

CORONAVIRUS -VACCINE AND TREATMENT DEVELOPMENT

An overview of treatment development for
COVID-19, including vaccine trials and antiviral
drug development

NOVEMBER 19, 2020



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Roadmap

- **Vaccine development**
- Treatment development



Vaccination has reduced infectious disease burden and can prevent up to 6 million deaths every year

Preclinical
87

Phase 1
37

Phase 2
17

Phase 3
13

Limited approval
6

Preclinical testing

- Animals such as mice or monkeys are given the experimental vaccine to see if their immune systems respond

Phase 1 safety trials

- A small number of people are given the vaccine to test safety and immune response

Phase 2 expanded trials

- The vaccine is given to hundreds of people split into groups by demographic characteristics to test differences in immune response

Phase 3 efficacy trials

- Thousands of participants are given either the vaccine or a placebo and scientists wait to determine if those given the vaccine are infected and compare differences between the 2 groups
- This phase further tests vaccine's ability to stimulate the human immune system

Combined phases

- Used to accelerate vaccine development
- For example, some COVID-19 vaccines are now in Phase 1/2, which means that there are testing hundreds of people for the first time

Approval

- Phase 3 trial results are reviewed to determine vaccine approval
- A vaccine may receive emergency use authorization before getting formal approval during a pandemic



Approximately 85% of congressional districts across the US are conducting COVID-19 clinical trials

Clinical trials across the US

US CHAMBER OF COMMERCE; AS OF OCTOBER 20, 2020

1-10 trials 11-35 trials 36-70 trials 71-150 trials 150+ trials



877
Ongoing clinical trials across all 50 states



Operation Warp Speed facilitates vaccine development with a public-private sector alliance

1 What is the goal?

- To produce and deliver 300 million doses of an effective, safe COVID-19 vaccine to the American public with the initial doses available by January 2021

2 Who is involved?

- Operation Warp Speed (OWS) is a partnership between HHS, CDC, NIH, BARDA, DoD, and private firms working on developing effective vaccines
- HHS Secretary, Alex Azar, and Acting Defense Secretary, Christopher Miller, oversee the project

3 How is it funded?

- The CARES Act allocated \$10 billion, plus flexible additional funding for this project
- BARDA received \$6.5 billion for countermeasure development and NIH received \$3 billion from Congress for research

4 What's the plan?

Vaccine development

- The project selects the most promising candidates for government aid and support
- Protocols for clinical trials are overseen by HHS rather than the companies

Vaccine manufacturing

- DoD and the CDC work with companies to coordinate manufacturing capacity simultaneously as vaccine efficacy is assessed

Vaccine distribution

- DoD and the CDC work with companies to develop a plan to deliver the future vaccine in a safe and quick manner

Highlight of drug manufacturers working to develop preventative vaccines for COVID-19 (1/4)



Many companies developing vaccines and treatments have received **funding** from federal entities like the **Biomedical Advanced Research and Development Authority (BARDA)** and the **National Institute of Allergy and Infection Diseases (NIAID)** along with global organizations like the **Coalition for Epidemic Preparedness Innovations (CEPI)**.

Genetic Vaccines

Genetic vaccines use genes from the novel coronavirus to stimulate a response in the human immune system.

Company	Stage	Details
Moderna & NIH	Phase 3 and part of Operation Warp Speed	<ul style="list-style-type: none"> Received funding from CEPI and began phase 3 clinical trials on July 27 On November 16, announced vaccine is 95% effective in preventing cases of severe infection and demonstrated efficacy among participants of color and 65+ Will likely file for FDA's emergency use authorization in the next few weeks
BioNTech, Pfizer & Fosun Pharma	Combined Phase 2/3 and part of Operation Warp Speed	<ul style="list-style-type: none"> Results from phase 1/2 in US and Germany revealed moderate side effects such as sleep disturbances and sore arms Trump administration awarded \$1.9 billion to deliver 100 million doses of vaccine by December 2020 and to acquire 500 million more doses Preliminary trials from November 8 yielded 90% efficacy rate and plan to apply for FDA's EUA by the end of November Potential complication for administration: must be freezeed in -80 degrees Celsius climate until injected
Imperial College London & Morningside Ventures	Combined Phase 1/2	<ul style="list-style-type: none"> Phase 1/2 began on June 15
Arcturus Therapeutics & Duke-NUS Medical School	Combined Phase 1/2	<ul style="list-style-type: none"> California-based company has partnered with the Singapore medical school to develop a "self-replicating" mRNA vaccine Phase 1/2 launched at Singapore General Hospital in August On November 9, the company announced positive immune responses from an early trial analysis

SOURCE MarketWatch, New York Times, Axios Vitals

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Highlight of drug manufacturers working to develop preventative vaccines for COVID-19 (2/4)

Protein-Based Vaccines		<i>Protein-based vaccines use a coronavirus protein or fragment to stimulate an immune response.</i>
Company	Stage	Details
Novavax	Phase 3 and part of Operation Warp Speed	<ul style="list-style-type: none"> Phase 3 trials in UK and US If trials succeed, expect to allocate 100 million doses to US by Q1 of 2021 In early November, the company announced that it will be delivering 40 million doses to Australia
Clover Biopharmaceuticals	Phase 1	<ul style="list-style-type: none"> Vaccine to be used in conjunction with a vaccine being developed by GSK Phase 2 trials to begin by the end of 2020
Sanofi and GlaxoSmith Kline	Combined Phase 1/2 and part of Operation Warp Speed	<ul style="list-style-type: none"> Clinical trials started in September; Phase 3 planned for December US announced payment of \$2.1 billion to support vaccine development and for 100 million doses Plan to provide 200 million doses to COVAX for global vaccine equity efforts
Finlay Vaccine Institute	Combined Phase 1/2	<ul style="list-style-type: none"> The vaccine contains a part of the spike protein, called RBD, along with two : proteins from a bacteria and aluminum hydroxide to boost immune system response to RBD spike protein
Kentucky BioProcessing	Phase 1	<ul style="list-style-type: none"> Developing a tobacco-based vaccine based on <i>Zmapp</i> used to treat Ebola Uses a species of tobacco to make viral proteins

Highlight of drug manufacturers working to develop preventative vaccines for COVID-19 (3/4)

Viral Vector Vaccines		<i>Viral vector vaccines use viruses to transport the coronavirus genes into a human body's cells to provoke an immune response.</i>
Company	Stage	Details
AstraZeneca & University of Oxford	Combined Phase 2/3 and part of Operation Warp Speed	<ul style="list-style-type: none"> Vaccine based on the chimpanzee adenovirus Phase 2/3 trials in England and phase 3 in Brazil, South Africa, UA Phase 3 paused on Sept 6 due to adverse reaction and resumed on October 23 with FDA approval
CanSino Biologics	Phase 3 and limited approval in China	<ul style="list-style-type: none"> Approved by the Chinese military as a "specially needed drug" on June 25 Announced phase 3 trials to begin in Saudi Arabia, Russia, and Pakistan
Beth Israel Deaconess & Johnson & Johnson	Phase 3 and part of Operation Warp Speed	<ul style="list-style-type: none"> Vaccine out of adenovirus 26 Launched phase 3 trials in late October If approved, US to pay \$1 billion to secure 100 million doses
Gamaleya Research Institute	Phase 3 and approved for early use in Russia	<ul style="list-style-type: none"> Manufacture vaccine from adenovirus 5 and 26 Since news broke about vaccine's regulatory approval w/o conducting a phase 3 trial, Russia called the approval as of Aug 11 a "conditional registration certificate" Results from phases 1 / 2 , released after its limited approval, demonstrated that vaccine yielded coronavirus antibodies w/ limited side effects



Highlight of drug manufacturers working to develop preventative vaccines for COVID-19 (4/4)

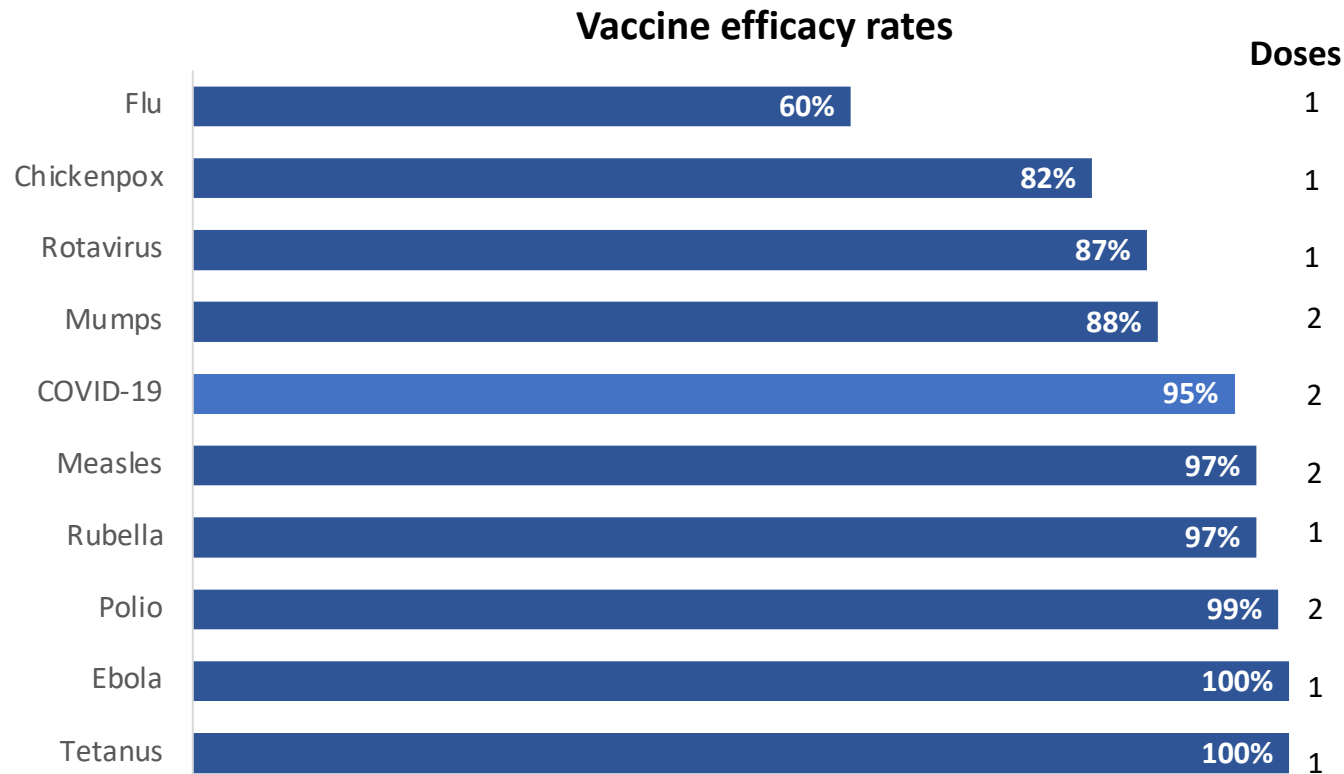
Inactivated Vaccines		
<i>Inactivated vaccines use a weak or inactive version of the coronavirus to stimulate an immune response.</i>		
Company	Stage	Details
Sinovac Biotech	Phase 3 and limited approval in China	<ul style="list-style-type: none"> • Currently in phase 3 trials in Brazil, Indonesia, and Turkey • Agreed to provide 40 million doses to Indonesia, if approved, by March 2021 • Preparing to manufacture for global distribution including the US in early 2021
Sinopharm	Phase 3 and limited approval in UAE	<ul style="list-style-type: none"> • Emergency authorization in UAE • Aim to have a vaccine ready by the end of 2020
Institute of Medical Biology at Chinese Academy of Medical Sciences	Phase 2	<ul style="list-style-type: none"> • Created vaccines for polio and hepatitis A • Currently in phase 2 trials using an inactive coronavirus
Bharat Biotech	Phase 3	<ul style="list-style-type: none"> • Working with the Indian Council of Medical Research and National Institute of Virology, currently in phase 3 clinical trials as of Oct. 23 • Aim to develop a vaccine by 2021

Repurposed Vaccines		
<i>Repurposed vaccines are currently used to protect against other, existing diseases.</i>		
Company	Stage	Details
Murdoch Children's Research Institute	Phase 3	<ul style="list-style-type: none"> • Australia-based research institute testing the Bacillus Calmette-Guerin vaccine • Vaccine was previously used to protect against tuberculosis



Frontrunner experimental COVID-19 vaccines are demonstrating high levels of efficacy

FDA had anticipated that the future COVID-19 vaccine would have a 50% efficacy rate, in line with the seasonal flu vaccine. Current reports from Pfizer and Moderna are showing their vaccine candidates with a 95% efficacy rate.



SOURCE: Axios Vitals

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Hackers are pivoting towards medical espionage as the race to develop COVID-19 vaccine heats up

China



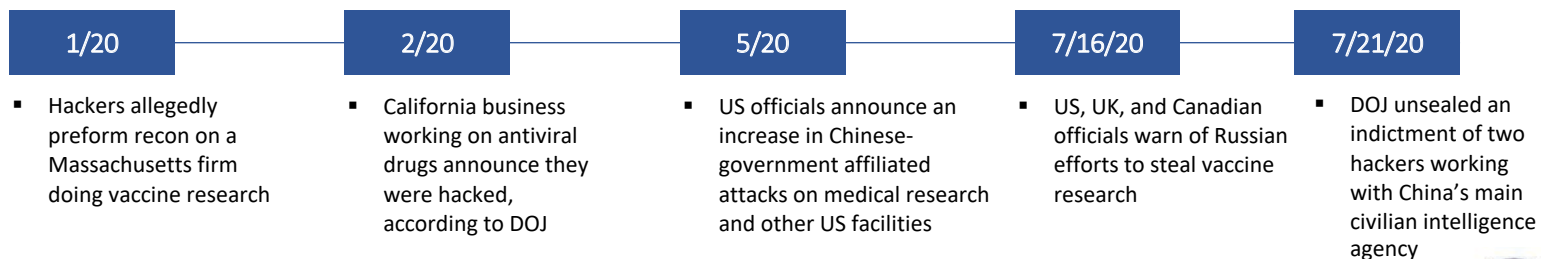
- DOJ unsealed an indictment charging two hackers of working with China's main civilian intelligence agency in a prolonged campaign targeting defense contractors, tech companies, dissidents, and COVID-19 researchers
- It is unclear if the attempts to steal COVID-19 research were successful, but hundreds of millions of dollars worth of related information was stolen over the decade-long course of the campaign, according to DOJ

Russia



- Security officials in the US, Britain, and Canada said that hackers belonging to Russian intelligence unit APT29, aka "Cozy Bear," are targeting vaccine research
- It is not clear if the hack attempts were successful
- Moscow denies the allegations

Timeline of major efforts to steal coronavirus research



CDC, NIH, and National Academies formed an equitable vaccine allocation oversight committee

NIH and CDC have requested the *National Academies of Sciences, Engineering, and Medicine* and the *National Academy of Medicine (NAM)* to form an oversight committee that will develop a framework for domestic and global policymakers to ensure equity in allocation practices for all future COVID-19 vaccines.

- Study to determine priorities for equitable vaccine distribution
- Factors such as health disparities among various populations and status of health, occupation, and geography will be considered
- Assess accessibility issues for communities of color to plan for vaccine distribution practices in the US

“While there has been a worldwide effort to accelerate development of safe and effective SARS-CoV-2 vaccines, there will inevitably be limited doses available for the first several months. We are pleased to be able to mobilize expertise quickly to respond to the government’s request for an independent study of priority-setting for the equitable allocation of potential vaccines for SARS-CoV-2...”

– National Academy of Medicine President, Victor Dzau

The committee’s first meeting took place on July 24 and included presentations from NIH Director Francis Collins and Director Robert Redfield from the CDC.

Roadmap

- Vaccine development
- **Treatment development**



Emergency use authorization (EUA) is overseen by the FDA

The Federal Food, Drug, and Cosmetic Act allows the FDA commissioner, in emergencies, to approve the use of unapproved medical products to diagnose, treat, and prevent serious and life-threatening diseases when no other FDA-approved alternative can combat the life-threatening disease.

Highlights of EUA issued for various medical products for the novel coronavirus

Issue Date of EUA	Product	Company
November 17, 2020	Prescription at-home testing kit	Lucira Health
November 9, 2020	Bamlanivimab, monoclonal antibody treatment	Eli Lilly
November 6, 2020	Antibody neutralizing detection kit	GenScript USA
October 15, 2020	At-home nasal swab collection kit	Clinical Enterprise
October 6, 2020	Molecular RT-PCR and sequencing	University of California, Los Angeles
September 22, 2020	Testing kit using saliva swab	Quadrant Biosciences
August 15, 2020	SalivaDirect, a real-time, molecular RT-PCR	Yale School of Public Health
May 1, 2020	Remdesivir, treatment to shorten length of hospital stay	Gilead Sciences



Remdesivir approved for emergency use in treating patients with severe cases of COVID-19

Remdesivir is an experimental, antiviral drug developed by biopharmaceuticals company, Gilead Sciences. The biopharma company has been researching this drug since 2009 and currently, its potency to treat Ebola, SARS, MERS, hepatitis C, and respiratory syncytial virus (RSV) are underway.



Gilead Sciences has been working with **China CDC** since January 2020 and **academic institutions in the U.S.** since February 2020 to test the safety and efficacy of the antiviral drug through **clinical trials**.



Results from a study done in China on patients with severe cases of COVID-19 demonstrated that **13.9%** of patients **given Remdesivir died**; whereas, **12.8%** of patients given the **placebo**. These findings were not statistically significant.



Results from the global, placebo-controlled NIAID clinical study demonstrated that patients taking a placebo recovered in 15 days, whereas **patients given Remdesivir recovered in 11 days**. A statement from the NIH also discussed the mortality rate difference, with the placebo group in this study having a death rate of 11.6% versus **8% for the group given the antiviral**.



Based on NIAID's findings, the FDA announced its **authorization of emergency usage** for *Remdesivir* on May 1, meaning it did not undergo the usual safety review protocol before being distributed as a viable treatment for patients with severe COVID-19. FDA announced another full approval for the drug in acute care settings in October.

Conflicting study data on *Remdesivir* treatment efficacy for patients hospitalized with COVID-19

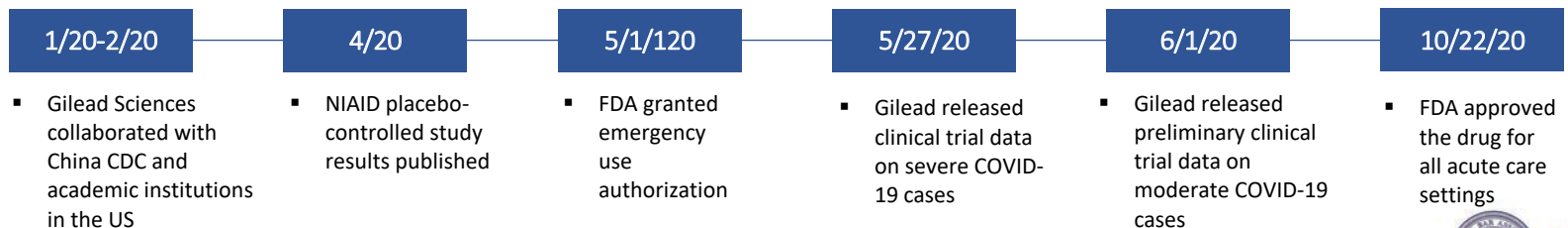
Overview of Gilead study results

- Gilead-sponsored clinical trials aim to assess outcome differences among patients hospitalized with severe and moderate cases of COVID-19 being treated with *Remdesivir* versus those receiving standard of care treatment alone.
- Among moderate cases of COVID-19, those treated with *Remdesivir* for 5 days were 65% more likely to show clinical improvements by day 11; clinical improvements were not statistically significant for those in the 10-day treatment group.
- Among severe COVID 19 cases, those treated with the drug for 5 days demonstrated similar levels of clinical improvement than those treated for 10 days.

Overview of WHO study results

- Results from WHO's Solidarity trial with over 2,700 participants across 30 countries demonstrated that *Remdesivir* did not reduce mortality, minimize hospital stay, or keep patients off ventilators significantly.
- Although scientists have raised questions regarding study design, there has been agreement that *Remdesivir* is most beneficial among patients with moderate COVID-19 and taken early after infection.

Timeline of *Remdesivir* clinical trials



S O U R C E Gilead, Firstpost, CNBC, Science, FDA, New York Times

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Efficacy of dexamethasone, a corticosteroid, in treating patients with severe cases of COVID-19



Study results from the University of Oxford's randomized, controlled clinical trial suggests that **dexamethasone decreases death** rates in hospitalized patients with severe COVID-19. Data released states dexamethasone reduced mortality by a **35% in patients on ventilators and 20% in patients on oxygen.**

Background: Dexamethasone, a common steroid, works by reducing inflammation, which results from an overactive immune response to the novel coronavirus. Without the steroid's presence, an overactive immune response can deteriorate the barrier between lungs and surrounding tissue causing lungs to fill with fluid and triggering acute respiratory distress syndrome.

Study details: Patients were randomly sorted into two groups: about 2,100 patients in the treatment group received a low dosage of dexamethasone and 4,300 received standard of care.

Results: Medical professionals have shared that if— after reviewing published study methods and data— dexamethasone does in fact reduce deaths by 1/3, it will be readily available to become the standard of care for patients with severe COVID-19.

Considerations



- Clinical significance in dexamethasone only applied to the sickest patients, who were either on a ventilator or receiving oxygen. There was no observed benefit to those not on respiratory support.
- There are no earlier randomized trials that suggest efficacy of steroid treatments on viral pneumonias like acute respiratory syndrome and H1N1.
- Japan's ministry of health recently approved the drug for a treatment option for COVID-19 patients.



FDA has authorized convalescent plasma for very sick, hospitalized COVID-19 patients



Convalescent plasma therapy works by giving patients infected with COVID-19 an infusion of antibody-rich plasma from patients who were able to recover from the novel coronavirus. Deriving treatments for diseases from patients who were able to recover from the disease is not new to medical experts and treatments using serum—plasma with its clotting factors removed—dates to the late 1800s.

Though research has begun to test this form of plasma therapy for COVID-19, research findings are still working to determine by **which mechanism** COVID-19 antibodies might work.

Current research is focusing on the **infusion of convalescent plasma** in hopes that it may boost a generalized response, or “passive immunity,” in a patient’s immune system until the patient’s immune system develops a targeted ability to fight the virus.

Researchers at the Icahn School of Medicine at Mount Sinai were able to identify differences in mortality rates from this study. There is a **12.8% death rate** for COVID-19 patients that received the antibody therapy versus a **24.4% death rate** for patients who did not.

Although already available to patients under expanded access programs, **the FDA announced an EUA for convalescent plasma on August 23, 2020**. This authorization presumes that convalescent plasma may be effective in treating COVID-19 and that benefits outweigh any risks.

The Trump administration has purported, inaccurately, that blood plasma has reduced COVID-19 mortality by 35% according to Mayo Clinic study results. The results, however, indicated that patients with mild cases who received antibody-rich plasma within 3 days of being diagnosed were **35% more likely to survive 30 additional days** compared to those who received plasma with low antibodies. There was no comparison to a placebo group in this study.



FDA revoked its emergency authorization use for hydroxychloroquine for COVID-19 treatment



Hydroxychloroquine and chloroquine have not been shown to be safe and effective in treating or preventing COVID-19. Normally, these drugs are used to treat or prevent malaria. Hydroxychloroquine is also approved to treat some autoimmune conditions.



Officials' stances:

- NIAID has issued a warning about using a combination of hydroxychloroquine and the antibiotic azithromycin, a duo that President Trump has called a "game changer"
- President Trump has repeatedly departed from experts' warnings, repeatedly calling for these drugs to receive more serious consideration from researchers and patients



Current uses and risks:

- Ongoing clinical trials are examining the usefulness of these drugs in treating or preventing COVID-19, including WHO's Solidarity Trials
- Through Emergency Use Authorization (EUA), FDA previously authorized their temporary use to treat the virus in hospitalized patients in some circumstances
 - On June 15, the FDA released a statement to **revoke temporary use of hydroxychloroquine and chloroquine**
 - The evidence supporting these drugs' potential benefits **did not meet legal criteria for approval of an EUA** and no longer outweighed potential side effects
- Side effects include heart rhythm problems that can lead to death
- At least one person has died from ingesting a form of chloroquine





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