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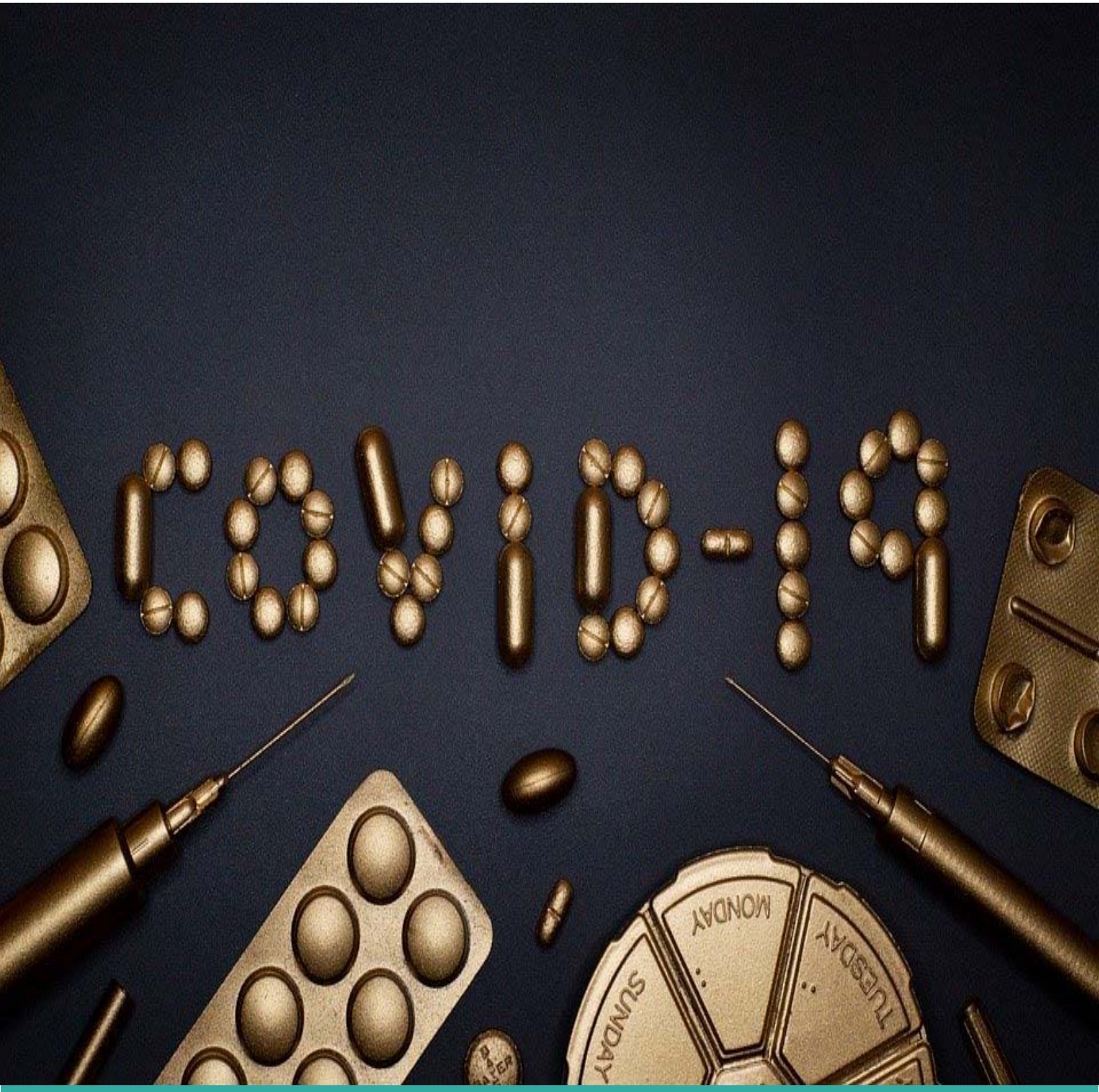
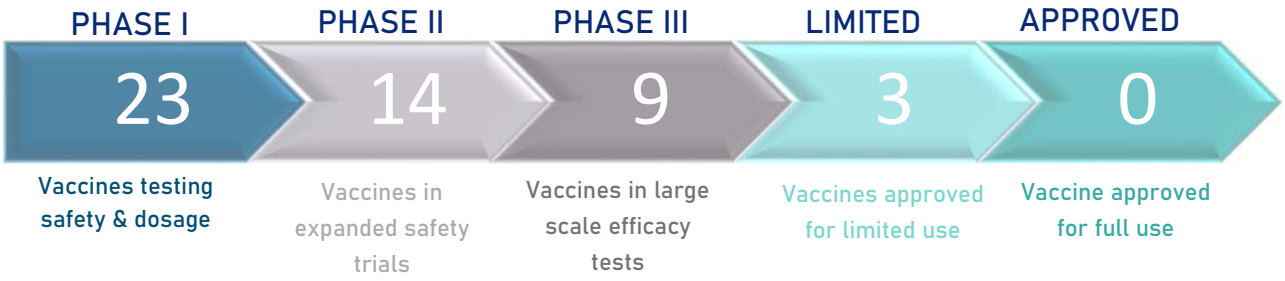


COVID 19 VACCINES | TREATMENTS

Report September 2020

COVID-19 VACCINES IN DIFFERENT PHASES



COVID-19 | GLOBAL CASE REPORT

Total Confirmed	Global Deaths
26,062,946	863,741

Researchers worldwide are working around the clock to find a vaccine against SARS-CoV-2, the virus causing the COVID-19 pandemic. Experts estimate that a fast-tracked vaccine development process could speed a successful candidate to market in approximately 12-18 months – if the process goes smoothly from conception to market availability.

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
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. Their Phase I/II trial reported that the vaccine was safe, causing no severe side effects. It raised antibodies against the coronavirus as well as other immune defenses. The vaccine is now in a Phase II/III trial in England, as well as Phase III 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. AstraZeneca has indicated they might be able to start delivering emergency vaccines as early as October, depending on the outcome of the studies. 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.

PHASE III APPROVED FOR LIMITED

The private Chinese company Sinovac Biotech is testing an inactivated vaccine called CoronaVac. In June the company announced that Phase I/II trials on 743 volunteers found no severe adverse effects and produced an immune response. Sinovac then launched a Phase III trial in Brazil in July and another in Indonesia the following month. 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.

PHASE III

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. Sinopharm's chairman said in August that the vaccine could potentially be ready for public use by the end of 2020. Sinopharm said that the Chinese government approved one of their two inactivated virus vaccines for emergency use in July, but it was not clear which one got the approval.

PHASE III

Sinopharm is also testing a second inactivated virus vaccine, this one developed by the *Beijing Institute of Biological Products*. In Phase 3 trials in the United Arab Emirates, 5,000 people are receiving the Wuhan Institute version, while another 5,000 are

receiving the Beijing Institute one. Sinopharm said that the Chinese government approved one of their two inactivated virus vaccines for emergency use in July, but it was not clear which one got the approval.

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. The government has bankrolled Moderna's efforts on a coronavirus vaccine with 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, After carrying out a Phase 2 study they launched a Phase 3 trial on July 27. The final trial will enroll 30,000 healthy people at about 89 sites around the United States. On August 11, the government awarded the company an additional $1.5 billion in exchange for 100 million doses if the vaccine proves safe and effective. 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.

PHASE III APPROVED FOR LIMITED

The Chinese company CanSinoBIO 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. On August 9, the Saudi

health ministry announced that CanSino Biologics would run a Phase 3 trial in Saudi Arabia, and later in the month they also started a trial in Pakistan.

PHASE III APPROVED FOR LIMITED

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РОССИЙСКОЙ ФЕДЕРАЦИИ

The Gamaleya Research Institute, part of Russia's Ministry of Health, launched a Phase 1 trial in June of a vaccine they called Gam-Covid-Vac Lyo. It is a combination of two adenoviruses, Ad5 and Ad26, both engineered with a coronavirus gene. In July, the chair of the upper house of Russia's Parliament said the country might start vaccine production by the end of the year. 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.

PHASE II / III

BIONTECH Pfizer FOSUN PHARMA

The German company BioNTech has entered into collaborations with Pfizer, based in New York, and the Chinese drug maker Fosun Pharma to develop their mRNA vaccine. In July, they posted preliminary results from their Phase I/II trials in the United States and Germany. They found that the volunteers produced antibodies against SARS-CoV-2, as well as immune cells called T cells that respond to the virus. Some volunteers experienced moderate side effects such as sleep disturbances and sore arms. On July 27, they announced the launch of a Phase II/III trial with 30,000 volunteers in the United States and other countries including Argentina, Brazil, and Germany.

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. If approved, Pfizer 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, but it has granted emergency use authorization to a few.

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

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 stops viruses from replicating 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 preliminary data from trials that began this spring suggested the drug can reduce 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.") These early results 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.

TENTATIVE OR MIXED EVIDENCE

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, but results from larger, well-designed clinical trials are still pending.

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

Dexamethasone | This 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

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.

Against the coronavirus, several of these drugs have offered modest help in some trials, but faltered in others. Drug companies Regeneron and Roche drug both recently announced that two drugs called sarilumab and tocilizumab, which both target the cytokine IL-6, did not appear to benefit patients in Phase 3 clinical

trials. Many other trials remain underway, several of which combine cytokine inhibitors with other treatments.

TENTATIVE OR MIXED EVIDENCE

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.

TENTATIVE OR MIXED EVIDENCE

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

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, and doctors sometimes use them on patients with Covid-19 who have clots. Many clinical trials teasing out this relationship are now underway. Some of these trials are looking at whether giving anticoagulants before any sign of clotting is beneficial.

SOURCE AND REFERENCE

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