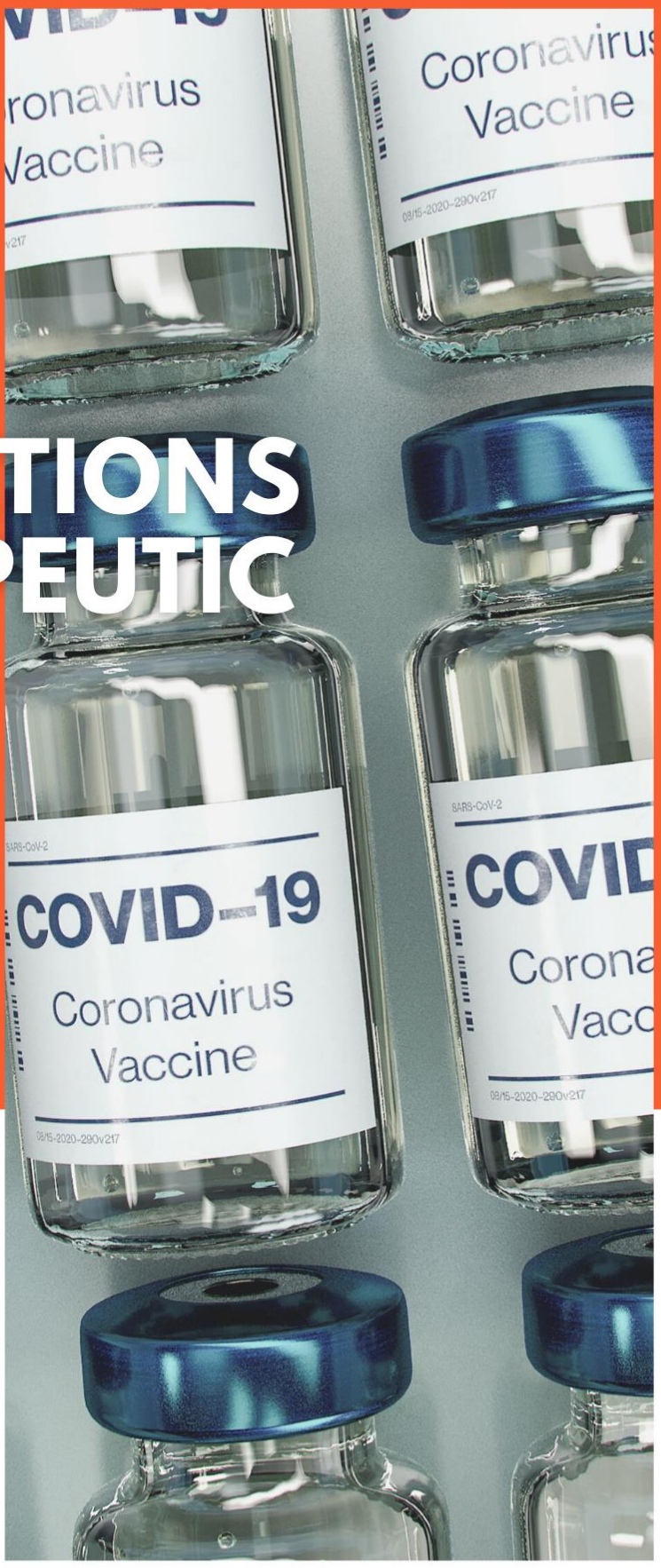
THE COVID-19 PANDEMIC & HAEMOGLOBIN DISORDERS

VACCINATIONS & THERAPEUTIC DRUGS



UPDATE
10 DECEMBER 21

THALASSAEMIA INTERNATIONAL FEDERATION

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UPDATE: 10 December 2021

"*Immunization is a key component of primary health care and an indisputable human right. It is also one of the best health investments money can buy. Vaccines are thus critical to the prevention and control of infectious-disease outbreaks. They underpin global health security and will be a vital tool in the battle against antimicrobial resistance*". – WHO https://www.who.int/health-topics/vaccines-and- immunization

"*Since the beginning of the pandemic, WHO has taken steps to prevent an "infodemic"— defined by the organization as "an overabundance of information and the rapid spread of misleading or fabricated news, images, and videos." WHO and the Wikimedia Foundation, the nonprofit organization that administers Wikipedia, have established a collaboration to expand the public's access to the latest and most reliable information about COVID-19*".

Information about the initiative is available at: https://www.who.int/news/item/22-10- 2020-the-world-health-organization-and-wikimedia-foundation-expand-access-to- trusted-information-aboutcovid-19-on-wikipedia

TIF shares the concerns of false information and misleading overabundance of information. This often happens in the effort to enhance hope to a population that is suffering not only from the disease itself, but also from its economic future, since lockdown/isolation practices are stifling the market economies of every country around the world. Hope however, must be based on realistic expectations and information.

For these reasons, TIF updates on new developments concerning vaccinations and new therapies are scanned for accuracy and are reviewed now more regularly.

Vaccines for SARS-CoV-2

The genetic sequence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was published on January 11, 2020, and the rapid emergence of research and collaboration among scientists and biopharmaceutical manufacturers followed. Various methods are used for vaccine discovery and manufacturing.

The U.S. Food and Drug Administration (FDA) has authorized **3 SARS-COV-2 vaccines** for emergency use (EUA) in the United States: Two are mRNA vaccines, the Pfizer-BioNTech COVID-19 Vaccine and Moderna COVID-19 Vaccine, whereas the third is a viral vector vaccine –the Janssen COVID-19 Vaccine. **The only vaccine to have gained full approval by the US regulatory health authority is the Pfizer vaccine, as of August 23.**

The European Medicines Agency (EMA) has given conditional marketing authorization to **4 SARS-CoV-2 vaccines**. Two are mRNA vaccines – Comirnaty or BNT-162b2 (Pfizer) and Spikevax (previously COVID-19 Vaccine Moderna), and the others are viral vector vaccines, the Vaxzevria (previously COVID-19 Vaccine AstraZeneca), and the Janssen COVID-19 Vaccine.

There are also 4 vaccines currently under rolling review by the EMA:

- **Sputnik V (Gam-COVID-Vac)**
- **COVID-19 Vaccine (Vero Cell) Inactivated (or Sinovac - CoronaVac COVID-19 Vaccine)**
- **Vidprevtyn (or Sanofi/GSK COVID-19 Vaccine)**
- **VLA2001 (Valneva)**

EMA has started evaluating an application for conditional marketing authorisation for **Novavax's COVID-19 vaccine, Nuvaxovid** (also known as NVX-CoV2373). The assessment will proceed under an accelerated timeline, and an opinion on the marketing authorisation could be issued within weeks if the data submitted are sufficiently robust and complete to show the efficacy, safety and quality of the vaccine.

The following 8 COVID-19 Vaccines have been granted Emergency Use Listing by the World Health Organization (WHO), as of December 10: Oxford/AstraZeneca, Serum Institute of India Covishield (Oxford/AstraZeneca formulation), Janssen (Johnson and Johnson), Moderna, Pfizer BioNTech, Sinopharm, Sinovac, and Covaxin (Bharat Biotech).

Status of COVID-19 Vaccinations in Major Countries and Regions

Globally, as of 7 December 2021, there have been **265,713,467 confirmed cases of COVID-19,** including **5,260,888 deaths,** reported to WHO. As of the same date, **7,952,750,402 vaccine doses have been administered.**

The COVAX scheme, co-led by Gavi-the Vaccine Alliance, the Coalition for Epidemic Preparedness Innovations (CEPI) and the World Health Organization (WHO), with the aim to accelerate the development and manufacture of COVID-19 vaccines and guarantee fair and equitable access for every country in the world, has shipped **over 610 million COVID-19 vaccines to 144 participating countries worldwide** (as of December 6).

Source: Gavi

Data provided by Our World In Data project at the University of Oxford, show that as of December 6, **55,2%** of the world population has received at least one dose of a COVID-19 vaccine, and **45%** is fully vaccinated. Only **6,3%** of people in low-income countries have received at least one dose. (see *Table 1*)

Millions of people in low-income and conflict-affected countries remain unvaccinated and, therefore, unprotected against COVID-19. According to data from the International Rescue Committee (IRC), as of December 6:

- Eight out of ten countries on the **IRC's 2021 Emergency Watchlist** are still less than 5% vaccinated with the Democratic Republic of Congo (0.06%), Yemen (1.16%), and South Sudan (1.17%) seeing the lowest coverage.
- Comparatively, the US, UK, Germany, and Sweden have vaccinated nearly 58%, 68%, 68%, and 70% of their populations respectively - and are starting to give booster shots to their populations.

- COVID-19 vaccine inequality is particularly pronounced in Africa, which has received just 2.8% of the world's vaccine doses, despite being home to 17% of the global population.

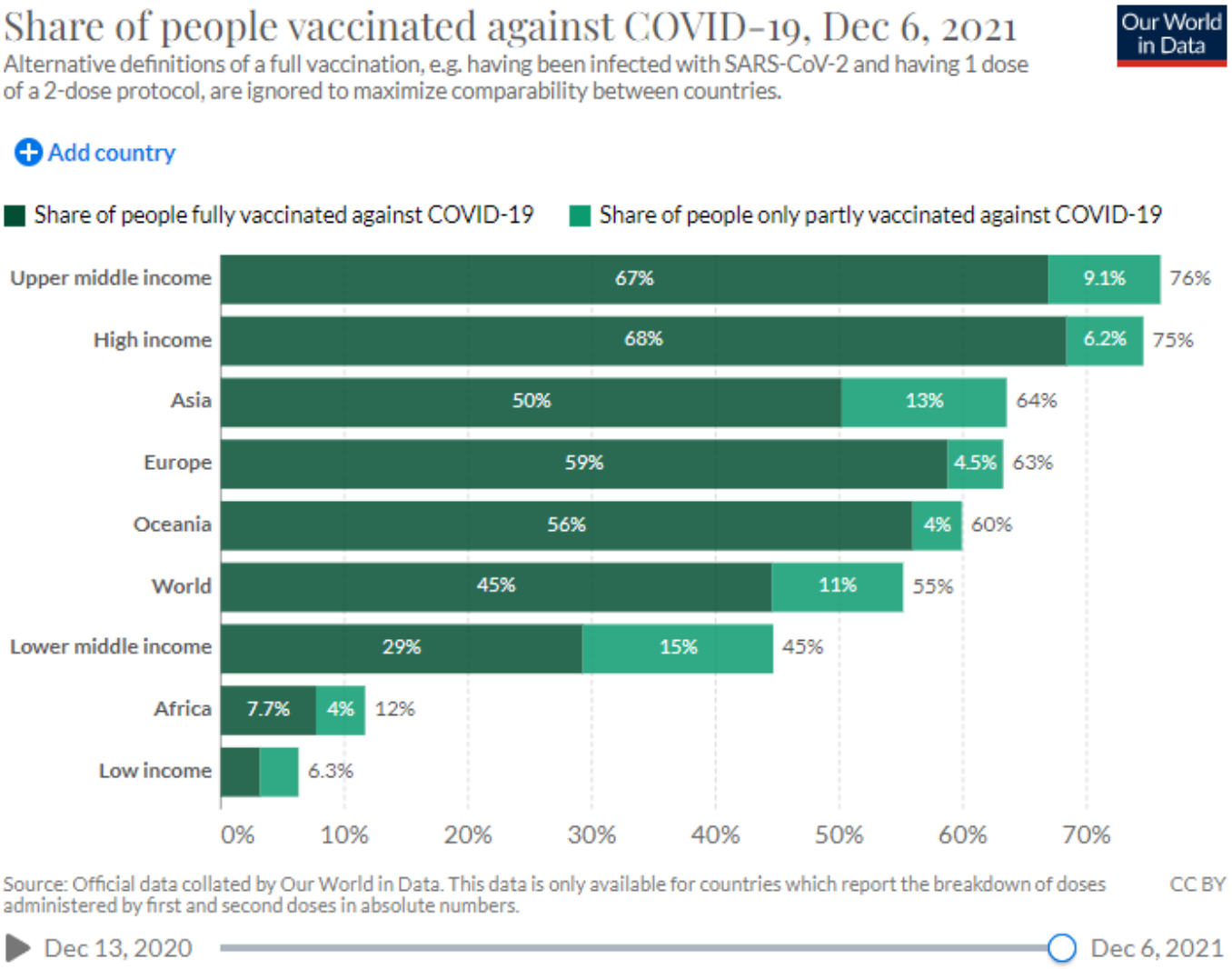


Table 1/ Our World in Data

An interactive COVID-19 Vaccination Rollout and Access Tracker per country is provided by Reuters HERE.

Development and Production of COVID-19 Vaccines

Scientists around the world are working faster than ever to develop and produce vaccines that can stop the spread of COVID-19, **with 136 vaccines now being in clinical development and another 194 in pre-clinical development** (information correct as of December 7).

Source: *WHO*

The development cycle of a vaccine from lab to clinic

PRECLINICAL TESTING: Scientists test a new vaccine on cells and then give itto **animals** such as mice or monkeys to see if it produces an immune response.

PHASE 1 SAFETY TRIALS: Scientists give the vaccine to a **small number of people** to test safety and dosage, as well as to confirm that it stimulates the immune system.

PHASE 2 EXPANDED TRIALS: Scientists give the vaccine to **hundreds of people** split into groups, such as children and the elderly, to see if the vaccine acts differently in them. These trials further test the vaccine's safety.

PHASE 3 EFFICACY TRIALS: Scientists give the vaccine to **thousands of people** and wait to see how many become infected, compared with volunteers who received a placebo. These trials can determine if the vaccine protects against the coronavirus, measuring what is known as the efficacy rate. Phase 3 trials are also large enough to reveal evidence of relatively rare side effects.

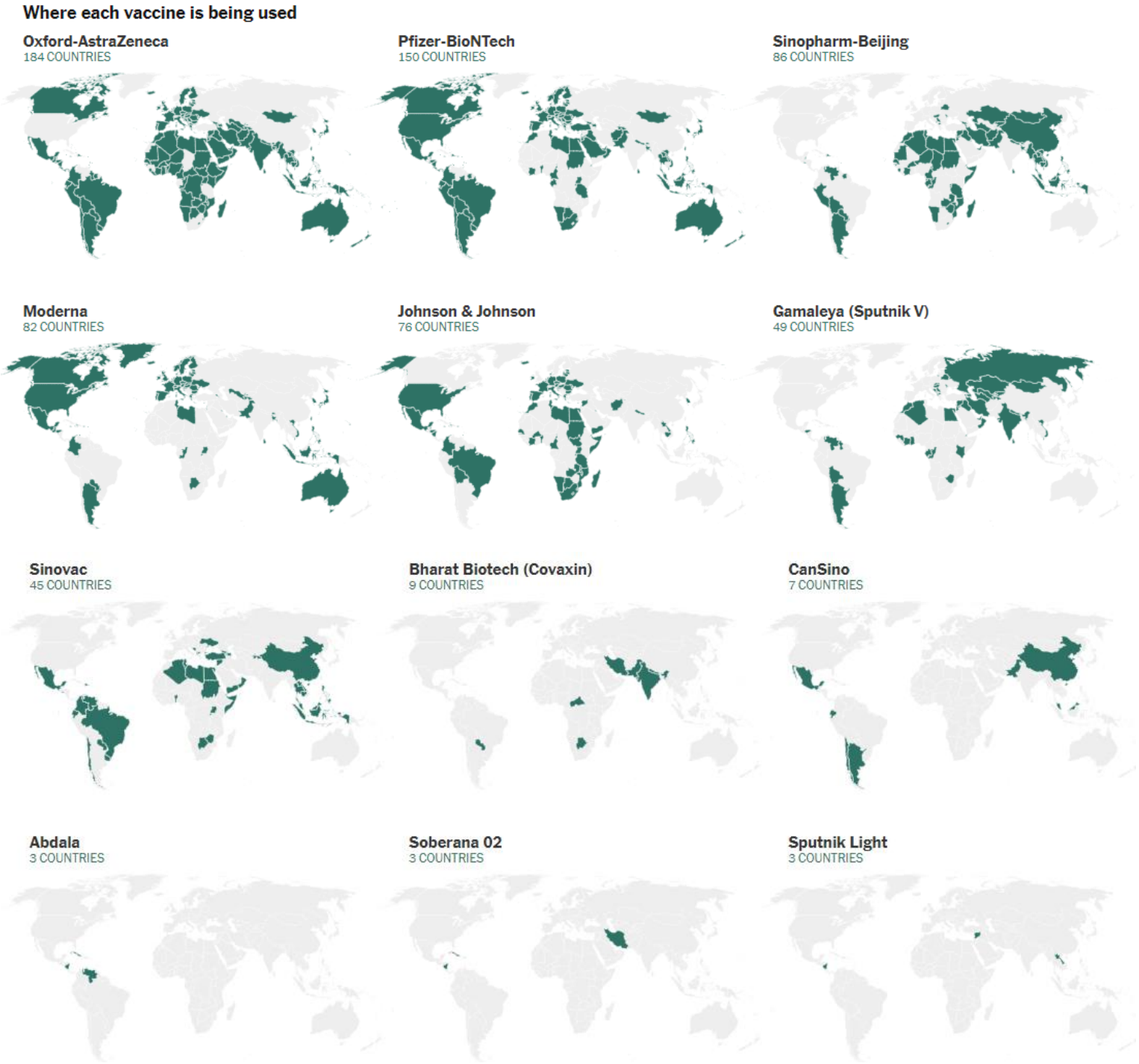
EARLY OR LIMITED APPROVAL: Many countries have procedures for providing emergency authorizations for vaccines, based on preliminary evidence that they are safe and effective. In addition, some countries such as China and Russia began administering vaccines before detailed Phase 3 trial data was made public.

APPROVAL: Regulators review the complete trial results and plans for a vaccine's manufacturing and decide whether to give it full approval.

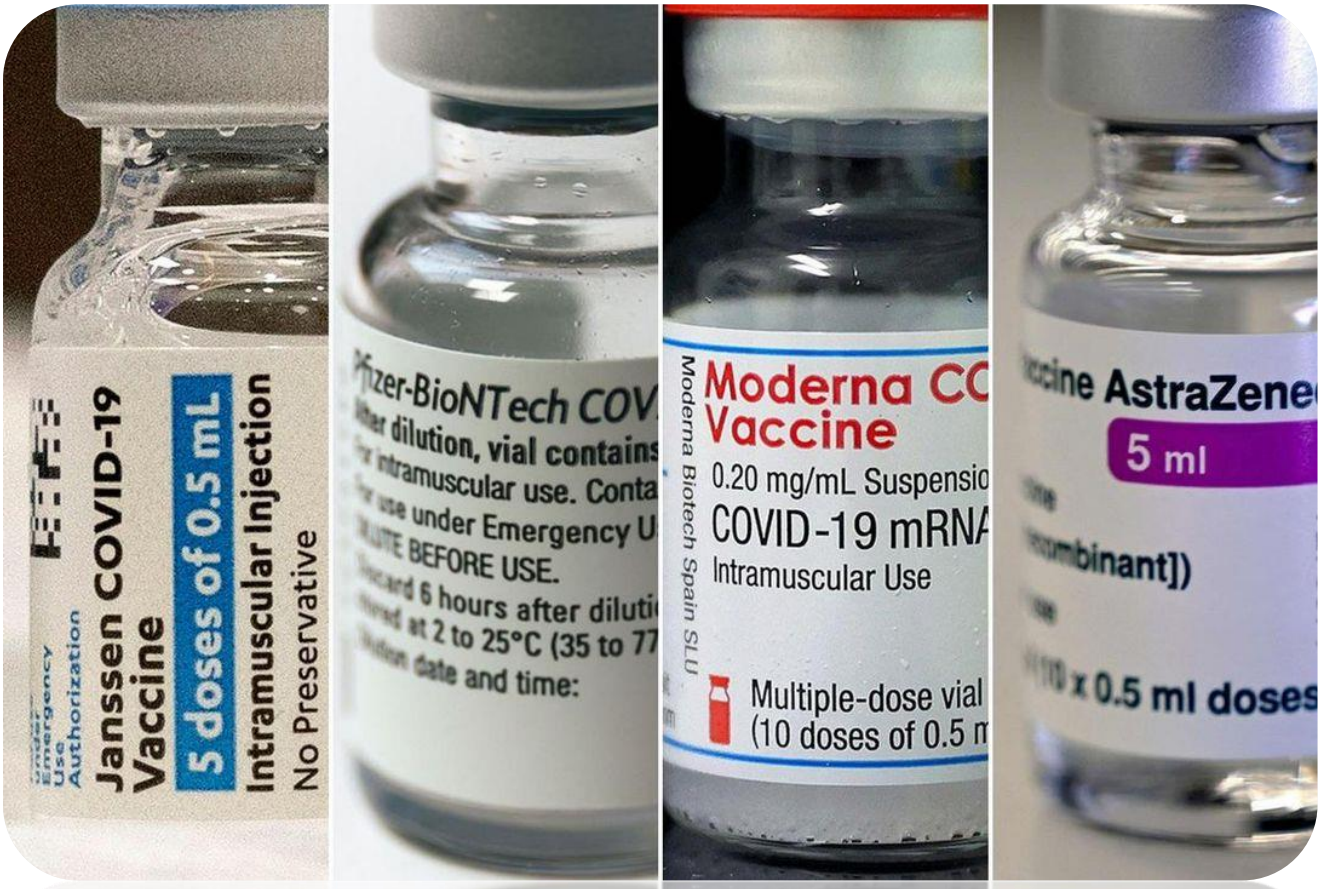
Until December 7, the top-3 used COVID-19 vaccines on a global scale, [according to the *New York Times Vaccines Tracker*](), are;

- the Oxford-AstraZeneca vaccine, in 184 countries or regions;
- the Pfizer vaccine, in 150 countries, and
- the Sinopharm-Beijing vaccine, in 86 countries

The below maps show where each vaccine is being utilized.



Pfizer/BioNTech, Moderna, AstraZeneca/Oxford & Janssen (J&J) Vaccines: A Head-to-Head Comparison



Pfizer-BioNTech

On December 11, 2020, this became the first COVID-19 vaccine to receive an FDA Emergency Use Authorization (EUA), after the company reported positive clinical trial data, which included news that the vaccine was up to 95% more effective than a placebo at preventing symptomatic disease. The vaccine has also received authorization by the European Medicines Agency (EMA) – the responsible regulatory body for the 27 EU Member States – on December 21, 2020.

On August 23, the FDA fully approved the Pfizer/BioNTech COVID-19 vaccine, making it the first vaccine against the novel coronavirus to receive full approval – all other vaccines have been granted Emergency Use Authorisation (EUA) by the authority. FDA Acting Commissioner, Janet Woodcock, MD, characterized the approval as a "milestone" in the pandemic, stating that *''the public can be very confident that this vaccine meets the high*

standards for safety, effectiveness, and manufacturing quality the FDA requires of an approved product''.

The Pfizer-BioNTech vaccine has had strict requirements involving how the vaccine is stored, requiring shipping in ultra-cold temperature-controlled units (-94 degrees Fahrenheit). In mid-February, the company submitted new data to the FDA demonstrating the stability of the vaccine at temperatures more commonly found in pharmaceutical refrigerators and freezers.

Recommended for: Adults, adolescents aged 12 years and older, and children aged 5 to 11 years. On October 29, the **FDA expanded emergency use authorization of the Pfizer-BioNTech COVID-19 Vaccine** to **include children 5 through 11 years of age. The EMA followed suit with a respective approval on November 25.** The FDA also **authorised the use of a single booster dose** of either the Pfizer or Moderna vaccines for all individuals 18 years of age and older after completion of primary vaccination, **on November 19**.

Dosage: Two shots, 21 days apart

Common side effects: Chills, headache, pain, tiredness, and/or redness and swelling at the injection site, all of which generally resolve within a day or two of rest, hydration, and medications like acetaminophen. On rare occasions (as in, 11 cases in 18 million vaccinations), mRNA vaccines have appeared to trigger anaphylaxis, a severe reaction which requires emergency treatment.

The FDA placed a warning label on the Pfizer vaccine regarding a "likely association" with reported cases of heart inflammation in young adults. This inflammation may occur in the heart muscle (myocarditis) or in the outer lining of the heart (pericarditis), and is considered important but uncommon—arising in about 12.6 cases per million second doses administered

How it works: This is a messenger RNA (mRNA) vaccine, which uses a relatively new technology. Unlike vaccines that put a weakened or inactivated disease germ into the body, the Pfizer-BioNTech mRNA vaccine delivers a tiny piece of genetic code from the SARS CoV-2 virus to host cells in the body, essentially giving those cells instructions for making copies of spike. The spikes do the work of penetrating and infecting host cells. These proteins stimulate an immuneresponse, producing antibodies and developing memory cells that will recognize and respondif the body is infected with the actual virus.

How well it works: Experts continue to learn about Pfizer's vaccine efficacy both in the laboratory and in the real world. Pfizer's initial Phase 3 clinical data presented in December showed its vaccine to have 95% efficacy.

A number of studies have focused on the vaccine and the various virus mutations. In early May,

the Pfizer vaccine was found to be more than 95% effective against severe disease or death from the Alpha variant and the Beta variant, in two studies based on real-world vaccinations.

As far as the Delta variant is concerned, two studies reported by Public Health England that have not yet been peer reviewed showed that full vaccination after two doses is 88% effective against symptomatic disease and 96% effective against hospitalization **(see below for more info on the Omicron variant).**

Moderna

Moderna's vaccine (Spikevax) was the second one authorized for emergency use in the U.S.—it received FDA EUA on December 18, 2020, as well as conditional marketing authorization by the EMA inEurope on January 6, 2021.

Moderna is also an mRNA vaccine, using the same technology as the Pfizer-BioNTech one and with a similarly high efficacy at preventing symptomatic disease. There are two key differences: The Moderna vaccine can be shipped and kept in long-term storage in standard freezer temperatures, and stored for up to 30 days using normal refrigeration, making it easier to distribute and store.

Also, the Moderna vaccine was slightly less effective in clinical trials—about 86%—in people who are 65 and older.

Recommended for: Adults 18 and older. On July 23, the EMA cleared the Moderna vaccine for children ages 12 to 17, and currently assesses the use of the Moderna vaccine among children aged 5-11. The United States currently authorizes the use of the Moderna vaccine for people 18 and older.

Dosage: Two shots, 28 days apart

Common side effects: Similar to the Pfizer vaccine, side effects can include chills, headache, pain, tiredness, and/or redness and swelling at the injection site, all of which generally resolve within a day or two. On rare occasions, mRNA vaccines have appeared to trigger anaphylaxis, a severe reaction that requires emergency treatment. The FDA placed a warning label on the Moderna vaccine regarding a "likely association" with reported cases of heart inflammation in young adults. This inflammation may occur in the heart muscle (myocarditis) or in the outer lining of the heart (pericarditis), and is considered important but uncommon—arising in about 12.6 cases per million second doses administered.

How it works: Similar to the Pfizer vaccine, this is an mRNA vaccine that sends the body's cells instructions for making a spike protein that will train the immune system to recognize it. The immune system will then attack the spike protein the next time it meets one (attached to a real SARS CoV-2 virus).

How well it works: Moderna's initial Phase 3 clinical data in December 2020 was similar to Pfizer's—at that point, both vaccines showed about 95% efficacy. This figure has changed over time. At six months after vaccination, the Moderna vaccine was shown to have efficacy of 90% against infection and more than 95% against developing a severe case, according to the company.

In June, Moderna reported that studies showed its vaccine is effective against the Beta, Delta, Eta, and Kappa variants, although it did show it to be about two times weaker against Delta than against the original virus **(see below for more info on the Omicron variant).**

Oxford-AstraZeneca

This vaccine is distinguished from some of its competitors by its lower cost—it is cheaper to make per dose, and it can be stored, transported, and handled in normal refrigeration for at least six months. It can also be kept in a regular refrigerator, unlike the vaccines from Pfizer and Moderna.

Despite initial pauses about its safety with blood clots, multiple health authorities, including the WHO, the European Medicines Agency and the International Society on Thrombosis and Hemostasis have agreed that the benefits of administering the vaccine outweigh the risks. The vaccine has not been approved by the FDA for use in the US, where the company is expected to seek full regulatory approval by December 2021.

READ HERE: WHO Interim recommendations for use of the ChAdOx1-S [recombinant] vaccine against COVID-19 (AstraZeneca COVID-19 vaccine AZD1222, SII Covishield, SK Bioscience)

Recommended for: Adults 18 and older.

Dosage: Two doses, 4 to 12 weeks apart

Common side effects: Headache, fatigue, nausea, tenderness, pain, warmth, redness, itching, swelling or bruising at the injection site, all of which generally resolve within a day or two.

How it works: This is a carrier vaccine, made from a modified version of a harmless adenovirus.

The final product contains the spike protein found in SARS-CoV-2. When that protein reaches the body's cells, the immune system mounts a defense, creating antibodies and memory cells to protect against an actual SARS-Cov2 infection.

How well it works: AstraZeneca updated its data analysis of its phase 3 trials in March, showing its vaccine to be 76% effective at reducing the risk of symptomatic disease 15 days or more after receiving the two doses, and 100% against severe disease. The company also said the vaccine was 85% effective in preventing COVID-19 in people over 65.

A paper in early February, cited 74.6% efficacy against the Alpha variant. However, the vaccine did not protect as well against mild and moderate cases in people infected with the Beta variant. Therefore, South Africa halted its rollout while scientists continue to study whether the vaccine can prevent severe illness and death in people infected with this variant. A British study found that the AstraZeneca vaccine provides 67% effectiveness against infection with the Delta variant. A Canadian study found that it had an effectiveness of 87% against hospitalization and death from the variant **(see below for more info on the Omicron variant).**

Janssen (Johnson & Johnson)

On February 27, 2021, the FDA granted emergency use approval for the Johnson & Johnson vaccine, followed by an EMA conditional marketing authorization on March 11. In comparison to the Pfizer and Moderna vaccines, this one is easier to store (in refrigerator temperature), and requires only a single shot, which has made it easier to distribute and administer.

Status: Emergency use in the U.S., the EU, the UK and other countries.

Recommended for: Adults 18 and older. While the vaccine is not yet available for children, the company says its vaccine provides strong protection for children as young as 12.

Dosage: Single shot.

Common side effects: Fatigue, fever headache, injection site pain, or myalgia (pain in a muscle or group of muscles), all of which generally resolve within a day or two. It has had noticeably milder side effects than the Pfizer and Moderna vaccines, according to the FDA report released in late February. No one suffered an allergic reaction in clinical trials for the vaccine, according to the company.

The FDA has attached two warnings to the Johnson & Johnson vaccine. In July, the FDA attached a warning after rare cases of the neurological disorder Guillain-Barré syndrome were reported

in a small number of vaccination recipients. Most of the cases occurred within 42 days after vaccination.

In April, the FDA added a warning label after ending a pause on the vaccine it had recommended "out of an abundance of caution" over an uncommon, but potentially serious, blood clotting disorder that occurred in a small number of recipients.

How it works: This is a carrier vaccine, which uses a different approach than the mRNA vaccines to instruct human cells to make the SARS CoV-2 spike protein. Scientists engineer a harmless adenovirus (a common virus that, when not inactivated, can cause colds, bronchitis, and other illnesses) as a shell to carry genetic code on the spike proteins to the cells.

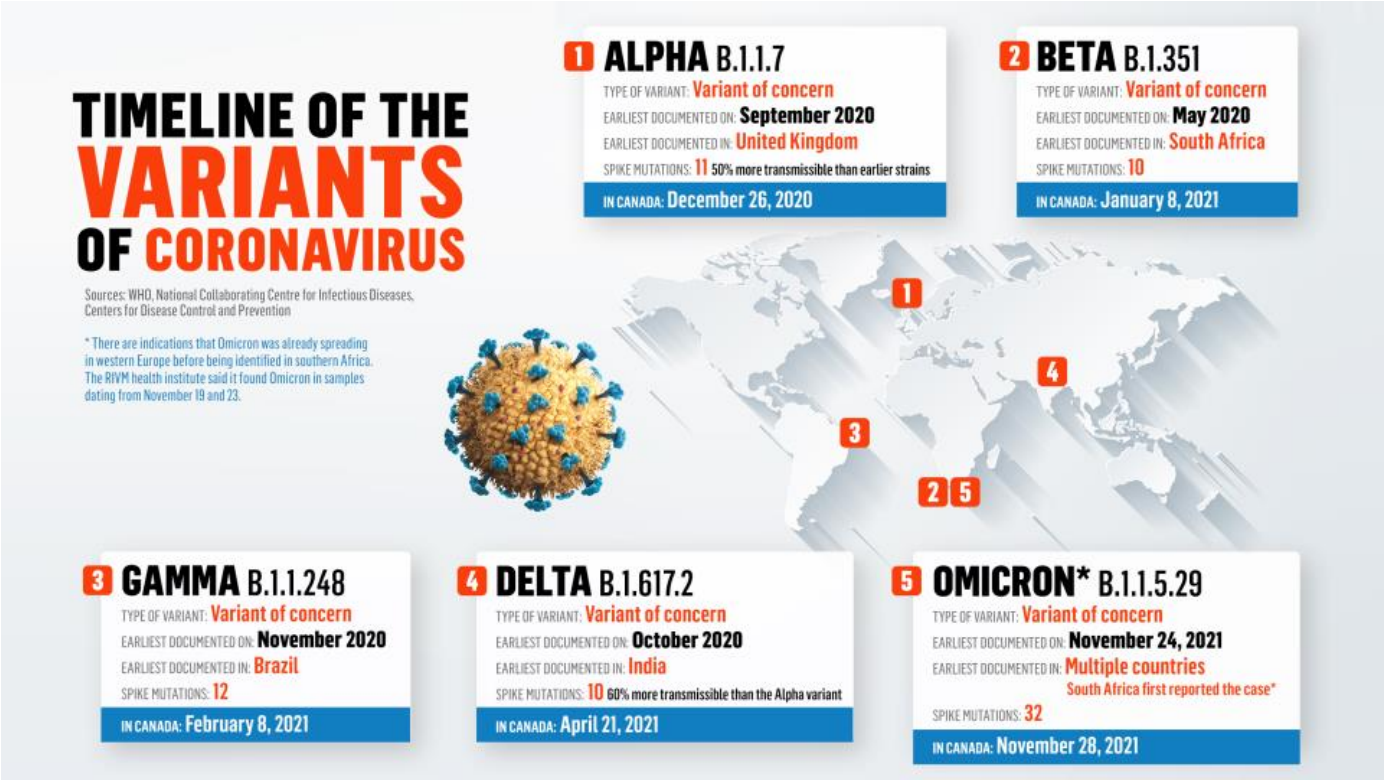
How well it works: 72% overall efficacy and 86% efficacy against severe disease in the U.S.

Johnson & Johnson found that its vaccine only had an efficacy of 52 percent in South Africa, where the Beta variant was dominant during the trial. As the Delta variant emerged in the summer of 2021, Johnson & Johnson released results of experiments indicating that their vaccine provided durable protection against it. However, another study from outside scientists suggested that the vaccine only weakly protects against Delta **(see below for more info on the Omicron variant).**

COVID-19 Variants & Vaccines' Effectiveness

All viruses – including SARS-CoV-2, the virus that causes COVID-19 – evolve over time. When a virus replicates or makes copies of itself, it sometimes changes a little bit, which is normal for a virus. These changes are called "mutations". A virus with one or more new mutations is referred to as a "variant" of the original virus.

As of December 10 and according to the WHO, there have been five (5) SARS-CoV-2 Variants of Concern (VoC) that have surfaced and undergone transmission across the globe.



Graphic by Jasna Baric/ CTV News

The **UK, Kent or Alpha variant** (also known as B.1.1.7), which became known in Britain in September 2020.

The **South Africa or Beta variant** (also known as B.1.351), first identified in South Africa in May 2020.

The **Gamma variant** (also known as P.1), which emerged in late 2020 in Manaus, the largest city in Brazil's Amazon region. It quickly became the predominant variant there and in several

other South American cities.

The **Delta variant** (also known as B.1.617.2), which emerged in late 2020 and quickly became the most common variant in India. It continued spreading around the world and is currently the dominant strain of the SARS-COV-2 virus across the world.

Omicron Variant: What We Know So Far

On November 24, 2021, a new variant of SARS-CoV-2, B.1.1.529, was reported to the World Health Organization (WHO). This new variant was first detected in specimens collected on November 11, 2021 in Botswana and on November 14, 2021 in South Africa.

The variant has an unusually large number of mutations, 60 mutations in total compared to the original Wuhan variant, several of which are novel and a significant number of which affect the spike protein targeted by most COVID-19 vaccines at the time of discovering the Omicron variant. This level of variation has led to **concerns regarding its transmissibility, immune system evasion, and vaccine resistance.** As a result, the variant was quickly designated as being "of concern", and travel restrictions were introduced by several countries in an attempt to slow its international spread. However, the variant has spread to over 50 countries by 7 December 2021. Accumulating epidemiological data from around the world also indicates re-infections are higher with Omicron.

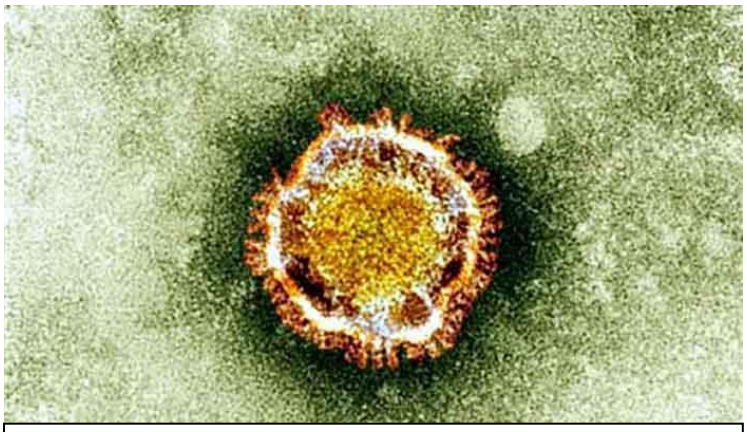
Photo: Thomas Faull/Alamy Live News

On December 7, long-time Director of the US National Institute of Allergies and Infectious Diseases (NIAID), Dr Anthony Fauci, said that the new variant is "*clearly highly transmissible*", adding as per its severity that "*it almost certainly is not more severe than the Delta variant*". He further added that lab experiments that tested the potency of antibodies from current vaccines against Omicron should come in the "*next few days to a week*"

How well will COVID-19 vaccines work against Omicron?

According to the US Centers for Disease Control and Prevention (CDC), current vaccines are expected to protect against severe illness, hospitalizations, and deaths due to infection with the Omicron variant. However, CDC stated that breakthrough infections in people who are fully vaccinated are likely to occur and the recent emergence of Omicron further emphasizes the importance of vaccination and boosters. CDC's perspective on the matter seems to be supported by most scientists at the moment who remain optimistic about the power of vaccines to safeguard people from the Omicron variant. *"It is extremely unlikely this variant will evade vaccines completely,"* Prof Peter Openshaw of Imperial College London said to The Guardian. *"The vaccines we have are remarkably effective against a range of other variants. Nevertheless, we need more lab and real world data to determine the degree of protection in those vaccinated."*

Several vaccine developers, including Pfizer, Moderna, and Johnson & Johnson, are already working on Omicron-specific shots. Pfizer´s Chief Scientific Officer, Mikael Dolsten, said an updated version of their vaccine could be ready to start mass-production as soon as March 2022.



This undated handout picture courtesy of the British Health Protection Agency shows the coronavirus seen under an electron microscope. I Photo Source AFP

On December 8, **Pfizer** announced that a third shot of the its COVID-19 vaccine offers protection against the Omicron coronavirus variant while just two doses show significantly reduced effectiveness against it, according to a preliminary study conducted by the vaccine makers.

In a joint statement, the companies said that while their current two-dose jab is "significantly less effective at blocking the virus," a booster shot "neutralized the Omicron variant in lab tests." There is also information from the Africa Health Research Institute published Tuesday, December 7, suggesting that the booster is likely to protect people from serious illness from the new variant.

Moderna's CEO, Stéphane Bancel, stated last week that there is a good chance current vaccines will not hold up as well against the Omicron variant. It would take three months for Moderna to produce a vaccine specifically targeting Omicron, Dr. Paul Burton, according to the company's Chief Medical Officer.

Dr. Mathai Mammen, **Johnson & Johnson's** Global Head of Research and Development, said that Omicron's presence shows that drugmakers must continue testing and monitoring COVID-19's

mutations, while adding that J&J is currently testing its vaccine against the newly emerged variant.

AstraZeneca's CEO, Pascal Soriot, has not said much publicly about the new variant or if the company will need to develop a new vaccine against it. Existing coronavirus vaccinations, no matter who produced them, likely will not perform well against Omicron, said Oxford Professor Sarah Gilbert, who helped create AstraZeneca's current jab. "*Until we know more, we should be cautious, and take steps to slow down the spread of this new variant,*" she told the BBC on December 6.

Emerging data from South Africa suggests increased risk of reinfection with Omicron, **WHO Director General, Tedros Adhanom Ghebreyesus**, told reporters on December 8, adding that "here is also some evidence that Omicron causes milder disease than Delta. He stressed, however, that more data is needed before drawing firm conclusions, and urged countries everywhere to boost their surveillance in order to help provide a clearer picture of how Omicron is behaving.

WHO experts underlined the importance of vaccination, highlighting that even if vaccines prove less effective against Omicron, as some data indicates, they are still expected to provide significant protection against severe disease.

Vaccines in Phase 3 Clinical Trials (listed as of December 10)

1. **Sinopharm Beijing and Wuhan Institute of Biological Products**, have produced two inactivated COVID-19 vaccines. The Beijing Institute's vaccine, **BBIBP-CorV**, was approved for emergency use in China on June 30, 2020. The Wuhan Institute's one was approved on July 23, 2020.

On 30 December 2020, Sinopharm announced the BBIBP-CorV vaccine's efficacy rate demonstrated in interim data from Phase 3 trials was 79.34%, without providing more details.

On May 7, WHO listed the Sinopharm COVID-19 vaccine for emergency use, giving the green light for this vaccine to be rolled out globally through COVAX. A further 42 countries, including Hungary, Venezuela, and Sri Lanka, have approved the vaccine. On August 2, the UAE Ministry of Health has approved the use of the Sinopharm vaccine against COVID-19 for children in the 3-17 years age group in UAE. The European Medicines Agency (EMA) has not yet reviewed it for use in the European Union.

On August 29, the U.A.E. mandated booster shots for all residents who received BBIBP-CorV. Results from a small-scale booster study showed that a third shot of the vaccine reversed a decline in antibodies after several months, Reuters reported on September 17.

A phase 4 trial was also registered in November to evaluate the immunogenicity, safety and persistence of a third dose of the vaccine in individuals aged 60 years and above with chronic bronchitis and chronic obstructive pulmonary disease.

2. **Valneva COVID-19 vaccine, VLA2001,** is a COVID-19 vaccine candidate developed by French biotechnology company **Valneva SE**, in collaboration with American company Dynavax Technologies.

   Rather than induce an immune response that targets just the spike protein of the coronavirus, the Valneva vaccine, also known as VLA2001, stimulates an immune response to the entire virus, in contrast to other vaccine candidates and existing vaccines targeting the virus' spike proteins.

   Phase 3 trials for the Valneva vaccine were carried out on more than 4,000 patients aged 18 years and older across 26 sites in the United Kingdom. The trials compared the immune response rates with those vaccinated with the Oxford AstraZeneca vaccines and results showed that VLA2001 generated a stronger immune response than the AstraZeneca vaccine – with higher levels of neutralising COVID-19 antibodies in the blood.

   On November 10, the European Commission approved a contract with Valneva providing the possibility to purchase almost 27 million doses of its vaccine in 2022, and on December 2 the European Medicines Agency (EMA)'s human medicines agency (CHMP) started a rolling review of VLA2001, following positive preliminary results.

3. **The Gamaleya National Research Center of Epidemiology and Microbiology** and the Russian Direct Investment Fund (RDIF) have reported that the **Sputnik V COVID-19 vaccine** showed a 97.6% efficacy. This was based on the analysis of data on disease infection rate among people receiving both shots of the vaccine.

   In February 2021, preliminary results of the phase 3 trials were reported in Lancet with a 91.6% efficacy rate – the percentage reduction of disease in a vaccinated group of people compared to an unvaccinated group under trial conditions. However, Sputnik V has become shrouded in controversy, largely due to the Institute's refusal to share important data on the drug. On August 11, Russian Health Minister, Mikhail Murashko, affirmed the shot to be around 83% effective against the Delta variant of coronavirus.

The Sputnik V is currently registered and certified in 71 countries. According to the Head of the Russian Direct Investment Fund, the vaccine should be approved by the WHO by the end of 2021.

4. The **Novavax Inc's** recombinant nanoparticle protein-based two-dose shot with Matrix-M adjuvant, **NVX-CoV2373 (Nuvaxovid),** is made with lab-grown copies of the spike protein that coats the coronavirus. That is very different from other widely used vaccines that deliver geneticinstructions for the body to make its own spike protein. The Novavax shots are easier to store and transport than some other options, and have long been expected to play an important role in increasing supplies in poor countries desperate formore vaccine.

In June, Novavax announced the vaccine had proved about 90% effective against symptomatic COVID-19 in a study of nearly 30,000 people in the U.S. and Mexico. It also worked against variants circulating in those countries at the time. Side effects were mostly mild. As for the highly contagious Delta variant, Novavax also announced that giving a booster six months after a second shot revved up virus-fighting antibodies that could tackle that mutant.

Novavax signed a deal with the EU on August 4 to supply up to 200 million doses and said it would complete the submission of data to the European Medicines Agency (EMA) for the vaccine's approval in Europe as early as the end of September. **On November 17, EMA received application for conditional marketing authorization of the vaccine. According to the Head of the European Medicines Agency (EMA), Emer Cooke, the vaccine could be authorized for use in the EU in the very near future.**

The company has also applied for authorization of Nuvaxovid in the United Kingdom, Australia, Canada, and New Zealand.

5. **ZF2001, trade-named Zifivax**, is an adjuvanted protein subunit COVID-19 vaccine developed by **Anhui Zhifei Longcom** in collaboration with the Institute of Microbiology at the Chinese Academy of Sciences.

ZF2001 employs technology similar to other protein-based vaccines in Phase III trialsfrom Novavax, Vector Institute, and Medicago. It is administered in 3 doses over a period of2 months.

ZF2001 was first approved for use in Uzbekistan and later China. Production capacity is

expected to be one billion doses a year. Phase II results published in The Lancet on the three-dose administration showed seroconversion rates of neutralizing antibodies of between 92% to 97%.

In July 2021, lab studies showed ZF2001 largely retained its neutralizing effect against Delta variant with a slight reduction. Serum samples from people vaccinated with ZF2001 showed a 1.2-fold reduction in neutralising effect compared against the original variant of COVID-19. By the same month, 100 million doses of the shot had already been administered in China and Uzbekistan.

On 7 September, the National Agency of Drug and Food Control of Indonesia (BPOM) published the emergency use authorization for Zifivax.

6. The vaccine **CVnCoV** is German clinical-stage biopharmaceutical company **CureVac's** mRNA-based vaccine candidate, which started development in January 2020. CVnCoV was being developed in collaboration with British pharma giant GlaxoSmithKline (GSK) and Bayer.

On 16 June 2021, CureVac said its vaccine showed inadequate results of 47% efficacy from its Phase III trial. The study involved 40,000 people in 10 countries in Europe and Latin America with at least 13 coronavirus variants circulating, the company said. Of those in the trial, there were 134 COVID cases among people two weeks after they had received the second dose. When sequencing the virus, only one was attributable to the original coronavirus strain. More than half (57%) were "variants of concern."

On October 12, CureVac announced that it decided to abandon its COVID-19 vaccine development and focus on its collaboration with GlaxoSmithKline (GSK) to develop second-generation messenger RNA (mRNA) vaccine candidates. The company also withdrew the application to the European Medicines Agency (EMA) for the approval of CVnCoV, and the latter ended its rolling review of the vaccine.

The biotech company has teamed up with GSK to produce a second-generation vaccine that targets variants with a "new messenger RNA backbone''.

7. Hyderabad-based vaccine manufacturer **Bharat Biotech International** announced the interim efficacy data for the Phase 3 trials of **Covaxin**, the first made-in-India coronavirus

vaccine.

In the trial results, Bharat Biotech and the ICMR said that Covaxin demonstrates an overall interim clinical efficacy of 78%. The efficacy against severe COVID-19 disease was 100%, the company said, but efficacy against protecting from asymptomatic COVID-19 infection dropped at 70%.

In July 2021, Bharat Biotech reported the vaccine to be 64% effective against asymptomatic cases, 78% effective against symptomatic cases, 93% effective against severe COVID-19 infection, and 65% effective against the Delta variant. On October 13, India recommended emergency use of the shot in the 2 to 18 age group, as the world's second-most populous nation expands its vaccination drive to include children.

On 3 November 2021, the WHO validated the vaccine for emergency use.

The governmental Indian Council for Medical Research (ICMR), which co-developed Covaxin with Hyderabad-based Bharat Biotech, has claimed that its COVID-19 vaccine may have an edge against other shots currently available when it comes to new variants.

Though very little is known yet, *"the virus may have less chance of escaping the immunity given by Covaxin than for other more targeted vaccines where the focus is principally on the spike protein,"* stated Samiran Panda, Head of Epidemiology and Infectious Diseases at ICMR.

8. **ZyCoV-D** is India-based **Zydus Cadila's** plasmid DNA vaccine candidate for COVID-19that targets the viral entry membrane protein of the virus.

In early animal studies, the firm reported that as well as generating neutralising antibodies post-vaccination, ZyCoV-D also induced T-cell response. ZyCoV-D can be stored at 2 to 8°C for the long term and at 25°C for a few months and is administered via Needle Free Injection System (NFIS).

On 1 July 2021, Cadila Healthcare reported the efficacy to be 66.6% against symptomatic COVID-19 and 100% against moderate or severe disease in its interim analysis of its Phase 3 trial data.

On August 22, the vaccine was approved for emergency use in India in adults and children aged 12 years and above, making it the 6th vaccine authorized for use in the country.

In an October 2021 interview, the managing director of Zydus Cadila said that the company was still waiting for a pricing plan from the Indian government before distributing the vaccine.

9. Kazakhstan's inactivated vaccine **QazCovid-in,** commercially known as **QazVac** and developed and tested in the **Kazakh Research Institute for Biological Safety Problems**, is currently in Phase 3 of clinical trials. The first preliminary results of QazVac clinical trials were published in Lancet's E Clinical Medicine journal on August 13.

The administration of the vaccine for the general population began at the end of April 2021. Kyrgyzstan is ready to use the Kazakh-made vaccine QazVac, right after recommendations from an independent experts committee. 25,000 doses were delivered to the country as humanitarian aid.

In September 2021, a study was published to EClincicalMedicine by The Lancet. The study's findings were that the *"QazCovid-in® vaccine was safe and well-tolerated and induced predominantly mild adverse events; no serious or severe adverse events were recorded in both trials."*

10. **Abdala (CIGB 66**) is one of three vaccine candidates for Covid-19 being developed in-house by **Cuba's Center for Genetic Engineering and Biotechnology (CIGB).**

Abdala is a protein vaccine that uses yeast as a receptor-binding domain (RBD) protein and alumina as an adjuvant and it is designed to be administered three times, at 14-day intervals.

On June 22, 2021, official Cuban government sources reported that the results of an initial study by the Cuban Center for Genetic Engineering and Biotechnology involving 48,290 participants found the vaccine, administered in 3 doses spaced 2 weeks apart, had a 92.28% efficacy rate at preventing symptomatic COVID-19.

On 9 July 2021, Abdala was approved for an emergency use authorization in Cuba.

In July 2021, Abdala started clinical trial phase I/II for children and adolescents aged 3-18.

The Abdala vaccine is one of a total of five candidate vaccines in Cuba, according to authorities there. Another, the two-dose Soberana 2, is also expected to be soon authorized for emergency use by CECMED. Both vaccines are then to be sent up for approval to the World Health Organization.

In September, Cuba agreed to sell 10 million doses of Abdala to Vietnam, which has granted the vaccine emergency authorization. In Venezuela, meanwhile, the National Academy of Medicine expressed concern over the lack of published scientific research on Abdala's safety and efficacy.

11. **Sinovac Biotech**, a private Chinese company, developed an inactivated vaccine called **CoronaVac** in early 2020.

On June 1st WHO validated the Sinovac-CoronaVac COVID-19 vaccine for emergency use, giving countries, funders, procuring agencies and communities the assurance that it meets international standards for safety, efficacy and manufacturing. Vaccine efficacy results showed an efficacy 50.65% against all symptomatic cases, 83.70% against cases that require medical treatment, and 100.00% against severe, hospitalized and fatal cases.

On August 10, Sinovac announced positive data on booster shots of CoronaVac, which induces strong immune response in adult and elderly populations.

Sinovac is now running a Phase 4 trial to evaluate how well such a booster can protect against Covid-19 in healthy adults.

On December 7, data from a study evaluating immunogenicity and safety of a third dose of CoronaVac and immune persistence of a two-dose schedule in healthy adults were published in The Lancet. Results suggest that a third dose of CoronaVac administered 8 months after a second dose effectively recalled specific immune responses to SARS-CoV-2, which had declined substantially 6 months after two doses of CoronaVac, resulting in a remarkable increase in the concentration of antibodies against the virus.

12. Sanofi–GSK COVID-19 vaccine, also known as **VAT00002** and **Vidprevtyn**, is a COVID-19vaccine candidate developed by **Sanofi Pasteur and GlaxoSmithKline (GSK)**. VAT00008 is a recombinant protein subunit vaccine containing the SARS-CoV-2 spike protein, which is produced in insect cells via a baculovirus vector.

In July 2021, **the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) started a rolling review of Vidprevtyn** (trade name), the COVID-19 vaccine developed by Sanofi Pasteur. The CHMP's decision to start the rolling review is based on preliminary results from laboratory studies (non-clinical data) and early clinical studies in adults, which suggest that the vaccine triggers the production of antibodies that target SARS- CoV-2, the virus that causes COVID-19, and may help protect against the disease. On September 2021, the Commission signed a contact with Sanofi to purchase up to 300 milion doses of the vaccine.

The company announced that its COVID-19 recombinant vaccine candidate is progressing in a Phase 3 efficacy and safety trial, following positive initial results from a phase 2 clinical trial. In that trial, the COVID-19 vaccine candidate was administered to 722 adults to assess the safety,

reactogenicity and immunogenicity of 3 doses and to identify an optimal vaccine dose. Results showed strong rates of neutralizing antibody response with 95% to 100% seroconversion following a second injection in all age groups (18 to 95 years old), across all doses.

In parallel, Sanofi has expanded its researchprogram to include a study of the vaccine as a booster dose.

13. **Nanocovax** is a Vietnamese COVID-19 vaccine candidate developed by **Nanogen Pharmaceutical Biotechnology JSC**. It is a subunit vaccine (SARS-CoV-2 recombinant spike protein with aluminum adjuvant).

In June 2021, Nanocovax entered phase III of clinical trials on 13,000 volunteers. The clinical trial Phase 3 (adaptive, multicenter, randomized, double-blind, placebo-controlled) enrolled volunteer subjects 18 years of age and older to evaluate the safety, immunogenicity, and efficacy of Nanocovax vaccine in participants.

Nanogen's chairman Ho Nhan said the firm had send its reports on the trials to the Ministry of Health for approval, claiming an efficacy rate of 90%. On September 18, the National Ethics Committee in Biomedical Research under the Ministry of Health had reviewed and approved the clinical trial results of the phase III of Nanocovax. According to President of the National Ethics Committee in Biomedical Research, Professor Truong Viet Dung, Nanocovax vaccine is safe and produces immune response.

14. The Chinese company **CanSino Biologics** developed **Convidecia** in partnership with the Institute of Biology at the country's Academy of Military Medical Sciences. The one- shot vaccine is based on an adenovirus called Ad5.

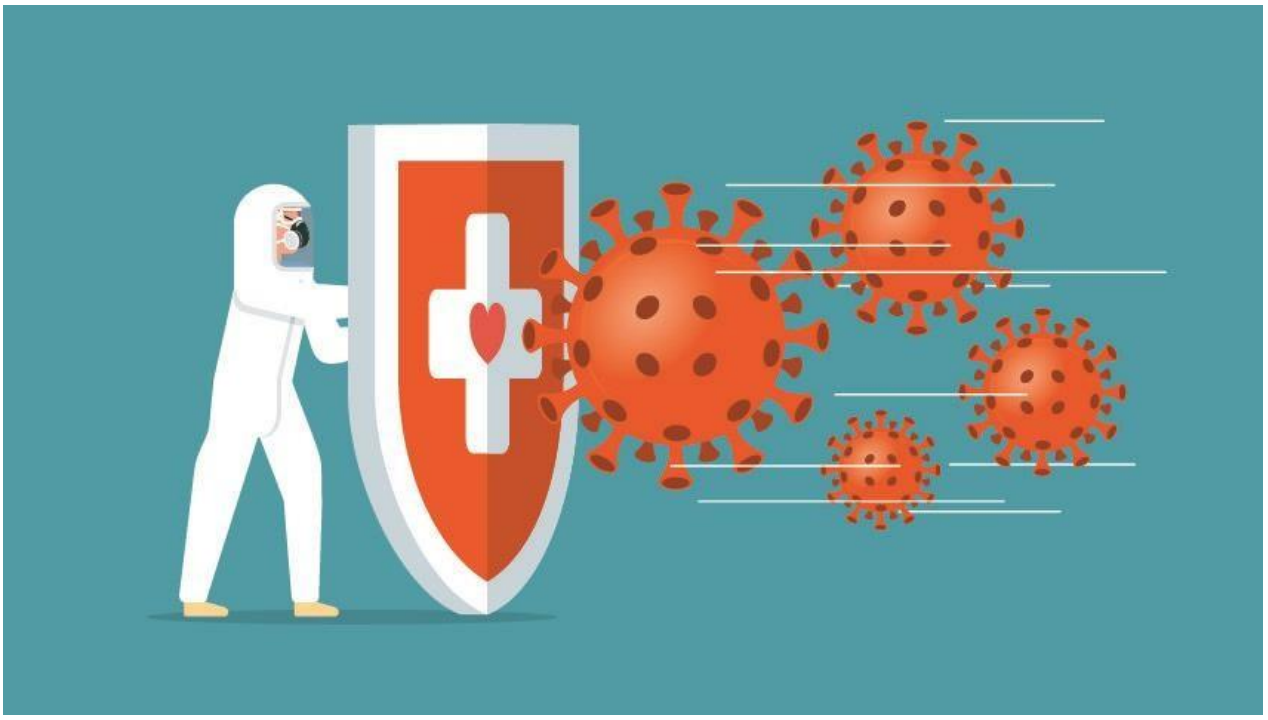
Starting in August 2020, CanSino began running Phase 3 trials in a number of countries, including Pakistan, Russia, Mexico and Chile. On Feb. 25, China announced the approval of the CanSino vaccine for general use. The company announced that its one-shot vaccine had an efficacy rate of 65.28% at preventing all symptomatic Covid-19 cases. The details of the trial have yet to be published. But on April 1, CanSino's chief scientific officer said that the efficacy of its vaccine could drop over time. He also floated the idea of using a booster shot six months after the first dose, though more clinical trial data is needed. Reuters reported on Aug. 5 that this drop could be as much as around 30 percent after six months.

On June 9, Reuters reported that the CanSino vaccine is being tested as a booster shot.

Resultsfrom a Chinese study, released on September 7, suggested that getting the CanSino booster shot after the Sinovac vaccine produced a stronger antibody response compared to a

third shot of the Sinovac vaccine. CanSino announced on Sept. 26 that a trial in children age 6 to 17 yielded positive results.

Therapeutic Drugs



Monlupiravir

The pharmaceutical firm Merck announced that an antiviral pill it is developing could cut hospitalizations and deaths among people with COVID-19 by half. The results have not yetbeen peer reviewed, but if the drug candidate, Molnupiravir, is authorized by regulators, it would be **the first oral antiviral treatment for COVID-19**, and could be an especially important tool in poor countries, where vaccine supply is low. By contrast, the other currently authorized drugs must be delivered intravenously or injected.

On October 11, Merck submitted its treatment Molnupiravir to the FDA, asking the health regulator to approve the pill for emergency use authorization, and plans to apply for emergency use or marketing authorization in other countries in the coming months. The company has already begun producing the pill, and has agreed to sell courses of the treatment to the United States and other countries if they get the green light.

Early trials of the drug showed significant promise in reducing the risk of hospitalization and death among at-risk patients with mild to moderate cases of COVID-19. An independent board of experts monitoring the trial recommended it be stopped early because of the promising results, the company said this month, a significant and telling development in a pharmaceutical

study.

A panel of experts, convened by the FDA on November 30, voted by a slim margin to recommend the agency authorize the COVID treatment developed by Merck, amid a vigorous debate about its risks and benefits. The expert panel voted 13-10 that Molnupiravir, should be authorized, although members expressed concerns that, if used in pregnancy it could cause birth defects.

Remdesivir

Remdesivir, an antiviral drug also known as Veklury, is currently **the only FDA-approved therapy for COVID-19**. It prevents SARS-CoV-2 from replicating by binding to RNA-dependent RNA polymerase, a keyenzyme the virus needs to propagate. It was approved in October 2020 for hospitalized COVID-19 patients ages 12 and up who weigh at least 88 lbs. Its original Emergency Use Authorization (EUA) has been revised to also allow for treatment of hospitalized pediatric patients under 12who weigh at least 7.7 lbs.

FDA also issued an EUA for the combination of remdesivir plus the oral JAK inhibitor barcitinib (Olumiant) in hospitalized patients with severe COVID-19, which is supported by the NIH guidelines. Gilead Sciences Inc said an analysis showed its antiviral remdesivir reduced mortality rates in hospitalized patients with COVID-19 and increased the likelihood of being discharged by day 28 after a five-day course of the treatment.

Remdesivir, which is approved or authorized for temporary use in approximately 50 countries worldwide, has been made available to 9 million patients, including 6.5 million people in 127 middle- and low-income countries. Data from a Phase 3 clinical trial found Remdesivir to be 87% effective at reducing hospitalizations in high-risk patients who were diagnosed early.

New findings by Gilead Sciences suggest that its antiviral COVID-19 treatment Remdesivir will continue to be active against the new omicron variant. "*Its antiviral activity has been confirmed in vitro against all major previously identified variants of SARS-CoV-2 including Alpha, Beta, Gamma, Delta, and Epsilon,*" Gilead said in a statement on December 1st. "*Due to the similarities in the viral RNA polymerase, these laboratory findings suggest that Remdesivir will also continue to be active against the Omicron variant and Gilead will conduct laboratory testing to confirm this analysis*".

Paxlovid

Pfizer has also submitted an application to the FDA for an emergency use authorization of its antiviral COVID-19 pill Paxlovid**,** which showed a high reduction in virus-related hospitalizations and deaths. According to an interim analysis, Paxlovid reduced the risk of Covid-19-associated hospitalisation or death by 89% in those who received treatment within three days of symptom onset. The drug was found to be so effective – just 1% of patients who received Paxlovid were hospitalised through day 28 compared to 6.7% of placebo participants – that its Phase II/III trial was ended early and regulatory submission to the FDA was filed sooner than expected. Moreover, while 10 deaths were reported on the placebo arm, none occurred among participants who received Paxlovid.

Like Molnupiravir, Paxlovid is administered orally, meaning COVID-19 patients can take the drug at home in the early stages of infection. The hope is that new antivirals like those from Merck and Pfizer will allow people with mild or moderate cases of coronavirus to be treated sooner, preventing disease progression and help avoid hospitals from being overwhelmed.

The drug fights the virus by inhibiting an enzyme it needs to replicate, whereas the vaccines target the the spike protein the virus uses to invade human cells, therefore Pfizer expects Paxlovid to be effective against the omicron variant and that it will manufacture 80 million courses of the pill, up from its original goal of 50 million. The Biden administration has already bought 10 million treatment courses of Paxlovid in a $5.29 billion agreement announced last month.

Pfizer is expected to submit full data on its Paxlovid to the FDA in the coming days.

Paxlovid is seen manufactured in Ascoli, Italy. Pfizer | Handout | via Reuters

Dexamethasone

Dexamethasone, a corticosteroid with potent anti-inflammatory effects, is recommended for use in many categories of patients hospitalized with COVID-19, but not for those with mild-to-moderate disease who are not in the hospital.

While it recommends against dexamethasone for those hospitalized but not on supplemental oxygen, the US National Institutes of Health (NIH) recommend it for in certain people hospitalized with severe COVID-19, who need supplemental oxygen, high-flow or noninvasive ventilation, and mechanical ventilation or ECMO. In September 2020, the EMA endorsed the use of dexamethasone in adults and adolescents (from twelve years of age and weighing at least 40 kg) who require supplemental oxygen therapy. Dexamethasone is also approved for NHS use by the UK government.

According to findings from the RECOVERY trial, dexamethasone use in those who required mechanical ventilation cut the risk of death by about 35% compared with usual care. Overall mortality also was lower in all hospitalized patients who received the drug.

Remarkable findings from a multidisciplinary study published in *Nature Medicine* show that while Dexamethasone might indeed have an effect in treating COVID-19, it likely does so only in men and female patients, at both the cellular level and at the population level, receive a limited benefit.

Tocilizumab

On June 24, the FDA issued an emergency use authorization (EUA) for the rheumatoid arthritis drug RoActemra (Tocilizumab) for the treatment of hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). RoActemra is not authorized for use in outpatients with COVID-19.

The FDA says that based on available scientific evidence, it is "reasonable to believe" that Tocilizumab may be effective in the treatment of COVID-19 for the authorized population and that the "known and potential benefits" of the drug outweigh the known and potential risks associated with the drug.

On December 6, Tocilizumab has received approval from the EMA for the treatment of adults with severe COVID-19 and who are in receipt of systemic treatment with corticosteroids and requiring supplemental oxygen or mechanical ventilation. The EMA's decision is based on an evaluation of data from a study of 4116 adults hospitalized with severe COVID-19 who required extra oxygen or mechanical ventilation and who had elevated levels of C-reactive protein.

The study found that the addition of Tocilizumab to standard treatment reduced the risk of death by 4% compared with standard treatment alone. 31% percent of patients in the tocilizumab arm died within 28 days of treatment (621 out of 2022) compared with 35% of patients receiving standard treatment alone (729 out of 2094).

The safety profile in patients receiving corticosteroids was favourable, however, the study data suggest an increase in mortality cannot be ruled out when the drug is used in patients who are not receiving systemic corticosteroids.

Anticoagulation

NIH recommends that all adults hospitalized for COVID-19 who are not pregnant should receive prophylactic anticoagulation to prevent venous thromboembolism (VTE). Pregnant patients hospitalized for severe COVID-19 should also get prophylactic anticoagulation unless it is contraindicated.

The agency notes that there are currently insufficient data to recommend either for or against the use of thrombolytics or higher-than-prophylactic-doses of anticoagulation in hospitalized patients outside of a clinical trial.

More trials are still underway, including many on aspirin, which is known to act as a blood thinner. But in June 2021, a large-scale randomized clinical trial found that aspirin had no significant impact on patient mortality. In sicker patients, clot buster drugs are being tested in the hope of helping combat respiratory failure.

Convalescent Plasma

Convalescent plasma has an FDA emergency use authorization to treat hospitalized COVID-19 patients. Only high-titer plasma is now authorized, however, and with restriction to hospitalized

patients who are early in their disease course or those who have impaired humoral immunity. The scope of authorization was narrowed last February, to specify the use of only high-titer plasma.

There is some evidence suggesting possible benefits of convalescent plasma in patients with COVID-19, but available data to date are largely from case reports or series; confirmation from additional randomized controlled studies is required. The Infectious Disease Society of America recommends against using convalescent plasma in hospitals and said there is no evidence yet supporting its use in people early in their infection.

Monoclonal Antibodies:
Monoclonal antibodies are manmade versions of the antibodies that our bodies naturally make to fight invaders, such as the SARS-CoV-2 virus. All three of the FDA-authorized therapies attack the coronavirus' spike protein, making it more difficult for the virus to attach to and enter human cells.

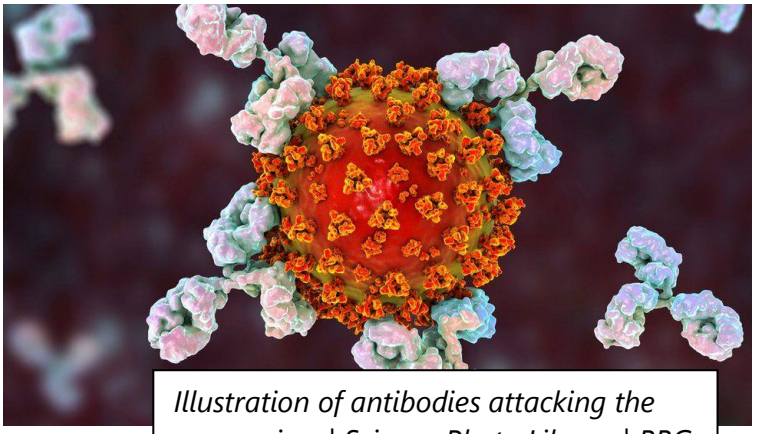


Illustration of antibodies attacking the coronavirus | Science Photo Library | BBC

The monoclonal antibody treatments that have Emergency Use Authorization (EUA) approval by the FDA are: a combination of casirivimab and imdevimab, called REGN-COV, made by Regeneron; a combination of bamlanivimab and etesevimab, made by Eli Lilly; and sotrovimab, made by GlaxoSmithKline. These treatments must be given intravenously in a clinic or hospital. These treatments are not currently authorized for hospitalized COVID-19 patients or those receiving oxygen therapy.

Ronapreve (casirivimab / imdevimab) is a monoclonal antibody treatment to prevent and treat COVID-19 developed by Regeneron Pharmaceuticals Inc. and Roche Pharmaceuticals GmbH. The drug contains a pair of antibodies created in a laboratory, and has been shown to lower hospitalisation or mortality from COVID by 70%, as well as shortening the duration of symptoms by four days. It can be administered through either injection or infusion.

It is intended for the treatment of COVID-19 in adults and adolescents from 12 years of age who do not require supplemental oxygen therapy and who are at increased risk of progressing to severe COVID 19, and for the prevention of COVID-19 in adults and adolescents aged 12 years and older.

On 20 August 2021, it was approved by the United Kingdom's Medicines and Healthcare

products Regulatory Agency for use in the UK. On October 12, the European Medicine Authority has started evaluating an application for the marketing authorisation of Ronapreve. EMA will assess the benefits and risks of Ronapreve under a reduced timeline and could issue an opinion within two months, depending on the robustness of the data submitted and whether further information is required to support the evaluation.

Bamlanivimab and etesevimab are two monoclonal antibodies developed by Eli Lilly. Although initially they showed promise, their prospects look much cloudier now.

On November 9, the FDA gave bamlanivimab emergency use authorization for mild to moderate C COVID-19. One early study suggested the drug reduced the risk of infected people becoming hospitalized. Another indicated that it can prevent people from getting COVID-19 in the first place. The company gave bamlanivimab to 965 healthy residents and staff members at nursinghomes. They found it reduced the risk of COVID -19 by 80%.

But some coronavirus variants that emerged in early 2021 proved resistant, leading the FDA to revoke its authorization for bamlanivimab alone as a COVID-19 treatment on April 19. Instead, the government allowed Lilly to sell a combination of bamlanivimab and etesevimab. They reasoned that if the coronaviruses could evade one drug they would still succumb to the other. In March 2021, Lilly reported that a combination of bamlanivimab and etesevimab produced an 87% reduction in COVID-19 related hospitalizations and deaths in a trial of 769 high- risk patients. The NIH COVID-19 treatment guidelines now recommend bamlanivimab and etesevimab for non-hospitalized COVID-19 patients who are at a high risk for their symptoms to worsen.

However, even this cocktail may prove ineffective in the long run. On May 26, the U.S. government warned that certain variants were proving resistant even to a combination of bamlanivimab andetesevimab. On June 25, the FDA paused the use of the two drugs across the United States because of the rise of the Beta and Gamma variants. The FDA reauthorized bamlanivimab andetesevimab in all states on Sept. 2. On Sept. 17, the FDA expanded its authorization to allow the combination to be administered to high-risk and unvaccinated patients who have been exposed to the virus.

On December 3, the FDA revised the emergency use authorization (EUA) of bamlanivimab and etesevimab (previously authorized for pediatric patients 12 years of age and older weighing at least 40 kilograms, or about 88 pounds), to additionally authorize bamlanivimab and etesivimab administered together for the treatment of mild to moderate COVID-19 in all younger pediatric patients, including newborns, who have a positive COVID-19 test and are at high risk for progression to severe COVID-19, including hospitalization or death. This revision also authorizes bamlanivimab and etesevimab, to be administered together, for post-exposure

prophylaxis for prevention of COVID-19 in all pediatric patients, including newborns, at high risk of progression to severe COVID-19, including hospitalization or death.

Sotrovimab works by binding to the spike protein on the outside of the COVID-19 virus. This is the same spike protein the body's immune system is trained to recognise with the Pfizer COVID vaccine. In May 2021, pharmaceutical company GlaxoSmithKline released data from a clinical trial. It compared sotrovimab to a placebo in 583 at-risk COVID-19 patients to see whether it prevented the disease progressing to the extent that the patient needed to be hospitalised or died. In the sotrovimab group (of 291 people), three patients saw their disease progress, compared to 21 in the placebo group (of 292 people). This amounts to an 85% reduction of disease progression in patients with mild to moderate COVID-19.

In May, the European drug regulator EMA also authorised sotrovimab to be used in adults and children aged over 12 with mild to moderate COVID-19, but who are at a high risk of progression to severe COVID-19.

Evusheld

Evusheld, also known as AZD7442l, is an antibody cocktail developed by British-Swedish multinational pharmaceutical and biotechnology company **AstraZeneca**.

AstraZeneca's antibody drug cut the risk of severe COVID-19 by at least 50% in a late stage study, the company announced on October 11. The injection contains two different antibodies developed from the blood of people who previously contracted COVID-19. It is the first drug of its kind shown to both prevent and treat COVID-19 in late- stage trials, the company said in a press release.

Late-stage trial results in August showed it reduced therisk of symptomatic COVID-19 by 77%. AstraZeneca looked at the drug's impact at day 29 of the TACKLE study, which is expected to follow participants for up to 15 months. AstraZeneca's early stage studies have previously shown that antibodies last at least nine months after the drug is given.

On December 8, the FDA issued an emergency use authorization for Evusheld, allowing the treatment to be used as a pre-exposure prophylaxis for COVID-19 among immunocompromised people.

Evusheld involves the administration of two monoclonal antibodies: tixagevimab and cilagavimab. They are meant to be administered as two separate and immediate intramuscular injections. The FDA said one dose of Evusheld may be effective at preventing COVID-19 for six months. The antibody cocktail was authorized only for people with moderately to severely compromised immune systems who may not mount an adequate immune response to vaccination, or for those with a history of severe adverse reactions to a COVID-19 vaccine and cannot receive one. It is only authorized for people who are not currently infected and who have not recently been exposed to a COVID-19-positive individual.

The EMA started a rolling review of Evusheld on October 14 and is expected to communicate further when a marketing authorization application for the medicine has been submitted.

Budesonide

In a pragmatic British trial, the inhaled corticosteroid budesonide (Pulmicort) shortened the duration of illness for outpatients at risk for severe disease, and diminished rates of hospitalization or death.

Inhaled budesonide is often used to treat asthma and chronic obstructive pulmonary disease, with no serious side effects associated with short-term use.

However, on May 27 the EMA's COVID-19 taskforce (COVID-ETF) has advised healthcare professionals that there is currently 'insufficient evidence' that inhaled corticosteroids, such as budesonide, are beneficial for people with COVID-19.

WHO to Test 3 Drugs as Possible COVID-19 Treatments

The WHO said it would begin testing three drugs currently used to treat other diseases to see if they can be used as treatments for COVID-19.

At a news briefing on August 11 from the agency's headquarters in Geneva, WHO Director General Tedros Adhanom Ghebreyesus said the organization, in its ongoing effort to find new treatments for COVID-19, will begin trials involving:

- ✓ **artesunate**, a treatment for severe malaria;

- ✓ **imatinib**, a drug for certain cancers; and
- ✓ **infliximab**, a treatment for immune system disorders such as Crohn's disease.

The WHO chief said the drugs were chosen by an independent panel of experts that evaluatesall the available evidence on all potential therapeutics. He added that the testing — known as the Solidarity PLUS trials — will involve thousands of researchers at more than 600 hospitals in52 countries.

Failed or Debated Therapies

Hydroxychloroquine

Both the WHO and the NIH recommend against the use of hydroxychloroquine -- with or without azithromycin -- for the treatment of COVID-19 in both hospitalized andnonhospitalized patients.

Findings from the RECOVERY trial showed that use of hydroxychloroquine did not reduce mortality among COVID-19 patients after 28 days, and in fact trended towards risk of death. Additionally, patients who received the antimalarial drug had a longer median hospital stay than those who received standard of care.

The FDA granted hydroxychloroquine emergency use authorization in March 2020, but rescinded it in June following the publication of these findings.

Another clinical trial based in Brazil and published in the New England Journal of Medicine found that hydroxychloroquine with or without azithromycin did not improve outcomes for hospitalized patients with mild-to-moderate COVID-19 after 15 days.

Several clinical trials and observational studies have found no benefit of using hydroxychloroquine to treat COVID-19. One retrospective cohort study based in Michigan, however, did show improved survival rates among patients that used the drug -- but the study did not account for confounders including ICU admission differences and dexamethasone use.

Ivermectin

The US recently issued a strong warning against the use of Ivermectin to treat patients of coronavirus disease. In a statement issued on August 21, the US Food and Drug Administration (FDA) said it has not approved Ivermectin for use in treating or preventing COVID-19 in humans as it is not a drug for treating viruses. *"You are not a horse. You are not a cow. Seriously, you all. Stop it!"* the FDA notably stated on Twitter.

The government body was sharply reacting towards the use of Ivermectin in Mississippi, the state worst hit by the Covid-19 pandemic across the United States. Several people were found using the drug to cure the viral disease. Mississippi's health department issued a warning that over 70 per cent of the recent calls to the poison department were from people who took Ivermectin bought at livestock supply centres, according to further reports.

There are some forms of the antiparasitic drug Ivermectin approved by the FDA for human use. Ivermectin is used to treat two conditions caused by parasitic worms: intestinal strongyloidiasis and onchocerciasis. There are also topical forms of ivermectin used to treat external parasites on people like head lice and skin conditions like rosacea. These forms of ivermectin are different from the ones given to animals.

Even the forms of ivermectin approved for human use are not without risks. Ivermectin can interfere with other medications such as blood thinners, the FDA said. In addition, overdosing on ivermectin can cause nausea, vomiting, diarrhea, low blood pressure, itching, hives, dizziness, balance problems, seizures, coma, and death.

Vitamin C

NIH states that there are insufficient data to recommend for or against the use of vitamin C (ascorbic acid) in COVID-19.

There are several ongoing clinical trials evaluating the efficacy of vitamin C for treating COVID-19, but few have been completed. A study of 56 hospitalized patients in China found that high-dose intravenous vitamin C was not effective at preventing mechanical ventilation over a 28-day period. Additionally, a randomized controlled trial of vitamin C and zinc showed no impact of either supplement on the course of symptoms in patients with mild illness.

Vitamin D

NIH states that there are insufficient data to recommend for or against the use of vitamin D in COVID-19.

While vitamin D deficiency has been associated with an increased risk of community-acquired pneumonia in older adults and children, no conclusive evidence shows it could be used to fight COVID-19.

In February, a large randomized Brazilian trial published in JAMA found no difference in length of hospital stay for those with moderate to severe COVID-19 given high-dose vitamin D or placebo.

Zinc

NIH states there are insufficient data to recommend for or against the use of zinc in COVID-19. It also recommends against zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial.

Protease Inhibitors

The NIH recommends against using lopinavir/ritonavir and other HIV protease inhibitors to treat COVID-19 in hospitalized and nonhospitalized patients because clinical trials have not shown clinical benefit in COVID patients.

The drugs did not demonstrate efficacy in two large randomized controlled trials of hospitalized patients -- including the RECOVERY trial and the WHO Solidarity Trial.

Colchicine

Neither the NIH nor WHO have any guidelines concerning this oral anti-inflammatory drug often used to treat gout, although it is still being investigated as a potential COVID treatment.

The colchicine arm of the RECOVERY trial was recently halted because an independent data monitoring committee found the drug wasn't helping hospitalized patients with COVID.

However, top-line results from the COLCORONA trial, which were announced in January via a press release, showed improved outcomes for patients with mild illness from COVID-19.