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Review Article

Recent Trends in Vaccine Development

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ABSTRACT

Vaccine development has undergone a paradigm shift over the last decade, moving from traditional empirical approaches toward rational, platform-based technologies. The rapid success of mRNA vaccines against COVID-19 highlighted the potential of nucleic acid platforms for fast, scalable, and adaptable responses to emerging pathogens. Recent trends include the refinement of mRNA vaccines through improved stability, delivery, and antigen design; the emergence of selfamplifying RNA (saRNA) and trans-amplifying RNA (taRNA) systems for dose-sparing and costeffective immunization; and continued optimization of viral vector vaccines to overcome preexisting immunity and enhance safety. Parallel advances in protein subunit, nanoparticle, and virus-like particle (VLP) vaccines have expanded the landscape by enabling highly targeted and durable immune responses. Synthetic biology, structural vaccinology, and artificial intelligence are being increasingly employed for antigen discovery, epitope mapping, and rational vaccine design. Delivery innovations, including next-generation lipid nanoparticles, intranasal sprays, microneedle patches, and thermostable formulations, are addressing critical barriers such as coldchain dependence and global accessibility. Novel adjuvants, particularly those engaging patternrecognition receptors (PRRs) like TLR and STING pathways, are enhancing both humoral and cellular immunity. Beyond infectious diseases, vaccines are now being explored for noncommunicable conditions such as cancer, autoimmune disorders, and neurodegenerative diseases, underscoring their therapeutic potential. Despite these advances, key challenges persist, including large-scale manufacturing, equitable distribution, vaccine hesitancy, regulatory harmonization, and the need for robust pharmacovigilance to monitor long-term safety. Future directions emphasize the development of universal and pan-pathogen vaccines, mucosal immunization strategies to block transmission at entry sites, and AI-driven, high-throughput pipelines for rapid vaccine design. Collectively, these trends represent a transformative era in vaccinology, with the potential to reshape global public health preparedness and response.

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INTRODUCTION

Vaccination is one of the most effective and sustainable public health interventions, responsible for preventing millions of deaths annually and controlling or eradicating life-threatening infectious diseases such as smallpox and polio. Traditional vaccine platforms—including live-attenuated, inactivated, and protein-

based subunit vaccines—have provided invaluable protection for decades. However, these approaches often require long development timelines, complex manufacturing processes, and may face limitations in addressing rapidly mutating pathogens, emerging infectious diseases, or specialized applications such as therapeutic vaccination for cancer.[13]

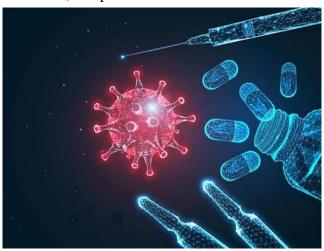


Fig 1: Vaccine

The COVID-19 pandemic marked a watershed moment in vaccinology, showcasing the ability of next-generation technologies to dramatically accelerate vaccine development, testing, and deployment. The rapid creation and global rollout of mRNA-based vaccines in less than a year demonstrated the flexibility and scalability of nucleic acid platforms, thereby redefining expectations for how vaccines can be designed and produced. This achievement not only transformed the immediate response to a global crisis but also catalyzed investment and innovation across other areas of vaccine research.[11]

In recent years, several transformative trends have emerged in the field of vaccine development. Nucleic acid vaccines, particularly messenger RNA (mRNA) and self-amplifying RNA (saRNA) platforms, have gained prominence due to their rapid adaptability, high immunogenicity, and

potential for dose-sparing effects. Viral vector-based vaccines continue to play a pivotal role, with improvements in vector design addressing concerns such as pre-existing immunity and vectorrelated adverse events. Similarly, advancements in protein subunit vaccines, virus-like particles (VLPs), and nanoparticle-based formulations have enhanced antigen stability, targeted immune activation, and durability of response.[2]

Another critical trend is the integration of synthetic biology, structural vaccinology, and artificial intelligence (AI) into vaccine design. These technologies enable rational antigen selection, epitope optimization, and predictive modeling of immune responses, thereby reducing the trial-and-error component of vaccine discovery. Additionally, the development of novel adjuvants and innovative delivery systems—

including lipid nanoparticles (LNPs), microneedle patches, and intranasal or oral formulations—are expanding the reach, effectiveness, and accessibility of vaccines, particularly in resource-limited settings. [13]

The goals of vaccination are also evolving. Beyond preventing infectious diseases, vaccines are being designed to provide universal or broadspectrum protection against rapidly mutating viruses such as influenza and coronaviruses. Moreover, vaccines are expanding into therapeutic domains, including oncology, chronic infections, and even non-communicable diseases, reflecting the growing versatility of modern vaccine platforms.[17]

Despite these promising developments, significant challenges remain. Issues such as large-scale manufacturing capacity, regulatory harmonization, equitable distribution, vaccine hesitancy, and robust safety monitoring continue to shape the global vaccine landscape. Addressing these challenges will be essential for translating scientific advances into real-world impact. This review aims to provide a comprehensive overview of recent trends in vaccine development, highlighting advances in platform technologies, delivery strategies, antigen design, and emerging applications. It also explores the challenges and future directions that will define the next era of vaccinology, ultimately underscoring transformative potential of vaccines in improving global health outcomes. [2]

Vaccines have long been recognized as one of the greatest achievements in biomedical science, providing safe, effective, and cost-efficient strategies for preventing infectious diseases and global morbidity and mortality. reducing Traditional vaccines, such as live-attenuated and inactivated formulations, played a critical role in controlling diseases like smallpox, polio, and measles. However, their limitations—including lengthy development timelines, complex manufacturing processes, and safety concerns in immunocompromised populations—have prompted the exploration of alternative strategies. Subunit and recombinant protein vaccines offered a safer alternative but often required strong adjuvants to achieve protective immunity.

The twenty-first century has ushered in a new era of vaccine development, driven by advances in biology, immunology, molecular biotechnology. The COVID-19 pandemic acted as a catalyst, accelerating the adoption and validation of novel platforms such as messenger RNA (mRNA) vaccines and viral vectors, which demonstrated unprecedented speed from genomic sequencing to large-scale deployment. The success of these platforms not only addressed a global emergency but also reshaped expectations for vaccine innovation, paving the way for their application in a broad spectrum of infectious and non-infectious diseases.[5][15]

RECENT TRENDS IN VACCINE DEVELOPMENT

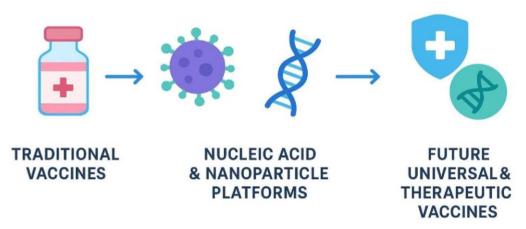


Fig 2: Recent trends in vaccine development

Recent trends in vaccine development highlight several paradigm shifts. Nucleic acid vaccines, including mRNA and self-amplifying RNA (saRNA), offer unparalleled flexibility, rapid design, and scalable production, enabling responses to emerging pathogens within weeks. Viral vector vaccines continue to be optimized for safety and immunogenicity, while recombinant protein and nanoparticle-based formulations allow precise antigen presentation and durable immune responses. Virus-like particles (VLPs) and nanoparticle display systems mimic natural viral structures, enhancing immunogenicity while maintaining excellent safety profiles.[2]

Beyond platform technologies, the field has embraced rational vaccine design through structural vaccinology, synthetic biology, and computational approaches. High-resolution structural biology techniques such as cryo-electron microscopy (cryo-EM) have enabled stabilization of key viral proteins in their most immunogenic conformations, while artificial intelligence (AI) tools assist in epitope prediction, antigen optimization, and immune response modeling. These approaches reduce reliance on empirical

thereby shortening discovery trial-and-error, pipelines. Vaccine delivery and formulation strategies are also undergoing rapid evolution. Next-generation lipid nanoparticles (LNPs), biodegradable polymers, and viral-like delivery systems are being tailored for enhanced stability, cellular targeting, and immunogenicity. Innovative delivery routes, including intranasal sprays, oral formulations, and microneedle patches, aim to improve patient compliance, elicit mucosal immunity, and expand access in lowresource settings. Additionally, thermostable vaccine formulations are being developed to overcome the challenges of cold-chain dependency, a major barrier in global vaccine distribution.

Importantly, the scope of vaccines is expanding from purely preventive measures against infectious diseases to therapeutic applications. Personalized cancer vaccines, autoimmune-modulating vaccines, and vaccines for chronic infectious diseases such as HIV, hepatitis, and tuberculosis are being actively investigated. The concept of universal vaccines, particularly for rapidly mutating viruses like influenza and

coronaviruses, is a major research focus. By targeting conserved epitopes or employing mosaic immunogens, researchers aim to achieve broad and long-lasting immunity, reducing the need for frequent updates. Despite remarkable progress, challenges remain. Global disparities in vaccine access, public hesitancy fueled by misinformation, manufacturing bottlenecks, and evolving regulatory landscapes continue to shape the vaccine ecosystem. Equally important is the need for robust post-marketing surveillance to ensure long-term safety and to build public trust. Thus, vaccine development today stands the intersection of innovation and necessity. The integration of modern biotechnology, computational power, and global collaborative frameworks has not only transformed the speed and scope of vaccine discovery but has also opened pathways for tackling complex diseases previously considered beyond the reach of immunization. This review provides a comprehensive overview of these emerging trends, highlighting key advances, challenges, and the future directions that will define the next generation of vaccines.[17]

Platform Technologies in Vaccine Development .

Vaccine platform technologies are modular systems that allow rapid adaptation to different pathogens by simply exchanging or modifying the antigen component, while keeping the core delivery system intact. Unlike traditional vaccines that required pathogen cultivation and lengthy inactivation or attenuation processes, platform technologies enable accelerated development, scalable production, and flexible design. Below is a detailed overview of the major platforms shaping modern vaccinology. [17]

PLATFORM TECHNOLOGIES IN VACCINE DEVELOPMENT

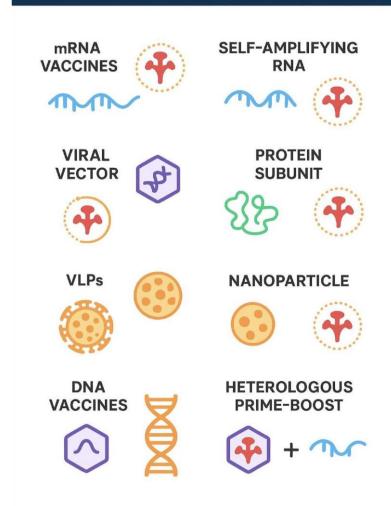


Fig 3: Platform technology in vaccine development

- 1) Messenger RNA (mRNA) Vaccines: mRNA vaccines represent a groundbreaking innovation, propelled into the spotlight during the COVID-19 pandemic. They deliver synthetic mRNA encoding a specific antigen (e.g., viral spike protein) into host cells, which then translate the message into protein and present it to the immune system.
- 2) Self-Amplifying RNA (saRNA) and Trans-Amplifying RNA (taRNA): saRNA builds upon mRNA technology by including replicase genes from alphaviruses, enabling intracellular amplification of the RNA template. This means

much smaller doses are needed to achieve the same level of immune response.

- Advantages:
- Dose sparing (10–100× lower doses than mRNA).
- Potentially lower production costs per dose.
- Prolonged antigen expression for stronger immunity.
- Recent developments:

- Early-stage clinical trials for COVID-19, influenza, and other viruses.
- Efforts to minimize immunogenicity of replicase proteins while maintaining efficacy.
- Combination with taRNA systems, where one RNA carries replicase and another carries the antigen, further increasing flexibility[2,6]
- 3) Viral Vector Vaccines: Viral vectors use engineered viruses (commonly adenoviruses, vesicular stomatitis virus, or modified vaccinia Ankara) to deliver genetic material encoding antigens.

Advantages:

- Strong induction of both antibody and T-cell responses.
- Potential for single-dose immunity.
- Well-studied safety profiles for certain vectors (e.g., adenovirus).

A Challenges:

- Pre-existing immunity to common viral vectors can reduce efficacy.
- Manufacturing complexity compared with RNA vaccines.

Recent trends:

- Use of rare human or non-human adenovirus serotypes to bypass pre-existing immunity (e.g., chimpanzee adenoviruses).
- Non-replicating vectors for safety;
 replicating vectors for enhanced immunogenicity.
- Applications in both prophylactic vaccines (Ebola, COVID-19) and therapeutic cancer vaccines. [15]

4) **Protein Subunit Vaccines:** These vaccines contain purified antigenic proteins or peptides rather than whole pathogens. They are often combined with adjuvants to enhance immunogenicity.

Advantages:

- Excellent safety profile with no risk of infection.
- Scalable production using recombinant DNA technology.
- Stable formulations with longer shelf life.

Recent trends:

- Structure-based antigen design (e.g., prefusion-stabilized viral proteins).
- Nanoparticle display systems that present multiple copies of an antigen to mimic viral structures.
- Use in universal influenza and pancoronavirus vaccine candidates.[6,4]
- 5) Virus-Like Particles (VLPs) and Nanoparticle Vaccines: VLPs mimic the structure of viruses but lack genetic material, making them non-infectious. Nanoparticle vaccines involve synthetic carriers that present antigens in a highly ordered, repetitive array.

♦ Advantages:

- Highly immunogenic due to multivalent antigen presentation.
- Safe and non-replicating
- Strong B-cell activation and neutralizing antibody responses.

Recent developments:

• Licensed vaccines (e.g., HPV, Hepatitis B) showcase clinical success.



- Modular nanoparticles designed to present multiple different antigens (mosaic vaccines).
- Ongoing work on nanoparticle-based HIV, influenza, and coronavirus vaccines.[11]
- 6) **DNA Vaccines**: DNA vaccines involve direct delivery of plasmid DNA encoding the antigen into host cells, which then express the protein.

Advantages:

- Stability at higher temperatures compared with RNA vaccines.
- Easy to produce and store.
- Induction of both cellular and humoral immunity.

Limitations:

- Relatively lower immunogenicity in humans compared with RNA vaccines.
- Need for delivery enhancements (e.g., electroporation, nanoparticle carriers).

♦ Recent progress:

• Several licensed veterinary DNA vaccines (e.g., fish and animal diseases).

- Human approvals in limited settings (e.g., India's ZyCoV-D COVID-19 DNA vaccine).
 [3]
- 7) **Heterologous Prime-Boost and Combination Platforms:** An emerging strategy is to combine multiple platforms to optimize immune responses. For example:mRNA prime + protein boost for durable immunity. Viral vector prime + RNA boost to broaden cellular and humoral responses. Multiantigen and multi-platform formulations for universal coverage. [11]

Delivery Formulations and Adjuvants:

The success of modern vaccines is not determined solely by the antigen or platform technology but also by the formulation used to stabilize and deliver it, as well as by adjuvants that modulate and enhance the immune response. Advanced formulations ensure antigen stability, bioavailability, and targeted delivery, while adjuvants shape the quality, magnitude, and duration of the immune response. Together, they represent critical components in next-generation vaccinology.[3]



Fig 4: Delivery formulation and adjuvants



1. Delivery Formulations

a. Lipid Nanoparticles (LNPs)[3]

- Role: Cornerstone of mRNA and selfamplifying RNA (saRNA) vaccines.
- Composition: Ionizable lipids, cholesterol, phospholipids, and PEG-lipids.
- Functions: Protect nucleic acids from degradation, promote cellular uptake, enable endosomal escape, and ensure cytoplasmic translation.

Recent advances:

- Targeted LNPs with ligands for dendritic cells.
- Thermostable LNPs reducing cold-chain requirements.
- PEG alternatives to reduce hypersensitivity.

b. Polymeric and Biodegradable Nanoparticles

- Examples: PLGA, chitosan, polyethyleneimine (PEI).
- Enable sustained antigen release, reducing need for multiple doses.
- Suitable for mucosal and oral vaccines.

c. Virus-Like Particles (VLPs) and Protein Nanoparticles

- Provide multivalent display of antigens in repetitive arrays.
- Enhance B-cell receptor cross-linking and neutralizing antibody production.
- Used in HPV and Hepatitis B vaccines, and under development for HIV and influenza.

d. Microneedle Patches

- Dissolving or coated microneedles deliver antigens to the dermis.
- Needle-free, painless, thermostable, and suitable for self-administration.

• Strong potential for mass vaccination campaigns.

e. Oral and Intranasal Formulations

- [1] Oral formulations use enteric-coated capsules, nanoparticles, or liposomes to protect antigens from gastric degradation.
- [2] Intranasal sprays induce mucosal immunity (IgA), blocking infection at the portal of entry.
- [3] Both routes improve compliance and avoid needle-associated risks.

2. Adjuvants

Adjuvants are substances added to vaccine formulations to enhance immune responses by promoting antigen uptake, modulating innate immunity, and shaping adaptive responses.

a. Classical Adjuvants

- Aluminum salts (alum): Oldest and most widely used adjuvant; promotes strong humoral immunity but limited cellular responses.
- Oil-in-water emulsions (MF59, AS03): Enhance antigen presentation and promote both antibody and T-cell responses.

b. Next-Generation Molecular Adjuvants

- Fig. 1. Toll-like receptor (TLR) agonists: CpG oligodeoxynucleotides (TLR9), monophosphoryl lipid A (MPLA, TLR4).
- Fig. 2. STING agonists: Trigger cytosolic DNA sensing pathways, inducing potent T-cell responses.
- Fig. 3. RIG-I agonists: Promote antiviral immunity through RNA sensing.



c. Combination Adjuvants

TABLE I. Modern vaccines use adjuvant systems (e.g., AS01 in Shingrix, containing MPLA + QS21 saponin) to generate robust humoral and cellular immunity.

TABLE II. Combinations provide synergistic effects by stimulating multiple innate pathways simultaneously.

d. Nanoparticle-Based Adjuvants

- Nanoparticles themselves act as immune potentiators by mimicking pathogenassociated patterns.
- Examples: gold nanoparticles, polymeric nanoparticles, and lipid-based carriers.

e. Mucosal Adjuvants

Cholera toxin B subunit and heat-labile enterotoxin derivatives are being investigated to enhance mucosal immune responses in oral and intranasal vaccines.

Changing Vaccine Goals:

Historically, vaccines were designed primarily to prevent infectious diseases by inducing protective immunity against bacterial and viral pathogens. However, with advances in immunology, molecular biology, and bioengineering, the goals of vaccination are shifting beyond traditional prophylaxis. Today, vaccine development is also directed toward therapeutic, cancer, and universal applications, as well as improving global access and acceptance.[7]

Therapeutic and Cancer Vaccines:

1) Therapeutic Vaccines: Unlike prophylactic vaccines, therapeutic vaccines aim to treat existing infections or chronic diseases.

Examples:

- HIV therapeutic vaccines designed to boost cytotoxic T-cell responses to control viral replication.
- Hepatitis B therapeutic vaccines to help clear chronic carriers.
- Tuberculosis vaccines under development to reduce disease progression.
- 2) Cancer Vaccines: Harness the immune system to recognize and destroy tumor cells.

Approaches Include:

- Peptide-based vaccines targeting tumorassociated antigens (e.g., MUC1, HER2).
- mRNA cancer vaccines encoding neoantigens unique to a patient's tumor (personalized oncology).
- Dendritic cell-based vaccines primed with tumor antigens (e.g., sipuleucel-T for prostate cancer).
- Combined with checkpoint inhibitors (e.g., anti-PD-1, anti-CTLA-4) to enhance immune response.
- Represents a paradigm shift where vaccines act as therapies, not just preventives. [10,14]

Manufacturing, Regulations, and Equity Challenges

1. Manufacturing Innovations and Barriers:

- mRNA and viral vector vaccines can be manufactured rapidly, but require coldchain logistics and highly specialized facilities.
- Scaling up manufacturing for global supply remains a challenge, especially for low- and middle-income countries (LMICs).
- New platforms (cell-free synthesis, modular bioreactors) aim to reduce costs and improve scalability.



1. Regulatory Frameworks:

- Accelerated approvals (e.g., Emergency Use Authorization during COVID-19) raised expectations but also highlighted gaps in longterm safety monitoring.
- Harmonization of global regulations is needed to speed approval without compromising safety.
- Stricter quality assurance and GMP compliance are essential for emerging technologies like gene-based vaccines.[23,15]

2. Equity Challenges:

- Vaccine nationalism and unequal distribution during COVID-19 highlighted the urgent need for fair allocation systems.
- The WHO's COVAX initiative attempted to address this but faced production and political barriers.
- Future efforts must prioritize local manufacturing hubs in LMICs and transparent pricing models.

Safety Surveillance and Public Acceptance

Safety Surveillance:

- Continuous pharmacovigilance systems are critical to detect rare but serious adverse events (e.g., myocarditis with mRNA vaccines, thrombosis with viral vectors).
- Digital health tools (apps, AI-driven monitoring) can enhance real-time safety data collection.
- Global collaboration (WHO, EMA, FDA) is vital for unified safety reporting.[19]

Public Acceptance:

- Vaccine hesitancy is now a major threat, fueled by misinformation, distrust in government, and cultural concerns.
- Transparent communication about risks and benefits is key.
- Community engagement, educational campaigns, and involvement of healthcare workers improve confidence. [19]

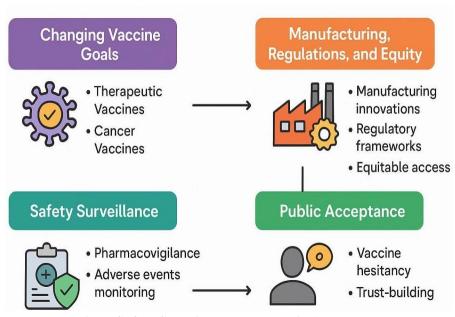


Fig 5: Safety Surveillance and Public Acceptance

CONCLUSION:

Recent trends in vaccine development highlight a paradigm shift from conventional approaches to advanced platforms such as mRNA, viral vectors, protein subunits, and nanoparticle-based vaccines. Innovations in delivery systems, formulations, and adjuvants are enhancing efficacy, stability, and accessibility, while expanding applications to therapeutic and cancer vaccines. Despite rapid progress, challenges in large-scale manufacturing, equitable distribution, regulatory oversight, safety monitoring, and public acceptance remain. Moving forward, the integration of cutting-edge technologies with global collaboration will be crucial to ensure safe, effective, and universally accessible vaccines for emerging and re-emerging health threats.

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