

# Understanding the Vaccine Development Process

## How Vaccines Work

The aim of vaccination is simple: to train the immune system to recognize disease-causing organisms like viruses or bacteria (the technical term is “pathogens”).

If a person is later exposed to the pathogen, the immune system can then recognize the threat and respond far more quickly than it would in the absence of vaccination.

The ideal outcome is the prevention of infection so that the pathogen never gains a foothold in the body. In some cases, it’s difficult to completely prevent infection, and the goal is to have the immune system respond rapidly and vigorously enough to prevent the pathogen from causing disease.

The main mechanism by which the immune system recognizes pathogens is similar to the children’s game in which different shapes have to be inserted into matching holes. The cells of the immune system have “receptors” that are like holes into which a piece of pathogen must fit in order to trigger an immune response.

If an immune system cell encounters a pathogen that matches its receptor, it swings into action, releasing infection-fighting substances and copying itself so that a swarm of immune cells are generated, all targeting the same pathogen.

A particular type of immune cell, B cells, are called upon to generate antibodies. Antibodies are Y-shaped proteins designed to stick to the specific pathogen and block it from replicating (referred to as “neutralization”).

When immune system cells encounter a pathogen for the first time, the process of responding is quite slow (days to weeks). But after a first encounter, immune cells become able to respond much more quickly if the same pathogen shows up again. This phenomenon is called immune system “memory,” and it’s the reason why vaccination is possible.

One way to think of it is that when an immune cell sees a pathogen it recognizes for the first time, the tools the cell needs to fight back need to be unpacked. After this process has occurred, the immune cell has all of its tools unpacked and ready to work immediately if the pathogen is seen again.

The ability of immune cells to develop memory and respond more rapidly to a second exposure to a pathogen explains why some childhood diseases like measles and mumps don’t happen again in adulthood.

Crucially, vaccines can duplicate this process and create immune system memory against a pathogen that a person has yet to encounter. This is how all vaccines work, including vaccines for COVID-19, which create immune system memory against the SARS-CoV-2 virus.

In some cases, including for COVID-19, vaccines can create higher and longer-lasting immune responses than are typically observed after infection.

## Vaccine Ingredients

Vaccine design is a technical process, but the goal is straightforward: to deliver a mimic of a pathogen into the body so immune cells with receptors that recognize it respond, unpack their tools, and become ready to react rapidly to any further

encounters. In other words, to create immune system memory against the pathogen.

Vaccines can achieve this goal by delivering selected proteins derived from a pathogen. Alternatively, a vaccine can deliver a killed (inactivated) or drastically weakened version of the pathogen that cannot cause disease.

Whatever the approach, the desired outcome is the same: to trigger immune cells with receptors that recognize the pathogen to respond and develop immune system memory.

For COVID-19, several leading vaccines use a technology called mRNA. This delivers a tiny amount of genetic code that acts as a blueprint for making the SARS-CoV-2 outer spike protein in the body (for a very short time). Immune cells with receptors that recognize the spike protein respond, creating immune system memory against SARS-CoV-2, including antibodies.

Other approaches include using harmless versions of certain viruses, particularly adenoviruses (similar to common cold), to briefly deliver the genetic code for the SARS-CoV-2 spike protein into the body.

In some cases, substances called adjuvants are included, which are designed to alert the immune system of the need to respond to the vaccine.

Often, more than one vaccination is given, spaced out over weeks or months. The idea is to further boost the number of immune cells and antibodies that recognize the pathogen (additional shots are called “boosters” for this reason).

## Vaccine Development Process

The speed of COVID-19 vaccine development has caused some people to question whether corners were cut. To address this concern, it's important to understand how scientists were able to be prepared in advance and how the process of establishing the safety and efficacy of vaccines works.

Selecting the ingredients to include in COVID-19 vaccines was made easier by prior research involving other viruses very similar to SARS-

CoV-2 (coronaviruses). This research had shown that the virus spike protein was a major target of the immune system. Furthermore, studies with the coronavirus named MERS (Middle Eastern Respiratory Syndrome) revealed a way of making a vaccine version of the spike protein that's better at inducing strong immune responses.

This approach was adapted for COVID-19 vaccine development within days of the genetic blueprint of SARS-CoV-2 being figured out and published online on January 10, 2020.

**Once vaccines are designed, they must go through a process of testing in clinical trials. The process determines if the vaccine is safe and works well enough to be made available to the public. The clinical trials proceed in three major phases:**

- **PHASE I:** focuses on safety and ability of the vaccine to induce immune responses in a small number (<100) of volunteers.
- **PHASE II:** typically assesses safety, immune responses, and potentially different dosing regimens in a larger number (>100) of volunteers.
- **PHASE III:** measures how well the vaccine protects against infection and/or disease in thousands of volunteers who are at risk of being exposed to the pathogen the vaccine is designed to protect against.

These steps can be accelerated by combining phases; for example, a phase I/II trial may allow progress from one phase to the next as results are analyzed, or merge elements from both phases into a single trial. Importantly, combining phases can speed the research process but it doesn't lessen or prevent the collection of information necessary to prove safety and efficacy.

Regulatory agencies, such as the U.S. Food and Drug Administration (FDA), review and authorize

trials each step of the way, to ensure they are ethical and appropriate for people to volunteer to participate in. Every volunteer is given an informed consent form that explains the potential risks of participation. Volunteers can only enroll if they sign the informed consent to confirm that they understand what's involved.

In some cases, large phase IV “post-marketing” trials are conducted after a vaccine is approved for use by the public, to study effects in broader populations or address specific questions that earlier phase trials did not fully answer.

Additional safeguards exist, such as manufacturing plant inspections and the Vaccine Adverse Event Reporting System (VAERS), which is a complex and thorough program designed to help track, mitigate, and understand any potential adverse reactions associated with approved vaccines.

COVID-19 vaccines have not skipped any of the steps of the vaccine development process. Due to the urgency of the pandemic, the approach of combining trial phases was used frequently, with ongoing FDA input to ensure the results supported moving ahead.

Phase III trials of COVID-19 vaccines quickly produced evidence of efficacy because they enrolled large numbers of people who were at a high risk of exposure to SARS-CoV-2. The high rate of exposure meant that clear differences in rates of symptomatic COVID-19 disease between recipients of vaccines and comparison dummy (placebo) shots were seen within months. This led to the emergency authorization of the first COVID-19 vaccines at the end of 2020.

The phase III trials are still ongoing and collecting information on the safety and efficacy of the vaccines. Thanks to an extraordinary effort on the part of community members, scientists and medical staff, key phase III trials enrolled diverse participants, with significantly higher proportions of Black, Indigenous, and People of Color (BIPOC) than ever achieved previously. This is important for establishing safety and efficacy across all populations that will use the vaccines, and for promoting trust in the vaccine research process.

On August 23, 2021, the FDA granted full adult approval for the COVID-19 vaccine manufactured by Pfizer, and others are expected to follow as sufficient safety and efficacy information becomes available.

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