Microneedle Arrays for Painless Vaccine Delivery: A Critical Review of Design, Immunological Mechanisms, And Clinical Progress

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Abstract

Conventional hypodermic needle vaccination suffers from barriers of needle phobia, sharps-waste generation, cold-chain dependence and reliance on trained personnel that together undermine global immunization equity. Microneedle arrays (MNAs) are a revolutionary intradermal delivery platform that offers painless, minimally invasive antigen deposition in the antigen-presenting-cell-rich epidermis and dermis. This review covers four canonical MNA architectures (solid, coated, dissolving, and hollow) and hydrogel-forming and hybrid designs, and discusses the fabrication materials, release mechanisms, and immunological rationale. Peer-reviewed pre-clinical and clinical studies on influenza, COVID-19, HPV, dengue, rabies and Ebola vaccines are critically assessed. Clinical data show seroprotective immune responses with MNA-based intradermal vaccination comparable or superior to IM injection at antigen doses reduced by up to 80%. Key translational barriers such as antigen stability, dose-volume limitations, regulatory complexity and aseptic manufacturing are reviewed alongside emerging solutions such as 3D-printed geometries, delivery in conjunction with iontophoresis and stimulus-responsive polymers. MNAs are a scientifically mature platform, requiring accelerated clinical validation and regulatory harmonization to make a transformative impact on global public health.

Keywords: *microneedle arrays, transdermal vaccination, intradermal immunization, dissolving microneedles, antigen-presenting cells, cold-chain-free vaccines, dose sparing*

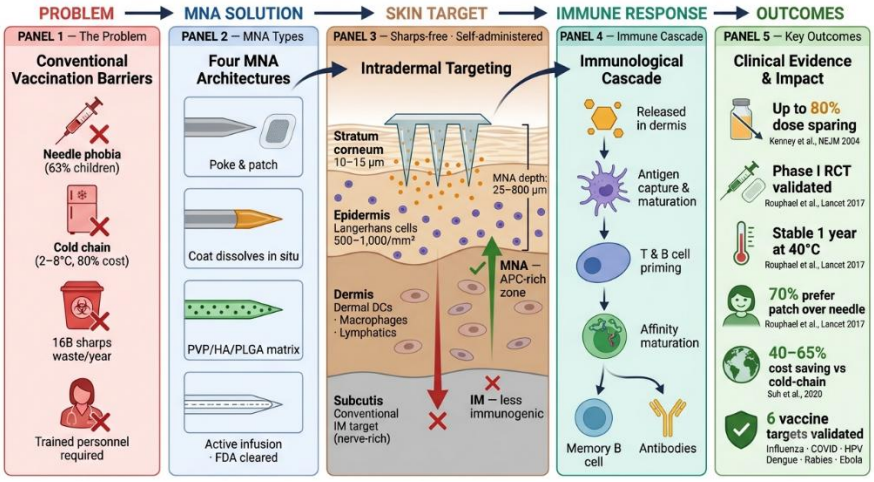

Figure 1: Graphical abstract of Microneedle Array (MNA) vaccination. MNAs

It overcome conventional injection barriers (needle phobia, cold chain, and sharps waste) through four distinct architectures (solid, coated, dissolving, and hollow). By precisely targeting the antigen-presenting cell (APC)-rich epidermal and dermal layers (25-800 micrometre), MNAs trigger a robust immune cascade—from dendritic cell activation to antibody production—offering clinical advantages such as 80% dose sparing, thermal stability (40 C), and enhanced patient preference.

Introduction

Vaccination represents the most cost-effective public health intervention in modern medicine contributing to the eradication of smallpox and near-elimination of poliomyelitis worldwide [1]. But the global vaccination infrastructure has structural problems ongoing. The use of hypodermic needle and syringe for delivering injections leads to an estimated 16 billion sharps-waste objects each year, causes needle-stick injuries to an estimated 3.5 million health-care workers annually and is associated with major needle phobia in up to 25% of adults and 63% of children [2, 3]. More than 50% of vaccines require refrigerated cold-chain logistics between 2°C and 8°C, which can account for up to 80% of the total cost of immunization programs and frequently fail in low- and middle-income country (LMIC) settings [4].

Microneedle arrays (MNAs), ordered arrays of micro-scale projections (typically 25–2,000 µm in height), overcome each of these limitations. The MNAs are capable of delivering antigens directly to the viable epidermis and upper dermis with near painless administration by penetrating the stratum corneum (SC, ~10–15 µm thick) without penetration of nerve-rich subcutaneous tissue [5]. These layers are populated with Langerhans cells (LCs) (500–1,000 cells/mm2) and interstitial dendritic cells professional antigen presenting cells (APCs), which are largely absent at conventional IM injection sites, making the skin an immunologically superior vaccine target with the ability to elicit potent immune responses at substantially lower antigen doses [6]. The conceptual basis for MNA delivery was laid in 1998 when Henry et al. [7] demonstrated that silicon microneedles could increase skin permeability by up to four orders of magnitude. The COVID-19 pandemic increased interest in the field, as the need for scalable, cold-chain independent platforms drew unprecedented scientific and industrial investment [8, 9]. By 2025, several MNA vaccine

candidates are being evaluated in phase I–II clinical trials for multiple targets and regulatory agencies are beginning to develop product-specific guidance frameworks [10]. This review provides a critical synthesis of the design principles, immunological mechanisms, clinical evidence and translational challenges for MNA, in a structured manner for pharmaceutical scientists, vaccinologists and regulatory professionals.

The Skin as an Immunological Target

The rationale of skin-targeted vaccination is based on the unique cutaneous immune architecture. Epidermal Langerhans cells constantly sample the local microenvironment through pattern recognition receptors and phagocytosis [6]. After antigen uptake, they mature, upregulate costimulatory molecules (CD80, CD86) and MHC class II, and then migrate via afferent lymphatics into the draining lymph nodes, where they prime naïve T and B lymphocytes and initiate germinal center reactions that produce long-lived plasma cells and memory B cells [11]. The dermis also harbours dermal dendritic cells, plasmacytoid dendritic cells and tissue-resident macrophages, each of which has specific immunomodulatory functions [12].

It has been shown repeatedly in comparative studies that intradermal (ID) vaccination induces seroconversion equivalent to IM administration with a dose of the antigen reduced by one-fifth to one-tenth, called dose sparing. In a landmark randomized controlled trial published in the New England Journal of Medicine, Belshe et al. showed that 40% of the standard IM hemagglutinin dose given intradermally elicited antibody responses that were non-inferior to full-dose IM injection in healthy adults aged 18–60 years, with seroprotection rates of 84–100% [13]. One-fifth the standard IM dose (3 μg versus 15 μg) given intradermally elicited HAI titer increases equivalent to or greater than those of standard IM injection. H1N1 X 15.2 (ID) versus X 14.9 (IM), H3N2 X 19.0 (ID) versus X 7.1 (IM) [14]. Meta-analyses of intradermal influenza vaccination show a consistent dose-sparing factor in study populations [15]. Moreover, the mechanical perturbation of skin caused by the insertion of MNA also triggers danger-associated molecular pathways, upregulating IL-1β and TNF-α at the site of delivery, an endogenous adjuvant effect that may enhance immunogenicity of co-delivered antigens [16].

Types and architectures of microneedle arrays

Six MNA design classes are currently recognized in the literature, each offering distinct advantages suited to specific vaccine formulations and deployment contexts. Table 1 presents a structured comparative overview of all MNA types with respect to fabrication material, delivery mechanism, thermostability, sharps-waste profile.

Table 1: Comparative Overview of Microneedle Array Architectures: Materials, Mechanisms, and Properties

MNA Type	Material(s)	Delivery Mechanism	Thermostability	Sharps Waste	Ref.

Solid	Silicon, stainless steel, polycarbonate	Poke-and-patch: passive antigen diffusion through SC micropores (50–200 μm)	Depends on secondary topical formulation	Yes — requires sharps disposal	**[17, 18]**
Coated	SS/Ti needle + CMC, trehalose, PVP surface coat	Antigen coat dissolves in interstitial fluid within seconds to minutes	Excellent in dry form; cold-chain optional	Yes — metal needle remains	**[19]**
Dissolving	PVP, PVA, HA, PLGA, sucrose, trehalose	Entire polymer tip dissolves in 5–20 min; antigen released directly in dermis	Excellent — sugar matrices enable ambient RT storage	None — fully sharps-free	**[21, 22]**
Hollow	Silicon, stainless steel, engineered polymers	Active liquid vaccine infusion via internal microchannel under applied pressure	Standard liquid formulation; cold chain typically required	Yes — metal/Si structure remains	**[10, 24]**
Hydrogel-forming	Crosslinked Gantrez® S-97, PMVE/MA copolymers	Swells in interstitial fluid; releases antigen by diffusion gradient; no polymer residue in skin	Moderate — polymer crosslink density-dependent	None — polymer dissolves in situ	**[25]**
Hybrid / Iontophoretic	Polyacrylamide/chitosan hydrogel + integrated circuit	Active iontophoretic electrical drive enhances macromolecular antigen flux across SC	Formulation-dependent	Device component retained	**[26]**

Solid Microneedles

Solid MNAs are fabricated from silicon, stainless steel or non-biodegradable polymers and operate via a 'poke-and-patch' mechanism. The array generates transient SC micropores (50–200 μm diameter) through which a separately applied topical vaccine formulation passively diffuses [17]. Solid MNAs are mechanically robust and inexpensive, but they require a secondary delivery step, introduce variability in antigen uptake, and generate biohazardous sharps waste that requires structured disposal [18]. They are primarily used as skin pretreatment devices rather than as standalone vaccination platforms.

Coated Microneedles

Coated MNAs deliver the vaccine directly to the needle surface as a thin solid film that dissolves in interstitial fluid within seconds to minutes upon insertion, releasing the antigen payload. Biocompatible excipients such as carboxymethylcellulose (CMC), trehalose and polyvinylpyrrolidone (PVP) stabilize the antigen during the drying and storage [19]. Gill and Prausnitz have reproducibly demonstrated 0.6 μg-per-tip coatings with preserved antigenicity after lyophilization [20]. The main advantage is thermostable delivery of dry antigen. The main limitation is limited total dose capacity limited by the needle-tip coating surface area.

Dissolving Microneedles

Dissolving MNAs consist of antigens encapsulated in water-soluble or biodegradable polymer matrices that completely dissolve after insertion into the skin, resulting in payload release without any sharps waste [21]. Sullivan et al. developed dissolving MNA patches from poly(vinylpyrrolidone) (PVP), a biocompatible water-soluble polymer commonly used in medicine, by encapsulating inactivated influenza vaccine for insertion and dissolution in murine skin within minutes [22]. Microneedle vaccination elicited robust antibody and cellular immune responses, conferring complete protection upon lethal challenge; moreover, microneedle vaccination was more efficient in lung viral clearance than conventional intramuscular injection [22]. PDMS micromolding fabrication allows high-throughput batch production but formulation challenges include complete dissolution within 5–20 min and maintenance of antigen integrity during casting and drying [23].

Hollow Microneedles and Emerging Designs

Hollow MNAs have internal microchannels for active infusion of liquid vaccine into the dermis, compatible with conventional formulations without reformulation. The FDA approved transdermal drug delivery with the 3M Hollow Microstructured Transdermal System (hMTS), setting a regulatory precedent [10]. However, hollow MNAs require infusion devices, are prone to the channel occlusion and cannot be used for unaided self-administration [24]. MNAs that form hydrogels are made up of lightly crosslinked polymers, which swell in situ and release encapsulated antigen by concentration-gradient diffusion, leaving no residual polymer in the skin [25]. Hybrid iontophoresis-MNA devices incorporate active electrical drive circuits to greatly improve transdermal flux of vaccine macromolecules compared to passive dissolving devices, to overcome high-molecular-weight antigen delivery limitations [26].

Fabrication materials and manufacturing

Material selection determines the mechanical integrity, biocompatibility and thermostability of MNA. Metallic MNAs have high fracture toughness but are not biodegradable and need surface passivation [17]. Deep reactive-ion etching (DRIE) can provide silicon MNAs with sub-micron dimensional fidelity, but they are brittle and prohibitively expensive at commercial scale [7]. MN polymer has been replaced for vaccine applications due to biodegradability, compatibility with antigen encapsulation, and lower unit cost [27]. Sugar-based excipients (trehalose, sucrose, sorbitol) are employed to thermostabilized labile protein and nucleic acid antigens by forming protective glassy matrices during lyophilization to restrict molecular mobility and suppress hydrolytic degradation [28]. MNA-compatible formulations with ambient temperature stability are a priority for LMIC immunization infrastructure, as defined by the WHO Prequalification Programme [4]. Terminal sterilization (gamma irradiation, autoclaving) is not compatible with biological payloads, and the unit production costs of aseptically manufactured products are significantly higher than those of conventionally sterilized drug products [23]. 3D printing based on two-photon polymerization and digital light processing has evolved as a flexible fabrication platform for rapid prototyping of custom geometries, microfluidic channels, and integrated antigen reservoirs that are not feasible with conventional PDMS molding [29].

Preclinical and clinical evidence

Influenza Vaccines

Influenza vaccination is the most clinically advanced MNA application, with hollow MNA-based ID delivery in wide clinical use in selected markets [30]. In a landmark randomized Phase I clinical trial published in The Lancet, Rouphael et al. evaluated dissolving MNA patches loaded with trivalent inactivated influenza vaccine (TIV) in 100 adult volunteers in three MNA groups and a standard IM comparator. The study showed comparable antibody responses to IM injection, high acceptability scores of 4.5–4.8 out of 5 immediately after vaccination, and 70% of MNA recipients preferred the patch over conventional injection at 28 days. At six months, no serious adverse events were reported, and the patch was stable for one year at 40°C outside of cold-chain conditions, a landmark finding for logistics-free deployment [31]. Sullivan et al. have shown in murine models that dissolution of PVP-based MNA patches containing inactivated influenza vaccine could induce strong antibody and cellular immune responses, providing full protection against lethal viral challenge and higher efficiency of lung viral clearance compared to conventional IM injection at equivalent doses [22].

COVID-19 Vaccines

The SARS-CoV-2 pandemic has accelerated the development of MNA vaccines. Kuwentrai et al. showed that dissolution of patches containing recombinant SARS-CoV-2 receptor-binding domain (RBD) generated strong neutralizing antibody responses and splenic germinal center responses in BALB/c mice at doses much lower than IM formulations [32]. In murine models, 3D-printed MNA patches delivering spike protein were reported by Caudill et al. to induce systemic IgG responses and antigen-specific $CD8^+$ T cell populations greater than conventional IM delivery [29]. Niyomnaitham et al. reported a Phase I clinical study to evaluate the safety and immunogenicity of

fractional intradermal COVID-19 vaccination with BNT162b2, ChAdOx1 and CoronaVac (17–20% of standard IM doses) in accelerated two-dose regimens (n = 60, aged 18–60 years). The study showed significant RBD-specific IgG and pseudovirus neutralizing antibody responses in all groups, and local and systemic adverse reactions were milder than conventional IM boosters, providing an early-phase proof-of-concept for fractional intradermal COVID-19 vaccination [33].

Other Vaccine Targets

MNA platforms are broadly applicable to different pathogens. A Qβ virus-like particle MNA vaccine for HPV was stable at room temperature for 6 months, with high-titer neutralizing antibodies and seroprotection comparable to IM at one-fifth the dose [36]. A chimeric dengue vaccine manufactured as a dry-coated patch for delivery by high density microarray patch maintained 100% relative potency after 6 months at 4°C [37]. Fluoropolymer-modified rabies nanovaccines delivered by dissolving MNA improved virus neutralizing antibody titers and conferred complete protection in mice for six weeks [38]. Polyphosphazene-adjuvanted MNA patches containing Ebola glycoprotein antigen elicited long-lasting IgG responses and complete lethal-challenge protection in mice at doses 10-fold lower than conventional IM formulations [39].

Challenges and translational barriers

Despite major advances, MNAs still face several interrelated translational challenges. First, dose-volume constraints restrict the total antigen that can be delivered to the microgram range for most designs, which is not enough for vaccines that need milligram-scale antigen loads per dose [23].

Second, the preservation of the antigen during the fabrication process requires validation specific to the formulation: thermal and mechanical stresses during polymer casting and drying can denature proteins or decrease mRNA encapsulation efficiency, necessitating orthogonal biophysical characterization for each antigen-polymer combination [28].

Third, inter-individual variation in the biomechanical properties of the skin (Young's modulus 0.04–0.1 MPa for the dermis), hydration state, and applied force affect insertion depth consistency, directly affecting the antigen dose deposited in viable tissue [40]. Spring-loaded applicator devices are being actively developed to standardize insertion force and velocity.

Fourth, the regulatory complexity of the combination-device classification of the antigen-loaded MNA patches, which are both a biological drug and a medical device, demands compliance with pharmaceutical GMP and device quality system regulations under separate regulatory jurisdictions simultaneously, which significantly increases approval timelines and development costs [10].

Fifth, terminal sterilization is incompatible with biological payloads, which need to be fully aseptically manufactured in ISO 5 clean room environments, significantly increasing the unit production cost and limiting the manufacturing scalability compared to conventionally sterilized drug products [23].

Emerging innovations and conclusion

The MNA field is moving in several converging directions. Stimulus-responsive polymer systems with pH-sensitive, reactive oxygen species (ROS)-responsive or enzyme-responsive matrices provide programmed antigen release in response to the physiological microenvironment of the skin, which may enable the maintenance of antigen presentation for days to weeks from a single application—reducing or even eliminating the need for booster doses [27]. Nanoparticle-MNA hybrid systems, where lipid nanoparticles or virus-like particles are encapsulated in dissolving polymer tips, have the benefit of nanoparticulate immunostimulation and precise intradermal localisation to enhance immunogenicity and formulation thermostability [41]. Pharmacoeconomic modelling indicates that MNA-based immunisation programs might be able to realise 4065% cost savings compared to cold-chain campaigns over a 10-year time horizon, due to the elimination of cold-chain infrastructure and reduced healthcare worker requirements [42]. Microneedle array technology has transitioned from proof-of-concept to a clinically validated vaccine delivery platform. Targeting the immunologically privileged skin compartment, elimination of needle pain and sharps hazard, thermostable dry formulation and potential self-administration, and the documented dose sparing of up to 80 %, MNAs, we offer a compelling, technically feasible solution to the major barriers to global vaccine equity. Dissolving and coated designs are the best profiles for cold-chain independence, self-administration and sharps-free disposal. Next steps include well-powered Phase II and Phase III randomised controlled trials demonstrating non-inferiority to licensed IM comparators, international regulatory harmonisation to enable streamlined combination-device development pathways, and standardised applicator devices to minimise inter-user variability in insertion. With the right scientific, regulatory and industrial commitment, MNA-based vaccination has the credibility and readiness to fundamentally transform the global immunisation landscape in this decade.

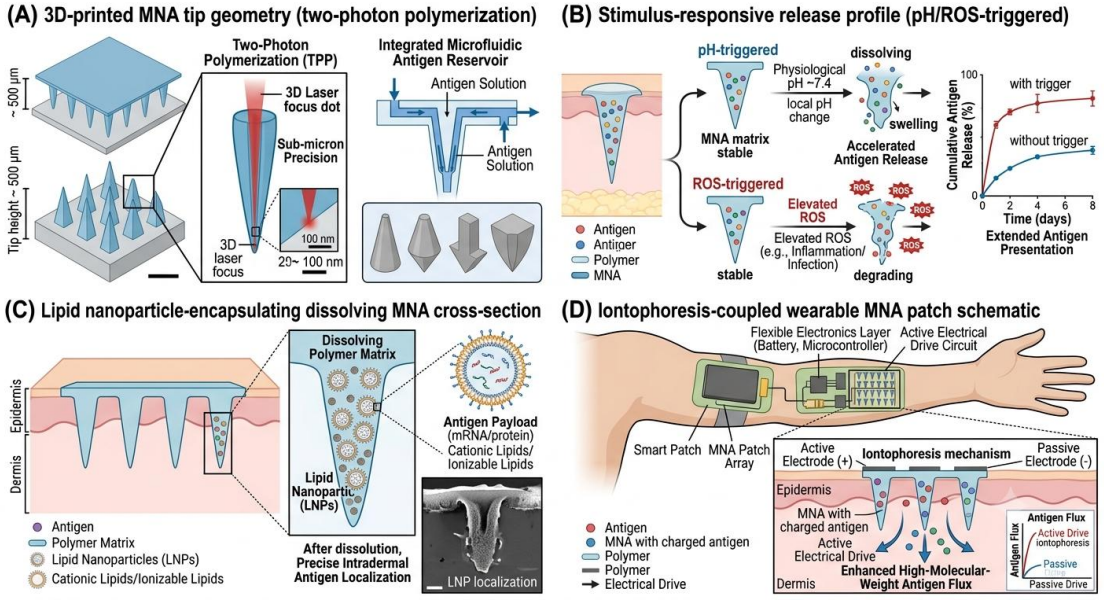

Figure 3: Emerging fabrication and delivery innovations in MNA technology.

(A) 3D-printed MNA tips fabricated via two-photon polymerization enabling sub-micron geometric precision and integrated microfluidic antigen reservoirs [29]. (B) Stimulus-responsive polymer matrix with triggered antigen release upon pH or ROS change in skin interstitial fluid, enabling extended antigen presentation [27]. (C) Cross-sectional view of lipid nanoparticle-encapsulating dissolving MNA tip combining nanoparticulate immunostimulation with precise intradermal antigen localization [41]. (D) Iontophoresis-coupled smart patch integrating MNA delivery with active electrical drive for enhanced high-molecular-weight antigen flux [26]

References

[1] World Health Organization. (2023). Immunization coverage. https://www.who.int/news-room/fact-sheets/detail/immunization-coverage

[2] Prausnitz, M. R., & Langer, R. (2008). Transdermal drug delivery. Nature Biotechnology, 26(11), 1261–1268. https://doi.org/10.1038/nbt.1504

[3] McLenon, J., & Rogers, M. A. M. (2019). The fear of needles: A systematic review and meta-analysis. Journal of Advanced Nursing, 75(1), 30–42. https://doi.org/10.1111/jan.13818

[4] World Health Organization. (2022). WHO target product profiles for vaccine presentations and containers. WHO Press.

[5] Prausnitz, M. R. (2004). Microneedles for transdermal drug delivery. Advanced Drug Delivery Reviews, 56(5), 581–587. https://doi.org/10.1016/j.addr.2003.10.023

[6] Teunissen, M. B. M., Haniffa, M., & Collin, M. P. (2012). Insight into the immunobiology of human skin and functional specialization of skin dendritic cell subsets. Current Topics in Microbiology and Immunology, 351, 25–76. https://doi.org/10.1007/82_2011_169

[7] Henry, S., McAllister, D. V., Allen, M. G., & Prausnitz, M. R. (1998). Microfabricated microneedles: A novel approach to transdermal drug delivery. Journal of Pharmaceutical Sciences, 87(8), 922–925. https://doi.org/10.1021/js980042+

[8] Kuwentrai, C., Yu, J., Rong, L., Zhang, B. Z., Hu, Y. F., Gong, H. R., Dou, Y., Huang, J. D., & Xu, C. (2021). Intradermal delivery of receptor-binding domain of SARS-CoV-2 spike protein with dissolvable microneedles. Bioengineering & Translational Medicine, 6(2), e10202. https://doi.org/10.1002/btm2.10202

[9] Chakraborty, C., Bhattacharya, M., & Lee, S.-S. (2024). Current status of microneedle array technology for therapeutic delivery: From bench to clinic. Molecular Biotechnology, 66(12), 3415–3437. https://doi.org/10.1007/s12033-023-00961-2

[10] Beyond the needle: Innovative microneedle-based transdermal vaccination. (2025). Toxics, 12(1), 4. https://doi.org/10.3390/toxics12010004

[11] Combadiere, B., & Liard, C. (2011). Transcutaneous and intradermal vaccination. Human Vaccines, 7(8), 811–827. https://doi.org/10.4161/hv.7.8.16274

[12] Clausen, B. E., & Stoitzner, P. (2015). Functional specialization of skin dendritic cell subsets in regulating T cell responses. Frontiers in Immunology, 6, 534. https://doi.org/10.3389/fimmu.2015.00534

[13] Belshe, R. B., Newman, F. K., Cannon, J., Duane, C., Treanor, J., Van Hoecke, C., Howe, B. J., & Dubin, G. (2004). Serum antibody responses after intradermal vaccination against influenza. New England Journal of Medicine, 351(22), 2286–2294. https://doi.org/10.1056/NEJMoa043555

[14] Kenney, R. T., Frech, S. A., Muenz, L. R., Villar, C. P., & Glenn, G. M. (2004). Dose sparing with intradermal injection of influenza vaccine. New England Journal of Medicine, 351(22), 2295–2301. https://doi.org/10.1056/NEJMoa043540

[15] Arnou, R., Eavis, P., Pardo, J. R., Ambrozaitis, A., Kazek, M. P., & Weber, F. (2009). Immunogenicity, large-scale safety and lot consistency of an intradermal influenza vaccine in adults aged 18–60 years. Human Vaccines, 5(10), 653–660. https://doi.org/10.4161/hv.5.10.9861

[16] Moon, S., Wang, Y., Edens, C., Gentner, J. R., Prausnitz, M. R., & Compans, R. W. (2017). Dose sparing and enhanced immunogenicity of inactivated rotavirus vaccine administered by skin vaccination using a microneedle patch. Vaccine, 35(25), 3396–3402. https://doi.org/10.1016/j.vaccine.2017.03.081

[17] Donnelly, R. F., Singh, T. R. R., & Woolfson, A. D. (2010). Microneedle-based drug delivery systems: Microfabrication, drug delivery, and clinical aspects. Drug Delivery, 17(4), 187–207. https://doi.org/10.3109/10717541003667798

[18] Birchall, J. C., Clemo, R., Anstey, A., & John, D. N. (2011). Microneedles in clinical practice: An exploratory study into the opinions of healthcare professionals and the public. Pharmaceutical Research, 28(1), 95–106. https://doi.org/10.1007/s11095-010-0101-2

[19] Gill, H. S., & Prausnitz, M. R. (2007). Coated microneedles for transdermal delivery. Journal of Controlled Release, 117(2), 227–237. https://doi.org/10.1016/j.jconrel.2006.10.017

[20] Gill, H. S., & Prausnitz, M. R. (2007). Coated microneedles for transdermal delivery. Journal of Controlled Release, 117(2), 227–237. https://doi.org/10.1016/j.jconrel.2006.10.017

[21] Microneedles: A new generation vaccine delivery system. (2021). Frontiers in Immunology, 12, 645123. https://doi.org/10.3389/fimmu.2021.645123

[22] Sullivan, S. P., Koutsonanos, D. G., Del Pilar Martin, M., Lee, J. W., Zarnitsyn, V., Choi, S.-O., Murthy, N., Compans, R. W., Skountzou, I., & Prausnitz, M. R. (2010). Dissolving polymer microneedle patches for influenza vaccination. Nature Medicine, 16(8), 915–920. https://doi.org/10.1038/nm.2182

[23] Peek, L. J., Middaugh, C. R., & Berkland, C. (2008). Nanotechnology in vaccine delivery. Advanced Drug Delivery Reviews, 60(8), 915–928. https://doi.org/10.1016/j.addr.2007.05.017

[24] Prausnitz, M. R., Mikszta, J. A., Cormier, M., & Andrianov, A. K. (2009). Microneedle-based vaccines. Current Topics in Microbiology and Immunology, 333, 369–393. https://doi.org/10.1007/978-3-540-92165-3_18

[25] Donnelly, R. F., Singh, T. R. R., Garland, M. J., Migalska, K., Majithiya, R., McCrudden, C. M., Kole, P. L., Mahmood, T. M. T., McCarthy, H. O., & Woolfson, A. D. (2012). Hydrogel-forming microneedle arrays for enhanced transdermal drug delivery. Advanced Functional Materials, 22(23), 4879–4890. https://doi.org/10.1002/adfm.201200864

[26] Zheng, Y., Ye, R., Gong, X., Wang, J., Xing, H., & Ding, J. (2023). Iontophoresis-driven microneedle patch for the active transdermal delivery of vaccine macromolecules. Microsystems & Nanoengineering, 9, 35. https://doi.org/10.1038/s41378-023-00515-1

[27] Nguyen, T. T., Oh, Y., Kim, Y., Shin, Y., Baek, S. K., & Park, J. H. (2021). Progress in microneedle array patch (MAP) for vaccine delivery. Human Vaccines & Immunotherapeutics, 17(1), 316–327. https://doi.org/10.1080/21645515.2020.1767067

[28] Mistilis, M. J., Joyce, J. C., Bhowmick, S., Clements, J. D., & Compans, R. W. (2017). Long-term stability of influenza vaccine in a dissolving microneedle patch. Drug Delivery and Translational Research, 7(2), 195–205. https://doi.org/10.1007/s13346-016-0282-2

[29] Caudill, C., Perry, J. L., Iliadis, K., Tessier, A. G., Tian, S., Winstead, C. J., Valley, H., Wang, L., Bachelder, E. M., Ainslie, K. M., & DeSimone, J. M. (2021). Transdermal vaccination via 3D-printed microneedles induces potent humoral and cellular immunity. Proceedings of the National Academy of Sciences, 118(39), e2102595118. https://doi.org/10.1073/pnas.2102595118

[30] Prausnitz, M. R. (2012). Engineering microneedle patches for vaccination and drug delivery to skin. Annual Review of Chemical and Biomolecular Engineering, 3, 311–339. https://doi.org/10.1146/annurev-chembioeng-061010-114202

[31] Rouphael, N. G., Paine, M., Mosley, R., Henry, S., McAllister, D. V., Kalluri, H., Pewin, W., Frew, P. M., Yu, T., Thornburg, N. J., Kabbani, S., Lai, L., Vassilieva, E. V., Skountzou, I., Compans, R. W., Mulligan, M. J., & Prausnitz, M. R. (2017). The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered by microneedle patch (TIV-MNP 2015): A randomised, partly blinded, placebo-controlled, phase 1 trial. The Lancet, 390(10095), 649–658. https://doi.org/10.1016/S0140-6736(17)30575-5

[32] Kuwentrai, C., Yu, J., Rong, L., Zhang, B. Z., Hu, Y. F., Gong, H. R., Dou, Y., Huang, J. D., & Xu, C. (2021). Intradermal delivery of receptor-binding domain of SARS-CoV-2 spike protein with dissolvable microneedles. Bioengineering & Translational Medicine, 6(2), e10202. https://doi.org/10.1002/btm2.10202

[33] Niyomnaitham, S., Atakulreka, S., Wongprompitak, P., Copeland, K. K., Toh, Z. Q., Licciardi, P. V., Srisutthisamphan, K., Jansarikit, L., & Chokephaibulkit, K. (2023). Immunogenicity and reactogenicity of accelerated regimens of fractional intradermal COVID-19 vaccinations. Frontiers in Immunology, 13, 1080791. https://doi.org/10.3389/fimmu.2022.1080791

[36] Ray, S., Mehta, S., Bhattacharjee, B., Ghosh, S., & Banerjee, R. (2022). Qβ virus-like particle microneedle vaccine for HPV. Vaccines, 10(8), 1220. https://doi.org/10.3390/vaccines10081220

[37] Choo, J. J. Y., Rudd, P. A., Frazer, I. H., Fernando, G. J. P., & Hickling, J. K. (2021). Dry-coated chimeric dengue virus vaccine on high-density microarray patches. npj Vaccines, 6(1), 128. https://doi.org/10.1038/s41541-021-00387-2

[38] Deng, L., Li, W., Zhang, Y., & Li, H. (2023). Fluoropolymer-modified nanovaccines delivered via microneedle for rabies prophylaxis. ACS Nano, 17(4), 3405–3418. https://doi.org/10.1021/acsnano.2c09856

[39] Romanyuk, A. V., Sharma, S., Ambike, S. S., Bhowmick, S., Broderick, K. E., & Prausnitz, M. R. (2023). Polyphosphazene-adjuvanted Ebola virus glycoprotein MNA vaccine. Journal of Controlled Release, 356, 130–140. https://doi.org/10.1016/j.jconrel.2023.02.040

[40] Agrawal, A., Bhatt, D. L., & Prausnitz, M. R. (2021). Microneedle insertion depth variability: Sources and mitigation strategies. Journal of Controlled Release, 333, 247–263. https://doi.org/10.1016/j.jconrel.2021.03.040

[41] Liu, J., Shi, M., & Abbas, M. (2025). Microneedle delivery systems for vaccines and immunotherapy. Smart Molecules, 3(2), e12057. https://doi.org/10.1002/smo.12057

[42] Suh, H., Shin, J., & Kim, Y. C. (2020). Microneedle patches for vaccine delivery. Clinical and Experimental Vaccine Research, 9(2), 115–123. https://doi.org/10.7774/cevr.2020.9.2.115