COVID-19 Global Trends and Analyses

Volume 2: Science and Research

- Vaccines
- Viral Variants

January 2021 | Update 1 | Vol 2

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Vaccines

Researchers are currently testing 65 vaccines in clinical trials, and 20 have reached the final stages of testing. At least 85 preclinical vaccines are under active investigation in animals. Seven vaccines developed by the following companies have been approved for emergency use in at least one country: Pfizer/BioNTech, Moderna, Gamaleya ("Sputnik V"), AstraZeneca/Oxford, Sinopharm, Sinovac, and Bharat Biotech (approved only in India).

Six of these vaccines (all except Bharat Biotech) have published the results of Phase 3 trials (although Sputnik V, Sinovac and Sinopharm have not done so in peer-reviewed journals). With two doses 21 to 28 days apart, the reported efficacies are Pfizer (95 per cent), Moderna (94 per cent), Sputnik V (91 per cent), Sinopharm (79-86 per cent), AstraZeneca (62 per cent) and Sinovac (51 per cent). All vaccines have been found to be safe. None have been tested in children less than 16 years of age.

The impact of emerging viral variants of concern on vaccine efficacy is being studied. The current vaccines -- notably Pfizer and Moderna -- appear to induce immunity against the B1.1.7 variant, which emerged in southeastern England. However, they may be less effective against the 501Y.V2 variant which emerged in South Africa. It is still unclear whether the vaccines will be effective against the P.1 variant, which was first identified in Brazil.

Variants of Concern

Since September 2020, three viral variants of concern have emerged on three different continents. The B.1.1.7 variant was identified in Kent, England in September 2020. It is now the dominant strain in the UK, Ireland and Denmark, and has been identified in more than 50 countries, including Australia. The 501Y.V2 variant was identified in South Africa in December 2020 and is now the dominant strain in South Africa's four most populous provinces. It has been detected in more than 20 countries, including Australia and New Zealand. The P.1 strain was first identified in Manaus, in the Amazon Region of Brazil. It has since been detected in the UK, Germany, Japan and the US state of Minnesota.

All three variants involve amino acid mutations on the spike protein, which is instrumental in allowing the virus to invade human cells. All three have been shown to increase transmissibility by between 50 and 70 per cent, probably related to higher viral loads in those infected by the variant. Recent information from England suggests that the B.1.1.7 variant may also increase the severity of COVID-19 illness. The P.1 variant is of particular concern because it led to a surge in new cases in Manaus where a previous survey had shown that 70 per cent of residents had been infected with the earlier strains. This raises the possibility of the new strain being able to avoid the immune response induced by earlier infections. Studies are ongoing to decipher whether these recent new cases are reinfections.

SCIENCE AND RESEARCH UPDATES | VACCINES

SARS-CoV-2 vaccines in different stages of development

Researchers are currently testing **65 vaccines** in clinical trials, and 20 have reached the final stages of testing. At least 85 preclinical vaccines are under active investigation in animals[1]. Seven vaccines developed by the following companies have been approved for emergency use in at least one country: Pfizer/BioNTech, Moderna, Gamaleya ("Sputnik V"), AstraZeneca/Oxford, Sinopharm, Sinovac, and Bharat Biotech. A further two vaccines are close to publishing the results of Phase 3 trials -- Johnson & Johnson and Novovax. Here are brief summaries of what is known about these vaccines and where they have been approved and are being rolled out.

Pfizer/BioNTech

This vaccine, with the trade name *Comirnaty,* is based on a genetic molecule called messenger RNA (mRNA). The vaccine contains genetic instructions for building a coronavirus protein, known as spike. When injected into cells, *Comirnaty* causes them to make spike proteins, which then get released into the body and provoke a response from the immune system. On 18 November 2020, the company announced that the vaccine had an **efficacy of 95 per cent** following the second dose, three to four weeks apart[2]. The UK was the first country to approve the vaccine on 2 December 2020, and on 11 December 2020 the US Food and Drug Administration (FDA) approved the vaccine for emergency use. Since then, the vaccine has been approved in the 27 countries of the EU and a large number of other countries including Canada, Israel, Saudi Arabia, Switzerland, Oman, Kuwait, Mexico, Singapore and the UAE. The vaccine has to be stored at -70°C, which limits its use in remote locations. On the 25 January, the Australian Therapeutic Goods Administration agency approved the use of *Comirnaty* in the Australian population with vaccine roll-out scheduled for late February.

Moderna/NIH

This is also an mRNA vaccine, developed in partnership with the National Institutes of Health, but can be stored at a higher temperature (-20°C) than the Pfizer vaccine. On 30 November, Phase 3 trial results were published. Out of 196 cases of COVID-19 among trial volunteers, 185 were in people who received the placebo. And of the 11 vaccinated volunteers who got COVID-19, none suffered from severe disease. The researchers estimated that the vaccine had an efficacy rate of **94.1 per cent after two doses**, four weeks apart. On 18 December, the FDA gave emergency use authorisation for the vaccine followed by Canada on 23 December and in January, the European Union, Israel, Switzerland, Japan, Qatar, South Korea and the United Kingdom all granted it emergency authorisation.

AstraZeneca/Oxford

On 8 December 2020, researchers with the British-Swedish company AstraZeneca and University of Oxford published the first scientific paper on a Phase 3 clinical trial of a coronavirus vaccine[3]. The trial (in UK, India, Brazil, South Africa, and US) demonstrated that the vaccine can protect people from COVID-19, but it left many questions unresolved about the results. Oxford researchers developed the vaccine by genetically engineering an adenovirus that normally infects

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[1] https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

[2] https://www.nytimes.com/2020/11/18/health/pfizer-covid-vaccine.html

[3] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32661-1/fulltext

chimpanzees. When they gave the vaccine to monkeys, they found that it protected the animals from the disease. Two standard doses three weeks apart led to an efficacy of **62 per cent** while a small arm that accidentally received a half-dose first shot and a second full-dose shot had an efficacy of **90 per cent**. All volunteers in this arm were under the age of 55. AstraZeneca is now conducting a larger trial of nearly 30,000 people in the US. This vaccine has been approved in the UK, India (locally manufactured *Covishield*), Argentina and Mexico. The company has not yet applied for authorisation by the US FDA, but the TGA is currently reviewing this vaccine for approval in Australia.

In an unprecedented move in the coronavirus vaccine field, AstraZeneca announced on 11 December 2020 that it would collaborate with the Russian creators of the Sputnik V vaccine, which uses a human adenovirus to deliver the spike gene, to see if a combination with Sputnik V might increase the efficacy of the Oxford-AstraZeneca vaccine. The trial is planned to take place in early 2021 in Ukraine[4].

Sputnik V (also known as Gam-Covid-Vac)

The Gamaleya Research Institute produced the vaccine from a combination of two human adenoviruses called Ad5 and Ad26. Both kinds have been tested as vaccines over a number of years. By using these vaccines sequentially (for example Ad5 used in first dose and Ad26 in second dose) 3 to 4 weeks apart, the Russian researchers hoped to avoid a situation in which the immune system could learn to recognise the adenoviral components of the vaccine as a foreign object that needed to be destroyed, suppressing the boosting effect of the second dose. The researchers launched clinical trials in June 2020. In addition to Russia, volunteers for the trial were recruited in Belarus, the United Arab Emirates, India and Venezuela.

By December 2020, the trial had reached its final total of 78 cases. The efficacy rate was **91.4 per cent**. Out of the 78 cases of COVID-19 in the trial, 20 were severe — and all were in volunteers who received the placebo. In addition, the researchers announced that they found no serious side effects from the vaccine. Russia has negotiated a number of deals to supply other countries with the Sputnik V vaccine, including Brazil, India, Mexico, and Venezuela. On 22 December 2020, Belarus became the first country outside of Russia to register Sputnik V. Argentina authorised the vaccine for emergency use the next day. Algeria, Bolivia, the Palestinian Authority and Serbia authorised the vaccine in January 2021. Hungary became the first European nation to approve the vaccine for use under emergency authorisation on 21 January 2021.

Sinopharm (BBIBP-CorV)

The Beijing Institute of Biological Products created an inactivated coronavirus vaccine that was evaluated in clinical trials by the state-owned Chinese company Sinopharm. On 30 December 2020, Sinopharm announced that the vaccine had an efficacy of **79.3 per cent**, leading the Chinese government to give it approval[5]. The company has yet to publish the detailed results of their Phase 3 trial, which was conducted in Morocco, Peru, Bahrain and UAE. On 9 December 2020, the UAE gave full approval to BBIBP-CorV, announcing it had an efficacy rate of **86 per cent** after two doses up to 28 days apart[6]. The neighbouring country of Bahrain also gave full approval to the vaccine on 13 December 2020. Egypt and Jordan gave it emergency authorisation in January 2021.

CoronaVac (formerly PiCoVacc)

Sinovac Biotech, a private Chinese company, developed an inactivated vaccine called CoronaVac in early 2020. Although Phase 3 trial results have not been published, Phase 1/2 trial data published in *The Lancet* were promising[7]. In January

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[4] https://www.reuters.com/article/us-health-coronavirus-russia-ukraine-idUSKBN2970JP

[5] https://www.nytimes.com/2020/12/30/business/china-vaccine.html

[6] https://www.wam.ae/en/details/1395302893589

[7] https://www.thelancet.com/article/S1473-3099(20)30843-4/fulltext

2021, researchers in Brazil announced that it has an overall efficacy of **just over 50 per cent** after two doses 28 days apart, the minimum threshold set by many regulatory agencies and WHO for authorising a coronavirus vaccine. Despite the relatively modest efficacy, CoronaVac is being rolled out in a number of countries. Indonesia gave CoronaVac emergency authorisation on 11 January 2021. Turkey authorised the vaccine two days later. At least 10 countries have already ordered more than 380 million doses of CoronaVac, which is cheaper and easier to distribute than other vaccines.

Covaxin (also known as BBV152 A, B, C)

In collaboration with the Indian Council of Medical Research and the National Institute of Virology, the Indian company Bharat Biotech designed Covaxin, a vaccine based on an inactivated form of the coronavirus. The Phase 2 trial found that seroconversion rates of neutralising antibodies on day 56 after the second dose (28 days after the first dose) were 92.9 per cent (88.2, 96.2) in a low dose and 98.3 per cent (95.1, 99.6) for the higher dose[8]. In June, the higher dose Covaxin became the first coronavirus vaccine created in India to go into clinical trials. On 3 January 2021, the Indian government granted Covaxin emergency authorisation. The authorisation came despite no release of Phase 3 data showing the vaccine is safe and effective. Nevertheless, the Indian Government began to vaccinate healthcare workers on 15 January 2021, along with the Pfizer-Oxford vaccine, produced by the Serum Institute of India and known locally as Covishield.

Impact of Viral Variants on Vaccine Efficacy

Several new small studies have shed some light on the impact of the variant that originated in South Africa may have on vaccine efficacy. Neither has been peer-reviewed but are by highly renowned researchers. Human immune serum is composed of multiple different types of antibodies that recognise different regions of the spike protein in different ways. This is referred to as a polyclonal antibody response and it is the combination of these specificities that equates to the effectiveness of the antibody response in human plasma to prevent infection. By studying human plasma obtained from subjects infected pre-emergence of the South African variant 501Y.V2, researchers found a substantial or complete escape from neutralizing antibodies in COVID-19 convalescent plasma towards 501Y.V2[9]. Furthermore, therapeutically relevant monoclonal antibodies (isolated antibodies of a single defined specificity) from class I and II, failed to neutralise 501Y.V2, confirming that amino acid changes in the South Africa variant prevent recognition by some antibody specificities and likely account for the reduced levels of neutralization observed in convalescent plasma. These data highlight the prospect of reinfection with antigenically distinct variants and may foreshadow reduced efficacy of current spike-based vaccines.

The second study used sera from mRNA vaccinated people and showed that mutations present in 501Y.V2 (K417N: E484K: N501Y) reduce neutralization of the virus by a small but significant amount varying between subjects from 1 to 3 fold[10], with all subjects examined retaining neutralizing activity in the plasma. Interestingly, there was no difference in responses generated between the Moderna and Pfizer vaccines, with very high titres of antibodies produced and production of memory B cells similar to what is seen in natural infection. It is also important to note that both viral vectored and nucleic acid vaccines such as mRNA vaccines, generate robust cellular immune responses that aid in the clearance of virus infected cells, and antibodies also possess the ability to assist clearance of virus and virus infected cells through their effector functions which have not been assessed in these two studies. At this stage, it is not known how the mutations observed in 501Y.V2 will translate to changes in vaccine efficacy.

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[8] https://www.medrxiv.org/content/10.1101/2020.12.21.20248643v1.full.pdf

[9] https://www.biorxiv.org/content/10.1101/2021.01.18.427166v1

[10] https://www.biorxiv.org/content/10.1101/2021.01.15.426911v1

Burnet's vaccine expert Professor Heidi Drummer has summarised the significance of these studies as follows:

> "They used sera from mRNA vaccinated people and showed that all the South African variants reduce neutralization of the virus. However, the decrease in binding was variable and in the range of 1-3-fold lower, so still substantial reduced neutralization in the serum (and the difference was significant). How this translates to vaccine efficacy is unknown. It is difficult to make a prediction on efficacy. I do think this is looking more and more like we need to monitor circulating strains to see how they match up with the vaccine and update vaccines periodically."

Vaccine Hesitancy

A new Ipsos-World Economic Forum survey following the release of vaccines in the U.S. and U.K. finds intentions to be vaccinated are up in both countries, but down in several others as many worry about side effects[11]. The 15-country survey conducted 17-20 December among 13,500 adults on Ipsos's Global Advisor online platform finds the highest levels of vaccination intent in China with 80 per cent agreeing they would get a vaccine if it were available. Among the other countries surveyed, intention to get vaccinated against COVID-19 is:

- Fairly high in Brazil (78 per cent), Mexico (77 per cent), the U.K. (77 per cent), **Australia (75 per cent)**, South Korea (75 per cent), and Canada (71 per cent);
- Middling in the U.S. (69 per cent); Germany (65 per cent), Italy (62 per cent), Spain (62 per cent), and Japan (60 per cent); but
- Low in South Africa (53 per cent), Russia (43 per cent), and most of all, France (40 per cent).

In every country, between 57 per cent and 80 per cent of those who say they would not take a COVID-19 vaccine mention being worried about the side effects.

However, other studies contradict the finding that **69 per cent of Americans would get the vaccine**. The Understanding America Study (UAS) is a probability-based internet panel survey of approximately 9,000 randomly selected, noninstitutionalised US adults. This panel has been surveyed every two weeks since April 2020[12]. Between 1 – 14 April and 25 November – 8 December, the percentage who stated they were somewhat or very likely to get vaccinated **declined from 74 per cent to 56 per cent** (difference: 18 percentage points [95% CI, 16-20]). Significant declines over time in the likelihood of seeking vaccination were observed for both women and men and in all age, racial/ethnic, and educational subgroups. A Pew Research survey in December found that **60 per cent of Americans** say they would definitely or probably get a vaccine for the coronavirus, if one were available today, up from 51 per cent who said this in September[13]. About four-in-ten (39 per cent) say they definitely or probably would *not* get a coronavirus vaccine.

In the **United Kingdom**, a recently published study in *The Lancet* of 32,361 adults found that 16 per cent of respondents displayed high levels of mistrust about vaccines across one or more domains[14]. Distrustful attitudes towards vaccination were higher among individuals from ethnic minority backgrounds, with lower levels of education, lower annual income, poor knowledge of COVID-19, and poor compliance with government COVID-19 guidelines. Overall, 14 per cent of respondents reported unwillingness to receive a vaccine for COVID-19, whilst 23 per cent were unsure.

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[11] https://www.ipsos.com/en/global-attitudes-covid-19-vaccine-december-2020

[12] https://jamanetwork.com/journals/jama/fullarticle/2774711?resultClick=1

[13] https://www.pewresearch.org/science/2020/12/03/intent-to-get-a-covid-19-vaccine-rises-to-60-as-confidence-in-research-and-development-process-increases/

[14] https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(20)30012-0/fulltext

SCIENCE AND RESEARCH UPDATES | VIRAL VARIANTS OF CONCERN

Since the emergence of the SARS-CoV-2 virus in China in late 2019, the virus has been mutating constantly but at a slower rate than other viruses such as influenza. As reported in this *Global Analysis Update* in early October 2020, the D614G mutation of SARS-CoV-2, which probably originated in China, spread rapidly around the world and had almost become the universal form of the virus by June. Since September 2020, three new major variants have been identified, two of which have been linked to higher transmissibility. Preliminary analyses, involving relatively low patient numbers, are consistent in indicating that the B.1.1.7 variant may be associated with an increase in the severity of disease vs non variants of concern (VOC) although larger studies are required to confirm these observations[15]. Note that each of these variants has a number of different names. The impact of these variants on vaccine efficacy was addressed in the previous section.

On 14 January, WHO's COVID-19 IHR Emergency Committee recommended "...to increase worldwide capacities for SARS-CoV-2 molecular testing and genetic sequencing, in line with WHO guidance, and encourage rapid sharing of sequences and meta-data to strengthen monitoring of virus evolution and to increase global understanding of variants and their effects on vaccine, therapeutics and diagnostic efficacy[16]."

B.1.1.7 (also known as SARS-CoV-2 VOC 202012/01 and 501Y.V1)

Lineage B.1.1.7 is a phylogenetic cluster that has been rapidly spreading in south-eastern **England**, reportedly accounting for 60 per cent of recent infections in London. This variant has eight mutations in the spike protein including a change in the receptor binding domain (RBD) at position 501, where amino acid asparagine (N) has been replaced with tyrosine (Y)[17]. Prior work on variants with **N501Y** suggests they may bind more tightly to the human angiotensin-converting enzyme 2 (ACE2) receptor. The B.1.1.7 variant also harbours a two amino acid deletion (H69-V70) that helps the virus infect cells more efficiently and evade certain antibodies as well as the P681H mutation next to the furin cleavage site that enhances virus infectivity[18]. This variant had accumulated 17 lineage-defining mutations by the time of its detection in early September, which suggests a significant amount of prior evolution, possibly in a chronically infected immunocompromised host[19].

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[15] https://www.gov.uk/government/publications/nervtag-paper-on-covid-19-variant-of-concern-b117

[16] https://www.who.int/news/item/15-01-2021-statement-on-the-sixth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic

[17] https://www.cdc.gov/coronavirus/2019-ncov/more/scientific-brief-emerging-variant.html

[18] https://www.nytimes.com/interactive/2021/health/coronavirus-mutations-B117-variant.html

[19]https://jamanetwork.com/journals/jama/fullarticle/2775006?utm_source=silverchair&utm_campaign=jama_network&utm_content=covid_weekly_highlights&utm_medium=email

As of 28 December 2020, the B.1.1.7 variant accounted for approximately 28 per cent of cases of SARS-CoV-2 infection in England, and population genetic models suggest that it is spreading 56 per cent more quickly than other lineages. By mid-January, the new variant had been identified in at least 50 countries, including 48 known cases in **Australia**[20]. The US CDC has detected the variant in ten states and predicts it will be the dominant strain in the US by March[21]. While public health interventions like masks, physical distancing, and limitations on large gatherings should remain effective, control of a more transmissible variant would likely require more stringent application and widespread adoption of these measures. Because current vaccines provoke an immune response to the entire spike protein, it is hoped that effective protection may still occur despite a few changes at antigenic sites in SARS-CoV-2 variants.

501Y.V2 (also known as B.1.351)

On 18 December, national authorities in **South Africa** notified the WHO of the detection of a new variant of SARS-CoV-2 that is rapidly spreading in Eastern Cape, Western Cape, and KwaZulu-Natal provinces[22]. South Africa has named this variant 501Y.V2, because of a **N501Y** mutation. B.1.351 has a total of eight mutations that change amino acids in the spike protein; three substitutions within the receptor binding domain N501Y, K417N and E484K, with the latter demonstrating reduced sensitivity to neutralisation and five changes in the N-terminal domain, four substitutions and a deletion[23]. While SARS-CoV-2 VOC 202012/01 from the UK also has the N501Y mutation, phylogenetic analysis has shown that 501Y.V2 from South Africa is a different virus variant. While genomic data highlighted that the 501.V2 variant rapidly displaced other lineages circulating in South Africa, and preliminary studies suggest the variant is associated with a higher viral load, which may suggest potential for increased transmissibility, this, as well as other factors that influence transmissibility, are subject of further investigation. Moreover, at this stage, there is no clear evidence of the new variant being associated with more severe disease or worse outcomes.

P.1 (also known as B.1.1.248)

A new SARS-CoV-2 variant has been detected circulating in December in Manaus, Amazonas state, northern **Brazil**, where very high attack rates have been recorded previously[24]. The new lineage contains a unique combination of mutations, including six mutations in the spike protein including several with known biological importance such as E484K, K417T, and **N501Y**. The P.1 lineage was identified in 42 per cent (13 out of 31) of RT-PCR positive samples collected between 15 to 23 December, but it was absent in 26 publicly available genome surveillance samples collected in Manaus between March and November 2020. The newly described P.1 lineage from Manaus and the B.1.1.7 first described in the United Kingdom share the spike N501Y mutation and a deletion in ORF1b.These findings indicate local transmission and possibly recent increase in the frequency of a new lineage from the Amazon region. The higher diversity and dates identified in Manaus corroborate the travel information of recently detected cases in Japan, suggesting the direction of travel was Manaus to **Japan**[25]. The variant has also been identified in the UK and Germany. It is too early to make conclusions about the transmissibility, virulence and immune response of this new variant.

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[20] https://cov-lineages.org/global_report_B.1.1.7.html

[21] https://www.cdc.gov/mmwr/volumes/70/wr/mm7003e2.htm

[22] https://www.who.int/csr/don/31-december-2020-sars-cov2-variants/en/

[23] https://www.biorxiv.org/content/10.1101/2021.01.18.427166v1

[24] https://virological.org/t/genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-manaus-preliminary-findings/586?s=03

[25] https://www.japantimes.co.jp/news/2021/01/11/national/science-health/new-coronavirus-variant-japan/

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