Transdermal approaches to vaccinations in the COVID-19 pandemic era

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Therapeutic Advances in Vaccines and Immunotherapy
2021, Vol. 9: 1–13
DOI: 10.1177/25151355211039073

***Abstract*:** The COVID-19 pandemic has necessitated rapid vaccine development for the control of the disease. Most vaccinations, including those currently approved for COVID-19 are administered intramuscularly and subcutaneously using hypodermic needles. However, there are several disadvantages including pain and fear of needlesticks, the need for two doses, the need for trained health care professionals for vaccine administration, and barriers to global distribution given the need for cold supply chain. Recently, transdermal techniques have been under investigation for vaccines including COVID-19. Microneedle array technology utilizes multiple microscopic projections from a plate which delivers a vaccine in the form of a patch placed on the skin, allowing for painless antigen delivery with improved immune response. In this review, we discuss challenges of existing vaccines and review the literature on the science behind transdermal vaccines including microneedles, current evidence of application in infectious diseases including COVID-19, and considerations for implementation and global access.

Keywords: access, COVID-19, microneedle, pandemic, patch, transdermal, vaccine

Received: 27 April 2021; revised manuscript accepted: 23 July 2021.

Introduction

Vaccines are biological formulations containing live or attenuated antigen that elicit an immune response, confer long-lasting immunity, and serve an essential role in reducing morbidity and mortality for numerous infectious diseases.[1] In 2020 alone, over 124 million cases of COVID-19 were diagnosed as part of the worldwide pandemic and over 2.74 million individuals lost their lives to the disease globally,[2] spurring prophylactic vaccine development and delivery into a global health priority. As of March 2021, 3 vaccines had been approved by the US Food and Drug Administration, an additional 289 experimental COVID-19 vaccines were in development, 66 were in clinical testing, and 5 had been authorized by regulatory authorities or the World Health Organization (WHO) internationally.[3] Numerous questions arose in the first few months following successful vaccine development regarding the prioritization, allocation, and distribution of vaccines. For example, over half of the initial reserved doses of COVID-19 vaccines were purchased by high-income countries which comprise just 14% of the world's population, potentially resulting in shortage of vaccines in low-income countries.[4]

One significant consideration in current vaccine development is the route of vaccine administration.[5–7] Most vaccines throughout history – including the currently approved vaccines for COVID-19 – have been administered intramuscularly and subcutaneously using hypodermic needles.[8,9] While effective at introducing antigens systemically for an immunogenic response, these modalities have several disadvantages, including pain with and fear of needlestick, limited thermostability, the need for trained health care professionals for vaccine administration, contamination of multidose vials, transmission of blood-borne

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disease through needlestick injuries, and generation of hazardous waste.[10–13] There have been additional challenges in determining the most equitable and efficient access to vaccines, such as overcoming supply-chain and distribution challenges to deliver vaccines to resource-limited regions, particularly where electricity for vaccine refrigeration is limited.[11,14,15] As vaccine development efforts continue to improve rapid and safe delivery of vaccines in a scalable manner, there has been increased attention given to other routes of vaccine administration.

Recent innovation efforts have investigated the potential for transdermal approaches such as microneedle (MN) patches as an alternative modality for painless drug delivery.[1,16–19] MN array technology utilizes multiple microscopic projections from a plate, which delivers a vaccine in the form of a patch placed on the skin; these patches allow for painless antigen delivery with potentially improved immune response due to their capacity for sustained release. Furthermore, MN patches deliver high concentrations of vaccine to the localized skin environment, which is rich in antigen-presenting cells and has the potential to elicit a dose-sparing effect that enables single-dose vaccine delivery.[4] This technique has been applied successfully to vaccine delivery in influenza and other infectious diseases.

More recently, transdermal techniques have been under investigation for the COVID-19 vaccine, with several research groups showing early evidence of success in *in vivo* models.[20,21] The successful development of MN patch vaccines has significant implications for the future of vaccine delivery and the reduction in burden of disease of COVID-19. In this review, we discuss the challenges of existing vaccine modalities, the science behind transdermal delivery including MN patch technology, types of MNs and fabrication, current evidence of COVID-19 MN vaccine efforts, strengths and weaknesses of the MN approach, and considerations for implementation.

Challenges of existing vaccine modalities and promise of transdermal approaches

Currently, vaccines are delivered via two main formulations: vials or ampoules for single or multidose administration, or prepackaged syringes for hypodermic needle injection.[22] While some vaccines are available orally – such as rotavirus, adenovirus, cholera, and typhoid – the vast majority of vaccinations are delivered via hypodermic needles, which are effective for systemic administration but have numerous adverse effects.[1] Hypodermic injection is a modality of drug administration using sterile needle encompassing intramuscular, intravenous, subcutaneous, and subdermal routes, and has multiple strengths. Given that these routes bypass the gastrointestinal tract, drugs can be delivered directly and rapidly systemically without first pass-effect nor need for an intact absorptive barrier. Furthermore, with proper technique, hypodermic administration allows for consistent, reliable drug delivery with 100% bioavailability. Despite these advantages, hypodermic needles also have numerous drawbacks.[13] A comparison of attributes between hypodermic needles and MN systems can be divided into three main categories: biological, psychological, and procedural (Table 1).

From a biological standpoint, hypodermic needles effectively deliver a bolus of antigen to trigger humoral immunity. However, it has been shown that bolus administration leads to rapid clearance of antigen, requiring booster vaccines to enhance antibody formation from memory B cells.[23] Furthermore, when multidose vials are not immediately used, repeated entry as well as prolonged open time increase risk of microbial contamination.[22] This risk is increased in low- and middle-income countries, where re-use of contaminated syringes is a common phenomenon due to limited resources, leading to transmission of blood-borne diseases.[22] A study examining rates of contaminated injections found that in 2000, contamination from injections caused up to one-third of new hepatitis B infections, 40% of new hepatitis C infections, and 5% of new HIV infections worldwide.[24] Even in developed countries, needlestick injuries remain a prevalent occupational hazard that prompts both anxiety of health care staff injured, as well as increased health care resource expenditure in diagnosis and prophylactic treatments.[22,25]

From a psychological standpoint, emotional trauma and fear of vaccines is a prevalent phenomenon, affecting up to 50% of adolescents and up to 30% of young adults.[26] Reasons for the phobia range from seeing injection needles to fear of associated pain, leading to poor

Table 1. Comparison of hypodermic injection and MN patch techniques.

Categories of attributes	Hypodermic injection[7–12,20,23–26]	MN patch[13,21,26–28]
Biological	**Advantage:** Rapid systemic drug delivery without first-pass effect. **Disadvantages:** Bolus administration leads to rapid antigen clearance, often requiring boosters Risk of bleeding, microbial contamination, and infection Risk of needlestick injury including with improper waste disposal, with potential for transmission of blood-borne diseases Adverse reactions at local injection sites, e.g. pain, erythema	**Advantages:** Enhanced humoral immunity through delayed antigen release. Minimal skin trauma, reduced skin bleeding, and pathogen introduction or contamination No needlestick injury risk during administration or waste disposal Minimal risk for transmission of blood-borne diseases **Disadvantages:** Adverse reactions at local application sites, e.g. allergic reaction, skin irritation Potential challenge of decreased permeability to larger, hydrophilic molecules
Psychological	Needle phobia leads to decreased patient compliance	Reduced needle phobia given painless injection
Procedural/ Distribution	**Advantage:** Cheaper to manufacture **Disadvantages:** Requires cold supply chain, access to electricity for refrigeration, which are expensive and limit vaccine access and distribution Requires trained personnel to administer	**Advantages:** No need for cold supply chain, facilitating increased vaccine access and distribution Can be self-administered **Disadvantage:** May be more expensive to manufacture depending on fabrication technology

MN, microneedle.

patient compliance. In a systematic review and meta-analysis by McLenon and Rogers,[26] the authors found that approximately one-fifth of adult patients and one-fourth of hospital employees avoid annual influenza vaccinations due to fear of needles, illustrating the significant impact of subjective perception of hypodermic needles in decision-making regarding vaccine compliance.

From a procedural standpoint, hypodermic needle administration of vaccines and drugs requires trained medical staff, which may be a major limitation in resource-poor environments. Furthermore, disposal of contaminated sharps waste requires specialized autoclaves and incinerators which are not always available in developing countries. As a result, individuals who are uneducated about the potential hazards of medical waste often become inadvertently infected with blood-borne diseases in the process of waste recycling.[27,28] In this setting, there is clearly a need for a safer, more effective modality for vaccine delivery.

Transdermal drug delivery systems (TDDSs) such as MN patches are a promising alternative to hypodermic needles for multiple reasons. As TDDSs do not stimulate nerves in the dermal layer of the skin, they do not cause pain, improving patient compliance.[29] Given that MN arrays are submillimeter in size, they cause minimal skin trauma, reducing risk of skin bleeding and pathogen introduction. From a psychological perspective, there is reduced concern for needle phobia given the small size of the needles on the patches and painless injection. Moreover, TDDSs allow for self-administration, giving patients agency over the vaccination process, reducing associated anxiety. From a biological standpoint, MN patches have also been shown to enhance humoral immunity due to their capacity for sustained antigen release, which allows for effective, single-dose vaccines.[23] From a procedural perspective, TDDSs reduce risk of contamination and unsafe injection practices leading to injury from sharps, and improper hazardous waste disposal, which cause an estimated 33,800 HIV infections, and 1.7 million hepatitis B infections, and 310,000

hepatitis C infections annually.[28] Overall, in terms of cost-efficiency, it is estimated that MN patches can potentially save over $2.6 billion to the US population over a single influenza season.[30] Because they do not require trained staff to administer, are single use, and are easily disposable, TDDSs reduce many barriers for point of care (POC) sites without risk of transmission of blood-borne pathogens to both staff and patients. Beyond their efficacy and safety, MN patches may also solve several challenges regarding vaccinations in developing countries through elimination of dependence on cold chain distribution and trained staff at the POC, as well as by reducing hazardous biological waste.[23]

Science of transdermal approach and MN array technology

The skin is a favorable target for drug delivery because of its robust immunogenicity and the fact that delivery to more confined spaces within the skin allows for higher antigen concentrations.[14] There are three layers in the skin – the epidermis (100–150 μm thickness) which contains the stratum corneum (10–20 μm thickness), and dermis (typically 3–4 mm thickness).[11] The epidermis and dermis are rich with keratinocytes, melanocytes, and Langerhans cells, which are the antigen-presenting cells that present antigens to T cells to activate the immune system. Given that the skin is both a strong physical barrier and also provides strong immunogenicity, transdermal vaccines must have the ability to penetrate through the stratum corneum and epidermis and target the antigen-presenting cells within the dermis. While several transdermal approaches have been studied in the literature including transdermal electroporation, sonophoresis, jet or powder injection, iontophoresis, and skin radiofrequency and laser ablation, the most widely applied technique is the MN patch or array.[1]

MN technology consists of a polymer-based plate with hundreds of microscopic needles usually 25–2000 μm in height that penetrate into the skin.[31] Their construction from strong water-soluble polymers allows them to penetrate the stratum corneum and epidermis before resting in the dermal interstitial fluid, where the coating covering the vaccine antigen dissolves and results in high concentration of local vaccine delivery.[1] Released vaccine is then taken up by antigen-presenting cells and presented to T cells for priming. In addition to the adaptive immunity from the antigen delivered, the mechanical stress of MN injection can induce a natural local innate immune response.[1] MNs are short enough to avoid pain receptors to reduce sensations of pain, providing a distinct benefit over conventional injections.[1,32]

Types of MNs and fabrication techniques

There are multiple categories of MNs including solid, drug-coated, hollow, and dissolving subtypes. Solid MNs work by physically disrupting the stratum corneum and creating microscopic pores for drug delivery. They are usually made from silicon, metal, ceramic, or polymer and are fabricated through isotropic, anisotropic, or silicon-etching processes, or 3D laser ablation.[11] While solid MNs have multiple advantages in their physical strength and stability, they have lower drug loading – the amount of drug applied on the needle surface – and are more likely to trigger skin inflammation, irritation, or infection due to biological incompatibility. Coated MNs are covered in agents that help stabilize the needles themselves and are fabricated through dipping or spraying. They are valuable for their strength and moderate drug dosing.[1,5,6] However, the drug may not remain adherent to coated MNs until delivery, as it may peel off or detach during storage. Hollow MNs are filled with the drug that are delivered directly into the site and constructed by a variety of techniques including microprojection arrays and microfabrication; while they allow for high doses of drug loading and more accurate dosing, there is significant risk of fracture from mechanical weakness and a chance of infection.[1,5,6] The last type of MN system is the dissolving MN, where fast-dissolving materials such as polymers or sugars are mixed with the drug or antigen in the matrix, and dissolve upon insertion into the skin to release the active ingredient.[5,33] This MN type is typically fabricated through a process called micromolding and has the potential for cost-effective fabrication with high drug loading; however, it is weaker and has poor biocompatibility. Both existing COVID-19 MN vaccines in development as of early 2021 use dissolving MN platforms.[10,21] The newest forms of MNs are constructed from hydrogel, which uptakes water and swell when inserted into the skin; drugs can either be incorporated into their

polymeric structure or be loaded and attached on top of the needles themselves.[34,35] Advantages of this technique include its higher drug loading capacity, superior biocompatibility, and ability to be fabricated into various shapes.[31,34] However, they have a limited rate of drug delivery because the drug is released in an initial burst then a steady state.[34]

There are multiple fabrication techniques for MN patches which have been well-explored in the literature, including etching, lithographic, and laser cutting. Micromolding is the most common method of constructing dissolving MNs whereby a polydimethylsiloxane (PDMS) mold is produced from a silicon or metallic mold.[36] The most common materials include silicon, metals, ceramic, silica, and polymers. The molding method involves microfabrication procedures such as photolithography, X-ray lithography, and UV lithography.[1] However, this method requires significant time and a sophisticated clean-room setup, which makes the technique expensive for large-scale vaccine development and delivery. Other methods include droplet-born air blowing to shape the polymer droplet to the MN, layer-by-layer assembly onto MNs, laser ablation to engrave a metal or polymer plate into a 3D geometry.[11,18]

The application of MN vaccine delivery systems for other diseases before the COVID-19 pandemic has been widely reviewed in the literature.[1,11,20] There have been numerous preclinical and clinical studies of vaccines using MN systems for a range of infectious diseases including influenza, BCG, MERS, polio, measles, rubella, hepatitis, and varicella zoster.[37–43] Of these, influenza has had the most robust studies, leading to currently commercially available MN vaccine delivery systems.[39,44] Prior studies have demonstrated similar immune responses between influenza vaccines delivered by conventional hypodermic injection and a dissolving MN influenza patch, and also have found no difference between self-administered influenza vaccine patches and patches administered by trained personnel.[37,45]

Current COVID-19 MN vaccine development efforts and early evidence

COVID-19 MN vaccine development efforts have met with early evidence of success (Table 2). A team at the University of Pittsburgh reported on an MN-delivery recombinant coronavirus (SARS-CoV-2) vaccine and conducted preliminary testing *in vivo* in mice models.[10] This research group previously showed that the spike (S) protein is an ideal vaccine target, as expression of SARS-CoV-S1 and MERS-S1 subunits resulted in a naturalization through antibodies compared with the full-length S1.[47] Kim and colleagues[10] fabricated their dissolvable MN carboxymethyl cellulose-based device against SARS-CoV-2 targeted against the S protein. Their study showed early evidence of SARS-CoV-2 vaccinated animals producing adequate antibodies for virus neutralization. In addition, they noted that MN delivery of the vaccines resulted in stronger immune responses than those administered by traditional methods, with observed virus-specific antibody responses 2 weeks after immunization.[10] Additional efforts demonstrated that the vaccine maintained potency even after gamma radiation sterilization,[10] an important step to eliminate microorganisms from medical devices to ensure safe use in humans.

The work of the University of Pittsburgh team has several notable strengths. The production of dissolvable MNs in quantities adequate for preclinical testing and generation of significant levels of antibody titers early on support feasibility of development, production, and preclinical testing of an MN vaccine against SARS-CoV-2. Limitations of the initially reported work include the lack of access to neutralization assays to ensure neutralizing antibody function, which may take up to 6 weeks to occur. Thus, it remains to be demonstrated whether there will be similar responses in immunized humans. Future studies should determine whether there is effective virus neutralization and protection from infection in animals immunized with the MN SARS-CoV-2 vaccine, and also investigate differences in immunogenicity between MN and traditional coronavirus vaccines.

A research team in Hong Kong (Kuwentrai and colleagues) has reported another dissolvable MN device developed for SARS-CoV-2 vaccination targeted against proteins in the receptor-binding domain (RBD) in the S1 subunit of the S protein in a formulation mixed with low-molecular weight hyaluronic acid.[21] They have reported that the

Table 2. Summary of COVID-19 MN vaccine studies.

Ref	MN Type	Study outcome	Strengths	Weaknesses	Future studies
Kim and colleagues[10]	Dissolvable MN carboxymethyl cellulose-based device	SARS-CoV-2 vaccinated mice produced adequate antibodies for virus neutralization Stronger immune responses than with traditional methods, with observed virus-specific antibody responses 2 weeks after immunization Vaccine maintained potency even after gamma radiation sterilization	Produced dissolvable MNs in quantities adequate for preclinical testing MN delivery resulted in significant levels of antibody titers	Unable to demonstrate neutralizing antibody function due to lack of access to neutralizing assays	Need to determine presence of effective virus neutralization and protection from infection in animals Need to investigate differences in immunogenicity between MN and hypodermal coronavirus vaccines
Kuwentrai and colleagues[21]	Dissolvable MN device with low-molecular weight hyaluronic acid	MN device was successful in penetrating mouse skin Significant B-cell antibody and IFN-gamma T-cell responses for 97 days	Demonstrated presence of T-cell IFN-gamma responses, which may serve as antiviral protective factors and may be as important as B-cell responses against SARS-CoV-2	Not effective for delivering mRNA, as there was no induced protein expression compared with bolus injection Variable titers of S protein receptor-binding domain antibodies compared with subcutaneous injection Expensive development, with high technical expertise and equipment required	Need to ensure sterility, as this MN vaccine was unable to be sterilized using steam, radiation, or gas after fabrication Need more consistent and precise deployment technique of the MN, as this study relied on thumb press technique
Kuwentrai and colleagues[46]	Dissolvable MN device with low-molecular weight hyaluronic acid	MN NP triggered both B-cell antibody responses as well as T-cell INF-gamma responses Demonstrated the presence of CD4 and CD8 T-cell markers in the lungs of mice immunized with NP	Provides evidence in support of NP as an alternative vaccine target to the S protein receptor-binding domain NP antibody titers were comparable with those produced by the subcutaneous injection method NP antibody activity was not affected by storage in a dehumidifier for a month	Expensive development, with high technical expertise and equipment required	Maintaining MN sterility in production laboratory sites, improving cost-effectiveness of MN fabrication, and creating applicators to ensure more standardized MN deployment Investigate the therapeutic potential of combining MN NP and MN S protein receptor-binding domain

IFN, interferon; MN, microneedle; NP, nucleocapsid protein.

MN device was not only successful in penetrating mouse skin but also resulted in significant B-cell antibody and Interferon-gamma T-cell responses.[21] The authors suggest that the T-cell Interferon-gamma responses may serve as antiviral protective factors and may be as important as B-cell responses against COVID-19.[21] Their observed antibody response was similar to that demonstrated by Kim and colleagues,[10] although for a longer time after administration, up to 97 days. In addition, the specific T-cell response detected by enzyme-linked immune absorbent spot (ELISpot), an assay measuring cytokine secretion, had not been shown by the previous study. They also found that the deployment of tips from the device took 10 s, facilitating quick

vaccination. However, one limitation of this study was that the MN method was not effective for delivering mRNA, as there was no induced protein expression compared with bolus injection. Another limitation was the high variation in titers of specific S protein RBD antibodies produced by the MN method compared with subcutaneous injection, which are possibly attributable to loss of antigen activity during MN formulation.[10] In addition, this technique is also quite expensive given the high technical expertise and equipment required. Another necessary step before clinical use of this technology includes ensuring sterility, as this MN vaccine is unable to be sterilized using steam, radiation, or gas after fabrication, and fabrication in a germ-free production laboratory site would require regulatory body support.[6] Finally, there is a need for a more consistent and precise deployment technique of the MN, as this study relied on thumb press technique which is user-dependent in terms of efficacy.

The same research team also developed a dissolvable MN targeted against the nucleocapsid protein (NP) of SARS-CoV-2.[21] They fabricated the MN patches through micromolding NP from *E coli* with hyaluronic acid with a PDMS negative mold. They showed that MN NP triggered both B-cell antibody responses as well as T-cell Interferon-gamma responses and demonstrated the presence of CD4 and CD8 T-cell markers in the lungs of mice immunized with NP.[21] The strength of this work is that it provides evidence in support of NP as an alternative vaccine target to the S protein RBD. In addition, the vaccine showed significant T-cell INF-gamma responses which are important protective factors against COVID-19. In addition, the researchers found that NP antibody titers were comparable with those produced by the subcutaneous injection method, and that NP antibody activity was not affected by storage in a dehumidifier for a month. Future directions include maintaining MN sterility in production laboratory sites, improving cost-effectiveness of MN fabrication, and creating applicators to ensure more standardized MN deployment.[21] The group also plans to investigate the therapeutic potential of combining MN NP and MN S protein RBD.

A fourth team based out of Swansea University has also reported exploration of a transdermal COVID-19 vaccine.[48] The Swansea group has reported that their vaccine platform can monitor biomarkers in the skin to measure vaccine efficacy in real time. At the time of this review, there were several announcements surrounding its pending development but no publicly released data. Finally, there are additional research groups funded through the Biomedical Advanced Research and Development Authority (BARDA) to create MN patches with the spike protein, though data are yet to be released regarding these efforts.[9]

Special considerations for global access and delivery of transdermal vaccines

As the COVID-19 pandemic continues to affect countries across the world, it is critical for countries to scale up vaccine production, distribution, and administration. There are many special considerations for the development and delivery of transdermal vaccinations in developing nations due to resource limitations.[28]

The challenges with current vaccine modalities are especially notable in developing countries, areas struck by natural disasters, human conflicts, and pandemics such as COVID-19. During these emergencies, there is often disruption of existing infrastructure; the lack of reliable transportation, electricity, or skilled staff to administer the vaccines creates tremendous logistical barriers to effective vaccination.[22,28] In low- and middle-income nations, the lack of reliable electricity and the costs involved in ensuring adequate refrigeration of vaccines during storage and distribution phases are particularly challenging. For instance, a study of cost to distribute vaccines in Vietnam found that 44% of the community health centers did not have access to consistent refrigeration.[49] The study found that key drivers of cost per vaccine were transportation (43%) and costs related to cold chain (depreciation as well as energy expenditure), which amounted to 25% of costs,[49] illustrating the potential for cost savings should cold chain not be required. Transdermal vaccines may address these issues in several ways.

Transdermal vaccines may provide broader access to developing nations given that they eliminate the need for a cold supply chain. Core to vaccination delivery is the distribution process, beginning from manufacture or point of origin, to storage, distribution, and eventually POC sites where the

vaccine is administered.[49] A critical component of vaccine delivery is cold chain storage, which requires vaccines to be refrigerated and transported in chilled, insulated boxes to maintain content integrity. Currently, the majority of hypodermic vaccines are packaged in three forms – prefilled syringes, liquid vials, or lyophilized vaccines.[49] Prefilled syringes are convenient and eliminate contamination of multidose vials, but are also expensive to prepare and require more space during transportation and storage. Liquid vials are more cost-efficient as more volume can be delivered in less space; however, they require drawing and filling of syringes at POC sites, which may lead to errors such as administration of wrong dosages, microbial contamination, and waste if the multidose vials are not fully utilized. Lyophilization, otherwise known as freeze-drying, can stabilize more labile vaccines for improved storage capacity. Such vaccines are initially formulated as liquids and then lyophilized to be shipped dry; this may be less cost-efficient, requiring liquid diluents necessitating cold chain capacity and be rehydrated at POC sites.[22] This is both costly from a storage standpoint and more time-intensive.

TDDSs such as MN patches have been proposed as an effective solution to many of these challenges. From a process standpoint, TDDSs require less storage space, are thermostable without need for cold chain supply, and do not need trained staff to apply.[28,50] As the transdermal patches are single use, they prevent vaccine waste from multidose vials, which have been estimated to be as high as 25% for liquid vials to 40% in lyophilized vaccines, an issue that is particularly severe in developing countries.[51]

MNs also have tremendous potential to help increase equitable global access to COVID-19 vaccines. However, mechanisms are needed to ensure affordable and sustainable provision of MN vaccines in low- and middle-income countries, which are more likely to lack financial resources to purchase vaccines. For example, wealthier countries secured pre-orders at higher prices and secured more COVID-19 vaccines than would be necessary to vaccinate their entire population, potentially precluding access for lower income countries. The lack of access for lower income countries may prolong the pandemic and increase the risk of additional viral mutations, potentially negating the efficacy of current vaccines.[3] As an attempt to mitigate this, the WHO facilitated the creation of the COVID-19 Vaccine Global Access (COVAX) Facility, a global allocation mechanism whose aim is to help provide all countries with access to a diversified vaccine portfolio at low prices, with different price points for high- and low- to middle-income countries. Despite this, however, the wealthiest countries have secured over 70% of early doses of the five leading vaccines directly from the developers.[3] This highlights the need for regulation of MN patch distribution to ensure equity across countries.

Implementation considerations and recommendations

There are several considerations for implementation of transdermal vaccinations including vaccine development, public education, understanding public perceptions and eliciting widespread support across cultural contexts, and ensuring equitable access and distribution.

There are several challenges in the development of MN vaccines for COVID-19 that need addressing before their widespread implementation. Significant challenges include device fabrication, optimization of antigen dose and formulation, manufacturing capacity, and minimizing cutaneous adverse reactions such as skin irritation, allergic reaction, and the rare possibility of needles being left in the skin.[11,29] Furthermore, MN patches require even, consistent application to the skin for adequate vaccine delivery. Devices to assist in this process are also currently being researched. It is important to note that there have been promising advances in MN patch technology over the past three decades. For example, MNs may now be fabricated using laser ablation techniques at a low cost, without requiring a clean room. In addition, novel Micro-Projection Arrays techniques have demonstrated clinical efficacy in both preclinical and clinical trials.[1] More research and resources are needed toward improving scalability of TDDSs as a first line modality for vaccines.

Future vaccine development efforts should focus on ensuring and testing vaccine efficacy, stability and sterility to ensure safe use in humans, and should explore different application devices.

More studies will be needed to prove that MN vaccines are of at least equal efficacy to hypodermic vaccines, as administration otherwise may not be ethical. In addition, patients may report preference for vaccines delivered via injection, even if painful, over a painless but less-effective MN alternative.[52] Following manufacturing, there is also a need for more research and efforts into the effect on the supply chain; while theoretically MNs should be easier to store and distribute given they are much smaller, there is no need for cold chain, and there is a reduced risk of sharps, the true thermostability in extreme climates must be explored. Finally, further development efforts should also focus on sterilization methods that can make MNs more feasible for safe use in humans.

Importantly, the implementation of MN technology would require public support of this route of administration; focus groups and surveys have already shown widespread public support for MN usage. A survey of adults in the United States vaccinated by Intanza, a MN patch vaccine for influenza, showed that 96.6% were 'satisfied' or 'very satisfied' and 93.7% would choose to receive future vaccination through MN patch if given the option.[53] Other studies have shown that children have positive views on MN use as an alternative to hypodermic needles and that parents felt positively about MN monitoring for infants.[54,55] A study by Birchall and colleagues showed that patients and health care providers felt that the potential benefits included reduced pain and reduced tissue damage, especially for children and patients afraid of needles. These studies provide encouraging evidence of public acceptance of this technology which will be critical for successful deployment.

Widespread adoption of this technology will also require public education efforts, especially around self-administration and avoidance of misuse. Studies have shown that subjects without prior experience were successfully able to self-administer MNs with a short set of instructions and with excellent outcomes.[31,52,53] One study conducted by Donnelly and colleagues[31] gave volunteers an informational leaflet and short teaching by a pharmacist and found that application of MN array had comparable increases in transepidermal water loss (TEWL), a measure of skin barrier function, whether the MNs were self-applied by novice volunteers, the researcher, or the experienced personnel, thus indicating that all subjects inserted the MNs to relatively similar depths as each other. This provides an example of how development of informational handouts and expert teaching may be effective methods of education, as participants felt that MN could be easily used by the public if given a similar form of instruction and possibly with use of a placebo to practice before the real vaccine. Additional education methods such as short instructional videos could easily be shared through digital platforms to highlight best practices for transdermal vaccine administration.

Subjects in the prior study of MN application raised concerns about knowing whether the correct dose had been administered; other research has also suggested subjects felt it would be important to have an indicator on the device to show the user that the correct dose had been delivered.[52] While early education and implementation efforts have shown evidence of success, special attention may need to be given to ensure adequate education for those with barriers to access including patients with low literacy, low English proficiency, elderly populations, or those who may not have access to a health facility to receive in-person training.

In addition to public education, it will be important to ensure public acceptance and implementation of education efforts across cultural contexts. First, different populations may have different perceptions of, and comfort levels with, MN technology for COVID-19 vaccine. One systematic review of COVID-19 vaccine acceptance rates across 33 countries found that low rates of vaccine acceptance were found in the Middle East, Russia, Africa, and several European countries, many of which were under 60%.[56] These low rates may pose barriers for control of COVID-19 and suggest the need for additional considerations for acceptance of MN vaccines, which may also carry different public perceptions. COVID-19 vaccine hesitancy differences across countries may correlate with belief in the natural origin of the novel coronavirus, with some observed differences potentially attributable to increased threat perception and out-group mistrust.[57] Even within countries such as the United States, it is important to acknowledge different perceptions of vaccinations among demographic groups. For

example, African Americans are more likely to report structural barriers to vaccination and hesitation about vaccines.[58,59] Thus, community efforts will be necessary to help educate the public and also address public perceptions of MN vaccines to ensure adequate awareness and implementation in a culturally sensitive manner that does not exacerbate existing health disparities.

There is also evidence to suggest that self-administered MNs can improve vaccination coverage and cost-effectiveness,[1] and that 30% of previously unvaccinated individuals would be amenable to vaccination if offered MN technology.[54] For example, one analysis showed that MN patches for influenza vaccination could increase both efficacy and compliance, preventing about 402,000 influenza cases a year in the United States, saving third-party payers $102 million and society $416 million.[30] In a study examining the cost-effectiveness of measles vaccination using hypodermic needle injections *versus* MN technology, it is estimated that MN vaccination costs $0.95 (range $0.71–1.18) per dose compared with syringe and needle administration, which costs $1.65 (range $1.24–2.06) per dose. While these early studies have suggested the cost-effectiveness of MN technology as well as satisfaction and support for MN,[60] there needs to be additional assessment and education to ensure optimal vaccine delivery. Thus, while these early studies have suggested satisfaction and support for MN and that such vaccines can be successfully administered by patients, there needs to be additional assessment and education to ensure optimal vaccine delivery.

As hypodermic vaccinations will likely continue to be an option while MN vaccines are initially deployed, considerations will need to be made for whether certain populations should be prioritized in accessing this technology. For example, 92% of public and health care professionals think that children in particular would benefit from MN vaccine administration given the painless and easy administration, and prior studies of measles vaccines in children have demonstrated efficacy.[52] In addition, the single-dose administration may make it more attractive to deliver to populations who are harder to reach and with barriers to access to vaccines. For example, when the single-dose Janssen/Johnson & Johnson vaccine was approved in the United States, there was an increase in usage among homeless populations, who traditionally face access challenges.[61] Similarly, the single painless administration of MN vaccinations may make them a useful modality to reach additional populations for whom two doses of a hypodermic needle vaccine may be less desirable.

Conclusion

Transdermal approaches including MN array technology represent a promising method of vaccine delivery with potentially significant advantages over hypodermic injections including painless delivery, increased immune response, increased efficacy and safety, and increased global access to vaccines. MN patches have already been applied successfully to vaccine delivery in influenza and other infectious diseases, and early preclinical studies of MN array vaccine development against SARS-CoV-2 show promise of success. Successful implementation efforts will include optimization of vaccine development, assessing public perceptions, promoting public education across cultural contexts, and ensuring equitable access and distribution.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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