

## PART 1

# How Do You Prepare for a Pandemic of a Virus That Doesn't Exist Yet?

By Polly Shulman

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When the COVID-19 pandemic struck in early 2020, the world was caught by surprise. Scientists learned that people were dying from a new virus in China. On January 30, 2020, the World Health Organization issued its highest level of warning. In many areas, schools, businesses, public venues, and houses of worship shut down overnight. Classrooms were empty. Some parents worked at home and tried to teach their children too. Other parents had to find safe places for their children while they went out to work. As infected patients crowded into hospitals, medical workers had to make short supplies of personal protective equipment last.

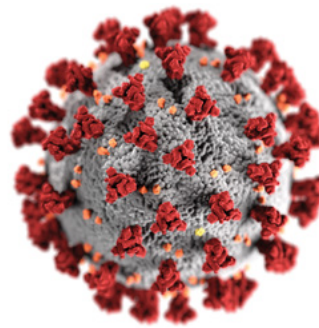
**Epidemiologists** are doctors and scientists who study how diseases spread. The word comes from *epidemic*, which means a widespread occurrence of a disease in a community at one time. When an epidemic spreads to the whole world, it's called a pandemic. To epidemiologists, the COVID-19 pandemic was not a surprise at all. They had known for years that a new coronavirus could jump from animals to humans and spread quickly across borders. They had been preparing for a pandemic like this. How did they know? How could they prepare for a pandemic of a brand-new virus? swimming speed is 2 meters per second (4.5 mph). That speed doesn't use too much energy. At that speed a blue whale can cruise around and migrate long distances with very little effort. But when it needs to, it can also swim in bursts as fast as 48 kph (30 mph).

## But First, What Is a Virus?

A **virus** is just a bit of genetic code wrapped in a protein shell. In fact, scientists don't even agree on whether viruses are living things. A virus can do very little on its own. It needs a host organism to replicate and survive. When a virus infects a host cell, it attaches to the cell's cellular membrane. Then it inserts its genetic material into the host cell. Once inside, the viral genetic material can force the host to make copies of the virus. The host uses its own organelles, such as its ribosomes, to do this. Once the new virus copies are ready, the host releases them. Then the copies can go on to infect new cells, repeating the cycle.

Viruses are all around us and in us, and in other living organisms, too. Most aren't harmful to humans. Some actually help us. Some of these helpful viruses inhabit our intestinal tract. Some viruses have evolved with us and contributed important genetic material to our own genomes. But as most of us know from sick days or worse, many viruses are harmful.

COVID-19 is caused by a virus called SARS-CoV-2 (**Fig. 1**), which belongs to a group called coronaviruses. (COVID stands for "coronavirus disease." The "19" comes from 2019, the year it began infecting humans. SARS-CoV-2 stands for "severe acute respiratory syndrome coronavirus 2.") Coronaviruses get their name from the protein spikes on their surface. Scientists thought those spikes resembled the spikes on a crown. Coronaviruses that infect humans are pretty common. Four strains of coronavirus are responsible for about 20 percent of the cases of the common cold.



**Figure 1. A Model of SARS-CoV-2, the Virus Responsible for COVID-19**

The red parts are called spike proteins. They give the coronavirus its name because they look like the points on a crown. © CDC/Alissa Eckert, MS; Dan Higgins, MAMDan Higgins, MAM

## Why Are Novel Viruses Dangerous?

A **novel** virus is simply a virus that humans have not yet encountered before. Most novel viruses that infect humans are **zoonotic**. They start out in other animals, then jump to humans. Scientists think SARS-CoV-2 probably began in a bat. Other novel viruses have started in pigs and birds, among other animals. Our immune systems remember viruses they have encountered before. Therefore, if we get infected with the viruses again, our bodies know how to fight them. But we haven't built up these defenses against novel viruses. They can spread easily.

Coronaviruses are **respiratory pathogens**. They infect the cells in our respiratory system—the nose, throat, larynx, trachea, lungs, and so on—when we take a breath. They can spread easily through the air from person to person. The time it takes for a person to develop symptoms after being infected is called the **incubation period**. Respiratory pathogens tend to have short incubation times. This means there's a brief period in which to stop them from spreading. That makes them hard to control. As a novel respiratory virus SARS-CoV-2 was well positioned to cause a pandemic.

## What's a Pandemic?

A pandemic is defined not by how deadly or terrifying a disease may be. It is defined by how widely it spreads. The Centers for Disease Control and Prevention, or CDC, is the national public health agency of the United States. It defines a pandemic as “an event in which a disease spreads across several countries and affects a large number of people.”

Of course, a pandemic can be deadly and terrifying! The Spanish flu pandemic of 1918 is an example. That pandemic killed between 50 million to 100 million people worldwide. Another example is the ongoing HIV/AIDS pandemic, which has killed about 81 million people so far. By contrast, acute hemorrhagic conjunctivitis, commonly known as pink eye, became a pandemic in 1981. It is mostly just annoying.

## Meet the Scientists

*Dr. Jennifer Nuzzo, Pandemic Preparedness*

Dr. Jennifer Nuzzo is an associate professor at the Johns Hopkins Bloomberg School of Public Health and a senior scholar at the Johns Hopkins Center for Health Security. She is an epidemiologist who focuses on preparing and responding to disease outbreaks and pandemics.



**Figure 3. Dr. Jennifer Nuzzo**

Dr. Nuzzo is an epidemiologist at Johns Hopkins University. She studies whether governments have the tools they need to respond to pandemics. © Johns Hopkins Center for Health Security

Nuzzo wrote a report in 2019 about how a coronavirus pandemic was likely. “I’m an epidemiologist, but I spend a lot of time studying policies and practices, and whether governments have all the tools they need to be able to respond to outbreaks, epidemics, or pandemics,” she explains. She runs a project called The Outbreak Observatory. The purpose is to study responses to disease outbreaks, identifying what worked well and what needs to be improved. “It’s really important to study outbreaks, because if you can stop outbreaks, you can prevent them from becoming epidemics. Or growing even larger, into pandemics,” she says.

Nuzzo recalls two earlier experiences with novel coronaviruses. The first was in 2003. A coronavirus now called SARS-CoV-1 jumped from animals to humans and went on to cause an outbreak of Severe Acute Respiratory Syndrome (SARS). It sickened about 8,000 people worldwide. Then in 2012 another novel coronavirus, MERS-CoV, spread from camels to people in Saudi Arabia. It caused Middle East Respiratory Syndrome (MERS). Unlike COVID-19, SARS and MERS did not go on to become pandemics. However, Nuzzo and other scientists were able to learn a great deal about coronaviruses by studying them.

*Dr. Lisa Cooper, Health Equity*



**Figure 4. Dr. Lisa Cooper**

Dr. Cooper is a Bloomberg Distinguished Professor at Johns Hopkins University School of Medicine and Bloomberg School of Public Health. She is also the director of The Johns Hopkins Center for Health Equity. © Johns Hopkins University

Dr. Lisa Cooper is a physician and social epidemiologist who has spent her career studying disparities in healthcare. “Health inequities cause a huge burden of human suffering and increased healthcare costs,” says Cooper. Health inequities are avoidable differences in health among

different groups of people. “They cause reduced productivity. They can even contribute to civil unrest,” she says.

Pandemics affect everyone. But they don’t affect everyone equally, Cooper explains. The COVID-19 pandemic made the long-standing worldwide problem of health inequities more apparent. Differences in opportunities have resulted in more injury, death, violence, and sickness in different social groups. People who belong to racial or ethnic minority groups and people with lower income levels are more likely to become more ill, at younger ages, than richer people and members of a majority group.

Cooper points to racial and ethnic disparities in cardiovascular disease, one of the most common and dangerous diseases in the United States. For example, in 2018 African Americans were 30 percent more likely to die of heart disease than non-Hispanic whites. And Native Americans were 50 percent more likely to be diagnosed with coronary heart disease than White Americans. Cooper also points to disparities in maternal and infant mortality. African Americans die in and around childbirth at about three to four times the rate of White Americans. And African-American and Native American babies die before their first birthday at much higher rates than White babies.

It’s tempting to blame differences in genes for these outcomes, but it would be wrong. “Health disparities are not caused, for the most part, by biological differences between people of different social groups,” says Cooper. “They’re caused by exposures to things in our environment. And by the way we distribute our resources within our society.”

Many of these disparities have deep historical roots. Cooper says, “European settlers in America forced Native people off their land. They spread smallpox, killing a large proportion of the Native population. They brought and enslaved people from Africa and elsewhere and forced them to labor for generations under horrific conditions. In the early 1930s, housing policies and real estate lending practices expanded homeownership opportunities for Whites while confining African



Americans to crowded neighborhoods with more pollution, less green space, and less access to healthy food, safe schools, and healthcare.”

## **Preparing to Develop and Distribute a COVID-19 Vaccine**

With COVID-19 spreading across the planet, it was vital to develop a vaccine as fast as possible. Fortunately, scientists had been working on developing coronavirus vaccines since the SARS epidemic in 2003. They had also spent decades working on a powerful, flexible new type of vaccine that would allow them to quickly design vaccines for specific viruses. Vaccine researchers developed the first COVID-19 vaccines in record time. But first, they needed to make sure the vaccines were safe and effective. They do this through clinical trials.

### **Stop and Think**

- 1.** If a novel coronavirus emerges, what do you need to know about it in order to take public health measures?
- 2.** What do you need to know about a novel coronavirus in order to develop a vaccine?
- 3.** What steps need to be taken to make sure that a new vaccine is effective and safe to use?

## PART 2

# The Vaccine Trials: How Do You Develop a Vaccine for a Novel Disease in Less Than a Year?

By Polly Shulman

Dr. Julie Ledgerwood has been studying vaccines since 2002. She's the chief medical officer and deputy director of the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID). That's part of the National Institutes of Health (NIH) in Bethesda, Maryland. For her job, she has conducted more than 60 clinical trials of vaccines and treatments targeting diseases that include HIV, flu, malaria, Ebola, and Zika. She and her team also oversaw clinical trials of a vaccine for COVID-19. Today, this vaccine is known as the Moderna COVID-19 vaccine.



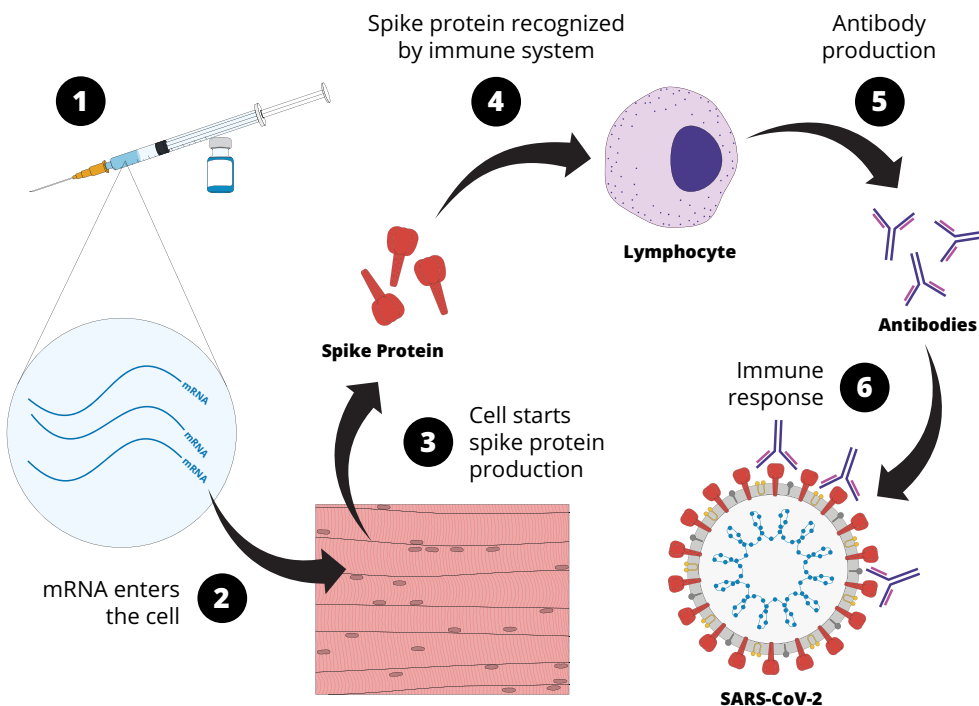
**Figure 1. Dr. Julie Ledgerwood**

© Julie Ledgerwood

A **vaccine** protects us from a virus by introducing proteins from the virus into the body. That way the immune system learns to recognize them. Then, when the virus invades, the immune system will recognize the proteins on the virus. It will know the virus is an invader and will attack it. Traditional vaccines introduce the proteins into the body directly, in the form of an inactivated or weakened virus. The Moderna COVID-19 vaccine is an example of a new type of vaccine. This new type is called an **mRNA vaccine**. mRNA vaccines work somewhat differently than traditional vaccines. They don't introduce the protein itself. Instead, they



introduce mRNA containing instructions for making the protein. The mRNA stands for messenger, because that's the molecule's function. It carries instructions from the DNA in a cell's nucleus to the ribosomes, the cell's protein-building center, located outside the nucleus.



**Figure 2. How mRNA Vaccines Work**

© Ramin Rahni / AMNH

When you get a shot of an mRNA vaccine, the mRNA is taken up by the muscle cells in your arm. There the ribosomes get to work making the protein, just as if they had received their instructions from their boss, the cell nucleus. They make a protein that sticks up from the surface of the SARS-CoV-2 virus. It's called the **spike protein**. When the muscle cells are done making the protein, the body's immune system detects them on the surface of the cells. The immune system prepares to recognize and combat the virus itself if the virus ever invades.

## How Were mRNA Vaccines Developed?

The Moderna and Pfizer COVID-19 vaccines are the first mRNA vaccines to receive authorization for use. However, scientists have been studying the technology for decades. “The idea for using mRNA as a vaccine platform originated by the early 2000s,” Ledgerwood says. Back then, several groups tried to make mRNA technology work in animals other than humans. But it was difficult. The test subjects had bad reactions to the vaccine and it didn’t protect them. Their immune systems recognized the mRNA and attacked it before their bodies could use it to make proteins.

Researchers worked on the problem for years. They continued to make improvements to mRNA technology. First they figured out a way to keep the immune system from fighting the mRNA so hard. Then they did research on SARS-CoV-1, a virus very similar to SARS-CoV-2. They discovered they could make a prototype mRNA vaccine for that virus. Another coronavirus appeared in 2012. That one, the MERS virus, first appeared in camels (**Fig. 3**). Researchers made a prototype mRNA vaccine for MERS too. So when SARS-CoV-2 became a pandemic, they were ready to use the technology to make a vaccine. “These kinds of efforts really paved the way for rapid development of SARS-CoV-2 vaccine,” says Ledgerwood.



**Figure 3. Testing for MERS**

A scientist swabs the nose of a dromedary camel to test the sample for MERS coronavirus.

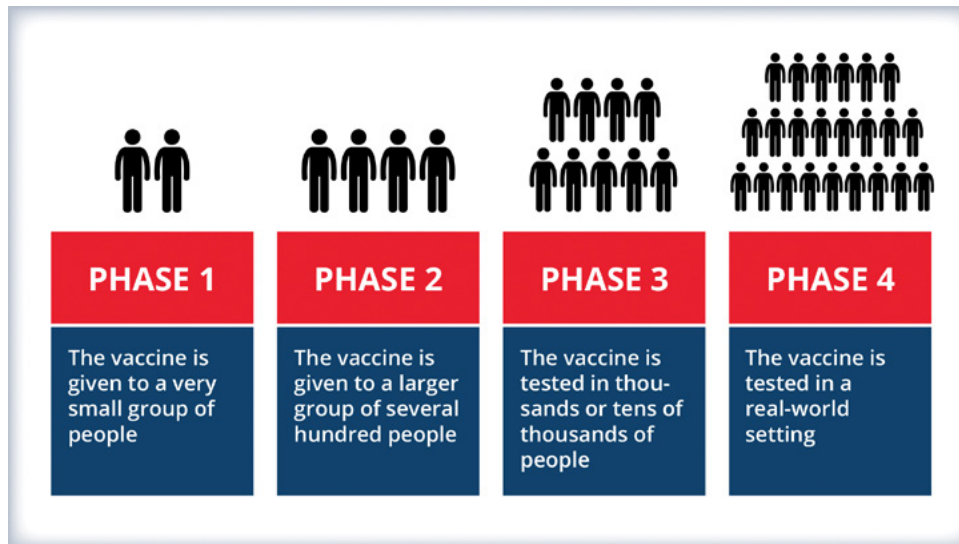
© NIAID

Fast-forward to December 2019. There was a lot of concern about this outbreak in China, says Ledgerwood. Nobody knew yet how big the outbreak would be. Nobody even knew whether the virus could spread from person to person. Still, scientists and public health leaders wanted to be prepared. “On about January 15, we decided, let’s do this. Let’s work with our collaborators at Moderna to make a prototype vaccine for SARS-CoV-2, test it in some animals, test it in some people,” Ledgerwood recalls. It was a big risk, but they wanted a vaccine to be ready if it was needed.

It soon became obvious that a vaccine was indeed needed. COVID-19 was spreading fast around the world. It was killing patients and overwhelming hospitals. “In response to the COVID pandemic, there was this unprecedented response,” says Ledgerwood. “It was all hands on deck. Everyone was all in. HIV researchers, influenza researchers, Ebola researchers, coronavirus researchers, public health officials, immunologists, epidemiologists. Everyone came together. Groups of researchers across the country were essentially raising their hands and saying, ‘I’ll participate in any of these clinical trials to help get an answer quickly.’ Volunteers were saying, ‘I’ll do it—I’ll be in the trial.’”

## How Are Vaccines Tested?

To find out whether a vaccine is safe and effective, scientists conduct **clinical trials (Fig. 4)**. (Scientists conduct clinical trials for drugs, medical devices, and treatments, too.) They determine all the details in advance. The details include how many subjects will be tested. They also include what results the researchers need to get for the trial to end and for the vaccine to be considered safe and effective. The statisticians help create a protocol. (Statisticians are scientists and mathematicians who specialize in collecting and analyzing large quantities of data.) “Every clinical trial is conducted based on a protocol—a document maybe 50 to 100 to 200 pages long,” says Ledgerwood. “It defines everything that will be done in that trial. It’s approved by ethics boards and regulators like the FDA [Food and Drug Administration].” Data safety monitoring boards oversee clinical trials to keep the subjects safe and make sure the data are valid.



**Figure 4. Stages of Clinical Trials**

Before it is tested in people, the vaccine is tested in the lab. When it is given to human volunteers, it is tested for safety first in a very small group of people. In the second phase of the trial, it is given to a somewhat larger group to further study its safety and effectiveness. In the third phase, it is given to a very large group of volunteers to determine its efficacy. In the fourth phase, the vaccine is tested in real-world settings to determine its effectiveness under various conditions. © AMNH

Vaccine trials consist of four phases:

- **Phase one.** The vaccine is given to a very small group—tens of people, maybe a hundred, says Ledgerwood. The purpose is to see whether it’s safe in healthy people. In this phase, researchers want to be sure “there aren’t common intolerable reactions, and the immune response looks promising,” she explains.
- **Phase two.** The vaccine is given to a somewhat larger group of several hundred people. The purpose is to further study its safety and to figure out the best way to give doses. “Do you need one shot or two shots? If you need two shots, how much time between them? That interval is really important for the immune response to have a chance to do its very best,” says Ledgerwood.
- **Phase three.** The vaccine is given to a much larger group, generally in the thousands or tens of thousands. “You’re looking for people

who are at risk for the disease,” says Ledgerwood. Safety is still critically important. That’s because less common reactions might show up with a larger group of people. But the main aim of this phase is **efficacy**. Subjects are randomly assigned to two groups. Those in one group receive the mRNA vaccine. Those in the other receive a shot of salt water instead of the mRNA vaccine. That’s called a **placebo**. These two groups are compared to see how well the vaccine protects people from illness. The researchers need to prevent people’s beliefs from influencing their interpretation of the outcome. To do that, they make the trial **double blind**. That means they make sure neither the volunteers nor the scientists know who is getting the real vaccine and who is getting the placebo. Only members of the trial’s data safety monitoring board have this information. Before the trial begins, the scientists designing it will determine what results the vaccine will need to meet to demonstrate that it works. If it meets those results, the vaccine developers can apply to the FDA for authorization and eventually approval. That will allow the vaccine to be administered.

- **Phase four, or post-marketing trials.** “These are generally performed in the real-world setting to assure continued evaluation of safety and efficacy of a product,” says Ledgerwood. They may include tests conducted in particular populations. These may include children, people with certain health conditions, or those at high risk for the disease.

## **How Were the mRNA Vaccine Trials Different?**

The COVID-19 mRNA vaccine trials followed all the established rules for vaccine trials, says Ledgerwood. “The main difference was the pace and the efficiency at which we were able to perform them. There was a reason for that. We were dealing with a worldwide pandemic that we really hadn’t seen in at least 100 years. It was like nothing any of us had experienced.”

Ledgerwood compares the COVID-19 vaccine development to building a house. With a crew of the usual size, say 10 people, working five days a week, seven hours a day, your house might be finished in a few months.

“But let’s say you need to build it in a week. How might you do that? Well, you could work around the clock. You could have a crew of 100 people. You could have more efficient machinery in place. You can get it done faster. All the same steps are taken, but much more efficiently.” That’s exactly what happened with the COVID-19 vaccine trials. “Instead of dozens of people managing a trial, we had hundreds or thousands. Instead of 20 sites, we had 100, so that we could enroll volunteers quickly, we could get the data quickly, we could analyze the data quickly and report it to the FDA and the public quickly. It was all hands on deck working literally around the clock seven days a week to gather this data to make these vaccines available.”

They also saved time by running processes at the same time instead of one at a time. Usually vaccines are not manufactured at large scale until after they are known to be effective. That makes sense. Drug manufacturers don’t want to risk making millions of doses of something they might not be allowed to sell. In the case of COVID-19, though, the vaccines were manufactured while they were still being tested. It was a big gamble financially. But it paid off in lives saved.

All of that took money. “The efforts to develop and procure COVID vaccines were very well funded by the US government, well into the tens of billions,” says Ledgerwood.

## **Choosing Test Sites**

Another reason they could test the COVID-19 vaccines so quickly? Because the pandemic itself was so big. A trial can’t end until a predefined number of people become sick. It has to be enough people so that they know for sure whether the vaccine is working. If infection rates are low, reaching that number will take a long time. Unfortunately for the victims of the virus, but fortunately for the vaccine trials, SARS-CoV-2 was spreading fast all over the world. The trials reached their number fast.



## Stop and Think

1. Explain how the mRNA vaccine works by drawing a model.
2. Compare and revise your plan for a clinical trial based on what you've learned about how the clinical trial for the Moderna vaccine was conducted.

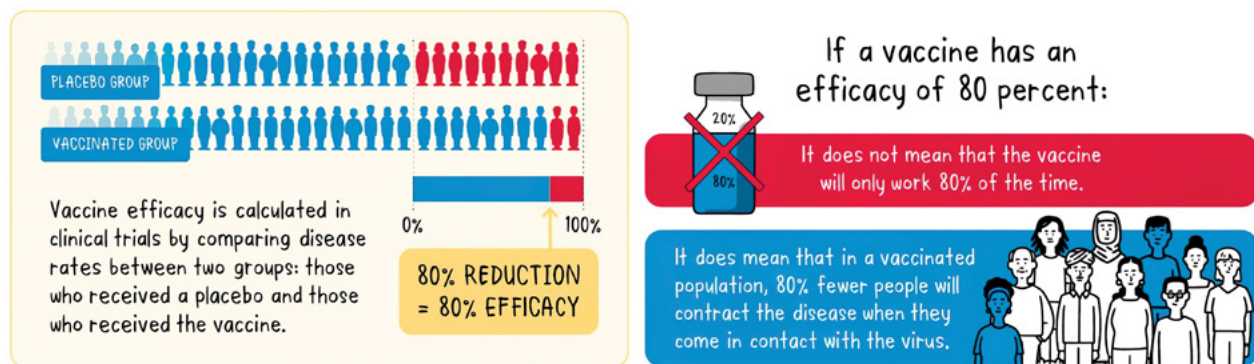
## PART 3

# Results—How Do We Know the Vaccine Is Safe and Is Effective?

By Polly Shulman

## Vaccine Efficacy

When researchers design trials to learn whether a vaccine works, they're looking for **vaccine efficacy** (Fig. 1). "Vaccine efficacy is the degree to which the vaccine protects people who have gotten [the vaccine] from getting infected," says Dr. Lisa Cooper. It's a precise number calculated from the data gathered in clinical trials.



**Figure 1. Vaccine Efficacy**

When epidemiologists talk about vaccine efficacy, they're using the term in a very precise way. They calculate the efficacy from data gathered in clinical trials. © WHO

The scientists conducting the trial gave one group of people a placebo shot of salt water. They gave another group the mRNA vaccine. Then they observed both groups to see who got sick. Once a predetermined number of people had gotten sick, the scientists compared the number of sick people who had received the placebo to the number of sick people who received the mRNA vaccine. Then they showed that comparison

as a percentage. That number is the vaccine's efficacy. For example, if a vaccine has a 95 percent efficacy, people who received the vaccine in the trial were 95 percent less likely to get sick than the people who didn't receive the vaccine.

It's important to note that 95 percent efficacy does not mean that 5 percent of people in the trial who got the vaccine got sick. Not everybody got sick, even without the vaccine. For example, some people were never exposed to the virus. Some people's immune systems protected them from illness. If the vaccine has 95 percent efficacy, then of the vaccinated people who would have gotten sick without the vaccine, only 5 percent of *those* people got sick. That adds up to many fewer people than 5 percent of the entire group.

Of course, the real world is messier than the world of a vaccine trial. Conditions are less controlled. **Vaccine effectiveness** describes how well the vaccine protects vaccinated people against sickness compared to unvaccinated people outside of clinical trials. Vaccine effectiveness is often a little lower than vaccine efficacy.”

Simple infection is not the whole story, though. Researchers also measure how much a vaccine protects people from getting very sick. Protecting people from needing treatment or hospitalization is important too. So is protecting them from dying from the disease. “We know the COVID-19 vaccines are effective because once we began to administer the vaccine to certain groups of people, we noticed that their death rates, hospitalization rates, and infection rates went down dramatically,” Cooper says. “For example, we started out with people over age 65, those who were very vulnerable to getting COVID-19 and dying from it. And we saw their death rates go down dramatically.”

## Trial Results

Let's take a closer look at the results of the phase three trial of the Moderna COVID-19 mRNA vaccine. The trial ran from July to October 2020. Some volunteers received a placebo shot. Others received a shot containing the vaccine. They were given two shots approximately one month apart. Both sets of volunteers were monitored for side effects and for COVID-19 until the trial ended. Typically, in clinical trials some volunteers become ineligible or drop out. In this trial, though, 96 percent of those enrolled received both injections. That's an unusually high rate for a trial of this size. In November 2020, the results were sent to the FDA, which approves vaccines for use.

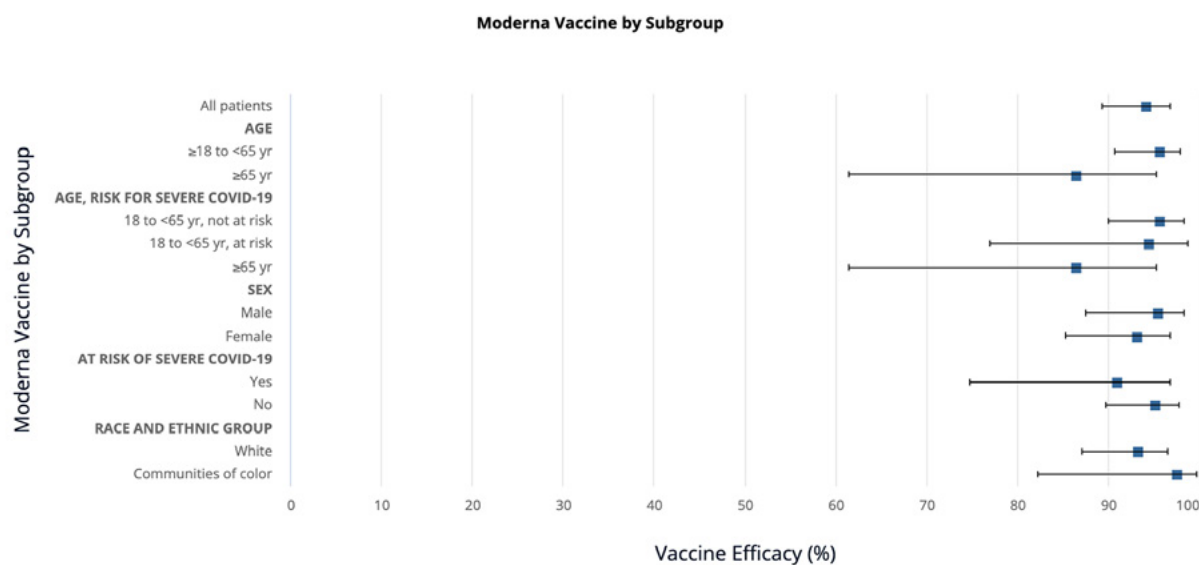
How did the researchers know when to end the trial? Dr. Robert DeSalle is a molecular biologist at AMNH. He explains, "When you're conducting a study like the Moderna vaccine clinical trial, you are looking for what's called a signal in the data." The researchers need to see such strong results that it would be impossible for the outcomes to have happened just by chance. "This signal says that the experiment has gone on long enough, and produced enough data, so the scientists can be confident in the results. It was obvious very quickly that the signal was going to be very, very strong and that the vaccines were very efficacious," he says.

The FDA guidance document for COVID-19 vaccines set goals in advance. It included at least 50 percent efficacy as a goal. The researchers hoped they could do even better. They aimed for at least 60 percent efficacy. Using this efficacy aim, statisticians calculated the number of volunteers necessary. (The trial enrolled 30,420 participants.) They calculated that the trials needed to run until at least 151 people had gotten a symptomatic case of COVID-19. That would give the researchers enough cases to know with 90 percent confidence that their conclusions about the vaccine's efficacy were true. And not just due to chance.

The protocol called for the data safety monitoring board led by the NIH to peek at the data at two points along the way. The first analysis of 95

COVID-19 cases was done by November 11, 2020. The results thrilled everyone. The vaccine efficacy was estimated at 94.5 percent. And the good news held. In the next analysis, ten days later, there were 196 cases and an efficacy of 95 percent. Analysis of the data showed that the vaccine was safe, and the side effects were tolerable. This data allowed for FDA emergency authorization of the vaccine.

## Vaccine Efficacy in Clinical Trials



**Figure 2. Vaccine Efficacy of Moderna COVID-19 Vaccine by Subgroup**

© Source: New England Journal of Medicine

## Safety

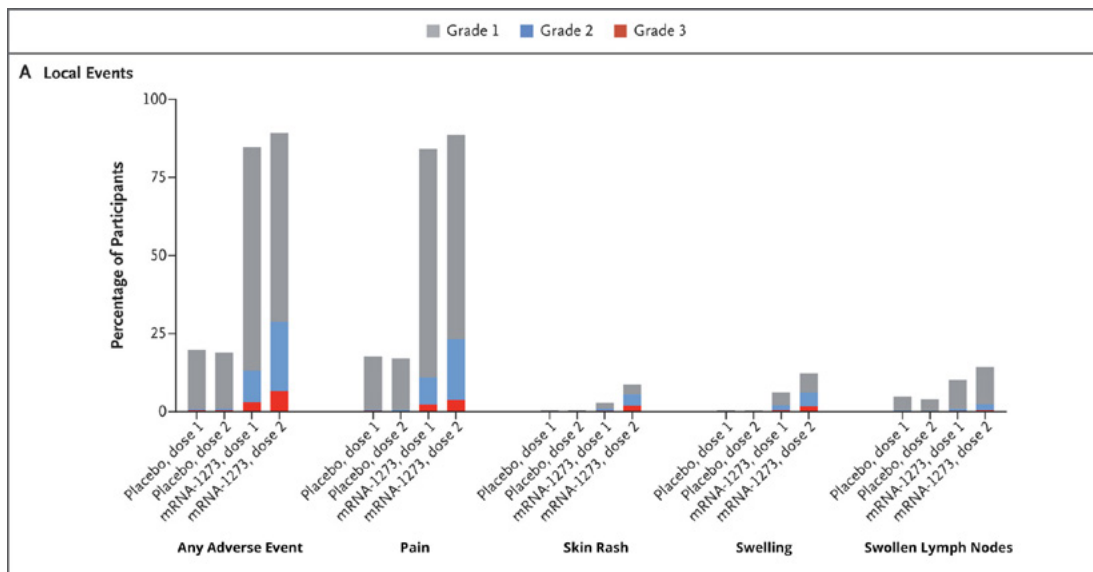
Efficacy was not the only important concern, of course. Before the vaccines could be used, the scientists and public health workers needed to know that they were safe. The trials also evaluated safety.

In the phase three Moderna COVID-19 mRNA vaccine trial, more volunteers who received the vaccine than the placebo experienced symptoms like tenderness, swelling, and pain at the injection site. The results were 84.2 percent vs. 19.8 percent for the first dose, and 88.6 percent vs. 18.8 percent for the second. These symptoms cleared up in four or five days. More volunteers who received the vaccine than the

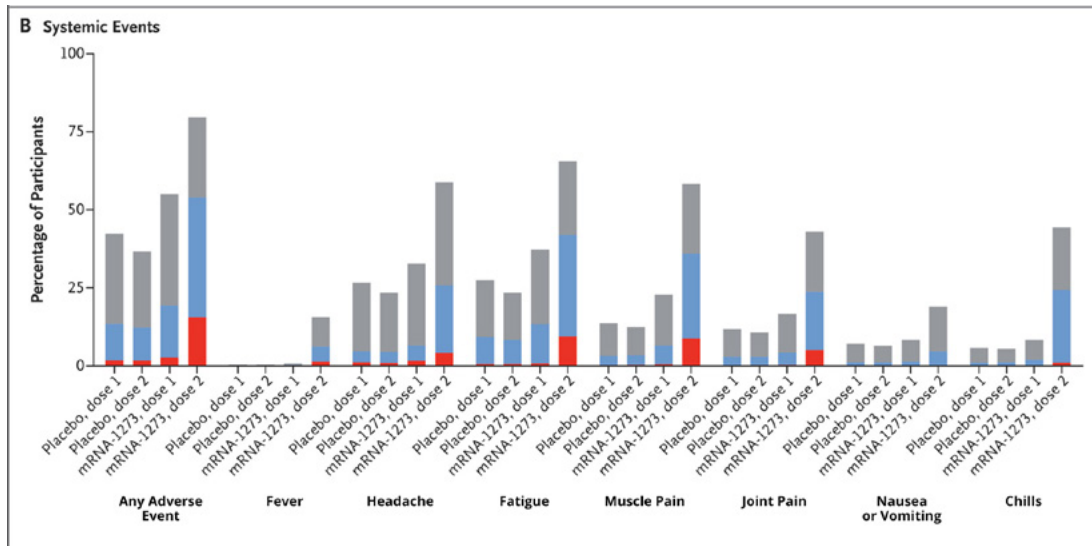
# Putting COVID-19 Vaccines to the Test

placebo experienced mild symptoms like fever, headache, and fatigue as well. The results were 54.9 percent vs. 42.2 percent for the first dose, and 79.4 percent vs. 36.5 percent for the second. However, the frequency of unexpected problems, severe issues, and death was similar in both the vaccinated and placebo groups (**Fig. 3**). It was low in both groups. That satisfied the scientists that the vaccine was safe.

“We do know from studies [of vaccines] that have been around for a very long time that when there’s going to be a safety issue, generally it happens within hours,” says Cooper. “Or certainly like within a week or two,” she adds. The volunteers in the COVID-19 mRNA vaccine trial were followed for up to six months. “We didn’t see safety issues come up in those groups. [That] means that the vaccine is safe,” she says.







**Figure 3. Reactions to the Vaccine**

This chart shows the percentage of trial participants who reported reactions within seven days after receiving a first or second dose of either the placebo or the Moderna COVID-19 mRNA vaccine. “Local Events” refers to reactions at the injection site, such as a sore arm or a rash. “Systemic Events” refers to reactions that involve other areas of the body, such as fevers, headaches, and joint pain. Grades 1, 2, and 3 refer to the severity of the reaction. Grade 3 is the most severe. © Source: New England Journal of Medicine

## Diversity in Vaccine Trials

Historically, vaccine trials have lacked diversity among their volunteers. Fewer people were likely to participate than in trials today. They were people who could afford to travel or take time off work. They were people who had the education to understand the trials readily. Some were able to learn about the trials simply because they already had a doctor, says Cooper. “And when the results came out, people wondered, if the vaccine’s only been tested in people who live in Northern Europe, does that mean that it would work for me? Because I live in South America or Africa.”

Now scientists recognize the importance of involving people from diverse environments and backgrounds in vaccine trials. “The racial distribution is supposed to represent as much as possible the geographic area where the trial is taking place. Or the population for whom the vaccine is intended,” explains Cooper. “It doesn’t always work out that way. But that’s what it should be. And sometimes what we do is over-

recruit people who are from minority groups. We want to make sure that there's an adequate number of those people in the trial so that we can look for differences between groups. And if we only recruit according to their representation in the overall population, we might not have enough people to be able to look at that.”

Communities of color were being hit hardest by the pandemic, both by numbers of cases and severity of outcomes. So the researchers were careful to enroll volunteers from different races and ethnicities. “About 60 percent of the participants in the Moderna mRNA trial, for example, were White. About 30 percent were either Black or had Hispanic ethnicity,” says Ledgerwood. “With a lot of effort, we were able to include a number of different, diverse groups in the trial. The other companies that tested COVID vaccines did the same thing. They all knew this was important.”

Characteristics	Placebo (N=15,170)	mRNA-1273 (N=15,181)	Total (N=30,351)
Sex — no. of participants (%)			
Male	8,062 (53.1)	7,923 (52.2)	15,985 (52.7)
Female	7,108 (46.9)	7,258 (47.8)	14,366 (47.3)
Mean age (range) — yr	51.3 (18–95)	51.4 (18–95)	51.4 (18–95)
Age category and risk for severe Covid-19 — no. of participants (%) <sup>†</sup>			
18 to <65 yr, not at risk	8,886 (58.6)	8,888 (58.5)	17,774 (58.6)
18 to <65 yr, at risk	2,535 (16.7)	2,530 (16.7)	5,065 (16.7)
≥65 yr	3,749 (24.7)	3,763 (24.8)	7,512 (24.8)
Hispanic or Latino ethnicity — no. of participants (%) <sup>‡</sup>			
Hispanic or Latino	3,114 (20.5)	3,121 (20.6)	6,235 (20.5)
Not Hispanic or Latino	11,917 (78.6)	11,918 (78.5)	23,835 (78.5)
Not reported and unknown	139 (0.9)	142 (0.9)	281 (0.9)
Race or ethnic group — no. of participants (%) <sup>‡</sup>			
White	11,995 (79.1)	12,029 (79.2)	24,024 (79.2)
Black or African American	1,527 (10.1)	1,563 (10.3)	3,090 (10.2)
Asian	731 (4.8)	651 (4.3)	1,382 (4.6)
American Indian or Alaska Native	121 (0.8)	112 (0.7)	233 (0.8)
Native Hawaiian or Other Pacific Islander	32 (0.2)	35 (0.2)	67 (0.2)
Multiracial	321 (2.1)	315 (2.1)	636 (2.1)
Other	316 (2.1)	321 (2.1)	637 (2.1)
Not reported and unknown	127 (0.8)	155 (1.0)	282 (0.9)

**Table 1. Demographic Characteristics of Trial Participants** © Source: New England Journal of Medicine

## Conclusion

Cooper stresses the importance of vaccination, which she calls “a community responsibility, something we all do to help each other.” Not everyone can get vaccinated. Some people are allergic to components of the vaccine. Some people have other health conditions that make it questionable for them. And some people may not have a strong immune response to vaccination. That can be true of the elderly and those with compromised immune systems. “So it’s not only for you that you get vaccinated, to protect yourself from getting sick,” says Cooper. “But it also helps other people around you who are vulnerable.”

### Stop and Think

1. Explain the difference between vaccine efficacy and effectiveness.
2. How is vaccine safety tested? Based on the results of the safety tests, what can you say about the safety of the Moderna mRNA vaccine?
3. Why is it important to consider the diversity of participants when designing a clinical trial?