Dissolving Microneedle Patches Match Injected Flu Vaccines While Enabling Self-Administration Without a Cold Chain

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Abstract

Seasonal influenza remains, year after year, a stubbornly persistent burden on global health systems, driving an estimated one billion infections and up to 650,000 respiratory deaths annually while straining economies through healthcare utilization and lost workplace productivity. Annual vaccination is still our best defense, yet the syringe-and-needle model that has dominated influenza immunization for decades carries costs of its own: needle phobia, occupational injury, a fragile cold chain, and a manufacturing pipeline that struggles to keep pace with a mutating virus. Microneedle (MN) array technology offers what may be the most credible alternative yet: patches, barely visible to the eye, that pierce only the outer skin layers, engage a dense network of Langerhans cells and dermal dendritic cells, and in doing so elicit immune responses that rival or exceed intramuscular injection at a fraction of the antigen dose. This review synthesizes evidence across immunological mechanisms, biomaterial engineering, clinical trial outcomes, and manufacturing science to characterize where the field currently stands and, more importantly, where the persistent "lab-to-clinic gap" remains unresolved. Dissolving microneedles emerge as the most clinically mature platform, offering dose-sparing, ambient thermostability, and needle-free self-administration validated across several Phase I/II trials. Yet no influenza microneedle patch has reached commercial licensure, a fact that reflects unresolved engineering, sterilization, and regulatory hurdles rather than scientific failure. We argue that closing this gap will require coordinated progress in current Good Manufacturing Practice scale-up, aseptic processing, and combination-product regulatory science, rather than further proof-of-concept studies alone.

Keywords

Microneedle vaccination; Seasonal influenza vaccine; Dissolving microneedle patches; Transdermal immunization; Skin-resident immune cells; Vaccine manufacturing scale-up; Lab-to-clinic translation

1. Introduction

Every winter, more or less on schedule, influenza arrives again. It is easy to become numb to the statistics after a while, yet they remain genuinely staggering: roughly one billion infections, three to five million cases of severe illness, and somewhere between 290,000 and 650,000 respiratory deaths worldwide each year (Jacoby et al., 2015; Taaffe et al., 2024; Mudaly et al., 2026). The economic shadow cast by these epidemics is nearly as

Significance | Microneedle patches could replace injectable influenza vaccines, eliminate cold-chain dependence and needle-related barriers while enable equitable, self-administered global immunization.

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consequential as the clinical one, with healthcare utilization and lost productivity together generating costs in the tens of billions of dollars annually (Jacoby et al., 2015; Mudaly et al., 2026). Annual vaccination remains, by a wide margin, the most effective tool available for blunting this recurring wave, yet the way that tool is delivered has changed remarkably little in the better part of a century (Tian et al., 2022; Goldin et al., 2025).

Licensed seasonal influenza vaccines are still administered almost exclusively by intramuscular or subcutaneous injection using a conventional hypodermic needle and syringe (Tian et al., 2022; Nguyen, 2025). This approach works, in the narrow sense that it reliably induces protective serum immunoglobulin G titers, but it drags along a set of well-documented drawbacks that quietly erode both individual compliance and global equity (Jacoby et al., 2015; Nguyen, 2025). Needle phobia, or trypanophobia, is not a marginal concern; it affects an estimated 20% to 50% of adolescents and young adults and is one of the more underappreciated drivers of vaccine hesitancy across otherwise willing populations (Jacoby et al., 2015; Nguyen, 2025; Adediran et al., 2025). On the provider side, the picture is not much better. Needlestick injuries have been reported by up to 56% of healthcare personnel at some point in their careers, carrying with them a real risk of bloodborne pathogen transmission, including Hepatitis B, Hepatitis C, and HIV, whenever needles are reused or sharps waste is mishandled (Raut et al., 2025; Nguyen, 2025). And because parenteral administration still requires trained personnel operating within a functioning clinical infrastructure, immunization throughput inevitably bottlenecks during seasonal peaks and pandemic emergencies, particularly in remote or resource-constrained settings (Jacoby et al., 2015; Nguyen, 2025).

Beyond the point of injection, logistics present their own quiet crisis. Conventional liquid influenza formulations are thermolabile, meaning the entire supply chain, from manufacturing floor to the patient's arm, depends on an unbroken cold chain held between 2 °C and 8 °C (Tian et al., 2022; Raut et al., 2025; Nguyen, 2025). Maintaining that temperature-controlled infrastructure costs an estimated $200 million to $300 million globally each year, and when it fails, as it often does in low- and middle-income countries, up to half of the affected vaccine stock can be lost to wastage (Nguyen, 2025). Manufacturing adds a further layer of fragility: the egg-based production process that still generates most seasonal influenza vaccine doses takes six to eight months from strain selection to release and is vulnerable to egg-adaptive mutations in the hemagglutinin protein, mutations that can subtly shift viral antigenicity and undercut real-world effectiveness whenever a strain mismatch occurs (Taaffe et al., 2024; Goldin et al., 2025; Mudaly et al., 2026).

There is, admittedly, a more subtle immunological gap as well, one that is easy to overlook amid the more visible logistical problems. Intramuscular delivery bypasses the mucosal immune system almost entirely, generating negligible secretory IgA in the upper respiratory tract, which happens to be exactly where influenza virus first makes contact with the host (Tian et al., 2022; Thakkar et al., 2026; Nguyen & Ho, 2026). Systemic humoral memory alone, in other words, is being asked to do a job that mucosal immunity is better suited for.

Taken together, these physical, logistical, and immunological shortcomings have prompted a search for delivery platforms that sidestep the hypodermic needle altogether, and microneedle (MN) array technology has emerged as perhaps the most promising candidate (Jacoby et al., 2015; Nguyen, 2025; Nguyen & Ho, 2026). This review sets out, in five parts, to evaluate that promise systematically: first, by examining the immunological mechanisms and comparative efficacy of transdermal delivery relative to intramuscular injection (Tian et al., 2022; Nguyen & Ho, 2026); second, by reviewing the biomaterial innovations that make ambient thermostability possible (Tian et al., 2022; Nguyen, 2025; Adediran et al., 2025); third, by synthesizing Phase I/II clinical trial findings and patient-reported usability (Gromer et al., 2024; Nguyen & Ho, 2026); fourth, by identifying the manufacturing, sterilization, and quality-control bottlenecks that continue to slow translation (Nguyen, 2025; Gattu et al., 2026; Nguyen & Ho, 2026); and fifth, by outlining a strategic regulatory and global-health roadmap for closing the lab-to-clinic gap that still separates this technology from routine clinical use (Jacoby et al., 2015; Ostrowsky et al., 2025; Nguyen & Ho, 2026).

2. Microneedle Vaccine Delivery: Advancing Thermostable, Needle-Free Influenza Immunization

2.1 Global Burden of Seasonal Influenza and the Case for Alternative Delivery

It is worth pausing, before turning to the technology itself,

to appreciate just how large a problem it is meant to solve. Influenza epidemics recur with almost metronomic regularity, and the global vaccine manufacturing base, while substantial, remains unevenly distributed and slow to pivot when strain composition changes from one season to the next (Goldin et al., 2025; Taaffe et al., 2024). Universal or broadly protective vaccine candidates are under active development, but they remain some years from routine deployment, which means that, for the foreseeable future, the field is working to improve delivery of the vaccines we already have rather than waiting for a fundamentally different antigen (Mudaly et al., 2026; Ostrowsky et al., 2025). Framed this way, the case for a delivery innovation such as microneedles is not merely technical elegance for its own sake; it is a pragmatic response to a burden that is not going away on its own (Jacoby et al., 2015; Taaffe et al., 2024).

2.2 Limitations of Conventional Parenteral Influenza Vaccination

Currently licensed seasonal influenza vaccines are overwhelmingly administered parenterally, via intramuscular or subcutaneous injection with standard hypodermic needle-and-syringe systems (Tian et al., 2022; Nguyen, 2025). This approach can and does induce protective serum IgG antibody titers, so its immunological adequacy is not really in question. What is in question, rather, is everything that surrounds the act of injection itself (Jacoby et al., 2015; Nguyen, 2025).

First among these concerns is pain and the anticipatory fear it produces. Hypodermic injections are intrinsically invasive, and the resulting needle phobia, affecting an estimated 20% to 50% of adolescents and young adults, is a documented and non-trivial contributor to vaccine hesitancy across otherwise health-conscious populations (Jacoby et al., 2015; Nguyen, 2025; Adediran et al., 2025). Second, and somewhat less visible to the general public, is occupational risk. Needlestick injuries have been reported by up to 56% of healthcare workers over the course of their careers, with attendant risk of bloodborne pathogen transmission, including Hepatitis B, Hepatitis C, and HIV, when needle reuse or improper sharps disposal occurs (Raut et al., 2025; Nguyen, 2025). Third, parenteral delivery is logistically demanding in a way that is easy to underestimate until a system is stressed: it requires trained medical personnel and functioning healthcare infrastructure, which constrains immunization throughput exactly when demand spikes, whether during a severe seasonal peak or a pandemic emergency, and especially in remote or low-resource settings (Jacoby et al., 2015; Nguyen, 2025).

Layered atop these delivery-specific problems is a supply-chain fragility that is arguably even harder to fix. Conventional liquid influenza vaccines are thermolabile and depend on an unbroken cold chain, maintained between 2 °C and 8 °C, from the point of manufacture to the point of administration (Tian et al., 2022; Raut et al., 2025; Nguyen, 2025). Sustaining that infrastructure costs an estimated $200 million to $300 million globally each year, and cold-chain failures are responsible for as much as half of all vaccine wastage in low- and middle-income countries (Nguyen, 2025). Manufacturing itself compounds the problem: egg-based production, still the dominant method, requires a six- to eight-month cycle from strain selection to release and remains susceptible to egg-adaptive hemagglutinin mutations that can alter antigenicity and reduce real-world effectiveness whenever the circulating strain drifts from the vaccine strain (Taaffe et al., 2024; Goldin et al., 2025; Mudaly et al., 2026).

Finally, there is an immunological limitation that receives comparatively less attention than pain or logistics, but which may matter just as much for protection. Intramuscular delivery fails to meaningfully engage mucosal immune networks, producing negligible secretory IgA in the upper respiratory tract, the very tissue where influenza virus first establishes infection, and relying instead almost entirely on systemic humoral memory to do the protective work (Tian et al., 2022; Thakkar et al., 2026; Nguyen & Ho, 2026).

2.3 Microneedle Technology: Structure, Mechanism, and Classification

To move past these constraints, researchers have turned to the skin itself, not merely as a barrier to be pierced but as an immunologically active organ worth engaging directly. Microneedle (MN) array technology has emerged from this shift, offering a transdermal alternative to the hypodermic needle (Jacoby et al., 2015; Nguyen, 2025; Nguyen & Ho, 2026). Physically, microneedles are arrays of micron-scale projections, typically between 100 and 1000 μm in height, mounted on a patch backing not unlike an adhesive bandage (Jeong et al., 2020; Nguyen & Ho, 2026). Applied to the skin, they penetrate the outermost stratum corneum barrier and deliver antigen directly into the vascularized epidermis and superficial dermis, all while

remaining well short of the deep dermal nociceptors responsible for sharp pain, which is precisely why administration is essentially bloodless and reported to be minimally uncomfortable (Tian et al., 2022; Jeong et al., 2020; Nguyen & Ho, 2026).

Structurally, the field has converged on five broad categories: solid, coated, dissolving, hollow, and hydrogel-forming microneedles (Nguyen, 2025; Nguyen & Ho, 2026; Gattu et al., 2026), summarized schematically in Figure 4. Solid microneedles work through a "poke-and-patch" mechanism, creating transient microchannels that are then covered with a topically applied vaccine formulation (Nguyen, 2025; Nguyen & Ho, 2026). Coated microneedles reverse the order, applying a dry vaccine film directly to the needle surface so that a single "coat-and-poke" step delivers antigen as the film dissolves within seconds of insertion (Gattu et al., 2026; Nguyen, 2025; Nguyen & Ho, 2026). Hollow microneedles behave much like miniaturized hypodermic needles, delivering liquid formulations through internal bores under pressure-driven flow, a "poke-and-flow" approach (Gattu et al., 2026; Nguyen, 2025; Nguyen & Ho, 2026). Hydrogel-forming microneedles take yet another route, swelling on contact with interstitial fluid to form conduits through which antigen diffuses from an attached reservoir, a "poke-and-swell" mechanism (Gattu et al., 2026; Nguyen & Ho, 2026).

Among these five, dissolving microneedles (DMNs) have pulled ahead as the most clinically advanced class for vaccine delivery, and for reasons that are fairly intuitive once stated (Tian et al., 2022; Nguyen, 2025; Nguyen & Ho, 2026). Constructed from water-soluble, biocompatible polymers and sugars such as trehalose, pullulan, carboxymethylcellulose, and hyaluronic acid, DMNs encapsulate antigen within a solid matrix that dissolves rapidly in dermal interstitial fluid upon insertion, a "poke-and-release" process that leaves no biohazardous sharps waste behind (Nguyen, 2025; Nguyen & Ho, 2026). Formulating the antigen into a dry, solid-state polymeric glass has the further, rather elegant consequence of enhancing thermostability at ambient temperature, shielding fragile protein structures from thermal degradation and permitting storage at 37 °C or even 40 °C for weeks to months without refrigeration (Tian et al., 2022; Nguyen, 2025; Nguyen & Ho, 2026). That combination of properties reduces cold-chain dependency, simplifies supply logistics, and, perhaps most importantly for global reach, opens the door to self-administration or deployment by minimally trained personnel (Jacoby et al., 2015; Nguyen & Ho, 2026).

It is also worth noting that architectural innovation within the dissolving-microneedle class has continued beyond the basic single-antigen patch. Compartmental Microneedle Arrays (CMAs) and related partition-loading strategies physically separate distinct antigens, for instance influenza B/Yamagata and B/Victoria lineages, or split-virus influenza antigen alongside respiratory syncytial virus prefusion F protein, into spatially segregated, non-overlapping sectors of a single patch (Jeong et al., 2020; Fan et al., 2025). This matters because co-formulating multiple antigens in one liquid solution often triggers intra-vaccine interference or physical complexation that undermines immunogenicity; keeping antigens apart until the moment they dissolve in the skin appears to eliminate that interference and restore strain-specific neutralizing antibody responses (Jeong et al., 2020; Fan et al., 2025).

2.4 Cutaneous Immunology and the Dose-Sparing Advantage

Why does the skin work so well as an immunological target in the first place? The short answer is antigen-presenting cell density. The cutaneous microenvironment is unusually rich in specialized antigen-presenting cells (APCs), namely epidermal Langerhans cells and dermal dendritic cells, positioned almost as sentries just beneath the surface (Tian et al., 2022; Nguyen, 2025; Nguyen & Ho, 2026). Once antigen is deposited intradermally, these resident APCs internalize it, process it, and carry it to draining lymph nodes, where they help drive germinal center reactions, follicular T helper (Tfh) cell expansion, and downstream systemic and mucosal B- and T-cell responses (Jeong et al., 2020; Nguyen & Ho, 2026). This full cascade, from initial skin penetration through to systemic and mucosal antibody production, is illustrated in Figure 1.One practical consequence of this targeted engagement is dose-sparing, and the magnitude reported across studies is, frankly, difficult to ignore. Because APCs in the skin are so effective at capturing and presenting even small quantities of antigen, microneedle delivery can achieve equivalent or superior antibody titers, microneutralization, and protective efficacy using a fraction, sometimes a 3- to 6-fold reduction, of the standard intramuscular antigen dose (Jeong et al., 2020; Nguyen & Ho, 2026). For a

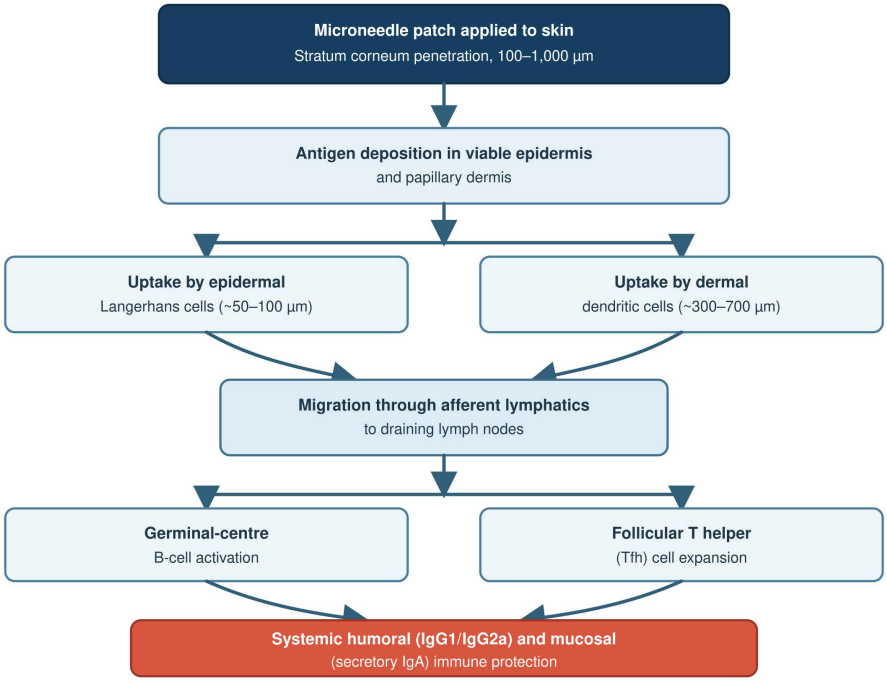


Figure 1. Cutaneous immune cascade following microneedle-mediated antigen delivery. Microneedle penetration of the stratum corneum deposits antigen within the viable epidermis and papillary dermis, where it is captured by epidermal Langerhans cells and dermal dendritic cells. These antigen-presenting cells migrate via afferent lymphatics to draining lymph nodes, driving germinal center B-cell activation and follicular T helper (Tfh) cell expansion, which together generate systemic humoral (IgG1/IgG2a) and mucosal (secretory IgA) immunity. Referenced in Sections 2.4 and 4.2 (adapted from Jeong et al., 2020; Nguyen & Ho, 2026).

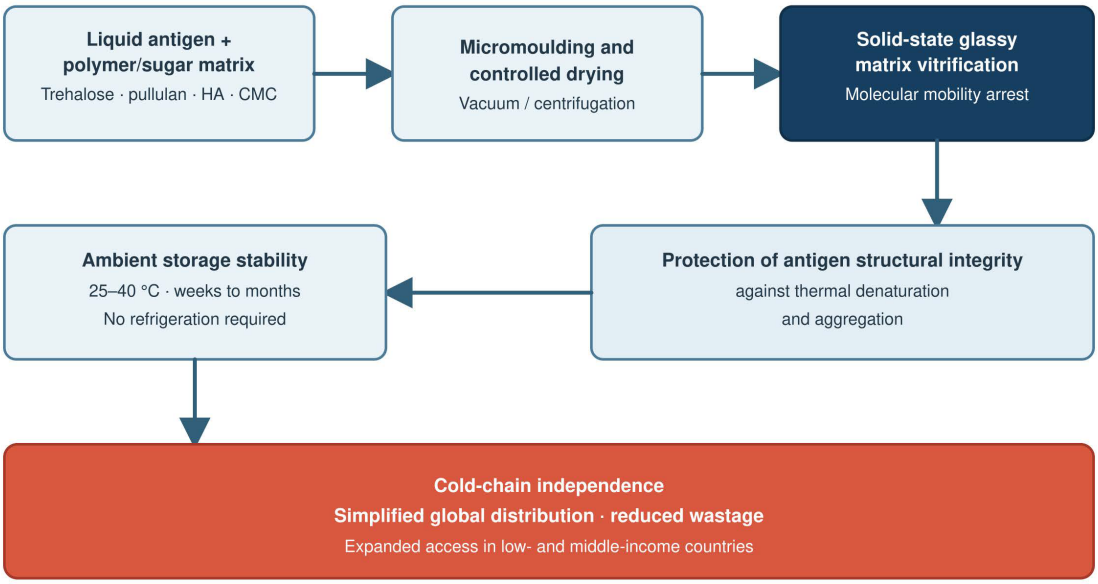


Figure 2. Solid-state matrix vitrification pathway underlying microneedle thermostability. Liquid antigen combined with sugar/polymer matrix components (trehalose, pullulan, hyaluronic acid, or carboxymethylcellulose) is micromolded and dried into a glassy solid-state matrix that restricts molecular mobility and protects antigen structure, enabling ambient-temperature storage (25–40 °C) for weeks to months and bypassing cold-chain dependence entirely. Referenced in Sections 2.5 and 4.3 (adapted from Tian et al., 2022; Nguyen & Ho, 2026).

vaccine enterprise perpetually short on manufacturing capacity relative to global demand, that kind of antigen efficiency is not a minor footnote; it could meaningfully expand the number of doses producible from a fixed antigen supply (Goldin et al., 2025; Jeong et al., 2020).

2.5 Biomaterial Engineering for Ambient Thermostability

None of these immunological advantages would matter much in practice without a matrix capable of protecting the antigen outside the cold chain, and this is where biomaterial science becomes central to the story. Formulating microneedles requires selecting polymers that are mechanically strong enough to pierce skin yet still dissolve quickly enough to release their payload, all without compromising antigen structure along the way (Tian et al., 2022; Adediran et al., 2025). Blends of disaccharides, trehalose being the most widely used, together with higher-molecular-weight polysaccharides such as pullulan or hyaluronic acid, have proven capable of producing sharp, mechanically robust needles that fully dissolve within 10 to 15 minutes of skin insertion (Tian et al., 2022; Adediran et al., 2025).

The thermostabilizing mechanism itself, summarized in Figure 2, rests on a fairly well-understood physical principle: incorporating antigen into a dry, solid-state polymeric glass restricts molecular mobility, effectively locking fragile protein structures in place and shielding them from the thermal denaturation and aggregation that would otherwise occur in a liquid formulation (Nguyen, 2025; Nguyen & Ho, 2026). Whole inactivated virus, virus-like particles, and subunit antigens embedded in trehalose/pullulan or hyaluronic acid matrices have been shown to retain hemagglutinating activity and immunogenicity after storage at 25 °C, 37 °C, or even 40 °C for weeks to months, without any refrigeration at all (Tian et al., 2022; Nguyen, 2025; Nguyen & Ho, 2026). This ambient thermostability is, arguably, the single most consequential logistical benefit of the platform: it bypasses the cold chain outright, simplifies global distribution, lowers shipping costs, and expands realistic access in precisely the low- and middle-income settings where cold-chain infrastructure is least reliable (Jacoby et al., 2015; Tian et al., 2022; Raut et al., 2025).

Beyond simple sugar-matrix formulations, the field has begun coupling microneedles with more sophisticated nanovaccine architectures, encapsulating whole virus, recombinant antigen, or nucleic acid payloads within poly(lactic-co-glycolic acid) (PLGA) microparticles or deoxycholic acid-modified polyethylenimine nanoparticles to create sustained-release depots within the dermis (Wang et al., 2023; Adediran et al., 2025; Nguyen & Ho, 2026). When loaded into dissolving microneedles, these particulate systems appear to prolong uptake by Langerhans cells and dermal dendritic cells, promoting balanced Th1 and Th2 immune profiles alongside the more immediate antigen release already provided by the dissolving matrix itself (Wang et al., 2023; Adediran et al., 2025).

3. Methods

Because this review synthesizes and interprets an existing evidence base rather than generating new laboratory data, our "methods" are, more precisely, a review methodology: a structured, reproducible account of how the literature underlying this manuscript was identified, screened, and synthesized. We describe it here in enough detail that another investigator, following the same steps, should arrive at a substantially similar evidence set, consistent with expectations for transparent reporting in a PubMed-indexed narrative or scoping review.

Search Strategy and Information Sources. We searched PubMed/MEDLINE as the primary database, supplemented by cross-referencing of citation lists within retrieved articles and targeted searches of Scopus and Google Scholar to capture recent preprints and conference-associated publications not yet indexed in MEDLINE. Search terms combined controlled vocabulary (MeSH terms, where applicable) and free-text keywords using Boolean operators, structured broadly as: ("microneedle*" OR "microarray patch*" OR "dissolving microneedle*" OR "transdermal vaccin*") AND ("influenza" OR "seasonal influenza" OR "hemagglutinin") AND ("vaccin*" OR "immuniz*" OR "immunogenicity" OR "clinical trial"). Searches were restricted to English-language publications, with no lower date limit imposed, given that foundational mechanistic and clinical work in this field dates back over a decade (Jacoby et al., 2015).

Eligibility Criteria. Studies were considered eligible if they reported original preclinical (in vitro or animal model) or clinical (Phase I–III trial) data on microneedle-based delivery of influenza vaccine antigens, or if they provided substantive technical, biomaterial, or regulatory analysis directly relevant to microneedle vaccine translation.

Review articles, editorials, and conference abstracts lacking primary data were excluded from the evidentiary synthesis but were, where appropriate, retained as background or contextual sources. Studies addressing microneedle delivery of non-influenza antigens were included selectively, and only where they illustrated a biomaterial, formulation, or manufacturing principle with direct relevance to influenza vaccine translation (for example, gamma-sterilization stability data from a SARS-CoV-2 microneedle candidate, or thermostability data from an orthopoxvirus microneedle platform) (Kim et al., 2025; Zou et al., 2026).

Study Selection and Data Extraction. Titles and abstracts identified through the search strategy were screened for relevance against the eligibility criteria above, and full texts of potentially eligible articles were then retrieved and assessed in detail. From each included study, we extracted, where reported: microneedle platform type and structural class; matrix biomaterial composition; antigen payload and dose; storage and thermostability data; immunogenicity endpoints (hemagglutination inhibition titers, seroconversion and seroprotection rates, mucosal and cellular immune markers); reactogenicity and safety outcomes; and, for clinical studies, participant acceptability and self-administration feasibility. Data were organized into structured comparative tables (Tables 1–4) to permit synthesis across heterogeneous study designs.

Synthesis Approach. Given the methodological heterogeneity across preclinical and clinical studies, spanning different animal models, antigen platforms, and trial phases, we opted for a narrative and thematic synthesis rather than formal meta-analysis. Findings were organized around five recurring themes that emerged consistently across the literature: structural and mechanistic classification, cutaneous immunology and dose-sparing, biomaterial and thermostability engineering, clinical safety and usability, and manufacturing/regulatory translation. This thematic structure, rather than a chronological or purely descriptive one, was chosen deliberately to mirror the translational pathway a candidate vaccine must actually traverse, from bench-level mechanism through to regulatory approval, and it directly informs the organization of the Results section that follows.

4. Synthesis of Evidence on Influenza Microneedle Vaccination Platforms

4.1 Structural Diversity and Delivery Mechanics

Analysis of the assembled literature identifies six functionally distinct structural classes of microneedle arrays engineered for vaccine delivery, summarized in Table 1 and depicted schematically in Figure 4: solid, coated, dissolving, hollow, hydrogel-forming, and compartmental/partition-loaded arrays (Gattu et al., 2026; Nguyen, 2025; Nguyen & Ho, 2026). Solid microneedles, operating by a "poke-and-patch" mechanism, generate high mechanical strength but require a two-step application and are limited by rapid microchannel closure within 15 to 30 minutes (Gattu et al., 2026; Khatik et al., 2025). Coated microneedles simplify this to a single "coat-and-poke" step, though their antigen payload is constrained to under 10 µg per needle (Fernando et al., 2018; Gattu et al., 2026; Nguyen, 2025). Dissolving microneedles, evaluated across the largest and most clinically mature evidence base, achieve full biodegradability and zero sharps waste (Adediran et al., 2025; Nguyen & Ho, 2026; Tian et al., 2022). Hollow microneedles retain compatibility with existing liquid formulations but carry a documented risk of lumen occlusion during insertion (Gattu et al., 2026; Nguyen, 2025), while hydrogel-forming platforms accommodate larger reservoir volumes at the cost of slower, diffusion-limited release kinetics (Gattu et al., 2026; Nguyen & Ho, 2026). Compartmental and partition-loaded arrays, a more recent architectural innovation, physically separate co-formulated antigens and have demonstrated relative standard errors in dose uniformity below 7%, effectively eliminating the intra-vaccine interference that otherwise compromises multivalent formulations (Jeong et al., 2020; Fan et al., 2025).

4.2 Cutaneous Immune Orchestration and Dose-Sparing OutcomesTurning to immunological outcomes, the evidence converges on skin-resident antigen-presenting cells, principally epidermal Langerhans cells and dermal dendritic cells, as the mechanistic driver behind microneedle efficacy (Nguyen, 2025; Thakkar et al., 2026), a cascade traced in full in Figure 1. Antigen delivered intradermally is captured locally, transported to draining lymph nodes, and used to drive germinal center B-cell activation and follicular T helper (Tfh) cell expansion, ultimately yielding systemic humoral and mucosal immune output (Norizwan & Tan, 2025; Wang et al., 2023). Imaging and pharmacokinetic studies indicate that

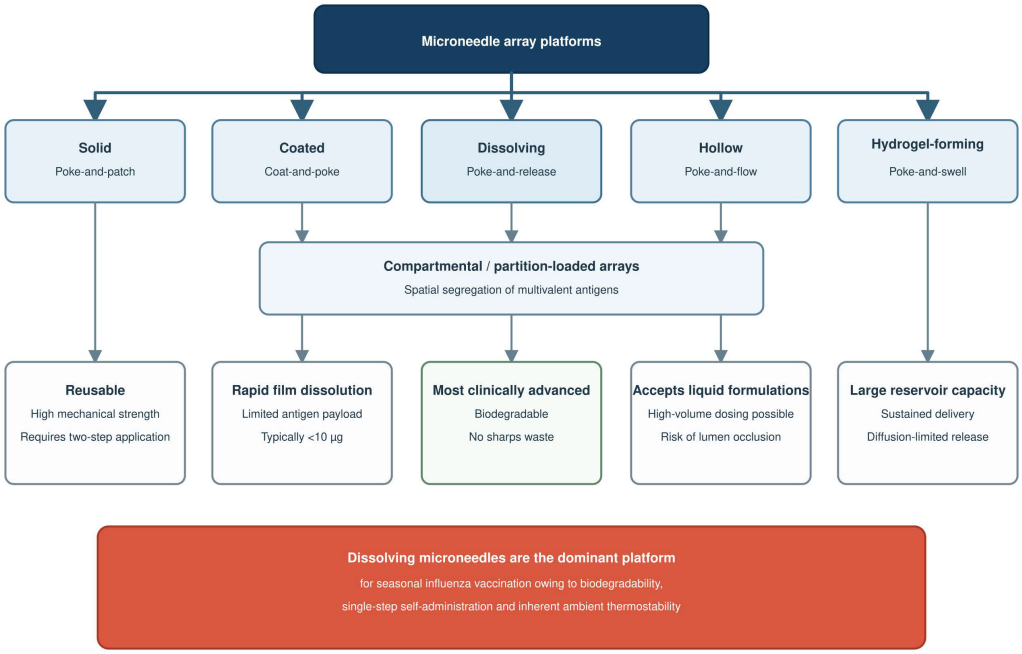


Figure 3. Structural classification of microneedle array platforms for vaccine delivery. The five principal architectural classes, solid, coated, dissolving, hollow, and hydrogel-forming microneedles, are distinguished by their release mechanism and key performance trade-offs. Compartmental and partition-loaded arrays represent a cross-cutting architectural innovation, most often applied to dissolving platforms, that physically segregates multivalent antigens to prevent intra-vaccine interference. Referenced in Sections 2.3 and 4.1, and complements Table 1 (adapted from Gattu et al., 2026; Nguyen & Ho, 2026).

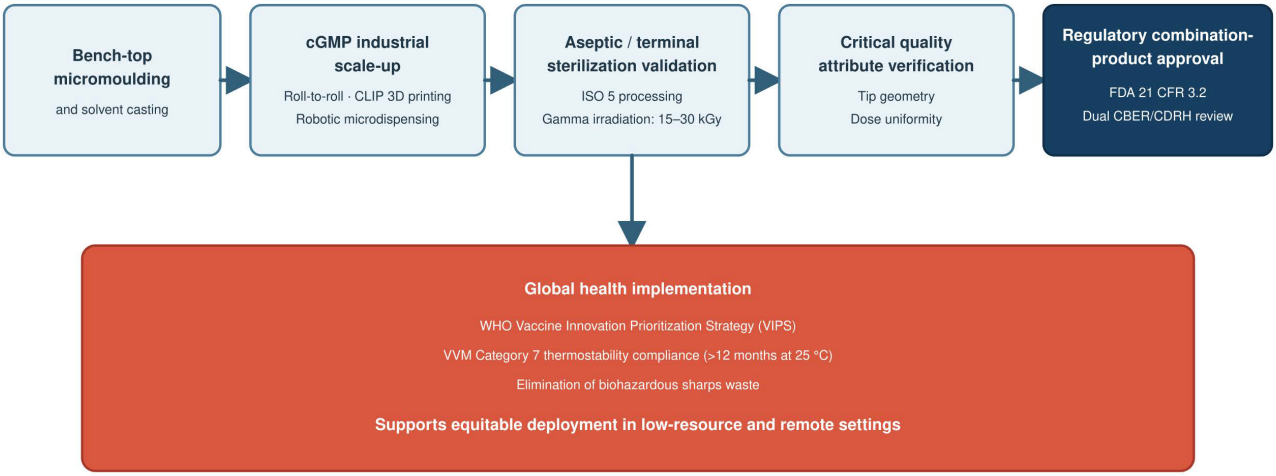


Figure 4. Translational pathway from laboratory-scale fabrication to regulatory approval and global deployment of influenza microneedle vaccines. Progression from benchtop micromolding to cGMP industrial scale-up, validated sterilization, critical quality attribute verification, and combination-product regulatory approval (FDA 21 CFR 3.2, dual CBER/CDRH review) underlies equitable global health implementation frameworks such as the WHO/Gavi Vaccine Innovation Prioritization Strategy. Referenced in Sections 4.5 and 5.3, and complements Table 4 (adapted from Gattu et al., 2026; Nguyen & Ho, 2026).

particulate antigens persist at the application site for up to three days, a sustained presentation window that appears to enhance germinal center reactions relative to the comparatively brief antigen exposure of an intramuscular bolus injection (Nguyen & Ho, 2026; Rouphael et al., 2021).

Two outcomes follow directly from this mechanism. First, dose-sparing efficiency: across multiple preclinical and clinical evaluations, transdermal delivery produced immune responses equivalent to, or better than, intramuscular injection using 3- to 6-fold less antigen (Fernando et al., 2018; Forster et al., 2020; Nguyen & Ho, 2026). High-density microarray patches delivering just 2.5 µg of hemagglutinin per strain, for instance, achieved hemagglutination inhibition titers and seroprotection rates non-inferior to a full 15 µg intramuscular dose (Fernando et al., 2018; Forster et al., 2020). Second, and perhaps more consequential for protection against a respiratory pathogen specifically, dissolving microneedles loaded with whole inactivated virus, recombinant subunit antigen, or PLGA microparticles elicited balanced Th1/Th2 antibody responses alongside measurable antigen-specific secretory IgA in lung washes, a mucosal response essentially absent following intramuscular injection (Adediran et al., 2025; Tian et al., 2022; Wang et al., 2023).

4.3 Biomaterial Formulations and Ambient Thermostability Performance

Table 2 compiles the biomaterial formulation strategies reported across the reviewed literature, and several themes recur. Trehalose/pullulan blends, at approximately equal weight ratios, retained full hemagglutination activity and mechanical penetration strength after four weeks of storage at 37 °C under 0% relative humidity (Tian et al., 2022), a thermostabilization pathway summarized in Figure 2. PLGA microparticle encapsulation within hyaluronic acid or trehalose matrices preserved encapsulation efficiency above 90% while inducing robust serum IgA, IgG, and lung-wash sIgA responses alongside CD4+/CD8+ T-cell expansion (Adediran et al., 2025). DNA nanovaccines condensed with deoxycholic acid-modified polyethylenimine and embedded within dissolving microneedles retained transfection efficiency through the molding and storage process while eliciting germinal center responses and cross-reactive neutralizing antibodies protective against lethal influenza challenge in mice (Wang et al., 2023). Perhaps most striking from a stability standpoint, a gamma-irradiated recombinant subunit vaccine embedded in a sugar matrix showed under 3% protein degradation after 19 months at room temperature, and under 3% additional degradation following a further month at a punishing 42 °C, compared with over 23% degradation in a liquid control formulation held under equivalent conditions (Kim et al., 2025).

4.4 Clinical Trial Evidence, Reactogenicity, and Usability

Table 3 summarizes clinical trial evidence, and the picture that emerges is, on balance, reassuring. In the landmark TIV-MNP 2015 Phase I trial (NCT02438423), a dissolving microneedle patch delivering inactivated trivalent influenza vaccine produced hemagglutination inhibition geometric mean titers and seroprotection rates non-inferior to intramuscular injection in healthy adults, while also generating higher neuraminidase inhibition titers and expanded circulating Tfh cell populations (Gromer et al., 2024; Rouphael et al., 2017; Rouphael et al., 2021). The high-density microarray patch (Nanopatch) platform demonstrated 6-fold dose-sparing in a separate Phase I trial, with local reactogenicity limited to mild, transient erythema that resolved without intervention (Fernando et al., 2018; Forster et al., 2020). The Vaxess MIMIX platform showed sustained-release depot kinetics and durable antibody responses in a dose-escalation study (Garg et al., 2024), while the hollow-needle MicronJet600 device achieved 50% dose-sparing in young adults and superior antibody responses in elderly populations across Phase I–III evaluation (Gattu et al., 2026; Jacoby et al., 2015; Nguyen, 2025). Notably, a pediatric measles–rubella microneedle trial conducted in The Gambia elicited 93% measles and 100% rubella seroconversion in infants, offering encouraging, if indirect, evidence that the platform can perform reliably in operationally demanding, low-resource field settings (Adigweme et al., 2024).

Across these trials, patient acceptability was consistently favorable: more than 70% of participants expressed a clear preference for microneedle patches over conventional injection, and self-application success rates approached 100% under minimal supervision (Jacoby et al., 2015; Rouphael et al., 2017), a pattern of findings summarized visually within Table 3.

4.5 Manufacturing Scale-Up, Quality Control, and Regulatory Translation

Table 1. Structural Classification, Mechanisms, and Architectural Innovations of Microneedle Vaccine Delivery Platforms. This table compares the five principal structural classes of microneedle arrays used for vaccine delivery, together with the compartmental/partition-loaded design variant, across insertion mechanism, constituent materials, key advantages, technological limitations, and representative influenza-relevant applications. It is intended to orient the reader to the mechanistic and material trade-offs that determine platform selection for a given vaccine formulation, and should be read alongside Figure 3, which depicts these relationships schematically.

Microneedle Class	Mechanism & Insertion Dynamics	Key Materials	Advantages	Limitations	Applications & References
Solid Microneedles	Poke-and-patch: creates microchannels (50–100 μm) before topical vaccine application	Silicon, titanium, rigid polymers (PLA); height 100–900 μm	High mechanical strength; reusable; compatible with electroporation	Two-step protocol; rapid channel closure (15–30 min); variable absorption	DNA vaccines, hepatitis B/influenza pretreatment (Gattu et al., 2026; Nguyen & Ho, 2026)
Coated Microneedles	Coat-and-poke: dry vaccine film dissolves within seconds to minutes of insertion	Metal/silicon core with trehalose/cellulose film coating	Single-step application; rapid, precise dosing; no liquid sharps	Payload <10 μg per needle; coating shear-off risk; humidity-sensitive	Inactivated influenza; HD-MAP/Nanopatch (Fernando et al., 2018; Nguyen & Ho, 2026)
Dissolving Microneedles	Poke-and-release: matrix fully dissolves in interstitial fluid within 2–15 min	Trehalose, pullulan, CMC, hyaluronic acid, PVP/PVA	Biodegradable; zero sharps waste; self-administration; ambient stable	Tip volume limits dose; hygroscopic softening; drying protocol sensitivity	Seasonal TIV/QIV, WIV, PLGA microparticles (Adediran et al., 2025; Tian et al., 2022)
Hollow Microneedles	Poke-and-flow: pressure-driven liquid infusion through internal bores	Silicon, glass, metal; height 300–1500 μm	Uses standard liquid formulations; larger volume delivery	Lumen occlusion risk; fluid leakage; lower mechanical resistance	MicronJet600; influenza, polio, rabies (Gattu et al., 2026; Nguyen, 2025)
Hydrogel-Forming Microneedles	Poke-and-swell: hydrogel swells with interstitial fluid to form conduits	Cross-linked Gantrez S-97, GelMA, methacrylated HA	Large reservoir capacity; intact removal, no residue	Slower diffusion-limited release; variable swelling	Protein/peptide antigens, biomarker sampling (Gattu et al., 2026)
Compartmental / Partition-Loaded Arrays	Spatially segregated delivery within non-overlapping patch sectors	Segmented backing with coated or dissolving microprojections	Eliminates intra-vaccine interference between co-formulated antigens	Complex multi-reservoir manufacturing; alignment precision required	Multivalent influenza, influenza–RSV combinations (Fan et al., 2025; Jeong et al., 2020)

Table 2. Matrix Biomaterials, Nanovaccine Formulations, and Ambient Thermostability Performance. This table synthesizes representative biomaterial formulation strategies for influenza and related antigens delivered by dissolving microneedles, detailing the stabilization mechanism, demonstrated storage performance under elevated ambient temperature, and the resulting immunological profile. It illustrates the material-science basis for cold-chain-independent vaccine storage discussed in Section 2.5 and Figure 2.

Formulation Platform	Antigen Payload	Stabilization Mechanism	Thermostability Performance	Immunological Profile	Reference
Trehalose/Pullulan (50:50)	Whole inactivated influenza virus (A/California/07/2009 H1N1)	Glassy-state vitrification with crystallization inhibition	Retains hemagglutination activity after 4 weeks at 37 °C, 0% RH	Serum IgG/IgG1/IgG2a comparable to IM; protective lung clearance	Tian et al. (2022)
PLGA microparticles in HA/trehalose	Inactivated influenza A (H1N1 pdm09, H3N2)	Double-emulsion encapsulation shielding antigen	>90% encapsulation efficiency retained after solid-state molding	High serum IgA/IgG, lung sIgA, CD4+/CD8+ expansion	Adediran et al. (2025)
DCA-PEI nanoparticles in DMNs	Mosaic influenza A DNA nanovaccine (mH1/mH3)	Polymer condensation enabling lysosomal escape	Retains transfection efficiency through molding/storage	Germinal center responses; cross-reactive neutralization	Wang et al. (2023)
HA/trehalose with gamma sterilization	Recombinant SARS-CoV-2 S1 subunit vaccine	Sugar-matrix vitrification with 15–30 kGy gamma irradiation	<3% degradation after 19 months RT + 1 month at 42 °C	Antigen-specific IgG for 70 weeks; strong neutralization	Kim et al. (2025)
PHBV & CMC depot	Inactivated influenza A (H1N1, H3N2) or VLPs	Polymeric depot with water-soluble needle tips	Preserves HA activity at 25–37 °C without cold chain	Balanced Th1/Th2 humoral and cellular responses	Nguyen & Ho (2026)
PEOX solvent-cast	Lyophilized tetanus toxoid	Suspension casting avoiding aqueous dissolution stress	Avoids reconstitution/drying denaturation cycles	97% insertion efficiency; 69% intradermal delivery	Lu et al. (2026)

Table 4 and Figure 3 turn to the translational bottlenecks that, despite this favorable immunological and clinical evidence, have so far kept every influenza microneedle candidate short of commercial licensure. Industrial scale-up remains a primary constraint: moving from benchtop micromolding or solvent casting to high-throughput, cGMP-compliant automated manufacturing, whether through roll-to-roll casting, robotic nanoliter dispensing, or continuous liquid interface production, requires substantial capital investment and dedicated process analytical technology (Gattu et al., 2026; Nguyen & Ho, 2026). Sterilization presents a second, more subtle challenge, since conventional terminal sterilization methods (autoclaving, ethylene oxide, gamma or electron-beam irradiation at high dose) can denature protein antigens or damage polymer matrices, pushing manufacturers toward either aseptic isolator processing at Grade A/ISO 5 conditions or carefully validated low-dose gamma irradiation protocols (Nguyen, 2025; Kim et al., 2025; Nguyen & Ho, 2026). Quality control adds a third layer of complexity, requiring tight control over needle tip sharpness, intra-patch dose uniformity, mechanical fracture force, and resistance to moisture-driven softening during storage and transport (Nguyen, 2025; Gattu et al., 2026; Lu et al., 2026; Tian et al., 2022). Finally, regulatory pathways remain genuinely complex: authorities including the U.S. FDA, operating under 21 CFR 3.2, classify microneedle patches as combination products, triggering dual evaluation of both the biologic payload and the delivery device by separate regulatory centers (Nguyen, 2025; Nguyen & Ho, 2026).

5. Bridging the Lab-to-Clinic Gap in Influenza Microneedle Vaccination

5.1 Interpreting the Immunological and Clinical Case for Microneedles

Stepping back from the individual findings, what does this body of evidence actually tell us? Taken as a whole, it makes a fairly compelling case that microneedle delivery is not merely a laboratory curiosity but a genuinely viable clinical alternative to intramuscular injection for seasonal influenza vaccination (Tian et al., 2022; Nguyen & Ho, 2026). The immunological rationale is mechanistically sound rather than merely empirical: the skin's dense population of Langerhans cells and dermal dendritic cells provides a biologically plausible explanation for the dose-sparing effects observed across multiple independent trials, and it is difficult to attribute a consistent 3- to 6-fold dose reduction, replicated across different platforms and research groups, to chance or bias alone (Fernando et al., 2018; Forster et al., 2020; Jeong et al., 2020). The added benefit of mucosal secretory IgA induction, largely absent following conventional intramuscular delivery, may prove especially consequential for a respiratory pathogen whose first point of contact is precisely the mucosal surface that intramuscular vaccination fails to engage (Tian et al., 2022; Thakkar et al., 2026).

5.2 Persistent Translational Bottlenecks

And yet, for all of this promise, it is worth asking honestly why, a full decade after the first published Phase I trial data (Jacoby et al., 2015; Rouphael et al., 2017), no influenza microneedle patch has reached the market. The answer, based on the evidence synthesized here, seems to lie less in biology than in engineering and regulatory science (Nguyen, 2025; Gattu et al., 2026). Sterilization is perhaps the least appreciated of these hurdles outside the field itself: a formulation that performs beautifully in a research-scale, aseptically handled batch may behave quite differently once subjected to the terminal sterilization methods that regulators typically expect for a commercial biologic-device combination product (Kim et al., 2025; Nguyen & Ho, 2026). Manufacturing scale-up carries a similar tension between laboratory feasibility and industrial reproducibility; a benchtop micromolding process that yields excellent needles one batch at a time does not automatically translate into a continuous, cGMP-validated production line capable of supplying a national immunization program (Gattu et al., 2026; Nguyen & Ho, 2026).

5.3 Strategic Pathways to Regulatory Approval and Global Health Equity

If closing this gap is the goal, then the roadmap implied by the evidence points toward several concrete, if not necessarily easy, priorities. Regulatory harmonization is probably the most actionable near-term step: because microneedle patches are classified as combination products requiring dual evaluation of drug and device components, early and sustained engagement with regulators, ideally informed by consistent Critical Quality Attribute benchmarks such as those summarized in Table 4, could meaningfully shorten review timelines (Nguyen, 2025; Nguyen & Ho, 2026). Investment in aseptic and low-dose irradiation sterilization validation, rather than reliance on conventional high-dose methods known to damage

Table 3. Clinical Trials, Human Usability, Immunogenicity, and Reactogenicity Profiles of Influenza (and Related) Microneedle Platforms. This table summarizes Phase I–III clinical trial evidence for microneedle vaccine platforms, including trial identifiers, antigen dose, study population, immunogenicity outcomes, safety/reactogenicity findings, and patient-reported acceptability. It underpins the clinical translation evidence discussed in Section 4.4 and directly supports the dose-sparing and preference findings cited throughout the Discussion.

Trial / Platform	Vaccine & Dose	Study Population	Immunogenicity & Dose-Sparing	Reactogenicity & Safety	References
TIV-MNP 2015 (NCT02438423)	Inactivated TIV, 15 µg HA/strain	Phase I RCT, 100 healthy adults (18–49)	HAI titers non-inferior to IM; higher NAI and Tfh expansion	Mild transient erythema/itching; systemic AEs comparable to IM	Gromer et al. (2024); Rouphael et al. (2017, 2021)
Nanopatch HD-MAP	TIV/monovalent, 1.5–15 µg HA	Phase I RCT, 100 healthy adults	6-fold dose-sparing: 2.5 µg HD-MAP ≈ 15 µg IM dose	Mild local erythema/edema, fully resolving; no systemic concerns	Fernando et al. (2018); Forster et al. (2020)
Vaxess MIMIX MAP (NCT06125717)	Monovalent H1N1	Phase I dose-escalation, healthy adults	Sustained-release depot kinetics; durable HAI titers	Mild, self-limiting local reactogenicity; no serious AEs	Garg et al. (2024)
MicronJet600 (hollow MN)	Commercial liquid influenza vaccines	Phase I–III, young/pediatric/elderly cohorts	50% dose-sparing in young adults; superior response in elderly	Mild local pain; reduced myalgia vs. IM	Gattu et al. (2026); Jacoby et al. (2015)
Gambian Measles–Rubella MNP (NCT04394689)	Live-attenuated MR vaccine	Phase I/II, 45 adults, 120 toddlers, 120 infants	93% measles, 100% rubella seroconversion in infants	Favorable pediatric safety profile; mild transient reactions	Adigweme et al. (2024)

Table 4. Industrial Scale-Up, Sterilization, Quality Control, and Regulatory Pathways for Influenza Microneedle Vaccine Translation. This table outlines the principal translational and manufacturing domains that constitute the remaining lab-to-clinic gap for influenza microneedle vaccines, including the specific technical barrier, current engineering solutions, associated critical quality attributes, and regulatory classification. It provides the evidentiary basis for the translational roadmap proposed in Section 5.3 and is illustrated schematically in Figure 4.

Domain	Technical Barrier	Engineering Solutions	Critical Quality Attributes	References
Industrial Scale-Up	Benchtop micromolding too slow for commercial demand	Roll-to-roll casting, robotic micro-dispensing, CLIP 3D printing	Needle height ±5%; tip radius 1–25 µm; fracture force >0.10–0.87 N	Gattu et al. (2026); Khatik et al. (2025)
Sterilization Assurance	Conventional sterilization denatures protein antigens	Aseptic isolator (Grade A/ISO 5); low-dose gamma (15–30 kGy)	Sterility Assurance Level = 10; retained HA bioactivity	Kim et al. (2025); Nguyen (2025)
Quality Control & Stability	Moisture uptake softens tips; brittleness causes fracture	High-Tg sugar formulation; nitrogen purging; foil packaging	Penetration efficiency >95%; dissolution <10–15 min	Lu et al. (2026); Tian et al. (2022)
Regulatory Approval	No standardized guidance for combination products	Dual CBER/CDRH review; 21 CFR Part 4; ISO 10993 testing	Classified as Combination Product (FDA 21 CFR 3.2)	Gattu et al. (2026); Nguyen & Ho (2026)
Global Deployment	Distribution bottlenecks; sharps waste hazards	Solid-state vitrification for room-temperature storage	VVM Category 7 (>12 months at 25 °C)	Jacoby et al. (2015); Raut et al. (2025)

protein antigens, appears to be a second priority worth prioritizing given the encouraging stability data already reported for gamma-irradiated subunit formulations (Kim et al., 2025). Third, and this may be the point most relevant to global health equity, the demonstrated ambient thermostability of dissolving microneedle platforms, several of which showed minimal antigen degradation after months at 25 °C to 40 °C, positions this technology unusually well to serve low- and middle-income settings where cold-chain infrastructure remains the single largest driver of vaccine wastage (Raut et al., 2025; Tian et al., 2022; Nguyen, 2025). Prioritization frameworks such as the Vaccine Innovation Prioritization Strategy, coordinated among Gavi, WHO, the Bill & Melinda Gates Foundation, and UNICEF, already recognize this potential and could serve as a coordinating mechanism for translational investment (Nguyen & Ho, 2026).

5.4 Limitations of This Review

This review is not without limitations, and it seems only fair to name them plainly. As a narrative rather than a formally registered systematic review, our synthesis, while structured and reproducible in its search strategy, does not include a formal risk-of-bias assessment or meta-analytic pooling of effect sizes across the heterogeneous studies included (see Methods). Much of the underlying clinical evidence remains confined to Phase I and early Phase II trials in relatively small, largely healthy adult cohorts, and comparatively little data yet exists in the pediatric, elderly, or immunocompromised populations who arguably stand to benefit most from a needle-free, thermostable delivery platform (Adigweme et al., 2024; Garg et al., 2024). Larger, adequately powered Phase III trials, together with parallel investment in manufacturing science, will ultimately be needed before any firm conclusions about population-level effectiveness, or realistic timelines to licensure, can be drawn with confidence.

6. Conclusion

Microneedle delivery reframes seasonal influenza vaccination around the skin's own immunological strengths rather than around the limitations of a hypodermic needle. By engaging Langerhans cells and dermal dendritic cells directly, dissolving microneedle patches achieve dose-sparing, mucosal immune engagement, and ambient thermostability that conventional intramuscular injection simply cannot match, while also addressing needle phobia, sharps waste, and cold-chain fragility in one integrated platform. Phase I and early Phase II trials consistently support safety, immunogenic non-inferiority, and strong patient preference. What remains is not further proof of biological concept but sustained investment in cGMP-compliant manufacturing, validated sterilization protocols, and harmonized combination-product regulatory pathways. Closing this lab-to-clinic gap will require genuinely interdisciplinary collaboration among immunologists, materials scientists, manufacturing engineers, and regulators, but the underlying case for microneedle-delivered influenza vaccination is, at this point, difficult to dismiss.

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