

PART 3

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

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Vaccine Efficacy

When researchers design trials to learn whether a vaccine works, they're looking to determine **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.

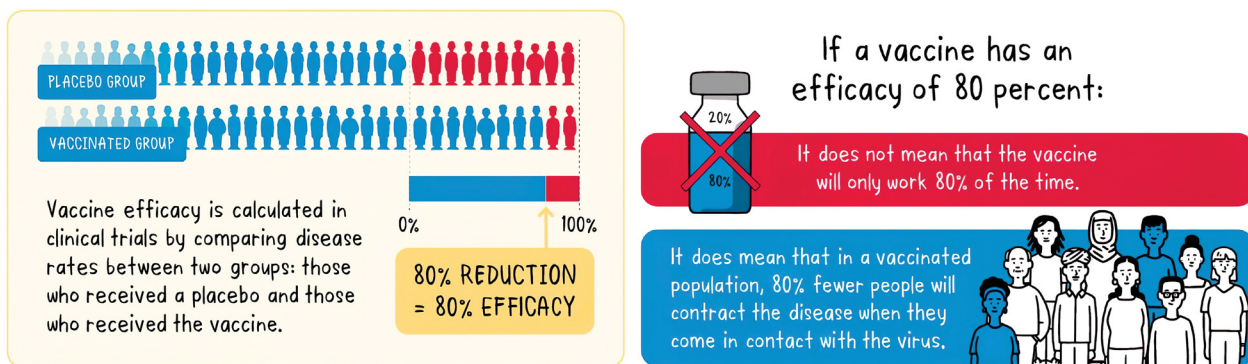


Figure 1. Vaccine Efficacy

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 in the trial a dummy shot of salt water, gave another group the vaccine, and 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 dummy shot to the number of sick people who received the real vaccine. Then they expressed that comparison as a percentage. That number is the vaccine's efficacy. For example, if a vaccine has a 95 percent efficacy, that means 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 never encountered the virus, or their 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. Because of the messiness of the uncontrolled variables, vaccine effectiveness is often a little lower than vaccine efficacy.

Simple infection is not the whole story, though, as Dr. Lisa Cooper emphasizes. Researchers also measure the extent to which a vaccine protects people from getting sick enough that they require treatment or hospitalization, and whether they end up 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. “So, 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

To better understand vaccine efficacy, 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—a shot of salt water. Others received a shot containing 100 micrograms of vaccine. They were given their shots approximately one month apart. Both sets of volunteers were monitored for side effects and for symptomatic COVID-19 until the trial ended. Typically in clinical trials some volunteers become ineligible or drop out, but in this trial 96 percent of those enrolled received both injections, an unusually high rate for a trial of this size. 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, a molecular biologist at AMNH, 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, a statistical signal.” The researchers need to see such strong results—for example, the event they were looking for occurring so often or with such high intensity—that it would be impossible for the outcomes to have happened just by chance. “This is what tips

researchers off that they're onto something. 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 developed by the different pharmaceutical companies were very efficacious," says DeSalle.

The FDA guidance document for COVID-19 vaccines set at least 50 percent efficacy as an endpoint goal and aimed for at least 60 percent efficacy. Using this efficacy aim, statisticians calculated the number of volunteers necessary (the trial enrolled 30,420 participants) and calculated that the trials needed to run until at least 151 people had contracted a symptomatic confirmed case of COVID-19. That would give the researchers enough cases to determine with 90 percent confidence that their conclusions about the vaccine's efficacy were true, rather than just due to chance.

The protocol called for the data safety monitoring board led by the NIH to take a peek at the data at two points along the way. The first planned interim analysis of 95 COVID-19 cases were observed by November 11, 2020. The results thrilled everyone. The vaccine efficacy was estimated at 94.5 percent. And the good news held. In the formal analysis, on November 21, 2020, there were 196 cases and an efficacy of 94.1 percent. Analysis of the safety data showed that the vaccine was safe and well tolerated, and this data allowed for FDA emergency authorization of the vaccine.

Vaccine Efficacy in Clinical Trials

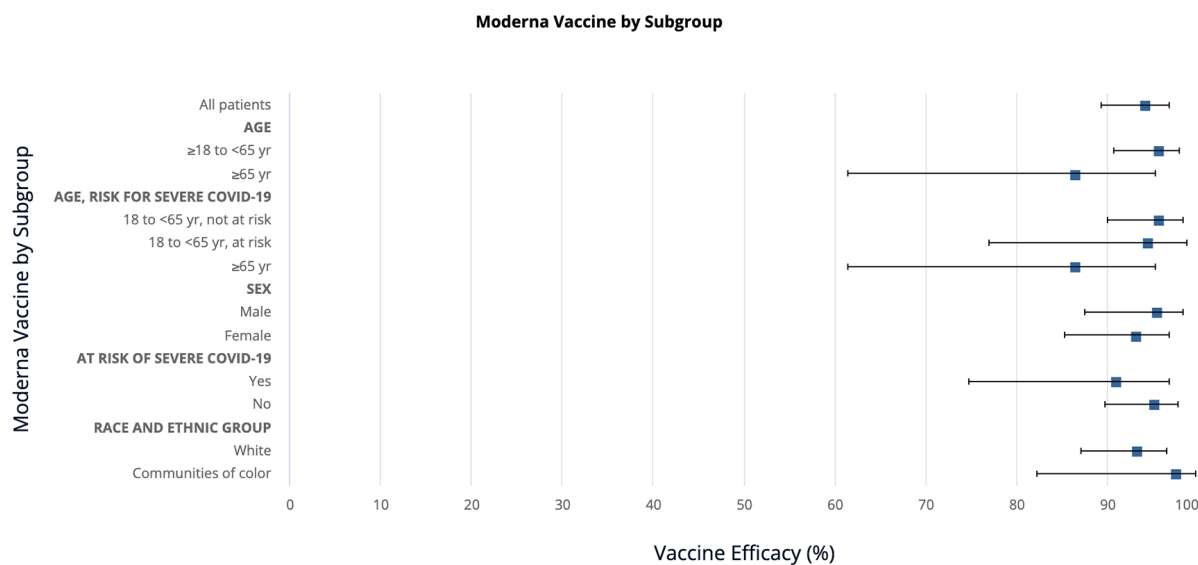


Figure 2. Vaccine Efficacy of Moderna COVID-19 Vaccine by Subgroup

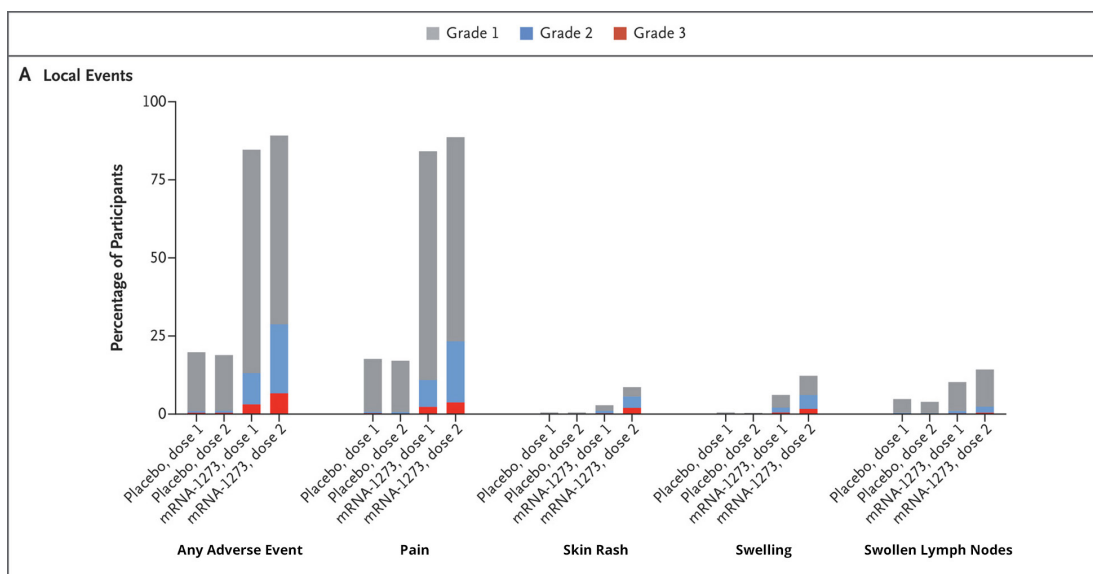
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Safety

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 (84.2 percent vs. 19.8 percent for the first dose, and 88.6 percent vs. 18.8 percent for the second). These symptoms resolved in four or five days. More volunteers who received the vaccine than the placebo experienced mild systemic symptoms like fever, headache, and fatigue as well (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—and low—in both the vaccinated and placebo groups (**Fig. 2**). 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 for the most part, or certainly like within a week or two,” says Cooper. The volunteers in the COVID-19 mRNA vaccine trial were followed for up to six months, “and we didn’t see safety issues come up in those groups, [which] means that the vaccine is safe,” she says.



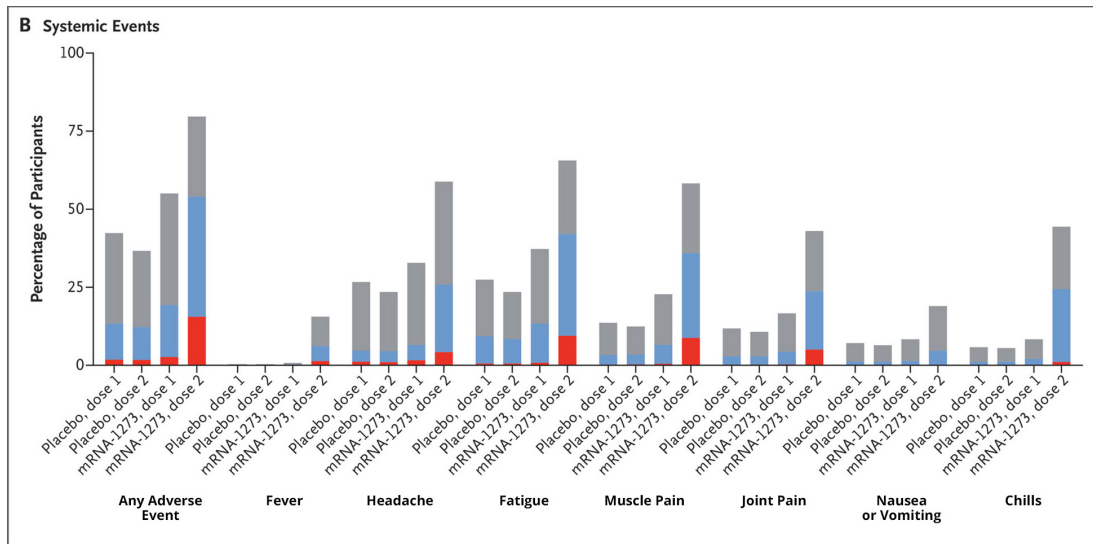


Figure 3. Reactions to the Vaccine

This chart shows the percentage of trial participants who reported any of a list of reactions within seven days after receiving a first or second injection 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, and “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, with Grade 3 being the most severe. © Source: New England Journal of Medicine

Diversity in Vaccine Trials

Historically, vaccine trials have lacked diversity among their volunteers. The people most likely to participate were those who could afford to travel or take time off work, who had the education to understand the trials readily, or who were able to learn about them 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 actually oversample or over-recruit people who are from minority groups, because 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.”

Because communities of color were being hit hardest by the pandemic, both by numbers of cases and severity of outcomes, 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, and about 30 percent were either Black or had Hispanic ethnicity,” says Ledgerwood. “With a lot of effort, it worked out that 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 (%) [†]			
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 (%) [‡]			
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 (%) [‡]			
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 or have other health conditions that make it questionable for them. And some people, such as the elderly and those with compromised immune systems, may not have a strong immune response to vaccination. “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?