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# Setting Bigger Targets for Next-gen Vaccines

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**New vaccine platform technologies could dramatically shorten the period from research to development, clinical trials, and vaccination. Reimagining R&D approaches in vaccine design and vaccine immunology may hold the key to significantly elevate the health impact of vaccines. Experts worldwide are adopting novel research approaches in the molecular design of vaccines, and vaccine technology platforms. India is seeing increasing interdisciplinary research, and a rise in cutting-edge technological interventions in fundamental and translational research. The time is ripe for boosting out-of-the-box R&D approaches in vaccinology. Letâ??s explore further.**



The National Institute for Allergy and Infectious Diseases (NIAID), one of the 27 institutes and centres that make up the National Institutes of Health (NIH) of the US, referred to next-generation vaccines as those with enhanced breadth of protection to variants, improved durability, and enhanced ability to block infection/transmission relative to currently approved vaccines. The Coalition for Epidemic Preparedness Innovations (CEPI), a global partnership working to accelerate the development of vaccines and other biologic countermeasures against epidemic and pandemic, describes vaccine technology platforms as technologies that are essential for rapid responses to emerging viral threats.

Essentially, vaccine platform technologies are systems that use the same basic components as a backbone but can be adapted for use against different pathogens by inserting new genetic or protein sequences. Rational vaccine design, developed using suitable vaccine technology platforms, could thus present significant advantages in immunisation. Creating such an unprecedented disease agnostic vaccine technology platform can empower the world to be ready for future pandemics. Studies have shown that next-generation vaccines can enable a higher spectrum of protection against multiple variants, increased durability, and minimal safety concerns due to side effects while increasing their immunogenicity.

Each vaccine's utility or efficiency is determined by its formulation, adjuvants, and mode of action. The efficacy of the vaccination depends on numeral properties like the generation of antibodies, memory cells, and cell-mediated immunity.

Studies on COVID-19 immunisation have shown that next-generation vaccines hold promise in generating long-lasting, broad immunity against virus variants. Since the launch of the first COVID-19 mRNA vaccine, continuous developments in improving mRNA vaccine technology for the SARS-COV2 virus are underway all over the globe. Research approaches from reverse vaccinology and immunoinformatics to continuous-replicating mRNA carrying the antigen of interest are being used to develop new vaccine platforms and improve the current lot of next-generation vaccines. For the larger goal of enhanced immunogenicity, researchers are exploring new antigenic epitopes, the role of immune cell subtypes, and unique adjuvant or delivery vehicles to generate better immune responses.

Approaches such as exploiting the role of mRNA modifications in attuning their immunogenicity, stability, and translational efficiency are important examples. Research into mRNA modifications has yielded multiple candidate mRNA therapeutics undergoing clinical or preclinical trials, as well as effective SARS-CoV vaccines. The COVID-19 mRNA vaccine highlights that using structurally modified mRNA allows for increased dose tolerance and may be better for eliciting a rapid antibody response. The new mRNA COVID-19 vaccine of Moderna, mRNA-1283, designed for multiple SARS-CoV-2 strains found to offer improved neutralising antibody response in individuals more than 65 years of age.

A team from the Yong Loo Lin School of Medicine at the National University of Singapore and Monash University, Australia has engineered a COVID-19 vaccine using a novel vaccine platform to fuse the receptor binding domain of the spike protein of the SARS-COV-2 virus to Clec9A antibody (an antibody against the receptor on dendritic cells presenting antigen to T and B cells to generate immune response). This construct showed long-lasting immunity till 21 months in a preclinical study after only a single dose. This would be a promising approach against waning immunity and a useful strategy for adults above 60 years by eliminating the need for repeated boosting.

The platform of the vaccine, number of doses for immunisation, the production capacity, and vaccine storage condition are all important for the rapid development of the vaccine from laboratory to clinical trials and approval. In addition, vaccine designs that can reduce safety concerns hold the advantage of crossing regulatory hurdles and approval stages in a reasonably short period. Moreover, a focus on next-generation vaccines and novel delivery methods, such as intranasal vaccines, may exhibit more effective and user-friendly vaccination strategies. This can prove crucial in India, owing to factors like the emergence of tropical infections, an overall vaccine hesitancy, a large population to vaccinate, and enabling wide-spread accessibility of vaccines, especially in rural areas.

Fostering an ecosystem for R&D in vaccinology could aid in directing focus toward vaccine discovery, vaccine design, and formulation, as well as vaccine administration methods. Experts across different verticals in this field are now making efforts to build an infrastructure to deliver effective but economical vaccines. This could help to achieve a better sense of preparedness for emerging diseases as well as an all-round improvement of the health impact of vaccines, particularly in the cases of HIV, dengue, malaria, and tuberculosis, which have been outsmarting scientists for decades. In addition, some at-risk groups show even low responses to the vaccines or the existing vaccine have severe side effects and need further development of suitable or more immunogenic vaccines (e.g., for elderly individuals or infants).

Given this scenario, enhancing efforts in the development of next-generation vaccines can hold a promise in protection against emerging and re-emerging infections.

**Next-gen vaccines in India**

Nucleic acid vaccines, viral vector-backbone-based vaccines, and protein subunit vaccines are vaccine platforms being explored for new-generation vaccine developments in many countries. The advent of the COVID-19 pandemic brought the mRNA technology to the forefront. Beyond Pfizer and Moderna, who were pioneering leaders in bringing mRNA vaccine platform to the community, the indigenously developed 'GEMCOVAC-19' vaccine is the only third mRNA vaccine to be approved for COVID-19 in the world, and is the very first mRNA vaccine developed in India in June 2023. Developed by Pune-based Gennova Biopharmaceuticals in collaboration with Department of Biotechnology (DBT), this Omicron-specific mRNA (booster) vaccine 'GEMCOVAC-OM' is thermostable, which does not require ultra-cold chain infrastructure used for other approved mRNA-based vaccines, making it easy for deployment pan India. It is delivered intradermally using a needle-free injection device system.

Upon Drug Control General of India (DCGI) approval for 'GEMCOVAC-OM' for Emergency Use Authorisation (EUA), in June 2023, **Dr Jitendra Singh, Union Minister (Independent Charge), Ministry of Science and Technology**, commended the efforts of the DBT said, "I take great pride in DBT fulfilling its mission yet again, enabling technology-driven entrepreneurship through creating this indigenous mRNA-platform technology. We have always supported technology-driven innovation towards the creation of a 'future-ready' technology platform in line with the Prime Minister's vision of Aatmanirbharta." He added, "Infrastructure to deploy vaccines in India, including LMICs, at 2-8°C exists today & this innovation is tailored for the existing established supply-chain infrastructure. The vaccine does not need ultra-low temperature conditions for transport and storage."

**Dr Rajesh S Gokhale, Secretary, DBT, and Chairperson, Biotechnology Industry Research Assistance Council (BIRAC)** said "Strategic infusion of funds is essential to drive and create an ecosystem for technological innovation. DBT did just that when it provided support for the development of the nation's first mRNA-based platform technology in 2021-22 and development of GEMCOVAC-19' vaccine. This is a disease-agnostic platform and can be used to make other vaccines in a relatively short developmental timeline."

Researchers at IIT-Delhi, led by **Dr Jayanta Bhattacharya at the institute's Centre for Biomedical Engineering**, developed a novel nanovesicle presenting spike protein on the surface of the dendritic cell-derived extracellular vesicles (DEVs) for use as a potential vaccine platform against SARS-CoV-2. Their research explored an approach to establish the immunogenic nature of DEVs and could demonstrate that a low dose of DEVs induces antibodies to inhibit SARS-CoV-2 infection in vitro. This warrants that with this approach, IIT Delhi researchers effectively developed a COVID-19 vaccine

prototype using the body's own immune cells.

iNCOVACC, Bharat Biotech's intranasal vaccine for COVID-19, was designed and developed on a novel adenovirus vector. The vaccine demonstrated stimulation of a broad immune response and has the advantage of being non-invasive and needle-free with high compliance. Additionally, the vaccine design and development protocol allows for scalable manufacturing, to even meet global demand. The DCGI under the Central Drug Standards Control Organisation (CDSCO) has granted permission for the sale or distribution of iNCOVACC for immunisation against SARS-CoV-2 virus infection for the age group? 18 years, for restricted use in emergency situations in public interest. The iNCOVACC vaccine is perhaps an all-round example of a rational vaccine design on a new-generation vaccine technology platform with intranasal delivery as compared to injections.

Zydus Cadila's ZyCoV-D, the world's first and India's indigenously developed DNA-based vaccine for COVID-19 is another significant milestone. It was developed by Zydus Cadila in partnership with the DBT, and implemented by BIRAC under the Mission COVID Suraksha. The vaccine received approval for EUA from the DCGI in August 2021, just over a year since the COVID-19 pandemic hit India. The plug-and-play technology on which the plasmid DNA platform is based can be easily adapted to deal with mutations in the virus, such as those already occurring. In addition, studies have shown, including Zydus's own analysis, that DNA vaccines are stable at higher temperatures, making storage and distribution easier.

A tetravalent dengue subunit vaccine, DSV4, developed by the International Centre for Genetic Engineering and Biotechnology (ICGEB) is a single-component, non-replicating '4-in-1? vaccine based on a virus-like particle (VLP) platform, produced using the methylotrophic yeast *Pichia pastoris.* In 2016, ICGEB transferred the dengue vaccine technology licence to Sun Pharma for further development. Process scale-up has been conducted in the Sun Pharma affiliated biotech company in Germany in 2019, and has been brought back to India for in-house development under the National Biopharma Mission, Government of India. A GMP facility of Sun Pharma is being established in Bangalore and efforts are being made to reach Phase 1 efficacy trials.

**What does the future hold?**

While India is a global leader in manufacturing vaccines, vaccine research, especially the development of next-generation vaccine technologies, are thus far relatively unexplored waters. Having an infrastructure for enabling rapid production of economical and safer vaccines in shorter time frames will allow our public health system to stay poised to fend off emerging diseases. Conventional vaccine development approaches have primarily involved live attenuated or inactivated whole pathogens. These approaches followed largely empirical design and developmental cycles. Additionally, attempts for R & D of traditional platforms of vaccines can take up to several years, which will fail to align with the expectations for fast response and control of epidemics and pandemics of an emerging or re-emerging pathogen.

Indian companies have entered into collaborations with global pharmaceutical firms and research institutions to leverage advanced technologies and expertise. The government is funding and providing regulatory support through DBT and the Indian Council of Medical Research (ICMR).

While next-generation vaccines can have their advantages, several major vaccine candidates that have evolved in India are based on traditional live attenuated and inactivated whole organism-derived approaches. These have proven to be immensely successful models for India, as chronicles of vaccines like MMR, OPV, and BCG, among others, have demonstrated for decades.

COVID-19 has resulted in an innovation surge in vaccine development globally and in India. While traditional vaccine development and delivery platforms have proven to be a successful model for India for many decades, it stands to reason that with pathogens evolving to adapt, it will be crucial for humans to evolve vaccine strategies to stay on top.

***Shivani Thakar***

***shivani.thakar@biospectrumindia.com***