

Medical News & Perspectives

COVID-19 and mRNA Vaccines—First Large Test for a New Approach

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On January 10, Chinese researchers posted the novel coronavirus' RNA sequence on a preprint server. Immediately, scientists who study genetic vaccines turned their efforts to the emerging pathogen that causes coronavirus disease 2019 (COVID-19). They knew that rapid response genetic platforms could shave precious weeks to months off development, crucial during a pandemic.

They were right. When the [first US clinical trial](#) for a vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began just 66 days later, volunteers received mRNA-1273, a messenger RNA (mRNA) candidate codeveloped by biotechnology company Moderna, Inc and the National Institute of Allergy and Infectious Diseases (NIAID).

On July 27, based on [encouraging early results](#), mRNA-1273 and another mRNA vaccine candidate, BNT162b2 from BioNTech and Pfizer, both entered phase

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3 trials, which together will enroll an estimated 60 000 volunteers. The milestone came "at a remarkably rapid pace compared to the usual pace for vaccine preparation," National Institutes of Health (NIH) Director Francis Collins, MD, PhD, said at a press briefing that day. Results could be available as early as this fall, NIH officials said.

Despite the unprecedented speed, mRNA vaccines are clinically unproven. No commercially available vaccines use the platform and, until now, it hasn't been tested in large-scale human trials. With COVID-19, that's all set to change. Experts said in interviews that if the technology pans out, the pandemic could help to usher in a new plug-and-play approach to vaccinology.

The Genetic Advantage

Current antiviral vaccine designs can be [described](#) as falling into 2 camps: protein based or gene based. Protein-based vaccines deliver the immune system-stimulating antigen to the body. This category includes whole-inactivated (killed) vaccines, as in the polio and flu shots, and



subunit vaccines and virus-like particles, like in the hepatitis B and human papillomavirus vaccines.

Gene-based vaccines take a different tack. They carry the genetic instructions for the host's cells to make the antigen, which more closely mimics a natural infection. In the case of coronaviruses, the antigen of interest is the surface spike protein the virus uses to bind and fuse with human cells. "You're not giving them the protein—you're giving them the genetic material that then instructs them how to make that spike protein, to which they make an antibody response that hopefully is protective," University of Pennsylvania vaccinology professor Paul Offit, MD, explained in a [JAMA livestream](#) in June.

The approach isn't entirely unfamiliar. In live-attenuated vaccines, like the measles, mumps, and rubella shot, weakened viruses incorporate their genetic instructions into host cells, causing the body to churn out viral copies that elicit antibody and T-cell responses. In newer gene-based designs—viral vector, DNA, and mRNA vaccines—scientists synthesize and insert genetic instructions from the pathogen of interest to induce immune responses.

The viral vector technique transports genetic information in a less harmful virus—often a common cold-causing adenovirus—that's sometimes engineered so it can't replicate in the host. DNA and mRNA vaccine designs deliver naked nucleic acids or, more recently, encapsulate them in a carrier nanoparticle. Within each of these versatile platforms, the same production and purification methods and manufacturing facilities can be used to make vaccines for different diseases.

These highly adaptable techniques were waiting in the wings when COVID-19 hit. "The people who jumped on this right away are the people who had vaccine platforms that were conducive for this that were simply sitting there," said Louis Picker, MD, associate director of the Oregon Health & Science University's Vaccine and Gene Therapy Institute. "All they had to do is basically figure out what part of [the virus] they were going to put in the vaccine and then run with it."

Thanks to research beginning in 2002 on the severe acute respiratory syndrome coronavirus and then the Middle East respiratory syndrome coronavirus, which emerged a decade later, scientists knew to focus their initial attention on the novel

coronavirus' spike protein. They also already knew which genetic modifications would stabilize the spike in its "prefusion" configuration—important for a robust and safe antibody response—and those that would make the mRNA less inflammatory and therefore safer. They had also learned how to purify mRNA to rid it of contaminants and how to protect it from degrading too quickly in the body by encasing it in lipid carrier molecules. These delivery vehicles, already in use with therapeutic small interfering RNAs, also help mRNA cross the cell membrane and may even have an immune-stimulating adjuvant effect.

Many of these [innovations](#) weren't possible until recently, according to Barney Graham, MD, PhD, deputy director of the NIAID Vaccine Research Center. "Over the last 10 years, vaccinology has just changed radically," he said. "I've been doing this kind of work for a long time and the kinds of things that can be done now, the technologies available, the way we can understand things in a very detailed level is really stunning to me."

Unlike conventional vaccines, mRNA vaccines aren't grown in eggs or cells, a time-consuming and costly process. At their essence, these vaccines are simply chemicals catalyzed in test tube or a tank. This makes them easier to develop quickly and—at least theoretically—at scale, although they've never been mass-produced before.

"We were making RNA within a week or so" of the SARS-CoV-2 sequence being published, said Drew Weissman, MD, PhD, who researches mRNA vaccines at the University of Pennsylvania Perelman School of Medicine. That speed propelled development: according to Weissman, both groups currently testing nucleic acid-based vaccines in phase 3 trials licensed his team's mRNA formulation from the university.

Why mRNA?

As of August 20, thirty [potential vaccines](#) against COVID-19 were in clinical trials, with another 139 in preclinical development, including both gene- and [protein-based](#) candidates. But genetic approaches have a potential immunological advantage. In addition to eliciting antibodies and CD4+ helper T cells, they recruit CD8+ cytotoxic T cells, also known as killer T cells, through the major histocompatibility class I pathway.

According to Otto Yang, MD, an infectious disease researcher and clinician at the

University of California, Los Angeles, David Geffen School of Medicine, the body's cells only display viral proteins on their surface through this pathway if those cells themselves have produced the proteins. "If you just inject a protein or inject a dead virus, it doesn't get into that pathway and doesn't get displayed that way, and so the T cells don't get stimulated," he said.

Even among the gene-based platforms, distinct advantages exist. In cutting out the viral vector, both DNA and mRNA vaccines eliminate the risk of preexisting immunity against it, which can limit effectiveness. "If your immune system clears a vector before it will actually get into the cells, that's a big problem," Yang said. Such immunity could also be more common in some geographic areas than others, rendering a vectored vaccine more or less effective depending on the region.

Preexisting immunity could explain why a non-replicating viral vector COVID-19 candidate from CanSino Biologics Inc and several Chinese institutions elicited less-than-impressive neutralizing antibody levels in a [phase 1 trial](#). Preexisting neutralizing antibodies to the vector, the human adenovirus 5, known as Ad5, [ranges](#) from up to 69% in the US to 80% in Africa. Of additional concern, Offit said in an [August livestream](#), more than a decade ago, men with preexisting Ad5 immunity had an [increased risk](#) of acquiring HIV infection after receiving an experimental Ad5-vectored HIV vaccine.

To get around these issues, [ChAdOx1 nCoV-19](#), a non-replicating viral vector candidate in phase 3 trials from AstraZeneca and the University of Oxford, uses an adenovirus that infects chimpanzees instead of humans. But, it's possible that cross-reacting preexisting immunity to human adenoviruses could still diminish the response.

According to Weissman, mRNA vaccines also have a leg up on DNA vaccines. In a DNA vaccine, the genetic material must first enter the host cell's nucleus. From there, messenger RNA is created, which travels out of the nucleus into the cytoplasm, where protein is formed from it. However, genetic information can only enter the nucleus when the cell is dividing, making the process inefficient.

Researchers are trying to solve this problem using electric pulses to increase DNA uptake into cells at the time of vaccination. But the mRNA platform simply by-

passes that step. "Ninety-five percent of cells that meet the RNA take it up and make protein, so it's an incredibly efficient process," Weissman said.

Proof Is in the Pudding

The first 4 COVID-19 vaccine developers with published clinical trial data all used either a non-replicating adenovirus or mRNA platform. The US government is betting on some of these new technologies. Under the auspices of its [Operation Warp Speed](#) vaccine development initiative, it has already purchased hundreds of millions of doses of ChAdOx1 nCoV-19, mRNA-1273, BNT162b2, and an investigational non-replicating viral vector [vaccine](#) in early trials from Johnson & Johnson-owned Janssen Pharmaceutical Companies, as well as other candidates. Doses should be standing by if or when any of these are approved.

All eyes are now on safety and effectiveness. Non-replicating viral vector vaccines, while a relatively recent approach, have been studied extensively in HIV and other disease trials. Janssen's new [Ebola vaccine regimen](#), which uses 2 different non-replicating viral vectors, [received](#) European authorization in July.

mRNA vaccines haven't been clinically tested to the same extent, though. Researchers have studied investigational mRNA-based therapeutic antibodies and therapeutic cancer vaccines. But German firm CureVac and academic collaborators published phase 1 results from the first prophylactic [mRNA vaccine clinical trial](#), for a candidate against rabies, less than 3 years ago.

Since then, potential mRNA vaccines against [rabies](#), [influenza](#), [Zika](#), and a few other viruses have been studied in small, early-phase trials, many of which are still underway. In both rabies and influenza trials, the candidates stimulated promising but lower-than-expected neutralizing antibodies. Some moderate and severe injection site or systemic reactions were reported, although severe events were rare.

So far, in early COVID-19 trials, mRNA platforms have turned up encouraging results. "Certainly, these vaccines look like they're generating the immune response that we need, and the reaction profiles have not been associated with severe reactions," said Kathryn Edwards, MD, scientific director of the Vanderbilt Vaccine Research Program. But, she continued, "the real proof of the pudding will be the phase 3

trials where we see if the vaccine actually prevents disease." The US Food and Drug Administration has [said](#) that a COVID-19 vaccine will need at least 50% efficacy to be approved.

Tolerability could be another issue. "People will have to know that they may have some local reactions or feel like they're a little under the weather for a day or so after the vaccine," said Edwards, who is among the independent experts monitoring investigational COVID-19 vaccine safety. She and others said that, as with any new pharmaceutical product, phase 3 studies could also reveal more serious safety concerns and unexpected adverse effects could emerge later.

Speaking at the July 27 media briefing, Collins addressed concerns: "Yes, we're going fast. But, no, we are not going to compromise safety or efficacy." Experts say several factors argue for mRNA vaccines' safety. For one, mRNA can't cause an infection. It also doesn't enter the cell's nucleus, so the chance of its integration into human DNA is believed to be very low. In addition, the body breaks down mRNA and its lipid carrier within a matter of hours, assuaging some concerns about long-term risks.

However, this rapid degradation raises questions about mRNA vaccines' protective duration. Of added concern for vaccine durability, researchers in Hong Kong recently [confirmed](#) that a man with SARS-CoV-2 was later reinfected, although his second case was asymptomatic. Yang and colleagues found that [antibodies rapidly wane](#) among patients with mild COVID-19.

The current candidates' 2-dose regimens could help to overcome this, Yang noted, and their cell-mediated immunity should provide additional oomph.

Offit, who is a member of an NIH Accelerating COVID-19 Therapeutic Interventions and Vaccines working group, said that how long protection from any COVID-19 vaccine lasts likely won't be known until after a product is approved and put into use. But, as Picker put it, a vaccine that's safe and effective for even a finite amount of time could be enough to "break the back of the pandemic."

Beyond COVID-19

If an mRNA vaccine works, the implications could stretch far beyond COVID-19. Success could pave the way for the platform's widespread use for both emerging and established pathogens.

"We are really making great strides in vaccine development, which will hopefully change the way vaccines are approached in the future," said Amesh Adalja, MD, a senior scholar at the Johns Hopkins University Center for Health Security.

One such advance might be thermostable vaccines that don't have to be frozen or refrigerated, something scientists say mRNA might enable. Chinese researchers recently [showed](#) that a potential mRNA-based SARS-CoV-2 vaccine could be stored at room temperature for at least a week.

Weissman is trying to develop a more potent second-generation mRNA vaccine that protects with a single shot. He's also set his sights on a universal coronavirus vac-

cine using the genetic platform. "We've had 3 coronavirus epidemics in the past 20 years," he said. "The next time this happens, we'll have a vaccine already made, ready to be shipped out and used very quickly to prevent the pandemic from taking over."

Before COVID-19, his team was working on [mRNA flu vaccines](#), as well as candidates for genital herpes and HIV. Influenza viruses acquire variations from season to season, making them excellent candidates for a rapid "vaccine on demand" platform.

In Weissman's view, mRNA has the potential to be truly transformative. In a soon-to-be-published study, he said he combined mRNA for 20 antigens for different diseases in the same vaccine. All 20 elicited good responses in mice. In theory, he said, it might one day be possible for children to get 2 shots that cover their more than 50 vaccinations.

He's not alone in that belief. The authors of a recent [review article](#) wrote that mRNA vaccines that "can simultaneously target multiple antigens, and pathogens will have broad utility for a range of diseases, reduce the number and frequency of vaccinations, and alleviate healthcare worker burden."

Much of this could rest on the success or failure of an mRNA COVID-19 vaccine—and hopes are high. "I think this is an opportunity for that technology to shine," Yang said. ■

Additional Reporting: Elena Guobye.

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