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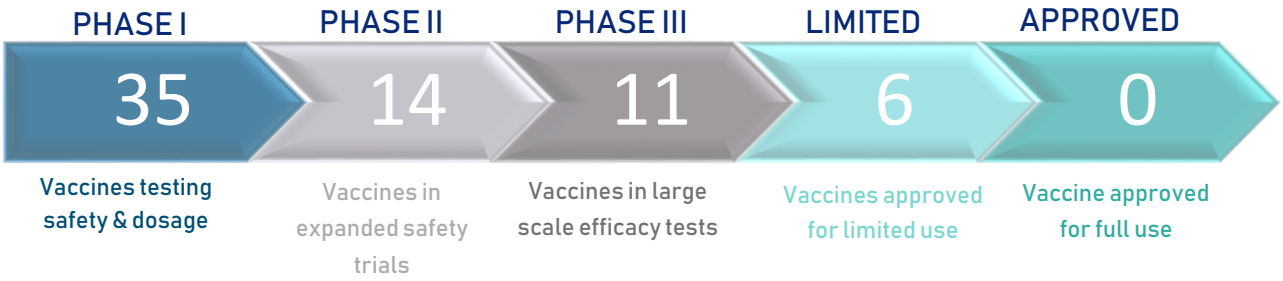
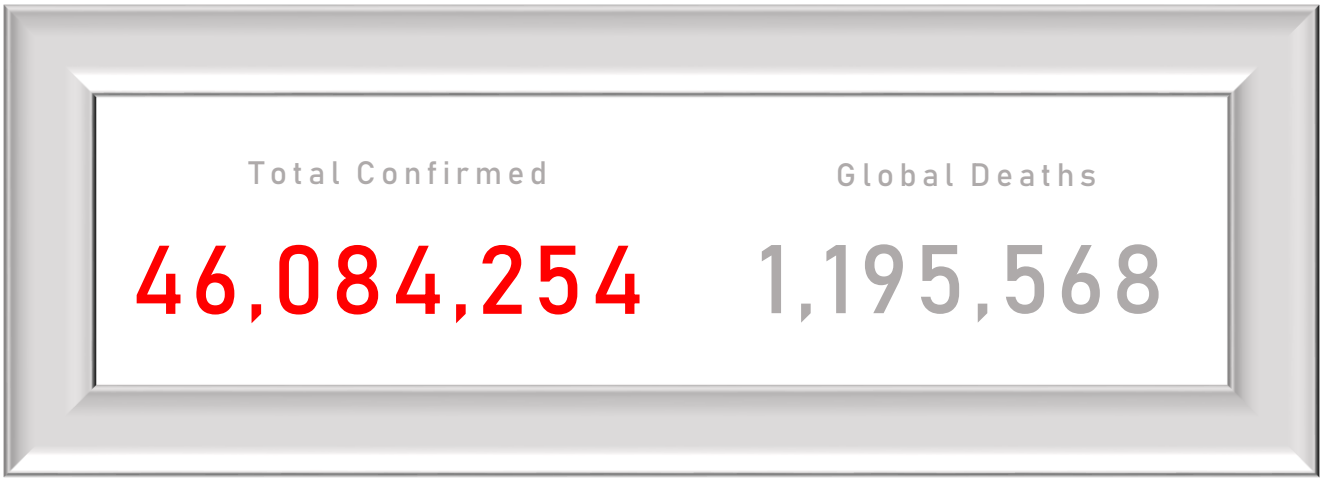
COVID 19 VACCINES | TREATMENTS

Report November 2020

COVID-19 VACCINES IN DIFFERENT PHASES



COVID-19 | GLOBAL CASE REPORT



Vaccines typically require years of research and testing before reaching the clinic, but scientists are racing to produce a safe and effective coronavirus vaccine by next year. Researchers are testing 49 vaccines in clinical trials on humans, and at least 88 preclinical vaccines are under active investigation in animals.

Work began in January with the deciphering of the SARS-CoV-2 genome. The first vaccine safety trials in humans started in March, and now 10 have reached the final stages of testing. Some trials will fail, and others may end without a clear result. But a few may succeed in stimulating the immune system to produce effective antibodies against the virus.

While these vaccines may potentially prevent infection, they cannot cure the disease.

Here is the status of leading vaccines that have reached Phase II and III

LEADING CANDIDATES

FARTHEST ALONG*	CLINICAL PHASE
Univ. of Oxford/AstraZeneca	III
Sinovac/Instituto Butantan	III
Wuhan Inst./Sinopharm	III
Moderna	III
CanSino Biologics	III
Janssen Pharma	III
Bharat Biotech	III
Novavax	III
BioNtech/Fosun/Pfizer	II/ III

**Ranked by entry into latest phase of development. Clinical phases move when it is publicly reported that the product has been dosed in a trial.*

PHASE III

AstraZeneca The British-Swedish company AstraZeneca and the University of Oxford developed a vaccine based on a chimpanzee adenovirus called ChAdOx1. In May, the United States awarded the project $1.2 billion in support for 300 million doses should the vaccine prove effective. A study on monkeys found that the vaccine protected the animals from the disease. In a Phase 1/2 trial, the vaccine developers did not detect any severe side effects. They found that the vaccine raised antibodies against the coronavirus as well as other immune defenses. The vaccine began Phase 2/3 trials in England and India (where it's known as Covishield). In addition, AstraZeneca launched Phase 3 trials in Brazil, South Africa, and the United States. In August the European Union reached an agreement for AstraZeneca to deliver 400 million doses if the trials yield positive results. The company has said their total manufacturing

capacity for the vaccine, if approved, stands at two billion doses. India's Serum Institute has already produced millions of doses to be used in trials. On Sept. 6, AstraZeneca halted global trials of the vaccine to investigate one volunteer, who developed a form of inflammation called transverse myelitis. Within a week, the trials began in all countries except the United States. Meanwhile, a newspaper in Brazil reported on Oct. 21 that a volunteer in the trial there died of Covid-19. While AstraZeneca would not comment on the case, the trial was not paused, which led outside experts to conclude that the volunteer must have received a placebo. On October 23, the F.D.A. authorized the restart of the trial.

PHASE III APPROVED FOR LIMITED

sinovac

The private Chinese company Sinovac Biotech is testing an inactivated vaccine called CoronaVac. In June the company announced that Phase 1/2 trials on 743 volunteers found no severe adverse effects and produced an immune response. Sinovac then launched a Phase 3 trial in Brazil in July, followed by others in Indonesia and Turkey. On Sept. 16, they registered a Phase 1/2 trial of the vaccine for children. While Sinovac has yet to release late-stage trial data, on Oct. 19 officials in Brazil said that it was the safest of five vaccines they were testing in Phase 3 trials.

Reuters reported that the Chinese government gave the Sinovac vaccine an emergency approval for limited use in July. In October, authorities in the eastern Chinese city of Jiaxing announced they were giving CoronVac to people in relatively high-risk jobs, including medical workers, port inspectors and public service personnel. Meanwhile, Sinovac has been preparing to manufacture the vaccine for global distribution, reaching an agreement to supply Indonesia with at least 40 million doses by March 2021. In September, Yin Weidong, the CEO of Sinovac, said the company planned on worldwide distribution of the vaccine in early 2021 — including the United States.

PHASE III

SINOPHARM

武汉生物制品研究所有限责任公司
WUHAN INSTITUTE OF BIOLOGICAL PRODUCTS CO.,LTD.

The Wuhan Institute of Biological Products developed an inactivated virus vaccine, which the state-owned Chinese company Sinopharm put into clinical tests. The Phase 1/2 trial showed that the vaccine produced antibodies in volunteers, some of whom experienced fevers and other side effects. They launched Phase 3 trials in the United Arab Emirates in July, and in Peru and Morocco the following month. Over the summer, the company later

said, the government gave it approval to inject hundreds of thousands of people with its two experimental vaccines. On Sept. 14, the U.A.E. gave emergency approval for Sinopharm's vaccine to use on health care workers.

PHASE III

moderna NIH National Institutes of Health *Turning Discovery Into Health*

Moderna develops vaccines based on messenger RNA (mRNA) to produce viral proteins in the body. They have yet to bring one to the market. In January, they began developing a vaccine for the coronavirus and since then the government has bankrolled Moderna's efforts, providing nearly $1 billion in support. In partnership with National Institutes of Health, they found that the vaccine protects monkeys from the coronavirus. In March, the company put the first Covid-19 vaccine into human trials, which yielded promising results. The vaccine has progressed into Phase 3 testing, which began on July 27. In October, the company announced that they had finished recruiting all 30,000 participants in the study, including 7,000 people 65 years or older. Moderna's trial protocol, which the company shared in September, indicates they will wait until a significant number of volunteers become sick before seeing how many of them were vaccinated. They also observe whether any participants suffer adverse events, investigating any serious cases to see if the vaccine was the cause or just a coincidence. If their results meet the FDA's benchmarks, Moderna could potentially apply for an emergency use authorization by the end of 2020.

On the business side, Moderna lost a patent dispute in July over some of their vaccine technology. The following month, the company stated that it could not be certain it was the first to make the inventions claimed in their patents, including its coronavirus vaccine. Meanwhile, the company has entered deals with several countries to supply the vaccine if it's approved. On Aug. 11, the United States government awarded the company an additional $1.5 billion in exchange for 100 million doses if the vaccine proves safe and effective. Moderna has made similar deals with Canada, Japan, and Qatar.

PHASE III APPROVED FOR LIMITED

CanSinoBIO

The Chinese company CanSino Biologics developed a vaccine based on an adenovirus called Ad5, in partnership with the Institute of Biology at the country's Academy of Military Medical Sciences. In May, they published promising results from a Phase 1 safety trial, and in July they reported that their Phase 2 trials demonstrated the vaccine

produced a strong immune response. In an unprecedented move, the Chinese military approved the vaccine on June 25 for a year as a "specially needed drug." CanSino would not say whether vaccination would be mandatory or optional for soldiers. Starting in August, CanSino began running Phase 3 trials in a number of countries, including Saudi Arabia, Pakistan and Russia.

PHASE III

A decade ago, researchers at Beth Israel Deaconess Medical Center in Boston developed a method for making vaccines out of a virus called Adenovirus 26, or Ad26 for short. Johnson & Johnson developed vaccines for Ebola and other diseases with Ad26 and have now made one for the coronavirus. In March they received $456 million from the United States government to support their move towards production. The vaccine has provided protection in experiments on monkeys. Johnson & Johnson began Phase 1/2 trials in July and launched a Phase 3 trial with up to 60,000 participants in September. Unlike other vaccines in Phase 3 trials, theirs only requires one dose instead of two. In August, the federal government agreed to pay $1 billion for 100 million doses if the vaccine is approved. The European Union reached a similar deal on Oct. 8 for 200 million doses. The company is aiming for production of at least a billion doses in 2021. On Oct. 12, Johnson & Johnson announced it put its trial on pause to investigate an adverse reaction in a volunteer. The trial resumed eleven days later. Despite the delay, the company expects to get results by the end of the year.

PHASE III

In collaboration with the Indian Council of Medical Research and the National Institute of Virology, the Indian company Bharat Biotech designed a vaccine called Covaxin based on an inactivated form of the coronavirus. Studies on monkeys and hamsters found that it provided protection against infection. When the company launched clinical trials in July, reports circulated that the vaccine would be ready by Aug. 15. But the C.E.O. of Bharat told reporters it would be available no sooner than early 2021. On Oct. 23, the company announced they were initiating a Phase 3 trial.

PHASE III

Maryland-based Novavax makes vaccines by sticking proteins onto microscopic particles. They've taken on a number of different diseases this way; their flu vaccine finished Phase 3 trials in March. The

company launched trials for a Covid-19 vaccine in May, and the Coalition for Epidemic Preparedness Innovations has invested $384 million in the vaccine. In July the U.S. government awarded $1.6 billion to support the vaccine's clinical trials and manufacturing.

After getting promising results from preliminary studies in monkeys and humans, Novavax launched a Phase 2 trial in South Africa in August. The blinded, placebo-controlled trial on 2,900 people will measure not just the safety of the vaccine but its efficacy. The following month, Novavax launched a Phase 3 trial enrolling up to 15,000 volunteers in the United Kingdom. It could potentially deliver results by the start of 2021. A larger Phase 3 trial is in development to launch in the United States by the end of November.

If the trials succeed, Novavax expects to deliver 100 million doses for use in the United States by the first quarter of 2021. In September Novavax reached an agreement with the Serum Institute of India, a major vaccine manufacturer, that they said would enable them to produce as many as 2 billion doses a year.

PHASE II / III

BIONTECH Pfizer FOSUN PHARMA

The German company BioNTech entered into collaborations with Pfizer, based in New York, and the Chinese drug maker Fosun Pharma to develop an mRNA vaccine to be given in two doses. In May they launched a Phase 1/2 trial on two versions of the vaccine. They found that both versions caused volunteers to produce antibodies against SARS-CoV-2, as well as immune cells called T cells that respond to the virus. They found that one version, called BNT162b2, produced significantly fewer side effects, such as fevers and fatigue, and so they chose it to move into Phase 2/3 trials. On July 27, the companies announced the launch of a Phase 2/3 trial with 30,000 volunteers in the United States and other countries including Argentina, Brazil, and Germany. In an interim study, the companies reported that after getting the first dose, volunteers experience mostly mild to moderate side effects. On Sept. 12, Pfizer and BioNTech announced that they would seek to expand their U.S. trial to 43,000 participants. The following month, they gained permission to start testing the vaccine on children as young as 12 — the first American trial to do so.

In September, Dr. Albert Bourla, the chief executive of Pfizer, said the Phase 3 trial would deliver enough results as soon as October to show if the vaccine worked or not. President Trump touted their progress, hinting that a vaccine would be available before the election. But on Oct. 27, Dr. Bourla announced that the

volunteers in the trial had yet to experience enough cases of Covid-19 to determine if the vaccines work. Pfizer and BioNTech's vaccine, like almost all the others in clinical trials, requires two doses. In the summer, the companies began inking deals to deliver large orders to countries around the world. The Trump administration awarded a $1.9 billion contract in July for 100 million doses to be delivered by December and the option to acquire 500 million more doses. Meanwhile, Japan made a deal for 120 million doses, and the European Union arranged to purchase 200 million doses. If their vaccine is authorized, Pfizer and BioNTech expect to manufacture over 1.3 billion doses of their vaccine worldwide by the end of 2021.

Getting the vaccine from the factory to people's arms could pose some major challenges. Like Moderna's vaccine, Pfizer and BioNTech's preparation is based on mRNA, which falls apart unless it's kept in a deep freeze. As a result, the vaccine will have to be chilled to minus 80 degrees Celsius (minus 112 degrees Fahrenheit) until it's ready to be injected.

COVID-19 DRUG AND TREATMENT

The Covid-19 pandemic is one of the greatest challenges modern medicine has ever faced. Doctors and scientists are scrambling to find treatments and drugs that can save the lives of infected people and perhaps even prevent them from getting sick in the first place.

There is no cure yet for Covid-19. Only one treatment, a drug called remdesivir, has been approved by the F.D.A. for the disease, and research suggests it may provide only a modest benefit to patients. The F.D.A. has granted emergency use authorization to some other treatments, but their effectiveness against Covid-19 has yet to be demonstrated in large-scale, randomized clinical trials. Scientists are also studying a wide range of other potential treatments, but most are still in early stages of research.

WHAT THE LABELS MEAN

WIDELY USED: These treatments have been used widely by doctors and nurses to treat patients hospitalized for diseases that affect the respiratory system, including Covid-19.

PROMISING EVIDENCE: Early evidence from studies on patients suggests effectiveness, but more research is needed. This category includes treatments that have shown improvements in morbidity, mortality and recovery in at least one randomized controlled trial, in which some people get a treatment and others get a placebo.

TENTATIVE OR MIXED EVIDENCE: Some treatments show promising results in cells or animals, which need to be confirmed in people. Others have yielded encouraging results in retrospective studies in humans, which look at existing datasets rather than starting a new trial. Some treatments have produced different results in different experiments, raising the need for larger, more rigorously designed studies to clear up the confusion.

BLOCKING THE VIRUS

Antivirals can stop viruses such as H.I.V. and hepatitis C from hijacking our cells. Scientists are searching for antivirals that work against the new coronavirus.

PROMISING EVIDENCE F.D.A. APPROVED
EVIDENCE IN CELLS, ANIMALS & HUMANS

Remdesivir | Remdesivir, made by Gilead Sciences under the brand Velkury, is the first drug to gain approval from the F.D.A. for the treatment of Covid-19. It works by interfering with the creation of new viruses, inserting itself into new viral genes. Remdesivir was originally tested as an antiviral against Ebola and Hepatitis C, only to deliver lackluster results. But a randomized controlled trial published in May concluded the drug reduced the recovery time of people hospitalized with Covid-19 from 15 to 11 days. (The study defined recovery as “either discharge from the hospital or hospitalization for infection-control purposes only.”) The trial did not show any effect on mortality.

The F.D.A. responded to this data in May by issuing an emergency authorization for remdesivir's use in critically ill patients who need supplemental oxygen. In August, they expanded that approval after researchers found that patients with less severe forms of Covid-19 seemed to benefit modestly from a five-day treatment course of remdesivir. The revised approval allows the use of the drug on all patients hospitalized with Covid-19, regardless of how severe their disease is. The move was criticized by some experts who said the F.D.A. had expanded remdesivir's use without strong evidence to back the change. On Oct. 3, doctors treating President Trump said he had begun a five-day course of intravenous remdesivir. On Oct. 22, the F.D.A. gave full approval to the drug for use in patients 12 years and older.

Even with approval, it remains to be seen how useful remdesivir is as a treatment against Covid-19. In October, the World Health Organization released the results of the largest randomized clinical trial on remdesivir so far in a manuscript that has not yet been published in a peer-reviewed journal. When the researchers gave the drug to 2,750 patients hospitalized for Covid-19, they got disappointing results. Remdesivir showed no evidence of reducing mortality, keeping patients off ventilators, or shortening their stay in the hospital. While some experts were critical of how the study was designed, most agreed that remdesivir might perform best in patients who are earlier in their disease course.

On Oct. 28, Gilead Sciences said that remdesivir has brought in $873 million in revenues so far this year.

TENTATIVE OR MIXED EVIDENCE EVIDENCE IN HUMANS

Favipiravir | Originally designed to beat back influenza, favipiravir blocks a virus's ability to copy its genetic material. A small study in March indicated the drug might help purge the coronavirus from the airway. Larger, randomized trials are now underway.

Putting Out Friendly Fire

The most severe symptoms of Covid-19 are the result of the immune system's overreaction to the virus. Scientists are testing drugs that can rein in its attack.

PROMISING EVIDENCE EVIDENCE IN HUMANS

Dexamethasone and Other Corticosteroids | Corticosteroids — often called steroids for short — are used to tamp down inflammation and for conditions such as allergies and asthma. In the 1960s, doctors began using them as a treatment for pneumonia and other severe respiratory illnesses, but the results of clinical trials were inconclusive. The Covid-19 pandemic brought a new interest in these drugs, and a raft of new clinical trials were launched.

In June, a steroid called dexamethasone was the first shown to reduce Covid-19 deaths. A study of more than 6,000 people found that dexamethasone reduced deaths by one-third in patients on ventilators, and by one-fifth in patients on oxygen. It may be less likely to help — and may even harm — patients who are at an earlier stage of Covid-19 infections, however. In its Covid-19 treatment guidelines, the National Institutes of Health recommends only using dexamethasone in patients with Covid-19 who are on a ventilator or are receiving supplemental oxygen.

In September, researchers reviewed the results of trials on dexamethasone, along with two other steroids, hydrocortisone and methylprednisolone. Overall, they concluded, steroids were linked with a one-third reduction in deaths among Covid-19 patients.

On Oct. 4, President Trump's doctor announced he was receiving dexamethasone to treat his Covid-19, despite his upbeat assessment of the president's health.

TENTATIVE OR MIXED EVIDENCE EVIDENCE IN HUMANS

Cytokine Inhibitors | The body produces signaling molecules called cytokines to fight off diseases. But manufactured in excess, cytokines can trigger the immune system to wildly overreact to infections, in a process sometimes called a cytokine storm. Researchers have created a number of drugs to halt cytokine storms, and they have proven effective against arthritis and other inflammatory disorders. Some turn off the supply of molecules that launch the production of the cytokines themselves. Others block the receptors on immune cells to which cytokines would normally bind. A few block the cellular messages they send. Depending on how the drugs are formulated, they can block one cytokine at a time, or muffle signals from several at once. Researchers are now trying out a number of different cytokine inhibitors against Covid-19 in clinical trials. So far, the results are mixed. In some trials, the drug tocilizumab has shown some evidence of reducing deaths, but has failed to help in others. A similar drug, sarilumab, did not appear to benefit patients

in Phase 3 clinical trials. Another drug, baricitinib, which can affect many types of cytokines at once, has shown some promise when doctors used it in combination with the antiviral drug remdesivir.

Other Treatments

Doctors and nurses often administer other supportive treatments to help patients with Covid-19.

WIDELY USED

Prone positioning | The simple act of flipping Covid-19 patients onto their bellies opens up the lungs. The maneuver has become commonplace in hospitals around the world since the start of the pandemic. It might help some individuals avoid the need for ventilators entirely. The treatment's benefits continue to be tested in a range of clinical trials.

WIDELY USED EMERGENCY USE AUTHORIZATION

Ventilators and other respiratory support devices | Devices that help people breathe are an essential tool in the fight against deadly respiratory illnesses. Some patients do well if they get an extra supply of oxygen through the nose or via a mask connected to an oxygen machine. Patients in severe respiratory distress may need to have a ventilator breathe for them until their lungs heal. Doctors are divided about how long to treat patients with non-invasive oxygen before deciding whether or not they need a ventilator. Not all Covid-19 patients who go on ventilators survive, but the devices are thought to be lifesaving in many cases.

TENTATIVE OR MIXED EVIDENCE EVIDENCE IN HUMANS

Anticoagulants | The coronavirus can invade cells in the lining of blood vessels, leading to tiny clots that can cause strokes and other serious harm. Anticoagulants are commonly used for other conditions, such as heart disease, to slow the formation of clots. Doctors sometimes use them on patients with Covid-19 who have clots, but there's no clear evidence of what benefits and risks they offer to people with the disease. On Sept. 10, the National Institutes of Health announced three large randomized clinical trials to evaluate anticoagulants on people with Covid-19 who have not yet been hospitalized, people who are being treated in hospitals, and people who have been sent back home.

TENTATIVE OR MIXED EVIDENCE EVIDENCE IN HUMANS

Vitamin and mineral supplements | Our bodies need vitamins and minerals to work properly. Some researchers are investigating whether supplements might help against Covid-19, but there's no strong evidence yet that they prevent infections or speed up recovery from them.

Vitamin C is known to tamp down inflammation, and so some researchers are investigating whether it can help with the immune system's overreaction to Covid-19 in several clinical trials. But no convincing data showing a benefit has emerged yet. It's also important to bear in mind that it's possible to ingest too much vitamin C, causing symptoms including diarrhea and nausea.

Vitamin D has also attracted attention. Along with promoting good bone health, it may play some roles in helping immune cells function. Some studies have found an association between low levels of vitamin D and higher rates of Covid-19. But such studies cannot establish that this deficiency was the cause of those disease rates. It may be that populations who suffer high rates of vitamin D deficiency are getting hit harder by the coronavirus for other reasons, including poorer access to health care or underlying conditions like obesity. Some clinical trials are underway to test whether vitamin D can help Covid-19 patients. In an Oct. 2 statement about President Trump's treatments for Covid-19, his doctor announced he was taking Vitamin D.

In that same announcement, Trump's doctor also said he was taking zinc. This mineral helps proteins throughout the body function, and people with zinc deficiencies are at higher risk of getting sick with infectious diseases. A 2010 study on the coronavirus that causes SARS found that zinc can put the brakes on the replication of the virus in cultures of cells. Small clinical trials are now underway to see if zinc can provide any benefit to people with Covid-19 or even prevent it. As of yet, however, there is no evidence that it does either. The NIH Covid-19 guidelines recommend against zinc to prevent of COVID-19, except in a clinical trial.

SOURCE AND REFERENCE

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