

# Want to Know More About mRNA Before Your COVID Jab?

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## — A primer on the history, scope, and safety of mRNA vaccines and therapeutics

by [Kristina Fiore](#), Director of Enterprise & Investigative Reporting, MedPage Today December 3, 2020

Clinicians will start rolling up their sleeves in just a few weeks to get their first doses of COVID-19 vaccines, both of which use mRNA technology to induce an immune response.

For those who want more information on the history and science of mRNA vaccines and therapeutics before getting their jab, here's a primer.

### **How It Works**

Biologically, messenger RNA is transcribed from DNA and travels into a cell's cytoplasm where it's translated by ribosomes into proteins.

For the Pfizer/BioNTech and Moderna vaccines, the synthesized mRNA is cloaked in a lipid nanoparticle in order to evade the immune system when it's injected. Once it's inside a cell, the

ribosomes will get to work pumping out the spike protein of SARS-CoV-2.

The immune system then mounts a response to that protein, conferring immunity to the virus without ever having been infected by it.

Essentially, instead of pharma producing the proteins via an expensive and difficult process, mRNA enlists the body to do the work. The capability to produce mRNA so rapidly is one reason these vaccines are out front in the global race for a COVID-19 vaccine.

### **Never Been Done Before?**

That's not completely true. While an mRNA vaccine has never been on the market anywhere in the world, mRNA vaccines have been tested in humans before, for at least four infectious diseases: rabies, influenza, cytomegalovirus, and Zika.

In 2017, German biotech CureVac [published results in \*The Lancet\* opens in a new tab or window](#) for a phase I trial of its mRNA rabies vaccine, and in January of this year the company issued results [via press release opens in a new tab or window](#) from a phase I trial of its low-dose rabies mRNA vaccine.

Last year, Moderna and German researchers published the phase I results of [two mRNA vaccines against influenza opens in a new tab or window](#). In January, Moderna announced results of its phase I study of an [mRNA vaccine against cytomegalovirus opens in a new tab or window](#), and just this past April as the pandemic raged, the company reported interim data from its [mRNA vaccine against Zika opens in a new tab or window](#).

### **Medical News from Around the Web**

In a paper in [Nature Reviews Drug Discovery](#) opens in a new tab or window, Drew Weissman, MD, PhD, of the University of Pennsylvania in Philadelphia and an early pioneer of mRNA technology, and colleagues wrote that early results from the rabies and flu mRNA vaccines "were somewhat modest, leading to more cautious expectations about the translation of preclinical success to the clinic."

The team noted that in both trials, immunogenicity was "more modest in humans than was expected based on animal models, a phenomenon also observed with DNA-based vaccines, and the side effects were not trivial."

Some indication of immunogenicity can also be gleaned from the COVID vaccine trials. Topline final results with the Pfizer/BioNTech showed [95% effectiveness](#) opens in a new tab or window in preventing symptomatic infection within 2 months of the second dose. Moderna's vaccine showed an [efficacy rate of 94.1%](#) opens in a new tab or window in final phase III results. Both products appeared [very effective in preventing severe illness](#) opens in a new tab or window as well as more moderate cases.

Durability of these effects remains an open question. However, [follow-up data from a phase I study of Moderna's product](#) opens in a new tab or window, spanning 4 months after the first dose, showed a persistent neutralizing antibody response, though with modest declines over that period, particularly in older participants.

### **What Do We Know About Safety?**

While the flu and rabies vaccines appeared to be "safe and reasonably well tolerated," Weissman and colleagues wrote, trials did show "moderate and in rare cases severe injection site

or systemic reactions."

Their chief safety concerns, which they said should be closely watched in future trials, were about local and systemic inflammation, as well as keeping tabs on the "expressed immunogen" and on any auto-reactive antibodies.

"A possible concern could be that some mRNA-based vaccine platforms induce potent type I interferon responses, which have been associated not only with inflammation but also potentially with autoimmunity," they wrote. "Thus, identification of individuals at an increased risk of autoimmune reactions before mRNA vaccination may allow reasonable precautions to be taken."

The authors also noted that extracellular RNA could contribute to edema, and cited a study that showed it "promoted blood coagulation and pathological thrombus formation."

"Safety will therefore need continued evaluation as different mRNA modalities and delivery systems are utilized for the first time in humans and are tested in larger patient populations," they wrote in the paper, which was published in 2018.

Systemic effects have definitely been seen with the two mRNA COVID vaccines, with news reports quoting participants as complaining of symptoms like "bad flu." While Pfizer/BioNTech reported [no serious safety concerns opens in a new tab or window](#) with their COVID-19 vaccine, patients did experience grade 3 fatigue and headache at rates of 3.8% and 2%, respectively.

Moderna did not release figures for adverse events in announcing final topline results, but said there were "no new serious safety concerns." [Interim data from the company's phase III trial opens in a new tab or window](#), analyzed when 95

infections had been recorded, did include adverse event rates: fatigue (9.7%), myalgia (8.9%), arthralgia (5.2%), headache (4.5%), pain (4.1%), and erythema/redness at the injection site (2.0%).

### **Why Did Earlier Vaccines Stall?**

"A major factor is that there's not a sense of urgency," Dennis Burton, PhD, of Scripps Translational Research Clinic in La Jolla, California, told *MedPage Today*.

Zika has been relatively contained; rabies vaccines are already sufficiently effective; and influenza remains a difficult target, Burton said.

While tolerability may have been an issue, safety wasn't, he said. "There's no risk of incorporation into host chromosomes, and levels of mRNA and protein will decline and clear."

"We know broadly that the overall approach is pretty safe," Burton said, but noted that it was important that adverse events are monitored and followed up.

He cautioned that just based on the sheer number of people who will be vaccinated for COVID-19, events will occur, and most will likely be unrelated to the vaccine. If people feel that concerns about those events are adequately addressed, they should be less likely to harbor reservations about taking the vaccine, and more inclined to help achieve the levels of herd immunity needed to end the pandemic.

"One of the things we're most concerned about is that people won't get vaccinated," he said. "But the risks of this disease are going to be way higher than the risks associated with vaccination."

### **What Else Do I Need to Know?**

Introducing synthetic mRNA into cells also holds promise as a type of replacement therapy for diseases in which production of vital proteins is inadequate or defective. It could thus hold advantages over gene therapies and protein replacement: less risky than the former, less frequent dosing than the latter, and cheaper than either.

Preclinical work on therapeutic mRNA [goes back at least to 1990](#)[opens in a new tab or window](#), with successful protein production seen in mice. Two years later, [a study showed](#)[opens in a new tab or window](#) that mRNA injected into the hypothalamus of rats with a genetic mutation enabled production of vasopressin and reversed their diabetes.

But those early results didn't garner substantial interest in mRNA therapeutics due to concerns about mRNA instability, high innate immunogenicity, and inefficient delivery, Weissman and colleagues wrote. "Instead, the field pursued DNA-based and protein-based therapeutic approaches."

[Finally, in 2005](#)[opens in a new tab or window](#), Weissman and Katalin Kariko, who is now a senior vice president at BioNTech, modified the mRNA so that it could evade immune detection and boost protein production, according to an [article in STAT](#)[opens in a new tab or window](#). This is considered one of the groundbreaking moments in mRNA therapeutics, experts told *STAT*.

Since then, the technology has been used not just in vaccines for infectious diseases, but also as a means to rev up the immune system to battle cancer. mRNA can target tumor-associated antigens expressed mainly by cancerous cells, like certain growth factors. These therapeutic -- rather than prophylactic -- vaccines have been tested in a range of cancers,

including acute myeloid leukemia, multiple myeloma, glioblastoma, melanoma, prostate cancer, and others.

There are fewer trials of regular therapeutics, but one that has garnered some attention is [an mRNA heart failure therapy being developed by Moderna and AstraZeneca opens in a new tab or window](#) that encodes for vascular endothelial growth factor A. Preclinical studies showed new blood vessel creation and improved cardiac function, and a phase I study in diabetic patients [published in \*Nature Communications\* in 2019 opens in a new tab or window](#) showed enhanced blood flow, which could indicate "therapeutic potential for regenerative angiogenesis."

Whether the apparent success of Pfizer and Moderna's vaccines will spark a wave of mRNA therapeutic development remains to be seen, but Burton cautioned that the coronavirus spike protein "does seem to be a particularly easy target."

"Will RNA work for all vaccines? I don't think we can say that yet," Burton said. "It's a huge leap forward. It's very quick to make and has a lot of advantages. But I think SARS-CoV-2 is an easy test relative to some of the other viruses we have to deal with."



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