

New vaccine approaches present new possibilities, but new challenges

The COVID-19 pandemic has put new vaccine technologies into the spotlight and accelerated their development.

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Mark Zipkin

The pace of development for vaccines against SARS-CoV-2 was extraordinary. RNA vaccine company Moderna was shipping vials for clinical testing at the US National Institute of Allergy and Infectious Disease (NIAID) just 6 weeks after accessing a draft of the virus's genome, built upon decades of research and platforms years in the making. In one regard, the timing of the pandemic was fortuitous, in that novel vaccine technologies that could be rapidly applied to respond to the threat had already been evaluated in clinical trials. But it also laid bare the work left to do to prepare for the future.

The foundation for the latest wave of vaccine technologies rests on government and industry investments in basic research and novel technology platforms, says Gary Nabel, President and CEO of multispecific immunotherapy company ModeX Therapeutics. Nabel cofounded ModeX in 2020 after leaving Sanofi, where he had been CSO since 2012, following more than a decade as head of the Vaccine Research Center at NIAID. According to Nabel, improved understanding of both viruses and human immunology over the past few decades has allowed for the rational design of vaccines in a way that was never possible before. For example, "There really has been an explosion in our understanding about both the determinants of viral spikes that can be recognized by neutralizing antibodies, and the mechanisms by which viruses can enter cells," he said. "Those two things together gave a lot of insight."

Other factors were important as well, Nabel says. For one, in the USA, the experience of previous viral outbreaks prepared government agencies such as the Food and Drug Administration

(FDA), which carved a clear regulatory path for vaccines via Emergency Use Authorizations (EUAs), and the Department of Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA), which handled vaccine procurement under Operation Warp Speed.

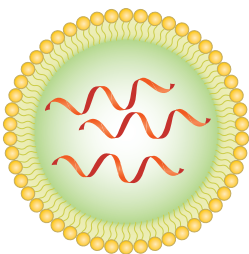
Pandemic proving ground

All three COVID-19 vaccines that have been issued EUAs by the FDA are built on platforms so new that they still haven't produced a fully approved vaccine in the USA (Fig. 1).

The first two COVID-19 vaccines granted an EUA are based on the mRNA platforms pioneered by Moderna and German immunotherapy company BioNTech, which partnered with Pfizer for clinical development, manufacturing, commercialization and distribution of vaccines for COVID-19 in March 2020. mRNA encodes a protein—in the case of COVID-19 vaccines it is the SARS-CoV-2 spike protein, which the virus needs to bind and invade human cells. The mRNA vaccines prompt human cells to produce the protein, recognize it as a foreign antigen and make antibodies, mimicking the natural immune response to a viral infection.

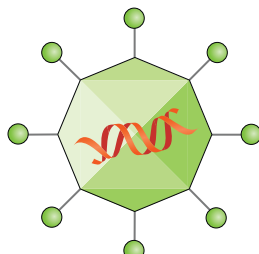
Moderna spent years exciting investors with its mRNA platform and endeavoring to live up to it. In 2018, it closed a \$604 million IPO, the biggest ever for a biotechnology company. On the eve of the pandemic, Moderna had 11 vaccines or therapies in early-stage clinical trials, while BioNTech had 6 cancer vaccines in the clinic. Still, it took nearly \$1 billion from Operation Warp Speed to push Moderna's COVID-19 vaccine through phase 2

a mRNA-based vaccines



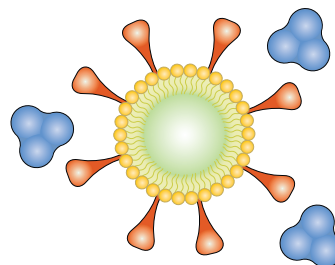
Lipid nanoparticles transport mRNA encoding the COVID-19 spike protein into cells

b Adenovirus-vector based vaccines



Adenovirus vectors carry the DNA encoding the COVID-19 spike protein into cells

c Recombinant protein vaccines



Nanoparticles coated with recombinant COVID-19 spike proteins are administered with an adjuvant

Fig. 1 | Comparison of selected vaccines in development against COVID-19. a | Nucleic acid vaccines. **b** | Adenovirus-based vaccines. **c** | Recombinant protein vaccine plus adjuvant.

and phase 3 clinical trials. Operation Warp Speed also signed a manufacturing agreement worth up to \$1.525 billion in August 2020. BioNTech and Pfizer signed a \$2 billion manufacturing contract for their COVID-19 vaccine through Operation Warp Speed in July 2020, but did not receive R&D funding.

The adenovirus platform at Johnson & Johnson's Janssen unit that produced the third SARS-CoV-2 vaccine to receive an EUA, JNJ-78436735, was slightly more mature, having scored its first European Commission approval last July with the Ebola vaccine Zabdeno. Adenovirus vaccines have been tested in the clinic for years, but had struggled to take hold until recently. In the 1990s, adenoviruses were explored as delivery vehicles for gene therapies in diseases such as cystic fibrosis, but their tendency to provoke an immune response was more desirable in a vaccine. The vaccines are based on recombinant adenoviruses, modified to block their ability to replicate or cause illness, that deliver genes for producing an antigen—again, in the case of JNJ-78436735 and others using viral vectors that have received regulatory approval in countries outside the USA, that means the SARS-CoV-2 spike protein.

One benefit to an adenovirus vector such as type 26 (Ad26) used in J&J's vaccine is that "it's a relatively easy virus to work with, to insert antigens in, and to make lots of vaccines with," said Jay Nelson, director of Oregon Health & Science University (OHSU)'s Vaccine and Gene Therapy Institute. Another is that the body recognizes it as a pathogen and mounts an immune response.

Testing the limits

There is a flipside to the body's pointed immune reaction to viral vectors that could limit their effectiveness though. "When you use a viral vector, you have to worry about two things: how prevalent that virus is in population, and if you give repeat administration, whether that could give an adverse response," said Nabel. According to Nabel, the immune system responds to both the adenovirus and the inserted gene, meaning anyone previously exposed to the natural variant of that adenovirus strain would generate antibodies to the vaccine. This pre-existing immunity to the vector effectively reduces the dose, and Nabel thinks it's one reason why Janssen might have wanted JNJ-78436735 to be a single dose: boosters may be less effective. "In many cases that can be a limitation," said Nabel, "because the immune system seems to do better, in general, when it sees the same thing more than once. That's how you generate memory responses."

For its part, Janssen—which has also tested Ad26 vaccines to prevent Zika, HIV, and respiratory syncytial virus (RSV)—has found no consistent pattern in clinical trials between baseline Ad26-neutralizing antibodies and immune response to its vaccines.

Other companies have attempted to lessen the issue by developing platforms based on adenoviruses that do not naturally infect humans. AstraZeneca's COVID-19 vaccine, Vaxzevria (AZD1222)—granted emergency authorization in the UK and conditional approval in Europe earlier this year—was developed at the University of Oxford based on a chimpanzee adenovirus, ChAdOx1. "A lot of people in developing countries have already been infected with adenovirus, but they wouldn't have been exposed to the chimpanzee one," said Nelson. AstraZeneca has not yet applied for an EUA in the USA.

Still, said Nelson, exposure to the vector in one vaccine might prevent an effective immune response to any future vaccines made from that vector.

And not all adenovirus vectors are the same. For example, adenovirus type 5 (Ad5) has been utilized by China's CanSinoBio for its Convidece vaccine, as well as in the booster following an Ad26-based prime dose in Russia's Sputnik V vaccine. But the approach has concerned some experts, including researchers who previously tested Ad5-based vaccines for HIV, who have linked it to increases in HIV infection.

mRNA vaccines are delivered in lipid nanoparticles, meaning they don't trigger the same immune response over multiple doses. As additional, resistant viral SARS-CoV-2 strains have emerged, mRNA companies have quickly developed boosters against the variants. But the lipids can still trigger some inflammation and immune response. "I suspect that's at least part of the reason why people get these side effects when they get an mRNA vaccine," said Nabel, though he adds that can likely be improved in the future.

Today most mRNA vaccines have stabilization issues that require ultracold storage throughout the supply chain. That requires sophisticated logistical solutions, said Philippe Denoel, Head of External R&D for GlaxoSmithKline (GSK) vaccines. "We have all seen in one year how important this technology platform is, it allows very fast development of vaccine candidates. But it's not going to be the one and only solution for the future."

The next wave

All of the current platforms have their limitations, which has kept academics and companies looking to improve on or build on existing technology. One area of broad possibility is adjuvants, which only recently began to advance beyond traditional adjuvants resembling those used in vaccines since the 1930s. Adjuvants improve the potency of vaccines by boosting immune responses, making them extremely important for vulnerable populations, including the elderly, that have reduced immune function, said Nelson. At least one COVID-19 vaccine candidate nearing potential regulatory authorization, Novavax's NVX-CoV2373, combines a full-length SARS-CoV-2 spike protein in a recombinant nanoparticle with a saponin adjuvant, and it has been highly efficacious in phase 3 testing.

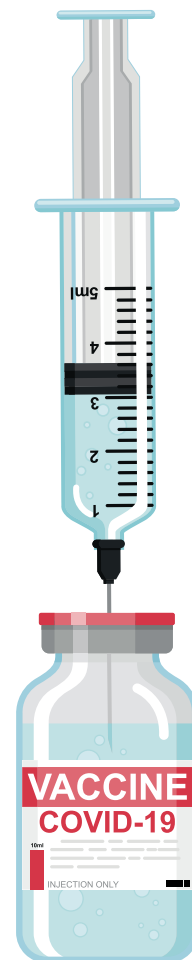
Another example is Shingrix, a vaccine developed from GSK's AS01 adjuvant platform and approved by the FDA in 2017 to prevent shingles in adults aged 50 years and older. AS01 is a liposome-based adjuvant with two immunostimulants that GSK has also used to develop a malaria vaccine, Mosquirix, which is approved in Europe. "We've seen with Shingrix that using an adjuvant has made all the difference between having an OK vaccine versus one that's really quite effective," said Nabel.

Denoel says investments in the AS01 platform also led to the development of additional adjuvants such as AS03, which has been used to improve on GSK's influenza and COVID-19 vaccine candidates. "The adjuvant platform has been a major investment for us in research and development over 25 years," he added.

Others are using the limitations of existing platforms to inspire new approaches. Nelson took cues from adenovirus research as his team developed VIR-1111, an HIV vaccine delivered instead by a replication-impaired, persisting cytomegalovirus. No adenovirus-based vaccine for HIV has made it to phase 3 testing, and Nelson suggested that they are better suited for acute infections like COVID-19. The cytomegalovirus approach "might be a way to get around persistent infections, like simplex or other herpesviruses." Vir Biotechnology licensed the platform through a merger with the OHSU spinout, TomegaVax and now has VIR-1111 in phase 1 trials.

Nabel also noted that nanoparticle technologies are promising approaches. "In the lab, we can mount specific parts of virus to synthetic nanoparticles, which will spontaneously assemble and present them in an array to the immune system," triggering a more active immune response, he added. Other companies, including Capricor Therapeutics and Codiak BioSciences, are developing exosomes—naturally derived nanoparticles—as potential vaccine delivery systems.

GSK has several other vaccine technologies in development, says Denoel. One is through a partnership with LimmaTech Biologics, to develop next-generation recombinant glycoconjugate vaccines. The company is also tapping a structural biology platform, exploring how vaccine antigens like the RSV prefusogenic fusion protein structure and the coronavirus spike protein can inform future vaccine development.



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Investing in the future

Infectious disease research is a team sport, by any measure. “It’s a different business model from other therapeutics,” said Nabel. The number of patients tends to vary, year on year, and vaccine trials require large sets of patients.

Funding for research and development is often bolstered by public bodies and public–private partnerships. Partnership is foundational to GSK’s approach, says Denoel, and support from the Bill & Melinda Gates Foundation and other funders was crucial for development of Mosquirix. He also noted that the Wellcome Trust, and public funders like BARDA and the NIH have been necessary for GSK’s work on Ebola, and the Innovative Medicines Initiative—a public–private partnership developed by the European Commission—brings an important support to the development of new pertussis and RSV vaccines.

The European Commission is also launching its response to BARDA, the European Health Emergency Preparedness and Response Authority (HERA), this year. Denoel called this a welcome addition to the world of biopreparedness.

Public funding in particular has been notable in the past year as governments signed huge procurement deals that provided the financial incentives to get COVID-19 vaccines across the finish line, such as the \$456 million vaccine order signed in March 2020 by Johnson & Johnson—before its clinical trials had even begun—with BARDA. But Vered Caplan, CEO of personalized cell and gene therapy company Orgenesis, notes that many vaccine technologies, including mRNA, might not exist without basic research funding from NIH. “We should look at where these technologies are coming from,” she said. “This is taxpayer money being invested into academic institutes. This information belongs to everyone, in a way we don’t always realize.”

NIH priorities guided the creation of Nelson’s institute two decades ago, down to the interdisciplinary staff he recruited. “I hired in people that would have their own programs,” he said, “but the idea was, we would all work together on programs,

because we knew that the NIH was going to be funding people in this direction. And that’s been quite successful.” The institute has two contracts with NIH to develop new adjuvants—one of the institute’s priorities, he said—including one working with immunotherapy company Inimmune. “The NIH has been extremely helpful in forming these types of partnerships, which I think are really necessary to get new vaccines out there,” he said.

Still, there are some things that can’t be done in an academic lab. It was the Gates Foundation, working with OHSU on its HIV vaccine, that pushed several OHSU researchers to co-found Vir, said Nelson, which raised \$143 million in an IPO in 2019 and now has a market cap of \$6.3 billion. “We couldn’t take it any further, we needed somebody that had expertise in vaccine manufacturing and clinical trials,” Nelson added.

Pre-pandemic, private investment had been more supportive of viral vaccine-adjacent companies, like BioNTech and Moderna, which focused more in areas like immunotherapy. “I wish that it could be the reverse, that thanks to investments in infectious disease, or biopreparedness vaccine technologies, this could instead open up opportunities for the treatment of other important situations like oncology, antibiotic resistance or non-communicable diseases” said Denoel. He remains optimistic, however. “I think the situation has somewhat changed, they realize that infectious disease offers not only opportunities to bring solutions to important medical needs and public health, but also could translate into some kind of financial returns for them.”

Viral vaccines remain risky business, though. “We’ve had a little bit of an infusion of talent and resources,” said Nabel. “I don’t know how long that will last. The same thing happened with Ebola—as soon as it was no longer a threat, everybody said, ‘Forget that, who wants to work on Ebola vaccines?’ Only time will tell whether COVID-19 has the same fate.

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