



## Repurposing of drugs and leading vaccines work against COVID-19

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### ABSTRACT

The novel coronavirus disease 19 (COVID-19) is a highly contagious and pathogenic viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first known case was reported / identified in Wuhan, China. In March 2020, the World Health Organization (WHO) declared it a 'pandemic' due to its Worldwide spread. Researchers have been trying to find a suitable treatment from available drugs like Dexamethasone, and Remdesivir to fight the novel coronavirus outbreak. AstraZeneca-SK Bio, Moderna, Pfizer-BioNTech and Janssen vaccines were added to the WHO's list of emergency use. Our review work highlights the repurposing of drugs and leading vaccines to counter COVID-19.

### Introduction

Coronaviruses are a large family of viruses that get their name from the halo of spiked proteins (S proteins) on their outer surface that looks like a crown under the microscope (Shereen *et al.*, 2020). The new coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused COVID-19 or 2019 Novel Coronavirus. On March 11, 2020, the World Health Organisation (WHO) declared this ongoing lethal disease a global pandemic (Bayat *et al.*, 2021). Even though SARS-CoV-2 has 79% similarity with SARS-CoV and 50% similarity with MARS-CoV, the infectivity and spreading rate of SARS-CoV-2 is higher than other coronaviruses (Noor, 2021). This explains the importance of developing a treatment or vaccine quickly. Reports suggested that the high spreading rate of SARS-CoV-2 maybe because of the mutation capability that makes it highly transmittable. SARS-CoV-2 has undergone 4400 amino acid substitutions and thousands of mutations since early 2020. This spike protein, which is used to enter the host cell, has demonstrated 14 mutations (Shariare *et al.*, 2021). Some scientists believed that these mutations can modify the sensitivity of the virus to neutralize

antibodies. The drug development process is more challenging due to limited understanding of the molecular mechanism involved in SARS-CoV-2 infection. The host cell proteins and viral proteins are the crucial targets for drug targeting. These include furin activation site, viral spike glycoprotein, RNA polymerase and protease enzymes, host cell-ACE2 receptor, protease enzymes, etc (Shariare *et al.*, 2021). There are 2 categories for the treatments of COVID-19 – host cell proteins and targeting SARS-CoV-2 or improving the human immune system (Shariare *et al.*, 2021). Developing a new drug is a time-consuming process, thus repurposing an existing drug seems to be one of the few solutions for the pandemic. Repositioning old drugs to treat COVID-19 is an attractive strategy as the information about the side effects, safety profile and posology are known (Gautret *et al.*, 2020). As per the clinical studies, antivirals reduce the viral load by targeting the enzymes of SARS-CoV-2 hence interfering with the viral cycle (Joshi *et al.*, 2021).

#### Challenges

The genome-based standard technology called reverse-transcriptase polymerase chain reaction

(RT-PCR) is the basis for several diagnostic tests for COVID-19, although none of these tests is fully standardized. The RT-PCR test can identify viral genetic material, only if there is an adequate RNA in the sample. Therefore, in early stage of infection, there is not usually enough RNA material before someone begins to feel sick (Shariare *et al.*, 2021). Hence, the RT-PCR test could deliver false-negative results and less useful information for asymptomatic patients. One of the challenges for scientists is to find an ideal animal model for testing. The SARS-CoV-2 uses the cellular surface protein angiotensin-converting enzyme 2 (ACE2) to invade host cells and the ACE2 of the mouse (*Mus musculus*) does not adequately bind with the viral spike protein (Muñoz-Fontela *et al.*, 2020). Thus, none of the animal models mimics the severe or critical patterns correlated with mortality as seen in humans with COVID-19 (Ehaideb *et al.*, 2020).

The World Health Organisation (WHO) has added some vaccines to the emergency use list. Moreover, old drugs are repurposed to fight COVID-19. Here, we discuss a few old drugs and leading vaccines that work to counter COVID-19.

### **Rapid Repurposing of Drugs**

The following section contains a summary of some of the medications being tested as treatments for COVID-19. Few of these drugs were later not recommended for use in the treatment of COVID 19 patients by WHO, FDA and other agencies due to more harm than good and/or had limited effect due to efficacy reasons.

#### **1. Hydroxychloroquine with Azithromycin**

Hydroxychloroquine is an antimalarial drug and according to a small study by French scientists published in the International Journal of Antimicrobial Agents, hydroxychloroquine with antibiotic azithromycin might be effective against COVID-19 (Gautret *et al.*, 2020). The COVID-19 virus attaches to a small particle in the cell called a lysosome. The lysosome cell has an acidic medium for the virus to thrive. Hydroxychloroquine competes for the same site on the lysosomes and makes the cell less acidic or more alkaline. As a result, the virus is unable to replicate within the cell and dies (Singh *et al.*, 2020).

#### **2. Dexamethasone**

Dexamethasone is a steroid that reduces inflammation. According to Oxford University's RECOVERY clinical trial, a low dose of

dexamethasone increases the survival rate of COVID-19 patients who need respiratory support (Ledford, 2020). In a trial, led by Oxford University, about 2,100 hospital patients were given dexamethasone and compared with more than 4,300 who were not. The risk of death for patients on ventilators was lowered from 40.7% to 29%, while the risk of death for patients using oxygen was reduced from 25% to 21.5% (Mahase, 2020).

#### **3. Favipiravir**

Favipiravir is an antiviral, used to treat influenza. Studies revealed that favipiravir inhibits the RNA-dependent RNA polymerase (RdRp) that is crucial for COVID-19 viral replication (Joshi *et al.*, 2021). An open-label multicenter trial involving 240 patients with COVID-19 from China concluded that those who got the drug tended to have a significantly high clinical recovery rate (Joshi *et al.*, 2021).

#### **4. Remdesivir**

Remdesivir is an antiviral drug used to fight Ebola. Remdesivir inhibits RNA-dependent RNA polymerase (RdRp) by imitating a part of the viral RNA and replacing it in the replicating site (Beigel *et al.*, 2020). Therefore, the virus fails to replicate further. According to the clinical trials, Remdesivir can reduce the recovery time from 15 to 11 days and the mortality rate from 11.6% to 8% in participants (National Institutes of Health, 2020).

#### **Vaccines**

While the drugs listed above may be useful to treat COVID-19, there are also vaccines in use to produce immunity. The following section contains information on the leading vaccines and vaccine candidates.

#### **1. AstraZeneca Covid-19 vaccine**

The coronavirus vaccine ChAdOx1 nCoV-19 or AZD1222 was developed and tested by the University of Oxford in collaboration with the British-Swedish company AstraZeneca (Corum and Zimmer, 2021). The SARS-CoV-2 virus has spiked protein that is used to enter human cells. The researchers added the gene of the spike protein into chimpanzee adenovirus, known as ChAdOx1. Adenovirus causes cold or flu-like symptoms. The adenovirus tough protein coat protects the genetic material inside (Corum and Zimmer, 2021). Therefore, this vaccine doesn't have to stay frozen. If refrigerated at 38–46°F (2–8°C) the vaccine can last for at least six months (Corum and Zimmer,

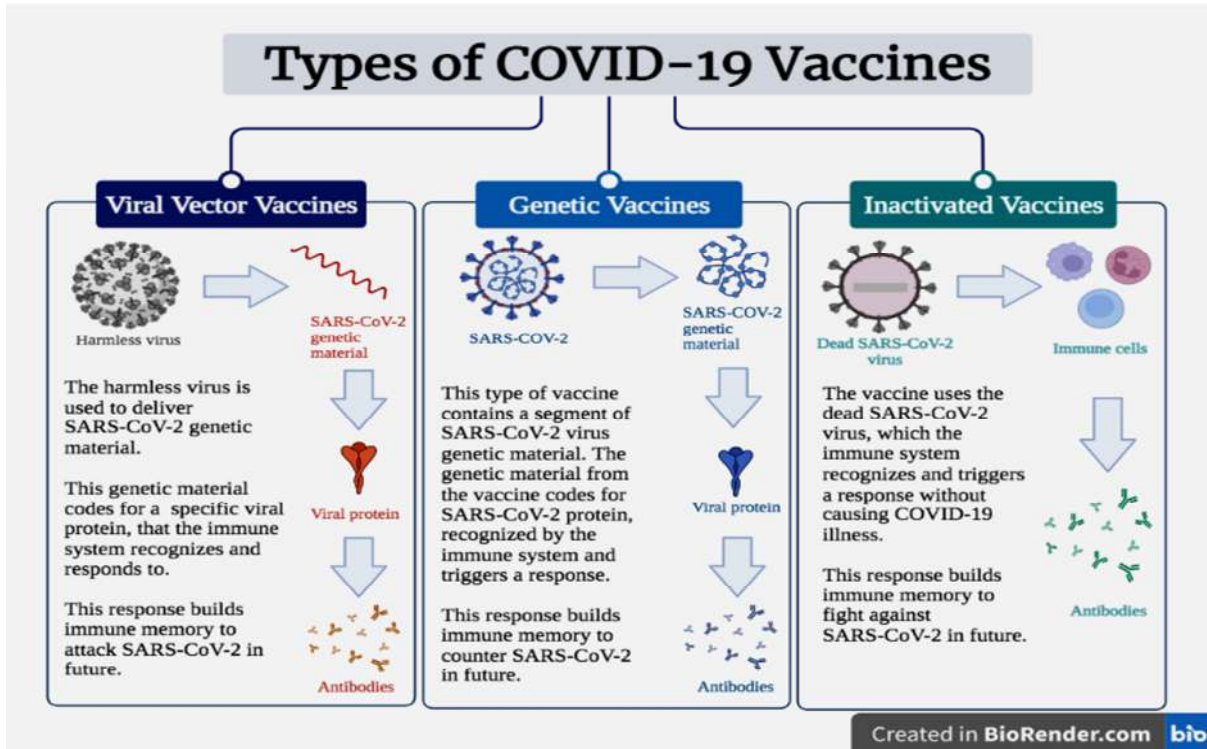


Figure 1: Summary of Types of COVID-19 Vaccines. Created with BioRender.com

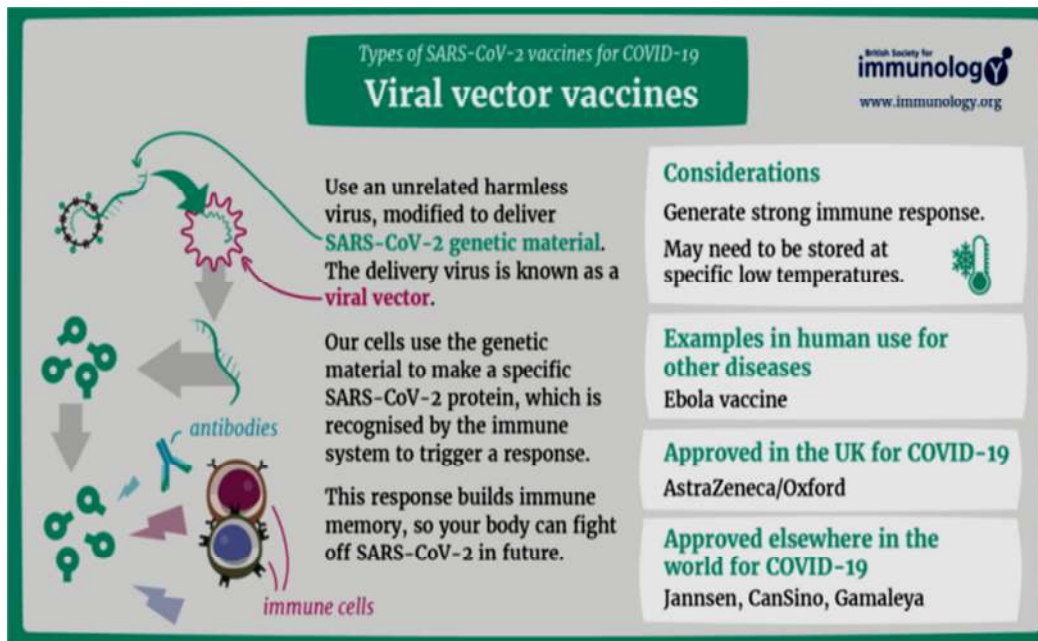
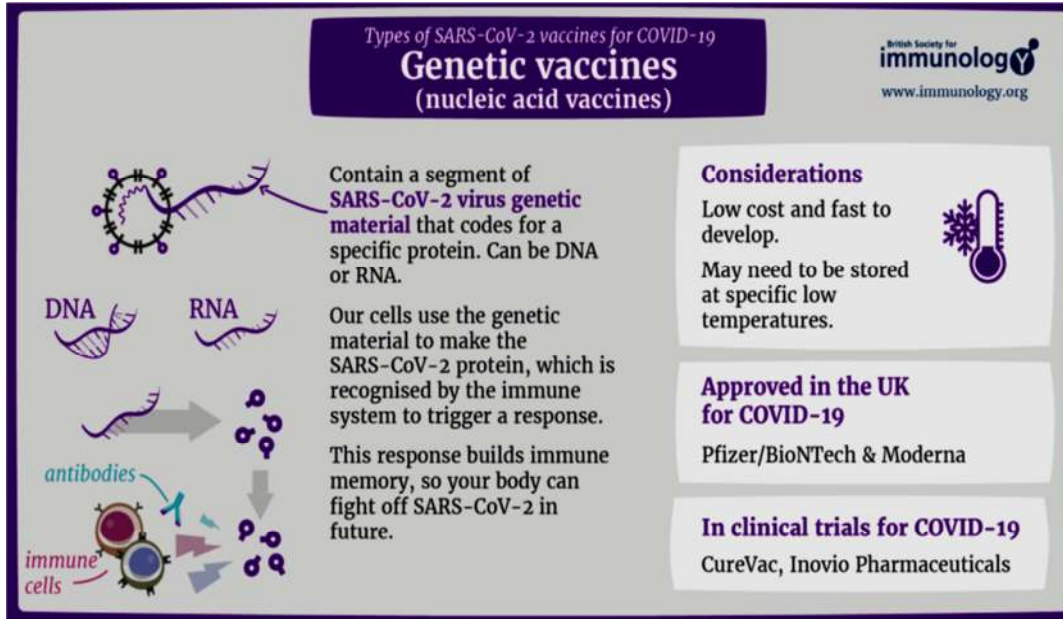


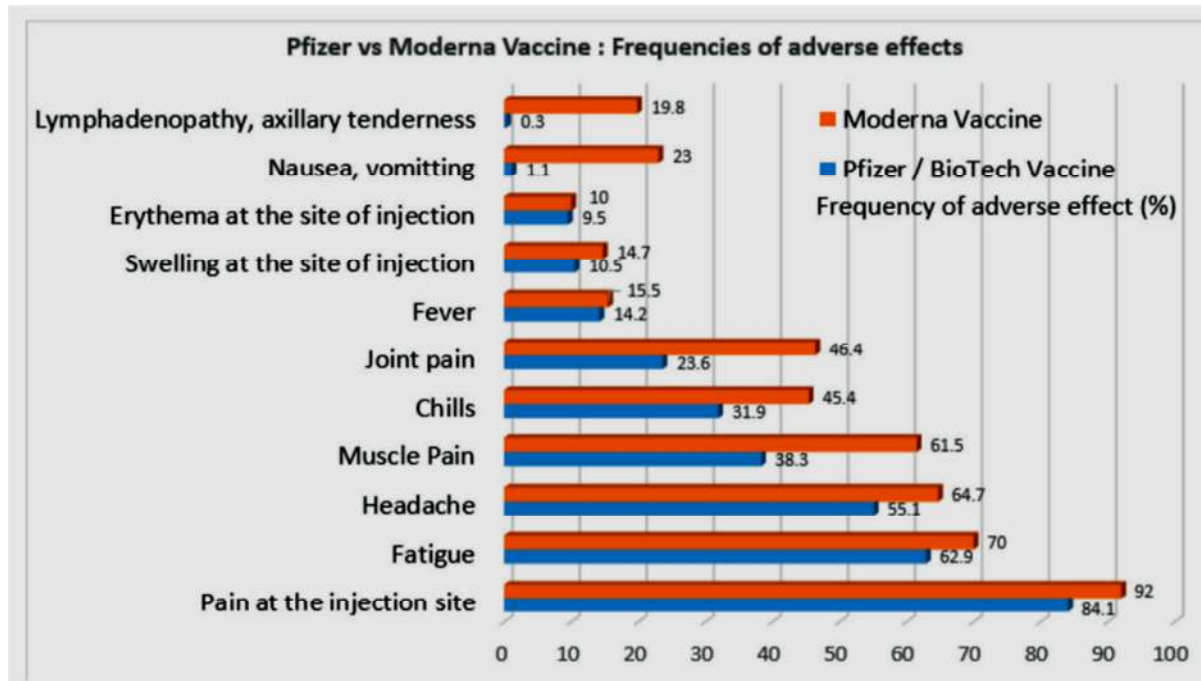
Figure 2: COVID-19 Viral Vector Vaccines.

British Society for Immunology. (2021). *Types of vaccines for COVID-19*. <https://www.immunology.org/coronavirus/connect-coronavirus-public-engagement-resources/types-vaccines-for-covid-19>



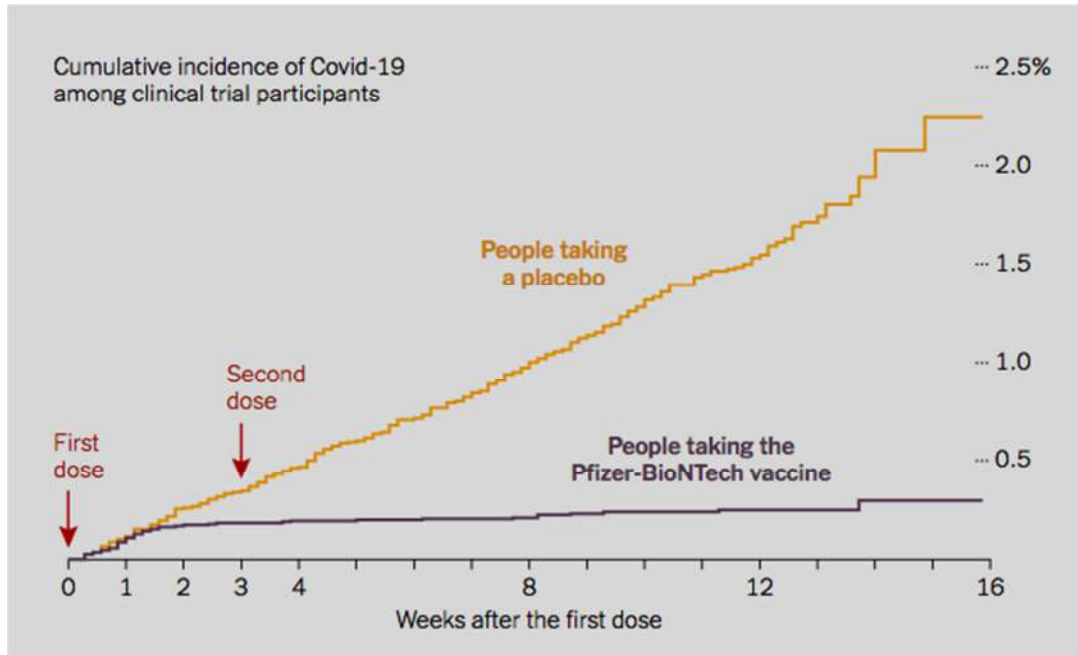
**Figure 3: COVID-19 Genetic Vaccines.**

British Society for Immunology. (2021). *Types of vaccines for COVID-19*. <https://www.immunology.org/coronavirus/connect-coronavirus-public-engagement-resources/types-vaccines-for-covid-19>



**Figure 4: Comparison of frequencies of adverse effects between Pfizer-BioNTech and Moderna Vaccines.**

Meo, S. A., Bukhari, I. A., Akram, J., Meo, A. S., & Klonoff, D. C. (2021). *COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna Vaccines*. *European Review for Medical and Pharmacological Sciences*, 25, 1663–1669. <https://www.europeanreview.org/wp/wp-content/uploads/1663-1669.pdf>




**Figure 5: A preliminary study showing Pfizer-BioNTech vaccine protection compared with people taking a placebo.**

Corum, J., & Zimmer, C. (2021, August 4). *How the Pfizer-BioNTech Covid-19 Vaccine Works*. The New York Times. <https://www.nytimes.com/interactive/2020/health/pfizer-biontech-covid-19-vaccine.html>

Types of SARS-CoV-2 vaccines for COVID-19

## Inactivated vaccines




**Contain killed SARS-CoV-2 virus.**  
The killed virus is recognised by the immune system to trigger a response without causing illness.  
This response builds immune memory, so your body can fight off SARS-CoV-2 in future.

**Considerations**  
May need to be administered with an adjuvant to boost immune response.


**Examples in human use for other disease**  
Influenza vaccine

**Approved elsewhere in the world for COVID-19**  
Sinovac, Sinopharm, Bharat Biotech

**In clinical trials for COVID-19**  
Shifa-Pharmed, Chinese Academy of Medical Sciences



*immune cells*      *antibodies*































www.immunology.org

**Figure 6: COVID-19 Inactivated Vaccines.**

British Society for Immunology. (2021). *Types of vaccines for COVID-19*. <https://www.immunology.org/coronavirus/connect-coronavirus-public-engagement-resources/types-vaccines-for-covid-19>

### How some of the Covid-19 vaccines compare

Company	Doses	Storage
<b>RNA</b>		
 <b>Pfizer (BioNTech)</b>		 -80 to -60°C (6 months) and 2 to 8°C (for up to 5 days)
 <b>Moderna</b>		 -25 to -15°C (6 months) and 2 to 8°C (for 30 days)
<b>Viral vector</b>		
 <b>Oxford-AstraZeneca</b>		 2 to 8°C (6 months)
 <b>Sputnik V (Gamaleya)</b>		 -18.5°C (liquid form) 2 to 8°C (dry form)
 <b>Johnson &amp; Johnson (Janssen)</b>		 2 to 8°C (3 months)
<b>Inactivated virus</b>		
 <b>CoronaVac (Sinovac)</b>		 2 to 8°C
 <b>Sinopharm</b>		 2 to 8°C
 <b>Covaxin (Bharat Biotech)</b>		 2 to 8°C
<b>Protein-based</b>		
 <b>Novavax</b>		 2 to 8°C

Source: Wellcome Trust, BBC research 

**Figure 7: Comparison of COVID-19 Vaccines.**

BBC News. (2021, May 7). *Sinopharm: Chinese Covid vaccine gets WHO emergency approval.* <https://www.bbc.com/news/world-asia-china-56967973>

2021). After entering the cell, the adenovirus engulfs the virus in a bubble and leaves the bubble to inject its DNA into the nucleus (Corum and Zimmer, 2021). Although the adenovirus cannot replicate itself, the coronavirus spike protein gene is read by the cell and transcribed into messenger RNA (mRNA). Spike proteins are formed when

mRNA is translated. These spike proteins form spike and protein fragments that migrate to their surface and stick out their tips (Corum and Zimmer, 2021). The immune system recognises these protruding spikes and spikes protein fragments afterwards. Helper T cells activate B cells, causing them to produce and pour out antibodies that target

the spike protein. Antibodies bind to coronavirus spikes, marking them for destruction and preventing them from connecting to other cells (Corum and Zimmer, 2021). The Oxford-AstraZeneca vaccine requires two shots four weeks apart. Depending on the dosage, the vaccination is either 62% or 90% effective (Financial Times, 2021).

## 2. Moderna Candidate Vaccine: mRNA-1273

US biotechnology company Moderna partnered with the National Institutes of Health to develop a coronavirus vaccine known as mRNA-1273 (Corum and Zimmer, 2021). According to clinical trials, the vaccine has an efficacy rate of more than 90% in preventing COVID-19 (Mishra, 2020). Moderna's vaccine uses mRNA that is read to make proteins (Noor, 2021). The mRNA is wrapped in oily bubbles made of lipid nanoparticles to protect it from being degraded by the body (S.A. Meo *et al.*, 2021). Moderna's vaccine should be stable for up to six months if stored at  $-4^{\circ}\text{F}$  ( $-20^{\circ}\text{C}$ ) (Corum and Zimmer, 2021). After injection, the vaccine releases its mRNA into cells and builds spike proteins. The immune system recognises these spike proteins and builds antibodies against them (Meo *et al.*, 2021). If an individual ever encounters the coronavirus, these antibodies can neutralize the virus. Moderna's vaccine requires two shots 28 days apart. Additionally, the US Food and Drug Administration (FDA) authorized the Moderna vaccine for emergency use (Tanne, 2020).

## 3. Pfizer-BioNTech

BioNTech partnered with Pfizer to develop a coronavirus vaccine called BNT162b2 (Bernal *et al.*, 2021). According to clinical trials, the vaccine has an efficacy rate of over 90% in preventing COVID-19 (Corum and Zimmer, 2021). The Pfizer-BioNTech vaccine is based on the coronavirus's genetic instructions for making spike protein, just like the Moderna vaccine. The vaccine storage temperature is between  $-80^{\circ}\text{C}$  and  $-60^{\circ}\text{C}$  to remain viable (Meo *et al.*, 2021). The vaccine introduces mRNA into the cells to develop the spike proteins. The body recognizes this protein and creates antibodies that can fight off future SARS-CoV-2 infections (Corum and Zimmer, 2021). The Pfizer-BioNTech vaccine requires 2 injections 21 days apart. A preliminary study

indicates that the Pfizer vaccine offers strong protection about 10 days after the initial dose as compared with people taking a placebo (Bernal *et al.*, 2021). The Pfizer vaccine is safe and immunogenic for adolescents aged 12 to 15 years old, according to a recent study published in the New England Journal of Medicine with an efficacy of 100% against COVID-19 from 7 days after dose 2 (Frenck *et al.*, 2021).

## 4. Sputnik V

The Sputnik V or Gam-Covid-Vac coronavirus vaccine was created by the Gamaleya National Research Institute of Epidemiology and Microbiology in Moscow (Jones and Roy, 2021). A study published by Gamaleya showed that two doses of the vaccine had an efficacy rate of 91.6% (Corum and Zimmer, 2021). Sputnik V is based on the coronavirus's genetic instructions for building the spike protein. Unlike the Moderna and Pfizer-BioNTech vaccines, Sputnik V uses double-stranded DNA. It is a vector vaccine based on adenovirus DNA, a cold virus (Jones and Roy, 2021). The researchers added the gene for the coronavirus spike protein to Ad26 and Ad5, two types of adenoviruses to invade cells but not replicate (Corum and Zimmer, 2021). After Sputnik V is injected, the adenoviruses enter the cell and engulf the virus in a bubble. After leaving the bubble, the adenovirus injects DNA into the nucleus. The gene for the coronavirus spike protein is copied into messenger RNA or mRNA. After translating mRNA, spike proteins are produced by the cell (Corum and Zimmer, 2021). The immune system recognises these protruding spikes and begins to generate antibodies in response. This prepares the immune system to fight coronavirus when it encounters it for real. Sputnik V requires two doses 21 days apart (Jones and Roy, 2021). This vaccine uses two different versions for the first and second doses. The researchers used one type of adenovirus, Ad26, for the first dose, and another, Ad5, for the second dose (Corum and Zimmer, 2021). The theory is that by combining two separate formulae, the immune system will be boosted even more and will provide longer-lasting protection. In addition, a version of the vaccine known as Sputnik Light uses only the first dose and skips the second dose (Corum and Zimmer, 2021).

## 5. Covaxin

An inactivated coronavirus vaccine called Covaxin is manufactured by the Indian company Bharat Biotech partnered with the Indian Council of Medical Research and the National Institute of Virology (Kumar *et al.*, 2021). Researchers doused a large stock of the coronavirus with beta-propiolactone that inactivated coronaviruses by bonding to their genes, but their proteins, including spike, remained intact (Corum and Zimmer, 2021). The inactivated viruses were then drawn off and mixed with adjuvant, an aluminium-based chemical that stimulates the immune system to boost its reaction to a vaccine (Kumar *et al.*, 2021). When injected into the body, B cells produce antibodies that target the spike protein (Corum and Zimmer, 2021). Covaxin requires two doses 4-12 weeks apart. According to the preliminary data from its phase 3 trial, Covaxin's efficacy rate is 80.7% (Kumar *et al.*, 2021).

## 6. Sinopharm Vaccine

Another inactivated coronavirus vaccine called BBIBP-CorV was developed by the Beijing Institute of Biological Products (Corum and Zimmer, 2021). According to clinical trials run by Sinopharm, the vaccine has an efficacy rate of 79%. The WHO also announced a similar efficacy estimate of 78.1% (Corum and Zimmer, 2021). The Beijing Institute researchers collected three coronavirus variants from Chinese hospitals to create BBIBP-CorV (Corum and Zimmer, 2021). One of the variants was chosen because it could rapidly expand in monkey kidney cells cultivated in bioreactor tanks. After mass-production of coronaviruses, the researchers drenched them in a chemical called beta-propiolactone, which rendered the coronaviruses inactive. After that, researchers mixed them with a tiny amount of an adjuvant to boost immune system response to a vaccine (Corum and Zimmer, 2021). Once vaccinated with BBIBP-CorV, B cells produce antibodies that target the spike protein to prevent the virus from invading cells. The Sinopharm vaccine is to be given in two doses three to four weeks apart (Corum and Zimmer, 2021).

## 7. Covishield

Covishield is being developed by Oxford University in collaboration with AstraZeneca and their manufacturing and trial partner is Serum Institute of India (Inbaraj *et al.*, 2021). Covishield

or AZD-1222 uses a viral vector made from a weakened version of a common cold virus (called an adenovirus) from chimpanzees (Pramod *et al.*, 2021). When the vaccine is injected, the immune system recognizes the spike protein and builds antibodies against it. There are two doses of Covishield given 12-16 weeks apart. According to the phase 3 clinical trials, the vaccine showed an efficacy of 67% (95% confidence interval [CI]: 57%-74%) against symptomatic SARS-CoV-2 infection (Pramod *et al.*, 2021). Covishield was added to the Emergency Use List (EUL) by the World Health Organisation (WHO).

## 8. Johnson & Johnson Vaccine

Johnson & Johnson developed a coronavirus vaccine called JNJ-78436735 or Ad26.COVS.2.S (Sadoff *et al.*, 2021). It is a single dose vaccine with an efficacy rate of 85% against COVID-19. The vaccine is based on the coronavirus's genetic instructions for building the spike protein. It uses double-stranded DNA. The researchers used Adenovirus 26 (common cold virus) and added the gene for the coronavirus spike protein to it (Corum and Zimmer, 2021). The Johnson & Johnson team used a modified adenovirus so that it would not cause any illness inside the cells. The vaccine can be refrigerated at 36–46°F (2–8°C) for up to three months (Corum and Zimmer, 2021). Once the disabled adenovirus is inside, the cell engulfs the virus in a bubble. The adenovirus breaks free from the bubble and pushes its DNA into the nucleus. The gene for the coronavirus spike protein is copied into mRNA. The cell's molecules read the mRNA sequence and begin assembling spike proteins. These spike proteins migrate to the cell surface and are recognized by the immune system (Corum and Zimmer, 2021). The immune system begins producing antibodies and activates other immune cells that target the spike protein. If ever encountered the virus that causes COVID-19 the immune system has antibodies to fight it.

### Vaccine Coming Soon:

#### Corbevax

Corbevax is a “recombinant protein sub-unit” vaccine, which suggests that the corbevax is made from the spike protein of SARS-CoV-2 (Raghavan, 2021). When injected into the body, an immune response is developed against the injected spike protein. Hence, the body will already have an immune response ready when the real virus



attempts to infect the body. In India, Corbevax has been approved for Phase III clinical trials (Raghavan, 2021). The manufacturer of Corbevax is Biological E, a Hyderabad-based company. For the first time, India has placed an advance order of 300 million doses for a vaccine that has not received emergency use authorisation (Sharma, 2021). Corbevax is administered in two doses. This vaccine is also predicted to be among the most affordable vaccinations available in the country.

**Conclusion** The COVID-19 pandemic has

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