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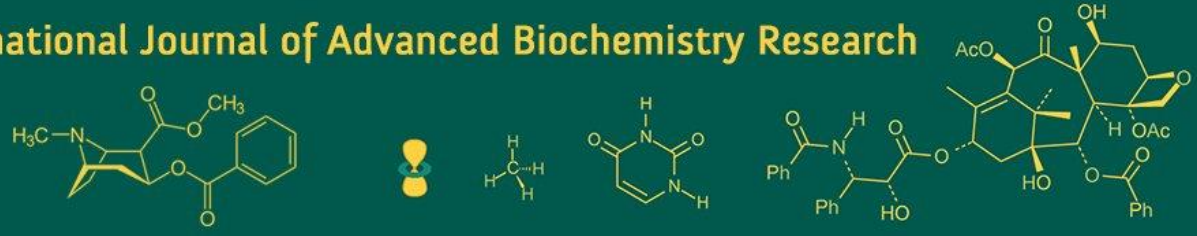

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mRNA vaccines in infectious disease control: Current progress and future perspectives

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Abstract
Messenger RNA (mRNA) vaccines have emerged as a transformative platform in vaccinology, offering rapid development, high flexibility, and scalable production. Preclinical and clinical studies have demonstrated their potential against a variety of pathogens, including HIV-1, rabies virus, Ebola virus, Zika virus, Nipah virus, and coronaviruses. The application of lipid nanoparticle (LNP)-encapsulated mRNA has been particularly promising, eliciting both humoral and cellular immune responses in animal models and early-phase human trials. However, challenges such as nucleotide modification errors, double-stranded RNA contamination, optimizing delivery systems, and understanding long-term immune memory remain significant hurdles for widespread deployment. Despite these limitations, mRNA vaccines uniquely fill the gap between emerging pandemic threats and the timely availability of effective immunization. With continued refinements in design, purification, and delivery technologies, mRNA vaccines are poised to become a cornerstone not only for infectious disease prevention but also for cancer immunotherapy and passive antibody transfer strategies.

Keywords: mRNA vaccines, lipid nanoparticles, HIV-1, emerging infectious diseases, Ebola virus, Zika virus, Nipah virus, COVID-19, immunotherapy, vaccine development, future prospects

1. Introduction

Vaccination has long stood as a cornerstone of public health, playing a pivotal role in controlling and eradicating devastating infectious diseases such as smallpox and polio. By training the immune system to recognize and combat pathogens, vaccines have saved millions of lives and continue to be a vital tool in global disease prevention. In recent years, advances in biotechnology have paved the way for innovative vaccine platforms, among which RNA vaccines represent a transformative leap forward. Unlike traditional vaccines that rely on weakened or inactivated pathogens, RNA vaccines use genetic material to instruct cells to produce specific antigens, eliciting a targeted immune response. This novel approach offers unprecedented speed, flexibility, and scalability in vaccine development, as demonstrated during the rapid deployment of mRNA-based vaccines against the SARS-CoV-2 virus [1].

RNA vaccines function by delivering a synthetic messenger RNA (mRNA) sequence into the body, which human cells then use to produce a harmless piece of the target pathogen—typically a viral protein. This protein acts as an antigen, triggering the immune system to mount a defense without causing disease. One of the most compelling advantages of RNA vaccines is their streamlined production process: the RNA can be synthesized in the lab from a DNA template using standardized biochemical reactions, bypassing the need for cell cultures or egg-based systems used in conventional vaccines. This not only accelerates development timelines but also reduces manufacturing costs and enhances responsiveness during pandemics or emerging outbreaks [2].

There are several types of RNA vaccines currently under development, including non-replicating mRNA vaccines, self-replicating mRNA vaccines, and dendritic cell-based mRNA vaccines, each with unique mechanisms and applications. While RNA vaccines offer significant benefits over DNA-based counterparts—such as improved safety due to their non-integrative nature and transient expression—they are not without challenges. Issues related to stability, delivery, potential immunogenicity, and storage requirements remain active areas of

research. Nevertheless, the success of mRNA vaccines in clinical settings, particularly during the COVID-19 pandemic, has validated their potential, opening new frontiers for combating infectious diseases, cancer immunotherapies, and personalized medicine [3].

2. Design and Structural Optimization of mRNA Vaccines

The development of messenger RNA (mRNA) vaccines relies on *in vitro transcription* (IVT), a cell-free process that synthesizes antigen-encoding RNA from a DNA template. Typically, a plasmid containing the gene of interest under a bacteriophage promoter (e.g., T7, SP6, or T3) is linearized and used as a template for transcription in the presence of recombinant RNA polymerase and nucleoside triphosphates. This generates a synthetic mRNA molecule designed to be delivered into host cells, where it directs the production of pathogen-specific antigens to elicit targeted immune responses [4]. After transcription, the DNA template is removed using RNase-free DNase to prevent unwanted immune activation. A functional IVT mRNA molecule includes several key structural elements: an open reading frame (ORF) encoding the target antigen, 5′ and 3′ untranslated regions (UTRs) that regulate translation and stability, a 5′ cap (7-methylguanosine, m7G) to protect against exonucleases and enable ribosome binding, and a poly(A) tail (optimally 120-150 nucleotides) to enhance mRNA stability and translational efficiency [5].

To maximize translational fidelity and minimize immune overactivation, several modifications are incorporated during IVT. Anti-reverse cap analogs (ARCAs) are used to ensure correct 5′ cap orientation, improving binding to the eukaryotic initiation factor eIF4E and enhancing protein expression [6]. Post-transcriptional purification—commonly achieved via high-performance liquid chromatography (HPLC) or FPLC—is critical to remove immunostimulatory contaminants such as double-stranded RNA (dsRNA), residual DNA, and truncated transcripts, which can trigger innate immune sensors and reduce vaccine efficacy [7]. Rigorous quality control assessments of mRNA integrity, purity, and immunogenic potential are essential before advancing candidates to preclinical or clinical testing [8].

3. Self-Amplifying mRNA Vaccines

Self-amplifying mRNA (saRNA) vaccines represent an advanced platform designed to enhance antigen expression and immunogenicity. Derived from positive-strand RNA viruses such as Sindbis, Semliki Forest, and Venezuelan equine encephalitis viruses, saRNA constructs include genes encoding viral RNA-dependent RNA polymerase (RdRp), while the structural genes are replaced with the antigen of interest [9]. Once delivered into host cells, the RdRp replicates the RNA genome intracellularly, leading to high-level amplification of the mRNA and sustained antigen production from very low initial doses. This dose-sparing effect was demonstrated in influenza vaccine studies, where only 50 ng of saRNA elicited strong antibody responses—40 times more potent than conventional non-replicating mRNA. Notably, the large size (9-11 kb) and molecular properties of saRNA confer a natural tropism for antigen-presenting cells (APCs), enabling efficient uptake even without advanced delivery systems [10].

Despite these advantages, saRNA vaccines face significant challenges. The large transcript size complicates production and increases susceptibility to degradation, requiring optimized IVT and purification protocols. Intracellular replication activates innate immune sensors like RIG-I and MDA5, leading to type I interferon (IFN-α/β) production, which may inhibit translation and reduce antigen yield. Additionally, repeated administration may be limited by immune responses against the viral replicase proteins, similar to the vector immunity seen with viral platforms. Ongoing research focuses on balancing immunogenicity with translational efficiency through sequence engineering, nucleoside modifications, and improved delivery vehicles to fully realize the potential of saRNA vaccines.

4. Mechanism of Action

In living organisms, genetic information is stored in DNA, which serves as the blueprint for protein synthesis. However, DNA does not directly produce proteins. Instead, it is transcribed into a transient intermediary molecule called messenger RNA (mRNA), which carries the genetic instructions to ribosomes—the cellular machinery responsible for protein translation. RNA-based vaccines harness this fundamental biological process by delivering synthetic mRNA into host cells. This engineered mRNA encodes a specific antigen, typically a viral or pathogen-derived protein. Once inside the cell, the host's translational machinery reads the mRNA sequence and produces the antigenic protein. These newly synthesized antigens are then processed and displayed on the cell surface via major histocompatibility complex (MHC) molecules, where they are recognized as foreign by antigen-presenting cells (APCs) and other components of the immune system (Pardi *et al.*, 2018).

The presentation of these antigens activates both the innate and adaptive immune responses. Dendritic cells and other APCs stimulate T cells and B cells, leading to the production of antibodies and the development of antigen-specific immune memory. This primary immune response "trains" the immune system to recognize the pathogen without causing disease. If the individual is later exposed to the actual pathogen, the immune system rapidly mounts a robust secondary response—characterized by faster antibody production and stronger cellular immunity—thereby preventing or mitigating infection. This ability to mimic natural infection while maintaining a strong safety profile is one of the key strengths of RNA vaccine technology.

5. mRNA Vaccine Constructs and Intracellular Delivery Mechanisms

Two primary types of mRNA vaccine platforms have been developed: non-replicating mRNA (NRM) and self-amplifying mRNA (SAM). NRM vaccines consist of a protein-coding sequence (CDS) flanked by 5′ and 3′ untranslated regions (UTRs), a 5′ cap (m7G), and a poly(A) tail, all of which enhance mRNA stability, translational efficiency, and cellular delivery [4, 5]. Once delivered into the cytoplasm, the mRNA is directly translated by host ribosomes into the target antigen, which may undergo post-translational modifications before being processed and presented to the immune system. In contrast, SAM vaccines are derived from alphavirus genomes and include genes encoding RNA-dependent RNA polymerase (RdRp) in addition to the antigen of interest [10]. After cellular uptake, the RdRp is translated first, enabling intracellular

amplification of the mRNA and leading to prolonged and high-level antigen expression from a minimal initial dose—offering significant dose-sparing advantages. However, the larger size of SAM constructs and their inherent immunostimulatory potential pose challenges for manufacturing and immune modulation.

6. Delivery Strategies for *in vivo* and Ex Vivo Applications

The successful delivery of mRNA vaccines critically depends on advanced carrier systems, with lipid nanoparticles (LNPs) emerging as the most effective and clinically validated platform. LNPs encapsulate mRNA, protecting it from ribonuclease degradation and facilitating cellular uptake through endocytosis. Within the endosome, ionizable lipids in the LNP respond to acidic pH, promoting membrane fusion or destabilization and enabling endosomal escape—thereby releasing mRNA into the cytoplasm for translation [3]. This mechanism supports robust antigen expression and activation of both MHC class I and II pathways, driving potent humoral and cellular immune responses [11]. An alternative strategy involves *ex vivo* loading of dendritic cells (DCs), where patient-derived DCs are transfected with mRNA—typically via electroporation—and reinfused to stimulate strong T-cell immunity, a method particularly explored in cancer immunotherapy [3]. While direct administration of naked mRNA or physical delivery methods (e.g., gene guns) has shown limited success due to instability and poor uptake, LNP-based delivery has proven highly effective *in vivo*, especially via intramuscular or intradermal routes. The clinical success of LNP-formulated mRNA vaccines, such as those against SARS-CoV-2, underscores their pivotal role in enabling the rapid development and deployment of safe and potent mRNA-based therapeutics.

7. Adjuvanticity in mRNA Vaccines

mRNA vaccines possess intrinsic self-adjuvanticity due to the inherent immunostimulatory properties of RNA, which activate innate immune sensors such as Toll-like receptors (TLR3, TLR7, TLR8) and cytoplasmic receptors RIG-I and MDA5. This recognition triggers signaling cascades that induce type I interferon production, promote dendritic cell maturation, and enhance antigen presentation—critical steps in initiating robust and durable adaptive immune responses [12]. This built-in adjuvant effect reduces or eliminates the need for traditional external adjuvants, contributing significantly to the high immunogenicity of mRNA-based platforms. To further amplify and shape immunity, exogenous adjuvants such as recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) have been co-delivered, demonstrating enhanced antigen-specific responses and a shift toward protective Th1-biased immunity in preclinical models, with several candidates advancing into clinical trials for cancer immunotherapy. Similarly, administration of mRNA encoding FLT3 ligand has been shown to improve dendritic cell recruitment and activation, boosting antitumor efficacy in mice.

An innovative evolution of this strategy involves encoding the adjuvant itself as an mRNA within the vaccine formulation, enabling endogenous, localized, and sustained expression of immune modulators such as GM-CSF, IL-2, CD80, or CD40 ligand (CD40L). This approach ensures coordinated expression of both the antigen and adjuvant in the same cell, enhancing immune synergy while circumventing the stability and delivery challenges associated with recombinant proteins. For example, GM-CSF-encoding mRNA has been shown to enhance cytotoxic T lymphocyte (CTL) activity in a dose-dependent manner and promote long-lasting memory T-cell responses. CD40L-encoding mRNA, in particular, activates professional antigen-presenting cells (pAPCs) via CD40 signaling, creating a positive feedback loop that amplifies T-cell priming and antigen presentation. In preclinical tumor models, CD40L-adjuvanted mRNA vaccines have demonstrated significantly improved tumor control compared to non-adjuvanted formulations. These findings highlight the potential of mRNA-encoded adjuvants to precisely modulate immune responses, although optimal dosing, timing, and safety profiles require further optimization for broad clinical translation [12].

8. Clinical Development of mRNA Vaccines

mRNA vaccines have rapidly advanced through clinical development as a versatile and agile platform for combating infectious diseases, beginning with rabies as a key proof-of-concept pathogen. Rabies was among the first targets due to its well-characterized genome and the established role of the viral glycoprotein (RABV-G) in eliciting neutralizing antibodies. The first clinical candidate, CV7201—a lyophilized, non-nucleoside-modified mRNA vaccine formulated with protamine—demonstrated robust humoral and cellular immune responses in preclinical models, including mice and pigs. However, early human trials revealed variable immunogenicity highly dependent on delivery method, despite an acceptable safety profile. This highlighted the critical importance of delivery optimization, leading to the adoption of lipid nanoparticles (LNPs) that protect mRNA from degradation and enhance cellular uptake. Subsequent LNP-formulated vaccines administered intramuscularly or intradermally elicited strong, durable immune responses in animal models, solidifying the feasibility of mRNA technology for prophylactic vaccination. Similarly, promising results have been achieved in veterinary applications, including protection against foot-and-mouth disease virus [13] and rabies in preclinical species [14], while LNP-encapsulated mRNA vaccines against Powassan virus demonstrated cross-protective immunity in mice.

The platform's flexibility has enabled rapid expansion into human infectious diseases, most notably influenza and HIV-1. mRNA-based influenza vaccines encoding hemagglutinin (HA) have shown broad protection against homologous and heterosubtypic strains, overcoming a major limitation of traditional egg-based vaccines—antigenic mismatch due to egg-adaptive mutations that impair neutralization of circulating H3N2 strains [15]. By encoding the exact wild-type sequence and relying on host-cell processing, mRNA vaccines produce structurally authentic antigens, enhancing immunogenicity and enabling rapid response to emerging variants [3]. Clinical trials for pandemic-prone strains like H10N8 and H7N9 have demonstrated strong immunogenicity and safety, with LNP-formulated H1N1 vaccines showing potent protection in animal models [16]. In contrast, HIV-1 vaccine development remains challenging due to viral diversity and immune evasion. Strategies include LNP-delivered mRNA encoding broadly neutralizing antibodies, which conferred complete

protection in humanized mice, and dendritic cell vaccines that induce antigen-specific T-cell responses, though clinical benefit has been limited [3]. Early-phase intranodal trials showed immunogenicity, but a Phase II study was discontinued due to lack of efficacy, underscoring the need for improved antigen design and delivery. Nonetheless, these collective advances—from rabies and influenza to HIV and beyond—demonstrate the transformative potential of mRNA vaccines in addressing both established and emerging infectious threats.

9. mRNA Vaccines in Cancer Immunotherapy

The application of mRNA vaccines in oncology has evolved rapidly since the pioneering work of Boczkowski *et al.* (1996), who first demonstrated that dendritic cells (DCs) electroporated with tumor-derived or antigen-specific mRNA (e.g., ovalbumin) could induce potent antitumor immune responses in mouse models [17]. Since then, mRNA-based cancer vaccines have emerged as a powerful strategy to stimulate cytotoxic T lymphocyte (CTL)-mediated immunity against tumor-associated antigens (TAAs) and patient-specific neoantigens derived from somatic mutations. A key example is the TriMix platform—a combination of mRNAs encoding CD70, CD40L, and constitutively active TLR4—which, when co-delivered with tumor antigen mRNA into DCs via electroporation, induced tumor regression in approximately 27% of patients with advanced melanoma, demonstrating clinical feasibility [3]. The flexibility of mRNA platforms enables both off-the-shelf and personalized vaccine designs. In melanoma, tumor sequencing allows for the identification of unique neoantigens, followed by rapid synthesis of individualized mRNA vaccines tailored to each patient's mutanome [4]. Delivery methods—including intradermal, intranodal, and intratumoral routes—combined with advances in LNP and electroporation technologies, have improved *in vivo* mRNA delivery and antigen presentation. Although early trials in prostate cancer and other malignancies show immunogenicity, further research is needed to determine whether these immune responses translate into durable clinical benefits. Nevertheless, the adaptability, speed, and potency of mRNA vaccines position them as a transformative tool in the future of cancer immunotherapy.

10. Immunity Induced by mRNA Vaccines

The immunogenicity of mRNA vaccines hinges on their ability to engage the innate immune system, which acts as the initial sensor of foreign RNA. Upon delivery—typically via lipid nanoparticles (LNPs)—the mRNA is taken up by antigen-presenting cells (APCs), where it is recognized by pattern recognition receptors (PRRs) such as Toll-like receptors (TLR3, TLR7, TLR8) in endosomes and cytosolic sensors including RIG-I, MDA5, and LGP2. TLR3 detects double-stranded RNA (dsRNA) and signals through TRIF to activate IRF3 and NF-κB, while TLR7 and TLR8 recognize single-stranded RNA (ssRNA) via the MyD88 pathway, both leading to the production of type I interferons (IFN-α/β) and pro-inflammatory cytokines. In the cytoplasm, RIG-I senses short dsRNA with 5′-triphosphates, and MDA5 detects long dsRNA (>2000 bp), signaling through the adaptor protein MAVS (IPS-1) to induce robust interferon responses. NOD2 has also been shown to contribute to IFN-β production via IPS-1. This innate immune activation promotes dendritic cell maturation, enhances antigen presentation, and creates a stimulatory microenvironment essential for initiating adaptive immunity.

While innate immune activation is crucial for vaccine efficacy, its magnitude and timing must be carefully balanced to avoid suppressing antigen expression and adaptive responses. Excessive or premature type I interferon signaling can trigger antiviral defense mechanisms—such as activation of PKR and OAS—that inhibit mRNA translation and promote degradation, reducing antigen yield. Furthermore, if IFN exposure precedes T cell receptor (TCR) engagement, STAT1-driven anti-proliferative and pro-apoptotic pathways may dampen T cell expansion. In contrast, when IFN signaling follows antigen recognition, STAT4 activation supports the differentiation of $CD8^+$ T cells into cytotoxic effectors. To optimize this balance, modern mRNA vaccines incorporate nucleoside modifications (e.g., pseudouridine), use highly purified transcripts to remove dsRNA contaminants, and leverage LNP delivery to enhance cytosolic delivery while modulating immune sensing. These strategies enable sufficient innate stimulation to drive immunogenicity without compromising protein expression. The resulting antigen is processed and presented via MHC class I and II pathways, activating both cytotoxic $CD8^+$ T cells and $CD4^+$ helper T cells, which in turn support B cell activation and the production of neutralizing antibodies. This coordinated interplay between innate and adaptive immunity underpins the potency, durability, and protective capacity of mRNA vaccines [18].

11. mRNA Vaccines in Emerging Infectious Diseases Control

mRNA vaccines hold significant promise for combating emerging infectious diseases, with several candidates demonstrating strong immunogenicity and protective efficacy in preclinical and clinical studies, despite no licensed products currently available for this category. For Ebola virus (EBOV), mRNA vaccines encoding the viral glycoprotein (GP) have been tested using modified dendrimer and lipid nanoparticle (LNP) delivery systems, showing protective immunity in mice and guinea pigs [19], with ongoing clinical evaluation led by Moderna in collaboration with the WHO. Similarly, an LNP-encapsulated mRNA vaccine for Zika virus (ZIKV), encoding the prM-Env proteins and formulated with 1-methylpseudouridine to reduce innate immune activation, induced potent neutralizing antibodies in mice and nonhuman primates and prevented fetal demise in pregnancy models. This candidate has advanced into Phase I/II clinical trials (Moderna Inc.). For Nipah virus (NiV), preclinical studies in Syrian hamsters have demonstrated that LNP-formulated mRNA encoding the soluble Henipavirus glycoprotein (sHeVG) can confer protective immunity [20]. The most transformative advancement came during the COVID-19 pandemic, when the SARS-CoV-2 mRNA-1273 vaccine, developed by Moderna and NIAID, rapidly progressed from design to Phase I trials within weeks and ultimately became the first mRNA vaccine to receive emergency use authorization and full regulatory approval, marking a historic milestone in vaccinology and validating the platform's potential for rapid response to global health threats.

12. Conclusion and Future Perspectives

The field of mRNA vaccines is still in its infancy, yet it has already demonstrated remarkable potential in revolutionizing vaccinology. Unlike traditional platforms, mRNA vaccines offer flexible, scalable, and relatively rapid production with the added advantage of being cold chain-independent, thereby providing a practical solution for global vaccine distribution. Their ability to bridge the gap between emerging pandemic infections and the timely supply of effective vaccines makes them an invaluable tool in future outbreak preparedness.

However, several challenges remain to be addressed. The improvement of potency, optimization of delivery systems, and a deeper understanding of immune memory mechanisms are key areas that require further research. Technical concerns, such as purification of double-stranded RNA contaminants using HPLC and minimizing translation inefficiencies, must be refined to enhance safety and efficacy. Moreover, incomplete or imperfect nucleotide modifications can negatively affect stability and immunogenicity, highlighting the need for precision in vaccine engineering. Looking ahead, the prospects of mRNA vaccines are highly encouraging. Ongoing advancements in nanoparticle-based delivery platforms**,** structural modification of nucleotides, and mechanistic studies on long-term immune responses are expected to pave the way for safer, more effective, and durable mRNA vaccines. While clinical validation in diverse populations is still evolving, the promise of mRNA technology against infectious diseases and even cancers is undeniable, making it one of the most exciting frontiers in modern medicine.

13. Conflict of Interest

The authors declare no conflict of interest.

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