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A DETAILED REVIEW ON VACCINE DELIVERY TECHNOLOGIES

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ABSTRACT

Vaccine delivery technologies have progressed from conventional needle-and-syringe administration toward advanced systems designed to improve antigen protection, intracellular delivery, immunogenicity, patient acceptability and mucosal protection. Recent developments include lipid nanoparticles (LNPs) for messenger RNA (mRNA), microneedles and microarray patches for minimally invasive skin delivery, and nanoparticle-based oral, buccal, intranasal and inhaled systems. This review evaluates recent peer-reviewed literature published from 2022 onward. Particular attention is given to formulation principles, delivery mechanisms, advantages, limitations, safety, stability and manufacturing. LNPs have become an important enabling technology for mRNA because they protect RNA and facilitate cellular uptake and intracellular release. Microneedles and microarray patches may reduce pain, sharps waste and dependence on trained personnel. Oral and intranasal systems aim to stimulate mucosal immunity at pathogen-entry sites. Despite rapid progress, stability, dose uniformity, biological barriers, scale-up and regulatory requirements remain important challenges. Future vaccine delivery will require integration of formulation science, nanotechnology, device engineering and manufacturing.

1. INTRODUCTION

One of the best preventive measures in public health is vaccination, but the effectiveness of a vaccine depends not only on the antigen but also on how it is prepared and administered. Traditional intramuscular, subcutaneous, and intradermal injections have established therapeutic paths and offer consistent dosage. Injections, however, may cause discomfort, worry about needles, the need to dispose of sharps, and a reliance on qualified staff. These restrictions have prompted the creation of needle-free and minimally invasive delivery methods.[1–2]

The importance of delivery mechanisms has been shown by the success of mRNA vaccines. Carrier systems are necessary to preserve the nucleic acid and promote cellular uptake because naked mRNA is prone to destruction and has low membrane permeability.[3–5] LNPs' composition affects stability, biodistribution, and immunological activation, and they can encapsulate mRNA and facilitate endosomal escape.[4-7,19-22]

Concurrently, alternative sites of immunization are being investigated, including the skin and mucosal surfaces. While microarray patches offer a patch-based structure, microneedles can deliver vaccine into skin layers that are high in immune cells.The goal of oral and intranasal delivery systems is to create immunity at mucosal surfaces.[8,17-18,25-27]

2. AIM

To assess how current developments in vaccine delivery technology might enhance vaccine stability, immunogenicity, safety, administration, and accessibility.

3. OBJECTIVES [1–27]

1. To examine new developments in both traditional and cutting-edge vaccination administration systems.

2. To assess how improved delivery technologies can enhance cellular absorption, immunogenicity, stability, and antigen protection.

3. To contrast oral, intranasal, and inhaled vaccine administration methods, lipid nanoparticles, microneedles, and microarray patches.

4. To determine the main benefits, restrictions, safety issues, and production difficulties related to new vaccine delivery systems.

5. To talk about future prospects for creating vaccine delivery systems that are secure, reliable, patient-friendly, and scalable.

4. METHODOLOGY[1–37]

Recent peer-reviewed journal articles published after 2022 were used to create a narrative literature review. The necessary literature-discovery source was Google Scholar, and publication data were verified by consulting journal and bibliographic records. Vaccine delivery technology, mRNA delivery, lipid nanoparticles, microneedle vaccine, microarray patch, intranasal nanoparticle vaccine, oral vaccine delivery, mucosal vaccination, and inhaled mRNA delivery were among the search concepts. A total of twenty-seven journal articles were chosen and numbered in accordance with the in-text citations.

5. CONVENTIONAL VACCINE DELIVERY

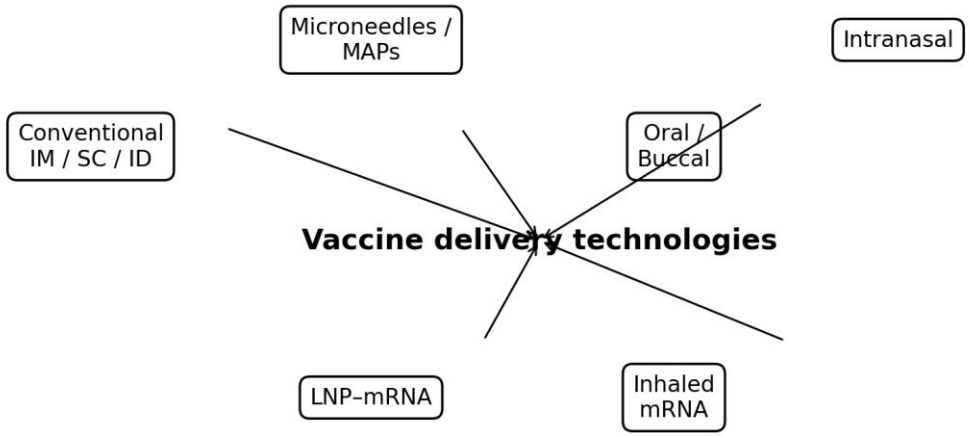


Figure 1. Overview of major vaccine delivery routes and enabling technologies.

For several vaccines, intramuscular, subcutaneous, and intradermal injection are still accepted methods. Repeatable dosing, a wealth of clinical knowledge, and well-established quality-control protocols are their key advantages. Injections, however, necessitate needles and may present challenges with regard to pain, needle phobia, disposing of sharp objects, and qualified staff.[1–3]

Because dendritic cells and other antigen-presenting cells are found in the skin, intradermal injection is especially pertinent to advanced delivery. Without using a traditional hypodermic needle, microneedles take advantage of this cellular milieu by forming minuscule passageways.[1-2,9,15]

6. NANOTECHNOLOGY-BASED VACCINE DELIVERY

Particle size, morphology, surface characteristics, payload loading, and release can all be controlled thanks to nanotechnology. Nanoparticles can enhance their interaction with biological membranes, shield antigens from deterioration, and make it easier for antigen-presenting cells to absorb them.dé[6-7] [28,32]

Lipid nanoparticles, liposomes, polymeric nanoparticles, protein-based nanoparticles, and hybrid systems are examples of significant platforms. Transport thru biological barriers and immune-cell absorption can be influenced by size, charge, hydrophilicity, stiffness, and surface properties.[6-8]

Adjuvant and carrier roles can also be combined by nanoparticles. Co-localization of antigen and immune-stimulating components may be supported by this, although more complicated formulations necessitate more manufacturing, characterisation, and regulatory requirements.[6-7]

7. mRNA VACCINE DELIVERY AND LIPID NANOPARTICLES

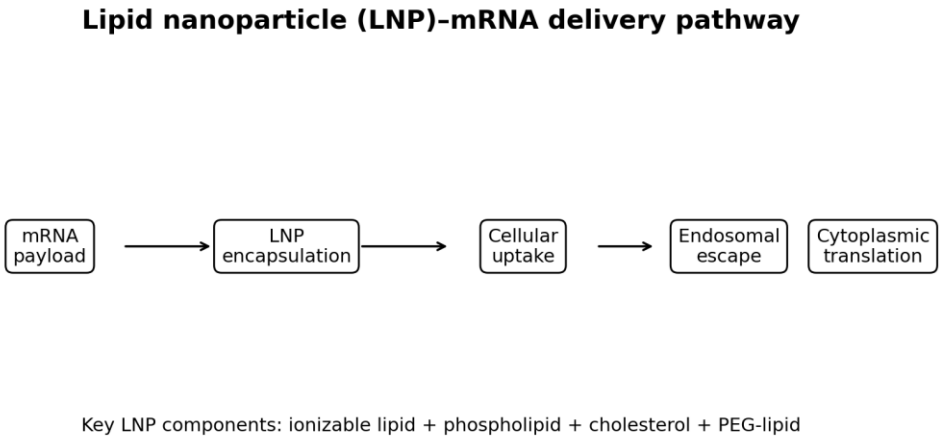


Figure 2. Simplified pathway of LNP-mediated mRNA vaccine delivery.

Because host cells generate the encoded antigen after delivery, mRNA is a desirable vaccine platform. Free mRNA, however, has poor cellular permeability and is fragile. LNPs aid in cellular absorption and intracellular release while protecting RNA.[3–5]

Ionizable lipids, helper phospholipids, cholesterol, and PEG-lipids are typically found in LNPs. For RNA complexation and endosomal escape, the ionizable lipid is especially crucial.[4–5] Particle size, encapsulation, stability, transfection, and immunological response are all influenced by composition.[4–7,19]

The components of LNPs have the ability to affect innate immune activation, making them more than just passive carriers. As a result, formulation design needs to strike a compromise between tolerable tolerability and efficient immune activation.[1–22] Although nebulization can affect particle stability, inhaled LNP-mRNA systems are also being studied for mucosal vaccination.The [23]

8. MICRONEEDLE-BASED VACCINE DELIVERY

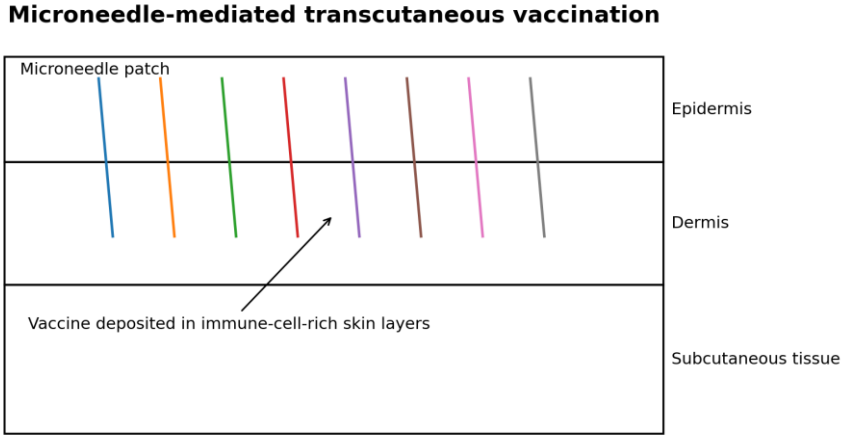


Figure 3. Schematic representation of microneedle-mediated transcutaneous vaccination.

Microscopic projections called microneedles are intended to penetrate the stratum corneum and apply vaccination to the outermost layers of the skin. Investigations have been conducted into hollow, coated, dissolving, and other designs. [1–2,9,15]

Because vaccine-containing matrices can dissolve after insertion and potentially reduce sharps waste, dissolving microneedles are especially appealing. For better distribution and storage, detachable and dissolvable designs have also been investigated.[14,16]

Microneedles offer a transcutaneous delivery method for nucleic acid vaccinations. Nevertheless, it is necessary to regulate mechanical strength, applicator performance, antigen stability, dosage uniformity, and insertion reliability. [1–2,9,15]

9. MICROARRAY PATCHES

Microneedle structures and a patch format are combined in microarray patches. Compactness, easier administration, less handling of sharp objects, and increased acceptability are possible advantages. Although immunogenicity depends on formulation, antigen, device, and research methodology, recent systematic evidence shows promising safety, usability, and acceptance.[10-11 29,36,37]

Scalable production, dose consistency, packaging, quality assurance, and regulatory assessment are necessary for mass vaccination. Because even a plain-looking patch requires consistent insertion and sufficient skin contact, applicator design is also crucial. [12–13]

10. ORAL AND BUCCAL VACCINE DELIVERY

Due to its lack of needles and potential to boost mucosal immunity, oral immunization is appealing. However, mucus, digestive enzymes, acidic pH, and other physiological barriers are encountered by vaccines. These elements may weaken antigen delivery to immune-inducing locations.[8,27]

Mucoadhesive systems and nanoparticles are being studied to enhance antigen uptake, residence time, and protection. Mucus contact and transport can be influenced by particle size, charge, hydrophilicity, and stiffness. Another mucosal route is buccal administration, which can extend residence time by using mucoadhesive formulations.[6,8,27]

11. INTRANASAL VACCINE DELIVERY

The goal of intranasal vaccination is to produce cellular and local antibody responses in the respiratory mucosa.Rapid mucociliary clearance, which can shorten the duration of antigen residency, is a significant drawback. Thus, research is being done on pathogen-mimicking carriers, mucoadhesive systems, and nanoparticles.[17-18,25-26 30–32,35]

Intranasal nanoparticle systems have shown promise in recent research for improved humoral and cellular responses as well as widespread influenza protection.Additionally, advanced assessments point to nanotechnology as a key avenue for enhancing intranasal vaccination.[17-18,26 31,32]

12. INHALED mRNA DELIVERY

Pulmonary delivery extends mucosal vaccination toward the lower respiratory tract. LNP-mRNA formulations may provide local antigen expression, but aerosol generation and nebulization can destabilize nanoparticles.[23] Charge-assisted stabilization has been investigated to improve LNP stability during inhalation and preserve delivery performance.[23,30,33]

Controlling aerosol particle size, deposition, dose repeatability, device compatibility, and patient technique are all necessary for a successful inhaled vaccination. Therefore, it is necessary to optimize both formulation and inhaler design.[33]

13. ADJUVANTS AND CO-DELIVERY

Adjuvants increase vaccine-induced immunity's strength or quality. Antigen and immune-activating components can be administered jointly thanks to nanoparticles' dual roles as transporters and potential immunostimulatory effects.[7]

Innate immune signaling and, hence, the effectiveness and acceptability of mRNA vaccines can be influenced by the composition of LNP.Sufficient immune activation without excessive inflammatory reactions is the goal of rational design. By delivering several components to the same antigen-presenting cells, co-delivery systems may enhance antigen presentation even further.[19-21]

14. COMPARATIVE EVALUATION

Different pharmacological and therapeutic needs are met by various delivery systems. While cutting-edge platforms seek to enhance convenience, targeting, mucosal protection, or nucleic acid delivery, conventional injections offer proven dependability.[1–2,4–18,19–27,29,30,34]

Conventional injection: dependable on the needle yet proven and repeatable. Although LNP-mRNA is particularly successful at delivering RNA inside cells, its stability and formulation are difficult. Microneedles are minimally invasive and can be applied topically, although control is needed for both insertion and dose consistency. Microarray patches are a convenient patch format, however scaling up production and compliance with regulations is still difficult. Oral systems can be mucosal and handy, but they are impacted by gastrointestinal obstacles. Targeting the respiratory mucosa, intranasal systems must contend with mucociliary clearance. Although it needs strong nebulization stability, inhaled LNP-mRNA shows promise for pulmonary delivery.

Platform	Route	Major advantage	Key limitation	Maturity
Conventional injection	IM/SC/ID	Proven, repeatable dosing	Pain, sharps, trained staff	Established
LNP–mRNA	Parenteral / emerging mucosal	Protects RNA; intracellular delivery	Stability, formulation, safety	Advanced
Microneedles / MAPs	Transdermal	Minimally invasive; lower sharps burden	Dose uniformity; scale-up	Translational
Oral / buccal	Mucosal	Needle-free; mucosal potential	GI/mucosal barriers	Developing
Intranasal	Respiratory mucosal	Local + systemic immunity	Mucociliary clearance	Developing
Inhaled mRNA	Pulmonary	Lower-respiratory targeting potential	Nebulization stability	Early-stage

15. ADVANTAGES

Improved cellular uptake, targeted or controlled administration, and protection of delicate antigens and nucleic acids are all possible with advanced vaccine delivery systems.[4–7] While oral and intranasal solutions can offer needle-free administration and possibly enhance mucosal immunity, microneedles and microarray patches can minimize invasive needle use and sharps handling. [1–2],[9–18],[25–27]

Lipid chemistry can be altered to affect delivery using the modular platform that LNPs offer. When production and storage needs are properly met, patch and mucosal technologies may potentially lessen reliance on skilled workers and provide greater access to vaccination. [4–7] ,[12–14], [19], [27]

16. LIMITATIONS

There are significant drawbacks to advanced delivery techniques. Control over RNA integrity, lipid composition, particle properties, storage stability, and immune activation is necessary for LNP-mRNA products.Consistent insertion, mechanical strength, dose homogeneity, packing, and dependable applicators are all necessary for microneedles and microarray patches.[1–2], [4–7], [9–16],[19–22]

Intranasal systems are impacted by mucociliary clearance, while oral systems must contend with acid, enzymes, and mucosal barriers. Nebulization and aerosolization problems are introduced by inhaled systems.The For a number of developing platforms, manufacturing scale-up, repeatability, and regulatory characterisation continue to be significant translational obstacles.[8,12-13,22-23,25-27]

17. SAFETY, STABILITY AND MANUFACTURING

The delivery system and vaccine payload must be taken into account while evaluating safety. Biological reactions and tolerability for mRNA-LNP products can be influenced by lipid content, particle characteristics, and innate immune activation.[19-22]

Because RNA can break down and nanoparticles can aggregate or alter their structure, stability is essential. Therefore, proper formulation, buffering, packaging, and storage conditions are crucial.[4–5] Additionally, during nebulization, inhaled materials must maintain stability.[23]

Particle size, composition, antigen content, sterility, and encapsulation efficiency must all be controlled throughout manufacturing. Control of mechanical characteristics, patch homogeneity, and applicator performance is also necessary for microneedle and MAP products.[12–16]

18. FUTURE PERSPECTIVES

Nanotechnology, biomaterials, immunology, and device engineering will probably all be incorporated into future vaccine delivery. Improved ionizable lipids and targeting techniques may make LNPs more programmable.[4,7,19] Improved applicators, stable formulations, and scalable manufacturing could lead to advancements in microneedle and MAP systems.[10-16]

Another important approach is mucosal vaccination. By producing protection at pathogen-entry sites, intranasal and oral systems may supplement systemic vaccination.[25-27]If dose repeatability and formulation-device compatibility are shown, inhaled mRNA systems could increase respiratory vaccination.[23]The most beneficial platform will strike a compromise between immunogenicity and user acceptability, safety, stability, affordability, manufacturing, and regulatory viability. [34,35]

19. CONCLUSION

Recent research shows that vaccine delivery systems are rapidly diversifying.[34] While microneedles and microarray patches provide promise minimally invasive substitutes for traditional injections, LNPs have made effective mRNA delivery possible. To enhance mucosal vaccination and increase the number of accessible administration routes, oral, buccal, intranasal, and inhaled systems are being developed.[1–27 29–33,36,37]

There isn't a single delivery method that works well for all vaccines. The features of the antigen, the intended immune response, the route, stability, manufacturing capacity, safety, and the clinical setting should all be taken into consideration when making a decision. Reproducible manufacturing, long-term stability, device-formulation compatibility, patient acceptability, and clinical evaluation should be given top priority in future research. [34–37]

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