COVID Research Brief: Vaccines for COVID-19
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Key Messages/Shorter Answer (Soundbite):[1]

- A massive effort is underway to develop a vaccine for COVID-19 using exciting new technologies.
- Not all vaccines currently being developed to prevent COVID-19 will be successful. Safety issues or a lack of protection will halt some.

- Ultimately, it is likely we'll need a repertoire of COVID-19 vaccines to offer widespread protection. Different vaccine formulations will ensure vaccination is safe and effective for all members of society, including infants, children, the elderly and people with weakened immune systems.

- Before being licensed for wide use, new vaccines have to first be tested to see if they are safe and effective.
- Phase 3 is the final phase of testing in humans to determine if a vaccine is safe and effective and will be approved by the Food and Drug Administration (FDA)
- Initial supplies of a COVID-19 vaccine would be for those at highest risk of infection or at the highest risk of serious illness and death.
- None of the vaccines in clinical trials in the United States at present are being tested in children, so initial approval of vaccines will not include an indication for children. Testing in children will almost certainly follow approval for adults (18 yo and older).

Types of Vaccines:

1. **DNA/RNA-based**

DNA and RNA vaccines use fragments of genetic material made in the lab. These fragments code for a part of the virus (such as its spike protein). After the vaccine is injected, your body uses instructions in the DNA/RNA to make copies of this virus part (or antigen). Your body recognises these and mounts an immune response, ready to protect you the next time you encounter the virus.

Pros

- these vaccines can be quickly designed based on genetic sequencing alone

- they can be easily manufactured, meaning they can potentially be produced cheaply

- the DNA/RNA fragments do not cause COVID-19.

Cons

- there are no approved DNA/RNA vaccines for medical use in humans, hence their alternative name: next-generation vaccines. So they are likely to face considerable regulatory hurdles before being approved for use

- as they only allow a fragment of the virus to be made, they may prompt a poor protective immune response, meaning multiple boosters may be needed

[1] https://www.astho.org/COVID-19/Q-and-A/

- there's a theoretical probability vaccine DNA can integrate into your genome.

The speed at which these vaccines can be designed, needing only the genetic sequence of the virus, is why these vaccines were among the first to enter clinical trials.

An RNA vaccine, mRNA-1273, being developed by Moderna and the US National Institute of Allergy and Infectious Diseases, advanced to clinical testing just two months after the virus was sequenced.

2. Virus vectors

These vaccines use a virus, often weakened and incapable of causing disease itself, to deliver a virus antigen into the body. The virus' ability to infect cells, express large amount of antigen and in turn trigger a strong immune response make these vaccines promising.

Examples of viruses used as vectors include vaccinia virus (used in the first ever vaccine, against smallpox) and adenovirus (a common cold virus).

Pros

- highly specific delivery of antigens to target cells and high expression of antigen after vaccination

- often a single dose is enough to stimulate long-term protection.

Cons

- people may have existing levels of immune protection to the virus vector, reducing the effectiveness of the vaccine. In other words, the body raises an immune response to the vector rather than to the antigen

- low-scale production of some virus-vectored vaccines means they are less cost-effective.

One high-profile example is the University of Oxford/AstraZeneca vaccine AZD1222, based on a modified chimpanzee adenovirus.

3. Inactivated

Inactivated vaccines are a tried and trusted method of vaccination. It's the technology used in the vaccine against poliovirus and in some types of flu vaccines. Inactivated vaccines contain viruses treated with heat, chemicals, or radiation so they cannot replicate, but can still trigger an immune response.

Pros

- a known technology, generally considered safe

- can be used in people with weakened immune systems.

Cons

- low immunogenicity, so requires multiple boosters.

The Chinese government is testing an inactivated COVID-19 vaccine.

4. Live-attenuated virus

Live-attenuated vaccines are among the most successful existing vaccine strategies, already used to protect against measles and polio. These contain virus weakened in the lab. The virus is still viable (live) but cannot cause disease. After vaccination, the viruses in these vaccines grow and replicate, stimulating an excellent immune response.

Pros

- strong protection as vaccine mimics the natural infection process
- cost effective for large-scale manufacturing with a familiar regulatory approval pathway
- single immunization without needing extra molecules (adjuvants) to stimulate the immune system.

Cons

- very rare potential to revert to a disease-causing state
- limited use in people with weakened immune systems due to potential safety concerns
- can require cold storage, which may limit potential for distribution.

Several live-attenuated COVID-19 vaccine candidates are currently in preclinical trials.

5. Protein subunit

Subunit vaccines do not contain live components of the virus, but are made from purified pieces of the virus (protein antigens) that trigger an immune response. Again, this is an existing technology, used for instance in hepatitis B vaccines.

Pros

- with no live components, subunit vaccines are generally thought to be safe
- can be used in people with weakened immune systems and other vulnerable populations.

Cons

- the protein antigens that best elicit an immune response must be investigated in detail
- can stimulate an insufficient immune response meaning that protection is likely to require multiple boosters or for the vaccine to be given with an immune system stimulant.

<u>Current vaccines in development</u> (https://vaccinemapper.nd.edu/)

- Globally
  - 198 total developers with around 200 vaccine candidates in development
  - 160 vaccine candidates in pre-clinical development; 37 in Phase 1, 2 or 3 clinical trials
- In the United States
  - 50 total developers
  - 6 vaccines funded by the federal government through HHS Biomedical Advanced Research and development Authority (BARDA) as part of Operation Warp Speed

See below:

Vaccine	**Company**	**Doses**	**Storage requirements**	**Trials**
BNT162: mRNA-based vaccine	Pfizer, BioNTech	Two, 21 days apart Intramuscular Diluent reguired	Minus 80 degrees	Phase 3
mRNA-1273: mRNA-based vaccine	Moderna	Two, 28 days apart Intramuscular	Minus 20 degrees	Phase 3
AZD1222: Replication-deficient viral vector vaccine (adenovirus from chimpanzees)	Astra Zeneca	Two doses Intramuscular	2-8 degrees	Phase 3 – on hold in US
JNJ-78436735: Non-replicating viral vector	Johnson& Johnson/Janssen	One dose Intramuscular	2-8 degree storage and administration	Phase 3
Recombinant SARS-CoV-2 Protein Antigen +AS03 Adjuvant	Sanofi Pasteur and GSK	Two doses	2-8 degrees	Phase 1/2
NVX-CoV-2373 vaccine Protein subunit	Novavax/Emergent Biosolutions	Two doses Intramuscular	2-8 degrees	Phase 1/2
rVSV G-CoV2: Vesicular stomatitis virus vectored vaccine delivering SARS-CoV-2 Spike glycoprotein	Merck and IAVI	NA	NA	

Concerns about rapid development of COVID 19 vaccines

- Many are concerned that there is political pressure to approve a COVID 19 vaccine before all the data are analyzed from Phase 3 clinical trials
- Pfizer and BioNTech, AstraZeneca, GlaxoSmithKline, Johnson & Johnson, Merck, Moderna, Novavax, and Sanofi have all signed a joint safety and efficacy **pledge** earlier this month, saying they wouldn't cut any corners during the R&D process.
- The Food and Drug Administration (FDA) decides when vaccines can be used by the general public.
- After approval by the FDA, the Advisory Committee on Immunization Practices (ACIP) will release recommendations for use of the vaccines, including recommended priority groups for vaccination when available vaccine is in short supply.