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COVID-19 timeline
Global situation

SCIENCE CORONAVIRUS COVERAGE

Dozens of COVID-19 vaccines are in development. Here are the ones to follow.

Here are the COVID-19 vaccine prospects that have made it to phase three trials and beyond.

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PUBLISHED NOVEMBER 9, 2020

More than 150 coronavirus vaccines are in development across the world—and hopes are high to bring one to market in record time to ease the global crisis. Several efforts are underway to help make that possible, including the U.S. government's Operation Warp Speed initiative, which has pledged \$10 billion and aims to develop and deliver 300 million doses of a safe, effective coronavirus vaccine by January 2021. The World Health Organization is also coordinating global efforts to develop a vaccine, with an eye toward delivering two billion doses by the end of 2021.

It can typically take 10 to 15 years to bring a vaccine to market; the fastest-ever—the vaccine for mumps—required four years in the 1960s. Vaccines go through a three-stage clinical trial process before they are sent to regulatory agencies for approval—which can be a lengthy process itself.

Even after a vaccine is approved, it faces potential roadblocks when it comes to scaling up production and distribution, which also includes deciding which populations should get it first—and at what cost. Many vaccines also stay in what's called phase four, a perpetual stage of regular study. (Here's how we'll know when a COVID-19 vaccine is ready.)

Given the urgent need, some vaccine developers are compressing the clinical process for SARS-CoV-2 by running trial phases simultaneously. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, has stated that independent Data and Safety Monitoring Boards can end trials early if their interim results are overwhelmingly positive or negative. Meanwhile, the Trump Administration pressured the U.S. Food and Drug Administration to quickly approve a vaccine by Election Day, which some observers worried was politically motivated. By mid-October, several states—including California, New York, and West Virginia—announced plans to independently review the data for any vaccine the FDA approves. On November 7, the presidential election was called for Democratic challenger Joe Biden.

While the FDA has agreed to expedite the approval process, on October 6 the independent federal agency released more stringent safety standards that had been initially opposed by the White House. In a meeting on October 23, the primary advisory panel for the FDA approval process appeared hesitant to issue an emergency use authorization—which allows the use of an unapproved medical product in a life-threatening situation—to any vaccine candidate. Members said doing so could interfere with ongoing trials; participants may drop out of the trials to ensure they receive the actual vaccine rather than the placebo, which would muddy the data and make it close to impossible to prove the efficacy of a vaccine. CDC director Robert Redfield, vaccine developers, and the FDA have also said it's unlikely a vaccine will be widely available until the middle of 2021.

Vaccine prospects

The COVID-19 candidates, like all vaccines, essentially aim to instruct the immune system to mount a defense, which is sometimes stronger than what would be provided through natural infection and comes with fewer health consequences.

To do so, some vaccines use the whole coronavirus, but in a killed or weakened state. Others use only part of the virus—whether a protein or a fragment. Some transfer the coronavirus proteins into a different virus that is unlikely to cause disease or even incapable of it. Finally, some vaccines under development rely on deploying pieces of the coronavirus's genetic material, so our cells can temporarily make the coronavirus proteins needed to stimulate our immune systems. (Find out more about vaccines and how they work.)

Though it's too soon to say which candidates will ultimately be successful, here's a look at the prospects that have reached phase three and beyond—including a quick primer on how they work and where they stand.

Pfizer

Name: BNT162b2

Who: One of the world's largest pharmaceutical companies, based in New York, in collaboration with German biotech company BioNTech.

What: This vaccine candidate relies on injecting snippets of a virus's genetic material, in this case mRNA, into human cells. They create viral proteins that mimic the coronavirus, training the immune system to recognize its presence. Any successful vaccine based on this technology would be the first mRNA vaccine approved for human use. This vaccine requires two doses taken 21 days apart.

Status: On July 27, Pfizer and BioNTech launched a trial that combines phase two and three by enrolling a diverse population in areas with significant SARS-CoV-2 transmission. It has expanded the trial to include 44,000 people across multiple countries. Preliminary results of phase one/two data show the vaccine produces antibodies and T-cell responses specific to the SARS-CoV-2 protein. And on November 9, the companies announced that an interim analysis of the phase three study shows the vaccine is more than 90 percent effective in preventing COVID-19 with no serious safety concerns—but as yet they have provided no data to back the claim.

The project is aiming to apply for emergency authorization from the FDA after the third week in November, even though the drug regulator has recently indicated it is moving away from the prospect of such an authorization. Pfizer has signed a nearly \$2 billion contract with the U.S. government to provide 100 million doses by December 2020—an agreement that goes into effect when and if the drug is approved and delivered—and hopes to supply 1.3 billion doses by the end of 2021.

Bharat Biotech

Name: COVAXIN

Who: An Indian biotechnology company, in collaboration with the Indian Council of Medical Research and the National Institute of Virology.

What: COVAXIN uses an inactivated, or non-infectious, form of the coronavirus that can no longer cause disease but can still provoke an immune response. This vaccine requires two doses that are administered 14 days apart. Results posted online in September but not yet peer reviewed show that the vaccine produced antibodies in monkeys. Bharat Biotech Executive Director Sai Prasad also told Reuters in October that preliminary results from early vaccine trials found more than 90 percent of human participants developed antibodies.

Status: On October 23, Bharat Biotech announced it has received approval to start phase three trials in 26,000 participants at more than 25 centers across India.

Novavax

Name: NVX-CoV2373

Who: A biotechnology company based in Gaithersburg, Maryland.

What: Novavax has bioengineered the coronavirus's spike proteins, the parts that help the virus invade cells but cannot replicate or cause COVID-19. Its vaccine candidate combines those proteins into a knucklebone-shaped nanoparticle. This can be injected along with its proprietary Matrix-M adjuvant—a compound that stimulates immune cells—to elicit an immune response. The vaccine is administered in two doses, 21 days apart. On September 2, a study of the company's phase one trial published in the New England Journal of Medicine found that the vaccine was safe and produced coronavirus antibodies at a higher level than is seen among those who have recovered from COVID-19. It also stimulated T cells, another arm of the human immune response.

Status: On September 24, Novavax announced the launch of its phase three trial in the United Kingdom, which will evaluate the vaccine in up to 10,000 people, both with and without underlying conditions. Up to 400 participants will also be vaccinated against the seasonal flu as part of a sub-study that will help determine whether it is safe to give patients both vaccines at the same time.

Johnson & Johnson

Name: JNJ-78436735

Who: One of the world's largest multinational corporations, based in New Jersey, that specializes in healthcare and pharmaceutical products.

What: Johnson & Johnson is developing an adenovector vaccine, which introduces a piece of DNA from SARS-CoV-2 into the common cold-causing adenovirus that has been genetically changed so that it can't replicate in the body. This vaccine builds on the technology Johnson & Johnson used to develop an Ebola vaccine as well as vaccine candidates for Zika and HIV. In July, a study published in Nature showed that the vaccine elicited neutralizing antibodies in monkeys and provided "complete or near-complete" protection with just one dose.

Status: On September 23, Johnson & Johnson announced the launch of a phase three ENSEMBLE trial to evaluate the safety of the vaccine—and how well it works—among up to 60,000 adults from a variety of countries. The trial will include "significant representation" from older populations and those with underlying conditions that make them more susceptible to COVID-19. On October 12, Johnson & Johnson announced that it has paused these trials for an independent safety review due to an unexplained illness in a participant. The company didn't provide any details, in part to protect the patient's privacy, but said that illnesses and accidents are expected in large clinical studies. What's more, study pauses are routine for clinical trials and aren't typically reported. On October 23, the company announced it will resume trials.

Moderna Therapeutics

Name: mRNA-1273

Who: A Massachusetts-based biotech company, in collaboration with the National Institutes of Health.

What: This vaccine candidate also relies on injecting snippets of mRNA into human cells to trigger an immune response. This vaccine requires two doses, four weeks apart. (*Here's how mRNA vaccines work.*)

Status: On July 27, Moderna announced it had started the third phase of its clinical trials, even as it continues to monitor phase two results. Preliminary findings from phase one have shown that healthy subjects—including elderly patients—produced coronavirus antibodies and a reaction from T cells. Phase three will test the vaccine in 30,000 U.S. participants; Moderna says it is on track to deliver at least 500 million doses per year beginning in 2021, thanks in part to the deal it has struck with Swiss manufacturer Lonza that will allow it to manufacture up to one billion doses a year. In September, however, Moderna's chief executive Stéphane Bancel told the New York Times that it was unlikely the vaccine would be widely available in the first half of 2021.

University of Oxford

Name: ChAdOx1 nCoV-19

Who: The U.K. university, in collaboration with the biopharmaceutical company AstraZeneca.

What: Oxford's candidate is what's known as a viral vector vaccine, essentially a "Trojan horse" presented to the immune system. Oxford's research team has transferred the SARS-CoV-2 spike protein—which helps the coronavirus invade cells—into a weakened version of an adenovirus, which typically causes the common cold. When this adenovirus is injected into humans, the hope is that the spike protein will trigger an immune response. AstraZeneca and Oxford plan to produce a billion doses of vaccine that they've agreed to sell at cost.

Status: Preliminary results from this candidate's first two clinical trial phases revealed that the vaccine had triggered a strong immune response—including increased antibodies and responses from T-cells—with only minor side effects such as fatigue and headache. It is in phase three of clinical trials, aiming to recruit up to 50,000 volunteers in Brazil, the United Kingdom, the United States, and South Africa. On September 8, AstraZeneca paused the trials for a safety review due to an adverse reaction in one participant in the U.K. The details remain unclear, though the company has described the pause as a "routine action." After an investigation by independent regulators, the trials resumed in the U.K., Brazil, South Africa, and India in September and resumed in the U.S. a month later.

Sinovac

Name: CoronaVac

Who: A Chinese biopharmaceutical company, in collaboration with Brazilian research center Butantan.

What: CoronaVac is an inactivated vaccine that uses a non-infectious version of the coronavirus to provoke an immune response.

Status: On July 3, Brazil's regulatory agency granted this vaccine candidate approval to move ahead to phase three, as it continues to monitor the results of the phase two clinical trials. Preliminary results in macaque monkeys, published in Science, revealed that the vaccine produced antibodies that neutralized 10 strains of SARS-CoV-2. Sinovac has also released preprint results of its phase two human trial that likewise showed the vaccine produced antibodies with no severe adverse reactions. Phase three will recruit nearly 9,000 healthcare professionals in Brazil. Sinovac will also conduct phase three trials in Indonesia and Bangladesh.

Sinopharm

Name: None

Who: China's state-run pharmaceutical company, in collaboration with the Wuhan Institute of Biological Products.

What: Sinopharm is also using an inactivated SARS-CoV-2 vaccine that it hopes will reach the public by the end of 2020. Preliminary findings from two randomized trials, published in JAMA, have shown the vaccine can trigger an antibody response with no serious adverse effects. The study did not measure T cell-mediated immune responses. These results are significant, though, as they are the first published data from human clinical trials for a COVID-19 vaccine that uses a whole, inactivated virus.

Status: On September 29, the *New Yorker* reported that Sinopharm is filing its application to China's regulatory commission for approval of the vaccine, which could arrive sometime in October. The story also notes that hundreds of thousands of Chinese civilians have already been vaccinated under the government's emergency-use approval. China began to inoculate medical workers and other high-risk groups with the Sinopharm trial vaccines in July, making it the first experimental vaccine available to civilians beyond clinical volunteers. Also in July, Sinopharm launched its first phase three trial among 15,000 volunteers—aged 18 to 60, with no serious underlying conditions—in the United Arab Emirates. The company selected the UAE because it has

a diverse population made up of approximately 200 nationalities, making it an ideal testing ground. Sinopharm will also undertake phase three trials in locations such as Peru and Bahrain.

Murdoch Children's Research Institute

Name: Bacillus Calmette-Guerin BRACE trial

Who: The largest child health research institute in Australia, in collaboration with the University of Melbourne.

What: For nearly a hundred years, the Bacillus Calmette-Guerin (BCG) vaccine has been used to prevent tuberculosis by exposing patients to a small dose of live bacteria. Evidence has emerged over the years that this vaccine may boost the immune system and help the body fight off other diseases as well. Researchers are investigating whether these benefits may also extend to SARS-CoV-2, and this trial has reached phase three in Australia. Though as of April 12, the World Health Organization says there is no evidence that the BCG vaccine protects people against infection with the coronavirus.

Status: In April, researchers from the Murdoch Children's Research Institute began a series of randomized controlled trials that will test whether BCG might work on the coronavirus as well. They aim to recruit 10,000 healthcare workers in the study.

CanSino Biologics

Name: Ad5-nCoV

Who: A Chinese biopharmaceutical company.

What: CanSino has also developed a viral vector vaccine, using a weakened version of the adenovirus as a vehicle for introducing the SARS-CoV-2 spike protein to the body. Preliminary results from phase two trials, published in *The Lancet*, have shown that the vaccine produces "significant immune responses in the majority of recipients after a single immunisation." There were no serious adverse reactions documented.

Status: Though the company was still technically in phase two of its trial, on June 25, CanSino became the first company to receive limited approval to use its vaccine in people. The Chinese government has approved the vaccine for military use only, for a period of one year. On August 15, Russian biopharmaceutical company Petrovax announced it had launched the first phase three clinical trial of Ad5-nCoV.

The Gamaleya National Center of Epidemiology and Microbiology

Name: Sputnik V

Who: A Russian research institution, in partnership with the state-run Russian Direct Investment Fund.

What: Gamaleya has developed a viral vector vaccine that also uses a weakened version of the common cold-causing adenovirus to introduce the SARS-CoV-2 spike protein to the body. This vaccine uses two strains of adenovirus, and it requires a second injection after 21 days to boost the immune response. Russia has not published any data from its clinical trials, but officials with the institute state that they have completed phases one and two. The researchers also claim the vaccine produced strong antibody and cellular immune responses.

Status: Despite the lack of published evidence, Russia has cleared the Sputnik V vaccine for widespread use and claimed it as the first registered COVID-19 vaccine on the market. Russia reports that it will start phase three clinical trials on August 12; the World Health Organization, however, lists the Sputnik V vaccine as being in phase one of clinical trials.

Editor's note: This story was originally published on July 31. It is regularly updated as developments occur.

9

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