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MICRONEEDLE SYSTEMS FOR PAINLESS VACCINATION- REVIEW ARTICLE

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Abstract:
Transdermal vaccination with biodegradable microneedles is an area that is growing swiftly. Painful microneedles are one of the major drawbacks for people when it comes to vaccination. This has, therefore, led to a major focus in biomedical research on the development of a method for pain-free vaccination using microneedles. Microneedles are an array of micron-sized needles that can be used for the efficient and pain-free transdermal delivery of vaccine agents. Moreover, microneedle-based vaccination holds many advantages over the intramuscular injections of vaccines. These advantages include higher immunogenicity because targeted skin deliveries in the epidermis and dermis, which have a high number of antigen-presenting cells like Langerhans cells and dendritic cells. Microneedle patches appear much like a Band-Aid. They also have other advantages, which include no cold chain necessary. And potentially could be used for self-administration. The major advantage of microneedle-based vaccination is the controlled release of antigens in various forms, namely solutions and suspensions. The microneedle-based patch for particulate vaccine holds a great promise because of the beneficial effects of particulate antigen and minimally invasive vaccine strategies. However, to make microneedle-based vaccines successfully translatable, various challenges and requirements, which include accurate dosage measurement, proper formulation, and sterility, need to be met. This review will help the audience become aware of the growing advancements in microneedle-based vaccine-delivery devices.

KEYWORDS: *Needle phobia, vaccine, transdermal, skin, microneedles.*

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INTRODUCTION:

Most vaccines are delivered through the hypodermic needle, ranging from the intramuscular to the subcutaneous injection methods. Despite the development of other methods of vaccine delivery, including oral, intranasal, intradermal, and transdermal, the injection methods are the predominant medium for vaccine delivery today (1). According to various health reports, "Vaccination is important to the community to induce herd immunity, specifically when 70% of the population is immunized."(2). A vaccine is a biological product that involves a weakened or attenuated microorganism, its toxins, or surface antigens intended to induce an immune response (3). More recently, biologics involving nucleic acids such as DNA-based biologics, including plasmid or RNA-based biologics, messenger RNA, have been developed as safe and effective biologics, intended to induce cellular immunity (4). Vaccines have long been delivered by hypodermic needles (4). Vaccines work by triggering the body's natural defences, enabling it to recognize and resist foreign invaders, such as viruses or bacteria. Vaccination offers a safeguard against these diseases by giving a boost to the individual's immunity, thus reducing their susceptibility to infections as well as their ability to spread the infection to others. With every individual being inoculated, the spread of the infection can be controlled, as it also safeguards those who are unable to receive vaccinations owing to certain illnesses, age, or conditions (5). Nonetheless, developed vaccinations are also facing hurdles regarding their safety as well as stability. Moreover, fear of needles might also hamper the large-scale inoculation of vaccinations among people. In such an aspect, "microneedles" might offer a possible solution (1).

> Early development of microneedles focused on delivering low doses of drugs into the skin. However, over the past decade, microneedles have gained significant attention as a platform for vaccine delivery. This growing interest has been largely driven by recent efforts to develop novel, painless vaccines (4,6).

In recent years, because of improved knowledge of skin immunology and developments in electronics that made it easier to accomplish, there have been technological breakthroughs related to skin transplantation, such as the production of these micro-scale devices (7). The development of the microneedles is primarily aimed at the transdermal delivery of low-drug, low-molecular-weight compounds into skin, taking advantage of their affinity for bypassing the stratum corneum barrier without causing tissue damage. However, in recent years, there has been an increasing trend in vaccine development that aims at overcoming the current barriers to improve the accessibility of vaccine antigens. Microneedle-based vaccine has shown significant attention because of the following benefits: pain-free administration, targeted delivery to the skin, possibility of self-administration, improved patient compliance, and simplified logistics (possibility for self -administration and reduced need for cold chain)

In addition, these needles are not easily self-administered unless the individuals have received specialized training in injection technique and needle disposal (7)

RATIONALE FOR THE USE OF MICRONEEDLES IN VACCINES:

For these reasons, other delivery methods are given attention with regard to vaccine administration. Using skin as a route for vaccination introduces microneedles as another mode of delivery system. MN is a minimally invasive transdermal delivery method with no pain perceived upon administration. This is attributed to the fact that MNs are sufficiently long to perforate the skin without reaching the nerve ending that perceives pain (8). MNs may deliver vaccine via physical puncture of the stratum corneum (9), hence offering painless drug administration, thereby avoiding complications from hypodermic needles. Further, there will be fewer requirements for the trained personnel (10), while averting the possibility of prick injections from accidental needle contact and disposal needs.

MNs function through the delivery of the antigens to the epidermis and dermis layers of the skin through the use of APCs in the skin (13). Intradermal administration of the vaccines through MNs has effectively induced an immune response similar to that obtained through SC and IM administration in different studies (11). Additionally, a larger dose can also be administered to the skin environment through the use of MNs. Consequently, the obtained effect is the principle of the dose-sparing method, which would reduce the required vaccine and hence lower toxicity (12). In terms of stability, vaccine delivery through MNs has many benefits over other delivery systems. The vaccine can be formulated in a solidified for that is more stable at the highest temperatures when compared with a liquid vaccine. In addition, being a dry form, the vaccine**,** along with its excipients, can improve its thermostability (13). There is no need for the reconstitution, and this reduces the associated cost of the cold chain (14). As a consequence, an MN offers a more preferable choice over traditional injections (15).

TYPES OF MICRONEEDLES:

Solid Microneedles:

Solid microneedles are normally used as a pretreatment technique for the skin. The microneedles are punctured into the skin and then pulled out, making minute pores on the surface of the skin. The stratum corneum is damaged, making it easy to cross, thereby improving permeability to a great extent. After that, a drug patch is applied to the surface to be influenced, as it can pass through the minute pores to reach inside (14). For maintaining the structural integrity of solid microneedles, it is important that they possess strong mechanical strength to penetrate into the stratum corneum. In this context, silicon, metals, and ceramics are often utilized. These microneedles are usually processed by the microfabrication methods, such as dry etching and micro molding. Even polymer-based microneedles have revealed potential. However, they possess weaker mechanical strength when compared to others. Solid microneedles have revealed potential applications in vaccine and therapeutic transcutaneous delivery systems. These systems have shown promising results in preclinical studies. Certain technological challenges are associated with these devices. These include biphasic administration procedure (15), the possibility of the dermal residue deposits of metals (16), and control needed to modulate release rates of therapeutics (17). These issues led to the development of other forms of microneedles, such as coated and hollow microneedles.

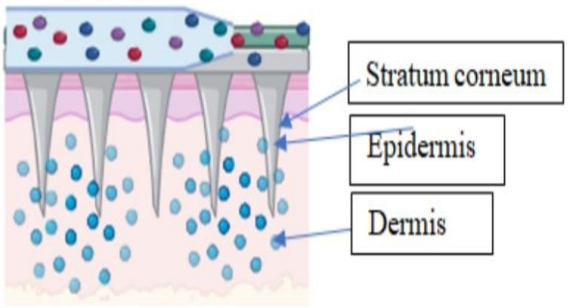

FIGURE 1: solid microneedles

Hollow Microneedles:

Hollow microneedles (HMNs) are micro- injection devices that mimic conventional hypodermic needles. They have been designed to deliver liquid pharmaceutical agents through the skin. These microneedles possess internal lumens that allow for the controlled transport of relatively large volumes of therapeutic substances, offering advantages over solid or coated microneedle types. (18,19).

Fabrication can be achieved using various MEMS-based techniques such as laser micromachining, deep reactive ion etching, X-ray lithography, and chemical etching. Common materials include metals, ceramics, glass, and silicon, chosen for their mechanical and structural properties (20).

Delivery mechanisms rely on either pressure-driven flow (5–20 psi) or passive diffusion from drug reservoirs (4). Hollow microneedles can deliver up to several hundred microliters at infusion rates of 50–300 nL/min (21). Arrays of HMNs enhance delivery efficiency and spatial coverage, provided uniform pressure distribution is maintained to avoid leakage.

HMNs have demonstrated successful vaccine delivery for diseases like influenza, HPV, polio, and plague, with or without adjuvants (21). They can elicit strong humoral and cellular immune responses, often at lower doses than traditional injections.

However, challenges persist, including lumen blockage, drug leakage, needle breakage, and variability in skin resistance, all of which can affect performance and safety.

Overall, HMNs offer a promising, minimally invasive transdermal delivery platform, particularly suitable for targeted vaccine administration to immunologically rich skin layers. Continued research is needed to overcome technical limitations and optimize their clinical application (22,23,24).

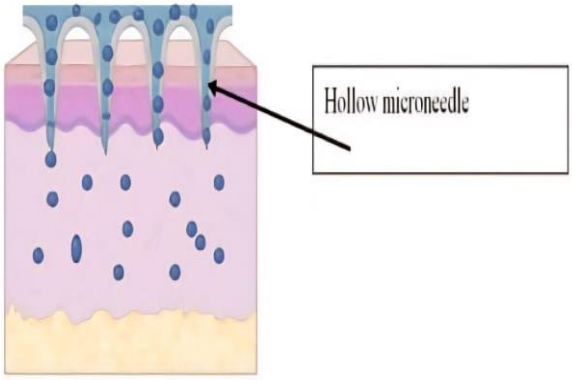

FIGURE 2: Hollow Micronnedle

Coated Microneedles:

The technology of coated microneedles involves the use of solid microstructures that are coated with therapeutic agents using solution or dispersion-based coating methods. Different methods of fabrication are employed, including dip coating, spray deposistion and precision inkjetting (25,26). Enhancement of formulation variables is of utmost importance for the antigenic effectiveness to

remain stable, most especially for different vaccines (27,28).

Components of typical formulations include viscosity additives, stabilizers, and immunological adjuvants, each of which is of great importance in determining the integrity of the coating and effectiveness of therapeutic agents (29,30,31).

This technology has applications for an entire range of vaccine studies, including prophylactics for infections such as influenza, flu virus, human papillomavirus, hepatitis B and C viruses, bacillus Calmette-Guérin (BCG), measles, and poliovirus. The coated microneedle shows several distinct advantages over the usual hypodermic needle method of delivering therapeutic compounds. These include the quick release of the medicated agent, the ability for bioavailability, dosing consistency, and suitability for small or large biological molecules for the treatment or prevention of disease (28).

Therapeutic loading capacity remains a primary limitation of coated microneedle systems, largely dictated by coating thickness and microneedle geometry (32). To address these constraints, several strategies have been developed, including optimization of array dimensions, increased needle density, and the application of electrostatic layer-by-layer (LbL) coating techniques (33,27). These innovations have significantly improved the efficiency of vaccine delivery, particularly against viral pathogens and cancer-associated antigens.

Yet, despite such developments, issues still lie ahead in translating basic science into medicine. These include non-uniform distribution of the drug, overall capacity for loading, repeatability, and scale-up. In manufacturing, for instance, Kim et al. Showed that the highest amount of inactivation. The flu vaccine could be loaded at 7-8ug in five needle arrays (34). This exemplifies that there is still an imminent need for innovative formulation and design concepts in patch development that improve efficiency and the overall amount that can be delivered (35). Promising clinical results also began to appear. Successful delivery of influenza vaccines by high-density influenza vaccine microneedle patches was shown in phase 1 clinical trials conducted by Vaxxas Pty., which showed very good tolerability, safety, and a six-fold reduced dose compared to the traditional intramuscular route without compromising immune responses (36). Other benefits mentioned were its dose sparing and superior thermostability, rendering it unnecessary to rely on cold chain distribution. Indeed, this was further supported by the intact antigen compositions of coated influenza vaccines that were found to be stable at 40 degrees, demonstrating their applicability even in resource-limited regions (37).

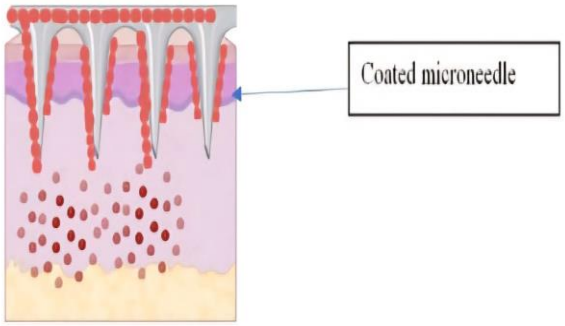

FIGURE 3: Coated Microneedle

Dissolving Microneedles:

Biocompatible, water-soluble, and biodegradable polymers or saccharides are basic materials in preparing dissolvable microneedles. These transdermal drug delivery systems are designed to use a poke and release process of dissolution of microneedles in the skin upon penetration, to ensure easy release and systematic diffusion of the loaded drugs (38). These microneedles have been found to offer a unique advantage over solid microneedles and hollow microneedles, especially due to simplified production methods and one-step patch delivery (27). The preparation process involves micro-moulding, where micro-solidification of aqueous solutions of materials to be used is carried out in molds of specific shapes. Various polymeric, saccharide materials such as polyvinylpyrrolidone, polyvinyl alcohol, hyaluronic acid, chitosan, polycaprolactone, carboxyl-methylcellulose, and poly (lactic-coglycolic acid) are used to prepare microneedles (39).In addition, selecting these materials requires careful consideration of factors such as compatibility, solubility, and mechanical properties to facilitate skin penetration (29). Also,cell-friendly materials should be used to prepare microneedles for fragile molecules such as proteins, peptides, and vaccines, which require mild process conditions to retain their biologic functions (32).

Dissolving microneedles have proven to be very promising for the stability of antigens at room temperature and thus solved issues associated with cold chains for various antigens like influenza, malaria, and hepatitis B. Moreover, the storage stability studies showed full maintenance of the adenovirus vaccine's immunopotency even when the adenovirus vaccine was prepared as a dissolving microneedle array and subjected to accelerated storage conditions (40degrees and 75%RH for 8-12weeks). Moreover, the stability

of the vaccine remained unaffected for six months at the intermediate storage conditions (40).

Swelling Microneedles:

Swelling microneedle (MN) systems represent an innovative platform for painless and minimally invasive vaccination. These systems are typically composed of hydrogel-forming polymers that, upon insertion into the skin, rapidly absorb interstitial fluid and swell, creating microchannels for efficient antigen delivery. Unlike dissolving microneedles, which dissolve completely within the skin, swelling microneedles maintain their structural integrity, allowing for controlled and sustained release of vaccine payloads. Upon insertion into the skin, these microneedles rapidly swell by absorbing interstitial fluid (ISF), enabling controlled drug release while preserving their structural integrity for safe removal. Their natural ability for extracting and retaining ISF makes swelling microneedles a promising tool for diagnosis, where they take advantage of biomarker-dense characteristics of ISF (41).

Porous Microneedles:

Porous microneedles are emerging as a promising tool in transdermal drug delivery due to their ability to enhance therapeutic administration via micro/nanoscale channel networks. These microneedles are fabricated using biocompatible materials such as metals (e.g., titanium, stainless steel), ceramics (e.g., alumina), and polymers (e.g., PLGA, PDMS, cellulose acetate). Metallic and ceramic microneedles, produced through sintering and anodization, offer high mechanical strength and controlled porosity. However, polymers are favored for simpler, cost-effective manufacturing. The porous structure enables high drug-loading capacity, allowing these microneedles to act as self-contained delivery systems for both liquid and solid drugs upon insertion into the skin.

COMPOSITION OF MICRONEEDLES:

A wide range of materials can be used to make microneedle arrays, all of which are approved by the FDA (20). Silicon was the first material to be used to make microneedles, which proved very useful due to its high flexibility, enabling microneedles with a wide range of shapes and sizes to be made. But there are a number of disadvantages associated with the microneedles made of silicon, such as a high cost of production, a prolonged process, and multi-step processing (44). Metals, such as stainless steel and titanium, which have been widely recognized as biocompatible materials for a very long time, are also widely used to make microneedles. For example, silica glass can be employed to construct microneedle patches with various shapes and sizes of microneedles at a faster and smaller manufacturing level.

Although being relatively strong, silica glass is brittle and mostly demands manual fabrication. By contrast, carbohydrates offer a more convenient method for the fabrication of microneedles on patches because they can easily be formed from hot melts or slurry material. Moreover, the use of carbohydrates as components for the preparation of dissolvable microneedles makes the drug delivery system completely non-toxic and very cheap to use. Some common carbohydrates that can be used as components for the preparation of dissolvable microneedles include maltose, sucrose, and mannitol. A major constraint for the use of carbohydrate-based microneedles is the requirement for high temperature during the fabrication process, hence limiting the drugs that can be combined. Moreover, they are very sensitive to temperature and humidity. Consequently, FDA-approved polymers for the fabrication of dissolvable microneedles include polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), hyaluronic acid, and polylactic acid, which are widely employed due to their biocompatibility, biodegradability, low toxicity, sufficient mechanical strength for skin penetration, and cost-effectiveness (20,45,46).

FACTORS AFFECTING MICRONEEDLES EFFICACY:

However, to achieve better MN efficiency, there must be an optional design feature (low insertion force and high fracture force). Such an optional design is influenced by various factors, such as MN dimension, tip size and sharpness, speed and force of application, size density, and interspace among MNs.

MN Geometry:

Geometry is a significant aspect in microneedles (MNs) that has been shown to directly impact the mechanical strength and penetration efficiency, as well as comfort. It has been found that the more vertices a polygon has in the MN design, the greater the mechanical strength (11). It has been a common observation that the MN design is done on a pyramid or a cone with a width-to-height aspect ratio between 1:1 and 1:3 (44).

Research reveals that microneedles with sharp edges, such as those with a triangle and square base, can insert deeper compared to microneedles with hexagonal shapes (47, 48).

Tip Diameter and Sharpness:

The diameter of the tip of the microneedle affects the insertion depth, and the sharpness significantly affects and controls the force of penetration. Sharpness that is excessive may affect the integrity and strength of the microneedle, thereby resulting in breakages (49). Romgens etal determined that it is vital to have sharp-tipped microneedles that have a tip diameter of less than 15 µm to have effective drug delivery, especially in vaccine delivery

Application Velocity and Force:

Application velocity and force are critical factors for the effective penetration of microneedles (MNs). It is essential to apply enough force in order to break through the stratum corneum and make microspores, which will help in drug delivery (50). It has been shown that the application force of 15–20 mN would be adequate for the successful insertion of a microneedle (51,52). It might be necessary, however, to apply the needles using controlled application devices to minimize variability in manual application (27).

Length:

The length of microneedles plays a crucial role in drug delivery systems. The microneedle should be of sufficient length to traverse over the outer cutaneous barrier and then target the dermis, thereby providing minimum drug loss and optimal drug uptake. Larger microneedles with higher volume capacity for drug delivery are more ideal, but this could lead to pain due to nerve endings. Some reports indicate microneedles with a height of less than 750 µm are less painful (53, 54). Optimally, their length needs to be drug-dependent, with shorter needles possibly required for highly permeable drugs, while longer needles are preferred for rapid drug delivery, since they target the dermis rich in blood vessels (40).

Density and Microneedle (MN) Interspace

Higher Needle Density: Increases the number of microchannels, allowing for greater drug diffusion and higher drug loading.

Bed of Nails Effect: When too many needles are packed together, insertion becomes difficult because the applied force is distributed across all needles. This means more pressure is required for skin penetration.

Solution – Varying Needle Lengths: Using microneedles of different lengths in the same array can reduce the overall insertion force needed, mitigating the bed of nails effect.

ADVANTAGES OF MICRONEEDLE-BASED PAINLESS VACCINATION:

Transdermal microneedles show long-term efficacy advantages over existing techniques of immunization by needle and syringe delivery. These novel needles ensure a small amount of microbes are carried, along with easy, painless delivery with less neural stimulation and pain perception. The delivery across assures no hemorrhage and entry of pathogens, with easy development, which can be easily done with or without medical assistance, thus ensuring easy immunization, especially in developing areas (46). Easy development helps to increase complications associated with vaccination, especially for multi - dose immunization (47).

Microneedles reduce the risk for both needlestick injury and cross-contamination exposures while optimizing the process for disposal. With the advantages for use, as well as the optimization for dosage, high-level immunogenic reaction, and improved rates for vaccination, the continually reduced cost for immunization delivery is achieved (48). Furthermore, microneedles demonstrate broad compatibility across vaccine categories, including live, inactivated, and subunit formulations (49,50), generating comparable or superior immunogenic response relative to traditional vaccination methods (51,52).

Microneedle technology greatly improves vaccine distribution, allowing targeted delivery to the vascularized dermis and epidermis, thereby triggering antigen-presenting cells and facilitating high antigen-specific antibody production (53). From the aspect of the pharmaceutical stability, there exists a certain n distinguished advantage in vaccine delivery by microneedles. Due to the solid formulation in microneedle vaccine technology, there exists greater thermal stability than in liquid vaccine formulations. This greatly facilitates thermostability when there exist certain stabilized excipients of dry vaccine form (63). This clearly does not require any reconstitution or utilization of cold chains (16) and makes microneedle technology a distinguished alternative to conventional injections (54).

The methodology of application for microneedle systems depends on the configuration and may employ either direct pressure or specialized applicators designed to combat the viscoelastic properties and mechanical resilience the skin provides. Vaccines may also be added through surface or embedded directly within the microprojections, which help to improve stability properties. These technology advancements have been reported to provide several benefits, which include the absence of needle=stick injuries,

needles as a source of anxiety, cross-contamination, or the need for specialized or skilled personnel. Various benefits can be offered by the combined approaches offered by the microneedle systems, which include optimized dosing, improved thermal stability, reduced dependencies for cold chain transport, vaccine versatility, and improved access, especially by the resource -limited sites, making the technology a promising alternative for current methods of injections (16,54,55).

VACCINE CHARACTERISTICS AND LIMITATIONS OF MNs IN VACCINE DELIVERY

According to the literature, MNs have been applied as carriers for various types of vaccine formulations, which include whole inactivated virus vaccine, subunit vaccine, DNA vaccine, plasmid, recombinant protein vaccine, or antigen vaccine (56,57,58,59,60). In an ideal vaccine for MN delivery, though, the vaccine should be thermostabilized with preserved antigenicity after processing, like sterilization (62).

Moreover, each type of MN chosen for delivery has its advantages and disadvantages. For example, hollow MNs may be appropriate for liquid vaccine delivery. However, this type of MN needs an injector and skilled personnel. Moreover, the formulation needs to be considered, especially the formulation that is less stable in the liquid form. Coated MNs can easily be injected and can deliver a stable solid vaccine formulation. However, the need for an applicator and formulation procedures may be required for successful delivery. Finally, dissolving MNs has the same characteristics, with the additional advantage that it dissolves into the skin without leaving sharp residues (61). Furthermore, the dose accuracy of MN is less accurate compared with hypodermic needles. The MN needs to be carefully injected vertically to prevent losing the dose and penetration uniformity. Stratum corneum varies among individuals. Skin condition may also affect the dose delivery/bioavailability (63).

FUTURE PERSPECTIVES OF MICRONEEDLE-BASED SYSTEMS:

Immunization programs remain the cornerstone of epidemic preparedness and control, especially in a world where new pathogens may emerge rapidly. While nucleic acid–based vaccines (mRNA, DNA) have proven their worth in speed and adaptability (e.g., the COVID-19 vaccines), the delivery technology still represents a major frontier. Microneedle (MN) systems hold strong promise to transform how vaccines are administered, especially in scenarios where conventional injections face logistical, behavioral, or infrastructural barriers.

Microneedle platforms offer compelling advantages: painless or minimally painful delivery, self- or minimally trained administration, reduced sharps waste, and potential stabilization of antigens in dried or solid forms. These features make them especially attractive for remote or resource-limited settings, needle-phobic populations, mass immunization campaigns, and areas with broken cold-chains. At the same time, several scientific, technical, and regulatory challenges must be overcome before full development.

CONCLUSION:

Microneedle -based delivery systems have already shown considerable potential in the area of vaccination, with the capacity for accurate delivery of vaccine doses into specific layers of the skin. This could specifically help improve both safety profiles as well as the bioavailability rates associated with vaccine administration. Recently, an improved comprehension of cell-mediated or mucosal immunity has given considerable insight into immunological correlates associated with vaccine -induced immunity. Nonetheless, both areas of vaccine delivery remain in their early stages. In the long run, it is necessary to work towards the development of specific designs that promote rapid, large-scale immunization (63). Moreover, the use of microneedle-based vaccine delivery may present its specific benefit within high-risk groups, which include older individuals, immunocompromised patients, or cancer patients with decreased immune responsiveness, presently requiring novel, improved immunization strategies (64). Recently, there has been considerable interest in the use of microneedle-based vaccine delivery platforms, with considerable funding offered by the National Institute of Health, amounting to a grant worth US$10 million to further explore these developments for an influenza vaccine within the realm of clinical trials (65,66).

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