"Long COVID"

Pandemic Continues To Reshape the Vaccine Sector

Gareth Macdonald

Vaccines have saved millions of lives during the COVID-19 pandemic. Estimates vary, but according to one study, inoculations against SARS-CoV-2 reduced "excess deaths" worldwide by 63% — equivalent to nearly 20 million people — during 2020 alone (**1**). Although the coronavirus pandemic has underlined the benefit of vaccine innovation, it also has highlighted some weaknesses in how such life-saving products are developed, manufactured, and distributed. How well the biopharmaceutical industry addresses those weaknesses using knowledge gained over the past few years will determine the effectiveness of its response to future health emergencies and endemic diseases in general.

Clinical Acceleration

The pandemic has had some positive effects on the vaccine sector, says Jeff Fischer (cofounder of Longhorn Vaccines & Diagnostics). Specifically he cites the speed with which SARS-CoV-2 vaccines moved through clinical development as an example:

"COVID-19 changed the way the industry thinks about timelines and surrogate endpoints. In the beginning of the pandemic, leading companies created new vaccines — messenger RNA (mRNA), viral vector — in a historically short amount of time." Developers then identified ways to accelerate early clinical studies. "They did some quick animal studies to check for neutralizing activity. The phase 1 studies were more about immunogenicity, looking at antibody levels and neutralizing antibodies (nAbs). Those are considered 'surrogate endpoints.'" In the future, Fischer says, "the use of surrogate endpoints to speed up vaccine development will be an important component in developing new vaccines during health emergencies and for vaccines [for which it is] difficult to generate large enough infections to prove efficacy."

Other experts are more cautious. In a 2022 study, a team of academic researchers examining post-COVID vaccination strategies warned about the potential pitfalls of opting for surrogates when viral variants are circulating (**2**): "Surrogate endpoints can be valuable, but they should be interpreted within the context of changing knowledge base and changing virus. For example, we now know that Omicron breakthrough infections induce overall higher neutralization titers against all different variants of concern, and BA.2.12.1 and BA.4/BA.5 can substantially escape nAbs induced by both vaccination and infection." The authors conclude that "investigators will need to be prepared to reevaluate study samples and to select an adaptive design that could allow for reevaluation of surrogate markers."

Messenger RNA Technology

In addition to prompting developers to rethink clinical trials, COVID-19 also firmly established the reputation of mRNA as a modality. Both Pfizer–BioNTech's Comirnaty and Moderna's Spikevax products, for example, use mRNA to induce in vivo production of the SARS-CoV-2 "spike" protein, which elicits a protective immune response to subsequent viral exposure.

As innovations during the pandemic moved mRNA technology into the mainstream, the industry realized that vaccines could be developed quickly. It took just 326 days from release of the virus's original genetic sequence to emergency authorization of a safe and effective vaccine. Accelerating development is a major focus for the vaccines industry, according to In-Kyu Yoon (executive director of vaccine research and development at the Coalition for Epidemic Preparedness Innovations, CEPI).

Yoon says that "mRNA vaccines were a game changer in our response to COVID-19 and are poised to play a key role in preparing for and responding to future health emergencies." That's largely due to the technology's flexibility as a rapid-response platform on which new vaccine candidates can be designed and quickly made ready for clinical testing and subsequent scale-up, potentially within days from the moment a new viral threat is identified.

The same technology also has been tested in other therapeutic areas (**3**). In December 2023, for example, Merck — known as MSD outside of the United States and Canada — and Moderna began a phase 3 trial of a therapeutic vaccine for lung cancer, V940 (mRNA-4157).

Next-Generation mRNA Technology: COVID-19 vaccines have proven that mRNA can be effective. However, Yoon says that further development and investment is needed for the technology to fulfill its potential. "Current mRNA vaccines have limitations. They have the potential to provoke local reactions or short-term fever. Relative to other types of vaccine, they are also, at present, expensive to manufacture and require costly and complex cold-chain storage and transportation infrastructure."

To try and address those issues, CEPI — which is backed by the Bill and Melinda Gates Foundation, the Wellcome Trust, and a number of governments – has launched programs to advance the next generation of RNA-vaccine platform technologies. "We have just launched a new partnership with the Houston Methodist Research Institute (**4**) looking at the potential of 'circular RNA' vaccines," Yoon says. And CEPI recently launched a project with Korean-based biotechnology company Lemonex (**3**) to advance its DegradaBALL mRNA drug-delivery technology, which could both minimize post-mRNA vaccination side effects and improve access to future vaccines.

"If effective," Yoon says, "these updated and improved mRNA-based vaccines could progress this new scientific era of mRNA vaccinology even further. But it's important to note that we cannot 'put all our eggs in one basket' and wholly rely on mRNA vaccine technologies. Diversification is key, and it may be the case that other types of vaccine technologies, such as viral-vector platforms or recombinant-protein vaccines, provide better protection against certain pathogens with epidemic or pandemic potential."

Rapid-Response Vaccines

Recognizing that need for diversification, CEPI also is supporting several other "rapid-response" vaccine platforms, including the ChAdOx technology created by the University of Oxford's Jenner Institute in the United Kingdom. The platform leverages chimpanzee adenoviral vectors to deliver antigenic gene sequences to human cells.

"ChAdOx is one of a handful of technologies with proven capability as a platform," Yoon explains, "on which safe and effective vaccines can be quickly developed and manufactured at scale and low cost. Supported by a commitment of up to US$80 million of CEPI funding, our strategic partnership with the University of Oxford launched in August 2023 to harness the ChAdOx platform and develop prototype vaccines against high-risk viral families." The technology could be adapted swiftly if a new viral threat is identified.

Furthermore, CEPI is funding the development of thermostable, sublingual vaccine films with biotechnology company Jurata Thin Film in Houston, TX. If successful, that technology could help expand access to vaccines in underserved regions. CEPI also partnered recently with Algenex in Spain to explore whether moth chrysalises could act as "living bioreactors" to accelerate new vaccine production. And the organization is examining the role that artificial intelligence (AI) could play in future pandemic preparedness and response.

"Our AI projects are looking to analyze the structure of viral families known to cause human disease," Yoon says. CEPI wants to identify potential antigenic targets to help inform vaccine design and guide the prioritization of viral families with potential epidemic or pandemic risk.

Vaccine Innovation

Coverage extension — ensuring that vaccines will protect against as many viral variants as possible — also has emerged as a research focus as a result of the pandemic. The first COVID-19 vaccines were highly effective, but their efficacy declined in the months that followed as viral variants mutated. Some subsequent versions of the vaccines have not shown the same ability to protect against symptomatic infections and instead are limited to reducing severe symptoms in specific populations.

In response, the industry and its stakeholders are focusing on development of vaccine technologies that will be resistant to pathogens' ability to mutate. Some products have emerged based on monoclonal antibodies (mAbs) that are designed to extend the duration of coverage. A notable example is Sanofi and AstraZeneca's Beyfortus (nirsevimab-alip) respiratory syncytial virus (RSV) vaccine, which the US Food and Drug Administration (FDA) approved in 2023 (**5**).

Further Reading

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Another impact of COVID-19 has been a renewed focus on vaccine efficacy. Patients, governments, and healthcare systems want vaccines to work. That demand has been loud and clear, according to Fischer. "The pandemic and early stages of the postpandemic timeframe have required companies to focus on developing vaccines that provide significantly more effectiveness than current vaccines. In the cases of influenza and COVID-19, vaccines need to have broader coverage to demonstrate the ability to prevent symptomatic disease — and last longer. Some companies are looking at combination vaccines [for] influenza and COVID-19. Others are developing combinations that pair a target where vaccines currently exist with a disease where there aren't any current vaccines."

The focus on efficacy has prompted some merger and acquisition (M&A) activity. In December 2023, AstraZeneca announced plans to buy Seattle-based Icosavax, citing as a key motivation the latter's combination protein virus-like particle (VLP) vaccine that targets both RSV and human metapneumovirus (hMPV) and is entering phase 3 trials.

Manufacturing Capacity

COVID-19 also put a spotlight on vaccine production, with the main realization being that the biopharmaceutical industry struggled to meet demand, particularly for developing regions. Dutch researchers found a number of reasons for that, including a lack of manufacturing facilities and technology-transfer personnel, critical shortages in raw materials, and restrictive protectionist measures (**6**): "More resilience and robustness must be integrated into the vaccine production chain, and low-/middle-income countries should be empowered to manufacture vaccines themselves."

That conclusion is in keeping with an earlier CEPI study, which identified Africa, Southeast Asia and the Western Pacific, the Middle East, and Latin America and the Caribbean as areas where additional vaccine production capacity is needed most (**7**). Those findings inform the organization's push to expand the global footprint of vaccine production, Yoon says. The organization has created a manufacturing network that focuses on vaccine makers in the Global South near areas that are at high risk of outbreaks caused by deadly viral threats such as Lassa fever, Nipah, disease X, and other prioritized pathogens with epidemic and pandemic potential.

"We currently have four partners in the network," Yoon says, citing Serum Institute of India, Aspen in South Africa, Institut Pasteur de Dakar in Senegal,

and Bio Farma in Indonesia. "There is a lot of movement across the regional vaccine manufacturing space, so we also just announced that we now will be hosting the Regionalised Vaccine Manufacturing Collaborative (RVMC), a global initiative to convene, match-make, and provide support across various regional manufacturing initiatives."

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Continued from ***page 1***

genetically engineered human breast-cancer cell line that is designed to present tumor antigens to patient immune cells, enhancing tumor destruction.

Protein-Subunit Vaccines: Because of their efficacy and rapid development timelines, vaccines based on messenger RNA (mRNA) played a significant role in abating COVID-19 public-health emergencies around the world. However, challenges remain for the modality. BPI editors BPI editors speak with the head of SK bioscience's biological R&D headquarters to learn why established production platforms for protein-subunit vaccines will be key to mitigating future infectious-disease outbreaks.

Multiserotype Glycoconjugate Vaccine Processing: Glycoconjugate vaccines comprise immunogenic carrier proteins linked chemically to specific polysaccharides, which can be isolated from a target pathogen or (increasingly) expressed recombinantly in microbial hosts. Although the complexity of chemical coupling historically has made such vaccines difficult to produce, researchers are leveraging bacterial technologies to couple glycans and carriers, helping to decrease costs. However, drug companies still need greater understanding of basic steps in glycoconjugate manufacturing. BPI associate editor Josh Abbott speaks with a Penn State researcher whose team has provided key insights into sterile filtration of multivalent glycoconjugate products based on studies of a Pfizer meningitis vaccine.

Innovation Is Key

As both data and life sciences advance, innovative technologies are developed to address questions that arise with real-world applications. CEPI's Dimki Patel spoke at the January 2024 CASSS Well-Characterized Biotechnology Products (WCBP) symposium held in Washington, DC. She described an ambitious goal that the organization has set forth: "Vaccines should be ready for initial authorization and manufacturing at scale within 100 days of recognition of a pandemic pathogen, when appropriate." With an eye looking back at the difficulties associated with mRNA vaccines, CEPI focuses part of that mission on drug-delivery technologies, especially associated with thermostability and alternative presentations. Patel highlighted microarray patches in development at Vaxxas that could improve the stabilization and delivery of mRNA vaccines; aVaxziPen's thermally stable, needle-free method for delivering vaccines as a solid dose; and Jurata Thin Film's formulation of room-temperature–stable vaccines for sublingual application. And she described regulatory strategies such as templates and master files for platform technologies that could set innovative products up now for future success. The recent pandemic may have given many such developments a head start.

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