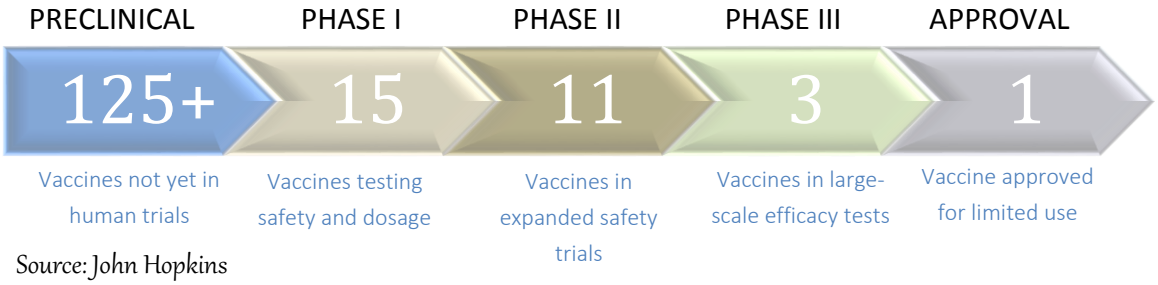
Vaccines and Treatments

July 5, 2020

COVID 19 - VACCINES IN DIFFERENT PHASES



Source: John Hopkins

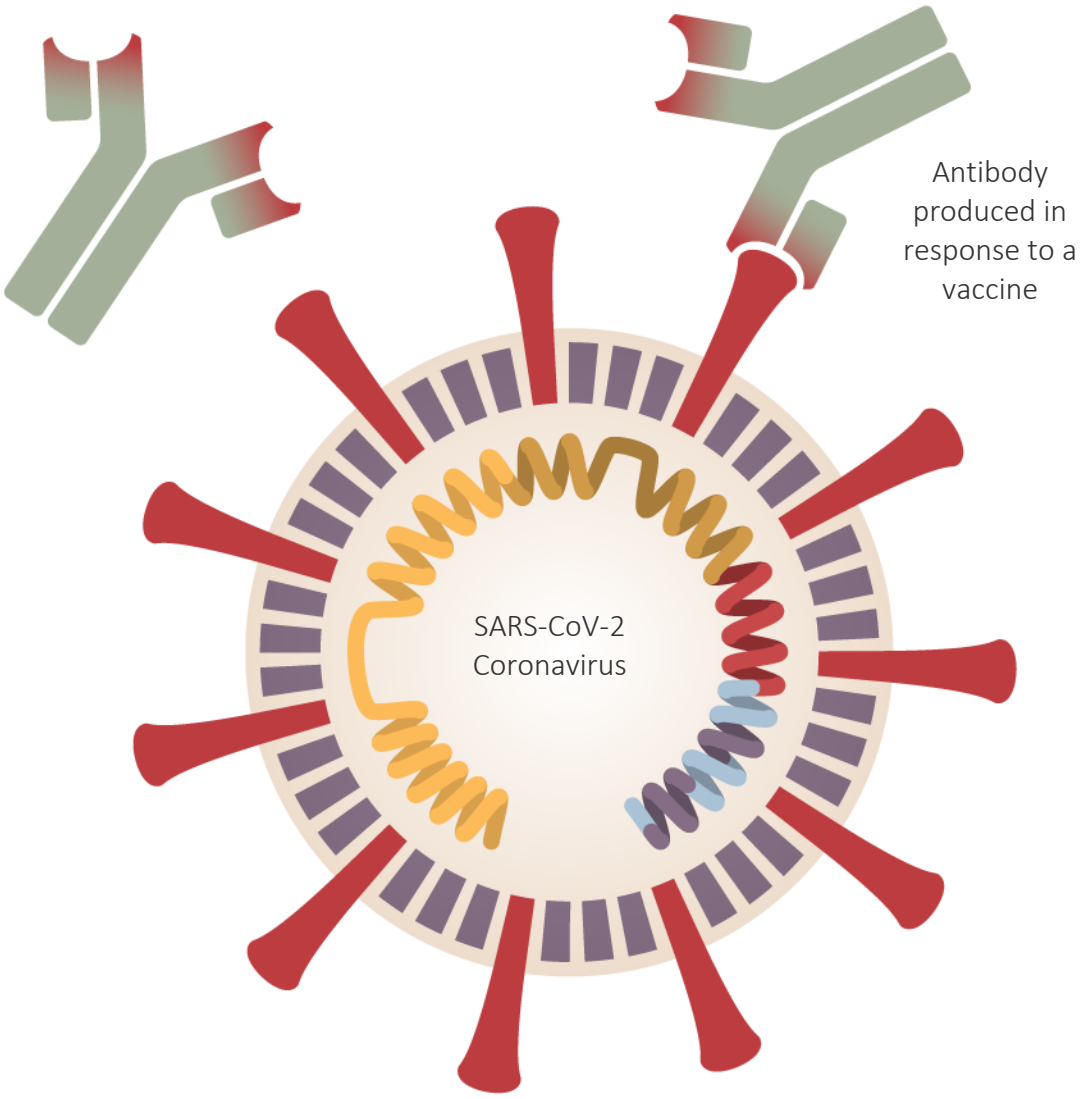
COVID 19 – GLOBAL CASE REPORT

Researchers around the world are developing more than 145 vaccines against the coronavirus, and 21 vaccines are in human trials. Vaccines typically require years of research and testing before reaching the clinic, but scientists are racing to produce a safe and effective vaccine by next year.

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 all the vaccines that have reached trials in humans, along with a selection of promising vaccines still being tested in cells or animals.

LEADING CANDIDATES	
FARTHEST ALONG*	CLINICAL PHASE
Wuhan Inst./Sinopharm	II / III
Univ. of Oxford/AstraZeneca	II / III
CanSino Biologics	II
Moderna	II
Inst. Of Medical Biology	II
Sinovac	II
Beijing Inst./Sinopharm	II
BioNtech/Fosun/Pfizer	I / II
Imperial College London	I / II
Novavax	I / II

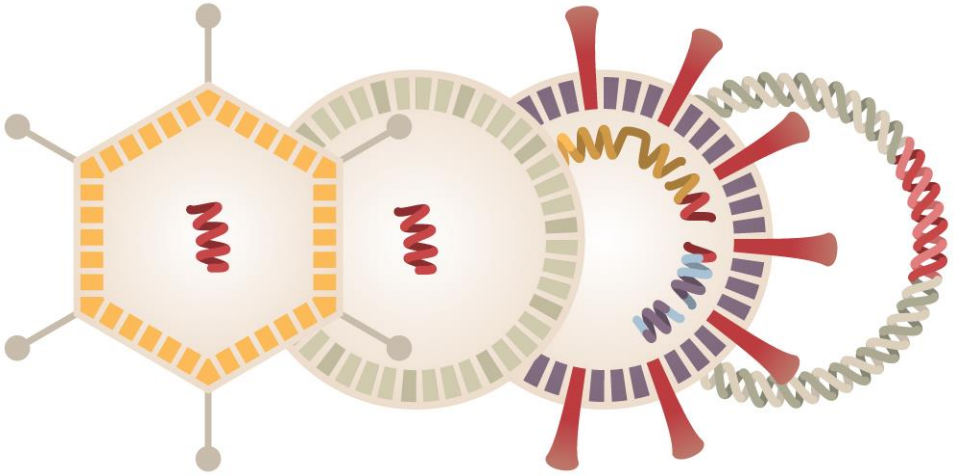


Indian vaccine-maker Zydus Cadila is approved for Phase I/II trials.

- **The Japanese company AnGes begins Phase I/II trials.**
- **The Indian company Bharat Biotech will begin Phase I/II trials.**
- **The Australian company Vaxine launched a Phase I trial.**
- **A vaccine by CanSino Biologics was approved for military use.**

THE VACCINE TESTING PROCESS

The development cycle of a vaccine, from lab to clinic



PRECLINICAL TESTING: Scientists give the vaccine to **animals** such as mice or monkeys to see if it produces an immune response.

PHASE I SAFETY TRIALS: Scientists give the vaccine to a **small number of people** to test safety and dosage as well as to confirm that it stimulates the immune system

PHASE II EXPANDED TRIALS: Scientists give the vaccine to a **small number of people** to test safety and dosage as well as to confirm that it stimulates the immune system.

PHASE III EFFICACY TRIALS: Scientists give the vaccine to **thousands of people** and wait to see how many become infected, compared with volunteers who received a placebo. These trials can determine if the vaccine protects against the coronavirus.

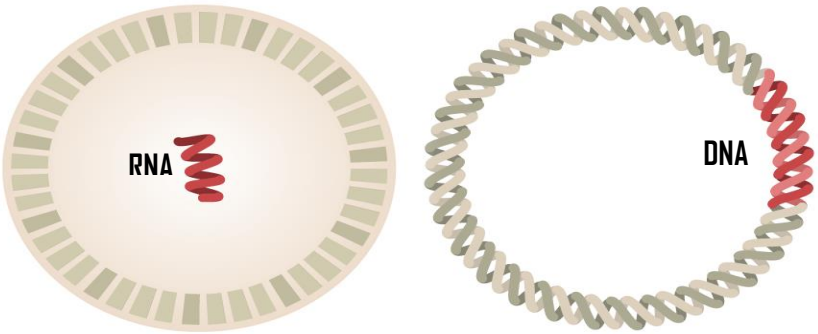
APPROVAL: Regulators in each country review the trial results and decide whether to approve the vaccine or not. During a pandemic, a vaccine may receive emergency use authorization before getting formal approval.

WARP SPEED: The U.S. government's Operation Warp Speedprogram is expected to name five or more vaccine projects to receive billions of dollars in federal funding before there's proof that the vaccines work. We will update the tracker and label the Warp Speed projects when there is an official announcement.

COMBINED PHASES: Another way to accelerate vaccine development is to combine phases. Some coronavirus vaccines are now in Phase I/II trials, for example, in which they are tested for the first time on hundreds of people.

GENETIC VACCINES

Vaccines that use one or more of the coronavirus's own genes to provoke an immune response.



PHASE II

moderna

Moderna's vaccine dazzled the stock market in May with Phase I data on just eight people, only to see its stock price drop when experts had a lukewarm reaction to the results. The vaccine uses messenger RNA (mRNA for short) to produce viral proteins. The American company is eyeing Phase III trials in July and hopes to have vaccine doses ready by early 2021.

PHASE I **PHASE II**

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. On July 1, they announced that all the volunteers for their Phase I/II trial produced antibodies against SARS-CoV-2, while some experienced moderate side effects such as sleep disturbances and sore arms. In an interview, Pfizer's CEO said that he hoped his company could begin delivering vaccines in October, providing hundreds of millions of doses by the end of 2020, and then up to a billion by the end of 2021.

PHASE I PHASE II

Imperial College London MORNINGSIDE

Imperial College London researchers have developed a “self-amplifying” RNA vaccine, which boosts production of a viral protein to stimulate the immune system. They began Phase I/II trials on June 15 and have partnered with Morningside Ventures to manufacture and distribute the vaccine through a new company called VacEquity Global Health.

PHASE I PHASE II

Zydus dedicated to life

Indian vaccine-maker Zydus Cadila has created a DNA-based vaccine. On July 3 they announced approval to start human trials, becoming the second company in India to enter the Covid-19 vaccine race after Bharat Biotech.

PHASE I PHASE II

AnGes 大阪大学 OSAKA UNIVERSITY

On June 30, the Japanese biotechnology company AnGes announced they had started safety trials on a DNA-based vaccine, developed in partnership with Osaka University and Takara Bio.

PHASE I

INOVIO POWERING DNA MEDICINES

On June 30, the American company Inovio announced they had interim Phase I data on their DNA-based vaccine. They found no serious adverse effects, and measured an immune response in 34 out of 36 volunteers. They plan to start Phase II/III trials this summer.

PHASE I

CUREVAC

In March, the Trump administration unsuccessfully tried to entice CureVac to move its research from Germany to the United States. In June, the company launched Phase I trials of its mRNA vaccine. The company said its German facility can make hundreds of millions of vaccine doses a year.

PHASE I

Genexine

The Korean company Genexine started testing the safety of a DNA-based vaccine in June. They anticipate moving to Phase II trials in the fall.

PHASE I

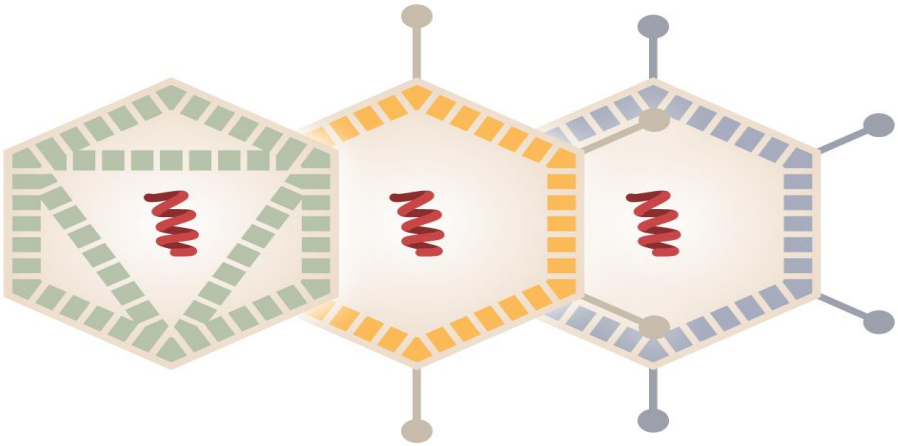
In June, Chinese researchers at the Academy of Military Medical Sciences, Suzhou Abogen Biosciences and Walvax Biotechnology announced they would start their country's first safety trials on a mRNA-based vaccine, called ARCoV. Earlier studies on monkeys reportedly showed protective effects.

PRECLINICAL

The French pharmaceutical company Sanofi is developing an mRNA vaccine in partnership with Translate Bio. On June 23, they announced they were planning Phase I trials in the fall.

VIRAL VECTOR VACCINES

Vaccines that use a virus to deliver coronavirus genes into cells and provoke an immune response.



PHASE II 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. The vaccine is in a Phase II/III trial in England and Phase III trials in Brazil and South Africa. The project may deliver emergency vaccines by October. In June, AstraZeneca said their total manufacturing capacity stands at two billion doses.

PHASE II LIMITED APPROVAL

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 I safety trial. Unpublished data from Phase II trials demonstrated the vaccine produced a strong immune response, leading the Chinese military to approve it on June 25 for a year as a "specially needed drug." CanSino would not say whether vaccination would be mandatory or optional for soldiers.

PHASE I

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РОССИЙСКОЙ ФЕДЕРАЦИИ

The Gamaleya Research Institute, part of Russia's Ministry of Health, launched a Phase I trial in June of a vaccine they call Gam-Covid-Vac Lyo. It is a combination of two adenoviruses, Ad5 and Ad26, both engineered with a coronavirus gene.

PRECLINICAL

Beth Israel Lahey Health
Beth Israel Deaconess Medical Center

Johnson & Johnson

Researchers at Beth Israel Deaconess Medical Center in Boston are testing an adenovirus called Ad26 in monkeys. Johnson & Johnson announced in June that they would start Phase I/II trials in late July.

PRECLINICAL

MASSACHUSETTS EYE AND EAR

NOVARTIS

The Swiss company Novartis will manufacture a vaccine based on a gene therapy treatment developed by the Massachusetts Eye and Ear Hospital. A virus called an adeno-associated virus delivers coronavirus gene fragments into cells. Phase I trials are set to begin in late 2020.

PRECLINICAL

MERCK iavi

The American company Merck announced in May it would develop a vaccine from vesicular stomatitis viruses, the same approach it successfully used to produce the only approved vaccine for Ebola. The company is partnering with IAVI.

PRECLINICAL

MERCK THEMIS

Merck is also working with Themis Bioscience, an Austrian firm it is acquiring, to develop a second vaccine, which will use the measles virus to carry genetic material into patients' cells.

PRECLINICAL

VAXART

Vaxart's vaccine is an oral tablet containing an adenovirus that delivers coronavirus genes. They are preparing for Phase I trials this summer.

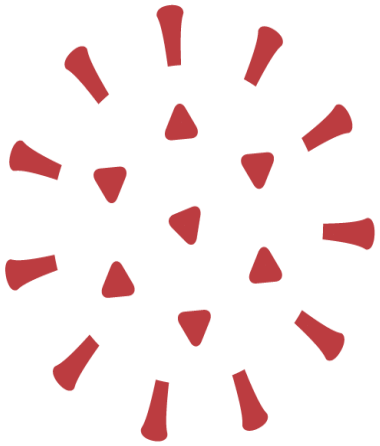
PROTEIN BASED VACCINES

Vaccines that use a coronavirus protein or a protein fragment to provoke an immune response.

PHASE I PHASE II

NOVAVAX
Creating Tomorrow's Vaccines Today

In May, the Maryland-based Novavax started a Phase I/II trial on a vaccine made up of microscopic particles carrying fragments of coronavirus proteins. The Coalition for Epidemic Preparedness Innovations is investing $384 million in the project.



PHASE I

In June, the company Anhui Zhifei Longcom began Phase I trials in China for a vaccine that is a combination of viral proteins and an adjuvant that stimulates the immune system. The company is part of Chongqing Zhifei Biological Products and has partnered with the Chinese Academy of Medical Sciences.

PHASE I

The Australian company Vaxine launched a Phase I trial in July. Their vaccine combines viral proteins with an adjuvant that stimulates immune cells.

PRECLINICAL

After the SARS epidemic in 2002, Baylor College of Medicine researchers began developing a vaccine that could prevent a new outbreak. Despite promising early results, support for the research disappeared. Because the coronaviruses that cause SARS and Covid-19 are very similar, the researchers are reviving the project in partnership with the Texas Children's Hospital.

PRECLINICAL

A vaccine in development by the University of Pittsburgh, called PittCoVacc, is a skin patch tipped with 400 tiny needles made of sugar. When placed on the skin, the needles dissolve and deliver virus proteins into the body.

PRECLINICAL

A vaccine from Australia's University of Queensland delivers viral proteins altered to draw a stronger immune response. In June, the university and the company CSL announced a partnership to start Phase I trials, which could lead to millions of doses a year starting in 2021. GSK is providing an adjuvant to further stimulate the immune system.

PRECLINICAL

SANOFI gsk

In addition to their mRNA vaccine, Sanofi is developing a vaccine based on viral proteins. They are producing the proteins with engineered viruses that grow inside insect cells. GSK will supplement these proteins with adjuvants that stimulate the immune system. Sanofi has said it could produce at least 600 million doses a year if the vaccine succeeds in trials.

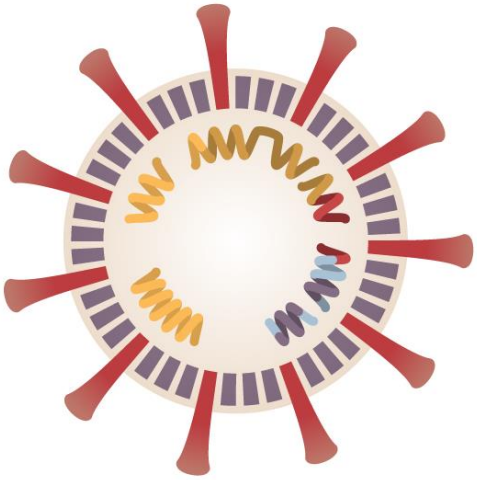
WHOLE VIRUS VACCINES

Vaccines that use a weakened or inactivated version of the coronavirus to provoke an immune response.

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.

After promising early testing, the state-owned Chinese company Sinopharm announced in June that it would be moving into Phase III trials. They reached an agreement with the United Arab Emirates to start testing the efficacy of an inactivated virus vaccine in the Gulf state.



PHASE II

INSTITUTE OF MEDICAL BIOLOGY
CHINESE ACADEMY OF MEDICAL SCIENCES

Researchers at the Institute of Medical Biology at the Chinese Academy of Medical Sciences, which has invented vaccines for polio and hepatitis A, started a Phase II trial of an inactivated virus vaccine in June.

PHASE I PHASE II

sinovac

The private Chinese company Sinovac Biotech is testing an inactivated vaccine called CoronaVac. On June 13 the company announced that Phase I/II trials on 743 volunteers found no severe adverse effects and produced an immune response. Sinovac is preparing Phase III trials in China and Brazil and is building a facility to manufacture up to 100

million doses annually.

PHASE I PHASE II

In collaboration with the Indian Council of Medical Research and the National Institute of Virology, the Indian company Bharat Biotech de signed a vaccine called Covaxin. It is an inactivated rabies virus engineered to carry proteins from the coronavirus. Phase I/II trials are scheduled to begin this month. The Indian Council of Medical Research reportedly envisions having the vaccine ready for public use on August 15, but this target has been met with skepticism.

REPURPOSED VACCINES

Vaccines already in use for other diseases that may also protect against Covid-19.

PHASE III

The Bacillus Calmette-Guerin vaccine was developed in the early 1900s as a protection against tuberculosis. The Murdoch Children's Research Institute in Australia is conducting a Phase III trial, and several other trials are underway to see if the vaccine partly protects against the coronavirus.

COVID 19 - THERAPEUTICS

As the COVID-19 pandemic continues, researchers and manufacturers are moving potential therapeutics into clinical trials at a dizzying pace. The search is on to find treatment candidates that lower mortality rates and lessen the severity of COVID-19.

To date, three therapeutics are approved to treat COVID-19: dexamethasone in the United Kingdom; Avigan (favilavir) in China, Italy and Russia; and Veklury (remdesivir) in Japan.

Potential therapies are being examined in several large international trials. The largest, SOLIDARITY, is led by the World Health Organization (WHO). More than 100 countries have joined SOLIDARITY to evaluate high-profile treatment candidates for COVID-19.

FRONTLINE CANDIDATES

DRUG: VEKLURY (REMDESIVIR) | Medication class: Antiviral | Developer: Gilead Sciences
Original use: Treatment for Ebola and Marburg virus infections
Rationale: Veklury, an intravenous drug that inhibits viral replication, has shown in vitro and in vivo activity against SARS-CoV-2. It was originally developed as a treatment for Ebola that ultimately proved less effective than other therapies, but has shown effectiveness in animal studies against other coronaviruses.
Regulatory actions: As studies of Veklury have shown reduced time to clinical improvement for COVID-19 patients, countries have started allowing its use outside of trial settings. Japan is the only country so far to approve Veklury for COVID-19, but Singapore's Health Sciences Authority and the EMA in Europe have conditionally approved Veklury for use in patients with COVID-19 12 years of age and up. FDA allows the use of Veklury for COVID-19 under an EUA based on preliminary results of NIH's ACTT trial. However, FDA has warned Veklury should not be used with hydroxychloroquine or chloroquine phosphate, as it may reduce antiviral activity. In the UK, Veklury has received a positive scientific opinion under the Medicines and Healthcare products Regulatory Agency (MHRA) Early Access to Medicines Scheme, which will allow adults and children with COVID-19 access to the medication if they meet additional criteria.
Trials: Remdesivir is being evaluated in the following high-profile trials:
DisCoVeRy (Recruiting): *A phase 3 trial in France examining Veklury alongside lopinavir/ritonavir, interferon beta-1a, hydroxychloroquine, and standard of care (NCT04315948)*
SOLIDARITY (Recruiting): *Veklury is a treatment arm of the WHO SOLIDARITY trial.*
SIMPLE (Active, Not Recruiting): *Two Phase 3 international studies from Gilead are examining moderate (NCT04292730) and severe COVID-19 cases (NCT04292899)*
ACTT (Not Recruiting): *NIAID is conducting a phase 3 trial of 800 patients receiving either Veklury or placebo (NCT04280705).*
Capital Medical University (Suspended/Terminated): Two phase 3 trials in China from Capital Medical University looking at mild/moderate (NCT04252664) and severe COVID-19 cases (NCT04257656).
A late-stage trial evaluating Veklury in pediatric patients with COVID-19.
A Phase 2 trial of 40 participants across multiple trial sites in the U.S. evaluating Veklury with and without the oral broad-spectrum anti-viral drug merimepodib (NCT04410354).
Status: SOLIDARITY and DisCoVeRy are currently recruiting. NIAID's trial has stopped early and patients in the placebo group are being given the option to receive the study drug.
Outcomes: Veklury is beginning to show promise as a therapy that improves time to clinical improvement—but not improvement in mortality—for patients with COVID-19.

THERAPY: CONVALESCENT PLASMA | Medication class: Immunoglobulin

Rationale: Researchers have theorized that convalescent plasma could be used as passive immunotherapy in other coronaviruses such as MERS and in SARS-CoV-2 to help neutralize the virus.

Trials: Convalescent plasma is being evaluated against placebos, other treatments, and standard of care in a number of high-profile trials.

NYU Langone Health and Albert Einstein (Recruiting): *A Phase 2 trial of 300 participants is being conducted to determine the efficacy and safety of convalescent plasma compared with receiving sodium lactate or saline solution (NCT04364737).*

Brigham and Women's Hospital (Recruiting): *Investigators are examining how high-titer convalescent plasma from recovered COVID-19 patients performs against standard plasma in a group of 200 participants (NCT04361253).*

Cedars-Sinai Medical Center (Recruiting): *In collaboration with Johns Hopkins, researchers are testing whether multiple doses of convalescent plasma could help COVID-19 patients in intensive care receiving mechanical ventilation (NCT04353206).*

Johns Hopkins (Recruiting): *Researchers are leading three of their own trials involving convalescent plasma, evaluating its potential for prophylaxis (NCT04323800), the effects of treating children exposed to or infected with COVID-19 (NCT04377672), and its ability to reduce COVID-19 related complications and mortality (NCT04373460).*

Baylor Research Institute (Not Recruiting): *A team is examining whether convalescent plasma fares better than receiving oxygenation in a phase 1 trial (NCT04333251).*

Stanford University (Not Recruiting): Researchers are examining the effects of convalescent plasma on reducing COVID-19 respiratory symptoms compared with standard plasma (NCT04355767).

Stony Brook University (Invitation): *Convalescent plasma is being tested against standard donor plasma in a phase 1/2 randomized trial of 500 participants, with a primary outcome of number ventilator-free days at day 28 (NCT04344535).*

Outcome: A medRxiv pre-print paper analyzing safety data from 5,000 hospitalized adults indicated convalescent plasma appears safe for use. In the first peer-reviewed study of convalescent plasma, 19 of 25 patients (76%) with severe COVID-19 who received convalescent plasma had clinical improvement. In a safety update published in Mayo Clinic Proceedings, mortality improved from 12% as reported in the pre-print to 8.6%. A randomized clinical trial of 103 patients with severe COVID-19 published in JAMA by researchers from China showed a non-significant clinical improvement in 51.9% of patients compared with improvement in 43.1% of patients who received standard treatment (P=.26). However, the trial was halted early due to the decrease in COVID-19 patients in China during the study period, which could have contributed to the study being underpowered to detect a clinically significant result.

Regulatory actions: On 24 March, the FDA allowed the use of convalescent plasma from recovered cases of COVID-19 for patients with "serious or immediately life-threatening COVID-19 infections under an emergency investigational new drug (eIND) application. On 9 April, healthcare company Grifols announced they were partnering with BARDA to create a COVID-19 treatment based on convalescent plasma.

DRUG: AVIGAN (FAVILAVIR/AVIFAVIR) | Medication class: Antiviral agent
Manufacturer/Distributor: Fujifilm Toyama Chemical (as Avigan) and Zhejiang Hisun Pharmaceutical | Approved Indication: Avigan is approved in China and Italy to treat COVID-19. Avifavir, a generic form of Avigan, has been approved to treat COVID-19 in Russia. | Rationale: Reports from officials in China have said Avigan is clinically effective against COVID-19. | Trials: There are six trials in China evaluating favilavir against other antivirals such as baloxavir and marboxil in patients with COVID-19. Fujifilm announced a phase III clinical trial to evaluate the safety and efficacy of Avigan in Japan for patients of COVID-19. In Canada, Appili Therapeutics announced they are conducting a Phase 2 trial of favilavir with 760 participants in long-term care facilities, which includes both residents and staff. A 330-person trial of avifavir in Russia is ongoing.
Outcome: Recent data appears to show lack of efficacy of Avigan in treating COVID-19. A study published in the pre-print server medRxiv of 240 patients that evaluated favilavir against the influenza drug umifenovir (brand name Arbidol) showed neither drug was more effective at improving the clinical recovery rate of patients. Interim data from Japan suggested the favilavir was not effective in treating mild or moderate cases of COVID-19, according to independent reporting from Kyodo News.
Status: Trials have various dates of completion.

DRUG: DEXAMETHASONE | Medication class: Glucocorticoid
Manufacturers/Distributors: Various (Dextenza, Ozurdex, others)
Approved Indications: Rheumatic and skin diseases, allergies, asthma
Rationale: Dexamethasone has been selected as a potential therapy due to its potential for reducing the inflammation associated with cytokine release syndrome in patients with COVID-19. | Regulatory Actions: In response to positive preliminary results, the UK has approved dexamethasone for use in the country as a COVID-19 treatment.
Trials: The drug is currently being evaluated as a treatment arm of the RECOVERY trial.
Outcomes: Preliminary results from the RECOVERY trial indicate dexamethasone may help reduce mortality in patients with COVID-19. Of 2,104 patients randomized to receive dexamethasone, there was a 35% reduction in mortality among patients on ventilators (P = .0003), and a 20% reduction in mortality for patients receiving oxygen (P = .0021).

DRUG: KALETRA (LOPINAVIR-RITONAVIR) | Medication class: HIV protease inhibitor
Developer: AbbVie | Approved US Indication: Kaletra is indicated in combination with other antiretrovirals to treat HIV-1 infection in adults and in pediatric patients 14 days and older. | Rationale: Kaletra has been effective against SARS, showing in vitro activity against the disease in a 2004 study. Countries hard hit by COVID-19, such as Italy, have recommended the drug combination as a treatment for the novel coronavirus.
Trials: High-profile trials of Kaletra are evaluating the drug alone and in combination with other COVID-19 therapeutic candidates.
Tongji Hospital (Recruiting): *A Phase 4 randomized controlled trial of Kaletra is evaluating the drug against arbidol hydrochloride and oseltamivir (NCT04255017).*

A study in South Korea is pitting Kaletra against hydroxychloroquine in patients with mild cases of COVID-19 (NCT04307693), Kaletra alone and in combination with interferon-beta are two arms of the WHO SOLIDARITY trial. The UK-based RECOVERY trial is also evaluating Kaletra, but has stopped randomization to this treatment arm.
Lopinavir and ritonavir are also being evaluated together with abacavir and lamivudine as the drug QuadraMune in up to 500 patients with COVID-19 in a trial sponsored by Therapeutic Solutions International (NCT04421391).
Outcomes: Findings are beginning to indicate that Kaletra may not result in clinical improvement from COVID-19.
Evidence for use: A study published in The Lancet of 127 patients randomized 2:1 to receive a combination of interferon beta-1b, Kaletra and ribavirin, or Kaletra alone and found the combination therapy was more effective than treating with Kaletra on its own.
Evidence showing no benefit: A randomized, controlled trial published in the New England Journal of Medicine showed no therapeutic benefit for Kaletra in patients with cases of severe COVID-19. After publication of this trial, some researchers have noted clinicians have stopped using the therapy. A journal pre-proof study by researchers from Guangzhou Medical University in China published in the journal Med found no difference in COVID-19 outcomes between 34 patients who received Kaletra, 35 patients who received arbidol and 17 patients who took no antiviral medication. In the RECOVERY trial, researchers found no clinical benefit for hospitalized patients taking Kaletra.
Status: The trial from researchers in South Korea is expected to be completed in May. The Tongji Hospital study is expected to be completed by July. Trial completion dates of the studies based in China vary, with the earliest completion dates listed in late April. SOLIDARITY is currently recruiting. RECOVERY has stopped randomizing to its Kaletra arm after finding no clinical benefit for the drug.

THERAPEUTIC: REMICADE (INFLIXIMAB) | Developer: Janssen
Medication class: Chimeric monoclonal antibody biologic
Approved Indication: Autoimmune diseases (rheumatoid arthritis, Crohn's disease, psoriasis, psoriatic arthritis, ankylosing spondylitis)
Rationale: Remicade is a tumor necrosis factor inhibitor that been proposed as a potential treatment for cytokine release syndrome associated with COVID-19.
Trials: Together with the monoclonal antibody namilumab, Remicade is being tested in patients hospitalized with COVID-19 in the multi-arm CATALYST trial of therapeutics led by researchers from the Universities of Birmingham and Oxford. Researchers hope one or both therapy will help alleviate serious symptoms of the disease.

SOURCE AND REFERENCE

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