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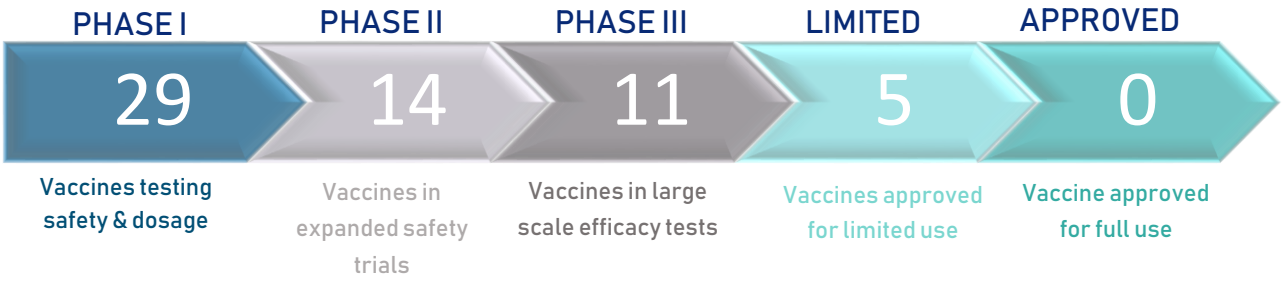
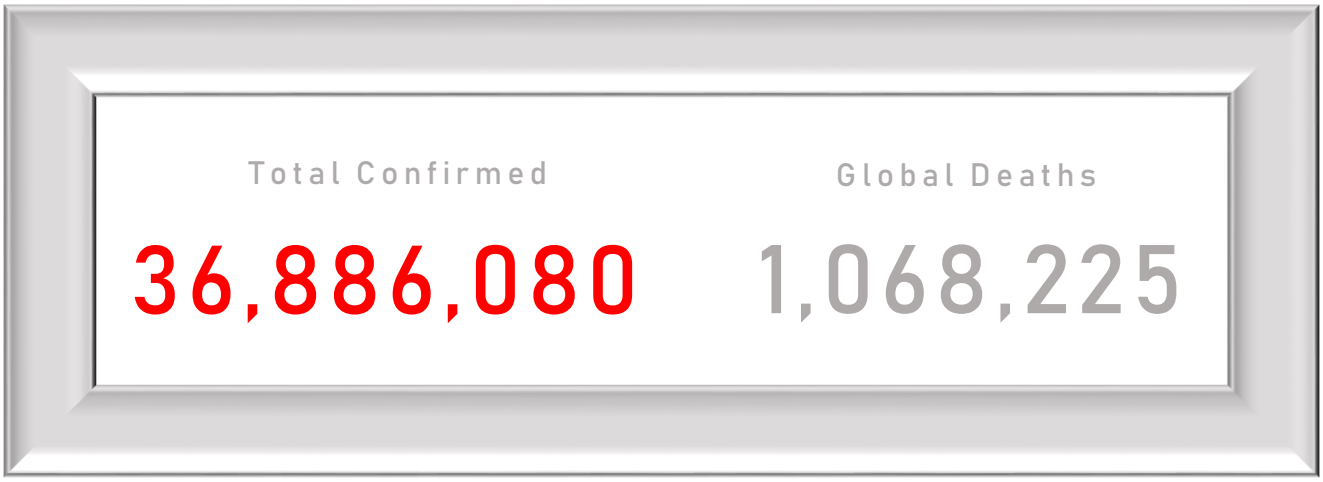
COVID 19 VACCINES | TREATMENTS

Report October 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 44 vaccines in clinical trials on humans, and at least 92 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, but the road ahead remains uncertain. 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.

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
Beijing Inst./Sinopharm	III
Moderna	III
CanSino Biologics	III
Janssen Pharma	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

A vaccine in development by the British-Swedish company AstraZeneca and the University of Oxford is based on a chimpanzee adenovirus called ChAdOx1. A study on monkeys found that the vaccine provided them protection. In May, the United States awarded the project $1.2 billion in support. In their 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, as well as 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 resuming. As of now, however, the United States is still keeping its trial on pause as the F.D.A. investigates.

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. Reuters reported that the Chinese government gave the Sinovac vaccine an emergency approval for limited use in July. Meanwhile, Sinovac has been preparing to manufacture the vaccine, 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

SINOPHARM Sinopharm also began testing a second inactivated virus vaccine, this one developed by the Beijing Institute of Biological Products. After running early clinical trials in China, they launched Phase 3 trials in the United Arab Emirates and Argentina. 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 before Sinopharm shared data indicating it was safe and effective.

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 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. The final trial is enrolling 30,000 healthy people at about 89 sites around the United States. On Aug. 11, the government awarded the company an additional $1.5 billion in exchange for 100 million doses if the vaccine proves safe and effective. Canada agreed in September to acquire 20 million doses. In July, Moderna lost a patent dispute 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. On Sept. 17, Moderna shared their protocol for determining if their vaccine was safe and effective. They planned to wait until a significant number of volunteers became sick with Covid-19 and then see how many had been vaccinated. It may take till the end of 2020 or early 2021 to reach the necessary numbers.

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

Johnson & Johnson

Beth Israel Lahey Health
Beth Israel Deaconess Medical Center

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. In August, the federal government agreed to pay $1 billion for 100 million doses if the vaccine is approved. The company is aiming for production of at least a billion doses in 2021.

PHASE III APPROVED FOR LIMITED

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РОССИЙСКОЙ ФЕДЕРАЦИИ

The Gamaleya Research Institute, part of Russia's Ministry of Health, launched clinical trials in June of a vaccine they called Gam-Covid-Vac. It is a combination of two adenoviruses, Ad5 and Ad26, both engineered with a coronavirus gene. On Aug. 11, President Vladimir V. Putin announced that a Russian health care regulator had approved the vaccine, renamed Sputnik V, before Phase 3 trials had even begun. Vaccine experts decried the move as risky, and Russia later walked back the announcement, saying that the approval was a "conditional registration certificate," which would depend on positive results from Phase 3 trials. Those trials, initially planned for just 2,000 volunteers, were expanded to 40,000. On Sept. 4, three weeks after Putin's announcement, Gamaleya researchers published the results of their Phase 1/2 trial. In a small study, they found that Sputnik yielded antibodies to the coronavirus and mild side effects. Meanwhile, Russia negotiated agreements to supply the vaccine to countries including Brazil, Mexico and India.

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.

In that same month, the Trump administration awarded a $1.9 billion contract 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. In September, the chief executive of Pfizer said they would know if the vaccine works as soon as October 2020. If approved, Pfizer has said they expect to manufacture over 1.3 billion doses of their vaccine worldwide by the end of 2021.

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. And even the most promising treatments to date only help certain groups of patients and await validation from further trials. The F.D.A. has not fully licensed any treatment specifically for the coronavirus. Although it has

granted emergency use authorization to some treatments, their effectiveness against Covid-19 has yet to be demonstrated in large-scale, randomized clinical trials.

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 EVIDENCE IN HUMANS

Remdesivir | Remdesivir, made by Gilead Sciences, was the first drug to get emergency authorization from the F.D.A. for use on Covid-19. It interferes with the creation of new viruses by 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, though retrospective data released in July hints that the drug might reduce death rates among those who are very ill.

The F.D.A. responded to this data in May by issuing an emergency authorization in May 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 is receiving a five-day course of intravenous remdesivir.

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. his cheap and widely available steroid blunts many types of immune responses. Doctors have long used it to treat allergies, asthma and inflammation. In June, it became the first drug shown to reduce Covid-19 deaths. That study of more than 6,000 people, which in July was published in the New England Journal of Medicine, 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.

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.

TENTATIVE OR MIXED EVIDENCE EVIDENCE IN HUMANS

Blood filtration systems | The F.D.A. has granted emergency use authorization to several devices that filter cytokines from the blood in an attempt to cool cytokine storms. One machine, called Cytosorb, can reportedly purify a patient's entire blood supply about 70 times in a 24-hour period. A small study in March suggested that Cytosorb had helped dozens of severely ill Covid-19 patients in Europe and China, but it was not a randomized clinical trial that could conclusively demonstrate it was effective. A number of studies on blood filtration systems are underway, but experts caution that these devices carry some risks. For example, such filters could remove beneficial components of blood as well, such as vitamins or medications. In September, a team of experts urged that blood filtration for Covid-19 be limited to randomized clinical trials.

TENTATIVE OR MIXED EVIDENCE EVIDENCE IN HUMANS

Stem cells | Certain kinds of stem cells can secrete anti-inflammatory molecules. Over the years, researchers have tried to use them as a treatment for cytokine storms, and now dozens of clinical trials are under way to see if they can help patients with Covid-19. But these stem cell treatments haven't worked well in the past, and it's not clear yet if they'll work against the coronavirus.

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.

SOURCE AND REFERENCE

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