Vol. 39 (2026): Proceedings of 2026 International Conference on Life Sciences and Health Engineering
—— Session 3: Health for All Populations: Forum on Public Health and Clinical Health Sciences
(PHCHS-LSHE 2026)
E-ISSN: 3105-0522 P-ISSN: 3105-0514
DOI: https://doi.org/10.70267/PHCHS-LSHE-2026.2026.39.103109

Development and Pharmacological Mechanisms of mRNA Vaccines

Hanyu Liu*

Friendship Christian School, Raleigh, United States

**Corresponding author: Hanyu Liu.*

Abstract

Messenger RNA (mRNA) vaccines are built on synthetic mRNA encoding a pathogen antigen. Nucleoside modification dampens innate immune overactivation, and lipid nanoparticles (LNPs) deliver mRNA into the cytoplasm, where it is translated into an antigen that simultaneously elicits humoral and cellular immunity. During the COVID-19 pandemic, two LNP-mRNA vaccines completed large-scale clinical validation, and the platform has since expanded to influenza and HIV. This review follows two lines: delivery and antigen expression, and immune responses. It first explains mRNA design, LNP delivery, and intracellular antigen expression; then analyzes how the expressed antigen, together with the mRNA and LNP components, triggers innate and adaptive immunity; then distinguishes COVID-19, influenza, and HIV applications by the maturity of their evidence; and finally discusses current technical bottlenecks and future directions.

Keywords

mRNA vaccine, lipid nanoparticle (LNP), immune activation, SARS-CoV-2, influenza

1. Introduction

Traditional vaccines differ widely in how they are made and how well they work. Live-attenuated vaccines provoke strong and durable immunity because the attenuated pathogen replicates and presents many antigens, but they carry a small risk of reversion to virulence and are unsuitable for severely immunocompromised individuals. Inactivated vaccines are safer but usually require multiple doses and adjuvants to achieve sufficient immunogenicity, and their manufacture depends on the production of large quantities of the inactivated pathogen. Protein-subunit vaccines are safe and precisely defined, but they are expensive to produce, often require adjuvants, and may not reproduce the native conformation needed for neutralizing antibodies. Viral-vector vaccines deliver antigen genes efficiently and induce both arms of immunity, yet pre-existing immunity to the vector can blunt responses, and manufacturing is relatively complex [1,2].

mRNA vaccines belong to the nucleic-acid vaccine class. Their antigen sequence can be revised quickly, and translation occurs in the cytoplasm without nuclear entry, so there is no risk of integration into the host genome [1]. Early naked mRNA was unstable, rapidly degraded by ribonucleases, difficult to deliver across cell membranes, and strongly stimulated innate immunity, thereby suppressing antigen translation. Two advances solved these problems: nucleoside modification (replacing uridine with N1-methylpseudouridine) reduced recognition by innate sensors and improved translation, while LNP delivery protected the mRNA and enabled cellular uptake [1,3,4].

Copyright © 2026 The Authors. All individual papers remain the copyright of their respective author(s) · Published by Zeus Academic Research Publishing Group

It should be emphasized that mRNA vaccines are not superior to traditional vaccines on every dimension. Their advantages should be separated into platform-level properties and vaccine-dependent attributes. At the platform level, mRNA vaccines do not require pathogen culture, enable rapid antigen sequence iteration, and express the complete antigen with native conformation in the cytoplasm [1,2]. However, the actual safety and immunogenicity depend on antigen design, formulation, dose, and host factors, and the platform itself has limitations in reactogenicity, cold-chain storage, and delivery dependence [3,5]. Comparisons with traditional vaccines should therefore be conditional rather than one-directional.

In 2020, two COVID-19 mRNA vaccines (BNT162b2 and mRNA-1273) were authorized, moving the technology into large-scale use [6,7,8]. The platform has since been extended to seasonal influenza (in clinical development) [9] and HIV (in exploratory research) [10,11]. The remainder of this review covers the design, delivery, and antigen expression of mRNA vaccines (Section 2); the pharmacological mechanisms of immune activation (Section 3); three representative applications at different stages of maturity (Section 4); and current technical bottlenecks (Section 5).

2. mRNA Vaccine Design, Delivery, and Antigen Expression

This section focuses on the delivery-to-expression chain—the pharmacokinetic side of the vaccine—while the triggering of immune responses is left to Section 3.

2.1 mRNA Molecular Design and Nucleoside Modification

The mRNA used in vaccines is a synthetic in vitro-transcribed sequence. From the 5′ end to the 3′ end, it comprises a 5′ cap, a 5′ untranslated region (UTR), an antigen-coding open reading frame (ORF), a 3′ UTR, and a poly(A) tail. The cap recruits ribosomes and protects against 5′ exonucleases; the UTRs regulate translation efficiency and stability; and the poly(A) tail stabilizes the mRNA and promotes translation [3].

Design involves several interdependent trade-offs. The cap can be added as a Cap 0 or the more translationally efficient Cap 1 structure. The choice of UTRs affects both the rate and the duration of antigen expression. The poly(A) length influences mRNA stability and translation, and codon optimization and GC-content adjustment adapt the sequence to host translation preferences. Purification removes double-stranded RNA (dsRNA) by-products of in vitro transcription, which would otherwise be recognized by innate sensors such as RIG-I. Nucleoside modification (for example, replacement of uridine with N1-methylpseudouridine) further dampens recognition by TLR3/7/8 and improves translation [3,4]. Importantly, higher translation does not automatically translate into a better immune response because some innate immune stimulation contributes to adjuvanticity; the design must balance translation and immunogenicity rather than maximize protein output alone [5].

2.2 LNP Delivery and Intracellular Fate

Naked mRNA is negatively charged, cannot easily cross the negatively charged cell membrane, and is rapidly degraded, so the LNP is an essential carrier. The classical mRNA LNP is self-assembled from four lipid components. The ionizable lipid is the functional core: it is electrostatically neutral at physiological pH, thereby reducing toxicity, and becomes protonated and positively charged inside the acidic endosome, where it disrupts the endosomal membrane and mediates endosomal escape, releasing mRNA into the cytoplasm. Helper phospholipids maintain the particle bilayer and assist membrane destabilization; cholesterol increases particle stability and membrane fusion; and PEG lipids reduce aggregation and prolong circulation time [3].

After intramuscular injection, the LNP distributes from the injection site, where it may acquire a protein corona of serum proteins that can influence uptake and clearance, and is taken up by local dendritic cells and macrophages or drains into lymph nodes. Following cellular uptake via endocytosis, the LNP must escape the endosome before the cargo is degraded in lysosomes; endosomal escape is inefficient, and only a small fraction of the internalized mRNA—often estimated at a few percent—reaches the cytosol, making this step a major bottleneck in LNP delivery [3,12]. The structure of the ionizable lipid strongly affects both escape efficiency and toxicity, and different lipid chemistries are being explored to close this gap [12]. After escape, the mRNA is translated in the cytoplasm by host ribosomes (Section 2.3).

Copyright © 2026 The Authors. All individual papers remain the copyright of their respective author(s) · Published by Zeus Academic Research Publishing Group

2.3 Intracellular Release, Translation, and Antigen Fate

Following endosomal escape, the mRNA is released into the cytoplasm and translated by host ribosomes into the encoded antigen protein [3]. The efficiency of endosomal escape determines how much mRNA reaches the cytoplasm and therefore how much antigen is expressed; because escape is inefficient, most internalized mRNA is degraded in lysosomes rather than translated [12].

The fate of the synthesized antigen then shapes the immune response. The proteasome processes antigen retained in the cytoplasm into peptides that are presented by MHC class I molecules. An antigen that is secreted or otherwise released from the cell can be taken up by antigen-presenting cells and presented by MHC class II molecules. The duration of antigen expression depends on the stability of the mRNA and the translated protein; transient expression generally lasts for days after a single dose, which is long enough to prime an adaptive response but short enough to avoid persistent antigenic stimulation [3,5]. These processing and presentation events connect the delivery-and-expression phase to the immune activation described in Section 3.

3. Immunological Activation and Pharmacological Mechanisms of the Immune Response

This section addresses the pharmacodynamic aspect, analyzing how the expressed antigen and the mRNA/LNP components trigger innate and adaptive immunity.

3.1 Innate Immunity: mRNA Nucleic-Acid Sensing and LNP Inflammation/Adjuvanticity

Innate immunity provides the activation signals on which adaptive responses depend, and the contributions of the mRNA and the LNP should be considered separately because the strength of the evidence differs.

Unmodified mRNA can be recognized by the endosomal Toll-like receptors TLR3, TLR7, and TLR8, as well as by the cytoplasmic RNA sensors RIG-I and MDA5. These receptors reside in distinct cellular compartments: TLR3/7/8 in the endosomes of immune cells, and RIG-I and MDA5 in the cytoplasm of most cells. Their activation triggers signaling cascades that induce type I interferons and inflammatory cytokines and, in the case of unmodified mRNA, also suppresses protein translation. Nucleoside modification markedly reduces this recognition, a mechanism supported by strong experimental evidence [4,5].

Type I interferon acts as a double-edged sword. On the one hand, it provides adjuvant-like signals that promote dendritic cell maturation and help launch adaptive immunity; on the other hand, strong interferon responses can inhibit antigen translation and cause inflammation. This trade-off is central to mRNA vaccine design [5].

In contrast, the “adjuvant” effect of the LNP is supported by weaker and partly debated evidence. Studies show that LNP components can promote dendritic-cell maturation and induce inflammatory cytokines, contributing to immunogenicity; however, the boundary between the contribution of the LNP and that of mRNA sensing is not fully clear, and the specific signaling pathways implicated (for example, those involving NLRP3 or STING) vary with LNP formulation and the experimental system. Evidence in this area should be read with several caveats: different ionizable lipids, doses, animal models, and routes of administration can yield different conclusions, and inflammatory pathways observed in animals cannot be assumed to translate directly to humans. It is therefore more accurate to say that the LNP can enhance immune responses, but that its mechanism depends on the formulation and that parts of the picture remain to be confirmed in human studies [5].

3.2 Adaptive Immunity: Antigen Presentation and T- and B-Cell Responses

Dendritic cells that take up mRNA-LNP migrate to draining lymph nodes and present antigen. Antigen synthesized in the cytoplasm is degraded by the proteasome, loaded onto MHC class I molecules, and presented to CD8+ T cells, activating cytotoxic T cells that kill infected cells. Antigen taken up from the extracellular space is presented on MHC class II molecules to CD4+ helper T cells; cross-presentation also allows exogenous antigen to enter the MHC class I pathway [3].

CD4+ T cells, particularly follicular helper T (Tfh) cells, support B cells in germinal-center reactions, where B cells undergo somatic hypermutation and affinity maturation to produce high-affinity neutralizing antibodies. Some activated B and T cells differentiate into memory B and memory T cells, which provide the basis for

Copyright © 2026 The Authors. All individual papers remain the copyright of their respective author(s) · Published by Zeus Academic Research Publishing Group

long-term protection and rapid recall responses [1,3]. Humoral and cellular immunity together constitute a protective response. It should be noted, however, that many traditional vaccines also induce cellular immunity, just with different strength and composition; the advantage of mRNA vaccines in this respect is conditional and most apparent for certain antigen designs and pathogen settings, rather than absolute [1].

3.3 Factors That Shape the Strength, Duration, and Quality of Immune Responses

"Rapid onset, long memory, and broad responses" do not apply uniformly to all mRNA vaccines. The strength, duration, and quality of the response are governed by several interacting factors, which can be grouped into formulation, vaccination strategy, host, and pathogen.

Formulation factors include the antigen design, the mRNA sequence and nucleoside modifications, and the LNP composition, all of which influence how much antigen is expressed and how strongly innate immunity is engaged. Vaccination strategy covers the dose and the immunization schedule (for example, prime–boost regimens), which determine the magnitude and persistence of antibody and T-cell responses. Host factors include age and immune status; older or immunocompromised individuals often mount weaker responses. Pathogen factors include the type of pathogen and its degree of antigenic variability, which influence protective efficacy [3,5].

The COVID-19 experience illustrates these effects: neutralizing antibody titers induced by mRNA vaccines decline over time, and booster doses are needed to maintain protection, so long-lasting memory cannot be assumed as a universal outcome of every mRNA vaccine [5,7,8].

4. mRNA Vaccines in Viral Infectious Diseases: From Established to Exploratory

COVID-19, influenza, and HIV differ markedly in the maturity of their evidence, so they are presented here along a gradient of established application, clinical development, and exploratory research rather than as equally developed directions. Each case follows the same structure—antigen design, clinical stage, and sample, key immunogenicity or efficacy results, safety, and current limitations—so that differences in evidence are clear.

4.1 COVID-19: An Established Application

The COVID-19 mRNA vaccines (BNT162b2 and mRNA-1273) encode the spike (S) protein of SARS-CoV-2, engineered with stabilizing mutations to maintain the prefusion conformation. In a phase 1 trial, mRNA-1273 induced strong neutralizing antibodies and T-cell responses in healthy adults [6]. In large phase 3 trials, BNT162b2 conferred approximately 95% efficacy against symptomatic COVID-19 in people aged 16 and older [7], and mRNA-1273 showed approximately 94% efficacy [8]. Both vaccines showed generally transient local and systemic reactogenicity, and serious adverse events were rare in the trial populations [7,8]. Their large-scale real-world use confirmed the platform's ability to respond rapidly to an emerging pathogen; when variants eroded protection, updated and multivalent mRNA vaccines could be produced quickly by changing the coding sequence. Current limitations include waning antibody titers and the need for periodic boosting [7,8].

4.2 Influenza: Clinical Development

Seasonal influenza viruses undergo continuous antigenic drift in the hemagglutinin (HA) protein, and egg-based vaccines have a long production cycle, so mismatches between predicted and circulating strains can reduce efficacy. mRNA vaccines do not depend on virus culture and can be updated quickly. In phase 1/2 randomized studies, nucleoside-modified mRNA influenza vaccines were well tolerated in healthy adults aged 18–85 and induced immune responses against multiple influenza strains [9]. By encoding HA together with neuraminidase (NA) and other antigens, the mRNA platform may broaden the range of protection. It should be noted that protective efficacy is still being confirmed in phase 3 trials and real-world studies [9].

4.3 HIV: Exploratory Research

The central difficulty of an HIV vaccine is that the Env envelope protein is highly variable, does not broadly induce neutralizing antibodies (bnAbs), and establishes latent reservoirs. mRNA-LNP can encode stabilized

Copyright © 2026 The Authors. All individual papers remain the copyright of their respective author(s) · Published by Zeus Academic Research Publishing Group

Env trimer antigens and, through prime–boost strategies, aim to drive bnAb-precursor B cells toward maturation [10]. Two phase 1 trials showed that mRNA-LNP immunization could drive early maturation of HIV bnAb precursors in humans, an important proof of concept [11]. It must be stressed, however, that this represents an early step on the immune pathway, not the generation of bnAbs with sufficient breadth and titer for protection. Sequential immunization and germline-targeting strategies, further booster-antigen design, and several key obstacles—most notably inducing antibodies with the required breadth and potency—remain before a protective vaccine can be realized [10,11].

5. Technical Bottlenecks and Future Directions

This section summarizes the main technical bottlenecks of the mRNA-LNP platform under six headings.

5.1 mRNA Stability and Delivery Efficiency

mRNA is susceptible to degradation by intracellular and extracellular nucleases, and its translation efficiency depends on the sequence and modifications. The delivery efficiency of the LNP determines how much mRNA reaches the cytoplasm and hence the level of antigen expression [3]. Improvements to stability and expression involve optimization of the cap, UTRs, and poly(A) tail, purification to remove dsRNA impurities, and lyophilization or novel formulations. A distinction should be drawn between formulation storage stability and the stability of mRNA after it enters the body; both matter, but are governed by different factors [3].

5.2 LNP Tissue Distribution and Targeting

Most LNP formulations preferentially accumulate in the liver and other organs, with limited targeting to lymph nodes and muscle, which constrains delivery precision. The development of more selective lipid formulations, targeting ligands, and organ-specific delivery strategies is an active area of research [3,12].

5.3 Inflammation and Reactogenicity

The mRNA and LNP components can induce local and systemic inflammatory responses, leading to pain, fever, and fatigue. It is useful to distinguish common reactogenicity, rare serious adverse events, and signals whose causality remains uncertain. In the phase 3 trials of the COVID-19 vaccines, reactogenicity was common but generally transient, and serious adverse events were rare [7,8]. Post-authorization surveillance has identified rare conditions, such as myocarditis in young males, as signals with low incidence and causality and mechanisms still under investigation; the balance between inflammation and immunogenicity remains an important optimization target [5,8].

5.4 Repeated Vaccination

Repeated administration may elicit immune responses against LNP components, particularly anti-PEG antibodies, which can affect the delivery and safety of subsequent doses. Anti-PEG antibodies are detectable in a proportion of the population even before exposure to PEGylated nanomedicines, and repeated dosing can raise them, leading to accelerated blood clearance in some settings [13]. Improvements under investigation include degradable PEG alternatives, other hydrophilic polymers, and reducing PEG exposure [13].

5.5 Storage Stability and Cold Chain

Most LNP-mRNA vaccines require cold-chain storage and transport, which place high demands on infrastructure and limit their use in resource-limited settings. Developing thermostable formulations—through improved lipid chemistry, lyophilization, or other stabilization approaches—is therefore an important priority to reduce cold-chain dependence [3].

5.6 Pathogen Variation and Immune Escape

Pathogen variation can erode vaccine-induced protection, as seen with SARS-CoV-2 variants and, more profoundly, with the highly variable Env of HIV. Antigen design and multivalent strategies are key to countering immune escape and broadening protection [10].

Copyright © 2026 The Authors. All individual papers remain the copyright of their respective author(s) · Published by Zeus Academic Research Publishing Group

Taken together, future directions include developing low-reactogenicity, targeted ionizable lipids; improving thermostability; designing multivalent and mucosally delivered vaccines; and optimizing antigen sequences to induce broad neutralizing antibodies against variable pathogens such as HIV [3,5,10,12,13].

6. Conclusion

mRNA vaccines rely on nucleoside-modified mRNA and LNP delivery to express antigen in native conformation in the cytoplasm and to activate both humoral and cellular immunity; the LNP serves as both a delivery vehicle and an adjuvant, although its adjuvant mechanism varies by formulation and remains partly unconfirmed. The large-scale use of COVID-19 vaccines established the platform's feasibility; influenza vaccines are in clinical development, and HIV vaccines remain in exploratory stages. The technology still faces bottlenecks in mRNA stability, LNP targeting, reactogenicity, repeated administration, cold-chain storage, and immune escape. Rather than list all of these again, it is useful to close by summarizing where the evidence is most mature, where it is still debated, and where the highest-priority research questions lie. The strongest evidence concerns the protective efficacy and immunogenicity of the COVID-19 mRNA vaccines; the most debated questions concern the mechanistic basis of LNP adjuvanticity and reactogenicity; and the highest-priority research questions concern the induction of durable, broad protection against variable pathogens such as HIV [1,3,5,7,8].

References

[1] Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines—a new era in vaccinology. Nat Rev Drug Discov. 2018;17(4):261-279. doi:10.1038/nrd.2017.243.

[2] Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov. 2014;13(10):759-780. doi:10.1038/nrd4278.

[3] Chaudhary N, Weissman D, Whitehead KA. mRNA vaccines for infectious diseases: principles, delivery and clinical translation. Nat Rev Drug Discov. 2021;20(11):817-838. doi:10.1038/s41573-021-00283-5.

[4] Karikó K, Buckstein M, Ni H, Weissman D. Suppression of RNA recognition by Toll-like receptors: the impact of nucleoside modification and the evolutionary origin of RNA. Immunity. 2005;23(2):165-175. doi:10.1016/j.immuni.2005.06.008.

[5] Verbeke R, Hogan MJ, Loré K, Pardi N. Innate immune mechanisms of mRNA vaccines. Immunity. 2022;55(11):1993-2005. doi:10.1016/j.immuni.2022.10.014.

[6] Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2—preliminary report. N Engl J Med. 2020;383(20):1920-1931. doi:10.1056/NEJMoa2022483.

[7] Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603-2615. doi:10.1056/NEJMoa2034577.

[8] Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384(5):403-416. doi:10.1056/NEJMoa2035389.

[9] Branche A, Mulligan MJ, Maniar A, et al. A phase 1/2 randomized study to evaluate the safety, tolerability, and immunogenicity of nucleoside-modified messenger RNA influenza vaccines in healthy adults. Vaccines (Basel). 2025;13(4):383. doi:10.3390/vaccines13040383.

[10] Mu Z, Haynes BF, Cain DW. HIV mRNA vaccines—progress and future paths. Vaccines (Basel). 2021;9(2):134. doi:10.3390/vaccines9020134.

[11] Willis JR, Prabhakaran M, Muthui M, et al. Vaccination with mRNA-encoded nanoparticles drives early maturation of HIV bnAb precursors in humans. Science. 2025;389(6759):eadr8382. doi:10.1126/science.adr8382.

[12] Chatterjee S, Kon E, Sharma P, Peer D. Endosomal escape: a bottleneck for LNP-mediated therapeutics. Proc Natl Acad Sci USA. 2024;121(11):e2307800120. doi:10.1073/pnas.2307800120.

Copyright © 2026 The Authors. All individual papers remain the copyright of their respective author(s) · Published by Zeus Academic Research Publishing Group

[13] Kozma GT, Shimizu T, Ishida T, Szebeni J. Anti-PEG antibodies: properties, formation, testing and role in adverse immune reactions to PEGylated nano-biopharmaceuticals. Adv Drug Deliv Rev. 2020;154-155:163-175. doi:10.1016/j.addr.2020.07.024.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgment

This paper is an output of the science project.

Open Access

This chapter is licensed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/), which permits any noncommercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license and indicate if changes were made.

The images or other third party material in this chapter are included in the chapter's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the chapter's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder.



Copyright © 2026 The Authors. All individual papers remain the copyright of their respective author(s) · Published by Zeus Academic Research Publishing Group