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Accelerating Vaccine Development: Plug-and-Play Platforms for Emerging Infectious Diseases

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Abstract: Emerging pathogens underscore an urgent need for rapidly developed vaccines to minimize mortality and societal disruption. Traditional vaccine development requires time spans of years, making it ill-suited to fast-evolving viruses that can overwhelm healthcare systems and economies. In response, plug-and-play vaccine platforms offer a more agile solution. By reusing proven backbones, they reduce the repetitive safety and production steps otherwise required for each new pathogen, thus accelerating both regulatory approval and large-scale manufacturing. In parallel, artificial intelligence and computational tools enable faster antigen and epitope identification, more accurate immune response modeling, and improved vaccine design. These innovations have already shortened timelines and enhanced efficacy.

Keywords: Vaccine, vaccine platforms, mRNA, viral vector machine, recombinant protein

1. Introduction

Emerging infectious diseases, such as SARS, Ebola, Zika, and COVID-19, have posed significant global threats, causing high morbidity and mortality, overwhelming healthcare systems, and disrupting economies and societies [1]. These impacts are further exacerbated by climate change, urbanization, and increased human-animal interactions [2]. Rapid identification of new pathogens and the swift development of vaccines are therefore essential for pandemic preparedness and public health response.

Fast-developed vaccines are crucial for mitigating outbreaks, reducing severe disease, hospitalizations, and deaths, even amidst emerging variants like delta and omicron [3-4]. However, traditional vaccine development is lengthy and resource-intensive, often requiring *5–18 years* of work and substantial financial investment [5]. Live or inactivated vaccines demand extensive safety testing to prevent reversion to virulence or adverse immune reactions. Furthermore, cultivating pathogens in eggs or animal cell cultures can be slow, costly, and vulnerable to contamination or unwanted mutations that diminish vaccine efficacy. Geopolitical and economic barriers also hinder vaccine access. Manufacturing capacity is often concentrated in wealthier nations, resulting in delayed distribution to low-income regions, as observed during the 2009 influenza pandemic [6]. Regulatory requirements further slow progress, with multi-phase clinical trials traditionally conducted in sequence, limiting rapid response during outbreaks [7].

The COVID-19 pandemic highlights the urgency of overcoming these limitations. Continued mutation of SARS-CoV-2, such as variants XBB.1.5 or EG.5, threatens the effectiveness of existing vaccines through increased transmissibility and immune escape [8-9]. Traditional regulatory

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timelines are ill-suited for such rapidly evolving threats. Accelerated vaccine development, approval, and deployment are critical to reducing disease burden and protecting vulnerable populations. To meet this challenge, plug-and-play vaccine platforms offer a promising solution. Their modular design allows for rapid adaptation to new pathogens, supporting global health efforts to contain outbreaks swiftly and equitably.

2. Traditional vaccine development

Following an understanding of immune mechanisms, vaccine design must align pathogen biology with the desired immune response. Live attenuated vaccines mimic infection and induce robust immunity but require careful attenuation to avoid safety risks. Inactivated and subunit vaccines are safer but often need strong adjuvants and boosters to enhance immunogenicity [10]. Vector-based, DNA, and plant-derived vaccines offer innovative delivery platforms, though challenges like vector immunity or low expression persist [11]. Heterologous prime-boost strategies can enhance immune breadth by combining multiple approaches.

Antigen selection may involve targeting dominant proteins, multiple antigens, or novel candidates revealed through proteomics or reverse vaccinology [12]. Rapidly evolving pathogens require updated or multivalent designs. Proper antigen conformation and post-translational modifications also impact immunogenicity, alongside feasibility and compatibility with delivery systems [13].

Adjuvant choice further shapes immune quality, guiding Th1/Th2 balance or mucosal targeting [14]. Common adjuvants include alum, saponins, oil emulsions, and novel tools like cytokines or nanoparticles. Delivery routes—parenteral for systemic, mucosal for local immunity—affect antigen presentation and logistical feasibility, with options like oral baits or in ovo injection offering scalable solutions [15].

Preclinical testing validates antigen expression, dose, and safety in vitro and in vivo. Promising candidates enter field trials to assess real-world efficacy, immune duration, and operational practicality. Regulatory approval requires comprehensive data on consistency and safety. Post-licensure monitoring ensures continued effectiveness amid evolving pathogens and production conditions [16].

3. Preventative vaccine platforms

A plug-and-play vaccine platform concept refers to reusing an already validated, standardized "backbone," which allows manufacturers to retain the existing production steps, formulation, and controls, then insert the pathogen-specific gene of interest rather than rebuilding a vaccine from scratch [17]. This dramatically accelerates the development process because much of the safety, efficacy, and quality infrastructure is already established for the platform itself. Consequently, developers can bring updated or novel vaccines to clinical trials and eventual use far faster than with conventional methods [18].

3.1. mRNA vaccine platforms

In mRNA construct design, researchers begin by selecting the target antigen, typically a surface protein known to trigger strong immunity, by zeroing in on the most immunogenic region of the viral protein. Next comes sequence engineering, whereby the gene sequence is codon-optimized to match human translation preferences, while its 5′ and 3′ UTRs (untranslated regions) are engineered to boost expression and stabilize the transcript [19]. During in vitro transcription, a specialized 5′ cap such as m^7GpppN is added, sometimes co-transcriptionally using vaccinia capping enzymes, ensuring ribosome recognition and limiting innate immune activation [20]. A carefully chosen poly(A) tail, commonly 100 to 120 adenosine residues, further prolongs mRNA half-life. To mitigate unwanted

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inflammatory responses, developers often incorporate modified nucleotides, including pseudouridine or N^1-methylpseudouridine, to reduce pattern recognition by sensors such as TLR7/8 without compromising translation efficiency [21]. Strict quality-control checks then confirm that unwanted double-stranded RNA products are minimized and that the purified mRNA is properly capped, tailed, and free of contaminants. This multifaceted strategy ensures that the final mRNA construct is highly expressed, adequately stable, and elicits a robust immune response once delivered into human cells.

The mRNA vaccine platforms bring huge benefits. First, its remarkable flexibility expedites vaccine design, as a simple alteration of the nucleotide sequence accommodates novel variants or even entirely new targets, obviating the protracted culture and purification steps classically required by conventional platforms. Moreover, scalable and cell-free manufacturing [22] can be readily deployed under a unified Good Manufacturing Practice (GMP) [23] process, thereby streamlining large-scale production. This is a feature especially advantageous for generating and testing multiple mRNA constructs in parallel. Importantly, while mRNA vaccines do not incorporate live or replication-competent viruses, they induce robust cellular and humoral immunity through the endogenous expression of complex protein antigens, often obviating the necessity for exogenous adjuvants. Their amenability to rapid update cycles makes them particularly beneficial against viruses subject to antigenic drift [24] or shift, typified by seasonal influenza and SARS-CoV-2, and underpins a potent defense against potential pandemics. Consequently, this integrated balance of speed, flexibility, immunogenic potency, and scalability positions the mRNA platform at the forefront of addressing both persistent infections and hitherto intractable challenges.

Despite their clear advantages, mRNA vaccines also face distinct limitations. First, animal models can be poor predictors of human immunogenicity and side-effect profiles, making it challenging to infer long-term efficacy or rare adverse events from preclinical studies [25]. Second, the intramuscular route often induces weak mucosal responses in the upper respiratory tract, an important site of viral entry for pathogens like SARS-CoV-2 and influenza [26]. Dose selection and valency constraints arise from both reactogenicity ceilings and the need to split that content among multiple antigens in polyvalent formulations [27]. Preexisting immunity can also skew responses toward immunodominant antigens, diminishing de novo targeting of new variants [28]. Additionally, mRNA lipid nanoparticles frequently induce transient inflammatory reactions and rarely more serious issues such as myocarditis, prompting ongoing efforts to refine RNA sequences and delivery vehicles [29]. Finally, logistical and equity concerns persist [30], as current vaccines generally demand cold-chain infrastructure and have been less accessible in low-resource settings, emphasizing the need for thermostable formulations and broader capacity building in these regions.

3.2. Viral vector machine platforms

Viral vector machine platforms are constructed by genetically modifying a selected virus. They are usually well-documented to be safe or attenuated in humans, including adenovirus, measles virus, and vaccinia, to insert and express heterologous antigen genes while preserving or disabling replication competency as desired [31]. For RNA viruses, investigators typically employ reverse genetics, in which they clone the full-length viral genome in a cDNA format for manipulation, such as removing virulence or immune-evasion genes, and alter envelope glycoproteins [32]. Thus, “slots” to accommodate foreign gene inserts are generated. Subsequently, target antigenic genes, such as the spike protein from SARS-CoV-2, Ebola GP, or cancer neoantigens, are codon-optimized and placed under a suitable promoter sequence to ensure robust expression [33]. In some cases, transmembrane (TM) and cytoplasmic-tail (CT) domains from the parental vector are fused with foreign proteins to enhance incorporation into newly generated virions. Once this molecular construct is complete, it is rescued or reconstituted in complementing cells that provide any missing viral functions or structural components [34]. The resulting recombinant vector is then confirmed to achieve stable propagation

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in vitro, expresses the transgene at sufficiently high levels, and even retains a desired attenuation profile. Following this, the candidate undergoes scale-up production under GMP standards with extensive quality control. In parallel, the recombinant vector is evaluated in preclinical models, only after which does the vaccine proceed to human clinical trials. The construct's safety, immunogenicity, and protective efficacy are then systematically validated. In fact, researchers have developed diverse viral-vectored vaccines. Based on viral vector machine platforms, adenovirus-based COVID-19 vaccines, measles-vectored hemorrhagic fever, and oncologic immunotherapies elicit potent humoral and cellular immunity and can be produced in rapid and cost-effective manners [35].

Viral vector vaccines confer multiple distinct advantages that distinguish them from both traditional and other contemporary vaccine platforms. First, by partially mimicking natural viral infection, they often trigger robust T-cell immunity in addition to potent humoral responses. Second, flexible antigen design facilitates inserting a range of single or multiple foreign genes, including complex glycoproteins or antigenic polyprotein cassettes [36]. Moreover, some vectors are naturally suited to mucosal delivery—via intranasal or oral routes—and thus encourage strong sIgA production, simplifying administration and potentially enhancing vaccine uptake [37]. Notably, replicating viral backbones (e.g., vesicular stomatitis virus, paramyxoviruses) can enable single-dose efficacy because the transient in vivo replication amplifies antigen expression [38]. Many vector systems, including adenoviruses and vaccinia, also have well-established manufacturing pipelines, enabling high-titer scale-up and lowering costs. Additional safety layers, such as replication-deficient constructs or extensively passaged attenuated backbones, mitigate biosafety concerns [39]. Genetic engineering techniques allow precise genome manipulation, whether to attenuate pathogenic determinants or embed tissue-specific promoters in oncolytic constructs. Furthermore, although these vaccines are critical in combating emerging pathogens, they also hold broad potential for noninfectious applications.

Despite their demonstrated efficacy and adaptability, viral vector vaccines also face substantial challenges that can limit their widespread deployment. Safety considerations and preexisting immunity related to residual or neurovirulence in susceptible populations may attenuate vaccine-induced responses, prompting the exploration of rare or nonhuman adenoviruses to enhance immunogenicity [40]. Some vectors are further constrained by limited genomic capacity, restricting them to smaller inserts such as influenza-based platforms, while expanded transgenes in other systems can compromise viral replication. Manufacturing logistics likewise pose difficulties for specialized attenuated backbones with translational gaps where robust immunogenicity observed in animal models fails to consistently predict human trial outcomes. Finally, the risk of environmental shedding or inadvertent reversion to higher virulence requires rigorous biosafety oversight, especially for replication-competent vectors [41].

3.3. Recombinant protein/nanoparticle platforms

Recombinant protein/nanoparticle vaccine platforms generally begin by identifying an immunogenic region, such as a viral receptor-binding domain, and designing it for robust expression and stability in a suitable host (commonly mammalian cells, yeast, or E. coli). The selected antigen is often fused to signal peptides if secreted or scaffold proteins for nanoparticle assembly and then produced under GMP conditions [42]. To form nanoparticles, researchers typically use naturally occurring protein scaffolds such as ferritin or lumazine synthase or computationally designed scaffolds, into which the antigen is genetically plugged at specific positions [43]. These constructs self-assemble into ordered architectures, often 24- to 60-subunit particles, to enhance antigen presentation to B cells and improve immunogenicity [44]. After expression and secretion or cell lysis and column-based purification (affinity or size-exclusion chromatography), the nanoparticles undergo biochemical and biophysical characterization by dynamic light scattering, electron microscopy, or bio-layer interferometry to

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confirm correct folding, oligomerization, and antigenicity [45]. Immunogenicity is typically validated in small animal models, with formulations commonly adjuvanted with oil-in-water emulsions to further boost immune responses. The resulting recombinant protein/nanoparticle vaccine can then advance into clinical development with the same overarching QA/QC measures applied throughout once these critical steps demonstrate safety, purity, and robust immunogenicity.

Recombinant protein/nanoparticle vaccines excel in immunogenicity by leveraging the multivalent, geometrically precise display of target antigens on a self-assembling scaffold, which maximizes B-cell receptor cross-linking and typically amplifies antibody production beyond what monomeric or simple oligomeric formulations can achieve [46]. These platforms also incorporate robust scaffold architectures, whether adapted from natural proteins like ferritin or generated via computational design, to ensure structural stability and reduce the risk of antigen misfolding, even during large-scale production and lengthy storage [47]. Because the nanoparticles themselves are nonreplicating and noninfectious, they boast an excellent safety profile, making them well-suited for at-risk populations. Researchers can customize antigen valency, spacing, and orientation by engineering different nanoparticle scaffolds, thereby fine-tuning the immune response to optimize affinity maturation and potentially elicit broader, more cross-reactive protection. Moreover, recombinant protein scaffolds can be readily expressed in standard bacterial, yeast, or mammalian systems and purified with routine column-based methods, simplifying manufacturing under GMP conditions [48]. This molecularly defined nature also enables stringent quality control, ensuring consistent batch-to-batch performance. Finally, durability and breadth of immune responses often benefit from the repetitive, orderly antigen array on nanoparticles, which can be further enhanced through judicious selection of adjuvants, thereby reinforcing the platform's capacity to counteract evolving pathogen strains and deliver potent, long-lasting immunity [49].

Despite their demonstrated promise, recombinant protein/nanoparticle platforms face several important limitations that must be addressed in development. Partial T-cell coverage can arise if only antigenic fragments such as the receptor binding domain are used, potentially omitting critical T-cell epitopes present in the full-length antigen [50]. Design and engineering complexities can become substantial, since protein scaffolds and fused antigens must be meticulously matched for correct folding, assembly, or secretion. Manufacturing intricacies can arise when scaling up newly designed scaffolds or larger constructs, even though purification steps themselves remain relatively standard. These vaccines also often exhibit a strong reliance on adjuvants to induce robust T-cell immunity, raising costs and regulatory hurdles [51]. Interplay between antigenic geometry and secretion might lead to no construct secretion, underscoring the trial-and-error nature of fine-tuning this platform [52].

4. Future directions

Since the development of artificial intelligence (AI), the integration of AI into computational modeling has revolutionized the field of vaccine development. By leveraging machine learning, deep learning, and bioinformatics, AI has significantly accelerated the design, prediction, and optimization of vaccines. It has been offering solutions to traditional challenges such as antigen identification and epitope prediction, which are critical for triggering immune responses. For instance, PoxiPred, an AI-based tool, was developed to predict antigens and T-cell epitopes for poxviruses, identifying 16,817 potential T-cell epitopes with high accuracy [53]. Similarly, deep neural networks (DNNs) have been employed to predict B-cell epitopes for SARS-CoV and SARS-CoV-2, achieving an accuracy of 82% [54]. Reverse vaccinology (RV) combines genomics, proteomics, and AI to identify vaccine candidates by analyzing pathogen proteomes. AI algorithms, such as XGBoost and Random Forest, have been used to predict immune-recognition patterns, enabling the design of novel vaccines [55-56]. Immunoinformatic tools further enhance this process by predicting immunogenicity and optimizing vaccine constructs [57].

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AI-driven approaches optimize vaccine design by predicting protein structures, modeling immune responses, and refining delivery systems. mRNA vaccine design has been enhanced through AI, enabling the prediction of neoantigen structures and the optimization of lipid nanoparticle (LNP) formulations [58]. Additionally, evolutionary multi-objective optimization frameworks have been proposed to select effective peptide subsets for vaccines, balancing population coverage and peptide diversity [59].

The development of personalized vaccines is also facilitated by analyzing individual immune profiles and genetic data. For instance, the EDGE platform predicts peptide-HLA interactions, enabling the design of T-cell-inducing vaccines with high precision [60]. Machine learning models have been used to predict immune responses to live attenuated influenza vaccines (LAIV), paving the way for personalized vaccination strategies [55].

Overall, AI holds the potential to increase speed and efficacy, reduce the cost, enhance accuracy, and enhance scalability and flexibility of vaccine development. Here is a summary of the current application of AI in the field of vaccine development.

Table 1: Current application of AI in the field of vaccine development

AI Model	Application	Target Pathogen/Virus
PoxiPred	Prediction of antigens and T-cell epitopes	Poxviruses
Deep Neural Networks (DNNs)	Prediction of B-cell epitopes	SARS-CoV and SARS-CoV-2
EDGE Platform	Prediction of peptide-HLA interactions	Viral pathogens (e.g., HIV, influenza A)
Vaxign-DL	Prediction of vaccine candidates	Bacterial pathogens
VirusImmu	Prediction of viral immunogenicity	African Swine Fever Virus
XGBoost	Prediction of T-cell epitopes	SARS-CoV-2

5. Conclusion

Emerging pathogens continue to threaten global health by triggering epidemics and pandemics that strain healthcare systems, disrupt economies, and cause extensive loss of life. Traditional vaccine development with timelines spanning up to two decades cannot adequately meet the urgent demands posed by fast-evolving viruses. However, novel plug-and-play vaccine platforms are reshaping the landscape. By reusing a validated backbone for each new pathogen, plug-and-play platforms minimize repetitive safety and manufacturing steps, allowing for quicker regulatory approvals and faster vaccine deployment. Although current platforms, including mRNA, viral vectors, and nanoparticles, face unique challenges, ongoing research is improving safety profiles, stability, and global distribution. Simultaneously, artificial intelligence accelerates antigen discovery, epitope prediction, and immunogenicity testing, thus refining vaccine design and reducing development costs. These innovations have already shortened timelines for recent outbreaks like COVID-19 and continue to offer valuable insights for tackling emerging strains. This synergy paves the way for a future in which vaccine development can outpace emerging threats and safeguard public health worldwide.

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