IN DEPTH

Jennifer Haller receives the first administration of an mRNA vaccine, made by the biotech firm Moderna, against the pandemic coronavirus.

PHOTO: AP PHOTO/TED S. WARREN

INFECTIOUS DISEASES

Vaccine designers take first shots at COVID-19

Two candidate vaccines start trials while dozens more are rushed into development

By **Jon Cohen**

The coronavirus that for weeks had been crippling hospitals in her hometown of Seattle changed Jennifer Haller's life on 16 March—but not because she caught it. Haller, an operations manager at a tech company in the city, became the first person outside of China to receive an experimental vaccine against the pandemic virus, and in the days since, she has experienced an outpouring of gratitude. "There's been overwhelming positivity, love, and prayers coming at me from strangers around the world," Haller says. "We all just feel so helpless, right? This was one of the few things happening that people could latch on to and say, 'OK, we've got a vaccine coming.' Disregard that it's going to take at least 18 months, but it's just one bright light in some really devastating news across the world."

The vaccine Haller volunteered to test is made by Moderna, a well-financed biotech that has yet to bring a product to market (*Science*, 3 February 2017, p. 446). Moderna and China's CanSino Biologics are the first to launch small clinical trials of vaccines against coronavirus disease 2019 (COVID-19) to see whether they are safe and can trigger immune responses. (The CanSino vaccine trial also began on 16 March, according to researchers from the Chinese military's Institute of Biotechnology, which is collaborating on it.) As *Science* went to press, a World Health Organization tally of other vaccine candidates that could follow stood at 52 (see table, p. 15).

"This is a wonderful response from the biomedical community to an epidemic," says Lawrence Corey, a virologist at the Fred Hutchinson Cancer Research Center who has run many vaccine trials but is not involved with a COVID-19 effort. "It's both gratifying and problematic in the sense of how do you winnow all this down?"

Science's COVID-19 coverage is supported by the Pulitzer Center.

Broadly speaking, these vaccines group into eight different "platforms"—among them old standbys such as inactivated or weakened whole viruses, genetically engineered proteins, and the newer messenger RNA (mRNA) technology that is the backbone of the Moderna vaccine—and their makers include biotechs, academia, military researchers, and a few major pharmaceutical companies. On 30 March, Johnson & Johnson (J&J) announced what it said could be a $1 billion COVID-19 vaccine project, with about half the money coming from the U.S. Biomedical Advanced Research and Development Authority if milestones are met.

Many viruses, including HIV and hepatitis C, have thwarted vaccine developers. But the new enemy, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), doesn't appear to be a particularly formidable target. It changes slowly, which means it's not very good at dodging the immune system, and vaccines against the related coronaviruses that cause SARS and Middle East respiratory syndrome (MERS) have worked in animal models. Corey heads the United States's HIV Vaccine Trials Network, which has seen one candidate vaccine after another crash and burn, but he is optimistic about a SARS-CoV-2 vaccine. "I don't think this is going to be that tough."

One concern is whether people develop durable immunity to SARS-CoV-2, which is crucial given that vaccines try to mimic a natural infection. Infections with the four human coronaviruses that typically cause minor colds don't trigger long-lasting immunity. Then again, researchers have found long-

Corrected 1 April 2020. See full text.

lasting immune responses to the viruses causing SARS and MERS, and genetically they are far more like SARS-CoV-2. And unlike cold-causing viruses, which stay in the nose and throat, the new coronavirus targets the lower respiratory tract, where the immune response can be stronger, says Mark Slifka, an immunologist who studies vaccines at the Oregon National Primate Research Center. "When you get an infection in the lungs, you actually get high levels of antibodies and other immune cells from your bloodstream into that space."

Even with an all-out effort, Anthony Fauci, director of the U.S. National Institute of Allergy and Infectious Diseases (NIAID), predicts a vaccine "is going to take a year, a year and a half, at least." Side effects, dosing issues, and manufacturing problems can all cause delays. Already some are calling for an ethically fraught shortcut to speed up clinical trials: giving people candidate vaccines and then intentionally attempting to infect them (see sidebar, p. 16).

A vaccine candidate might also be made available to health care workers and others at high risk even before final efficacy trials are completed. Stanley Perlman, a veteran coronavirus researcher at the University of Iowa, suggests a vaccine that only offers limited protection and durability could be good enough—at first. "In this kind of epidemic setting, as long as you have something that tides us along and prevents a lot of deaths, that may be adequate," he says.

A BETTER SPIKE

On 13 January, 3 days after Chinese researchers first made public the full RNA sequence of SARS-CoV-2, NIAID immunologist Barney Graham sent Moderna an optimized version of a gene that would become the backbone of its vaccine. Sixty-three days later, the first dose of the vaccine went into Haller and other volunteers participating in the small trial at the Kaiser Permanente Washington Health Research Institute. In 2016, Graham had made a Zika virus vaccine that went from lab bench to first volunteer in what was then a lightning-fast 190 days. "We beat that record by nearly 130 days," he says.

The effort benefited from lessons Graham learned from his past vaccine efforts, including his work on respiratory syncytial virus (RSV). The search for an RSV vaccine has a checkered past: In 1966 a trial of a candidate vaccine was linked to the death of two children. Later studies identified the problem as vaccine-triggered antibodies that bound to the surface protein of the virus but did not neutralize its ability to infect cells. This antibody-viral complex, in turn, sometimes led to haywire immune responses.

Studying structures of the RSV surface protein, Graham discovered that it had different orientations before and after fusing with a cell. Only the pre-fusion state, it turned out, triggered high levels of neutralizing antibodies, so in 2013 he engineered a stable form of the molecule in that configuration. "It was so clear at that point that if you didn't have structure, you didn't really know what you were doing," Graham says.

The experience came in handy in 2015, when a member of Graham's lab made a pilgrimage to Mecca, Saudi Arabia, and came back ill. Worried that it might be MERS, which is endemic in Saudi Arabian camels and repeatedly jumps into humans there, Graham's team checked for the virus and instead pulled out a common cold coronavirus. It was relatively easy to determine the structure of its spike, which then allowed the team to make stable forms of the ones for the SARS and MERS viruses, and, in January, for SARS-CoV-2's. That's the basis of the Moderna COVID-19 vaccine, which contains mRNA that directs a person's cells to produce this optimized spike protein.

No mRNA vaccine has yet reached a phase III clinical trial, let alone been approved for use. But producing huge numbers of doses may be easier for mRNA vaccines than for traditional ones, says Mariola Fotin-Mleczek of the German company CureVac, which is also working on an mRNA vaccine for the new coronavirus. CureVac's experimental rabies vaccine showed a strong immune response with a single microgram of mRNA, suggesting 1 gram could vaccinate 1 million people. "Ideally, what you have to do is produce maybe hundreds of grams. And that would be enough," Fotin-Mleczek says.

Many companies are relying on time-tested techniques. Sinovac Biotech is making a SARS-CoV-2 vaccine by chemically inactivating whole virus particles and adding an immune booster called alum. Sinovac used the same strategy for a SARS vaccine it developed and tested in a phase I clinical trial 16 years ago, says Meng Weining, a vice president at Sinovac. "We immediately just restarted the approach we already know."

Florian Krammer, a virologist at the Icahn School of Medicine at Mount Sinai, says inactivated virus vaccines have the advantage of being a tried-and-true technology that can be scaled up in many countries. "Those manufacturing plants are out there, and they can be used," Krammer says.

CanSino is now testing another approach. Its vaccine uses a nonreplicating version of adenovirus-5 (Ad5), which also causes the common cold, as a "vector" to carry in the gene for the coronavirus spike protein. Other vaccine researchers worry that because many people have immunity to Ad5, they could mount an immune response against the vector, preventing it from delivering the spike protein gene into human cells—or it might even cause harm, as seemed to happen in a trial of an Ad5-based HIV vaccine made by Merck. But the same Chinese collaboration produced an Ebola vaccine, which Chinese regulators approved in 2017, and a company press release claimed its new candidate generated "strong immune responses in animal models" and has "a good safety profile."

Other COVID-19 vaccine platforms include a laboratory-weakened version of SARS-CoV-2, a replicating but harmless measles vaccine virus that serves as the vector for the spike gene, genetically engineered protein subunits of the virus, a loop of DNA known as a plasmid that carries a gene from the virus, and SARS-CoV-2 proteins that self-assemble into "viruslike particles." J&J is using another adenovirus, Ad26, which does not commonly infect humans, as its vector. These approaches can stimulate different arms of the immune system, and researchers are "challenging" vaccinated animals with SARS-CoV-2 to see which responses best correlate with protection.

Many researchers assume protection will largely come from neutralizing antibodies, which primarily prevent viruses from entering cells. Yet Joseph Kim, CEO of Inovio Pharmaceuticals, which is making a DNA COVID-19 vaccine, says a response by T cells—which clear infected cells—proved a better correlate of immunity in monkey studies of the company's MERS vaccine, which is now in phase II trials. "I think having a balance of antibody and T cell responses probably is the best approach."

Kim and others applaud the variety of strategies. "At this early stage, I think it makes sense to try anything plausible," he says. As Stéphane Bancel, CEO of Moderna, says, "Nobody knows which vaccines are going to work."

FINAL PRODUCTS

Spurring many of the efforts has been the Coalition for Epidemic Preparedness Innova-

Best shots

The World Health Organization has tallied dozens of vaccine candidates, based on a variety of technologies. Two have started human safety trials (*).

PLATFORM	CANDIDATES
Protein subunit	18
RNA	8*
DNA	3
Non-replicating vector	8*
Replicating vector	5
Inactivated virus	2
Attenuated virus	2
Viruslike particle	1

DATA: WHO

Corrected 1 April 2020. See full text.

Published by AAAS

Infect volunteers to speed a coronavirus vaccine?

As desperately as the world wants a shot that provides protection from the new coronavirus afflicting one country after another, proving that a vaccine works safely can be painfully slow. Clinical trials start with small numbers of people and at first only look for side effects and immune responses, slowly building up to a large study that tests efficacy—a process that will take at least 1 year for the new virus (see main story, p. 14). But as the scale of the pandemic becomes clearer, a provocative, ethically complicated proposal to shave many months off that timeline is gaining traction: Give people an experimental vaccine and then deliberately try to infect them.

Stanley Plotkin of the University of Pennsylvania, inventor of the current rubella vaccine, says a carefully designed "human challenge" trial could offer clear proof of a vaccine's worth at blinding speed. "We're talking 2, 3 months," says Plotkin, who has co-authored a commentary submitted for publication that describes how this might be ethically done. "People who are faced with a terrifying problem like this one will opt for measures that are unusual. And we have to constantly rethink our biases." A similar proposal from three other scientists was published this week in the *Journal of Infectious Diseases*.

Human challenge studies have been done ever since 1796, when Edward Jenner infected a boy with the smallpox virus after immunizing him with cowpox. Some are still underway for dengue, cholera, and other diseases (*Science*, 20 May 2016, p. 833). Today, such trials have careful designs and undergo extensive ethical reviews. Yet even researchers who conduct them argue against human challenges for the new coronavirus.

Matthew Memoli, an immunologist at the U.S. National Institute of Allergy and Infectious Diseases who stages human challenge studies of influenza, notes that the virus is so new it is not clear how often it makes people seriously ill or leaves them with long-term complications. "When you're going to give somebody a virus on purpose, you really want to understand the disease so that you know that what you're doing is a reasonable risk."

He also questions how quickly a proper human challenge of the new pathogen could be done. The challenge virus would first have to be grown under contamination-free, high-quality standards, and researchers would also have to determine the proper dosing of the challenge virus with, say, a monkey model, and confirm the dose in unvaccinated people.

Myron Levine, a vaccine researcher at the University of Maryland School of Medicine who has conducted challenge experiments for decades, doubts traditional clinical trials for vaccine candidates will be as slow as some fear. "I think we're going to move very, very fast," he says. Because of the high levels of new infections in many places, conventional trials will reveal a vaccine's worth on the same timeline as a human challenge, Levine says. "I cannot imagine that this would be ethical and would really speed up what we have to do."

Plotkin and other proponents of coronavirus challenge studies say risks could be reduced by only enrolling young adults, who seem to rarely suffer severe symptoms. To further decrease risks, the challenge could use a coronavirus strain from a person who had mild symptoms, a natural virus weakened in the laboratory, or a coronavirus mimic made by adding genes, such as the one for its surface "spike" protein, into a different, harmless virus.

Levine and Memoli agree that the risks would become more acceptable if an effective drug for the virus were available. And Seema Shah, a bioethicist at Northwestern University who also has strong misgivings, says the ethical scales might tip in favor of the experiment if the volunteers were people already "trained to take on these risks," like health care workers.

Shah would like to see a standing committee set up to address the ethics of challenge trials, especially during outbreaks, and spell out when they are justified. "The public is not familiar with these trials," she says. "They sound completely counterintuitive and opposed to the standard notion of what researchers or doctors are supposed to be doing."

Given the urgency, Shah adds, the vaccine community would be wise to quickly work out all the devilish details. "We're all going through these complicated emotions right now. If we're going to say we're making an exception to the standard way we do things, then we really have to get that right." —*J.C.*

tions (CEPI), a nonprofit set up to coordinate R&D for vaccines against emerging infectious diseases. So far, CEPI has invested nearly $30 million in vaccine development at Moderna, Inovio, and six other groups. "We have gone through a selective process to pick the ones that we think have the greatest likelihood of meeting our goals—which we think ought to be the world's goals—of speed, scale, and access," says CEPI CEO Richard Hatchett.

But he is rooting for other candidates as well. "We don't want to be in a situation where we have [one] successful vaccine and we have a contamination event [during manufacturing] and suddenly we don't have any vaccine supply."

CEPI invests in manufacturing facilities at the same time it puts money into staging clinical trials. "By doing things in parallel rather than in serial fashion, we hope to compress the overall timelines," Hatchett says. After reviewing phase I data and animal data, CEPI plans to move six of the eight products into larger studies to arrive at three that are worthy of full-scale efficacy trials that enroll perhaps 5000 participants. CEPI has less than $300 million in its coffers for fully developing a vaccine, however. and Hatchett estimates the price tag at $2 billion.

Seth Berkley, who heads Gavi, the Vaccine Alliance, argued in an editorial in *Science* last week that the world needs to come together even more to streamline the search for a COVID-19 vaccine. "If ever there was a case for a coordinated global vaccine development effort using a 'big science' approach, it is now," Berkley wrote, stressing that there must be extraordinary sharing of data, coordination of clinical trials, and funding. "You can't move 100 vaccines forward," he says.

Moderna and J&J both say that if everything goes perfectly, they could launch efficacy trials with about 5000 people in late fall and determine by January 2021 or so whether the vaccine works. Meng says, depending on approval from Chinese regulatory agencies, Sinovac could move its vaccine through small phase I and II tests by June. But, because of China's success at controlling its epidemic, the company may have to find another country that has high transmission of SARS-CoV-2 to stage an efficacy trial quickly.

Haller has had no serious side effects from the mRNA injected into her arm, but realizes that the phase I study will not determine whether the vaccine is effective. "The chances of the one that I got being really anything? I don't know," Haller says. "This is just the first of many, many vaccines, and it's just stupid luck that I was the first one." ■

With reporting by Kai Kupferschmidt.

Corrected 1 April 2020. See full text.

Vaccine designers take first shots at COVID-19

Jon Cohen

Science **368** (6486), 14-16.
DOI: 10.1126/science.368.6486.14