Vaccine Technologies Jockey for Primacy in Pandemic Response

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https://doi.org/10.1016/j.ymthe.2021.02.010

Stanley Plotkin is no stranger to viral outbreaks. In 1964, he helped put the “R” in MMR by designing the first vaccine against rubella. Commonly known as German measles, the virus was sweeping across the United States at the time, infecting some 12.5 million people, including tens of thousands of pregnant women who either lost their babies or had children with crippling, rubella-related birth defects.

Plotkin also worked on vaccines for chickenpox, rabies, anthrax, polio, and cytomegalovirus (CMV). He co-invented the rotavirus vaccine that is part of today’s childhood immunization schedule. And now, Plotkin is advising companies on the development of vaccines against the novel coronavirus, SARS-CoV-2, a pathogen unlike any he has encountered in his storied, decades-long career. “This is a disaster,” Plotkin says of the global pandemic. But for vaccinologists like him, “it’s a disaster from which we can really learn a lot.”

“Never before have we had so much vaccine development against the same target, permitting us to compare the different ways of making vaccines,” he says.

That target, the three-pronged spike protein that gives the coronavirus its crown-like appearance and name, is the major immunizing antigen found in the first two vaccines that won emergency approval from US regulators in December—one from Moderna, the other from Pfizer and its partner BioNTech. And it underpins dozens more potential coronavirus disease 2019 (COVID-19) vaccines that are now in various stages of development around the world (Figure 1).

With late-stage trial data from even the most advanced vaccine candidates still pouring in, it is too early to make definitive conclusions about which immunization approach is “best.” But already, the parallel development of so many technology platforms is yielding some important insights that could inform vaccine R&D strategies going forward, especially for emerging infectious diseases.

Shots on Goal

For starters, vaccines built on messenger RNA technologies clearly proved their worth. Going into the pandemic, only a dozen such vaccines—for rabies, influenza, and a handful of other viruses—had ever gone into human testing. Just one, for CMV, had progressed past phase I development. “What COVID did was showcase the strength of messenger RNA in a pandemic-like setting,” says Ron Renaud, chief executive of Translate Bio, a company with its own RNA-based coronavirus vaccine in development with partner Sanofi Pasteur.

The most obvious strength is speed. The Moderna and Pfizer-BioNTech shots shattered all development records for vaccines, a process that usually takes years. With both RNA vaccines, the design stage lasted only a few days. Mouse studies were performed in a matter of weeks. And clinical trials were completed in under 9 months.

What’s more, both vaccines proved to be around 95% effective at preventing disease, with reasonable safety profiles to boot. Few experts had foreseen those kinds of results. “I was stunned about the performance,” says Peter Palese, a virologist at the Icahn School of Medicine at Mount Sinai in New York City, who was not involved in either vaccine’s development.

Still, the RNA vaccines have their drawbacks. Raw materials that go into synthesizing nucleic acids and encapsulating them in lipid nanoparticles can be expensive. Side effects are typically worse than those from, say, a flu shot. The two-dose, prime-boost regimen comes with logistical challenges and compliance concerns. And distribution requires cold-chain handling to maintain the integrity of the RNA, a temperature requirement that has contributed to delays in mass vaccination campaigns around the world.

As such, other vaccines are still needed, especially to meet the huge demand for cheap and easy-to-store vaccines that can be readily integrated into health systems found in lower-income countries. “You want the vaccine that works in your context,” says Naor Bar-Zeev, a statistical epidemiologist at the Johns Hopkins Bloomberg School of Public Health in Baltimore, MD, who helped establish a national vaccine surveillance program in Malawi.

“For me, the key issue isn’t in the production of an efficacious vaccine,” Bar-Zeev adds. “The delivery aspects are going to be what differentiates one vaccine from another.”

Yet, several of the leading vaccine candidates that offer those kinds of delivery advantages have encountered development hiccups along the way. At best, the issues have simply pushed back timelines for late-stage human testing and eventual deployment. At worst,
they have called into question the clinical utility of vaccines already going into millions of people’s arms.

Take the adjuvanted recombinant protein-based coronavirus vaccines supported through the US government’s Operation Warp Speed project. Both faced months-long setbacks in their clinical programs, either because of antigen formulation issues (in the case of Sanofi and GlaxoSmithKline’s candidate) or because of manufacturing-related hold-ups (with Novavax’s product). Novavax ultimately demonstrated a vaccine efficacy of nearly 90% in a large UK study, but its North American trial was delayed.

Then there are the inactivated SARS-CoV-2 vaccines, many of which are already in widespread use despite limited or underwhelming data in large-scale clinical trials. For example, one from Sinovac Biotech that is available on an emergency basis in China, Turkey, and elsewhere proved to be little more than 50% effective in a phase III study involving more than 12,000 volunteers in Brazil.

Not Half Bad

Meanwhile, some vaccines that use replicating viruses to express the spike protein have underperformed. Earlier this year, for instance, Merck abandoned two vectored vaccine candidates—one built around vesicular stomatitis virus, the other around measles virus—after initial trials found that shots elicited only weak immune responses.

Vaccines built around replication-defective adenoviruses have had better success. According to interim analyses of phase III trial data, Janssen’s single-dose adenovirus (Ad) serotype 26 vector-based vaccine was 66% effective in preventing moderate-to-severe COVID-19 about a month after immunization; Russia’s Sputnik V vaccine, which involves a prime-boost regimen of two recombinant Ad vectors, a type 26 followed by a type 5, posted a 92% efficacy on the day of the second inoculation; and the two-dose chimpanzee Ad vectored vaccine from AstraZeneca and the University of Oxford proved to be 70% effective. But the AstraZeneca/Oxford vaccine has been mired in controversy because of a dosing error and patchy data.

German health authorities in January recommended against giving the vaccine to people over 65 years, citing a lack of evidence in the age group. And the clinical picture was muddied by the fact that a few thousand study participants accidentally received an initial half-dose of the COVID-19 jab (or the meningococcal vaccine control) before getting a full-dose for their second shot weeks later, a regimen that ultimately proved to be far more successful at preventing disease.

Despite the scientific uncertainties, regulators across Europe, India, Mexico, and elsewhere have even continued to tinker with the dosing strategy through their general vaccine rollouts. In the UK, for example, health authorities have elected to stretch out the interval between doses (both for the AstraZeneca/Oxford vaccine and for others available) as a way of immunizing as many people as quickly as possible. Some people in the country are even getting two different shots—one involving messenger RNA, the other with adenovirus—if matching vaccines are not available. There is little clinical data to support any of these alternative control measures.

Another big unknown about all the COVID-19 shots: how long does vaccine-induced immunity last? With the frontrunner vaccines, “we have efficacy data for maybe 2 or 3 months,” says Hildegund Ertl, a vaccine scientist at the Wistar Institute in Philadelphia, PA. But, she adds, “this virus isn’t going anywhere, and if efficacy starts waning, we will need to revaccinate.”

Continued viral evolution could further accelerate the process of compromised vaccine protection. Some fast-spreading variants of SARS-CoV-2, such as the B.1.1.7 lineage first identified in the UK, seem to be just as vulnerable to vaccine-induced immune responses as the original viral isolate from Wuhan, China. But others, including the B.1.351 variant from South Africa, harbor mutations that seem to compromise the vaccine integrity.

Unpublished lab experiments from Moderna, for example, found that the neutralizing power of the company’s vaccine was reduced 6-fold against B.1.351, while field experiments from Novavax and Janssen have shown that those vaccines have lower efficacies in South Africa, where B.1.351 is widespread, compared to other parts of the world where the variant is less common.

Several companies are now developing booster vaccine candidates tailor-made to the new variant’s unique mutational signature. Some additionally plan to test whether giving people extra doses of an original,
already-authorized vaccine offers another path to increased protection against emergent viral strains.

**Stop the Spread?**
Many researchers are also awaiting data on whether the vaccines reduce the spread of the virus in addition to warding off disease and death. If the shots block infections and curb contagiousness, they could hasten society’s return to normal life without the need for mask-wearing and social-distancing.

“But if we don’t have transmission-blocking effects,” says Daniel Larremore, a mathematical biologist at the University of Colorado Boulder, who has modeled vaccine prioritization strategies, “that will make a difference about whether we think we’re going to get to herd immunity—and how quickly we can open up.”

Trial investigators are intermittently drawing blood from study participants to determine if they have antibodies indicative of prior asymptomatic infections. A few studies also include routine genetic surveillance and testing of stool or saliva samples for signs of viral shedding. Plus, researchers are discussing ways to measure vaccine impact on transmission dynamics by studying spread between household contacts.

But society can ill-afford to wait for study conclusions. Immunization programs are moving full steam ahead, albeit with many distribution issues, even as many questions about the assorted vaccines and their technology platforms remain.

Plotkin is eagerly looking forward to the research results. In an ideal world, he says, if given the choice of vaccine, “I would want to be armed with the immunologic data: how high is the response? How broad is the response? How durable is the response? And I don’t have those answers yet.” By the end of 2021, however, “we’re going to have a hell of a lot more information.”

From what he has seen, Plotkin remains impressed by all the leading vaccine candidates. And at age 88, he knows that time—and risk for severe illness with COVID-19—are not on his side. So, “if I were offered a vaccine,” he says, “I would take it, almost regardless of which one it is.”

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