

Vaccines are important—but what are they, and how do they work?

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To say that the COVID-19 pandemic has disrupted our lives would be an understatement. Since March, when stay-at-home orders were first put in place, many of us have spent our time in our homes, avoiding crowds, wearing masks, social distancing, and working remotely, often while taking care of or homeschooling children.

In spite of all of this, the virus continues to spread and our lives remain far from normal. And while research into therapies and treatments for COVID-19 is advancing, there are still none that can prevent severe illness.

We've been told that a [vaccine](#) that provides full protection against SARS-CoV-2, the virus that causes COVID-19, offers the best chance for a return to normalcy. Getting one would allow people to go about their daily lives, free from worry of getting infected, as well as the need to social distance and wear masks.

Ideally, one or more of the many COVID-19 vaccines in development will prove to be effective. But even a vaccine that offers less than complete immunity would slow the virus's spread and could reduce the severity of the disease. Along these lines, the Food and Drug Administration (FDA) announced in July that it would approve any vaccines that demonstrated at least 50% efficacy against the coronavirus.

All of this may be confusing—and frustrating—to those of us who are simply trying to put one foot in front of the other during this pandemic. And the confusion surrounding COVID-19 vaccines may be compounded by the uptick in reporting about them—the trials, their efficacy, and their safety.

With this in mind, Yale Medicine offers this primer on vaccine basics—how they work, their different platforms, and the approval process—and what that means for a COVID-19 vaccine.

So how do vaccines actually work?

Basically, vaccines train the immune system to recognize [dangerous pathogens](#), like SARS-CoV-2, allowing the body to fight an infection without having to get sick.

"The immune system is like an orchestra. It has so many different players and instruments that need to work together to defend the body against invading pathogens," says Akiko Iwasaki, Ph.D., Waldemar Von Zedtwitz Professor of Immunobiology and Molecular, Cellular, and Developmental Biology at Yale School of Medicine. "The vaccine serves as the conductor to orchestrate the defense system."

How does this happen? When a pathogen infects the body, the immune system dispatches an army of different cells to clear the infection from the body. Two types of immune cells that make up this army—B cells and T cells—are particularly important for the development of vaccines.

What are B cells and T cells?

B cells and T cells move through the body, constantly on the lookout for pathogens. When they encounter one, they attach themselves to it via a structure on the pathogen's surface called an antigen. When B cells bind to antigens, they crank out thousands of antibodies, which in turn bind to other pathogens circulating in the blood and lymphatic fluid. These antibodies send chemical signals to other immune cells to come and help destroy the pathogen.

But what happens if a virus infects the cells? This is where T cells come in: A special type of T cell (called a "killer T cell") monitors the body's cells. Should these killer T cells detect an [infected cell](#), they kill it in order to prevent the infection from spreading to other cells.

After ridding the body of a pathogen, some B and T cells live on as [memory cells](#). These memory cells can live for years—even decades—preserving their knowledge of these pathogens. If the immune system sees them again, the memory cells will recognize them and launch a swift and powerful immune response that kills the pathogens before they can cause sickness.

If you had chickenpox as a child, for example, your immune system will have developed an immunological memory against the virus that caused it. This memory protects you against reinfection. Recent studies suggest this may also be true for COVID-19. Some studies show that people who've recovered from COVID-19 develop memory B and T cells. But unlike with chickenpox, scientists don't yet know how long this immunological memory lasts with COVID-19 or how well it protects against reinfection. What's also not yet understood is what this means about the ability of a COVID-19 vaccine to provide long-term protection against the disease.

Because this is complicated, it's worth reiterating: It is the ability of memory cells to remember pathogens that confers immunity and protection against viral and bacterial pathogens they have previously confronted. Vaccines use this immunological memory.

But instead of exposing people to a dangerous pathogen that causes severe disease, a vaccine introduces the immune system to the pathogen in a way that does not make them ill, but which nevertheless prompts the immune cells to respond and create memory cells.

In this way, a vaccine against SARS-CoV-2 would work by introducing your immune system to the virus—or the virus's antigens—in a manner that does not cause COVID-19, but which still stimulates an immune response and the formation of an immunological memory.

How does a vaccine introduce a pathogen without making you sick?

Scientists have developed several ways to introduce a pathogen to the immune system without risking disease. One method—what's known as an "inactivated vaccine"—exposes the bacteria or virus to certain

chemicals, radiation, or heat to "kill" it, so that it is no longer able to infect human cells; this deactivated pathogen is what's in the vaccine. Alternatively, scientists might weaken a pathogen so that it is still able to infect cells but without causing sickness; these are known as live or attenuated vaccines.

Both methods have been used safely and effectively for several decades to protect people against a variety of diseases that were once common and serious. Examples include the Salk polio vaccine, as well as vaccines against measles, mumps, and rubella, among others.

Both inactivated and live attenuated vaccines for COVID-19 are currently under development worldwide. Sinovac Biotech, a company in China, produced an inactivated vaccine that has been approved there for emergency use, and several other inactivated vaccines are at various stages of development in China, India, and elsewhere. But one downside to inactivated viral vaccines is that they require considerable quantities of virus to be produced, which is a slow process.

New vaccine methods

Pharmaceutical companies and research laboratories are also exploring other ways to develop vaccines against COVID-19, beyond the methods discussed above.

For instance, several groups are working on carrier vaccines (also called virus vector vaccines), in which scientists genetically engineer an innocuous, or harmless, virus so that it carries genetic material that codes for the spike protein of SARS-CoV-2, the structure the virus uses to attach to and infect cells and which also serves as an antigen.

The genetically engineered virus acts as a Trojan Horse. When introduced into the body (via an injection, for instance), the virus infects

cells, but in so doing, it covertly delivers the genetic material for the spike protein—spurring the body's own cells to produce copies of it. Recognizing these spike proteins as outside invaders, the immune system mounts a defense against them, and, in the process, creates memory cells that should serve to protect against the coronavirus.

Some vector vaccines use viruses that have been modified so that they cannot replicate and consequently cannot cause illness, while others use viruses that cannot harm people. The University of Oxford-AstraZeneca team, CanSino, Johnson & Johnson, and several other companies are working to develop viral vector vaccines.

Still other companies like Moderna, Pfizer, and Inovio are working on RNA and DNA vaccines. Like carrier vaccines, RNA and DNA vaccines get the body's cells to generate copies of antigen proteins, only they do not use a viral vector to deliver genetic material. Instead, the genetic material, in the form of either DNA or messenger RNA, is introduced into the body directly.

The [genetic material](#) enters cells and instructs them to produce copies of the viral antigen. This stimulates an immune response and ultimately development of memory cells that can recognize and respond to the SARS-CoV-2 virus. DNA and RNA vaccines can be mass produced quickly and at reasonable cost.

One important caveat is that though it has been tried in the past, no vaccines have ever been successfully developed using these new types of vaccine platforms.

How are vaccines approved?

Before a vaccine can be used on the general population, it must first be carefully tested and vetted in an approval process intended to ensure that

it is both safe and effective.

Here in the United States, this process begins with what's called "preclinical research." This is when the vaccine is first tested on cell cultures and animals—not humans—to determine whether it safely produces the desired immune response.

If a vaccine passes the preclinical stage, it begins a three-phase trial.

- Phase 1: During Phase 1, the vaccine is given to a small group of healthy volunteers (between 10 and 100). This phase of the trial is focused on evaluating whether the vaccine is safe, though researchers also study its efficacy by determining whether it triggers an immune response.
- Phase 2: Vaccines that prove safe in Phase 1 move on to Phase 2. Here, hundreds of volunteers receive the vaccine. During Phase 2, researchers continue to assess the safety of the vaccine, though they also try to understand how the [immune system](#) responds to different doses of it.
- Phase 3: Phase 3 occurs after a vaccine successfully passes Phase 2. During this phase, thousands or even tens of thousands of volunteers receive either the vaccine or a placebo, but neither the researchers nor the volunteers know who gets which treatment.

The volunteers then live their lives as they normally would. Amid COVID-19, this means they are encouraged to social distance, wear masks, and follow other public health infection prevention guidelines. Researchers will track how many volunteers get COVID-19 and, to measure the effectiveness of the vaccines, follow them to learn whether those who received the vaccine were infected at lower rates than those who got the placebo. Researchers continue to monitor the vaccine's safety throughout the trial.

If, after all three phases, the vaccine is found to be safe and effective—if, in the example of COVID-19, it protects against infection or reduces severity of illness—then it is submitted to the FDA for approval. A multidisciplinary team of scientists reviews the data collected throughout the trial. And, if the data look good, the FDA will license the vaccine and the manufacturing process begins in order to produce mass quantities, so the general population can be vaccinated.

Is safety monitored after the vaccine is approved?

Even after the approval of a vaccine, the FDA and Centers for Disease Control and Prevention (CDC) continue to monitor its safety. Anyone involved in the use or distribution of vaccines including patients, pharmacists, health care providers, and vaccine manufacturers can report side effects through the Vaccine Adverse Event Reporting System (VAERS).

In all, this process of vaccine development, from preclinical research to licensure and vaccine production, usually takes a decade or longer. The fastest vaccine ever successfully developed—a mumps vaccine produced by Merck in the 1960s—still required four years.

But with the COVID-19 pandemic still among us, vaccine researchers are rushing to develop vaccines in record time, perhaps within a year or so from the start of initial vaccine research.

But experts like Iwasaki do not see this as cause for alarm. "The vaccine candidates undergo rigorous testing before being approved by the FDA," she says. "Even though the timeline is rushed to develop COVID-19 vaccines, the evaluation of safety and efficacy is not being compromised."

Provided by Yale University

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