COUNTDOWN TO A CORONAVIRUS VACCINE

The race is nearly complete, but distributing the doses will be a breathtaking challenge.

By Carolyn Kormann

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Thirteen pharmaceutical companies have made it into late-stage clinical trials.

Illustration by Virginia Gabrielli

On a hot afternoon in August, Debbie Honeycutt walked into the crowded waiting room of the Medical Center for Clinical Research, an experimental-treatment facility tucked inside a squat office building in San Diego. She was volunteer number four hundred and ten out of four hundred and sixty-six that the clinic had recruited to test a potential coronavirus vaccine. After a brief screening, a research assistant led her into an exam room, where a doctor administered a nasal-swab test and performed a physical examination. Honeycutt, who is sixty-nine years old, with short white hair and a matter-of-fact disposition, spent much of her career as a fund-raiser in the fields of education and science. This would be her sixth time volunteering in a clinical trial, and it had never felt more important. In the seven months since the first cases of COVID-19 had been identified in the United States, 5.6 million people had been infected and a hundred and seventy-five thousand had died. Honeycutt, who lives alone in a tranquil suburb of San Diego—"the kind of place where you know all your neighbors"—had seen friends fall gravely ill. She also knew that the study needed people from high-risk demographics: over sixty-five, with underlying health conditions. She had high blood pressure. "They need guinea pigs," she said. "I believe in helping people."

A nurse gave Honeycutt an injection. Neither of them knew whether the liquid was a placebo or an experimental vaccine known as mRNA-1273. Developed by the Massachusetts-based biotech

company Moderna, the vaccine contains a microscopic chain of messenger RNA, the atom-size instructions for building proteins. No vaccine made from mRNA has ever been licensed for commercial use. After the injection, Honeycutt was kept under observation for thirty minutes, to be sure that it did not trigger an anaphylactic reaction; during that time, the vaccine, if that's what she'd been given, was crossing her cell membranes, into the cytoplasm, where the ribosomes would begin using its code to manufacture a defense against the virus. Honeycutt hoped that she had got the real thing. But, she said, "you don't know. It could be saline."

Honeycutt was one of thirty thousand volunteers nationwide, aged eighteen and older, in Moderna's Phase III trial—the final test of safety and efficacy before a company applies to the U.S. Food and Drug Administration for authorization. A Phase III clinical trial for an experimental vaccine is simple, at least in concept. Half the volunteers receive a placebo, and half receive the vaccine. No one can see who got what except the members of the Data and Safety Monitoring Board, an independent group of experts appointed by the National Institutes of Health. Once a predetermined number of volunteers develop symptomatic cases, the board members take their first peek at the data.

On the morning of November 11th, Moderna announced that it had hit that threshold. A few days later, the Data and Safety Monitoring Board held a call with Moderna's management and N.I.H. officials, telling them that, of ninety-five confirmed cases of COVID-19 among trial participants, ninety were in the placebo group. Eleven volunteers had developed severe cases; all of them were in the placebo group. The vaccine was nearly ninety-five per cent effective.

Pfizer, working with the Germany-based immunotherapy company BioNTech, was performing similar trials on its own vaccine, with forty-two thousand volunteers. A week earlier, Pfizer had released preliminary data showing that its vaccine was ninety per cent effective. Both companies still had to finish their trials, but the announcements were exciting. Medical experts, including the top doctors at both Pfizer and Moderna, had been hoping that the vaccines would be seventy to eighty per cent effective. "Something like ninety-five per cent was really aspirational," Anthony Fauci, the director of the National Institute of Allergy and Infectious Diseases, at the N.I.H., said.

“Well, our aspirations have been met. And that is really very good news.”

The two companies achieved these results in less than four months, an unprecedented pace, without any serious side effects. “It is difficult to convey to those outside the field how extraordinary this achievement has been,” Kathleen Neuzil, who is co-leading the federal network that designs and oversees coronavirus-vaccine trials, told me. “The science and manufacturing allowed these vaccines to be developed in weeks, not years.” Pfizer and Moderna have since applied to the F.D.A. for emergency-use authorization, which could allow the first doses to be shipped out before the end of the year.

On the evening after Honeycutt got her shot, she signed into an app on her phone to record her temperature and any symptoms. Her arm was sore. Otherwise, she felt unchanged. Both Moderna’s and Pfizer’s vaccines require two shots, roughly a month apart. After twenty-eight days, Honeycutt returned to the clinic for a second injection. The next morning, around nine o’clock, she started to get body aches and chills. Her temperature was slightly elevated, at 99.9 degrees. She bundled up and lay on the couch. By noon, her temperature was above a hundred. A few hours later, she felt better, she said, even excited: “I felt like I got the vaccine.”

The vaccine that had possibly kick-started Honeycutt’s immune system relies on a recent innovation. By now, just about everyone has seen images of the infamous spike protein, which the coronavirus SARS-CoV-2 uses to fuse to our cells, like a key in a lock. Traditional vaccines inject bits of weakened or inactivated virus, but Moderna’s and Pfizer’s coronavirus vaccines contain the molecular instructions—the mRNA—for making a replica of the SARS-CoV-2 spike. When injected into our body, the mRNA orders our cells to start producing spike proteins. Our immune system recognizes these new spike proteins as antigens, foreign invaders, and creates antibodies to neutralize them. Then, if the actual SARS-CoV-2 virus tries to breach our cells, our body will be prepared.

A crucial development has allowed Pfizer and Moderna to move quickly. The spike protein alters its form once it fuses with a cell in our body; after the lock is opened, the key changes shape. In

order for a vaccine to work, it has to present the body with the original key—the spike's delicate, unaltered form—so that the immune system can learn how to keep the lock closed. Several years ago, Barney Graham, the deputy director of vaccine research at the National Institute of Allergy and Infectious Diseases, and Jason McLellan, a professor at the University of Texas, were investigating another coronavirus, Middle East respiratory syndrome (MERS-CoV), in the hope of developing a vaccine. Earlier work on viruses suggested that, if they changed the genetic sequence slightly, the spike would retain its original shape. They tried two mutations on the MERS spike protein, which worked, resulting in a potent vaccine. "It was a big moment when we realized that the idea was transferrable from one virus to another," Graham told me.

In 2017, the N.I.H. partnered with Moderna to see how rapidly they could develop an mRNA vaccine if there were a pandemic; they accelerated the effort in mid-2019. Not long afterward, a mysterious cluster of viral pneumonia cases appeared in the city of Wuhan, China, and their experiment suddenly became real. On January 10th, Chinese researchers published the sequence of the SARS-CoV-2 genome. The next morning, Graham and his colleagues went to work developing a potential mRNA vaccine, using the stabilizing mutations from their research on MERS.

BioNTech, like Moderna, had been experimenting with mRNA vaccines. In late January, when Ugur Sahin, BioNTech's co-founder, realized that SARS-CoV-2 could cause a pandemic, the company began developing its own vaccine candidate. A few weeks later, Sahin called Kathrin Jansen, the head of vaccine research at Pfizer, and asked if her company would be interested in joining the effort. Jansen said that she had been planning to call him.

The Moderna and Pfizer vaccines are more similar than different. In both, the mRNA is encapsulated in a substance called a lipid nanoparticle, a shell of precisely formulated fat, which helps carry the mRNA into our cells. Like nearly every vaccine in use today, they also both require two doses. (The flu shot is a single dose, but a new one is required every year.) The first dose exposes the immune system to the antigen, which creates a population of antibodies that can respond to it. The second dose expands that population. Anyone who catches the coronavirus between the first and second shots—a real risk in a pandemic—would likely have protection from

severe disease, but no one knows yet the extent of that protection. Johnson & Johnson is currently testing a coronavirus vaccine, in a trial of sixty thousand people, that could work with just one shot. It might not provide durable protection, however, so in November the company started a second, global Phase III trial that will give two shots to as many as thirty thousand participants.

Thirteen companies worldwide have made it into late-stage, large-scale clinical efficacy trials. Back in April, to coördinate and accelerate this sprawling vaccine-development effort, Peter Marks, the director of the Center for Biologics Evaluation and Research, at the F.D.A., proposed a moon-shot program that, as a longtime "Star Trek" fan, he dubbed Project Warp Speed. Marks now leads the F.D.A. team that will make the final call on granting emergency-use authorization to the leading vaccine candidates. Acknowledging the stakes, he recalled a line from James Bond, in which the head of M.I.6 says, "This is the big one, 007. Do not screw it up."

Moncef Slaoui, the former head of vaccine development at GlaxoSmithKline, was eventually appointed the head of what is now known as Operation Warp Speed. The program has so far provided at least twelve billion dollars to pharmaceutical companies for researching, developing, and manufacturing vaccines and drugs, with the biggest contracts awarded to Moderna, Sanofi (which is partnering with GlaxoSmithKline), Novavax, Johnson & Johnson, and AstraZeneca. All of them except AstraZeneca are using Graham and McLellan's mutations. According to Graham, the original RNA technology came from Drew Weissman, a researcher at the University of Pennsylvania, whose work was also heavily funded by the N.I.H. "What do they say?" Graham said. "Success has many fathers, and failure is an orphan."

Pfizer and BioNTech decided not to accept funds from Operation Warp Speed. "I wanted to liberate our scientists from any bureaucracy," Albert Bourla, the C.E.O. of Pfizer, said in an interview on CBS's "Face the Nation." BioNTech did receive four hundred and forty-five million dollars in funding from the German government, and the two companies signed a contract with Operation Warp Speed to sell their first hundred million doses to the U.S., at a cost of around two billion dollars. They also relied on Graham and McLellan's publicly funded work when they created their vaccine's mRNA sequence.

In trials on mice and monkeys, as well as in Phase I trials on people, Pfizer and Moderna showed that their vaccines were safe and provoked robust immune responses. In May, companies and regulators began to suggest that a vaccine could be ready sooner than expected. "Once we started getting human data, then we really got more confident," Graham said. Pfizer and Moderna began Phase III trials on July 27th. Waiting for enough volunteers to get sick—typically the most time-consuming aspect of a Phase III trial—was not likely to take long: COVID-19 cases were surging around the country. The companies' stock prices soared as executives sold off their shares.

Donald Trump, too, tried to capitalize on the news. By summer, he was hyping the possibility that a vaccine could be ready before the election, although few public-health experts believed this timeline to be realistic. "You could have a very big surprise coming up," Trump said in a press conference. "We're going to have a vaccine very soon, maybe even before a very special date. You know what date I'm talking about."

Around the time of Trump's remarks, the COVID-19 Vaccine Confidence Project, a nonprofit effort to advise the F.D.A., began conducting focus groups with people most at risk: workers in health care, service, and retail, and members of underrepresented communities. Many respondents were skeptical about the haste with which the vaccines were being developed. "Some of our listening-session participants noted that they would want to wait months, or even years, before choosing to receive a vaccine," Susan Winckler, the C.E.O. of the Reagan-Udall Foundation, which is leading the project, said. In an online presentation, Winckler shared direct quotes from the respondents, a Greek chorus of worry: "When I hear the F.D.A. say they have a particular process, but then I hear the White House say they can cut that in half or negate it, it brings more distrust"; "I am suspicious that they are trying to get it out before the election"; "A lot of people don't trust the people who are making the vaccine because they are politically motivated, and we are all a bunch of guinea pigs."

Bourla, the Pfizer C.E.O., had an idea to quell some of these concerns. In early September, he and Sahin, of BioNTech, flew to Austria in a Pfizer jet to visit a vaccine-manufacturing facility. During the flight, Sahin said, they talked about the issue of public trust, and the risk that the vaccines

"could be politicized, and how to react to that." Bourla suggested that all the front-runners in the vaccine race publish an open letter, reaffirming their commitment to safety, scientific rigor, and ethics. Sahin thought that this was a great suggestion.

When Bourla returned to the U.S., he called Fauci, who told me that he strongly encouraged the pledge. Bourla rallied seven other companies, all of which were involved with Operation Warp Speed, and were likely aware that President Trump's wish to hasten the arrival of a vaccine was creating the impression that developers were taking shortcuts. "You can feel if the public gets insecure about what is going on," Sahin said. It seemed critical to be transparent about "the independence of this process from any political influence."

On September 8th, Pfizer, BioNTech, Moderna, AstraZeneca, GlaxoSmithKline, Sanofi, Johnson & Johnson, Merck, and Novavax released a joint pledge to "stand with science," to make the "safety and well-being" of vaccinated individuals their "top priority," and to "adhere to high scientific and ethical standards" for clinical trials and manufacturing. "So the pledge was 'Let's not try to jump the gun,' " Fauci told me. The race for a vaccine was becoming as much a public-relations effort as a scientific one.

A week and a half later, Moderna and Pfizer published their trial blueprints, which are usually kept secret until a vaccine study is complete. But the possibility that Pfizer might file for an emergency-use authorization before the election created more controversy. In the past hundred years, the F.D.A. has never granted an emergency-use authorization for a new vaccine. To address the public's concerns, the agency issued updated guidelines on October 6th, asking drugmakers to collect two months of safety data following the second injection before applying for an authorization. This made the possibility of a preëlection vaccine almost nil. Trump was outraged, and attempted to block the guidelines' release, a move that was widely condemned. In an abrupt reversal, the guidelines were cleared the next day. Still, the President tweeted, "New FDA Rules make it more difficult for them to speed up vaccines for approval before Election Day. Just another political hit job!"

To many observers, the F.D.A.'s guidelines represented the bare minimum of what was necessary to insure a safe and effective vaccine. The World Health Organization has advocated for no less than three months of safety data. Most side effects will occur in the first two to three months, so two months of follow-up safety data "is pretty much a base case," Scott Gottlieb, Trump's former F.D.A. commissioner, who sits on Pfizer's board of directors, said. "It's a short time frame, but it's appropriately aggressive given the circumstances." Doran Fink, the deputy director of the F.D.A.'s vaccine division, emphasized that the agency had tried to balance two imperatives: "having the amount of safety data that we thought was absolutely necessary" and "not withholding a vaccine that could have an impact."

Victoria Smith works as a family physician at an outpatient clinic owned by Ochsner Health, a network of hospitals and medical facilities across Louisiana. Back in March, New Orleans became one of the worst hot spots in the world, with a massive outbreak catalyzed in large part by the annual Mardi Gras celebration. Many of Smith's patients got severely ill. Some died. Since then, Ochsner's academic center has been running studies related to the virus, investigating how it has affected certain communities and how it might be treated. Two days after Pfizer's and Moderna's Phase III trials began nationally, Ochsner's chief academic officer told Smith that his staff had opened enrollment for Pfizer's trial. Smith signed up immediately. She knew that, as an African-American doctor, she could help establish trust in the vaccines. "I wanted to be a model to my patients, to communities of color," she said, "to encourage people to take part."

The companies were encouraged to recruit volunteers that reflected the country's demographics. In late August, Slaoui, the head of Operation Warp Speed, told Moderna's C.E.O., Stéphane Bancel, that the company had to slow down its trial in order to sign up more volunteers from Black and Latino communities, which have had much higher rates of infection and death during the pandemic than white communities have. The concern was not necessarily that physical responses to the vaccine might vary by race. "It was more to assure the public that the vaccine data, when it comes out, is applicable to everybody," Tal Zaks, Moderna's top doctor, told me. Moderna contacted leaders of historically Black universities and other academics with ties to Black and

Latino organizations. Slaoui joined a virtual town hall organized by Jesse Jackson's Rainbow/PUSH Coalition, in Atlanta, to ask for help in finding Black volunteers.

Moderna eventually recruited more than seven thousand Americans over the age of sixty-five, and more than five thousand with chronic conditions such as diabetes, obesity, and heart disease. Thirty-seven per cent of the study's participants were from communities of color, which have historically been underrepresented in clinical research. But, according to a Stat-Harris poll conducted in early October, there remains a significant racial discrepancy in vaccine confidence. Only forty-three per cent of Black Americans said that they would agree to receive a vaccine as soon as one was available, versus fifty-nine per cent of white Americans. "There's a long history in the United States of science being done on people of color and not with them," Smith said. "I'm thinking of the Tuskegee experiment." She continued, "So it is, I think, the work of our medical and scientific communities to decrease those disparities, but also to understand that mistrust and work to create trust."

On November 30th, Moderna announced that it had arrived at the end of its trial, with a hundred and ninety-six COVID-19 cases among more than thirty thousand volunteers. A hundred and eighty-five of the people who got sick had received the placebo, indicating an efficacy rate of ninety-four per cent. All thirty people who got severely ill, including one person who died, were in the placebo group. The data was consistent across age, race, and ethnicity. Among the volunteers who contracted COVID-19, twenty-nine identified as Latino, six as Black, four as Asian-American, and three as multiracial; thirty-three were older than sixty-five.

The results were remarkably similar to Pfizer's, which ultimately achieved an efficacy rate of ninety-five per cent. "The fact that two independent studies, with more than thirty thousand people in each one, both randomized and placebo-controlled, came to the same answer?" John Mascola, the head of the N.I.H. Vaccine Research Center, said. "That really gives you enormous confidence in their information."

And yet there is still an entrenched anti-vaccination movement to contend with. Falsehoods

circulating on social media claim that the vaccines will modify your DNA, and accuse Bill Gates of injecting people with location trackers. Francis Collins, the director of the N.I.H., said, "It is troubling, indeed, to see polls reflecting the vaccine hesitancy of Americans." He pointed to "a lack of information about what the real details of the vaccine safety and efficacy were," and "a lot of noise about it and a lot of conspiracy theories that have not helped." Fauci emphasized the importance of making the public aware of "the transparency and the independence of the process, which I think they may not fully appreciate when they hear things about rushing or influence from the outside." He noted the role of the Data and Safety Monitoring Boards, and the Vaccines and Related Biological Products Advisory Committee, an independent body that holds public meetings to debate safety and efficacy considerations of the F.D.A.'s vaccine-approval process.

During an all-day meeting of the committee, on October 22nd, Archana Chatterjee, the dean of the Chicago Medical School, noted the challenge of insuring the scientific rigor of vaccine development "in the face of a pandemic that is killing hundreds of thousands of people across the globe." She continued, "What we're being asked to do is build this plane as we fly it." The committee is expected to endorse Pfizer's request for an emergency-use authorization on December 10th. Marks, the F.D.A. regulator, said that the agency plans to issue a final authorization "days to weeks" later. (The committee will vote on Moderna's authorization on December 17th.)

For some, that won't be fast enough. On December 1st, Mark Meadows, Trump's chief of staff, met with the head of the F.D.A., Stephen Hahn, to discuss why the agency "hadn't moved faster to grant preliminary approval," Bloomberg reported. The next day, shortly after regulators in the U.K. granted an emergency-use authorization to Pfizer, Meadows reportedly summoned Hahn back to the White House. According to Mascola, of the N.I.H., there is a simple explanation for the F.D.A.'s timeline: Pfizer has presented "a very large and complex set of data," and "all that information has to be reviewed." Investigators must double-check who tested positive for COVID-19, and what follow-ups were conducted to determine the severity of symptoms. "So far we only have Pfizer and Moderna's word for it," Mascola said. "What everyone wants is the F.D.A.'s word

for it."

For months, hundreds of thousands of vials of Pfizer's and Moderna's vaccines have been sitting in a few manufacturing plants in the United States and Europe. Based on recommendations from the Centers for Disease Control and Prevention, health-care workers and the elderly or chronically ill—about twenty million people—will be the first to receive a vaccine in the U.S. Scaling up to six hundred million doses—then safely and equitably distributing those doses around the country, and making sure that as many people as possible get a vaccine, including the second shot—is a breathtaking logistical challenge. "Something as simple as a supply chain usually would take five or six years," Robert Johnson, the director of the Division of Influenza and Emerging Infectious Diseases at the U.S. Biomedical Advanced Research and Development Authority, said. "We're trying to do it in the course of a few months, with six candidates."

Pfizer plans to manufacture 1.3 billion doses globally in 2021, but its vaccine must be stored at minus ninety-four degrees Fahrenheit, making mass distribution even more complicated. The company has created dry-ice-packed shipping containers that can hold some five thousand doses, in two-millilitre glass vials. Once the containers arrive at their destination, they serve as temporary storage units for fifteen days, assuming that they are opened no more than twice a day and that the dry ice is replenished. Each container carries a G.P.S.-enabled thermal sensor that will track its location and temperature. On average, Pfizer will have twenty cargo flights a day carrying vaccines all over the world.

Moderna plans to manufacture between five hundred million and a billion doses globally in 2021. Its vaccine, which can be stored at normal refrigerator temperatures for thirty days, will be easier to distribute. Zaks, the doctor from Moderna, told me that some of the company's earlier efforts required storage at minus ninety-four degrees, but that there was no single "magic trick" that could easily be shared with Pfizer to apply to its vaccine. "It's not a simple sauce," Zaks said. "It is a collection of hundreds of small scientific steps." (The two companies have not collaborated, he added, at least not in any way "that has been publicly disclosed.")

Pfizer's and Moderna's vaccine-trial participants will be tracked for two years. A federal database, the Vaccine Adverse Event Reporting System, already monitors vaccination side effects. The C.D.C. has also created a smartphone-based program called V-SAFE, which will track the health of the roughly twenty million people who receive the first round of vaccines. "Long-term side effects are not common with vaccines," Larry Corey, a virologist and a co-leader of the network overseeing coronavirus-vaccine trials, told me. "But you do need to do surveillance to assure safety."

AstraZeneca, whose vaccine is cheaper to make and easier to store, was expected to be the next developer to file for an authorization. On November 23rd, the company announced that its vaccine candidate was, on average, seventy per cent effective. The results, however, were quickly called into question. The company had combined data from two different clinical trials, in the United Kingdom and Brazil, and from two different dosing regimens. A small group of participants had accidentally been given a half dose for their first shot. In this group, which also didn't include anyone over the age of fifty-five, the vaccine was ninety per cent effective. In the other, much larger group, the vaccine was just sixty-two per cent effective. One AstraZeneca executive called the half-dose accident "serendipity." But many industry experts saw a troubling lack of transparency, and a need for more data before the vaccine has a chance at authorization in the United States. An AstraZeneca spokesperson said in early December that the company is "continuing to further investigate these findings in order to establish the most effective dosing regimen."

For nonessential workers and otherwise healthy Americans, all that is known is that a vaccine will likely be available at doctors' offices and pharmacies sometime in late spring, and that it will be free. In order to achieve herd immunity and halt the pandemic, at least seventy per cent of the population will have to be vaccinated, according to Slaoui, the head of Operation Warp Speed. Only then will social distancing and universal mask-wearing no longer be strictly necessary. Operation Warp Speed has been generous in funding the vaccine's development, but the rollout has been left to the states, with little federal support or coördination. "We're talking about vaccinating three hundred million Americans with two doses," Prashant Yadav, a supply-chain

expert at the Center for Global Development, said. “For that, we need more infrastructure investment.”

Much of that effort will fall to the Biden Administration. Manufacturing supplies will be a concern—chemicals for making the vaccines, glass for vials, plastic for syringes, endless blocks of dry ice. The incoming Administration will need to develop outreach campaigns to educate the public, and make sure that local agencies have the resources to hire and train people to administer the vaccine. Hard decisions will also need to be made regarding who gets a vaccine and when. “The first round of high-priority people is somewhat easier,” Rick Bright, an immunologist on the President-elect’s COVID-19 task force, told me. The real challenge, he said, is choosing who comes next among “the other hundreds of millions of people across our country who are at high risk or have co-morbidities or are essential workers.”

Bright was the director of the Biomedical Advanced Research and Development Authority, until the Trump Administration demoted him in May. He quickly filed a whistle-blower complaint alleging that his “efforts to prioritize science and safety over political expediency” had led to his demotion. (Trump responded by calling Bright a “disgruntled employee.”) “There hasn’t been a lot of transparency from the current Administration about how complex the challenge is, once the vaccine is produced and pushed out from the factory,” Bright told me. A major difference in the Biden Administration’s approach, he added, was to “let science lead and not politics.”

Honeycutt, the Moderna-trial volunteer, has had no other side effects since receiving her second shot, in September. “Everything is good,” she told me, though her trial contact has said that Moderna will not share who got the vaccine “until sometime later.” Since she began the trial, 8.3 million more COVID-19 cases have been identified in the U.S., and ninety-eight thousand more people have died. “It’s imperative that people get their lives back,” Honeycutt said. “This has been very sad on so many levels.” But, she continued, “I think the fact that we have some people urging swiftness ahead of caution has been detrimental to the whole process. I worked in the sciences. People need rigor in examining data. This is the way science works.” ♦

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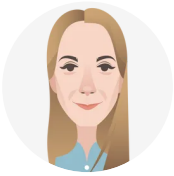

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