WHITE PAPER

Inoculating your vaccine portfolio for the future

The advantages and limitations of vaccine technology platforms

By Adi Natu, Joshua Hattem, Matt Furlow, Sara Ackermann and Amandeep Singh

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Ever since the advent of the first smallpox vaccine in 1796, the vaccine manufacturing landscape has undergone progressive transformation to surmount constraints and incorporate advancements to build better vaccines. In recent memory, the COVID-19 pandemic led to the approval of vaccines based on a variety of platforms—adenoviral vectors, mRNA, DNA, VLPs, protein subunits and inactivated vaccines. Each platform offers opportunities and challenges. Each offers new sophistication and complexity in addressing the high unmet need of infectious diseases across the globe. Figure 1 shows the timeline of when the first vaccines based on specific platforms were approved.

FIGURE 1:

Vaccine platform timelines, 1700s through present

Abbreviations:

VLP: viral-like particles; OMV: outer membrane vesicles; FDA: Food and Drug Administration; DCGI: Drugs Controller General of India; EUA: Emergency Use Authorization

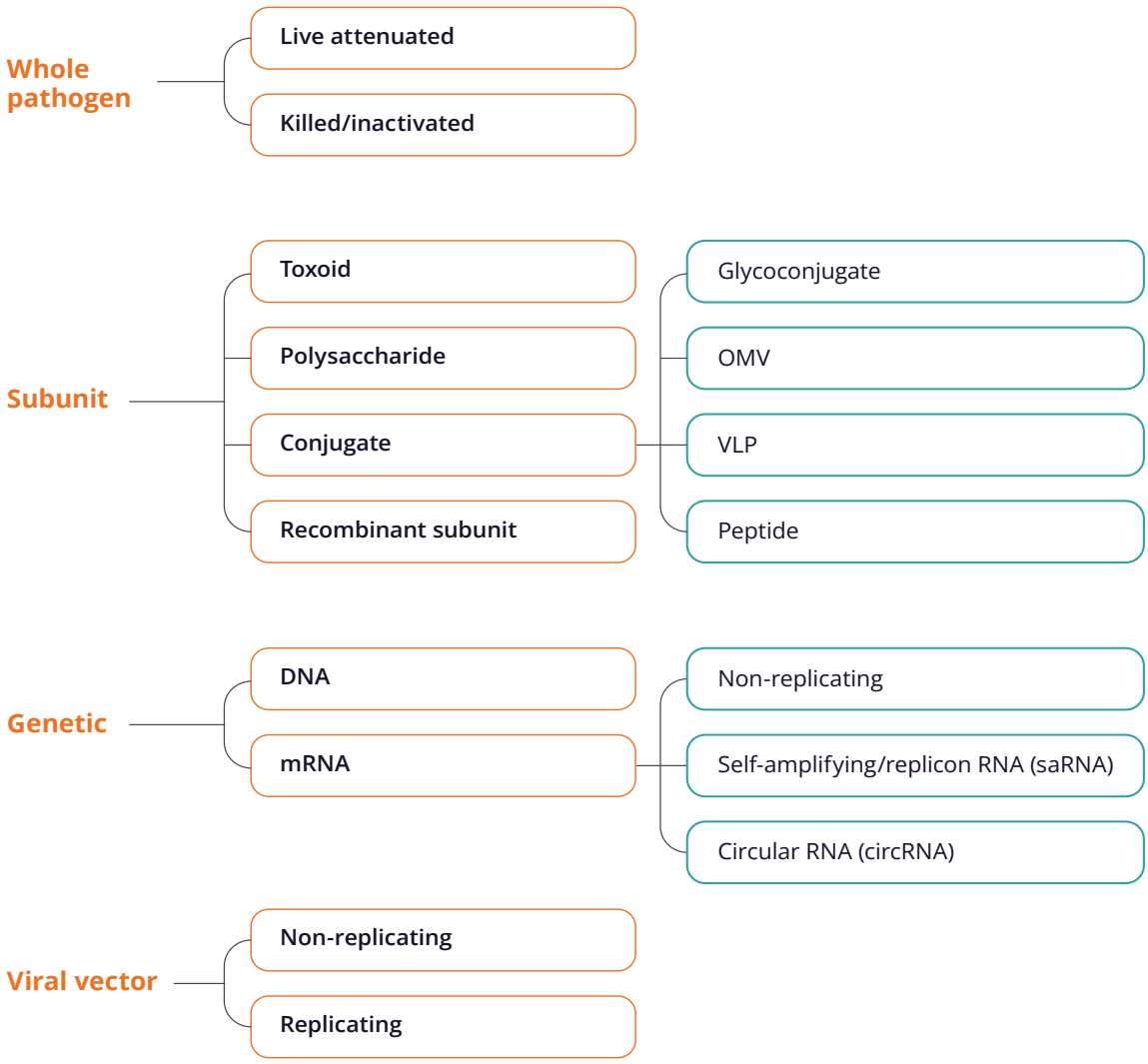
Source: Amr Saleh et al, "Vaccine development throughout history." Ummunize.org, "Vaccine history timeline."

Vaccine platform types and their benefits

Traditional vaccines, like whole pathogens or subunits, employ antigens derived either from intact pathogens or constituent elements like protein subunits or toxins to activate an immune reaction. The advent of novel approaches in immunogen design and genetic engineering has fostered the emergence of next-gen vaccine platforms, like viral vectors and genetic vaccines. Figure 2 shows a brief classification of the various platforms used today. Note that some platforms, like dendritic cells, which typically do not follow the conventional vaccine specifications are not included in the classification.

FIGURE 2:

Vaccine platform classifications



For decades, **whole pathogen vaccines (WPVs)** have served as the mainstay of immunization. Safety concerns associated with WPVs spurred the development of subunits, harnessing pathogen fragments instead. These can be protein subunit vaccines with specific isolated proteins from viral or bacterial pathogens, vaccines containing chains of sugar molecules (polysaccharides) found in the cell walls of some bacteria or conjugate subunit vaccines (where the polysaccharide chain is bound to a carrier protein to elicit an immune response). Virus-like particles (VLPs) and outer membrane vesicles (OMVs) are sophisticated subunit mimics of viral structures, possessing inherent adjuvanticity and improved immunogenicity compared to conjugates.

Recombinant subunit vaccine technology revolutionized antigen production, enabling rational design and heterologous expression systems. Viral antigens can be produced in diverse systems like E. coli yeast and mammalian cells. Further enhancements include immunopotentiation tags and targeted delivery to specific immune cells, significantly boosting immunogenicity. However, limitations like expression system scalability and expensive downstream processing can restrict accessibility. Modern vaccines like viral vector vaccines don't contain antigens, but rather use the body's own cells to produce them. These vaccines comprise viral particles with genetically modified genomes, incorporating one or more target genes that encode essential antigens. Although these encounter challenges related to scalability, their capacity to express diverse antigens and trigger both cellular and humoral immune response without the need of adjuvants positions them as promising platforms.

Genetic vaccines provide quick, scalable and standardized manufacturing options. Leveraging the power of DNA or RNA, these deliver a genetic blueprint for pathogen-specific antigens directly to recipient cells. This empowers cells to act as miniature antigen factories, triggering a tailored immune response. Potential advantages include the stimulation of broad immune responses (involving both B and T cells), the relative ease of large-scale vaccine manufacturing and the applicability across infectious and non-infectious diseases. However, genetic vaccines are limited by the need for complex and specialized delivery systems, relatively increased reactogenicity and supply chain and distribution complications due to stability issues and a need for cold chain.

Vaccine platform commercial parameters

"Although advanced vaccine platforms offer multiple advantages over traditional vaccines, a complete shift to modern platforms is neither feasible nor pragmatic," offered Bernadette Bourjolly, associate principal at ZS. Every platform is unique in its properties, and some may be more compatible than others, owing to heterogeneity associated with infectious diseases, geographies and population groups. Figure 3 displays the unique features of multiple platforms along with examples of vaccines developed using them.

FIGURE 3:

Vaccine platform benefits and challenges

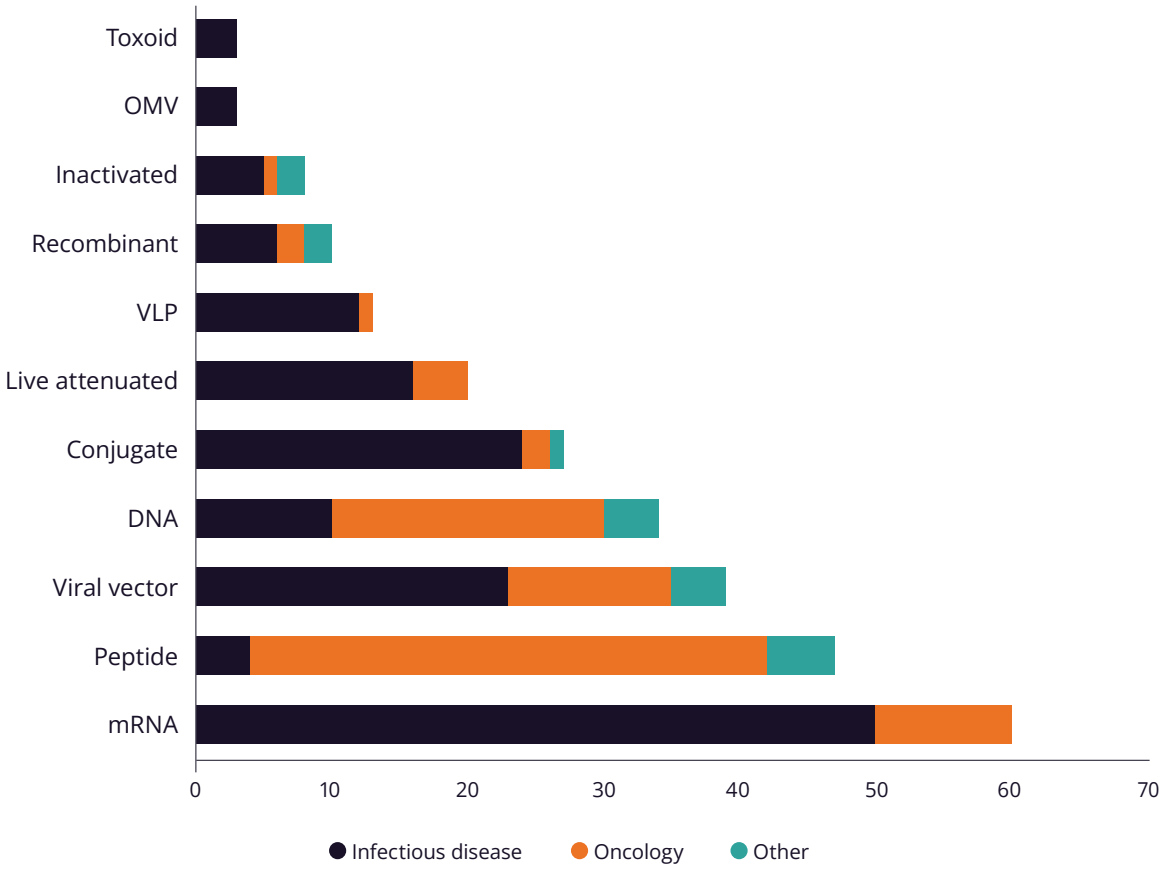
	Platform	Benefits	Challenges	Examples
Whole cell	Live attenuated	Excellent efficacy; no need of adjuvants; lifetime protection	Unstable; require cold chain; potential risk of safety hazard	MMR, varicella
	Killed	Comparatively stable, safer, inexpensive and simpler to manufacture	High dose; short-term protection; require adjuvants	Polio, influenza
Subunit	Toxoid	Mainly used against bacteria that produce toxins; less susceptible to changes in light, humidity and temperature	Multiple doses required; costlier and more complex than live and killed	Diphtheria and tetanus
	Polysaccharide	Safer than toxoids and whole cell	May need adjuvants; require booster doses; strain modification is challenging; age restrictions	Meningococcal ACWY, PCV23
	Glycoconjugate	Safer and more stable than polysaccharide; can be used in nearly all age groups	Need protein carriers and adjuvants; complex, costly, tedious and challenging to produce	PedvaxHIB (HiB), Menjugate (meningitis)
	OMV	Better efficacy; self-adjuvant properties; endotoxic effect; comparatively lower cost	Low yield is the main concern; complex to manufacture	VA-MENGOC-BC and Bexsero (Meningitis)
	VLP	High immunogenicity and self-adjuvant properties; present possibility to develop vaccines against enveloped viruses	More sensitive and need cold storage; high cost of manufacture; complex downstream processing	MalariVax (Malaria), Engerix-B (HBV) and Gardasil (HPV)
	Peptide	Fast and simple, easier large-scale manufacturing; high purity, safety and stability; time and cost efficient; potential applicability in therapeutic vaccines	Low immunogenicity; multiple doses; need special complex adjuvants; very low success rate	UB-612 (Phase 3, COVID-19), PVX-410 (Phase 1, cancer)
	Recombinant	Very strong immunogenicity, secure and safer than traditional vaccines, DNA recombinant vaccines are thermostable	Need adjuvants, multiple doses; very high cost, owing to expression system scale-up and downstream processing	Recombivax, FluBlok (Flu)
Viral vector	Replicating and non-replicating vectors	Powerful and long-lasting cellular responses; no strict need of adjuvants; less stringent storage and handling conditions; stable and safer than most vaccine platforms	Scalability is major bottleneck wherein multiple process steps and components increase risk of contamination; require extensive testing which increases costs	Ervebo (Ebola), Jcovden, Vaxzevria (COVID-19)
Genetic vaccines	DNA	Strong, long-term immunity; relatively safe; rapid and scalable manufacturing; broad applicability against pathogens and cancer; more stable than mRNA vaccine; easy to transport and store at ambient temperature	High cost; may require adjuvants; low or variable efficiency due to degradation by nucleases; low success rate	ZyCoV-D (COVID-19)
	Non-replicating mRNA	Good efficacy profile; self-adjuvant; rapidly designable and scalable; adaptable to various pathogens	Stability issues; need ultra-cold storage; short-term immune response; require boosters	Comirnaty, Spikevax (COVID-19)
	Self-amplifying/ Replicon RNA (saRNA)	Higher amount of protein expression; minimal dose of RNA required; longer immune response	Large sized and difficult to deliver in cell; shorter half-life, owing to degradation by nucleases	PF-07852352 (influenza)
	Circular RNA (circRNA)	Comparatively more stable than non-replicating mRNA; prolonged antigen coding tolerances	Delivery is complex	Pre-clinical

Sources:
Brittanica, "Benefits of vaccination." Ryan J. Malonis, Jonathan R. Lai and Olivia Vergnolle, "Peptide-based vaccines: current progress and future challenges."
Vaccines Europe, "Types of vaccines." Zrinka Matić and Maja Šantak, "Current view on novel vaccine technologies to combat human infectious diseases."

Continuously innovating and optimizing platforms across the scientific and technical spectrum is crucial to ensuring the readiness and ability to respond to evolving public health needs. The rich pipeline of vaccines portrays an optimistic future for the industry. More than 60 established and emerging players are evaluating more than 800 vaccine candidates across more than 50 indications. There is tremendous activity across modern platform-based vaccines (as seen in Figure 4).

FIGURE 4:

Pipeline vaccines across platforms for indication groups



Efforts across the industry to explore modern platforms to develop better vaccines for the future are increasing, and it is clear from recent trends that nearly all big players have made significant investments to broaden their modern platform portfolio. Most of the leading players seem interested, particularly, in mRNA after its recent success during the COVID-19 pandemic. Adi Natu, who leads the vaccines center of excellence at ZS, explained, “The decision to invest in a specific platform over another is context-dependent and there are numerous factors that inform these decisions spanning across multiple stages, from development through the distribution of a vaccine.”

FIGURE 5:

A heat chart representation of enablers and hurdles

Platform	Manufacturing and supply	Applicability across indications	Proof of efficacy	Ideal for
Live attenuated				Diseases requiring long-term immunity (e.g., pediatric vaccines like MMR, varicella). Potential in RSV.
Killed/inactivated				Use in immunocompromised people and pregnant women, inducing faster immune response (e.g., travel, outbreak vaccines like JE, hep A, flu).
Toxoid				Preventing diseases caused by potent bacterial toxins (e.g., tetanus, diphtheria, C. difficile).
Polysaccharide				Protecting high-risk groups from specific bacterial infections. Generally ineffective in children (e.g., pneumococcal).
Glycoconjugate				High potential of use against encapsulated bacteria (e.g., pediatric pneumococcal). Being tested for E. coli, N. gonorrhoeae.
OMV				Suitable for bacterial infections like meningococcal. Research underway for salmonella, pseudomonas, among others.
VLP				Promising, safe and effective against several pathogens (e.g., flu and HPV. Being evaluated for malaria, HIV, norovirus and chikungunya).
Peptide				Widest applicability across oncology, respiratory infectious diseases, autoimmune and chronic diseases.
Recombinant				Widespread use against viral infectious diseases. Being tested for oncology and chronic indications (e.g., acne).
Viral vector				Presents promise for use across infectious, oncology and chronic indications. Being actively tested in cancer trials.
DNA				High hope in oncology vaccines and chronic diseases like Alzheimer's. Recent success in COVID-19.
mRNA vaccine				Tremendous scope against rapidly mutating respiratory pathogens as well as latent infections and oncology.

Not enabling — Very enabling

Manufacturing and supply

Successfully establishing and operating a new platform calls for a careful consideration of the required infrastructure and capabilities, resource allocation and skill development. Both complexity and the agility of production and supply can greatly affect a platform's adoption.

Infrastructure and raw materials: Vaccine manufacturing requires specialized facilities with bioreactors, purification systems and aseptic filling lines. Securing consistent and high-quality raw materials like antigens, adjuvants, carriers and cell cultures affects production efficiency, and specialized auxiliary requirements can further add to the financial burden. Traditional platforms require minimal additional resources whereas modern platforms often necessitate their use. For example, platforms like live, inactivated toxoids and some subunit vaccines use simpler and more economical adjuvants like aluminum salts; however, peptide vaccines necessitate costly and intricate adjuvants, affecting overall production expenses. Complex carrier systems and delivery vehicles like lipid-nanoparticles required for genetic vaccines are expensive compared to those employed in conjugate vaccines. Referring to lentiviral vectors, Matt Furlow, associate principal at ZS, explained, "The complexity associated with their production, purification and delivery, combined with a high demand, owing to use across vaccines and gene therapy, is creating several issues with manufacturing and supply."

Production scalability: It's critical for organizations to be able to increase or decrease production rapidly and efficiently based on changes in demand, especially for pandemic preparedness and global health equity. A scalable system proves to be cost-effective, ensuring efficient resources utilization by matching demand and preventing waste. These types of systems are future-proof, as they easily expand to accommodate future growth, eliminating the need for costly infrastructure overhauls and ensuring long-term investment value. The mRNA platform stands out in terms of scalability and is widely appreciated across the industry. On the other hand, several successful platforms, like viral vector and recombinant, suffer because of tedious and complex expression systems as well as requirements of extensive downstream processing.

Storage, supply chain and distribution: These pivotal factors can severely affect the uptake of vaccines, even after efficient production. Reduced sensitivity to environmental stressors like light, pH and humidity support storage and supply in less stringent conditions, eliminate the need for a strict cold chain. Also, platforms with stability and shelf life allow for manufacturing and storing stockpiles of vaccine shipments, which can serve to meet any unexpected surge in demand. Platforms like inactivated, peptide, viral vector, recombinant and DNA vaccines generally exhibit greater stability compared to live and non-replicating mRNA vaccines. This stability makes them well-suited for wider distribution and deployment in challenging environments. However, extensive research is currently underway to develop temperature stable mRNA vaccine candidates successfully in the form of saRNA and circRNA.

Breadth of applicability of vaccine platforms

An adaptable or flexible platform with the versatility to generate vaccines for diverse indications with few modifications offers significant advantages in resource utilization in terms of cost, time, expertise, infrastructure and logistics. Joshua Hattem, principal in the pipeline, portfolio, and BD strategy space at ZS, explained, "Access to a modular and versatile technology can benefit the manufacturer in two ways: through IP rights or patent protection, and the ability to create vaccines for multiple indications from a single platform."

The plug-and-play nature of some platforms enables the quick development of vaccines for different diseases, with minimal modifications specific to pathogen components. Modern platforms are being extensively tested to develop vaccines for chronic and autoimmune diseases in addition to ones for infections. For example, the peptide platform is widely used for developing vaccines for Alzheimer's, obesity, uveitis, multiple sclerosis and more. Similarly, platforms like mRNA, DNA, viral vectors and peptides have applicability across latent and pandemic infections (like Zika and Ebola), across oncology for neoantigen vaccines and across chronic indications for therapeutic vaccines against hypertension and Crohn's disease.

The ability of a platform to potentially address a wider range of diseases presents hope to improve public health outcomes in diverse populations. This also fosters continuous innovation wherein the core platform serves as a foundation upon which advancements in delivery systems, adjuvants and targeting strategies can be readily integrated. From a manufacturer's standpoint, such platforms are more attractive as they present an opportunity to expand the addressable population significantly, thereby increasing market potential and return on investment. Investing in a single-use platform such as egg-based inactivated and live flu vaccines platforms carry inherent risks because of market fluctuations, waning demand or a scientific dead-ends, whereas access to a versatile platform like mRNA, viral vector or peptide can unlock diversity across the pipeline with a high probability of success for candidates.

Vaccine platform efficacy and proof of concept

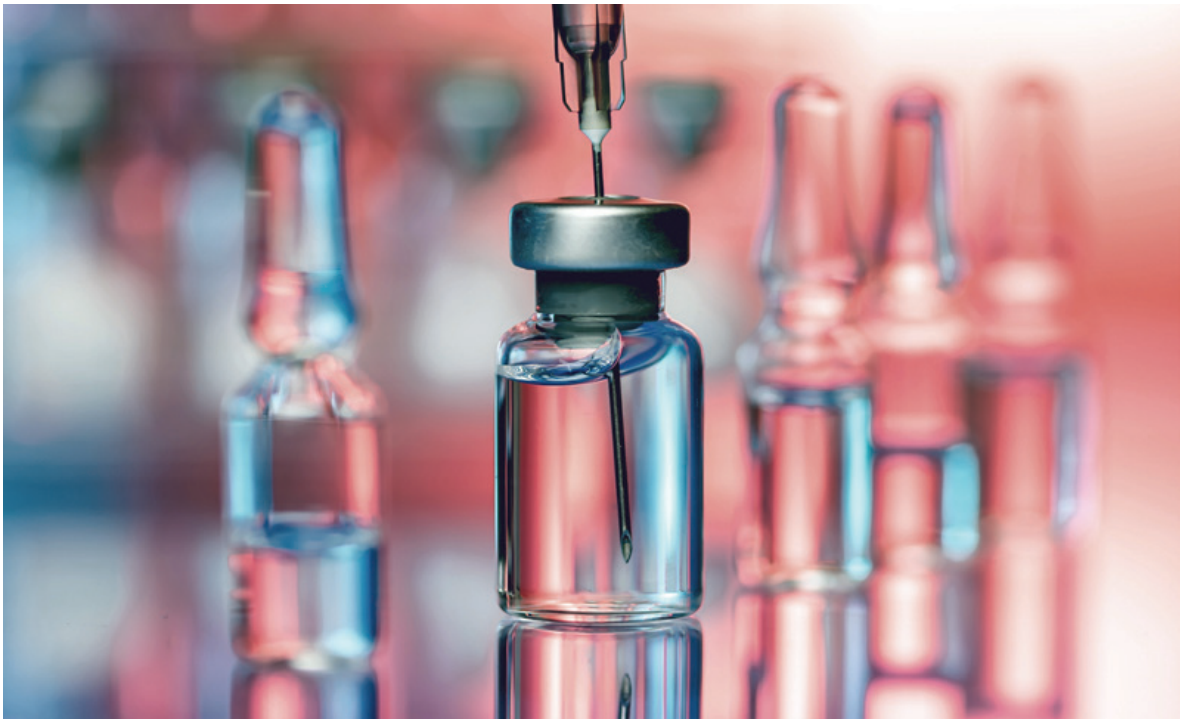
A good efficacy profile of a vaccine manufactured through a platform in comparison to the existing standard of care vaccines is paramount to its success. An example is the mRNA platform, where superior efficacy of the first COVID-19 vaccine, in contrast to other platforms like adjuvanted and inactivated, combined with other advantages have kickstarted a series of rapid investments in the platform for developing seasonal respiratory vaccines. On the other hand, the viral vector platform which proved successful in COVID-19 vaccine development led to failure in RSV, for instance. Similarly, despite numerous advantages, the peptide platform has been associated with multiple failures and has a lower probability of success. This platform has mainly been used for the development of cancer vaccines along with some vaccines for infectious diseases, like HIV and hepatitis C. No peptide vaccines have been approved by the FDA, although more than 500 peptides had progressed to clinical trials. This is mainly due to a lack of efficacy and failure to elicit a controlled, stable and prolonged immune response. Presently, only one peptide vaccine (EpiVacCorona developed by the

Russian VECTOR Center of Virology and Biotechnology) is approved for use, but the vaccine is only available in Russia and has attracted criticism owing to less efficacy than other available COVID-19 vaccines. It can be seen from numerous examples across the industry that no one platform can guarantee consistently good efficacy across indications.

Recommendations and industry reflections on vaccine platforms

Looking at the present, Sudharsan Parthasarathy, lead scientist at ZS Discovery, commented, "Growth strategies in the vaccine sector has now shifted to a two-pronged approach: A traditional focus on the target indications and to create opportunities for platform innovation." Major companies, like GSK and Pfizer, have been active in getting hold of different platform types, either by building the capability in-house or investing in the form of a merger, acquisition or collaboration. A robust portfolio should have multiple platforms in the right mix, made with thoughtful considerations. There's a lack of clear evidence that modern platforms alone are sufficient to address unmet need across the plethora of infectious diseases.

The decision and action to begin developing in a platform must be proactive and future focused. Efforts to innovate and evolve technologies for improvement should never cease however, as seen in the case of mRNA platforms moving from traditional to self-amplifying to circRNA and further. Several trends that arose from the pandemic—like the evolution in vaccine administration sites (e.g., retail pharmacies)—emphasized an expansion of adult vaccination, efforts to address vaccine hesitancy and promoted vaccine equity. All of this points to an increase in both vaccine manufacturing and its future demand.



About the authors

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Adi is a principal within ZS's value and access practice area. He leads global market access and pricing projects with several large and small biopharmaceutical clients. Adi's deep experience and thought leadership in the global market access and pricing space has been shaped over the past 14 years through strategic engagement with clients around the world, including North America, EU5, Japan, Latin America, Eastern Europe and Africa. His passion is in the intersection of science and business, helping clients define market access and pricing strategies for pipeline and inline assets. Adi's experience spans a variety of therapy areas, including oncology, vaccines, immunology and infectious diseases.

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Josh is part of ZS's pipeline and launch strategy practice, leading the Philadelphia-based team within the practice as well as ZS's portfolio strategy service line. Josh's focus is in helping pharmaceutical companies develop strategies for product development and commercialization. His passion is the intersection of science and business, helping clients develop cross-functional strategies for their products and portfolios as well as capabilities that bridge commercial, medical and clinical. He specializes in cross-functional challenges such as market mapping and market shaping, portfolio prioritization, market segmentation, value proposition development and evidence generation strategy.

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