

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. As the chief medical officer and deputy director of the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH) in Bethesda, Maryland, 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

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“A vaccine provides the immune system a peek at what that virus would look like if it were encountered,” she says. Viruses have DNA or RNA that encodes proteins, and the proteins are what our immune system reacts to. “Viruses generally have approximately 10 to 30 expressed proteins, but usually only one or two of those evoke a protective immune response that vaccines aim to replicate. They are often the proteins on the outer surface of the virus. In the case of coronavirus it’s the spike protein—that’s the piece that sticks up.”

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Traditional vaccines introduce those important 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 called an mRNA vaccine. This type of vaccine works somewhat differently than a traditional vaccine. (**Fig. 2**) It introduces not the protein itself, but mRNA containing instructions for making the protein. The m in mRNA stands for messenger, because that's the molecule's function. In nature, it carries instructions for making proteins from the DNA in a cell's nucleus to the ribosomes, the cell's protein-building machinery, located outside the nucleus.

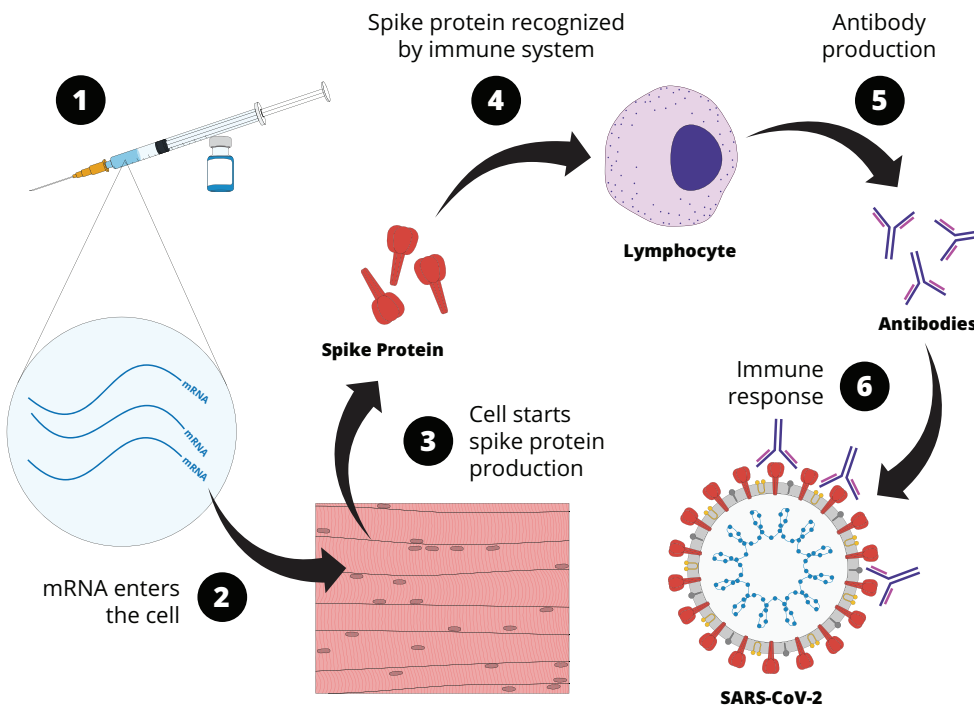


Figure 2. How mRNA Vaccines Work

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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. The mRNA never enters the cell nucleus, just the cytoplasm (the part of the cell outside the nucleus)—and it doesn't linger very long. When cells are done making the protein, the mRNA is degraded and the cells display the protein on their surfaces, where immune cells can spot them. That triggers the body's complex immune response. The immune system prepares to recognize and combat the virus itself, should it ever encounter it.

How Were mRNA Vaccines Developed?

While the Moderna and Pfizer COVID-19 vaccines are the first mRNA vaccines to receive authorization for use, 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 body’s innate immune system recognized the mRNA as foreign and went on the attack, causing intense symptoms like sore arms and fevers, and breaking down the mRNA, ultimately limiting the immune responses.

Then came a breakthrough. In 2005, researchers at the University of Pennsylvania figured out that if they made minor changes to the genetic code in the mRNA, the immune system wouldn’t react as strongly—but it would still deliver the desired immune response. A further important step was necessary: Biochemists at the University of British Columbia determined that the mRNA needed to be encased in a protective fatty coating. “Lipid nanoparticles protect the mRNA from being degraded on the way into the cells,” says Ledgerwood. Together, those advances made it possible to develop effective mRNA vaccines with side effects that people could tolerate.

By the time SARS-CoV-2 appeared on the scene, not only had mRNA vaccines come a long way, but scientists already knew quite a bit about coronaviruses generally. In fact, back in 2004, they’d even studied a DNA vaccine against a very similar virus, SARS-CoV-1, the virus that emerged in 2003.

“We had done research on SARS-CoV-1 here at the NIH at the Vaccine Research Center, and we studied a prototype vaccine for that virus encoding that spike protein,” says Ledgerwood. “We studied it in a very small group of healthy people, 10 people total, but it gave us enough information to know that if we encountered another virus like that, that spike protein could be safely delivered by gene-based vaccines and would induce an immune response.”

Then, in 2012, another coronavirus of concern emerged—Middle East Respiratory Syndrome (MERS), developed in camels (**Fig. 3**). By 2017, researchers Dr. Barney Graham and Dr. Kizzmekia Corbett of the Vaccine Research Center had developed a prototype vaccine with a stabilized version of the spike protein from the virus. When they gave the prototype vaccine to laboratory animals, the animals had an immune response. Fortunately, neither SARS-CoV-1 nor MERS reached pandemic level, so the vaccines never made it past the prototype stage. But “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.

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Fast-forward to December 2019. “There was a lot of interest and concern about what was happening with this outbreak in China,” says Ledgerwood. Nobody knew yet how big the outbreak would be or even whether the virus could spread from person to person, but 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 abundantly obvious that the vaccine was indeed needed. COVID-19 was spreading fast around the world, 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 in the government, the private sector, academia, industry. 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.’”

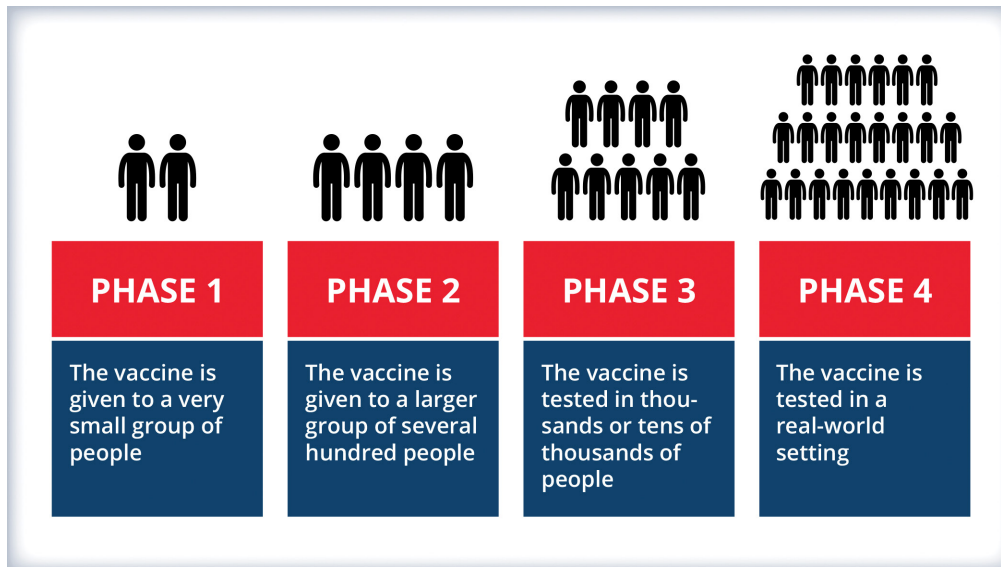


Figure 4. Stages of Clinical Trials

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 before it is given to a somewhat larger group, in the second phase, to further study its safety and effectiveness. In the third phase of the trial, 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

How Are Vaccines Tested?

To find out whether a vaccine (or a drug, medical device, treatment, etc.) is safe and effective, scientists conduct **clinical trials** (Fig. 4). They determine all the details in advance, including how many subjects will be tested and what criteria must be met for the trial to end and for the vaccine to be considered safe and effective. This is where the team’s statisticians really shine. “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.

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—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 to further study its safety and to determine the dosing regimen. “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, since with a larger group of subjects, less common reactions might emerge. But the main aim of this phase is **efficacy**. Subjects are randomly assigned to groups who receive either the vaccine or a placebo (a dummy vaccine, such as a shot of salt water), and these two groups are compared to see how well the vaccine protects people from illness. To prevent people’s beliefs from influencing their interpretation of the outcome, the trial is **double blind** in this phase—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 benchmarks the vaccine will need to meet to demonstrate that it works. If it meets those benchmarks, the vaccine developers can apply to the FDA for authorization and eventually approval, allowing the vaccine to be administered.

The scientists try to make sure the population of volunteers in clinical trials of vaccines represents the racial distribution in both the geographic area where the trial is taking place and the population for which the vaccine is intended. “That way people can be confident that nobody was left out of the testing process,” Dr. Lisa Cooper says. Historically these efforts have often fallen short, but the COVID-19 mRNA vaccine trials were successful in recruiting diverse volunteers.

- **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, such as 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.” This unprecedented crisis required unprecedented cooperation and scale.

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—it’s still built to code, and 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 simultaneously instead of one action 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. “One important aspect of our success was that 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 factor that allowed the COVID-19 vaccines to be tested quickly was the scale of the pandemic itself. A trial reaches an efficacy benchmark only when a predefined number of people have become sick, as determined in the protocol. If infection rates are low, reaching that benchmark 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.

To figure out where the virus would be spreading, Ledgerwood and her colleagues used a method called predictive analytics. “By integrating population demographic and emerging epidemiological data, we could start to assess which communities were at highest risk,” says Ledgerwood. “Then we populated the map with all of that data in it, with all of the potential participant sites that could participate in trials. Then the drug companies were able to choose sites that would allow them a broad population that might be at risk, based on all of that data.” For example, the phase three trial for the Moderna mRNA COVID-19 vaccine enrolled volunteers at 99 sites in 35 US states.

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.