Operation Warp Speed

Developing the COVID-19 Vaccine

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More than 40 vaccines against COVID-19 are currently under development, with researchers around the world using different techniques and targeting different sites on the virus. In the U.S., the federal government established Operation Warp Speed (OWS) to accelerate the availability of a safe and effective vaccine. This guide provides an overview OWS, the progress of the vaccines in the program, and the prospects for the rapid release of a COVID-19 vaccine.

Operation Warp Speed (OWS) was a government program to advance COVID-19 diagnostics, treatments, and vaccines through public-private partnerships.[1] **One goal of OWS was to provide a COVID-19 vaccine to the public by January 2021,** reducing the development time from years to months. OWS has partnered with at least six pharmaceutical and vaccine manufacturing companies to fund vaccine testing and development. In an unusual step, OWS also funded the manufacture of a vaccine during its final testing phase; however, the company involved also assumes a financial risk if ultimately, the vaccine is ineffective.

Clinical trials are required by the U.S. Food and Drug Administration (FDA) for each vaccine to make sure it is safe (meaning it causes no serious side effects) and effective (meaning it reduces the risk of getting COVID-19 by more than 50%). While OWS significantly accelerated the vaccine development phase, clinical trials were still required. Trial participants must be monitored for several months after receiving the vaccine to determine its safety and efficacy.

Traditionally, vaccines go through three phases before approval.
Phase 1 and Phase 2 trials must be completed first. However, for many of the OWS vaccines, these phases are being conducted simultaneously (a Phase 1/2 trial). During Phase 3, thousands of people participate. Afterward, the FDA reviews the trial data and can approve the vaccine for public use.

Phase 1 and 2	Phase 3
Small number of patients (20-500)	Large group of patients (30,000-60,000)
Questions What is an appropriate dosage? Are there any major side effects?	**Questions** What are the side effects? Does it work?

Types of COVID-19 Vaccines

Researchers used several types of vaccine technologies to develop a COVID-19 vaccine.[2]

Virus Vaccine: A virus, either weakened or killed, is used to create the vaccine. This approach links back to the method used to develop the first smallpox vaccine in the 1700s.

Viral-vector Vaccine: A well-researched virus, such as measles or adenovirus, is engineered to produce proteins found on SARS-CoV2 (the virus causing COVID-19) to generate an immune response. This technique has resulted in a few recent vaccines for other viruses, but it is a newer process that is not well understood. Some believe pre-existing immunity to the engineered virus could impact the vaccine's effectiveness.

Genetic Vaccine: The RNA or DNA of SARS-CoV2 proteins is inserted into cells, which then produce the virus protein to generate an immune response. This technique is unproven; no existing vaccines use this technology.

Protein-based Vaccine: SARS-CoV2 proteins are injected directly into the body. This technique was used in monkeys to create a vaccine against SARS (2003), but the technology has never been tested in humans.

OWS Vaccines Under Development

At least six potential vaccines are being funded under OWS; three were approved in the U.S. for emergency use, but are still being followed to determine side-effects and long-term immunity. During Phase 3, OWS vaccine candidates were simultaneously being manufactured. This allowed faster access to the vaccine, after the FDA approved it. However, there was a risk that resources were wasted for vaccines found to be unsafe or ineffective.

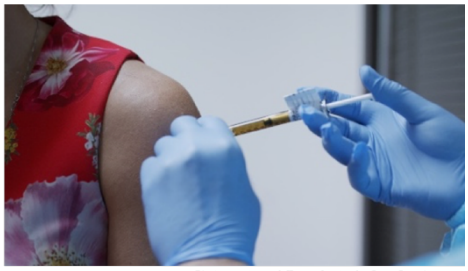

Photo courtesy of Texas Center for Drug Development

Pfizer/BioNTech • RNA-based Vaccine • Approved for Emergency Use

Phase 1, 2, 3 completed.[3]

This is a new vaccine technology that has not yet been used in a licensed vaccine. This vaccine requires two doses (affecting compliance) and must be frozen (making it challenging to get to low-resource areas). While Pfizer received OWS funding to provide the vaccine, it did not receive funding for the vaccine research and development.

Note: The FDA granted Emergency Use Authorization (EUA) for the vaccine on December 11, 2020.

Moderna • RNA-based Vaccine • Approved for Emergency Use

Phase 1, 2, 3 completed.[4]

This is a new vaccine technology that has not yet been used in a licensed vaccine. This vaccine requires two doses and must be frozen.

Note: The FDA granted Emergency Use Authorization (EUA) for the vaccine on December 18, 2020.

Johnson & Johnson • Viral-vector Vaccine • Approved for Emergency Use

Phase 1, 2, 3 completed. [5]

This vaccine uses an engineered adenovirus, which has already resulted in a licensed vaccine for Ebola. Unlike DNA- and RNA-based vaccines, this vaccine can be stored in a refrigerator (making it easier to distribute) and only requires a single dose (making compliance easier).

Note: The FDA granted Emergency Use Authorization (EUA) for this vaccine on February 27, 2021.

AstraZeneca/Oxford University • DNA-based Vaccine • Phase 3

Phase 1, 2 completed. **Phase 3** started Aug. 31 • 30,000 participants in the U.S.[6]

This is a new vaccine technology that has not yet been used in a licensed vaccine. This vaccine has been shown to produce an immune response but requires two doses and must be frozen.

Note: The vaccine was approved in several countries including the UK, South Africa and India, but U.S. approval is not anticipated until April 2021. Use of the vaccine was halted in South Africa because it was less effective on a new virus variant present in the region (B.1.351).

Novavax • Protein-based Vaccine • Phase 3

Phase 1, 2: completed. **Phase 3** started Dec 28.[7]

This vaccine uses a novel technology recently used for a flu vaccine that was developed in March 2020 (but not yet brought to market). Phase 3 trials will require two doses; results are expected in May 2021.

Sanofi/GSK • Protein-based Vaccine • Phase 2

Phase 1, 2 began in September 2020 with 440 participants across 11 sites in the U.S. **Phase 3** trials begin in 2021.

This vaccine uses existing vaccine technology from Sanofi's seasonal influenza vaccine and GSK's pandemic adjuvant (an ingredient to increase immune response).

Note: Sanofi entered into agreements with Johnson & Johnson and Pfizer to help produce their vaccines.

Endnotes

1. For more information on OWS, see "Coronavirus: Operation Warp Speed," U.S. Department of Defense, https://www.defense.gov/Explore/Spotlight/Coronavirus/Operation-Warp-Speed/.
2. For graphical descriptions of different types of vaccines see Ewan Callaway, "The race for coronavirus vaccines: a graphical guide," *Nature* 580 (2020): 576-577. https://doi.org/10.1038/d41586-020-01221-y.
3. Mark J. Mulligan, et al. "Phase 1/2 study of COVID-19 RNA vaccine BNT162b1 in adults," *Nature* 586 (2020): 589-593, https://doi.org/10.1038/s41586-020-2639-4. FDA. "Pfizer-BioNTech COVID-19 Vaccine VRBPAC Briefing Document" https://www.fda.gov/media/144245/download.
4. Lindsey R. Baden, et al. "Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine." NEJM (December 20, 2020). https://doi.org/10.1056/NEJMoa2035389.
5. FDA, "Janssen Biotech, Inc. COVID-19 Vaccine Ad26.COV2.S Sponsor Briefing Document," https://www.fda.gov/media/146219/download.
6. Pedro M. Folegatti, et al. "Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomized controlled trial," *The Lancet* 396 (2020):467-478, https://doi.org/10.1016/S0140-6736(20)31604-4. Merryn Voysey, et al. "Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim report analysis of four randomized controlled trials in Brazil, South Africa and the UK," *The Lancet* (2020). https://doi.org/10.1016/S0140-6736(20)32661-1.
7. Cheryl Keech, et al., "First-in-Human Trial of a SARS CoV 2 Recombinant Spike Protein Nanoparticle Vaccine," *medRxiv* (August 6, 2020), https://doi.org/10.1101/2020.08.05.20168435.

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