

## SHIELD OF VACCINE AGAINST THE SHARP BULLET OF COVID-19

\*<sup>1</sup>Kushal Nandi, <sup>1</sup>Prodipta Bhattacharyya, <sup>1</sup>Sagnik Chowdhury, <sup>1</sup>Suprodip Mandal, <sup>1</sup>Dr. Dhrubo Jyoti Sen and <sup>2</sup>Dr. Dhananjay Saha

<sup>1</sup>Department of Pharmaceutical Chemistry, School of Pharmacy, Techno India University, Salt Lake City, Sector-V, EM-4, Kolkata-700091, West Bengal, India.

<sup>2</sup>Deputy Director, Directorate of Technical Education, Bikash Bhavan, Salt Lake City, Kolkata-700091, West Bengal, India.

\*Corresponding Author: Kushal Nandi

Department of Pharmaceutical Chemistry, School of Pharmacy, Techno India University, Salt Lake City, Sector-V, EM-4, Kolkata-700091, West Bengal, India. DOI: <https://doi.org/10.17605/OSF.IO/H3498>

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**ABSTRACT**

A COVID 19 vaccine is a vaccine intended to provide acquired immunity against COVID-19. Prior to the COVID-19 pandemic, work to develop a vaccine against the coronavirus diseases SARS and MERS had established knowledge about the structure and function of coronaviruses, which accelerated development during early 2020 of varied technology platforms for a COVID 19 vaccine. By mid-December 2020, 57 vaccine candidates were in clinical research, including 40 in Phase I-II trials and 17 in Phase II-III trials. In Phase III trials, several COVID-19 vaccines demonstrated efficacy as high as 95% in preventing symptomatic COVID-19 infections. National regulatory authorities have approved six vaccines for public use: two RNA vaccines (tozinameran from Pfizer-BioNTech and mRNA-1273 from Moderna), two conventional inactivated vaccines (BBIBP-CorV from Sinopharm and CoronaVac from Sinovac), and two viral vector vaccines (Gam-COVID-Vac from the Gamaleya Research Institute and AZD1222 from the University of Oxford and AstraZeneca).

**KEYWORDS:** SARS, MERS, RNA vaccine.

**INTRODUCTION**

Many countries have implemented phased distribution plans that prioritize those at highest risk of complications such as the elderly and those at high risk of exposure and transmission such as healthcare workers. As of 3 January 2021, 12.3 million doses of COVID-19 vaccine had been administered worldwide based on official reports from national health agencies. Pfizer, Moderna, and AstraZeneca predicted a manufacturing capacity of 5.3 billion doses in 2021, which could be used to vaccinate about 3 billion people (as the vaccines require two doses for a protective effect against COVID-19). By December, more than 10 billion vaccine doses had been preordered by countries, with about half of the doses purchased by high-income countries comprising only 14% of the world's population.

**Planning & Investment:** During 2020, major changes in the overall effort of developing COVID-19 vaccines since early in the year have been the increasing number of collaborations of the multinational pharmaceutical industry with national governments, and the diversity and growing number of biotechnology companies in many countries focusing on a COVID-19 vaccine. According to the Coalition for Epidemic Preparedness Innovations (CEPI), the general geographic distribution of COVID-19 vaccine development involves organizations in North America having about 40% of the

world's COVID-19 vaccine research, compared with 30% in Asia and Australia, 26% in Europe, and a few projects in South America and Africa. Commitment to first-in-human testing of a vaccine candidate represents a substantial capital cost for vaccine developers, estimated to be from US\$14 million to US\$25 million for a typical Phase I trial program, but possibly as much as US\$70 million. For comparison, during the Ebola virus epidemic of 2013-16, there were 37 vaccine candidates in urgent development, but only one eventually succeeded as a licensed vaccine, involving a total cost to confirm efficacy in Phase II-III trials of about US\$1 billion.

**International organizations**

**Access to COVID-19 Tools (ACT) Accelerator:** The Access to COVID-19 Tools Accelerator (ACT Accelerator), or the Global Collaboration to Accelerate the Development, Production and Equitable Access to New COVID-19 diagnostics, therapeutics and vaccines, is a G20 initiative announced by pro-tem Chair Mohammed al-Jadaan on 24 April 2020. A call to action was published simultaneously by the World Health Organization (WHO) on 24 April. On 10 September, the UN and European Union cohosted the Inaugural Meeting of the Facilitation Council of the ACT-Accelerator, which had received \$2.7 billion of the \$35 billion necessary to secure the 2 billion COVID-19 vaccine

doses, 245 million treatments, and 500 million tests that the initiative deemed necessary to shorten the pandemic and speed economic global recovery. Sir Andrew Witty and Dr Ngozi Okonjo-Iweala have accepted to act as

Special Envoys to the ACT Accelerator from the WHO. During the Trump administration, the United States withdrew its financial support of the WHO, and did not support the ACT Accelerator.



Figure-1: COVID-19 Vaccine Picture.

The ACT Accelerator is a cross-discipline support structure to enable partners to share resources and knowledge. It comprises four pillars, each managed by two to three collaborating partners:

- Vaccines (also called "COVAX")
- Diagnostics
- Therapeutics
- Health Systems Connector

**Vaccines and COVAX:** A multinational collaboration, including the World Health Organization (WHO), the Coalition for Epidemic Preparedness Innovations (CEPI), GAVI, the Gates Foundation, and governments, formed the *Access to COVID-19 Tools (ACT) Accelerator*, to raise financial support of accelerated research and development, production, and globally-equitable access to COVID-19 tests, therapies, and licensing of vaccines, which are in a specific development program called the "COVAX Pillar". The COVAX Pillar has the goal of facilitating licensure of

several COVID-19 vaccines, influencing equitable pricing, and providing equal access for up to 2 billion doses by the end of 2021 to protect frontline healthcare workers and people with high-risk of COVID-19 infection, particularly in low-to-middle income countries. During 2020, major changes in the overall effort of developing COVID-19 vaccines since early in the year have been the increasing number of collaborations of the multinational pharmaceutical industry with national governments, and the diversity and growing number of biotechnology companies in many countries focusing on a COVID-19 vaccine. According to CEPI, the general geographic distribution of COVID-19 vaccine development involves organizations in North America having about 40% of the world's COVID-19 vaccine research, compared with 30% in Asia and Australia, 26% in Europe, and a few projects in South America and Africa.<sup>[1]</sup>

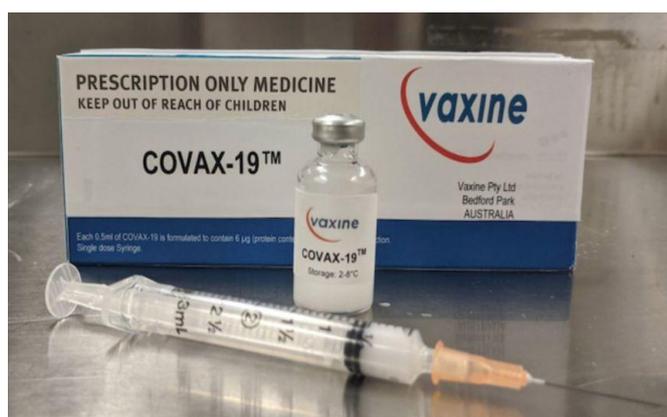


Figure-2: COVAX-19 & World's Demand to Develop Vaccine.

**Coalition for Epidemic Preparedness Innovations:** A multinational organization formed in 2017, CEPI is working with international health authorities and vaccine developers to create vaccines for preventing epidemics. CEPI has organized a US\$2 billion fund in a global partnership between public, private, philanthropic, and civil society organizations for accelerated research and

clinical testing of nine COVID-19 vaccine candidates, with the 2020–21 goal of supporting several candidate vaccines for full development to licensing. The United Kingdom, Canada, Belgium, Norway, Switzerland, Germany and the Netherlands had already donated US\$915 million to CEPI by early May. The Gates Foundation, a private charitable organization

dedicated to vaccine research and distribution, is donating US\$250 million in support of CEPI for research and public educational support on COVID-19 vaccines.

Over 2020 throughout the pandemic, CEPI was funding the development of nine vaccine candidates in a portfolio deliberately made diverse across different vaccine technologies to minimize the typically high risk of failure inherent in vaccine development. As of December, the vaccine research organizations and programs being supported by CEPI were Clover Biopharmaceuticals (vaccine candidate, SCB-2019), CureVac, Inovio, Institut Pasteur (vaccine candidate, MV-SARS-CoV-2), Moderna, Novavax, AZD1222 (University of Oxford-AstraZeneca), Hong Kong University, and SK bioscience (vaccine candidate, GBP510).

**Pharmaceutical companies:** Large pharmaceutical companies with experience in making vaccines at scale, including Johnson & Johnson, AstraZeneca, and GlaxoSmithKline (GSK), formed alliances with biotechnology companies, national governments, and universities to accelerate progression to an effective vaccine. To combine financial and manufacturing capabilities for a pandemic adjuvanted vaccine technology, GSK joined with Sanofi in an uncommon partnership of multinational companies to support accelerated vaccine development. By June 2020, tens of billions of dollars were invested by corporations, governments, international health organizations, and university research groups to develop dozens of vaccine candidates and prepare for global vaccination programs to immunize against COVID-19 infection. The corporate investment and need to generate value for public

shareholders raised concerns about a "market-based approach" in vaccine development, costly pricing of eventual licensed vaccines, preferred access for distribution first to affluent countries, and sparse or no distribution to where the pandemic is most aggressive, as predicted for densely-populated, impoverished countries unable to afford vaccinations. The collaboration of the University of Oxford with AstraZeneca (a global pharmaceutical company based in the UK) raised concerns about price and sharing of eventual profits from international vaccine sales, arising from whether the British government and university as public partners had commercialization rights. AstraZeneca stated that initial pricing of its vaccine would not include a profit margin for the company while the pandemic was still expanding. In early June, AstraZeneca made a US\$750 million deal allowing CEPI and GAVI to manufacture and distribute 300 million doses if its Oxford vaccine candidate proves safe and effective, reportedly increasing the company's total production capacity to over 2 billion doses per year. Commercialization of pandemic vaccines is a high-risk business venture, potentially losing billions of dollars in development and pre-market manufacturing costs if the candidate vaccines fail to be safe and effective. The multinational pharmaceutical company Pfizer indicated it was not interested in a government partnership, which would be a "third party" slowing progress in Pfizer's vaccine program. Further, there are concerns that rapid-development programs – like the Operation Warp Speed plan of the United States – are choosing vaccine candidates mainly for their manufacturing advantages to shorten the development timeline, rather than for the most promising vaccine technology having safety and efficacy.

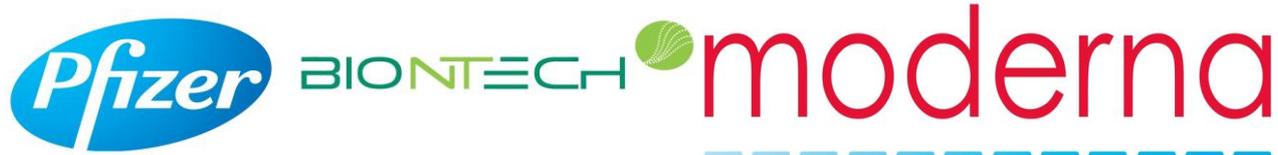


Figure-3: Companies That are trying to develop COVID-19 Vaccine.

### Development

**Background:** Prior to COVID-19, a vaccine for an infectious disease had never before been produced in less than several years, and no vaccine existed for preventing a coronavirus infection in humans. However, vaccines have been produced against several animal diseases caused by coronaviruses, including as of 2003 infectious bronchitis virus in birds, canine coronavirus, and feline coronavirus. Previous projects to develop vaccines for viruses in the family *Coronaviridae* that affect humans have been aimed at severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Vaccines against SARS and MERS have been tested in non-human animals.<sup>[2]</sup>

According to studies published in 2005 and 2006, the identification and development of novel vaccines and medicines to treat SARS was a priority for governments and public health agencies around the world at that time. As of 2020, there is no cure or protective vaccine proven to be safe and effective against SARS in humans. There is also no proven vaccine against MERS. When MERS became prevalent, it was believed that existing SARS research may provide a useful template for developing vaccines and therapeutics against a MERS-CoV infection. As of March 2020, there was one (DNA based) MERS vaccine which completed Phase I clinical trials in humans, and three others in progress, all of which are viral-vectored vaccines: two adenoviral-vectored (ChAdOx1-MERS, BVRS-GamVac), and one MVA-vectored (MVA-MERS-S).

## Early development



**Figure-4: NIAID (NIH) scientist researching COVID-19 vaccine examines agar plate. (30 January 2020).**

After the coronavirus was detected in December 2019, the genetic sequence of COVID-19 was published on 11 January 2020, triggering an urgent international response to prepare for an outbreak and hasten development of a preventive vaccine.

In February 2020, the World Health Organization (WHO) said it did not expect a vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative virus, to become available in less than 18 months. The rapidly growing infection rate of COVID-19 worldwide during early 2020 stimulated international alliances and government efforts to urgently organize resources to make multiple vaccines on shortened timelines, with four vaccine candidates entering human evaluation in March (see the table of clinical trials started in 2020, below). In April 2020, the WHO estimated a total cost of US\$8 billion to develop a suite of three or more vaccines having different technologies and distribution.

By April 2020, "almost 80 companies and institutes in 19 countries" were working on this virtual gold rush. Also in April, CEPI estimated that as many as six of the vaccine candidates against COVID-19 should be chosen by international coalitions for development through Phase II–III trials, and three should be streamlined through regulatory and quality assurance for eventual licensing at a total cost of at least US\$2 billion. Another analysis estimates 10 candidates will need simultaneous initial development, before a select few are chosen for the final path to licensing.<sup>[3]</sup>

In July 2020, Anglo-American intelligence and security organisations of the respective governments and armed forces, as the UK's National Cyber Security Centre,

together with the Canadian Communications Security Establishment, the United States Department for Homeland Security Cybersecurity Infrastructure Security Agency, and the US National Security Agency (NSA) alleged that Russian state-backed hackers may have been trying to steal COVID-19 treatment and vaccine research from academic and pharmaceutical institutions in other countries; Russia has denied it.

**Compressed timelines:** The urgency to create a vaccine for COVID-19, led to compressed schedules that shortened the standard vaccine development timeline, in some cases combining clinical trial steps over months, a process typically conducted sequentially over years. Multiple steps along the entire development path are evaluated, including the level of acceptable toxicity of the vaccine (its safety), targeting vulnerable populations, the need for vaccine efficacy breakthroughs, the duration of vaccination protection, special delivery systems (such as oral or nasal, rather than by injection), dose regimen, stability and storage characteristics, emergency use authorization before formal licensing, optimal manufacturing for scaling to billions of doses, and dissemination of the licensed vaccine. Timelines for conducting clinical research – normally a sequential process requiring years – are being compressed into safety, efficacy, and dosing trials running simultaneously over months, potentially compromising safety assurance. As an example, Chinese vaccine developers and the government Chinese Center for Disease Control and Prevention began their efforts in January 2020, and by March were pursuing numerous candidates on short timelines, with the goal to showcase Chinese technology strengths over those of the United States, and to reassure the Chinese people about the quality of vaccines produced in China.

## Preclinical research



**Figure-5: COVID-19 vaccine research samples in lab freezer.**

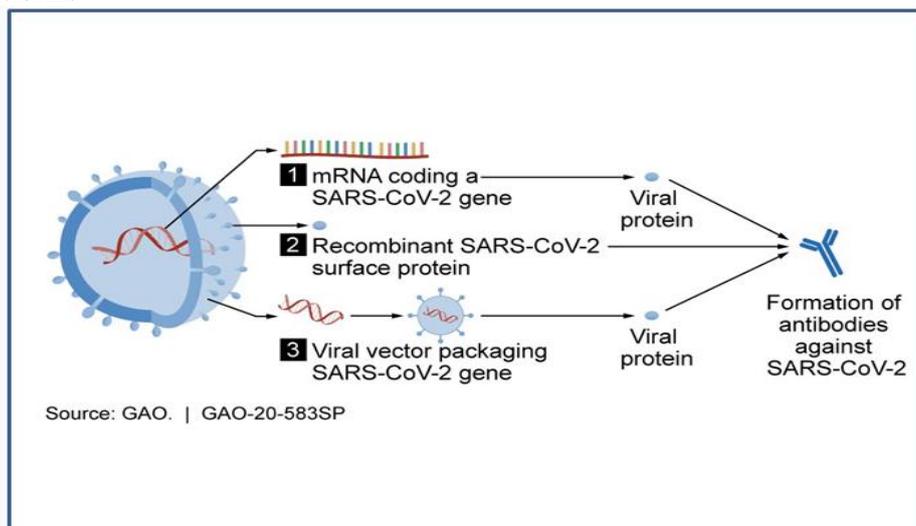
In April 2020, the WHO issued a statement representing dozens of vaccine scientists around the world, pledging collaboration to speed development of a vaccine against COVID-19. The WHO coalition is encouraging international cooperation between organizations developing vaccine candidates, national regulatory and policy agencies, financial contributors, public health associations, and governments, for eventual manufacturing of a successful vaccine in quantities sufficient to supply all affected regions, particularly low-resource countries.

Industry analysis of past vaccine development shows failure rates of 84–90%. Because COVID-19 is a novel virus target with properties still being discovered and requiring innovative vaccine technologies and development strategies, the risks associated with developing a successful vaccine across all steps of preclinical and clinical research are high.

To assess potential for vaccine efficacy, unprecedented computer simulations and new COVID-19-specific animal models are being developed multinationally during 2020, but these methods remain untested by unknown characteristics of the COVID-19 virus. Of the confirmed active vaccine candidates, about 70% are being developed by private companies, with the remaining projects under development by academic, government coalitions, and health organizations.<sup>[4]</sup>

Most of the vaccine developers are small firms or university research teams with little experience in successful vaccine design and limited capacity for advanced clinical trial costs and manufacturing without partnership by multinational pharmaceutical companies. Historically, the probability of success for an infectious disease vaccine candidate to pass preclinical barriers and reach Phase I of human testing is 41–57%.

## Technology platforms



**Figure-6: Potential candidates for forming SARS-CoV-2 proteins to prompt an immune response.**

As of September 2020, nine different technology platforms – with the technology of numerous candidates remaining undefined – were under research and development to create an effective vaccine against COVID-19. Most of the platforms of vaccine candidates

in clinical trials are focused on the coronavirus spike protein and its variants as the primary antigen of COVID-19 infection. Platforms being developed in 2020 involved nucleic acid technologies (nucleoside-modified messenger RNA and DNA), non-replicating viral

vectors, peptides, recombinant proteins, live attenuated viruses, and inactivated viruses.

Many vaccine technologies being developed for COVID-19 are not like vaccines already in use to prevent influenza, but rather are using "next-generation" strategies for precision on COVID-19 infection

mechanisms. Vaccine platforms in development may improve flexibility for antigen manipulation and effectiveness for targeting mechanisms of COVID-19 infection in susceptible population subgroups, such as healthcare workers, the elderly, children, pregnant women, and people with existing weakened immune systems.

**Table-1: Covid-19 platforms.**

COVID-19 vaccine technology platforms, December 2020		
Molecular platform	Total number of candidates	Number of candidates in human trials
Inactivated virus	19	5
Non-replicating viral vector	35	4
RNA-based	36	3
Protein subunit	80	2
DNA-based	23	2
Virus-like particle	19	1
Replicating viral vector	23	0
Live attenuated virus	4	0

**Challenges:** The rapid development and urgency of producing a vaccine for the COVID-19 pandemic may increase the risks and failure rate of delivering a safe, effective vaccine. One study found that between 2006 and 2015, the success rate of obtaining approval from Phase I to successful Phase III trials was 16.2% for vaccines, and CEPI indicates a potential success rate of only 10% for vaccine candidates in 2020 development.

An April 2020 CEPI report stated: "Strong international coordination and cooperation between vaccine developers, regulators, policymakers, funders, public health bodies and governments will be needed to ensure that promising late-stage vaccine candidates can be manufactured in sufficient quantities and equitably supplied to all affected areas, particularly low-resource regions." Research at universities is obstructed by physical distancing and closing of laboratories.

**Biosafety:** Early research to assess vaccine efficacy using COVID-19-specific animal models, such as ACE2-transgenic mice, other laboratory animals, and non-human primates, indicates a need for biosafety-level 3 containment measures for handling live viruses, and international coordination to ensure standardized safety procedures.

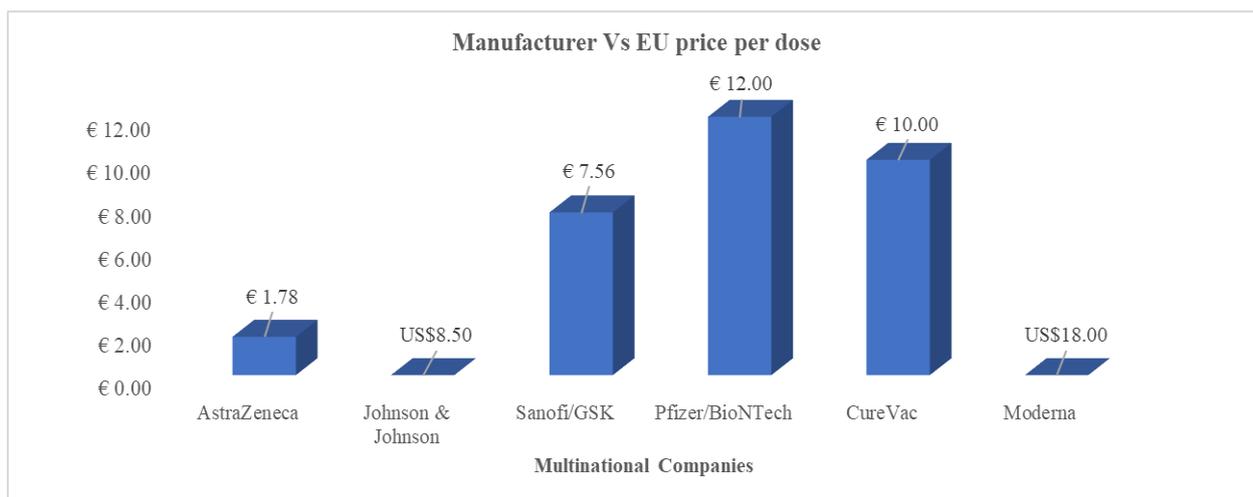
**Antibody-dependent enhancement:** Although the quality and quantity of antibody production by a potential vaccine is intended to neutralize the COVID-19 infection, a vaccine may have an unintended opposite effect by causing antibody-dependent disease enhancement (ADE), which increases the virus attachment to its target cells and might trigger a cytokine storm if a vaccinated person is later attacked by the virus. The vaccine technology platform (for example, viral vector vaccine, spike (S) protein vaccine or protein subunit vaccine), vaccine dose, timing of

repeat vaccinations for the possible recurrence of COVID-19 infection, and elderly age are factors determining the risk and extent of ADE. The antibody response to a vaccine is a variable of vaccine technologies in development, including whether the vaccine has precision in its mechanism, and choice of the route for how it is given (intramuscular, intradermal, oral, or nasal).

**Cost:** An effective vaccine for COVID-19 could save trillions of dollars in global economic impact, according to one expert, and would, therefore, make any price tag in the billions look small in comparison. In early stages of the pandemic, it was not known if it would be possible to create a safe, reliable and affordable vaccine for this virus, and it was not known exactly how much the vaccine development could cost. There was a possibility that billions of dollars could be invested without success.<sup>[5]</sup>

Once an effective vaccine would be developed, billions of doses would need to be manufactured and distributed worldwide. In April 2020, the Gates Foundation estimated that manufacturing and distribution could cost as much as US\$25 billion. From Phase I clinical trials, 84–90% of vaccine candidates fail to make it to final approval during development, and from Phase III, 25.7% fail – the investment by a manufacturer in a vaccine candidate may exceed US\$1 billion and end with millions of useless doses given advanced manufacturing agreements.

As of November 2020, companies subsidized under the United States' Operation Warp Speed program have set initial pricing at US\$19.50 to US\$25 per dose, in line with the influenza vaccine. In December 2020, a Belgian politician briefly published the confidential prices agreed between vaccine producers and the EU:



**Histogram: Price chart.**

**Supply of raw materials:** Globally, supplies critical to vaccine research and development are increasingly scarce due to international competition or national sequestration.

**Rollout:** Different vaccines have different shipping and handling requirements. For example, the Pfizer-BioNTech COVID-19 Vaccine (active ingredient tozinameran) must be shipped and stored between  $-80$

and  $-60^{\circ}\text{C}$  ( $-112$  and  $-76^{\circ}\text{F}$ ), must be used within five days of thawing, and has a minimum order of 975 doses, making it unlikely to be rolled out in settings other than large, well-equipped hospitals. The Moderna COVID-19 Vaccine vials require storage above  $-40^{\circ}\text{C}$  ( $-40^{\circ}\text{F}$ ) and between  $-25$  and  $-15^{\circ}\text{C}$  ( $-13$  and  $5^{\circ}\text{F}$ ). Once refrigerated, the Moderna COVID-19 Vaccine can be kept between  $2$  and  $8^{\circ}\text{C}$  ( $36$  and  $46^{\circ}\text{F}$ ) for up to 30 days.

### Trials



**Figure-7: Volunteer receives CoronaVac injection during Phase III trial.**

In April 2020, the WHO published an "R&D Blueprint (for the) novel Coronavirus" (Blueprint). The Blueprint documented a "large, international, multi-site, individually randomized controlled clinical trial" to allow "the concurrent evaluation of the benefits and risks of each promising candidate vaccine within 3–6 months of it being made available for the trial." The Blueprint listed a *Global Target Product Profile* (TPP) for COVID-19, identifying favorable attributes of safe and effective vaccines under two broad categories: "vaccines for the long-term protection of people at higher risk of COVID-19, such as healthcare workers", and other vaccines to provide rapid-response immunity for new outbreaks. The international TPP team was formed to 1) assess the development of the most promising candidate vaccines; 2) map candidate vaccines and their clinical trial worldwide, publishing a frequently-updated

"landscape" of vaccines in development; 3) rapidly evaluate and screen for the most promising candidate vaccines simultaneously before they are tested in humans; and 4) design and coordinate a multiple-site, international randomized controlled trial – the "Solidarity trial" for vaccines – to enable simultaneous evaluation of the benefits and risks of different vaccine candidates under clinical trials in countries where there are high rates of COVID-19 disease, ensuring fast interpretation and sharing of results around the world. The WHO vaccine coalition will prioritize which vaccines should go into Phase II and III clinical trials, and determine harmonized Phase III protocols for all vaccines achieving the pivotal trial stage.<sup>[6]</sup>

**Enrollment of participants:** Vaccine developers have to invest resources internationally to find enough

participants for Phase II–III clinical trials when the virus has proved to be a "moving target" of changing transmission rate across and within countries, forcing companies to compete for trial participants. As an example in June, the Chinese vaccine developer Sinovac formed alliances in Malaysia, Canada, the UK, and Brazil among its plans to recruit trial participants and manufacture enough vaccine doses for a possible Phase III study in Brazil where COVID-19 transmission was accelerating during June. As the COVID-19 pandemic within China became more isolated and controlled, Chinese vaccine developers sought international relationships to conduct advanced human studies in several countries, creating competition for trial participants with other manufacturers and the international Solidarity trial organized by the WHO. In addition to competition over recruiting participants, clinical trial organizers may encounter people unwilling to be vaccinated due to vaccine hesitancy or disbelieving the science of the vaccine technology and its ability to prevent infection.

Having an insufficient number of skilled team members to administer vaccinations may hinder clinical trials that must overcome risks for trial failure, such as recruiting participants in rural or low-density geographic regions, and variations of age, race, ethnicity, or underlying medical conditions.

**Adaptive design for the Solidarity trial:** A clinical trial design in progress may be modified as an "adaptive design" if accumulating data in the trial provide early insights about positive or negative efficacy of the treatment. The WHO Solidarity trial of multiple vaccines in clinical studies during 2020, will apply adaptive design to rapidly alter trial parameters across all study sites as results emerge. Candidate vaccines may be added to the Solidarity trial as they become available if priority criteria are met, while vaccine candidates showing poor evidence of safety or efficacy compared to placebo or other vaccines will be dropped from the international trial. Adaptive designs within ongoing Phase II–III clinical trials on candidate vaccines may shorten trial durations and use fewer subjects, possibly expediting decisions for early termination or success, avoiding duplication of research efforts, and enhancing coordination of design changes for the Solidarity trial across its international locations.

**Proposed challenge studies:** Challenge studies are a type of clinical trial involving the intentional exposure of the test subject to the condition tested, an approach that can significantly accelerate vaccine development. Human challenge studies may be ethically controversial because they involve exposing test subjects to dangers beyond those posed by potential side effects of the substance being tested. Challenge studies have been used for diseases less deadly than COVID-19 infection, such

as common influenza, typhoid fever, cholera, and malaria. The World Health Organization has developed a guidance document with criteria for conducting COVID-19 challenge studies in healthy people, including scientific and ethical evaluation, public consultation and coordination, selection and informed consent of the participants, and monitoring by independent experts. Beginning in January 2021, dozens of young adult volunteers will be deliberately infected with COVID-19 in a challenge trial conducted in a London hospital under management by the British government COVID-19 Vaccine Taskforce. Once an infection dose of COVID-19 is identified, two or more of the candidate COVID-19 vaccines will be tested for effectiveness in preventing infection.

**Vaccines:** As of 21 December, many countries and the European Union have authorized or approved tozinameran, the Pfizer–BioNTech vaccine. Bahrain and the United Arab Emirates granted emergency marketing authorization for BBIBP-CorV, manufactured by Sinopharm. In the United Kingdom, 138,000 people had received tozinameran by 16 December, during the first week of the UK vaccination programme. On 11 December 2020, the United States Food and Drug Administration (FDA) granted an Emergency Use Authorization (EUA) for tozinameran. A week later, they granted an EUA for mRNA-1273, the Moderna vaccine. CEPI classifies development stages for vaccines as "exploratory" (planning and designing a candidate, having no evaluation *in-vivo*), "preclinical" (in vivo evaluation with preparation for manufacturing a compound to test in humans), or initiation of Phase I safety studies in healthy people. Some 321 total vaccine candidates were in development as either confirmed projects in clinical trials or in early-stage "exploratory" or "preclinical" development, as of September.

Phase I trials test primarily for safety and preliminary dosing in a few dozen healthy subjects, while Phase II trials – following success in Phase I – evaluate immunogenicity, dose levels (efficacy based on biomarkers) and adverse effects of the candidate vaccine, typically in hundreds of people. A Phase I–II trial consists of preliminary safety and immunogenicity testing, is typically randomized, placebo-controlled, while determining more precise, effective doses. Phase III trials typically involve more participants at multiple sites, include a control group, and test effectiveness of the vaccine to prevent the disease (an "interventional" or "pivotal" trial), while monitoring for adverse effects at the optimal dose. Definition of vaccine safety, efficacy, and clinical endpoints in a Phase III trial may vary between the trials of different companies, such as defining the degree of side effects, infection or amount of transmission, and whether the vaccine prevents moderate or severe COVID-19 infection.



**Figure-8: Moderna & BioNTech.**

**Efficacy:** Pfizer-BioNTech and Moderna's COVID-19 vaccines are both mRNA vaccines, which use a copy of a natural chemical called mRNA to provoke the body's immune response. When the immune response is activated, it protects the body from acquiring an infection. The RNA is packaged in a similar manner in both vaccines, which requires the use of polyethylene glycol, the chemical suspected to induce allergic reactions in a few patients who had an allergic reaction to the Pfizer vaccine.<sup>[7]</sup>

Pfizer-BioNTech's vaccine contains

- A nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein of SARS-CoV-2
- Lipids, or fatty substances, including: (4-hydroxybutyl)azanediylobis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2-[(polyethylene glycol)-2000]-N, N-ditetradecylacetamide, 1,2-distearoyl-snglycero-3-phosphocholine, and cholesterol
- Potassium chloride
- Monobasic potassium phosphate
- Sodium chloride (salt)
- Dibasic sodium phosphate dihydrate
- Sucrose (sugar)

The Moderna vaccine contains similar ingredients such as:

- Messenger ribonucleic acid (mRNA)
- Lipids, or fatty substances, including: SM(sphingomyelin)-102, Polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC], and cholesterol
- Tromethamine

- Tromethamine hydrochloride
- Acetic acid
- Sodium acetate
- Sucrose (sugar)

The vaccine primarily contains salts and stabilizers in the forms of sugars and lipids, which don't cause allergic reactions.

Both vaccines are similar when it comes to ingredients. "The primary difference between the two is that the packaging of the RNA in the Moderna vaccine allows for storage in a regular freezer, compared to ultra-cold freezers required for the storage of the Pfizer vaccine.

The effectiveness of a new vaccine is defined by its efficacy. Several COVID-19 vaccines have demonstrated 80% efficacy and higher in Phase III trials, including mRNA-1273, Tozinameran, BBIBP-CorV, and Gam-COVID-Vac. In the case of COVID-19, a vaccine efficacy of 67% may be enough to slow the pandemic, but this assumes that the vaccine confers sterilizing immunity, which is necessary to prevent transmission. Vaccine efficacy reflects disease prevention, a poor indicator of transmissibility of SARS-CoV-2 since asymptomatic people can be highly infectious.

With BBIBP-CorV, Sinopharm announced a vaccine's efficacy was 79.34%, which was lower than the 86% announced by the United Arab Emirates on 9 December. The UAE had based its results on an interim analysis of Phase III trials conducted from July. While the UAE said it had reviewed Sinopharm's interim data analysis, there was no indication it had independently analyzed the raw data. It is unclear how Sinopharm drew conclusions from

the data, since the UAE did not state critical details of the analysis, such as the number of COVID-19 cases or the volunteers' ages.

With CoronaVac, Instituto Butantan said the vaccine is between 50% and 90% effective in Brazil, but withheld full results at Sinovac's request, raising questions about transparency as it was the third delay in releasing results. Separately on 24 December, Turkey released Phase III results from an interim analysis of 29 cases which showed an efficacy rate of 91.25% based on the data of 1,322 participants in a trial involving 7,371 volunteers, a confusing readout compared to Brazil.

**SARS-CoV-2 variant:** In mid-December 2020, a new SARS-CoV-2 variant (VOC-202012/01) was identified in the UK. While preliminary data indicates that this variant showed an estimated increase in reproductive number (R) by 0.4 or greater and an increased transmissibility of up to 70%, there is as yet no evidence for lower vaccine effectiveness.<sup>[8]</sup>

**Use of adjuvants:** As of September 2020, eleven of the vaccine candidates in clinical development use adjuvants to enhance immunogenicity. An immunological adjuvant is a substance formulated with a vaccine to elevate the immune response to an antigen, such as the COVID-19 virus or influenza virus. Specifically, an adjuvant may be used in formulating a COVID-19 vaccine candidate to boost its immunogenicity and efficacy to reduce or prevent COVID-19 infection in vaccinated individuals. Adjuvants used in COVID-19 vaccine formulation may be particularly effective for technologies using the inactivated COVID-19 virus and recombinant protein-based or vector-based vaccines. Aluminum salts, known as "alum", were the first adjuvant used for licensed vaccines, and are the adjuvant of choice in some 80% of adjuvanted vaccines. The alum adjuvant initiates diverse molecular and cellular mechanisms to enhance immunogenicity, including release of proinflammatory cytokines.



Figure-9: Covaxin & Covishield.

**Covaxin:** COVAXINTM, India's indigenous COVID-19 vaccine by Bharat Biotech is developed in collaboration with the Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV). The indigenous, inactivated vaccine is developed and manufactured in Bharat Biotech's BSL-3 (Bio-Safety Level 3) high containment facility. The vaccine received DCGI approval for Phase I & II Human Clinical Trials and the trials commenced across India from July, 2020. After successful completion of the interim analysis from the Phase 1 & 2 clinical trials of COVAXINTM, Bharat Biotech received DCGI approval for Phase 3 clinical trials in 26,000 participants in over 25 centres across India.

**Covishield:** The University of Oxford, AstraZeneca vaccine is a vaccine that aims to protect against COVID-19.

Manufacturer/developer: University of Oxford, AstraZeneca

Research name: AZD1222 (ChAdOx1)

Vaccine type: Non-Replicating Viral Vector

Administration method: Intramuscular injection

Serum Institute of India (SII), the world's largest vaccine manufacturer by volume, and Indian Council of Medical

Research (ICMR), the apex body in India for biomedical research, announce completion of enrolment of phase 3 clinical trials for COVISHIELD in India. ICMR and SII have further collaborated for clinical development COVOVAX (Novavax) developed by Novavax, USA and upscaled by SII. The partnership is a stellar example of private-public institutes collaborating to mitigate the dire consequences of the pandemic outbreak. ICMR has funded the clinical trial site fees while SII has funded other expenses for COVISHIELD. At present, SII and ICMR are conducting Phase 2/3 clinical trial of COVISHIELD at 15 different centres, across the country. It has completed the enrolment of all 1600 participants on 31 Oct 2020. COVISHIELD has been developed at the SII Pune laboratory with a master seed from Oxford University/Astra Zeneca. The vaccine made in UK is currently being tested in large efficacy trials in UK, Brazil, South Africa and USA. The promising result of the trials so far give confidence that COVISHIELD could be a realistic solution to the deadly pandemic. COVISHIELD is by far the most advanced vaccine in human testing in India. Based on the Phase 2/3 trial results, SII with the help of ICMR will pursue the early availability of this product for India. SII has already manufactured 40 million doses of the vaccine, under the at-risk manufacturing and stockpiling license from

DCGI. Furthermore, US-based Novavax has initiated its late phase trials in South Africa and in UK and will soon commence the same in the USA. SII has received the bulk vaccine and Matrix-M adjuvant from Novavax and will soon fill and finish them in vials. This vaccine formulated at SII (COVOVAX) will be tested in a Phase 3 trial in India and an application for the same to regulatory authorities will be made soon by ICMR and SII.

The Drug Controller General of India (DCGI) has formally approved Serum Institute's Covishield and Bharat Biotech's Covaxin vaccines for restricted emergency use against COVID-19 in India. Serum Institute's Covishield and Bharat Biotech's Covaxin are the two vaccines against COVID-19 that have received approval from India's Drug regulator for restricted emergency use in India. Covishield vaccine is developed by AstraZeneca and the University of Oxford. It is the Indian variant of AZD1222. Covishield vaccine is developed and manufactured by the Pune-based Serum Institute of India (SII) through a license from AstraZeneca and Oxford. That is it is a Recombinant Chimpanzee Adenovirus vector vaccine (Covishield), encoding the SARS-CoV-2 Spike (S) glycoprotein with technology transfer from AstraZeneca/Oxford University. The vaccine is a "non-replicating viral vector" that is it makes use of another weakened and genetically modified virus. It carries the code to make the spike protein that is the spike on the surface of the virus. It is supposed that the immune system of the body will recognise this protein as a threat and work on building antibodies against it. Now, the Covaxin vaccine, developed by Hyderabad-based Bharat Biotech in collaboration with the National Institute of Virology and uses a different platform.

Covaxin is an "inactivated" vaccine that uses the killed SARS-CoV-2 virus and has no potential to infect or replicate once injected and just serves to uplift an immune response. It is expected to target more than just the spike protein. It aims to develop an immune response to the nucleocapsid protein which is the cell of the virus that encloses its genetic material.

What does the approval mean?

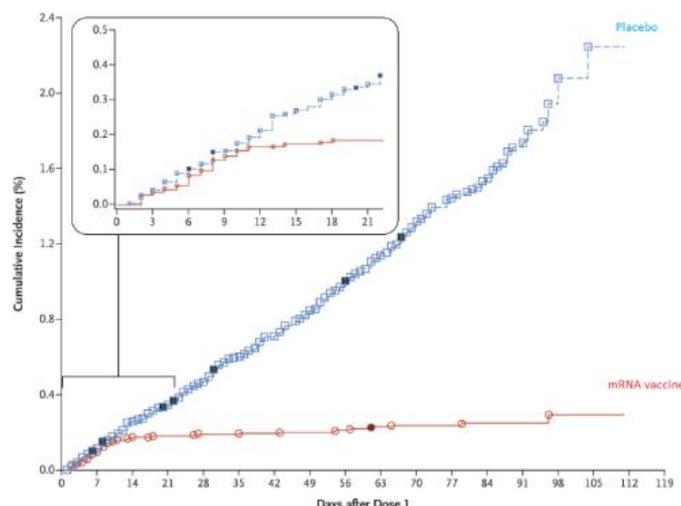
As mentioned above that both the vaccines received "restricted use approval in an emergency situation" just like an Emergency Use Authorisation that countries like the UK and US have been granting to companies including Pfizer, Moderna, and AstraZeneca for their vaccines. It means that the vaccines received approval for use despite the companies have not yet completed clinical trials. The government wanted a vaccine ready to use as the earliest for the COVID-19 pandemic. Also, the concern is about the mutation of the SARS-CoV-2 virus. Due to these new strains are found in countries like the UK and is also started to spread in the world including India.

Trial and efficacy of Covishield and Covaxin: As per DCGI, the Serum Institute submitted the data of Phase I clinical trial which was conducted over 23, 745 overseas participants and shows an overall result of 70.42 efficacy. In India, Phase-II/III was conducted on 1600 participants and the data was found comparable with the data from the overseas clinical studies. The clinical trial ongoing in the country by the firm and will continue. On approx. 800 participants, Bharat Biotech conducted phase one and two trials and also conducted several animal trials. The results have demonstrated that the vaccine is safe and provides a robust immune response. Its third trial is going on and about 22, 500 participants took part in it. As per the data available till date the vaccine has been found effective and safe. According to the Indian Express, All India Institute of Medical Sciences Director Dr. Randeep Guleria "This (approval for Covaxin) is like a back-up. If we find that cases don't rise, then we stick to the SII (Serum Institute of India's Covishield), till the Bharat Biotech data comes early next month. And if that data is found to be good enough, then they will get the same approval as the SII. Indirectly, looking at the safety profile, that (Covaxin) is a safe vaccine, although we don't know how efficacious it is. They (the regulators) have given, I would say, a green signal to start stockpiling in case we need it."

Who will get the vaccine first?

The country will be able to begin its mass vaccination programme as the two vaccines received approval. The government told SII and Bharat Biotech to keep "significant" doses ready so that they can be transported to over 30 Vaccination hubs in places including Lucknow, Panchkula, Chennai, and Delhi. After the company sends the vaccines, state governments are expected to mobilise the doses to the vaccination points. In the first slot, the vaccination points will be the healthcare facilities where nearly 70 lakh public and private health professionals will be vaccinated in a time span of three months. Next will be frontline workers who will get the vaccine and then the people aged 50 years and above. According to the Health Minister Dr. Harsh Vardhan, the government expected the first phase of vaccination and targeting around 30 crore people on priority which is to be completed by August 2021.

About Covishield and Covaxin Doses and storage temperature: Both the vaccines have to be administered in two doses and are to be stored at 2-8°C. In the last let us have a look at the Novel Corona Virus-2019-nCov-Vaccine. It is developed by M/s Cadila Healthcare Ltd. by using DNA platform technology. In India, the firm initiated Phase I/II clinical trial in more than 1000 participants which is still ongoing. The data suggest that the vaccine is safe and immunogenic with three doses when administered intradermally. The firm also received permission to conduct Phase-III clinical trials in 26,000 Indian participants as recommended by the Subject Expert Committee.



**Figure-10: Cumulative incidence curves for symptomatic COVID-19 infections after the first dose of the Pfizer-BioNTech vaccine (tozinameran) or placebo in a double-blind clinical trial.**

**Conclusion:** A recent survey shows many Americans are hesitant to get the COVID-19 vaccines, some citing fears of possible side effects and questions about effectiveness as reasons. Infectious disease experts stress that the data collected from the Pfizer/BioNTech and Moderna vaccine trials are very reassuring in terms of both efficacy and safety. Experts say it's important to think of the vaccine as a part of the overall COVID-19 prevention strategy. By accepting the vaccine, you will help our country achieve herd immunity. While two COVID-19 vaccines are now authorized for use in the United States, not everyone is eager to get in line once their priority group is called. According to a Kaiser Family Foundation survey published on December 15, about a quarter (27%) of the public are vaccine hesitant, saying they "probably or definitely would not get a COVID-19 vaccine even if it were available for free and deemed safe by scientists." The survey found that those who were hesitant to get a COVID-19 vaccine were worried about multiple things, including possible side effects (59%), lack of trust in the government to ensure the vaccines' safety and effectiveness (55%), and concerns that the vaccine is too new (53%). To address these concerns, Verywell spoke with infectious disease experts from all over the country.

**Concern 1: The vaccine was developed so fast. It must have been rushed and therefore isn't safe.**

The speed at which the Pfizer-BioNTech and Moderna vaccines were both developed and authorized is a stark contrast compared to how long other human disease vaccines have taken to create. The mumps vaccine, which held the previous record, took about four years. However, scientists can point to a few different reasons why the COVID-19 vaccines have a different timeline. A lot of events conspired to make the vaccines available so quickly, but it wasn't because of any shortcuts. Both vaccines made by Pfizer and Moderna are mRNA vaccines, and the mRNA platform was already in development (though not net used in a human vaccine).

By using a small part of the virus's genetic code (RNA), an mRNA vaccine shows cells how to make a coronavirus protein that our immune system can recognize and then respond to. After someone gets vaccinated, if they're exposed to COVID-19, their body will already have the antibodies to fight it off and keep it from entering cells. For example, the Moderna vaccine took the platform (mRNA) that they had for a MERS (Middle East respiratory syndrome) vaccine, and they swapped out the MERS genetic code and swapped in the SARS-CoV-2 genetic code. So, these vaccines didn't come out of nowhere; they came out of years of research and advances in technology. "While some vaccines use live virus or bacterium to teach our immune system how to fight the pathogens, an mRNA vaccine doesn't use the live virus, and therefore cannot give someone COVID-19", according to the Centers for Disease Control and Prevention (CDC). Additionally, mRNA from the vaccine never enters the nucleus of the cell, meaning it does not affect or interact with human DNA. The timeline behind the actual manufacturing of the vaccines had a huge impact on how quickly they could be deployed after authorization from the Food and Drug Administration (FDA). Usually, companies don't commit to manufacturing vaccines until they've been approved. And governments or healthcare systems don't buy vaccines until they've been approved. But what was really sped up under Operation Warp Speed was the commitment to purchase millions of doses of vaccine before they had been approved. That allowed manufacturing to rev up, even while the vaccines were going through the study and approval process.

**Concern 2: The government and health agencies have been giving mixed messages about COVID-19 since the beginning. Why trust them about a vaccine?**

A large complaint among Americans is the contradictory messages from the CDC and healthcare officials like Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID) at the National

Institutes of Health (NIH). For example, in an interview on March 8, 2020, Fauci said “there’s no reason to be walking around with a mask.” But by April 3, the CDC updated its previous advice and recommended people wear face coverings “in public settings when around people outside their household, especially when social distancing measures are difficult to maintain.” The part of the issue regarding these messages is that they had to change. And that’s because science—and the virus—is always evolving. The great news is that as we learn about the virus, we can update recommendations to reflect that latest data, which is what happened with the mask wearing. The objections to the vaccine are understandable because the vaccine is brand new, but it’s not entirely intellectually consistent with some of the other actions that we take and the other risks that we take day in and day out of our lives. When you go to the grocery store, you trust that the food you’re buying doesn’t contain salmonella and won’t make you sick. When you drive a car, you trust that your vehicle has passed industry safety regulations and won’t malfunction. But there are—and will—be rare occasions when that head of lettuce gives you salmonella, and the car you drive breaks down. Unless we are growing our own food and living off the grid, we have to establish some trust into societal norms.

### **Concern 3: The side effects of the vaccines haven’t been observed long enough.**

In clinical trial data presented to the FDA by Pfizer, the vaccine was well-tolerate in approximately 44,000 participants with no serious safety concerns. Side effects were mild, including fatigue and headache in fewer than 3% of participants. Moderna presented similar findings. The company reported that the majority of side effects among its 30,000 vaccine clinical trial participants were mild or moderate. After the first dose, 2.7% of participants reported pain at the injection site. The FDA says there is a “remote chance” that the Pfizer vaccine could cause a severe allergic reaction, which would occur within minutes or up to an hour after receiving the vaccine. Experts believe and agree with the science and data that prove the two COVID-19 vaccines approved for use in the U.S.—the Moderna and Pfizer-BioNTech vaccines, are safe and effective. Getting the vaccine when it becomes available to you will help our country reach herd immunity and play a pivotal part in getting back to normalcy.

### **REFERENCES**

1. Santiago, Jahleah (19 December). "A side-by-side comparison of the Pfizer/BioNTech and Moderna vaccines", 2020.
2. Beaumont, Peter (18 November). "Covid-19 vaccine: who are countries prioritising for first doses?". *The Guardian*, 2020.
3. Mullard, Asher (30 November). "How COVID vaccines are being divvied up around the world Canada leads the pack in terms of doses secured per capita". *Nature*, 2020.

4. So AD, Woo J (December 2020). "Reserving coronavirus disease vaccines for global access: cross sectional analysis", 2019.
5. Thanh Le T, Andreadakis Z, Kumar A, Gómez Román R, Tollefsen S, Saville M, et al. (9 April). "The COVID-19 vaccine development landscape". *Nature Reviews Drug Discovery*, 2020.
6. Gouglas D, Thanh Le T, Henderson K, Kaloudis A, Danielsen T, Hammersland NC, Robinson JM, Heaton PM, Røttingen JA (December). "Estimating the cost of vaccine development against epidemic infectious diseases: a cost minimisation study", 2018.
7. DiMasi JA, Grabowski HG, Hansen RW (May). "Innovation in the pharmaceutical industry: New estimates of R&D costs". *Journal of Health Economics*, 2016.
8. Sanger DE, Kirkpatrick DD, Zimmer C, Thomas K, Wee S (2 May). "With Pressure Growing, Global Race for a Vaccine Intensifies", 2020.