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REVIEW

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Microneedle technology for potential SARS-CoV-2 vaccine delivery

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ABSTRACT

Introduction: Microneedle fabrication was conceptualized in the 1970s as devices for painless transdermal drug delivery. The last two decades have seen considerable research and financial investment in this area with SARS-CoV-2 and other vaccines catalyzing their application to in vivo intradermal vaccine delivery. Microneedle arrays have been fabricated in different shapes, geometries, formats, and out of different materials.

Areas covered: The recent pandemic has offered microneedle platforms the opportunity to be employed as a vehicle for SARS-CoV-2 vaccine administration. Various modes of vaccination delivery and the potential of microneedle array-based vaccines will be presented, with a specific focus placed on recent SARS-CoV-2 research. The advantages of microneedle-based vaccine administration, in addition to the major hurdles to their en masse implementation, will be examined.

Expert opinion: Considering the widely acknowledged disadvantages of current vaccine delivery, such as anxiety, pain, and the requirement for professional administration, a large shift in this research sphere is imminent. The SARS-CoV-2 pandemic has catalyzed the development of alternate vaccination platforms, working to avoid the requirement for mass vaccination centers. As microneedle vaccine patches are transitioning through clinical study phases, research will be required to prepare this technology for a more mass production environment.

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Microneedles; skin vaccine; pain-free; minimally invasive; SARS-CoV-2; vaccination; vaccine patch; theranostics

1. Introduction

1.1. Vaccination

Infectious diseases have plagued society throughout recorded history, requiring the development of an increasing number of vaccine classifications to ensure these diseases can be managed. From the 19th century onwards vaccination researchers have been recording substances that inactivate microbes to elicit immunity, contributing to the increase in United Kingdom life expectancies from 40 to 81 years [1]. Critically, advancements have been made in laboratory technologies and a better understanding of how infection is hosted and transmitted. Most recently, the global collaboration and financial injection into the fight against SARS-CoV-2 has very significantly accelerated enhancements in understanding infectious disease, and vaccine technology in response to it. As of April 2022, the European Centre for Disease Prevention and Control (ECDC) reported 6,158,591 deaths from SARS-CoV -2 since 2020, with vaccinations such as those produced by Pfizer, Moderna, and the University of Oxford/AstraZeneca responsible for providing 81% protection against death in the UK alone [2,3]. Common vaccinations have long been required for certain employments e.g. BCG, Hepatitis B, Influenza, and Varicella vaccinations for individuals in care and medical professions. Vaccination enforcement remains, however, a contentious topic, with the SARS-CoV-2 vaccinations adding further to medico-scientific and political debate [4].

Vaccination delivery has been trialed through an array of modalities, broadly classified into mucosal and parenteral routes. Mucosal routes, including oral, nasal, and sublingual delivery, although can typically experience better patient compliance, suffer from limited bioavailability, and resultantly require elevated dosages. Parenteral vaccination routes encompass administration by means other than the mouth and alimentary canal, with common examples being intramuscular and subcutaneous injection routes. The current mode of vaccination delivery is intramuscular injection via a hypodermic needle and syringe; however, this modality is associated with a wide range of disadvantages, and is currently used due to necessity and financial limitations. Shortcomings of this approach vary from patient anxiety, and the potential for needlestick incidents, to the requirement for professional administration. Needle phobias and needle-related anxiety are major obstructions in the rollout of vaccinations, with studies reporting 24% and 63% of the parents and children, respectively, to experience trypanophobia, with this being the primary reason for immunization noncompliance in 7% and 8% of these groups, respectively [5]. In support of this, a recent study investigating vaccine hesitancy in an Irish population ($n = 105$) identified its prevalence as 6.7%, with 36.2% and 20% of the parents concerned about side effects and safety, respectively [6]. These studies collectively support the need for further development within the field of vaccine delivery, specifically for vaccinations through a minimally invasive MN approach to create increased uptake.

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Article highlights

- The preferred mode of vaccination delivery has not evolved since hypodermic needles were invented in 1852, despite the vaccination technology itself undergoing huge advancement
- The use of microneedles to create cavities in the skin for drug delivery was conceptualized in 1976, however the technology at the time prevented their advancement
- The SARS-CoV-2 pandemic has highlighted the need for advancement in medical devices for vaccine delivery, mitigating professional administration and cold-chain storage requirements
- Recent research has reported on novel microneedle array patches with impressive thermostability over prolonged periods
- Furthermore, microneedles have demonstrated significant dose sparing, with as great as 10-fold increases in immunogenicity compared to traditional delivery modes. This offers the potential to eradicate vaccine shortages, which was experienced during the SARS-CoV-2 pandemic.

Moreover, the worldwide prevalence of needlestick injuries spanning a healthcare worker's career is reported to be 56.2%, with individuals put at risk of exposure to diseases such as human immunodeficiency virus (HIV) and Hepatitis B and C [7]. A WHO-sponsored review published data revealing at least 50% of injections in sub-Saharan Africa, Asia, and the former Soviet Republic were unsafe, and risked patient exposure and contraction of blood-borne diseases such as HIV [8]. Furthermore, in circumstances whereby global health is dependent upon vaccine rollout speed, as with SARS-CoV-2, current delivery modalities are limited by the requirement for professional administration, due to the specific training required, and cold-chain storage conditions [9].

In an attempt to improve patient compliance and meet vaccination quotas, as well as minimize the risk of needlestick and eliminate the requirement for trained professionals, the scientific community investigated the oral administration route. The oral polio vaccine was the first to be developed, requiring three doses at set intervals to confer acceptable immunity, partially on account of the poor bioavailability of oral formulations [10,11]. Despite their favorability due to their noninvasive nature, oral formulations must withstand the hostile environments of the gastrointestinal (GI) tract, often rendering the drug less efficacious, requiring greater dosage, and therefore risking increased incidence of side effects [12].

1.2. The principles of vaccination

Vaccinations are medications that prime the body's immune system, arming it with highly specific defense mechanisms to fight a disease upon potential infection. They are used variously to stimulate the body's immune system depending on their classification. Summarized in Table 1 are the four generally accepted classifications of vaccinations; (i) whole pathogen, (ii) subunit, (iii) genetic, and (iv) viral vector vaccines [13]. Upon vaccine administration, the innate immune system provides the first of a two-pronged defense against non-self-pathogens. Independent of antigen generation, the nonspecific innate immune system deploys immune cells such as natural killer (NK) cells, macrophages, dendritic cells, neutrophils, and mast cells. These cells classically respond in a phagocytotic manner, with further protection generated through microbe activation of pattern recognition receptors (PRR), resulting in the production of pro-inflammatory cytokines. Furthermore, they enable the downstream transcription of interferon-stimulated genes (ISGs) through the JAK-STAT pathway, producing the antiviral cytokines type I and II interferons, and type II, responsible for the promotion of macrophage activation. This rapid response aims to prevent any spread of microbes throughout the body and tends to peak at 24-h post-exposure (Figure 1).

In the days following the innate immune response, the more specific, adaptive immune response is raised, deploying T lymphocytes and, arguably most importantly, B lymphocytes, for antibody production. This second prong of the immune system's defense is antigen-dependent, with antibodies raised against the unique epitope provided via vaccination. Following the clearance of the non-self-microbes, the T and antibody-producing B lymphocytes are reclassified as memory cells for the cleared infection. The antigen-experienced memory cells lie dormant until reinfection, upon which a rapid anamnestic response is raised to produce a more aggressive and robust memory CD4+ and CD8+ T cell response than the initial [14]. The ability of the memory cells to generate a more potent response is ultimately dependent on the lifespan of the cell and the infection it is primed against, with differing data reported on a disease-by-disease basis. Although too early to report on the long-term immunity of COVID, the preservation of memory cells has been credited with the lifelong protective immunity post-vaccination in multiple disease states, such as smallpox, with an 88-year follow-up study demonstrating no decrease in vaccination-specific antibody titer in 97% of the participants (n = 246) [15]. This longevity is not expected for COVID vaccinations, with the specificity of memory cells becoming a disadvantage upon the emergence of new variants. Promisingly, studies have reported the third vaccination to significantly diversify the population of memory B cells, in some cases enabling the production of antibodies capable of clearing a diverse range of variants, such as Omicron [16].

1.3. Parenteral vaccine delivery

The vaccination delivery route is crucial when establishing its formulation, with differing routes (summarized in Figure 1) having niche requirements, from gastroenteric-resistant coatings for oral vaccines to lipid membranes for RNA vaccines [17,18]. The formulation is designed specifically to ensure the greatest bioavailability and efficacy of the drug, ensuring suitable immunity can be conferred. Parenteral delivery routes are predominantly used for vaccination administration, as critically they offer greater bioavailability on account of bypassing the harsh environment of the gastrointestinal tract, providing ease of entry into the bloodstream for transfer around the body [19] (Figure 2).

To discuss parenteral routes of drug delivery, the skin must be discussed as both a barrier to be bypassed to enable drug delivery, and as an organ that can be harnessed to perpetuate the conferred immunity. A key feature of the skin is its barrier

Table 1. A summary of the four main vaccination classifications, their subclassifications, and examples.

Vaccine Type		Differentiating factor	Example	Ref
(i) Whole pathogen	Live attenuated	Whole pathogens 'weakened' via genetic modification to confer protective immune responses	Rotavirus vaccine	[13]
	Inactivated	Whole pathogens are killed to prevent the ability to replicate	Inactivated polio vaccine	[14]
(ii) Subunit	Recombinant protein	A small viral DNA section is transfected into a yeast/bacterial cell, which produces the viral protein. This is purified and included as the active pharmaceutical ingredient	Hepatitis B vaccine	[15]
	Toxoid	Toxins (inactivated toxins) are delivered to allow the immune system to recognize and mount a response, without the poisonous risk of the toxins	Tetanus vaccine	[16]
	Conjugate	Toxoid connected to a polysaccharide chain, to enable better recognition by the immune system, and resultantly confer heightened immunity	Meningococcal C vaccine	[17]
	Virus-like particles	Non-infectious molecules are synthesized to mimic viruses, displaying antigens, which can be recognized by the immune system	HPV vaccine	[18]
	Outer membrane vesicles (OMV)	Toxic antigens are removed from the outer membrane vesicles of bacteria, and suitable antigens which generate immune responses are key	Meningococcal B vaccine	[19]
(iii) Genetic	RNA	Viral mRNA enters the body via a lipid membrane, where it enters cells and is translated into the antigen protein. The mRNA degrades, and the antigen protein generates an immune response	Pfizer BioNTech SARS-COV-2 vaccine (BNT162b2) Moderna SARS-COV-2 vaccine (mRNA-1273)	[20] [21]
	DNA	Administered via electroporation, DNA is taken up into cells and transcribed to mRNA, followed by its transcription into antigen protein which stimulates immune response	Currently, no licensed vaccines	-
(iv) Viral vectored	Replicating	A nonpathogenic virus is used to deliver to human cells the genetic information for vaccine antigens, allowing the body to produce the viral antigens. Specifically, enabling the virus to replicate allows greater production of vaccine antigen, enhancing immunity. The presence of preexisting immunity to some viral vectors can lead to a reduction in efficacy.	Ebola vaccine	[22]
	Non-replicating	Viral vectors have the genes required for replication removed, and only allow for the delivery and production of the antigen protein. The presence of preexisting immunity to some viral vectors can lead to a reduction in efficacy.	Oxford-AstraZeneca SARS-COV-2 vaccine (AZD1222) Janssen SARS-COV-2 vaccine (Ad26.COV2.S)	[23] [24]

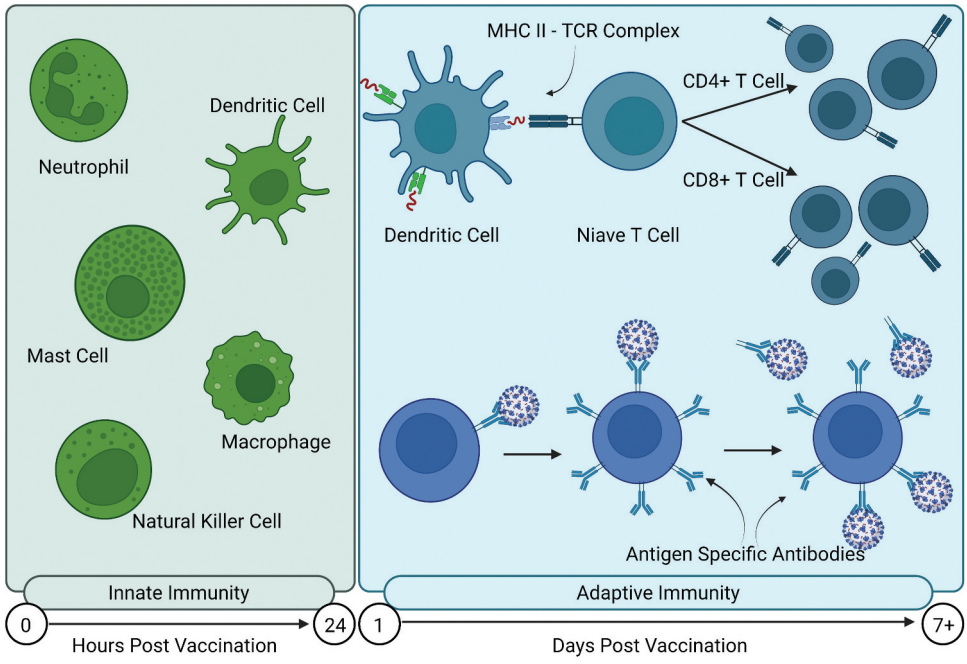

Figure 1. A schematic of the progression from innate to adaptive immunity relative to time post-vaccination. Created with BioRender.Com.

properties, which are essential for the preservation of human health. The *stratum corneum*, the outermost epidermal layer, prevents both the uncontrolled loss of water through the skin, while inhibiting the entry of undesirable materials [20]. With topical administration of drugs generally demonstrating poor efficacy, needles and syringes represent the current gold standard for vaccinations, by enabling the bypass of the corneocyte-containing lipid matrix forming the *stratum corneum* [20] (Figure 3).

Classically, hypodermic needles have been used to breach the *stratum corneum* barrier, injecting drugs into the muscular or subcutaneous tissue. Such depth of penetration is not necessary for immune response and may limit the conferred immunity generated (Figure 3). With respect to needle-free alternatives, topical ointments, and transdermal patch-style drug delivery are well established in terms of patient compliance and expense, with ease of self-application and manufacture a highly sought within the pharmaceutical industry. These

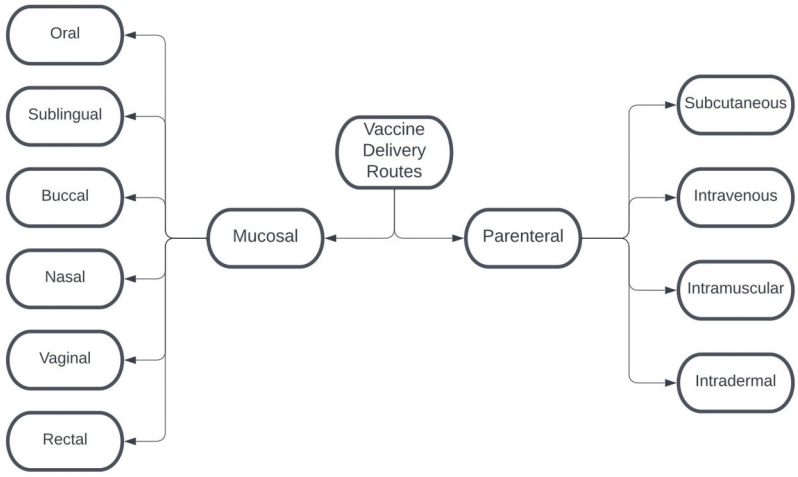

Figure 2. A schematic of the types of vaccine delivery routes.

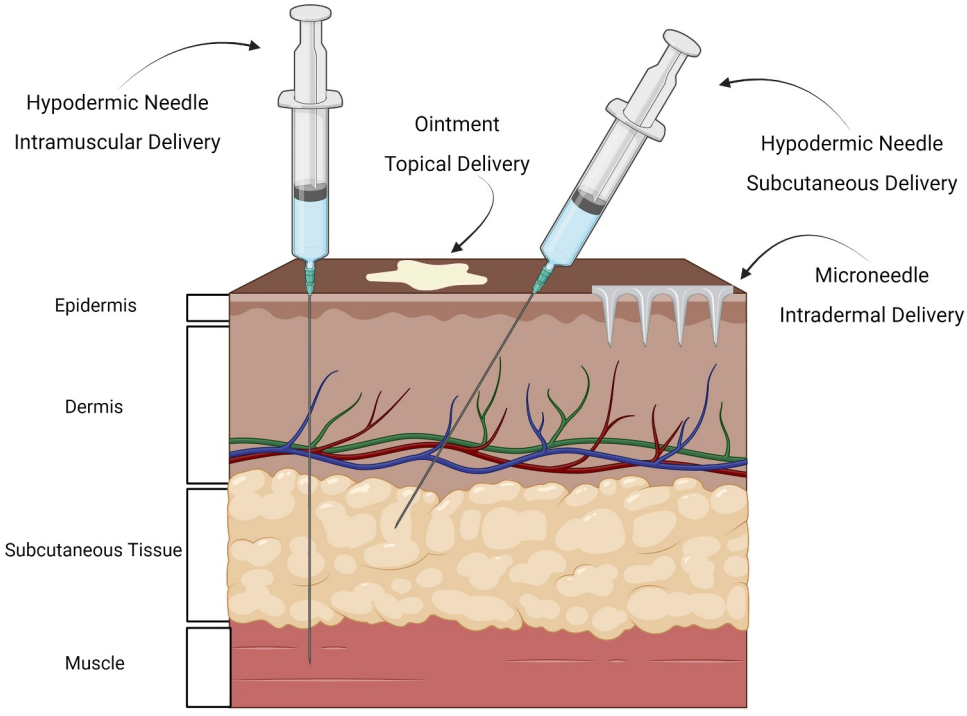

Figure 3. A comparison of the penetration of hypodermic needles, ointments, hypodermic needles, and MNs. Created with BioRender.Com.

noninvasive systems avoid the significant effects of hepatic first-pass metabolism, which is acknowledged to contribute to poor bioavailability through gastrointestinal incompatibility and premature metabolism. There are, however, hurdles to their widespread adoption, with the majority of drug formulations having a molecular weight in excess of the '500 Dalton rule' resulting in limited absorption through the skin [21].

As an active immune organ, the skin houses an arsenal of resources to raise an immune response to pathogenic or vaccine materials, which break the *stratum corneum*. Through direct targeting of the epidermis, interaction, and resultant contact with the dense network of the immune sentinel LCs can be maximized. This is crucial as LCs contribute to the determination of both the innate and adaptive immune response of the skin and retain the ability to migrate from the epidermis to draining lymph nodes, which may contribute to the dose-sparing potential of microneedles (MNs) [22,23]. Working in concert with LCs are epidermotropic and dendritic epidermal T lymphocytes, which are suggested to provide an early form of the more mature systemic T-cell immune surveillance [24]. On account of the recruitment of the aforementioned immune cells within the epidermis, the delivery of vaccination intradermally generates a humoral immune response equivalent to more traditional intramuscular and subcutaneous delivery routes with only a fifth of the standard dose [25]. This warrants significant investment into the

development, optimization, and commercialization of MN devices that can accurately, and reliability target the epidermis to harness this biological sink of immune potential.

2. Introduction to microneedle technology

MNs arrays were first theorized for drug delivery many decades ago, but only became the subject of development in the mid-1990s when microfabrication processing enabled their production [26]. Their application has been widely explored over the years in three main areas: cosmetics, diagnostics, and therapeutics. The geometry and design of the devices depend largely on the drug being delivered, but with a focus on ensuring minimal invasiveness to mitigate the pain experienced by the user. The MN length should be sufficiently long to penetrate the epidermis where there is interstitial fluid, whilst avoiding contact with nerves or triggering pain receptors in the muscle tissue.

MNs for drug delivery can be classified into four general categories: (i) solid; (ii) coated; (iii) dissolvable; and (iv) hollow. Following the discussion of these distinct categories, recent research investigating the delivery capabilities of MN arrays will be introduced

2.1. Solid MNs

Solid MNs are used for skin pre-treatment by creating micropores in the skin. An external drug reservoir, in the form of a patch, cream, gel, lotion, or ointment, is then applied to the pre-treated area [27]. This drug delivery method is termed 'poke and patch.' The drug diffuses into the skin for local treatment, and it can be further delivered to other body systems through capillaries in the skin compartment. This method, however, restricts this type of delivery to a bolus of drug, with sustained release not possible due to the pores in the skin healing rapidly [28]. The MN material must possess high mechanical strength to enable *stratum corneum* penetration. Although a sharper tip allows MN insertion into skin tissue with a smaller force, this critical dimension can be limited by the choice of material. Common materials used to produce solid MNs include silicon, metal, non-degradable, biodegradable polymers, and ceramics, with metal and silicon devices recognized to facilitate a smaller tip angle [29–33].

Fabrication of silicon solid MNs could involve isotropic dry etching and anisotropic wet etching methods [34–36]. A combination of both methods takes advantage of lower fabrication costs using wet etching methods and overcomes geometrical limitations imposed by anisotropic etching methods [34,37]. Metal MNs can be fabricated using laser cutting, metal electroplating, three-dimensional laser ablation, and wet etching methods [30,38–43]. Polymers used to produce MNs are often ultraviolet-curable, hence these MNs are not as mechanically strong as silicon and metal MNs [26]. Polymer MNs are typically made by photolithography into master structures that are used in mold-making for replication purposes. An inverse mold is formed by pouring a silicone polymer onto the master structure and allowing it to cure. Filling the mold with molten thermoplastics, namely polycarbonate and poly(methyl methacrylate) (PMMA), and allowing it to cool and solidify, forms non-degradable polymer MNs [44,45]. Biodegradable MNs, also known as dissolvable MNs, are discussed in section 2.3. Ceramic MNs can be fabricated by micro-molding and ceramic sintering, as well as lithography [33,46–48].

2.2. Coated MNs

Coated MNs are solid MNs, which have been externally coated with the drug to be delivered. The drug delivery method employed is termed 'coat and poke,' whereby the MNs are pushed into the skin and the drug coating is allowed to dissolve before the main body of the MNs is removed from the skin. The dimension of the MN tip and shaft is the limiting factor for the volume of drug that can be delivered, usually below 1 mg for small MN arrays [49]. The procedure for coating MNs often involved dipping or spraying [49–52]. Dipping each MN into microwells filled with a coating solution or into a thin layer of coating solution on a roller surface is a good strategy for coating the MN tips in isolation, avoiding contamination of the base substrate [49,50].

There are five considerations to be made when formulating the coating solution [49]; (i) coating wetting and spreading; (ii) water-solubility; (iii) mechanical strength; (iv) excipient biocompatibility; and (v) protection of the active pharmaceutical ingredient (API). Wetting and spreading of the coating solution on the MN substrate must be well-regulated to ensure uniformity of the coated layer, with surfactants and thickeners commonly used to enable formulation customization to provide the desired coating behavior [49,52–54]. Importantly, dried coatings require high mechanical strength for optimal adhesion to the MN substrate, enabling sound delivery following insertion into the skin [55]. Sound API delivery and stability is also impacted by the excipients and solvents used in the coating formulation, which may need to be recharacterized following the change in delivery mode [56]. Crucially, the coating procedure needs to be carried out without damaging the drug molecules, and the procedure needs to be compatible with industrial pharmaceutical manufacturing processes. Commonly, stabilizers can be used to protect the drugs, especially during the coating and drying processes [57]. A wide range of compounds can be coated onto MNs including small molecules, macromolecules, vaccines, DNA, and micron-scaled particles. However, in order to do so, each of the five above criteria must be considered and optimized [50–52,54,55,57–65].

Coated MN has the potential to facilitate sustained release, whereby the devices would be left implanted in the skin until the coating dissolves. This requires design changes, however, with a flexible base plate to conform with the deformation of the skin for user comfort, whilst mechanically strong enough for efficient, low-pressure penetration [28]. Furthermore, studies assessing the biocompatibility and biofouling of any potential material must be considered to ensure the device can be left implanted in the skin until complete drug release.

2.3. Dissolvable MNs

Dissolvable MNs deliver drugs via the 'poke and release' method, whereby the MNs are inserted into the skin and allowed to dissolve completely, releasing the drug. A major advantage of using these MNs is the absence of biohazardous sharp waste production. It is of paramount importance for dissolvable MNs to be composed of materials that are biocompatible and water-soluble to fulfil their function. Dissolvable MNs are fabricated using micro-molding methods, which involve dissolving materials in water and filling the solution into molds where solidification takes place [32,66–68]. These MNs can also be fabricated using drawing methods. During the fabrication process, it is critical to note that the encapsulation and solidification of drugs or compounds that are sensitive to heat should be done at moderate conditions to avoid any damage [56]. Moreover, drug encapsulation should be focused on the MN tips to ensure that the full volume of the drug is being delivered upon insertion of the MNs into the skin [69,70].

Cryogenic microneedles (cryoMNs) are an emerging design of MNs, formulated predominantly from substances including phosphate-buffered saline (PBS), dimethyl sulfoxide (DMSO), sucrose, and cells, fabricated using a PDMS mold. Beneficially, the cells delivered have the potential to be patient-derived, enabling the coveted approach of personalized therapeutics. The living cells are suspended within the cryoMNs are held within an optimized cell medium and have been pre-modified to carry out cell therapy, such as cancer immunotherapy or stem cell therapies [71,72]. To enable their fabrication, the devices require freezing at −60 and−80°C for 4 and 2 h respectively, before being further exposed to liquid nitrogen (−196°C) for 1 h. Although dependent on the composition of the device, cryoMNs have been reported to melt within 30 s of removal from liquid nitrogen into a 24°C room [71]. The cryogenic methodology enables the cells to retain viability, since melting follows insertion that enables cellular proliferation in the dermal layer leading to enhanced migration. Despite cryoMNs potential, widely acknowledged disadvantages to their deployment remain, notably their requirement for specific and extreme cold-chain transport and storage conditions, as well as surplus training for healthcare professionals to ensure correct use.

Dissolvable MNs have the greatest potential with respect to controlled release, a key advantage with respect to MN devices over hypodermic alternatives. They also offer the alternative for customization with respect to release, with different polymers resulting in different drug release outcomes. For example, hydroxypropyl cellulose (HPC) and hyaluronic acid (HA) are utilized for immediate-release MNs, and poly(lactic-co-glycolic acid) (PLGA) selected for their sustained-release properties [73]. Dissolvable MNs also enable their dissolution to be modified with respect to biological and environmental stimuli. In 2016, Hardy *et al.* produced hydrogel-forming MNs composed of crosslinked ethylene glycol dimethacrylate and poly (2-hydroxyethyl methacrylate) (PHEMA) to fabricate a photosensitive device measured to produce up to 160 h of light-mediated prolonged release [74]. It is important, however, to note that the complete dissolution of dissolving microneedles is difficult, which therefore can limit dosage. To maximize dosage, Chu and Prausnitz reported the fabrication of separable dissolvable MNs, with polymer dissolving tips detaching from the rigid metal shaft following insertion, allowing the tips to dissolve with sustained-release kinetics [75]. More recently, in 2019 Boopathy *et al.*, reported on their implantable, dissolving MN which were fabricated to sustain the intradermal delivery of an HIV subunit vaccination [76]. Promisingly, in comparison to the traditional bolus delivery mode, their reports detail enhanced B cell responses and significantly superior humoral immunity with a 16 and ~ 1,300 fold elevation in bone marrow plasma cells and serum IgG titers, respectively [76].

2.4. Hollow MNs

Hollow MNs have channels for substances to flow through. Like the 'poke and flow' method, which is similar to hypodermic injections, hollow MNs promote minimal invasiveness and inflict little or no pain. Once the MNs have penetrated the skin, the drug can be administered through pressure-driven flow or diffused from a drug reservoir without the application of additional pressure [77]. The former drug delivery method usually involves only individual MNs, whereas the latter method involves an array of hollow MNs [38,78]. Some advantages of delivering drugs by using the second method include a higher drug delivery rate compared to subcutaneous injection due to wider coverage, higher bioavailability, and potential for lymphatic targeting [79,80]. For the hollow MN array to deliver drugs effectively, equal pressure must be applied to all the MNs, without leakage. Fabrication of hollow MNs usually employs microelectromechanical systems (MEMS) techniques such as deep reactive ion etching of silicon, deep x-ray photolithography, integrated lithographic molding technique, laser micromachining, wet chemical etching, and microfabrication [38,81–84]. In addition, hollow MNs are also useful for the extraction of body fluids whereby glass and silicon hollow MNs have been employed for the extraction of interstitial fluid, whereas stainless steel hollow MNs have been employed for taking blood samples [85–88].

2.5. MN Arrays

MN arrays are not a subclassification of device design but are rather a description of the collation and orientation of individual devices. Typically, a hundred of these devices are arranged as a cluster on one device, to maximize the quantity of drug delivered by maximizing surface area. It is based on their potential as robust platforms for the delivery of higher quantities of drugs, arrays of MNs, as opposed to individual structures. Despite this potential, however, they have been criticized with respect to their critical dimensions and the insertion force required, often being referred to as potentially eliciting a 'bed of nails' effect. Recent studies have investigated MN arrays of varying materials, examining their fracture points and insertion forces relative to tip width and base diameters. Critical dimensions and material properties are beginning to be defined, for example, to minimize penetration

force, array pitch must be optimized, with 150 mm spacing recommended to minimize insertion force [89]. The degree of both axial and transverse mechanical loading on the device before must also be evaluated to ensure appropriate safety margins, with Park & Prausnitz recommending a Young's modulus of 3 GPa to prevent failure along the axial plane for polymeric MNs [90]. A recent study performed by Chang *et al.*, utilized ANSYS/LS-DYNA software to demonstrate the most appropriate shape for pharmaceutical delivery to be the tapered cone, due to its lowest insertion force and elite drug capacity, requiring a base diameter of <100 um to prevent *stratum corneum* damage [91]. In 2021, a complementary paper by Shu *et al.*, demonstrated the critical nature of pre-tension of the skin, with a reduction of 13% and 15% penetration force and efficiency, respectively, recorded for 10% strain [92]. Interestingly, the presence of an array base plate was evidenced to limit penetration efficiency by 27%, potentially suggesting a redesign of this basic structure to optimize array performance [92].

3. SARS-CoV-2

3.1. SARS-CoV-2 mode of action

The spike (S) protein of SARS-CoV-2 binds to ACE2, found throughout the body but particularly prevalent on the surface of cells within the lungs and heart, and is required for receptor attachment purposes and the activation of transmembrane protease serine 2 (TMPRSS2) [93]. Upon this dual binding and activation, the virion is endocytosed and uncoated via the host trypsin and furin-mediated proteolytic cleavage at the S1/S2 site of the S protein [94]. The proteins composing the nucleocapsid are degraded via proteosomes, allowing the release of the single-stranded viral RNA strand to be released into the cytoplasm of the host cell. Composed predominantly of non-structural proteins, the viral replication/transcription complex facilitates the replication and transcription of the viral genome. Proceeding this, through the utilization of host cell replication machinery, the positive viral genome is translated to protein from open reading frame 1a/b, crucially producing two polyproteins PP1A and PP1AB [94]. Containing within their sequencing two main proteases (Mpro/3CLpro and PLpro), the cleavage of PP1A and PP1AB into their functional components is facilitated [95]. Following their synthesis, structural proteins such as the membrane, nucleocapsid, S, and envelope proteins are synthesized in the cytoplasm and ultimately are transferred to the endoplasmic reticulum-Golgi intermediate compartment (ERGIC), where they undergo self-assembly ahead of vesicular exocytosis as a new viral particle, which can infect other cells [94]. Following the exocytosis of a new virion, the host's cell undergoes necrosis as a direct result of the stress imparted through viral replication and production.

3.2. SARS-CoV-2 pathology

The innate immune system initially recognizes the SARS-CoV-2 virus and, following the infection of type II alveolar cells and resultant replication as described above, the infected cells secrete proinflammatory cytokines *e.g.*, IL-1b and TNF-a to further activate an immune response. This presents as the initial mild SARS-CoV-2 symptoms of body aches and a persistent cough. Importantly, the cytokines IL8 and TNFa are released to recruit neutrophils and macrophages, stimulating their migration into the alveolar sac where they proceed to secrete IL8, and IL1, IL6, and TNFa, respectively [96]. Crucially, IL6 instigates vasodilation, permitting an influx of immune cells into the alveolus. Within the alveolus, necrotic and dead cells, either through immune mediated necrosis or cell death following viral infection, combine with plasma producing a protein-rich solution, leading to the classic symptom of shortness of breath, which can progress to pneumonia and acute respiratory distress syndrome (ARDS) [97]. In extreme cases, the immune system fails to dampen down its response, leading to an aberrant migration of pro-inflammatory cytokines into the circulatory system, resulting in a cytokine storm [97]. If not treated, this can result in multiorgan failure and death.

3.3. SARS-CoV-2 vaccination

To turn specifically to SARS-CoV-2 vaccinations, two classifications of vaccinations have been deployed: mRNA vaccines (Pfizer and Moderna) and adenovirus vaccines (Oxford/AstraZeneca and Janssen). MNs are an extremely attractive approach for vaccine rollout, especially in a world that continues to expand society into areas of untouched nature, increasing the risk of exposure to foreign pathogens. Furthermore, with a predicted 10% of SARS-CoV-2 vaccine hesitancy due to needle phobia, MNs represent hope for a significant portion of the population who struggle to access vaccinations through the currently available delivery modes [98]. It has been revealed by the World Health Organization (WHO) that, per annum, up to 50% of the vaccinations are wasted globally [99]. A large contributor to this is the thermal stability requirements of cold supply chain and storage at narrow temperature ranges of between 2–8°C, which has not only led to vaccine wastage in countries like the United Kingdom, but also impeded vaccination programme rollout to some African and Asian nations [99]. MN devices may potentially offer a minimally invasive and pain-free delivery route that bypasses the requirement for cold storage, providing solutions to two of the main roadblocks in the roll-out of SARS-CoV-2 vaccinations.

The following sections will briefly introduce each of the current SARS-CoV-2 vaccinations with regulatory approval (Food and Drug Administration (FDA) or European Medicines Agency (EMA), reviewing currently available research surrounding their delivery via an MN or skin patch platform.

3.3.1. Pfizer/BioNTech (Bnt162b2)

The Pfizer vaccination is comprised of a modified nucleoside RNA vaccination coded against the SARS-CoV-2 spike (S) protein, encapsulated in a lipid nanoparticle [100]. When introduced into the body, the RNA is translated into the S protein, which enables B cells to produce antibodies to neutralize the virus upon re-exposure. The S protein is required by the virus to gain entry to type 2 alveolar cells, specifically via the

angiotensin-converting enzyme 2 (ACE2) receptor [100]. Upon reinfection, memory B cells will raise antibodies against the S protein, binding to it and preventing its binding to the ACE2 receptor, resultantly preventing viral entry into type 2 alveolar cells [100]. Despite being the first vaccine granted for emergency-use authorization 7 months following the initiation of clinical trials, the Pfizer/BioNTech vaccine initially required very specific conditions to maintain thermal stability. Originally this formulation requiring transportation conditions of−70°C ± 10°C (15 days), followed by 2–8°C (5 days) for post-thaw storage conditions [101]. Following stability studies, more flexible storage and transportation conditions for the Pfizer-BioNTech vaccination (−25 - −15°C for 31 days) were announced by the FDA and EMA [102].

3.3.2. Moderna (Mrna-1273)

Also utilizing a lipid nanoparticle for encapsulation, the Moderna vaccination is a nucleoside-modified messenger RNA (mRNA) encoding the SARS-CoV-2 S protein [103]. When detected by the host's immune system, the mRNA is translated into the S protein, allowing antibodies to be raised against this viral binding and entry mechanism [103]. To maintain the thermal stability of the active pharmaceutical ingredients (APIs), the Moderna vaccination requires−50 - −15°C for transportation and storage, with post-thaw conditions of 2–8°C enabling stability for further 30 days [104].

3.3.3. Oxford/AstraZeneca (AZD1222)

Technically termed ChAdOx1nCoV-19, the Oxford/AstraZeneca vaccine utilizes a modified chimpanzee DNA adenovirus as a vehicle, delivering similar coding for the viral SARS-CoV-2 S protein to the cytoplasm of human cells where it later migrates to the nucleus for transcription and translation into protein [105]. Following its expression on the cellular surface, the protein aids the activation of T and B cells, raising a humoral, antibody-based response [106]. The Oxford/AstraZeneca vaccination has been recognized as potentially the most appropriate formulation for *en masse* roll-out with conventional hypodermic technologies, with specific regard to resource-constrained low- and middle-income countries, with 2–8°C required for transportation, storage, and distribution conditions [107,108].

3.3.4. Janssen (Ad26.Cov2.s)

The Janssen vaccine is the only SARS-CoV-2 vaccination that uses a non-replicating human adenovirus to deliver the genetic code for the full-length S protein [109]. Similar to the previously discussed vaccines, once the protein has been translated, it allows the induction of antibody-based humoral immune response by binding and preventing viral entry into type 2 alveolar cells [110]. This vaccine has been scrutinized, as it has been demonstrated to be less effective in some cases due to a degree of preexisting immunity to viral vectors [111]. As with the guidance for the Oxford/AstraZeneca vaccination, the Janssen formulation requires 2–8°C for transportation and an extended post-thaw storage capacity of 6 months [112].

4. MN technology for vaccinations

MN technology for healthcare applications such as vaccine delivery was introduced in 1995 to increase gene transfixion [113]. Microfabrication technologies based on silicon were being optimized. Silicon was the first choice of material, primarily used for the fabrication of MN arrays. However, in recent decades, polymeric materials, due to the ease of fabrication, have become popular as materials for high throughput fabrication. We review below the various infectious diseases where MN arrays have been extended for vaccine delivery application, providing some context to the early research of MN for vaccination, before discussing MN for SARS-CoV-2 research.

4.1. Early MN vaccination research

4.1.1. Influenza

The common flu (influenza) is a contagious respiratory illness caused by influenza A/B virion [114]. Widely available are two vaccination types: live attenuated influenza vaccines (LAIV) and inactivated influenza vaccines (IIV) [115]. Influenza places significant strain on health services worldwide, with the Center for Disease Control (CDC) reporting the flu to have caused up to 710,000 hospitalizations and 41 million illnesses between 2010 and 2020 in the USA alone [116]. Therefore, the convenience and potential for minimizing strain on healthcare infrastructure via MN-style delivery has generated widespread interest.

Influenza vaccination via MNs has had a significant amount of research attention and, resultantly, has rapidly progressed from animal models to human studies. A randomized controlled trial conducted by Van Damme *et al.* investigated the dose-sparing potential of intradermal influenza vaccination in healthy adults, finding reduced dosage delivered by MicronJet as comparable with full-dose IM vaccination [117]. This was built upon by Fernando *et al.*, who, in a Phase I clinical trial, investigated the immunogenicity of an influenza vaccine when delivered by a high-density MN patch, Nanopatch™ [117]. Promisingly, 69.9% of the participants reported their preference for an MN patch for future influenza vaccinations, with 98.6% reporting an overall positive experience with the novel devices [117].

4.1.2. Hepatitis

Hepatitis is a category of infectious diseases caused by the Hepatitis virus, which can be contracted through sexual contact, or sharing/second use of needles [118]. The severity of this condition and the high prevalence (355 million people infected with Hepatitis B and C combined in 2021) warrant research into simplified modes of vaccination, improving accessibility and reducing needlestick injury risk [119]. Recently, Cuevas *et al.*, utilized metal and dissolvable MN patches coated with antigen to immunize BALB/c mice and rhesus macaques, with both demonstrating immunogenicity with highly detectable levels of antibodies in the titer (above the 2 mIU/mL detection limit) [120]. Although this has the

potential for greater sustainability, high penetration forces induced mechanical failure, potentially impacting the pain experienced upon administration [120].

Most recently, exciting work has been published by Kim *et al.*, whereby dissolvable MNs with a dual-release pattern boosted the efficacy of Hepatitis B vaccinations in female BALB/c mice [121]. Specifically, HBsAg was included in the sustained-release PLA MN tip, and a bolus of HBsAg containing CMC coating showed excellent immunogenicity and immune priming after 20 min [121]. The novelty of this system is in its transferrable nature, whereby disease states which require simultaneous bolus and sustained release, such as those for Alzheimer's, can be delivered in a minimally invasive and pain-free manner [121].

4.1.3. Polio

The poliovirus is responsible for the disabling disease polio, which sees an infection of the spinal cord resulting in paralysis [122], with both an oral and liquid formulation of the inactivated poliovirus vaccine available [123]. Thanks to the continued use of these vaccinations, polio is considered to be eradicated in some countries such as the United States and the United Kingdom [124]. MN technology for the delivery of polio vaccinations was investigated in human studies as early as 2015, with Anand *et al.*, conducting a randomized controlled trial with healthy 6-week-old human infants that demonstrated considerable immune priming in comparison to the oral formulation [125].

Promising studies have emerged by Kolluru *et al.*, who have investigated the thermostability of vacuum-based molded dissolvable MNs composed of inactivated polio vaccine (IPV) and biodegradable and biocompatible polymers [31,126]. This study evidenced the MN patches to display significantly improved thermostability in the absence of cold-chain storage conditions, a huge advantage for the global rollout of vaccination programmes [126]. Most recently, a study has revealed the use of MN as a dual delivery platform for IPV and inactivated rotavirus vaccine (IRV), with the co-administration of a quarter dose via dissolving MN to demonstrate the potency of a full IM dose [127].

4.2. SARS-CoV-2

Recent years have seen MN research pivot, with groups almost unanimously focusing their explorations on MN delivery for SARS-CoV-2 vaccination, to contribute to society's collective strive to make vaccinations more accessible and expedite their availability on the market. Within the first year of the pandemic, a promising paper was released investigating the ability of mechanical micromilled MN arrays (MNA) to deliver SARS-CoV-2 S1 subunit vaccines containing a foldon trimerization domain to improve spatial mimicry of the native virus [128]. Initially focusing their research on the Middle East Respiratory Syndrome (MERS), Kim *et al.*, investigated the immunogenicity raised and antigen-specific antibody responses following both traditional subcutaneous and intracutaneous dissolving MNA, demonstrating the MNA to be more effective than subcutaneous injection in eliciting neutralizing antibodies for all vaccine candidates trialed [128]. The group report to have applied these methods to enable rapid production of MNA SARS-CoV-2 vaccinations with scalable processing methods. With data from an ongoing stability study yet to be published, the group report gamma radiated-MNA vaccines to elicit immunogenicity comparable with that of unsterilized devices [128]. Nevertheless, the data has not yet been released, though its prospects for terminal sterilization in a GMP environment are noteworthy.

Following the first global SARS-CoV-2 vaccination, specifically the Pfizer-BioNTech formulation, administration on 8 December 2020 8 December 2020, the MN research sphere began to erupt. 2021 saw a plethora of research released, reporting on a variety of MN devices such as dissolvable patches fabricated by Ortega-Rivera *et al.*, from the University of California [129]. Following the formulation of mono- and trivalent vaccine candidates, the devices were produced through micromolding and compared to two methods of subcutaneous delivery: traditional subcutaneous injection and implant-based vaccination [129]. Interestingly, active, and passive MN vaccinations were trialed. Previously reported as successful in the immunotherapy of dermal melanomas, active vaccinations contained magnesium microparticles to provide a driving force for the expulsion of vaccine from the device [130,131]. This effect did not translate to SARS-CoV-2 vaccination, however, and no enhanced efficacy was observed between the two MN patches. Furthermore, the simultaneously rapid dissolution of polymer containing the three active vaccine subunits produced a titer with reduced antibody levels, caused by decreased (10%) release of total vaccine dosage from the devices on account of the void volume contained in the base plate of the MN patch [129]. Nevertheless, the crucial finding that the MN patch, as with the two alternative vaccination modes, did produce neutralizing antibodies and balanced Th1/Th2 responses instill promise in this approach, with the increase in patch size suggested as a simple solution for clinical applications [129].

A novel approach was taken by Yin *et al.*, who investigated separable MN patches to co-administer an amphiphilic encapsulated immune adjuvant and an S or N protein-encoded DNA vaccine, following room temperature storage for a minimum of 30 days [132]. This removable backing technology enabled the biodegradable MNs to reside in the intradermal layer for several days and elicited both humoral and cellular immune responses, with storage having no impact on the immunogenicity invoked [132]. This investigation opens new avenues of research for MN devices that can be left in the skin, reducing the need for medical device waste and potential sharps hazards for users.

As a result of increased funding following the SARS-CoV-2 pandemic, new medical vaccination devices are rapidly emerging. Exciting work has been published by the Georgia Institute of Technology, with data published evidencing a well-tolerated, low-cost MN electrode ePatch [133]. This portable device utilizes a piezoelectric pulse that, following thumb pressure, enables an MN array with dense electrode spacing to create and deliver high electric field pulses to the epidermis [133]. With traditional electroporation widely reported to leave

enduring damage to the epidermis, the short length of the MNA prevented significant damage to the epidermal integrity of rat and murine skin [133]. Promising data has been reported following the use of the ePatch, with the delivery of the S protein inducing robust immunogenicity and specific antibody response, demonstrating a dose-sparing potential of 10-fold when compared to conventional intramuscular and intradermal DNA vaccination [133]. Further studies are required, however, to demonstrate the potential impact on the integrity of human tissue following electroporation with an MN patch and to perform investigations into pain ranking to ensure that combinations of this technology offer the same nociception benefits as previously reported.

A more traditional approach to MN for vaccination was utilized for the molding and drip coating for MNs for the delivery of inactivated SARS-CoV-2-based vaccines, which, although still required the limiting cold storage (4°C), focused on the potential of the patch enabling decentralized information storage [134]. After first demonstrating its effectiveness as a vaccination device, with antibody levels as well as IFNg and IL2 expressing CD8+ T cells rising in comparison with the free vaccine group and PBS-treated mice, the group reported loading the devices with dyes that were inserted in patterns [134]. This was suggested for accurate *in situ* recording of vaccination and administrated data in animals, limiting its use to animal trials.

CryoMNs have recently been fabricated by Yu *et al.*, to deliver the Pfizer-BioNTech mRNA vaccination using subcutaneous injection as a benchmark for delivery efficiency [135]. Fabricated via cryogenic micromoulding of pre-suspended cells, the devices required 10 s of mechanical thumb pressure for insertion at body temperature [135]. Promisingly, from a patient compliance perspective, any visual marks were absent after 24 h. Nevertheless, the advised 'thumb pressure' may not be translational due to variability arising from self-administration [135]. Unfortunately, although the cryoMNs successfully delivered the mRNA vaccine and induced immunogenicity, when compared with spike antibody titers, pseudoviral neutralizing assays, and specific T cell responses invoked from subcutaneous vaccination, the cryoMNs fall short [135]. Although a promising technology, with respect to reduced medical waste and increased speed of *en masse* vaccination, further research is required to address efficacy issues, sterilization procedures, and the requirement for cold storage.

As the number of global SARS-CoV-2 cases rises, surpassing the current total of 588 million, as an act of self-preservation, the virus particles mutate forming new variants and strains, some of which are a greater cause for concern than others [136]. The new variants were emerging at an alarming rate in Q4 2021 and Q1 2022, emphasizing the need for a drug delivery platform and vaccination, which induces greater immunogenicity across not just the ancestral variant, but emerging strains also. Resultantly, medical device research must run in parallel with the development of a broader spectrum of SARS-CoV-2 vaccinations. In that vein, building upon a paper released from their previously published work evidencing their MN patch to induce complete protection through a single-dose of spike vaccine, McMillan *et al.*, have recently reported their development of a trimeric SARS-CoV-2 protein subunit vaccine, delivered through an MNA patch fabricated via injection molding and comprising 5000 projections/cm^2 [137,138]. Using intradermal injection as a benchmark for invoked immunogenicity, vaccination was investigated with and without an adjuvant [137]. Although its efficacy against the omicron strain is unproven, the immune response measured against the SARS-CoV-2 alpha and beta variants was not only comparable to the ancestral variant but crucially, neutralizing antibodies and IgG levels were significantly higher than in the intradermal injection murine population [137]. This work holds significant promise for the delivery of multi-strain vaccinations without the requirement for medical professionals and cold-chain storage.

5. Key challenges facing MN introduction

The current barriers to effective global mass vaccination include: requirements for increased vaccine effectiveness, requirements for trained healthcare providers, requirements for an effective supply chain, risk of sharps, vaccine wastage due to multi-dose vials, need for vaccine reconstitution, and the cost of vaccine/vaccination. MN technologies, therefore, offer a potential platform for global mass vaccination.

Despite the associated advantages of MN technology, it would be remiss to not discuss the challenges accompanying the development and adoption of this technology. These can be generally grouped into five categories: (i) MN dimensions; (ii) safety; (iii) fabrication; (iv) regulation; and (v) sustainability.

5.1. MN dimensions

MN dimensions impact the ability of the device to puncture the skin, therefore impacting drug delivery. Factors such as the MN shape, e.g. cylindrical, canonical, volcano, tapered, and tip diameter, affect the insertion force required, with metal and metalloid needles such as aluminum and silicon currently boasting sharper tips and resultant lower insertion force than the popular polymeric alternatives [26]. Using glass MNs, a recent study revealed an insertion force to linearly rely on the tip frontal area, with blunt MN (60–160 µm) requiring a relatively high insertion force (0.08–3.04 N) [139,140]. Concerning vaccination, an MN with a tip diameter<15 µm has been reported to best penetrate the *stratum corneum* and epidermis, to access the LC-rich subdermal space [141]. Furthermore, the MN length is a critical dimension and is closely related to the medication delivered. An MN of excessive length, exceeding 4 mm, may result in bending upon insertion and potentially contact with the adipose tissue layer [142]. This houses numerous nerve cells, causing pain, and a limited blood vessel network. Therefore, if your medication requires diffusion through the circulatory system such as insulin, this is disadvantageous [142]. Conversely, short MNs limit drug delivery to the outermost skin layer, the epidermis, limiting drug diffusion and therefore restricting bioavailability. Finally, MN height determines loading dose, either by the surface area available for solid MNs, tip size for dissolving MNs, or bore size for hollow MNs [143]. Beneficially, however, low dosages are required for vaccinations in comparison to

insulin delivery for type 1 and 2 diabetes, especially when considering the dose-sparing potential of MNs facilitated through direct LC recruitment [144]. This is a limited demonstration of how no 'one size fits all' approach will be feasible for MN devices, and how not only drug type and disease state will impact the device required, but also individuals' skin characteristics. Therefore, there may be requirements for a diverse demand for MN dimensions, which may perturb the commercialization and clinical adoption of an MN product.

5.2. Safety

To replace the classic hypodermic needle, a safe though painful and invasive alternative, the safety of MN devices concerning the accuracy, stability, biocompatibility, and immune response must be proven. Silicon and silica glass MNs are accompanied by concerns over breakages following insertion, and any resultant irritation caused to the skin area, although demonstrated as 'not significant[ly] cytotoxic' by Bayliss *et al.* [145]. Polymeric MNs boast a better safety profile in this regard, as they offer the possibility of biocompatible, and even biodegradable, polymers, minimizing any potential skin irritation or toxicity [146]. Vaccination programmes are manufactured and distributed on a global scale; therefore, these studies should include long-term post-market surveillance, with a diverse testing pool. With a cutaneous layer geometry dependent on a variety of variables, MN with the same geometry and critical dimensions may demonstrate varying penetration and delivery efficacy.

With any medical device that is designed for penetration through the skin, or usage within the body, the risk of device fracture and remnants residing in the skin is extant and must be appropriately assessed. Currently, there is a lack of experimental methods that can consistently measure the penetration of MNs, and reliably assess any potential damage to target area tissue. In particular, the combination of MN devices with electroporation elicits a further risk of skin damage. The number and duration of pulses may be subjective, depending on the characteristics of an individual's skin, rendering keratinocytes and resident cells vulnerable to damage [147]. A particularly challenging example of this is intratympanic administration, which requires injection through the thin tympanic membrane, enabling its absorption through the round window membrane (RWM) and into the cochlea for the treatment of inner ear conditions [148]. Yu *et al.*, have recently published on this issue, reporting a single 3D-printed MN to perforate the RWM of a guinea pig, accurately and reliably, with complete injection site closure observed within 7 days [149]. Further studies must be performed to provide target area-specific safety data on penetration depth and penetration site closure.

5.3. MN fabrication

Regardless of the material, the MN fabrication process must be both streamlined and simplified to facilitate mass-scale production, enabling significant cost reduction than that seen currently at the research level. Furthermore, the reproducibility of fabrication must be demonstrated before MN devices can be rolled out *en masse*. A crucial challenge facing MN devices is sterilization. Whether this is via gas sterilization or liquid, the mode of sterilization must be compatible not only with the material of the device but also with the drug formulation itself in the case of dissolvable MNs. A further consideration, especially in the case of dissolving MNs, is the potentially detrimental impact of the fabrication process on the stability of the antigen or vaccine. Factors such as temperature, freeze-thawing, pH, and light exposure all impacting the integrity of the vaccine [150]. It is crucial that drugs delivered by MN are not impacted by the delivery mode and device fabrication, with vaccinations, specifically mRNA and viral vector vaccines susceptible to inactivation and resultantly poorer efficiency should conditions such as temperature and light exposure be uncontrolled. Given that lyophilization, or freeze-drying, has become almost standard practice to stabilize vaccines such as attenuated virus formulations, it is vital that more preventative approaches, and repeatable and accurate test methods, are developed to ensure the integrity of the APIs are not impacted by device processing.

5.4. Regulation

As a new medical device, MNs are subject to rigorous regulatory scrutiny. A significant obstacle arises because they must be filed in combination with a drug that uses the device, therefore prolonging the approval process; 'Regulation of combination products must take into account the safety and effectiveness questions associated with each constituent and the product as a whole' [151]. There is still a considerable degree of manufacturing-based research to be performed into precisely defining the current good manufacturing practice (cGMP) of this new medical device, with regulatory bodies such as the FDA and EMA concerned over the risk analysis and the sterile cGMP techniques [152]. As researchers better understand the concerns of these regulatory bodies, studies are rapidly being published covering stability testing and repeatable, accurate drug delivery, echoed by the rapidly increasing number of regulatory filings.

5.5. Sustainability

Sustainability, from sourcing to reuse and recycling, is a compulsory consideration of any new device or product. However, medical devices are generally exclusions to this rule, on account of the risk of cross-contamination and blood-borne diseases, therefore both hypodermic needles and syringes are currently single-use products [153]. Current hypodermic needle manufacture and usage have established a low standard concerning sustainability. This does not obviate the need for sustainability considerations when developing new MN products. As ever, there is a trade-off between performance and sustainability; a balance in which few products are classified as high-performing and high sustainability. Especially for medical devices, like MNs, performance is key, and this is a factor that must be considered when assessing their sustainability. Silicon MNs suffer when assessing their sustainability, requiring highly pure starting materials fabricated through water-intensive

processes [154]. Finally, biodegradable, dissolvable MNs present hope for a zero-waste future for injections, whereby the needles themselves dissolve whilst administering the drug, and the backing dissolves in water [155].

6. Expert opinion

One silver lining associated with the recent COVID-19 pandemic caused by the SARS-Cov-2 virus has been the opportunities presented for the repurposing of existing technologies to develop vaccines. Vaccine innovation is critically needed to reach global goals of equitable coverage. Researchers need to collaborate across disciplines such as medical engineering, clinical professionals, and drug development to drive vaccine product innovation. Microarray patches are a transformative novel delivery approach for global immunization. The motivation behind advancing MN-based skin vaccines includes: the transformation of vaccine delivery, suitability for SARS-CoV-2 vaccine delivery scenarios, its potential to address many of the key immunization barriers, have a positive impact on 'life course' immunization, and its contribution to global health security and pandemic preparedness.

Research projects on repurposing MN for self-administration of the SARS-CoV-2 vaccine were undertaken by academic and industry research organizations. Many scientific reports have been published around clinical studies on MN-based vaccine administration devices in the US (Stanford, Pittsburgh) and Australia (Queensland). Another interesting observation during the pandemic was the fact that regulatory approvals were expedited, and vaccines were approved for mass vaccination programs in record time. This offers MNA-based skin vaccines an opportunity to be commercially available on an accelerated timeline.

Clearly, MN-based skin vaccination platforms for SARS-CoV-2 vaccination have inherent advantages that encourage mass vaccine production and distribution, as opposed to bringing the masses to vaccination centers. This will benefit not only the healthcare systems around the world but also vulnerable subgroups, such as the elderly and pediatric populations. From employing 3D printing technologies, to mass-producing MN patches, to demonstrating 50× responses, MNA patches have thus far demonstrated potential solutions such as pain-free, self-administrable vaccine patches requiring minimal resources. These vaccine patches can also be made smarter by incorporating diagnostic potential, with the integration of the ability to track the antibodies produced as an immune response to the vaccination.

In terms of the potential of MNA-based SARS-CoV-2 vaccines to contribute to pandemic preparedness and response, they offer the advantages of access, simplified storage requirements, minimum resources, and good patient acceptability. They will enable dose-sparing of vaccines and reduce reliance on ancillary supply. Due to the single-dose presentation, they can reduce the risk of stock-outs and missed opportunities due to reluctance to open a multi-dose vial. Improved thermostability of SARS-CoV-2 MN vaccines could reduce cold chain requirements and facilitate use within the controlled temperature chain. Their ease of use could allow lesser trained staff to administer the vaccines and potentially enable needle-free self-administration, avoiding needle-stick injuries & simplifying waste disposal. These skin patches appear painless and safer than needles and syringes to recipients demonstrating improved immunogenicity and dose-sparing.

The human-centered design of MN products has been developed and tested as contraception devices whose commercial application is anticipated in the short term. MNA patches for vaccine delivery to increase equitable vaccine coverage in low- and middle-income countries have been prioritized under WHO's vaccine innovation prioritization strategy (VIPS) as part of the Gavi-vaccine alliance. A collaborative approach between the various academic and industrial groups working on MNA should help define the regulatory pathway for the MNA patches. Further, MN-based patches for the SARS-CoV-2 vaccine are highly likely to be commercially available following the completion of clinical studies and the clearer definition of the regulatory pathway.

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