FEATURE

How — and When — Can the Coronavirus Vaccine Become a Reality?

It is likely we'll eventually have a coronavirus vaccine — but perhaps not as quickly as some expect. From development, to clinical trials and distribution, ProPublica reporter Caroline Chen explains the tremendous challenges that lie ahead.

by Caroline Chen

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Series: Coronavirus

The U.S. Response to COVID-19

It's been six months since researchers in China said they had identified a novel coronavirus spreading in the city of Wuhan. Hope and desire for a vaccine to end the global devastation is growing with each passing week.

Almost every day, I hear people making plans around the eventual arrival of a coronavirus vaccine — office reopenings, rescheduled weddings, family reunions and international travel. In recent weeks, colleagues and friends have asked me with growing urgency: "When will we have a vaccine? Will it be any good?"

Help Us Report on Coronavirus

Are you a public health worker, medical provider, elected official, patient or other COVID-19 expert? Help make sure our journalism is responsible and focused on the right issues.

Note: If you develop emergency warning signs for COVID-19, such as difficulty breathing or bluish lips, get medical attention immediately. The CDC has more information on what to do if you are sick.

At the same time, other friends have been telling me, "When I hear that this is going to be the fastest vaccine developed ever, that doesn't make me feel good — it makes me feel nervous that they're going to cut corners."

These questions and concerns resonate with me. I, too, want a vaccine, but I want reassurance that it's truly safe and effective. So I talked to a dozen people in the vaccine world: scientists, pediatricians, pharmaceutical manufacturers, as well as staff at the National Institutes of Health and the Food and Drug Administration.

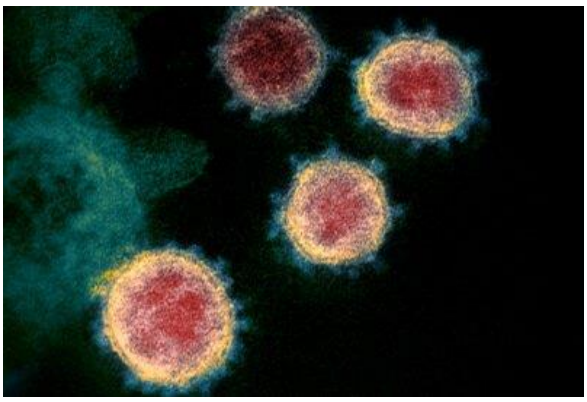
Let me tell you this up front: If you're imagining there'll be one golden day when a vaccine is approved and the pandemic will be over — *Finally! We can all crowd into one another's living rooms and resume choir practice again* — I'm afraid it won't be quite like that. But it will be the beginning of the end.

There's much to be hopeful about, and enormous challenges lie ahead. Let's dig in.

Scientists Are Optimistic About a COVID-19 Vaccine

Everyone I spoke to was optimistic that manufacturers would eventually develop a COVID-19 vaccine. This isn't just because there are so many scientists and pharmaceutical companies working on the endeavor, and so much money being poured into it, though that also raises the chance of success.

The goal of vaccine developers is to mimic a natural infection as closely as possible without getting a healthy individual sick. There are many ways to do this. You can give a person a weakened virus or a dead virus. You can also show the immune system just part of the virus. Many manufacturers are creating vaccines involving only the "spike protein," the part on the surface of the coronavirus that attaches to the human cell it is trying to enter. Once the immune system has learned what the spike protein looks like, when it encounters it again, as part of a real coronavirus, it should know how to defend itself.



A transmission electron microscope image shows coronavirus particles. Spike proteins on the outer edge of the virus attach to human cells. (Image Point FR - LPN/BSIP/Universal Images Group via Getty Images)

Dr. John Mascola, director of the Vaccine Research Center at the NIH's National Institute of Allergy and Infectious Diseases, said he is hopeful because our natural immune system, when healthy, is capable of handling the infection. "Most of the time, people recover from COVID-19, because their immune system eventually clears the virus," he said. He contrasted the coronavirus to HIV, for which scientists so far have struggled to create an effective vaccine: "In HIV, the natural immune

system is not effective and people get AIDS." In this virus's case, if we can mimic a natural infection closely enough, it's likely that a vaccine will work.

The Coronavirus Is Not the Flu. In This Case, That's Good News.

There are some vaccines that are extremely effective, like the MMR vaccine: One dose is about 93% effective at preventing measles; two doses (which is what's recommended) are about 97% effective.

Other vaccines aren't as perfect. The flu shot's effectiveness varies year to year. During the 2019-20 flu season, it was about 45% effective at preventing infections, according to the CDC. The year before, it was just 29% effective.

The experts I talked to said that the flu shot was an outlier because of the rapidly shifting nature of the influenza virus. Because of its frequent mutations, developers have to make each year's vaccine based on educated guesses on what strains of the flu virus will be circulating next year. Sometimes, they misjudge, resulting in a vaccine that doesn't exactly match up with the flu strains that are most prevalent the following season.

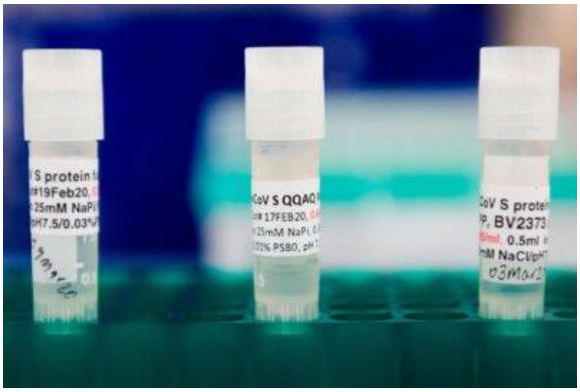
"Influenza changes year in, year out, and the people who get it tend to be extremes in age — elderly and children — so you don't tend to have as good an immune response," said Dr. Nicholas Kartsonis, infectious disease and vaccines clinical research lead for Merck, which has two COVID-19 vaccine candidates that it plans to start in human trials this year.

One lucky break COVID-19 vaccine developers have had is that this coronavirus hasn't mutated in any significant way so far, including, crucially, the part that is most visible to the immune system, that spike protein. So long as that remains true, the vaccine they make should match up with the virus that our bodies will encounter in the real world, meaning it'll likely work as intended. Given the stability seen so far in the coronavirus's genetic sequence, "I am hopeful that when we do develop a vaccine, it will provide long-term protection," Kartsonis said.

Even a Vaccine That's Not 100% Effective Could Be Good Enough

When vaccine manufacturers talk about "effective," there are two common definitions. One is preventing people from getting sick. The other is preventing people from getting infected at all. In the case of COVID-19, this could be a nontrivial difference.

We know now that many people infected with the coronavirus may be asymptomatic carriers, which means that they never feel sick or get symptoms like a cough or fever, even if they are, in fact, infected with the virus. So you can have a vaccine that is effective in that it prevents symptomatic COVID-19, but that doesn't mean it'll stop everyone from being infected.



Vaccine candidates developed by Novavax, an American company. (Andrew Caballero-Reynolds/AFP via Getty Images)

Let's be clear: A vaccine that can significantly reduce sickness would be fantastic. If a vaccine can reduce the severity of COVID-19 so that it's far less deadly, decrease hospitalizations and minimize symptoms even for those who catch it, that's a win.

"In terms of what you'd expect for approval, it should at least be 50% efficacy against symptoms and 70% against moderate to severe disease, to keep you out of the hospital," said Dr. Paul Offit, director of the vaccine

education center at the Children's Hospital of Philadelphia.

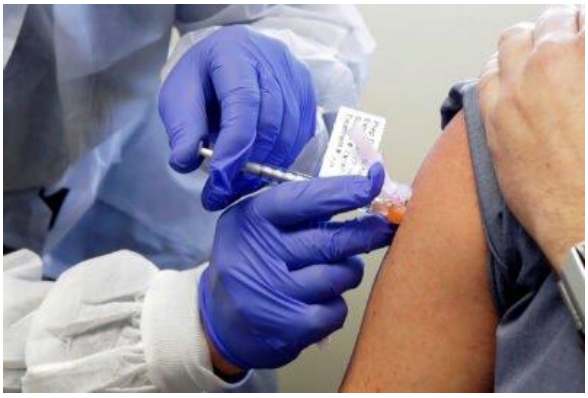
Even so, it's important not only to measure what the vaccine does, but also for politicians, health officials and journalists to clearly explain to the public exactly what it is that the vaccine is capable of doing. If it ends up that the first vaccine to go to market is "70% effective," we should be clear on whether it is 70% effective at reducing sickness or infection, so members of the public have the appropriate context and don't feel let down if they are vaccinated and still get a mild case of COVID-19.

Large Scale Trials Will Tell Us if the Vaccine Works

When experimental vaccines are tested, they usually go through three phases of clinical trials. The first phase is the smallest and focuses on safety, making sure that the product doesn't have any dangerous health effects. The second is a little larger, continuing to gather safety data while testing if the vaccine can induce an immune response, producing antibodies in participants. The third trial is the largest, and it needs to be big enough to confirm that the vaccine is actually effective in the real world.

Moderna Therapeutics is currently expected to be the first U.S. manufacturer to start a phase 3 trial. Candidates by AstraZeneca and Johnson & Johnson will follow, according to The Wall Street Journal. Moderna's trial is planned to begin in July and will enroll about 30,000 participants. Half will get the vaccine and half will get a placebo, according to Moderna's chief medical officer Dr. Tal Zaks. (I should disclose: Paul Sagan, chairman of ProPublica's board, is also one of Moderna's board members. That said, ProPublica's board members have no say in what reporters write about, nor do they know about articles before they are published.)

The participants will be tracked carefully throughout the study. If they have any symptoms related to COVID-19, they'll get tested to see if they have contracted the virus. The participants will also get blood drawn at regular intervals to get tested for antibodies, which will determine if they got infected but perhaps didn't know because they didn't develop symptoms.



A participant receives a shot in the first phase of Moderna Therapeutics' clinical trial in March. (Ted S. Warren/AP Photo)

"But wait!" you say. "Doesn't a vaccine also create antibodies? How can you tell by looking in a participant's blood whether the antibodies come from the vaccine or from an infection that the vaccine failed to prevent?" Excellent question.

At least for Moderna's vaccine trial, here's how they're going to tell the difference: Moderna's vaccine is what's known as an mRNA vaccine. Instead of using the actual virus or even a little bit of the virus, it uses a piece of genetic code, kind of like a recipe, that gives instructions for making the spike protein. Once injected into the arm and introduced into human cells, the cell's protein-making factories read the recipe and manufacture the spike protein, churning out copies for the immune system to check out. The immune system should then create antibodies that correspond to the spike protein, like a matching puzzle piece.

When you get infected by an actual coronavirus, however, there are more parts to it than just the spike protein. Your body will produce other antibodies that match up with other parts of the virus, including what's called the nucleoprotein, found inside the virus. We can also measure for those antibodies in a trial participant's blood, the NIH's Mascola

explained. So if we find so-called NP antibodies, that means you've been infected for real, because there's no way you could induce NP antibodies from the vaccine alone.

The Moderna trial is designed to end when a predetermined number of people have gotten sick, according to Zaks. Then, the study investigators will count up the number of people that have gotten sick in the placebo arm and compare it with the vaccine arm. Hopefully, there will be far fewer in the vaccinated cohort.

There's one more question that a phase 3 trial cannot answer: How long will protection last? Right now, we don't even know if people who have gotten sick via natural infection have lifelong immunity. The only way to find out how long a vaccine's protection lasts will be to keep tracking study participants and whether their antibody levels drop over time. We may end up needing periodic booster shots. Truly, only time will tell.

Shortcuts Involve Trade-Offs

To give you a sense of what a blistering pace we are attempting to move at, consider that under normal circumstances, it typically takes 10 to 15 years to develop a vaccine. Creating the HPV vaccine was a 15-year journey from key research findings in 1991 until the vaccine was approved, initially for the prevention of cervical, vulvar and vaginal cancers, in 2006. Merck's Ebola vaccine, one of the fastest ever to be approved in the company's history, still took about five years from start to finish in human trials, according to Merck.

The speed of the phase 3 trials depends on the rate of infection wherever people are enrolled. If there is a huge outbreak going on, people in the placebo group will get sick at a high rate, and the trial may be over in a matter of a few months. If infection rates are very low, however, the trial could drag on for months on end. Moderna hasn't announced its trial sites yet, but it will have sites "well dispersed" in the U.S. and is considering international trials as well, according to a spokesman.

"Fast-Tracking" a Coronavirus Vaccine Sounds Great. It's Not That Simple.

Among the many ways to shorten the vaccine development timeline, approving a treatment based on antibody data — without completing a phase 3 trial — could be contentious. This is why.

"There have been some European countries that wanted to be part of our trial, and we said: 'Look at your epidemiology, you're a victim of your own success — there's just not enough cases happening. It would take five years!'" Moderna's Zaks said. "So speed here is going to be enabled by what we anticipate is ongoing attack rates. We expect there will be infections amongst the participants on our trial."

Still, there have been discussions of some potential ways to speed up trials even more. One common proposal is to conduct what are known as challenge trials, in which vaccinated participants are deliberately "challenged" with the coronavirus to see if they get sick.

This idea was dismissed as unethical by some experts I interviewed. "We don't have a treatment — we can't guarantee to any volunteer that if we gave them a challenge with the actual virus, that it wouldn't make them very, very sick," said Dr. William Schaffner, professor of preventive medicine and infectious diseases at Vanderbilt Medicine. "That would make a lot of people very uneasy."

The other shortcoming of approving a vaccine via a challenge trial is that because of the

inherently risky nature of giving participants a live virus, challenge trials are typically very small. "That diminishes the safety database, and you need a large safety database to give us comfort to communicate to the public that we think that this is a safe vaccine," Schaffner said.

Another potential would be to green light use of a vaccine based on expected benefit, if manufacturers can show it reliably generates levels of antibodies in study participants that are similar to those found in people who have been naturally infected. Not everyone is a fan of that idea — some experts I interviewed told me that immune responses aren't always predictive of a vaccine's real-world capabilities. (Read more about this discussion.)

Children and Pregnant Women Won't Be First in Line

In the phase 3 trials currently being planned, the vaccines will be tested in adults. People over the age of 55 are being specifically recruited, and it's important to include them because the need for the vaccine in that demographic is particularly high.

One group that won't be in the initial set of phase 3 trials: children.

This is for two reasons. First, as a safety precaution, the NIH's Mascola explained. Traditionally, when running trials with an experimental vaccine or drug, developers make sure it's safe in adults before moving on to children. Second, for the COVID-19 vaccine specifically, the most acute need isn't in children.

This means that when the vaccine is first approved, it likely won't be available for those under 18, because it hasn't yet been studied in that population. However, Mascola said there are already discussions for how to run future trials for children. Moderna will eventually run trials in children, Zaks confirmed.

Another special population is pregnant women. They are also not going to be enrolled in the initial phase 3 trial for the Moderna vaccine, according to Zaks. But Mascola said that it's essential that that population eventually be studied. "If we're not able to immunize women of childbearing age, that excludes a large proportion of the population. There's a strong interest in getting those studies done," he said. "The FDA is encouraging companies/sponsors to include in their development plans studies that would provide data to support use of COVID-19 vaccines during pregnancy," the agency said in a statement.

The FDA added that it "strongly encourages the enrollment of populations most affected by COVID-19, specifically racial and ethnic minorities." African Americans have been disproportionately affected by the pandemic, contracting the virus and dying at higher rates.

Manufacturing "At Risk" Is a Safe Time-Saver

One strategy that everyone agreed was a safe way to save a whole lot of time without any risk to human health is what's known as "manufacturing at risk." This is one of the key components of the U.S. government's Operation Warp Speed, which is supporting five candidates with billions of dollars of federal funding.

Typically, drugmakers will manufacture only enough doses for clinical trials and make sure the trials are successful before starting mass production. Manufacturing at risk means that developers will instead begin mass production at the same time as clinical trials, which means that if a vaccine fails in human trials, they'll have to throw away all the product they've made, wasting money and materials. But if a product is successful, it means that the minute its trial is completed, there'll be millions of doses ready to go.

Manufacturing at a massive scale is no simple task. "If we're going to immunize 300 million people in the U.S. — we don't even do that with the flu vaccine every year — we need a lot of glass vials, we have to make sure we have printing supplies and paper to make the labels and package inserts, we need stoppers for the vials, and they all need to be made to a very high

standard. All this in addition to the raw materials to the vaccine itself," Schaffner said.

Mass production of H1N1 flu vaccines at Sinovac in 2009. (China Photos/Getty Images)

Pfizer and its partner, German company BioNTech, are planning to have a few million doses ready by the end of the year, and hundreds of millions of doses available in 2021, even though the first of their four vaccine candidates just began its first early-stage human trials in May. The companies are currently preparing manufacturing facilities in St. Louis, Andover, Massachusetts, and Kalamazoo, Michigan, as well as in Europe, according to Dr. Philip Dormitzer, Pfizer's vice president and chief scientific officer for viral vaccines.

Development Is the First Hurdle, Distribution Is the Next Challenge

On the day that a vaccine is approved, you'll find me jumping up and down in my apartment, cheering loudly enough to startle my neighbors. And then … I'll keep on washing my hands, wearing a mask and maintaining social distancing.

Why? Because I know that when a vaccine is first approved by the FDA, there won't be enough available for everyone who wants it. There will need to be a prioritization, with the vaccine given first to those who need it most: essential workers and the elderly. As a healthy adult who is fortunate to be able to work from home, I'll be nowhere near the front of the inoculation line.

Distribution is going to be a massive challenge. "There's a need to have in place a mechanism to ensure people who should get the vaccine get it," Dr. Walter Orenstein, associate director of Emory University's vaccine center, said. "We won't have 8 billion vaccines. So who should get priority, and how should it get delivered? We will need to remove barriers to access, including cost and distance."

In all likelihood, we'll have several vaccines that come to market and are in use at the same time, because of the unprecedented need to vaccinate so many people around the globe. No one company has the manufacturing capability to make it all.

There may also be differences in what works best for different countries and populations. Some of the vaccines will require cold shipping or storage. Some will require two doses (Moderna's is a two-dose vaccine, taken a month apart). All these variations will add to the complexity of delivery and distribution.

"Since I have gray hair, I'm trying to remind my colleagues that in previous distribution and prioritization schemes, flexibility is very important," Schaffner warned me. He has long worked with the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practice, which reviews data on vaccines and gives recommendations on which populations they should be used for. He is now on the COVID-19 vaccine working group. "Adverse events will come up that have to become investigated. There will be bumps in the road. War plans are great, until the war starts. Then you will have to be flexible."

Safety Monitoring Doesn't End After Trials Are Over

Vaccinating 15,000 to 20,000 people before approval should give regulators a large pool of data to help them understand what side effects are to be expected and help ensure that the vaccines that go to market don't have any major safety issues.

But of course, 20,000 people isn't 20 million or 200 million or 2 billion people.

"When we have tens of thousands of people being evaluated, we can at least pick up safety signals for serious adverse events for the more frequent adverse events," Orenstein said. "Now for very rare events, if it's 1 per million, you're not going to catch that in clinical trials."

What everyone wants to avoid is a repeat of the mass immunization program following the swine flu outbreak at Fort Dix in 1976. After 45 million doses were distributed, the vaccine was found to be associated with increased cases of Guillain-Barré syndrome, which can cause paralysis and sometimes death. Even worse, there wasn't actually a pandemic — the program had been launched in fears that the swine flu virus circulating among recruits at Fort Dix would cause a catastrophic outbreak. In the end, there was no transmission across the U.S., and the vaccination program was canceled.

So there will need to be some sort of mechanism to track and monitor for rare safety events even after the vaccine goes on the market. There is already a program to do so, which is the Vaccine Adverse Event Reporting System, run by the CDC.

While it may be impossible for a phase 3 trial to catch a very rare potential side effect, Offit, of the Children's Hospital of Philadelphia, points out that "it's not a risk-free choice to not get the vaccine, if the virus is still circulating."

He added, "If the data were clear that in 20,000 people it appears to be safe and highly efficacious, then you should get the vaccine, because if you're choosing not to get a vaccine, you're choosing to risk getting a natural infection, which could be fatal."

When Will a Coronavirus Vaccine Be Ready? Let Data Determine the Timeline.

The Trump administration's Operation Warp Speed has said it "aims to have substantial quantities of a safe and effective vaccine available for Americans by January 2021."

Experts I've spoken to have ranged in their optimism about that timeline. The NIH's Mascola said, "If a study is started in the summertime, it's possible that by the end of the year we'll have an answer."

Dr. Luciana Borio, former FDA acting chief scientist and current vice president at In-Q-Tel, a nonprofit strategic investment firm, concurred. "Depending on the results of the clinical trials, I think we might see some vaccine become available before the end of the year, but most people will have to wait for 2021."

Others were more cautious. Orenstein said he thinks there is a "real possibility" that we will have a vaccine by summer next year, "if everything goes well."

Vanderbilt's Schaffner said he prefers to avoid timelines altogether. "We're making the same mistake we made back in 2009 when we developed the H1N1 vaccine. We made the same statements and then it took more time than people anticipated, and when it finally came out, the media all said, 'It's a late vaccine!'

"So we overpromised and underdelivered in 2009, and we haven't learned that lesson. We are overpromising now, and I wish we wouldn't do that. I wish we would just say, 'We're working as hard as we can and we'll get it to you whenever it's finished, but we've got to do it right.' And that would be a much more solid message."

How America's Hospitals Survived the First Wave of the Coronavirus

ProPublica deputy managing editor Charles Ornstein wanted to know why experts were wrong when they said U.S. hospitals would be overwhelmed by COVID-19 patients. Here's what he learned, including what hospitals can do before the next wave.

Many of the experts I talked to stressed that they wanted to see the phase 3 trials run to completion, however long they took.

Dr. Brit Trogen, a pediatrics resident at NYU Langone, said she worries about political pressures on developers. "I consider vaccines to be one of the greatest public health achievements of the past few centuries, and I know the consequences of under-vaccinating, because I treat kids who are seriously ill with preventable illness," she said. "But I worry that at the first hint of something positive, politicians will swoop in and push for an early release beyond what the science allows."

Some also noted that vaccine hesitancy has been growing in the United States, thanks to a fervent anti-vaccination movement.

Dr. Peter Hotez, a vaccine scientist, professor and dean of the National School of Tropical Medicine at Baylor College of Medicine, said communication that focuses solely on speed "is very tone deaf to the fact that there's an aggressive anti-vax lobby that says that vaccines are rushed and aren't adequately tested for safety."

I brought these concerns to the FDA, as the agency will ultimately be the one to make the call on when there is sufficient data to approve a vaccine.

"We recognize that there are some that are concerned that 'rapid development' means that vaccine development steps are being skipped, but the FDA scientists will not cut corners in order to approve a vaccine," the agency responded. "The FDA will thoroughly evaluate the data submitted in support of a vaccine's safety and effectiveness, and will approve a vaccine for the prevention of COVID-19 only if the FDA determines that it is safe and effective for its intended use."

When I pause to really think about it, I am staggered by what an enormous undertaking is underway around the globe — and what lies ahead — to develop and distribute a COVID-19 vaccine to billions of people. There is so much at stake, both to give the world a vaccine as soon as possible, and also to not make any critical mistakes in the process. As I cheer on all of the developers, I hope that every country's leaders will let science and evidence guide decisions every step of the way.

I asked Zaks, of Moderna, what kind of pressure he felt, and he answered me in two ways. He said: "Every day and every minute counts." And then he told me this — that normally, when he works on vaccines, he never gets to meet the people that he's making the vaccine for. But this pandemic has been different. His future daughter-in-law is a second-year internal medicine resident in New York City, where the coronavirus has hit hard. "This one's personal," he said. "This one cuts close to home."

He's making this vaccine for her.

Chris Hendel contributed reporting.

Clarification, June 18, 2020: *This story was updated to clarify the time frame of the development of Merck's Ebola vaccine.*