

Intranasal mRNA vaccines: Targeting mucosal immunity through optimized delivery

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The COVID-19 pandemic highlighted the transformative potential of mRNA lipid nanoparticle (LNP) vaccines, yet their limited ability to induce mucosal immunity at respiratory entry points remains a significant challenge. Intranasal vaccination offers a promising strategy to elicit local immune responses at the primary site of respiratory pathogen entry, critical for preventing infections like SARS-CoV-2 and influenza.¹ In a recent study published in *Molecular Therapy Nucleic Acids*, Vu et al. demonstrated that while intranasal mRNA-LNPs efficiently transfect lung epithelial and immune cells, they fail to generate robust primary mucosal immunity, despite the success of LNPs in intramuscular applications, unless boosted in a primed context² (Figure 1). The study further revealed that cationic lipid DOTAP (1,2-dioleoyl-3-trimethylammonium-propane) enhances recall responses. These findings highlight fundamental gaps in mucosal immunobiology and the urgent need to refine LNP formulations, bridging cargo delivery and immunogenicity for effective respiratory tract-optimized vaccines.³

mRNA-LNP vaccines, such as those developed by Pfizer/BioNTech and Moderna, have revolutionized immunotherapy by enabling rapid antigen design and systemic immunity. However, intramuscular delivery, while effective for systemic protection, often fails to induce mucosal IgA, IgG, or tissue-resident memory cells critical for blocking respiratory pathogens at entry sites. Intranasal administration targets the respiratory mucosa, potentially enhancing local immunity and reducing transmission.⁴ Challenges include LNP stability, mucosal barrier penetration, and immune activation in the lung microenvironment.⁵ Vu et al.

address these by systematically comparing mRNA-LNP formulations (ALC-0315, SM-102, and MC3, with/without DOTAP) for their cargo delivery and immunogenicity in mouse models, revealing key insights into the decoupling of delivery efficiency and immune response.²

Vu et al. revealed a critical disconnect between mRNA-LNP delivery efficiency and immunogenicity in respiratory tissues. Using reporter systems in mouse models, they demonstrated that while formulations like ALC-0315 and MC3-DOTAP efficiently transfected lung epithelial/immune cells (2.95% and 0.65% of lung cells, respectively), they failed to elicit primary humoral or B cell responses even in pre-inflamed lungs with inducible bronchus-associated lymphoid tissue.² This contrasts sharply with robust immunogenicity observed after intramuscular administration. The incorporation of DOTAP, a permanent cationic lipid, increased LNP size (60–75 to ~120–125 nm) and shifted surface charge to positive, enhancing epithelial cell transfection (15.8% vs. 0.4% for ALC-0315) and modestly improving mucosal IgG in bronchoalveolar lavage fluid and nasal washes. It remained non-immunogenic as a primary vaccine. This selective enhancement suggests that cationic modifications may preferentially influence antigen trafficking rather than immune activation.⁶

The study's most promising finding involves the "prime-and-pull" vaccination strategy, where systemic priming followed by intranasal boosting enhanced both systemic and mucosal antibody responses. This approach effectively leverages pre-existing immune memory while directing it toward mucosal

compartments. The enhanced performance of DOTAP-containing formulations in this context suggests that optimized LNP properties can improve the recall of established immunity. This strategy may be particularly relevant for populations with universal prior exposure to respiratory pathogens, where booster vaccinations aim to enhance rather than establish immunity.²

Recent advances in mRNA-LNP vaccine technology have highlighted both the promise and challenges of intranasal delivery for respiratory pathogens. The work of Vu et al. underscores a key bottleneck; while standard and cationic LNPs can efficiently deliver mRNA to lung epithelial and immune cells, this does not always translate into robust mucosal immunity. Their findings, which reveal a disconnect between delivery and immune activation, emphasize the need for further innovation in LNP design and immunization strategies. However, recent studies demonstrate that these challenges can be overcome. For example, optimized LNP formulations and dosing regimens have enabled intranasal mRNA-LNP vaccines to induce strong mucosal and systemic antibody responses, and even sterilizing protection, in animal models of SARS-CoV-2 and influenza.⁷

In some cases, the immune responses and protection achieved by intranasal vaccination were comparable to those seen with intramuscular administration, provided that the LNPs were engineered for improved mucoadhesion and tissue penetration and appropriate antigen doses were used. While much of the focus has been on humoral responses, recent work also highlights the importance of T cell immunity. Intranasal mRNA-LNP vaccination can induce robust tissue-resident memory T cell responses in the lung, which are critical for sterilizing

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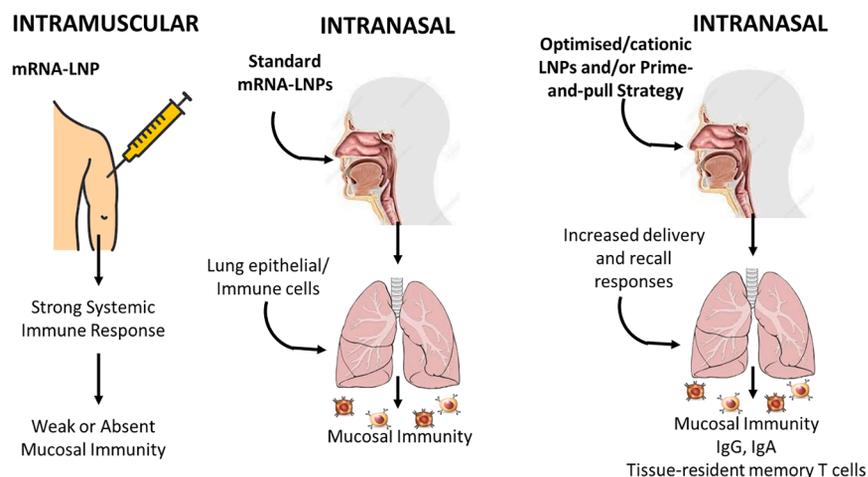


Figure 1. Schematic overview comparing intramuscular and intranasal mRNA-LNP vaccine delivery

While intramuscular administration induces strong systemic immunity but limited mucosal protection, standard intranasal LNPs efficiently deliver mRNA to the respiratory tract but fail to generate robust mucosal immunity. Optimized LNP formulations (cationic, muco-penetrating) and prime-and-pull strategies can enhance mucosal immune responses, bridging the gap between delivery and immunogenicity for effective respiratory vaccines.

immunity and long-term protection against respiratory pathogens and even mucosal cancers.⁸ Future studies should systematically assess both B and T cell responses when evaluating new intranasal mRNA vaccine candidates. Safety remains a central consideration for clinical translation. The addition of cationic lipids such as DOTAP can improve LNP delivery and immunogenicity but may also increase local inflammation. Encouragingly, preclinical studies in rodents and hamsters have shown that optimized cationic LNPs can be safe and effective at certain doses, though careful dose selection and further safety evaluation in humans are essential before broad application.^{3,9}

A recurring limitation in the field, also noted by Vu et al., is the reliance on model antigens such as ovalbumin. Recent successful studies have used pathogen-specific antigens and clinically relevant animal models, further supporting the translational potential of intranasal mRNA-LNP vaccines.⁵ Moving forward, the integration of advanced LNP designs, optimized dosing, comprehensive immune profiling, and rigorous safety testing will be critical for realizing the full potential of intranasal mRNA vaccines for respiratory and mucosal diseases.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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