REVIEW ARTICLE

Microneedle Patches for Pediatric Vaccination: Technology, Immunogenic Advantages, Clinical Evidence, and Future Implementation

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Abstract

Microneedle patches (MNPs) represent a disruptive new modality for pediatric vaccination that overcomes some of the most enduring barriers to needle-based immunization, such as pain, fear of needles, logistical challenges, and dependence on cold-chain transportation. Though current subcutaneous and intramuscular injections are effective, global disparities in vaccine coverage-apparently exacerbated by vaccine hesitancy, infrastructural impediments, and attrition associated with multiple-dose regimens-point to a need for new delivery platforms. MNPs enable antigen deposition in the immunologically rich epidermal and dermal layers, affording superior immunogenicity, dose sparing, and improved thermostability compared to conventional vaccine formulations. This review summarizes current evidence on microneedle design, pediatric-appropriate formulation considerations, and the immunological advantages of skin-targeted delivery. Early clinical data, including measles–rubella trials in infants, demonstrate favorable safety profiles and robust seroconversion rates comparable to injections, while preclinical studies highlight compatibility with multivalent and fractional-dose strategies. Manufacturing challenges, regulatory considerations, and ethical implications are discussed with an emphasis on pediatric-specific needs. Collectively, available data support MNPs as a promising modality for expanding global childhood immunization, particularly in low- and middle-income settings. Further large-scale pediatric trials and cost-effective industrial scale-up remain essential to accelerate their integration into routine immunization programs.

Key words: Microneedle patches, Pediatric vaccination, Transdermal delivery, Immunogenicity, Vaccine hesitancy, Dose sparing

INTRODUCTION

Vaccinations have drastically changed the health of children: Smallpox, polio and measles are now eradicated or well-controlled by massive vaccinations.[1] Vaccines prevent millions of deaths each year in children, during 2000–2023, an estimated 60.3 million measles deaths were averted by vaccination. During COVID-19 pandemic, vaccination of measles-containing vaccine had declined to 81%, the lowest level since 2008, leading to outbreaks among susceptible populations.[2] Although conventional subcutaneous (SC) or intramuscular (IM) delivery is efficient, it is challenged by pain, fear of needle injection and logistics demanded in both adult and pediatric settings, such as needle phobia in up to 20–30% of pediatric populations, causing hesitancy and refusal.[3] These issues are particularly more prevalent in low- and middle-income countries (LMICs) where cold chain infrastructure and appropriately trained staff are limited, resulting in vaccine wastage and inequitable access.[4]

Microneedle patches (MNPs) offer a promising alternative, as they consist of an array of needles at the micron scale, with patterns designed to deliver antigens across the stratum corneum into the viable epidermis or dermis, avoiding pain

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Received: 30-11-2025
Revised: 02-02-2026
Accepted: 12-02-2026

receptors at lower depths (Figure 1). Developed since the 1990s, MNPs offer painless administration, thermostability, dose-sparing potential, and ease of use by non-professionals, which may improve compliance in young children.[5].

This review examines the evidence for MNPs in pediatric vaccine delivery, drawing on studies from PubMed, Scopus, and Web of Science. It highlights the immunological advantages of skin-targeted delivery, the limited but existing clinical evidence in pediatrics, and the barriers to adopting this method. In addition, it discusses the future potential of MNPs to promote equitable global vaccination. Focusing on these areas, MNPs could significantly transform pediatric vaccination practices, supporting the World Health Organization's (WHO) goals for disease eradication.

NEED FOR ALTERNATIVE PEDIATRIC VACCINATION METHODS

A variety of factors influence the effectiveness and reach of pediatric immunization programs. One of the most common problems is acute anxiety or avoidance, which is considered one of the hallmark symptoms of needle phobia. Empirical evidence suggests that approximately 24% of parents report that their children fear injections, which is a significant factor contributing to overall resistance to influenza vaccination.[6] In Bologna, Italy, a cross-sectional survey of 169 parents found that 72.2% were initially hesitant to vaccinate their children against influenza. However, after being informed about non-injectable alternatives, more than 40.2% of these parents changed their decisions. This remarkable change thus highlights the need to address needle fear.[3]

Resistance due to needle phobia significantly impacts influenza vaccine uptake and increases the cost of vaccinations within urban and rural areas. International surveys report that 10–20% of caregivers delay repeated vaccinations due to discomfort with needle shots, indicating that this problem is not limited to a single website or geographic area. Logistical challenges with vaccine distribution and storage also exacerbate these issues, especially in poorer countries. These challenges include sterilizing the needles and retaining the bloodless chain between 2°C and 8°C.[6,7] When those necessities are not met, the overall effectiveness of vaccination applications is decreased, resulting in huge vaccine wastage ranging from 20% to 50%.[7] Achieving good enough vaccination coverage in the pediatric population is hard due to the logistically demanding situations and the use of multidose regimens. High charges of incomplete multidose regimens are connected to different factors, including limited access to fitness offerings, having more than one sibling requiring vaccination, and socioeconomic disparities. For example, completion charges may be as low as 70% in a few cases for sicknesses, together with hepatitis B, which requires multiple doses for full protection.[8]

The difficulty with pediatric vaccinations is compounded when children have weakened immune systems or chronic illnesses. Cultural and spiritual issues are also a barrier to adoption in some groups.[9] The COVID-19 pandemic has highlighted these issues as significant obstacles to vaccination, due to barriers in access and the spread of misinformation. This scenario outlines the need for developing pediatric vaccination strategies that can achieve large vaccination coverage and protection against preventable infections. Traditional vaccination techniques, despite their proven effectiveness, are complemented by new vaccination strategies, including nasal or oral vaccination, which are emerging as promising solutions to certain current challenges.[10] MNPs are a straightforward approach to such adversities, as they are reliable, minimally invasive platforms that do not cause pain and reduce logistical difficulties. MNP can enhance vaccination 15–25% in areas where vaccination hesitancy is not uncommon.[11] Moreover, MNPs could be applied more frequently in pediatric vaccination bundles, as studies have shown that parents prefer painless vaccination options for their children.[12]

OVERVIEW OF MICRONEEDLE TECHNOLOGY

Microneedle technology uses needle clusters, typically from 25 to 2,000 micrometers in length, to deliver drugs or vaccines through the outer layer of the skin.[5] In response to the limitations of transdermal delivery, advances in microfabrication in the 1970s led to the development of MNPs, which provided access to immunologically rich dermis without needles. During vaccination, MNPs promote immune responses, eliminate sharp debris, and reduce biohazard risk by depositing antigen directly into dense layers of antigen-presenting cells (APCs).[5,13] Because patches can be applied like bandages, the payload can be dissolved or released slowly, and they can be self-administered, their adaptability makes them suitable for mass vaccination.[14] Preclinical models of microneedles show thermal stability, with some formulations retaining more than 90% of their potency for several weeks at 40°C, unlike conventional vaccines, which are brittle.[15] MNPs have demonstrated dose-saving effects, requiring up to 10 times less antigen in influenza, measles, and human papillomavirus vaccines, thanks to their effective targeting of the skin. Although they are still in their early stages, human trials have confirmed safety and immunogenicity similar to injections.[16]

MNPs promise fewer injuries for pediatrics, as evidenced by animal studies showing lower inflammation and higher antibody titers in pediatric models. Customization to MNPs can be improved by integration with three-dimensional (3D) printing, enabling pediatric-friendly designs.[17] Scalability and cost remain obstacles, despite the potential, but continued advancements make MNPs a game-changing tool for universal immunization.[18]

TYPES OF MICRONEEDLES

Microneedles are classified according to their design and purpose, each of which is appropriate for a particular vaccination need, especially in pediatrics, where the least amount of invasiveness is crucial (Table 1).[19] Solid microneedles, which are made out of silicon, metal, or polymers, make micropores that can be used for topical administration (poke-and-patch) or direct poking to make the skin more permeable. They are less complicated because they don't require antigen encapsulation, but their pediatric viability may be limited by the number of steps involved in the formulation and manufacturing process.[20]

Micro needle vaccine formulations are sprayed or dip-coated onto a base substrate (like stainless steel) to create coated microneedles. Antigens are delivered by coatings that dissolve quickly after insertion; this type is effective for labile vaccines but struggles to consistently coat pediatric doses.[21]

Antigens are encapsulated within the needle matrix of dissolving microneedles, which are composed of biocompatible polymers such as hyaluronic acid or polyvinyl alcohol. The needle matrix disintegrates after insertion, allowing for controlled release without sharp removal.[22] They proved effective in measles-rubella patches and fully dissolved in minutes, making them perfect for single-dose pediatric application.[23]

Using cross-linked polymers like poly(methacrylic acid), hydrogel-forming microneedles expand when hydrated, creating a depot for prolonged release. Due to their adjustable release kinetics, they are promising for multidose pediatric schedules and enable reversible insertion, minimizing residue.[24]

Vaccine stability and ease of administration are key factors in vaccine selection. For pediatric vaccinations, dissolving and hydrogel types are most common due to their self-contained delivery and painless administration.[25]

FORMULATION CONSIDERATIONS FOR PEDIATRIC VACCINES

Antigen stability, biocompatibility, and pediatric-specific factors such as a smaller skin area and an immature immune system must be considered when developing vaccines for MNPs.[30] Excipients, such as sugars (trehalose) or polymers, stabilize structures and maintain more than 80% activity after lyophilization. As vaccines are proteins or live-attenuated virus, and are prone to denaturation during fabrication. Antigen loading for dissolving MNPs is achieved through micromolding, ensuring uniform distribution to prevent dose variability in children.[31] Sterilisation is important, and ethylene oxide or gamma irradiation is preferred over heat, which can affect live vaccinations. Compatibility with skin pH (4.5–5.5) enables the prevention of inflammation, and hypoallergenic materials are prioritized in pediatric formulations to minimise rare sensitivities.[32] Rotavirus and poliovirus models in rats have proven the importance of dose modification. MNPs reduce antigen requirements while preserving immunogenicity by allowing fractional dosing (e.g., 1/4 of the standard dose for polio).[33]

Viscosity optimization and cold chain independence, where thermostable formulations preserve potency at room temperature, assist reduce shear forces in the course of molding. In pediatric trials, age-suitable volumes are prioritized, and needle lengths of 500–700 µm are best for penetrating infant skin. All matters taken into consideration, these elements growth the viability of MNP for everyday formative years immunizations.[23]

IMMUNOLOGICAL BASIS OF MICRONEEDLE VACCINATION IN CHILDREN

Langerhans cells and dendritic cells are powerful APCs that trigger T- and B-cell responses. A strong B-cell and T-cell response is produced against the antigen, outperforming muscle-based uptake in the dermis and epidermis of the skin during IM delivery.[34] To protect pediatric mucosa from respiratory pathogens, MNPs target this layer, promoting cross-presentation and a balanced Th1/Th2 immunity.[35]

Increased circulating T follicular helper cells (cTFH: CD4+ CXCR5+ CXCR3+ ICOS+ PD-1+) following influenza MNP vaccination, up to 2 times higher than IM routes, show that intradermal delivery through MNPs enhances germinal center formation in children, whose immune systems are still developing.[36] This enhances neuraminidase inhibition and antibody avidity, both of which are crucial for broad protection. MNPs cause protective measles titers equal to full doses in preclinical pediatric models (such as juvenile rhesus macaques), with lower viral loads after challenge.[23]

Mechanisms involve the release of cytokines (interleukin-2 interferon-gamma) and the activation of monocytes (CD14+ CD16+), which fosters the development of memory B cells and long-term humoral responses. For children, this translates to dose-sparing, minimizing reactogenicity while boosting herd immunity.[37]

CURRENT EVIDENCE IN PEDIATRICS

Preclinical and early-phase trials are the primary sources of evidence supporting the use of MNPs in pediatric vaccination;

Table 1: Types of microneedles, materials, key characteristics, pediatric relevance

Type	Materials	Key characteristics	Pediatric relevance	References
Solid	Silicon, metals, polymers	Poke-and-patch; no encapsulation; reusable	Reduces initial pain but requires follow-up application; suitable for quick pre-treatment in clinics.	[26]
Coated	Stainless steel, gold	Surface-coated antigen; rapid dissolution	Fast delivery minimizes distress; challenges in dose uniformity for small children.	[27]
Dissolving	PVA, PLGA, hyaluronic acid	Encapsulated antigen; full dissolution	Self-contained and painless, ideal for home use, it enhances compliance in fearful children.	[28]
Hydrogel-forming	Poly (methacrylic acid)	Swells to form depot; sustained release	Low residue risk, gentle for sensitive infant skin.	[29]

PVA: Polyvinyl alcohol, PLGA: Polyglycolic lactic acid

Table 2: Summary of clinical trials using microneedle patches in children

Trial/Study	Vaccine	Population (*n*, Age)	Design	Key safety findings	Key efficacy/ Immunogenicity	References
Gambia phase 1/2	Measles-Rubella	Infants/Toddlers (240, 9–18 months)	RCT, double-blind	Mild induration (65–77%), discoloration (58-95%); no SAEs	93% measles, 100% rubella seroconversion; comparable to SC	[23]
Parental acceptability	General	Parents of children (32, N/A)	Qualitative focus groups	N/A (perceived)	High acceptance for pain reduction; barriers: unfamiliarity	[12]
Influenza phase 1 subset	Influenza	Adults (22, 18–49 year; extensible to peds)	RCT	Mild local reactions	Higher NAI titers, cTFH activation versus IM	[36]
Polio-rotavirus	Polio-Rotavirus	Rats (N/A)	Preclinical	No interference	Quarter-dose neutralizing Abs equivalent to full	[39]

*Preclinical but relevant for pediatric formulation. RCT: Randomized controlled trial, SAE: Serious adverse event, SC: Subcutaneous, IM: Intramuscular, NAI: Neuraminidase inhibition, cTFH: Circulating T follicular helper cells

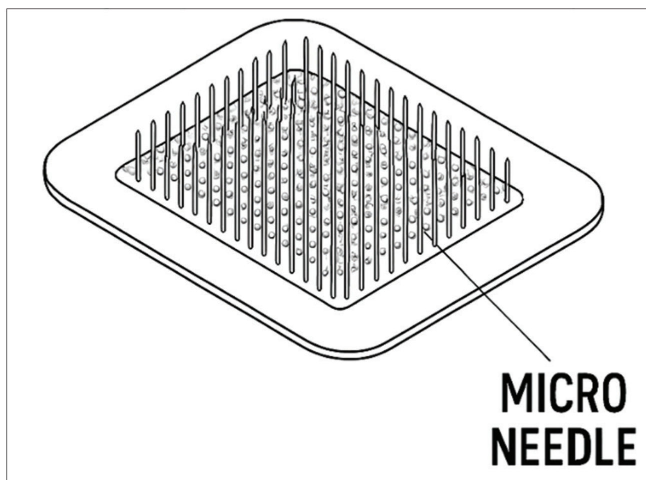

Figure 1: Schematic representation of a microneedle patch

however, due to logistical and ethical limitations, there is a limited amount of large-scale data available (Table 2).[38] A Phase 1/2 trial of a measles-rubella MNP in The Gambia (*n* = 240, ages 9–18 months) showed mild local reactions (induration in 65–77%, discoloration in 58–95%) but no serious adverse events, similar to those linked to SC injection.[23] Strong immunogenicity was demonstrated by 93% seroconversion for measles and 100% for rubella in infants using MNP, which matched SC rates.[23]

Parental acceptability is high; a qualitative study of 32 Irish parents revealed excitement about reduced discomfort and convenience, but concerns about unfamiliarity and delivery confirmation persisted, although these were mitigated by medical support.[12] A rat model of inactivated polio-rotavirus MNP demonstrated no interference with other vaccines; quarter-doses produced complete neutralizing antibodies, indicating pediatric dose-sparing. Due to their similar skin immunology, children can also benefit from the superior cellular responses (such as increased cTFH) shown in adult influenza MNP trials.[36,39]

Seven months after MNP, therapeutic data from non-human primates demonstrate protective titers against a measles challenge, with no viral shedding.[23] There are a few pediatric-specific trials; one small study found immune responses in kids, but there are not many specifics. More randomised controlled trials in various pediatric cohorts are crucial, but overall, MNPs show promise in terms of safety and efficacy.[40,41]

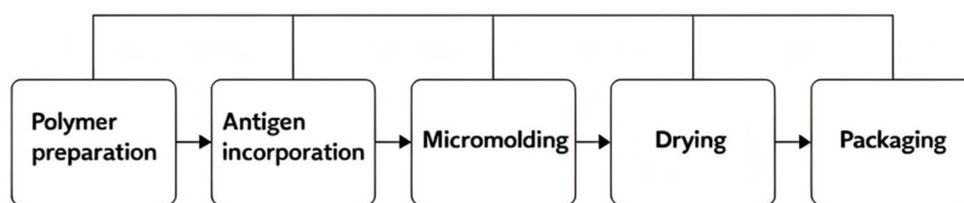

Figure 2: Microneedle manufacturing workflow

MANUFACTURING CHALLENGES AND STABILITY ISSUES

MNPs are synthesised through micromolding, coating, or 3D printing; however, there are particular challenges in scaling up those approaches for pediatric vaccines (Figure 2). Antigen loading variability, which can result from complex techniques like injection molding, can affect steady pediatric dosing.[42] Prioritizing hypoallergenic ingredients in pediatric formulations reduces the possibility of uncommon sensitivities while ensuring skin pH compatibility (4.5–5.5), which in turn helps reduce inflammation.[42] Rotavirus and poliovirus rat models demonstrate the importance of dose adjustment; fractional dosing (e.g., 1/4th for polio) enables MNPs to reduce antigen requirements without compromising immunogenicity.[43] Viscosity optimization and cold chain freedom minimise shear forces through casting, while thermostable formulations maintain strength at room temperature. Age-appropriate volume is the primary characteristic of pediatric tests, and the appropriate needle length to puncture a child's skin is between 0.5 and 0.7 mm. Taken together, these elements improve the feasibility of MNP for daily vaccination in the early years.[42,43]

Humidity management remains important throughout the garage, but trehalose buffers help prevent aggregation caused by polymer-antigen interactions.[43] Pediatric expenses increase by 20–30% due to the use of child-resistant packaging. Advances in polymer blends are improving stability and reducing production costs, despite ongoing challenges, including waste reduction and the need for regulatory-compliant sterile environments.[42]

Once these issues are resolved, it will become significantly easier to incorporate MNP into the routine vaccination program.

REGULATORY AND ETHICAL CONSIDERATIONS

MNP's guidelines are under development. They are now classified as combination products (device plus biologic) in accordance with Food and Drug Administration (FDA) and European Medicines Agency regulations.[44] The FDA's 2020 guidance on microneedling emphasizes the importance of conducting research on IM comparators for vaccines, as well as testing for biocompatibility, sterility, and overall performance.[45] Pediatric-specific guidelines recommend age-adjusted trials and pharmacokinetic studies, focusing on endpoints such as seroprotection rates. The WHO emphasizes user-friendliness and thermostability, particularly in LMICs, to promote global access through prequalification.[46,47]

Due to the need for parental consent and using children in fact series, pediatric trials present critical ethical consent issues. MNPs, being a newer and advance technological product of large companies that mainly aim to get profits, may also exacerbate disparities; therefore, ensuring equitable access is crucial.[48] To avoid coercion, open verbal exchange has to be part of moral vaccination practices. Individual rights and cultural variations need to be reputable in mandatory programs. Strict oversight is necessary to ensure compliance with ethical requirements.[44]

CLINICAL POTENTIAL AND FUTURE DIRECTIONS

MNPs display promise for medical use due to their accessibility and affordability. According to modeling, the cost of each measles case prevented via MNP is $1.66, whereas injections at 95% coverage cost $ 2.64, often due to logistical issues. By increasing pediatric coverage by 20%, they may make a sizable contribution to the eradication of polio and measles.[49] Multivalent patches, such as a 5-in-1 patch for regular vaccinations, and the combination of virtual fitness tools to display adherence, are examples of future developments.[44] Thermostable formulations, combined with mRNA and DNA vaccines, administered through MNPs, can offer fast responses throughout pandemics. Large-scale trials are crucial, particularly in LMICs.[38] Personalized pediatric dosing can be made viable by means of combining MNPs with wearable technology. With today's advances and ongoing innovation, MNPs may transform modern vaccination.[50]

CONCLUSION

The microneedle patch is a promising development for pediatric vaccine delivery, offering a practical, painless, and immunologically potent alternative to traditional injection methods for vaccine administration. MNPs achieve high-level humoral and cellular immune responses, dose-saving

advantages, and good parental acceptability by consistently targeting the skin's dense network of APCs. These attributes address some of the most important challenges in increasing childhood vaccination rates directly. Preclinical data support their development in polyvalent and thermostable formats. Early clinical successes, particularly with the measles-rubella patch, demonstrate its safety and efficacy in infants and young children. Despite manufacturing standardization, cost reduction, and regulatory approval still being outstanding, rapid advances in polymer engineering, 3D microfabrication, and thermostable antigen immobilization are gradually making production feasible. Their widespread global use will be based on ethics, including appropriate access and culturally sensitive distribution. MNPs may well revolutionize routine childhood vaccinations and reduce reliance on cold-chain logistics for vaccines, supporting vaccine-preventable disease elimination initiatives as ongoing research and larger pediatric studies progress. If development continues, these patches can be a significant part of the future of pediatric vaccination.

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Source of Support: Nil. **Conflicts of Interest:** None declared.