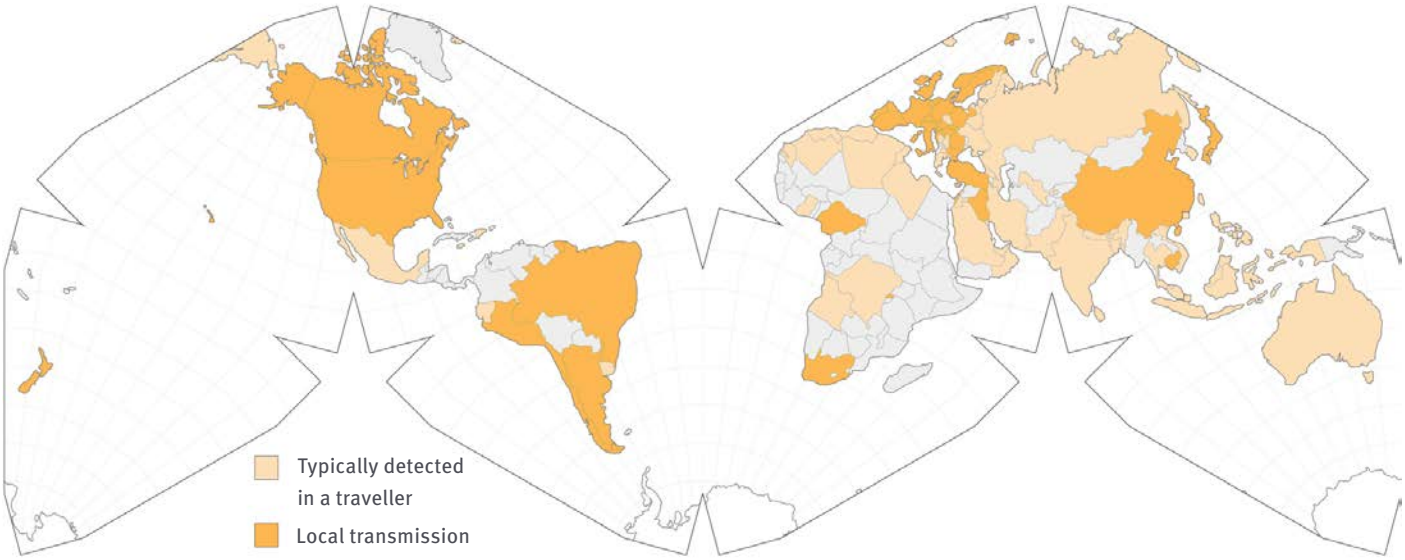


Alpha (B.1.1.7) variant

This variant has a mutation in the receptor binding domain of the spike protein at position 501, where the amino acid asparagine (N) has been replaced with tyrosine (Y). The shorthand for this mutation is N501Y. The N501Y mutation enables the virus's spike protein to more easily bind to human cells, which may make it more infectious.

Global spread of the Alpha (B.1.1.7) variant

The alpha variant has now been detected in 118 countries and territories, including Australia. Here is the worldwide distribution of the variant. It is the dominant strain in the UK, US, most of Europe, and the second most common strain in India. Source: New York Times Vaccination Tracker.



Beta (B.1.351) variant

This variant carries a mutation, called N501Y and contains other mutations of concern, including E484K and K417N. These two mutations are thought to explain why the beta variant appears to be better able to evade neutralising antibody responses elicited through natural infection or vaccination. Clinical trials of AstraZeneca, Johnson and Johnson and Novavax showed lower efficacies than in countries where the variant is not circulating. Currently there is no evidence to suggest that this variant has any impact on disease severity.

This variant was first identified in Nelson Mandela Bay, South Africa, in samples dating back to the beginning of October 2020. The variant spread from South Africa into Zambia and other neighbouring countries and was detected in the United States in January.

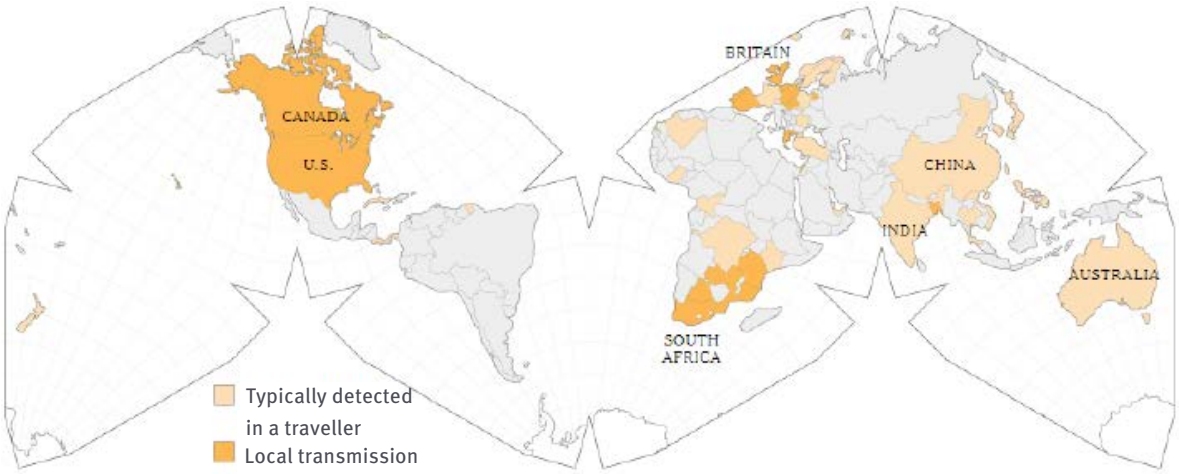
The beta variant has shown evidence of increased transmissibility, a considerable reduction in neutralisation by convalescent and post-vaccination serum, and significantly decreased neutralisation by monoclonal antibodies. The *NEJM* has published two peer-reviewed trials evaluating the efficacy of two vaccines — a replication-deficient chimpanzee adenovirus vector vaccine (AstraZeneca) and an adjuvanted, recombinant nanoparticle vaccine (Novavax) — against the beta variant. Both trials enrolled predominantly younger adults with high seropositivity to SARS-CoV-2 at trial entry. The trials were conducted with a backdrop of high symptomatic attack rates in the placebo group and a high prevalence of the beta variant among sequenced strains.

In the first trial, two doses of the AstraZeneca vaccine conferred no efficacy (point estimate, 10.4%; 95% confidence interval [CI], −76.8 to 54.8) against mild-to-moderate disease caused by the beta variant in previously seronegative participants. In the second trial, two doses of the Novavax vaccine had an efficacy of 49.4 per cent (95% CI, 6.1 to 72.8) against symptomatic Covid-19 caused by the beta variant while having high efficacy against the original strain.

In summary, the beta variant is demonstrating significant avoidance of the immune response induced by current vaccines although other data from Israel and the US suggest that the mRNA vaccines do confer immunity against the variant, if less so than against earlier variants, such as the alpha variant.

The variant has spread to at least 81 countries. It is the dominant strain in Comoros, Malawi, Botswana, Zimbabwe and Bangladesh. The worldwide dispersion of this variant is less than for the alpha variant as shown in the following figure. Source: New York Times Vaccination Tracker.

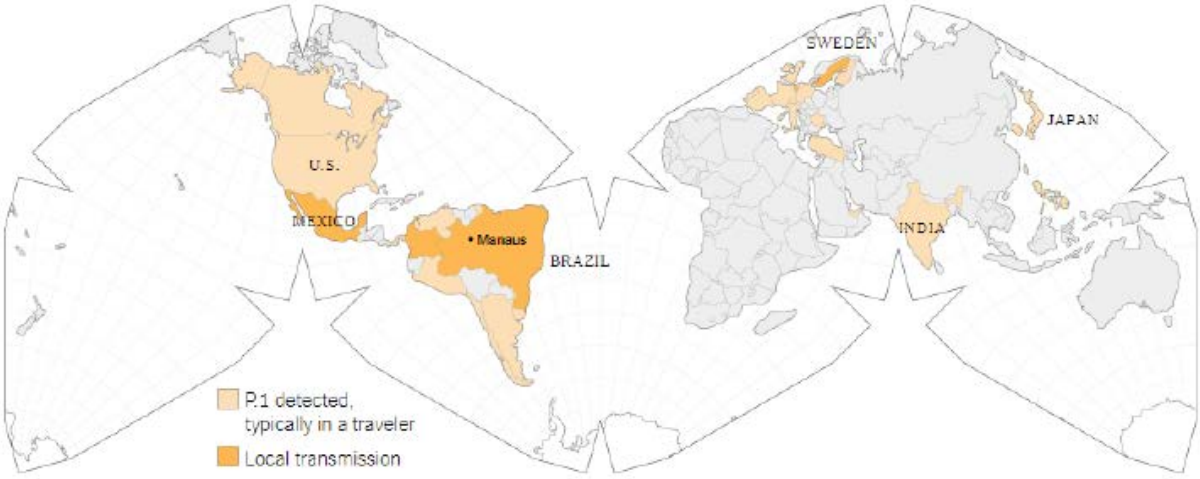
Global spread of B.1.351 variant



Gamma (P.1) variant

The gamma variant was first detected in samples from Manaus in the Amazonas state in northern Brazil in mid-December 2020. The gamma variant harbours the N501Y mutation in the spike protein and has an 'escape mutation' known as E484K, which also exists in the beta variant from South Africa and which in lab experiments has been found to help the coronavirus evade protective antibodies generated by earlier infections, as well as less susceptible to antibody-based drugs. Recent research suggests that the gamma variant is 2.5 times as infectious as the Wuhan strain. The variant accounts for 47 per cent of cases in Brazil and has spread to 40 countries. It is thought to be contributing to current COVID-19 surges in Argentina, Uruguay, Paraguay, Peru, Bolivia and Colombia. Source: New York Times Vaccination Tracker

The gamma (P.1) variant around the world



New Variants of Interest

A.VOI.V2 (Angola)

In order to rapidly characterise the spread of emerging variants of concern (VOC) and variants of interest (VOI), the Network for Genomic Surveillance in South Africa (NGS-SA) partnered with the Africa Centres for Disease Control and Prevention and the African Society of Laboratory Medicine through the Africa Pathogen Genomics Initiative to strengthen SARS-CoV-2 genomic surveillance across the African region.

On 15 January 2021, in response to the international spread of VOCs, the Angolan government instituted compulsory rapid antigen testing of all passengers arriving at the main international airport, in addition to the existing requirement to present a negative PCR test taken within 72 hours of travel. In March 2021, according to a *medRxiv* preprint NGS-SA received 118 nasopharyngeal swab samples collected between June 2020 and February 2021, a number of which were from incoming air travellers. From these, they produced 73 high quality genomes, 14 of which were known VOCs/VOIs and 12 were other lineages.

In addition, they detected a new VOI in three incoming travellers from **Tanzania** who were tested together at the airport in mid-February. The three genomes from these passengers were almost identical and presented highly divergent sequences within the A lineage. The GISAID database contains nine other sequences reported to be sampled from cases involving travel from Tanzania, two of which are basal to the three sampled in Angola.

This new VOI, temporarily designated A.VOI.V2, has 31 amino acid substitutions (11 in spike) and three deletions (all in spike). The spike mutations include three substitutions in the receptor-binding domain (R346K, T478R and E484K); five substitutions and three deletions in the N-terminal domain, and two substitutions adjacent to the S1/S2 cleavage site (H655Y and P681H). Several of these mutations are present in other VOCs/VOIs and are evolving under positive selection.

While they have only detected three cases with this new VOI, the authors state that it warrants urgent investigation as the source country has a largely undocumented epidemic and few public health measures in place to prevent spread within and out of the country. Tanzania has not reported a single case to WHO since April 2020 and has no plans to vaccinate its population against COVID-19.

New Vietnam Variant of Interest

Vietnam's Health Ministry announced on 29 May that it had detected a highly transmissible new variant of the coronavirus that has helped fuel a recent wave of infections in the country. Genetic sequencing by the National Institute of Hygiene and Epidemiology found the variant in at least four COVID-19 patients in the country. The Deputy Head of the Institute, said: "We discovered the Y144 deletion on spike protein S of the B.1.617.2 variant. This mutation is similar to the one found on the B.1.1.7 variant."

He said that the mutation on the Indian variant is not yet recorded by GISAID, a global science initiative and primary source that provides open access to genomic data of influenza viruses and the coronavirus responsible for the pandemic. The variant has not yet been named; however, viral cultures in the laboratory revealed that the virus replicated itself very quickly, he added, explaining why there are so many new cases in different locations in a shorter time frame.

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