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Review article

# Microarray patches for managing infections at a global scale

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ABSTRACT

Since the first patent for micro array patches (MAPs) was filed in the 1970s, research on utilising MAPs as a drug delivery system has progressed significantly, evidenced by the transition from the simple 'poke and patch' of solid MAPs to the development of bio responsive systems such as hydrogel-forming and dissolving MAPs. In addition to the extensive research on MAPs for improving transdermal drug delivery, there is a growing interest in using these devices to manage infectious diseases. This is due to the minimally invasive nature of this drug delivery platform which enable patients to self-administer therapeutics without the aid of healthcare professionals. This review aims to provide a critical analysis on the potential utility of MAPs in managing infectious diseases which are still endemic at a global scale. The range of diseases covered in this review include tuberculosis, skin infections, malaria, methicillin-resistant *Staphylococcus aureus* infections and Covid-19. These diseases exert a considerable socioeconomic burden at a global scale with their impact magnified in low- and middle-income countries (LMICs). Due to the painless and minimally invasive nature of MAPs application, this technology also provides an efficient solution not only for the delivery of therapeutics but also for the administration of vaccine and prophylactic agents that could be used in preventing the spread and outbreak of emerging infections. Furthermore, the ability of MAPs to sample and collect dermal interstitial fluid that is rich in disease-related biomarkers could also open the avenue for MAPs to be utilised as a minimally invasive biosensor for the diagnosis of infectious diseases. The efficacy of MAPs along with the current limitations of such strategies to prevent and treat these infections will be discussed. Lastly, the clinical and translational hurdles associated with MAP technologies will also be critically discussed.

## 1. Introduction

Since the cradle of civilisation, infectious diseases have ranked with wars and famine as major obstacles to human progress and survival. This group of diseases constitute a persistent and serious public-health threat at a global scale. Although some infections such as smallpox and poliomyelitis have been successfully eradicated, many diseases still persist within the community [1]. Against the constant outbreak of established infections, epidemics and in some instances, pandemics of new infectious diseases periodically emerge, greatly magnifying the global burden imposed by infectious diseases. For instance, the Covid-19 outbreak has resulted in severe mortality worldwide, impacting public health and economic welfare, as well as changing the behaviour of our society dramatically [2]. Reflecting upon decades of fundamental research into infectious diseases, evolutionary properties of pathogenic microorganisms and the dynamic, yet complex, relationships between microorganisms, their hosts and the environment have been determined [3]. It is believed that new infections emerge from animal reservoirs when ecological changes underpinned by evolutionary genetics increase the pathogen's opportunities to enter the human population, resulting in subsequent human-to-human transmission [4].

It was once predicted by academic leaders that due to the efficacy of antibiotics bacterial infections would be a thing of the past. However, as a result of the overprescribing of such agents, a viscous, yet predictive

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cycle has been established: a novel antibiotic is discovered that is subsequently followed by the emergence of a resistant pathogen that results in an untreatable infection with a high mortality rate [5]. Ideally, there should be a never-ending race to discover and develop a new range of antibiotics to treat infections and overcome ones that have grown resistant to the current armamentarium of antibiotics [5]. Unfortunately, relative to other areas such as cancer, cardiovascular and respiratory diseases, many pharmaceutical companies do not view the development of antibiotics as financially viable, causing us to reach an unsettling impasse in medicine, meanwhile the cases of antibiotic resistance continue to rise [5]. For instance, the so-called ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp.*) are the primary cause of a wide range of infections in humans ranging from dermal, lung and urinary tract infections. Worryingly, most of these organisms are now developing resistance against carbapenems which are considered the last line of defence against bacterial infections [6].

Since the serendipitous discovery of penicillin in 1928, the range and class of antibiotics utilised in clinical practice has evolved and expanded. Fundamentally, new groups of antibiotics are challenging to discover *via* the use of conventional approaches and resources resulting in companies exploring similar variants of current antibiotic chemophores [7]. In addition, despite being nearly a century since the discovery of the first antibiotic, the range of delivery strategies and technologies employed to delivered antibiotics has been limited to conventional oral tablets, suspension, topical creams and intravenous injection. In the late 1920s until the late 1940s, the majority of antibiotics used in managing infectious diseases consisted of small-molecules such as penicillin, sulphonamides, tetracyclines and nitrofurans. Due to their small size and physiochemical properties, most of these small molecule antibiotics are easily administered *via* the oral route. However, from the early 1950s to the late 2010s, the range of antibiotics that have been discovered has been more structurally diverse and, in some instances, consisted of large molecules such aminoglycosides, streptogramin, polymyxin and lipoglycopeptides. Most of these large antibiotics have poor oral bioavailability and necessitate administration *via* intravenous injections. This drug delivery route is not only invasive and painful but would require the aid of healthcare professionals.

In addition, oral antibiotic therapy has been shown to have a significant impact on gastrointestinal microbiome and may lead to dysbiosis in the gut. The reduction in microbial diversity along with the loss of beneficial commensal bacteria can lead to the establishment of chronic infections caused by *Clostridium difficile* and vancomycin-resistant enterococci [8,9]. Dysbiosis in the gut microbiome following antibiotic therapy has been shown to be a potential cause for the rise in antimicrobial resistance genes, which can be passed on into the faeces, ultimately leading to the release and spread of antibiotic resistance into the environment [10]. On the other hand, some antibiotic therapies, such as those required for the treatment of tuberculosis, consist of a multi-antibiotic regimen which can last for several months [11]. This treatment approach imposes a considerable pill burden on the patients which can lead to non-adherence and ultimately treatment failure. Clearly, there is an impetus to develop a unique drug delivery system that can simplify the complex antibiotic therapy. This drug delivery strategy should be capable of delivering multiple antibiotics payloads with minimal side effects, while simultaneously circumventing the issue of antibiotic-induced gut dysbiosis. Such an approach would provide a potential solution to mitigate patient adherence issues while reducing the risk of multi-drug resistance.

One of the drug delivery platforms that could be utilised to improve the delivery of antibiotics into and across the skin are microneedles or microarray patches (MAPs). Described as a hybrid between hypodermic needles and transdermal patches [12], MAPs are a biomedical microdevice consisting of arrays of micron scale projections that form transient channels within the skin upon application. These water filled channels could be utilised to deliver a wide array of therapeutics, ranging from small drug molecules [13] to large macromolecules [14]. The first microneedle patent was filed in 1976 by Gerstel and Place from Alza Corporation, and at the time it was predicted that such micron-scale needles could be employed to deliver drug molecules into and across the skin in a minimally invasive fashion [15]. However, it was not until the development of microfabrication tools within the microelectronics industry in the 1990s that research on using MAPs for drug delivery started to gain momentum [16]. The utilisation of microneedles for the delivery of antibiotics is of great therapeutic value, this is because MAPs have the advantage of conferring painless antibiotic delivery with minimal tissue damage, as the device only penetrates the non-innervated epidermis [17]. In addition, MAPs could also be employed for antibiotic delivery in cases where intravenous administration is challenging while mitigating the damaging effects of oral antibiotics administration. Besides that, the capability of inserting MAPs into the skin provides a unique opportunity for specific and precise delivery of therapeutics to treat localised skin infections. Also, exploratory studies on the views of patients and clinicians towards MAPs have highlighted that there is indeed a demand for the technology to be included in clinical interventions. It is estimated that the global transdermal drug delivery market will be worth $95.57 billion by 2025 [18]. From an economic standpoint, it is speculated that part of this market would potentially be dominated by microneedles as such devices offer an easy and pain free drug delivery strategy compared to the more painful hypodermic injection-based delivery of drugs such antibiotics. For readers who wish to understand further on the background of the MAP technology in detail, we would like to signpost them to the following dedicated reviews on this topic [19–24].

More importantly, MAPs have the potential to be utilised for not just the delivery of antibiotics for the treatment of common bacterial infections, but these systems may be broadly utilised for the management and potentially for the prevention of other infectious diseases through the delivery of prophylactic agents and vaccines. Decades of research within the field of immunology and infectious diseases have culminated with the development of potential vaccine candidates which could be administered as a means of preventing the spread of infectious diseases such as malaria [25], tuberculosis [26], Ebola and influenza [27]. The administration of these prophylactic vaccines would provide a powerful strategy by which we could control or even potentially eradicate these infectious diseases. Nevertheless, most of these vaccines necessitate administration *via* hypodermic injection which is both painful and requires the aid of a trained healthcare professional. It has been extensively described and shown that MAPs offer an elegant approach for the delivery of vaccines in a painless fashion to which the patient could even self-administer the vaccine from the comfort of their home [28]. This advantage may aid vaccine uptake within the global populous particular for individuals with trypanophobia. Furthermore, the ability of MAPs to puncture and embed micron size projections within the skin also offers the possibility for this drug delivery platform to be repurposed for the diagnosis of infectious disease. The insertion of MAPs into the skin will enable the system to be in direct contact with dermal interstitial fluid (ISF) that is rich with an assortment of health-related biomarkers. These biomarkers may be of heuristic value for the diagnosis of infectious diseases. This is because studies have shown that 83% of systemically circulating biomarkers are also found within the dermal ISF [29]. This is further corroborated by emerging studies that have begun to explore and demonstrate the utility of MAPs in the diagnosis of infectious diseases [30].

The first section of this review provides an overview on the application of MAPs in managing several infectious diseases. Some of the infectious diseases that are covered include tuberculosis, malaria, skin and soft tissue infections, methicillin-resistant *Staphylococcus aureus* infections and COVID-19. We have chosen this list of infections since tuberculosis, malaria, skin infections and COVID-19 are some of the most common infectious diseases that contribute to the highest disease

burden worldwide [31,32]. In addition, these diseases, particularly tuberculosis and malaria, exert an extensive social and economic burden within low- and middle-income countries (LMICs) where access to healthcare is usually poor [33]. Given the potential utility of MAPs to enable self-administration of medication and even be used for point-of-care testing, this technology may help in the management of these infectious diseases in LMICs. Regarding MRSA skin infections, they are fast becoming a growing health challenge at a global scale that involves a considerable burden on healthcare systems, since, for instance, a significant consumption of medical resources is required for their treatment [34]. The ability of MAPs to deliver antibiotics with high precision to the infected sites offers a potential new treatment and so, an alternative to change the strategy on how MRSA is currently managed. We acknowledge that HIV/AIDS also falls under the category of infectious diseases, however, there has been a detailed review on the application of MAPs for the treatment of HIV/AIDS [35]. The second section of this review highlights and discusses the translational considerations that need to be addressed for the successful transfer of MAP technologies from bench to bedside. It is hoped that this review will further inform clinicians, formulation scientists and researchers of the important role of MAPs in improving the treatment of the abovementioned conditions. Furthermore, this paper also aims to stimulate a paradigm shift towards the utilisation of MAPs for the treatment of infectious diseases at a global scale.

## 2. Microneedle technology in managing infectious diseases

### 2.1. Tuberculosis

Tuberculosis (TB) is an infectious disease and one of the leading causes of death worldwide, posing a major health, social and economic burden, primarily in low and middle-income countries [36]. The WHO reported that there were about 10 million cases of TB in 2018 and an estimated 1.5 million deaths worldwide, therefore, TB is claimed as the most infectious killer in the world [37]. There are several factors that affect TB incidence. This results in disparities of case distribution, including age, nutrition, vaccination and immune status [38–41]. Co-infections with the human immunodeficiency virus (HIV) play a major role in the TB disease development, as HIV causes immunodeficiency [42]. People living with HIV have an increased risk (16-27 times) in developing TB disease compared to those without HIV [43]. Moreover, diabetes mellitus (DM) also contributes to TB incidence, which is 2-3 times higher than in non-diabetic patients [44,45]. TB and DM are thought to exacerbate and worsen the course for the other [43,46,47]. TB increases the glycaemic levels in diabetic patients and causes an impaired glucose tolerance [47]. Additionally, TB also likely increases the susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and hence, worsens the effect that the Coronavirus disease 2019 (COVID-19), caused by this virus, has on the pulmonary system [48,49].

TB disease is triggered by the infection with an aerobic bacterium of the species Mycobacterium tuberculosis (MTB). These bacilli can attack many organs of the human body, lungs being the most common site of infection [50,51]. MTB is spread by airborne particles and can last several hours after expectoration [52]. MTB-containing droplets are dispersed in the air and transferred to other individuals by inhalation [53,54]. Once the infectious droplets are inhaled, the MTB bacilli are introduced to the airways. In most cases, inhaled MTB bacilli are blocked and removed by mucus secretion and cilia located in the upper parts of the airways [52]. If MTB bacilli escape the mucociliary system, they reach the lower part of the airways, where they are detected by alveolar macrophages [36]. Macrophages in alveolus can eliminate the invading MTB by recognising the mycobacterial lipoarabinomannan (LAM) antigen which is attached to the cell wall [52]. Considering the quality of the host's immune system and its ability to tackle the invading MTB, the MTB phagocytosis by macrophages can result in two possible outcomes, either successfully control of the MTB infection resulting in a latent TB, or progression to an active TB disease [52]. Pathophysiology of TB disease is illustrated and presented in Fig. 1.

Treatment for latent TB is given to people who meet the two following conditions, high risk of progression of the disease to active TB, and a positive result in either a tuberculin skin test or interferon gamma release assay test [36,55]. The WHO recommends a number of options for treating latent TB, including isoniazid monotherapy for 6-9 months, a combination of rifapentine and isoniazid for 3 months, combination of rifampicin and isoniazid for 3-4 months, or rifampicin monotherapy for 3-4 months [36,56]. Currently available treatment options for active TB consist of first-line drugs, (rifampicin, isoniazid, pyrazinamide, and ethambutol); and second-line drugs, such as injectable agents (streptomycin, kanamycin, amikacin, capreomycin and viomycin, ofloxacin, levofloxacin, gatifloxacin and moxifloxacin) and other oral agents (ethionamide, prothionamide, cycloserine, terizidone and para-aminosalicylic acid) [55,57,58].

Key issues related to the MDR-TB background are mismanagement in TB treatment and the transmission of unsusceptible MTB [43]. People with TB can progress to MDR-TB. This is caused by unfinished 6-month treatment due to poor adherence rate and lack of patient monitoring. The unsusceptible MTB can be further transmitted to individuals nearby, especially in low resources setting during the treatment. At this point, the WHO and supporting experts propose a number of strategic steps to control MDR-TB, including provision of a rapid diagnostic tool for MDR-TB detection, and addition of antibiotics from the second-line regime to the initial TB regime [43,55]. In 2016, the WHO released a new treatment guideline for a shorter MDR-TB regimen. This new regime contains seven drugs for a treatment duration of 9-12 months. It is indicated to be used only under specific conditions, for patients with either MDR-TB or rifampicin resistant-TB [59]. Despite the increase in treatment options, MTB resistance can possibly worsen if the combined drugs are still used inappropriately [36]. Although this regimen strategy is expected to positively affect MDR-TB treatment, more problems related to drug toxicities may appear and intensive monitoring is required due to the extended number and duration of drug exposure [36].

Beyond drug resistance, hepatoxicity has been reported as the most frequent adverse effect of first-line anti-TB medication due to daily repeated oral dosing in a long treatment duration. Approximately 28% of TB patients experienced an increase in alanine aminotransferase (ALT) levels, which is an enzyme associated with hepatocellular injury [60,61]. Additionally, gastric erosions and upper GI bleeding have also been reported as adverse effects and are associated with frequent administration of RIF [62]. Despite the fact that the conventional therapy of active TB has successfully saved 58 million lives in 20 years [43], oral administration is less effective in dealing with MDR-TB and tackling several adverse effect issues.

Conventional anti-TB drugs are administered orally. The ingested drugs directly enter the liver *via* the splanchnic circulation and undergo first pass metabolism [63]. By changing the conventional route of TB treatment into non-oral administration, the pre-systemic metabolism may be avoided, and thus, reduce the risk of liver injury. Moreover, the drug can directly reach the blood circulation without having to pass the gastrointestinal tract and relying on effective gastrointestinal absorption. Therefore, this route can also prevent the gastrointestinal bleeding induced by RIF administration. Besides, choosing more appropriate drug administration routes can have an effect on the risk of drug resistance. Zhang *et al.* reported that the development of antibiotic resistance may be minimised by administrating the drug through parenteral injection. Parenteral antibiotic delivery may prevent the unnecessary exposure of antibiotic to the gut microbiota [64]. Bearing this in mind, the transdermal route as an alternative drug administration site, may considerably delay antibiotic resistance, which in turn can control the progression of active susceptible TB into MDR-TB.

Several studies have assessed the delivery of antibiotics transdermally using both passive and active techniques. Caon *et al.*

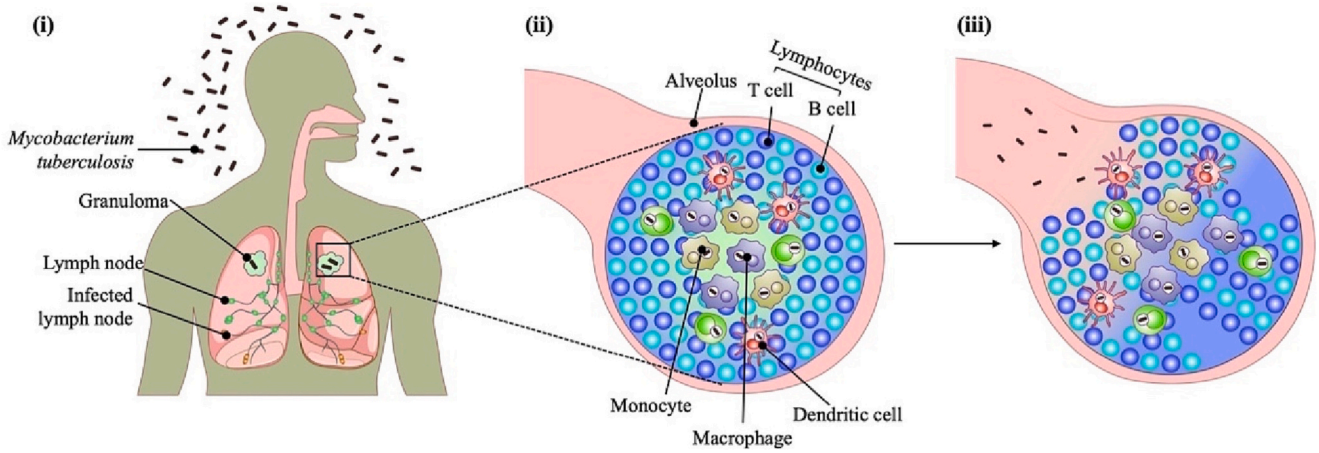


**Fig. 1.** Pathophysiology of TB. (i) Infection starts when the MTB-containing droplets are inhaled, enter the lung, and reside in alveoli. (ii) Macrophages and T-lymphocytes response to the invaded MTB by forming granulomas to limit the replication and spread. (iii) In less immunocompetent individuals, the granulomas fail to contain the infection, they break, and the bacilli can escape and spread to other organs.

investigated and compared the transdermal delivery of isoniazid incorporated with chemical enhancers, such as menthol, limonene, Transcutol®. The results showed that isoniazid could be efficiently delivered across the skin and the delivery positively correlated with the logP of chemical enhancers [65]. Furthermore, Hussain *et al.* formulated rifampicin into a nanoemulsion gel that can be a promising alternative to the conventional oral administration to treat TB disease. The results revealed that the plasma concentration following transdermal application was 4.34-4.74-fold higher than that recorded after oral administration [66]. The application of electrophoresis has been explored for TB treatment. Chen and co-workers have investigated the transdermal delivery of both rifampicin and isoniazid in a solution using electrophoresis for treatment of superficial TB and lymphadenitis [67,68]. However, this route can cause cell death and has the potential to damage heat-sensitive therapeutics for TB treatment, such as ethambutol [69]. Another approach that has been explored to improve TB treatment include MAP technologies. Research that employed the use of microneedles for the delivery of antibiotics for the management of TB disease was reported by Anjani *et al.* in 2021 [70]. By utilising hydrogel-forming microneedle array patches, Anjani and colleagues demonstrated promising results for the high dose delivery of four antibiotics, including rifampicin, isoniazid, pyrazinamide and ethambutol across dermatomed (350 μm) neonatal porcine skin over 24 hours. Based on *in vitro* results, this early proof-of-concept study showed that the utility of hydrogel-forming MAPs in combination of several types of drug reservoirs could be a promising approach to improve TB treatment *via* a simple and pain-free manner.

As a preventative medicine, the bacille Calmette-Guérin (BCG) vaccine is administered to infants as part of national vaccination programmes, including developing countries in which TB is highly prevalent. Using the 'poke and release' approach with dissolving microneedles, Chen and co-workers demonstrated a strong cellular immunity stimulation of BCG, which was comparable to intradermal administration. This study also showed that microneedles were able to completely avoid the local reactions in mice during vaccine administration [71]. Furthering this, BCG polysaccharide nucleic acid (BCG-PSN) loaded onto dissolving microneedles were prepared by Yan and co-workers in order to improve immunotherapeutic effect compared to an intramuscular injection. This study showed that the MTB infected mice from the microneedle delivery group secreted more IFN- γ than the intramuscular injection group. Therefore, BCG-PSN delivery *via* microneedles may provide an enhanced immunomodulatory response when compared to an intramuscular injection [72]. In addition to delivering BCG vaccines to prevent TB, Yan *et al.* have also explored plasmid DNA encoding Ag85B as a vaccine loaded in a dissolving MAP. Upon application to the skin, the microneedles undergo dissolution in dermal interstitial fluid, releasing DNA vaccine to antigen presenting cells within the skin and promoting superior immune response relative to intramuscular injection. This study showed that a microneedle delivery of Ag85B DNA vaccine might be a promising strategy to prevent TB [73].

Moving forward, other research groups have now explored the utility and feasibility of performing TB skin test for diagnostics using MAPs, illustrated in Fig. 2. Jin *et al.* pioneered the TB testing using polymeric microneedles in 2013. The group developed chitin microneedles and demonstrated the capability of delivering purified protein derivative (PPD) tuberculin into the skin for TB diagnosis in guinea pigs. This early proof of concept study showed that microneedles coated with PPD tuberculin are a useful tool for TB testing due to its ability in controlling the depth of delivery by customising the length of needles. As such, this particular advantage might overcome the issues associated with hypodermic needles used in a standard Mantoux test, which are more painful and have a higher test failure rate due to administration errors [74]. Moreover, Wang *et al.* developed a dissolving MAP as a new method for tuberculin skin test. Using hyaluronic acid, the group incorporated a PPD dose equivalent to that in the Mantoux test into a dissolvable microneedle system. The results showed that the dissolving microneedle array patches might be a promising alternative approach over conventional hypodermic injections [75]. However, despite several advantages that have been offered, microneedle technology is limited to the low specificity of PPD as the main TB antigen in tuberculin test. Therefore, for achieving a comprehensive improved method for TB diagnostic, some specific antigen that is secreted by MTB should be considered to replace PPD.

### 2.2. Malaria

Affecting over 240 million people worldwide each year, malaria is an infectious disease which accounts for 881,000 deaths every year, with nine out of ten deaths occurring in sub-Saharan Africa [76,77]. This mosquito-borne disease arises when the single celled protozoans known as *plasmodium* are injected into the human systemic circulation during a mosquito bite, a process known as a blood meal [78,79], illustrated in Fig. 3. Some of the common plasmodium that result in malaria are *P. falciparum, P. vivax, P. ovale, P. malariae,* and *P. knowlesi* [77]. However, it is known that *P. falciparum* is the deadliest species of plasmodium in humans [77]. On top of the health burden imposed by the disease, the economic impact of this infection is vast. It has been shown by economists through cross-country regression frameworks that malaria endemic countries typically suffered lower growth per capita income. This indicates that the disease itself directly affects the economic

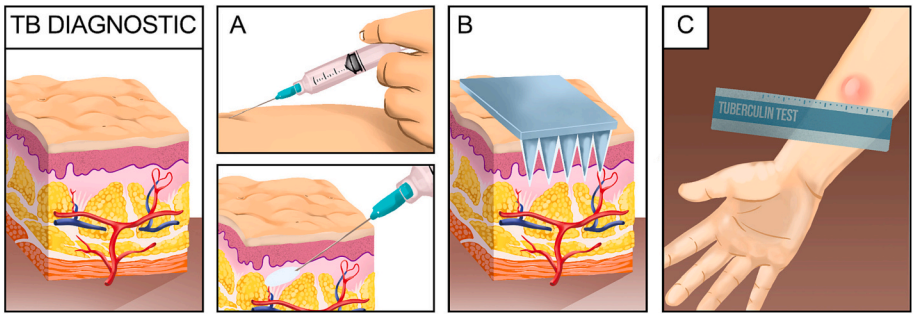


**Fig. 2.** Illustration of TB skin test. (A) Mantoux test with hypodermic injection, (B) utilization of MAP technology to deliver PPD tuberculin into the skin, (C) a firm swelling on the injection site following the tuberculin skin test.

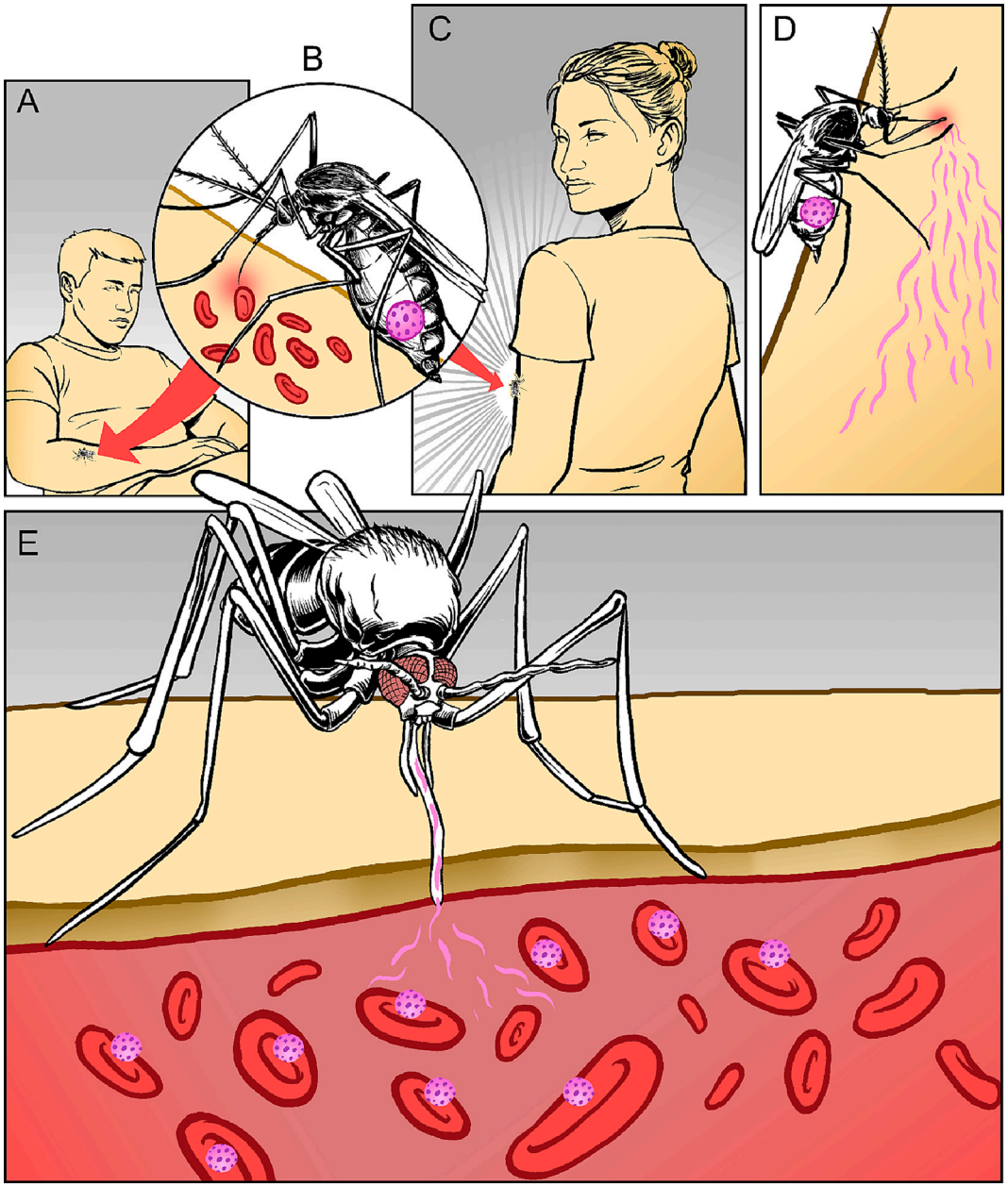


**Fig. 3.** Illustration of malaria infection. (A) Infected person is bitten by (B) female *Anopheles* mosquito which then carry the *Plasmodium* parasites, in the form of sporozoites. (C) The mosquito then bites a healthy person, (D, E) injecting the parasites into the skin, which the sporozoites migrate to reach capillaries, traverse the endothelium and reach the bloodstream and then pass quickly pass into human liver for the next stage of infection.

growth of nations if the disease is left unmanaged [80].

The risk of death due to malaria is exacerbated by the low adherence to conventional therapy as well as challenges associated with the health infrastructure in malaria endemic areas [81]. Furthermore, the high pill burden accompanying antimalaria pharmacotherapy is especially challenging in new-born and infant patient groups [77,82]. Therefore, there is a clear impetus to reformulate current treatments to provide a simple and straightforward administration strategy.

The major complication with malaria controls nowadays, especially in Africa and Southeast Asia, is drug resistance [77]. Parasite resistance to anti-malarials, including chloroquine, sulphadoxine-pyrimethamine, amodiaquine, mefloquine and quinine, has been reported in *P. falciparum species* [76]. In addition, a 70-80% treatment failure rate has been reported for chloroquine, which is the cheapest and most widely available anti-malarial drug [83]. Despite the fact that artemisinin derivates are the only class of anti-malarial agents that are still effective to *P. falciparum,* cross-resistance between two classes of anti-malarial agents can still occur, which can further contribute to the development of resistance [77].

With respect to symptoms associated with malaria, patients infected with *P. falciparum* experience persistent vomiting when they present to the hospital [82,83]. This eliminates the use of the conventional oral delivery route, thus necessitating an intravenous infusion and intramuscular injection. For instance, in May 2020, the Food and Drug Administration (FDA) approved Artesunate for Injection™ as a first line therapy for severe malaria in adult and paediatric patients [84]. Nevertheless, these routes require skilled health care workers, which is particularly challenging in low- and middle-income countries [85]. In light of this limitation, MAPs offer a suitable alternative to painlessly improve the delivery of anti-malarial drugs into the blood circulation *via* the transdermal route.

Recently, several studies have reported the delivery of anti-malarial drugs transdermally using MAP technology. Pawar and Shende synthesised a nanoparticle system loaded with lumefantrine using chitosan mediated gelation, optimising the system using 2 [2] factorial design [86]. In this work, it was shown that by loading the lumefantrine-nanoparticles and artemether into dissolvable MAPs, the researchers could control the release of both drugs in the *ex vivo* permeation studies, achieving up to 70% drug permeation across dermatomed porcine skin after 24 hours. Furthering this, artemether and lumefantrine dissolving MAPs were also formulated by Zanutto and co-workers [87]. In this study, the researchers prepared the nanosuspensions of artemether and lumefantrine individually and loaded the lyophilised powder into an aqueous blend of polyvinyl pyrrolidone and sodium hyaluronate, respectively. Following repeated MAP application to female C57BL/6JUnib mice, the results showed that the extended-release profile was achieved for both artemether and lumefantrine when compared to oral administration. Moreover, this approach also showed a promising result for antimalarial activity studies, which demonstrated a 99.5% reduction in parasitaemia in mice infected by *P. yoelii*. Accordingly, potential application of a novel MAP system could be effective in delivering antimalarial drugs to patients with malaria, specifically in low-resource settings.

In regards of malaria vaccine, Yenkoidiok-Douti *et al.* designed a system of dissolving MAPs loaded with *Plasmodium falciparum* surface protein P47 and cytosine-phosphate-guanine (CpG) [88]. In this work, the researchers use fish gelatin as the polymeric matrix of MAPs. Based on the results from *in vitro* cell studies, it was seen that the P47 and CpG released from MAP successfully generated TLR9 signal and triggered primary dendritic cells similarly to the pure compounds. Despite the lack of *in vivo* results within this study, it is worth highlighting the potential of MAPs to be used as one of the strategies to deliver malaria-based vaccines.

The application of MAP technologies is also marked in malaria blood testing. Jiang and Lilehoj developed a microneedle-based device for rapid detection of protein biomarkers in dermal interstitial fluid [89]. As a proof-of concept, they showed the ability of the device to detect one biomarker for malaria infection, *P. falciparum* histidine-rich protein 2 (PfHRP2), at low concentrations (16 ng/mL). Moreover, an addition of gold enhancement solution to both test and control lines can enhance the contrast of those two lines (test and control) and improve the sensitivity of detection of PfHRP2 to 8 ng/mL. In addition, the researchers demonstrated that this microneedle-based lateral flow assay (Fig. 4) requires less than 20 mins to complete each test. Such approaches provide a future for a simple and rapid diagnostic microneedle-based device, primarily for self-testing of malaria disease.

### 2.3. Skin and soft tissue infections

Characterised by microbial invasion into the skin and underlying tissues, skin and soft tissue infections are among the most common infections encountered in both ambulatory and hospital settings [90]. Skin and soft tissue infections is an umbrella term that encompasses a broad range of skin infections ranging from simple subcutaneous abscesses to severe necrotising infection [91]. The aetiology of skin and soft tissue infection can be very complex due to the diverse microbiome present within skin tissues. In healthy human skin, commensal bacteria typically secret molecules, such as lugdunin and serine protease glutamyl endopeptidase, which mitigate the propensity of skin infection arising from pathogenic microbial organism [92]. Nevertheless, changes to the skin microbiome termed dysbiosis may give rise to skin and soft tissues infections [93]. Some of the common organisms that cause skin and soft tissues infections are *Staphylococcus aureus, Pseudomonas aeruginosa, Enterococcus species, Escherichia coli* and *Beta-hemolytic Streptococcus* [91].

Ideally, the treatment choice for skin and soft tissue infection is tailored to the causative microorganism. In most cases, broad-spectrum antibiotics are prescribed empirically until clinical results are available to guide the treatment with narrow spectrum antibiotics. Gentamicin is an example of a broad-spectrum antibiotic that is used in the management of some skin infections [94]. However, the hydrophilic nature of the drug limits its permeation across the skin to treat deep-located infections. In addition, it is quite common for most antimicrobial agents that are used in the management of skin and soft tissue infections to display physicochemical properties that limits the permeation of the compounds to treat deeper seated skin infections. In light of this limitation, MAPs may aid the delivery of antibiotics into the skin, as illustrated in Fig. 5.

The development of antimicrobial MAPs was initially developed as an effort to mitigate the risk of infection that may be associated with the movement of microorganism through microchannels post microneedle insertion. Gittard and coworkers were among the pioneering researchers to fabricate antimicrobial MAPs for the treatment and management of localised skin infection. The group developed antimicrobial microneedles which were fabricated from polyethylene glycol 600 diacrylate *via* two photopolymerisation-micromolding, which were then coated with gentamicin sulphate. These microneedles were shown to release gentamicin *in vitro* and inhibit the growth of *Staphylococcus aureus,* as shown *via* agar plating assays [95]. It was apparent that during the early 2010s, coated MAPs were indeed the most common type of microneedles used to deliver potent antimicrobial agents for localised skin and soft tissue infections [96–98]. However, this class of MAPs suffer the issue of limited drug loading which may result in sub-inhibitory concentrations of the antimicrobial agents being delivered into the skin. Consequently, several researchers reported that this particular MAP system was ineffective in mitigating the growth of some strains of pathogenic microorganism [96,97,99]. From a clinical standpoint, delivering sub-inhibitory concentration of antimicrobial agents to infected skin could lead to detrimental effect, as this will not only result in poor treatment outcome but the sub-inhibitory concentration delivered will exert a selective evolutionary pressure on dermal microbiota that could lead to the development of antimicrobial resistant bacteria.

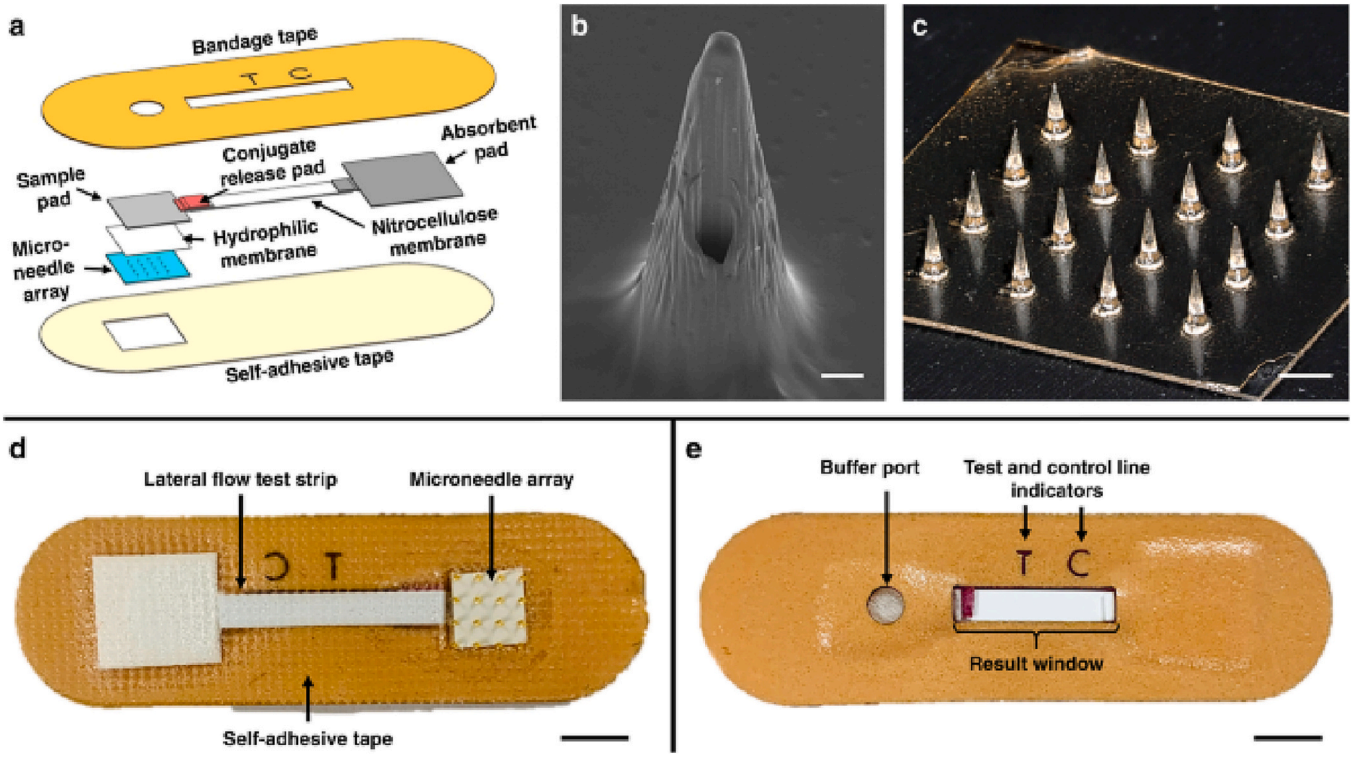


**Fig. 4.** (a) The design of the microneedle-based device. (b) Scanning electron micrograph of a single hollow needle (scale bar is 100 μm). (c) Digital image of microneedles (scale bar is 1 mm). (d) The underside and (e) topside views of device (scale bar is 6 mm). Adapted with permission from [89].

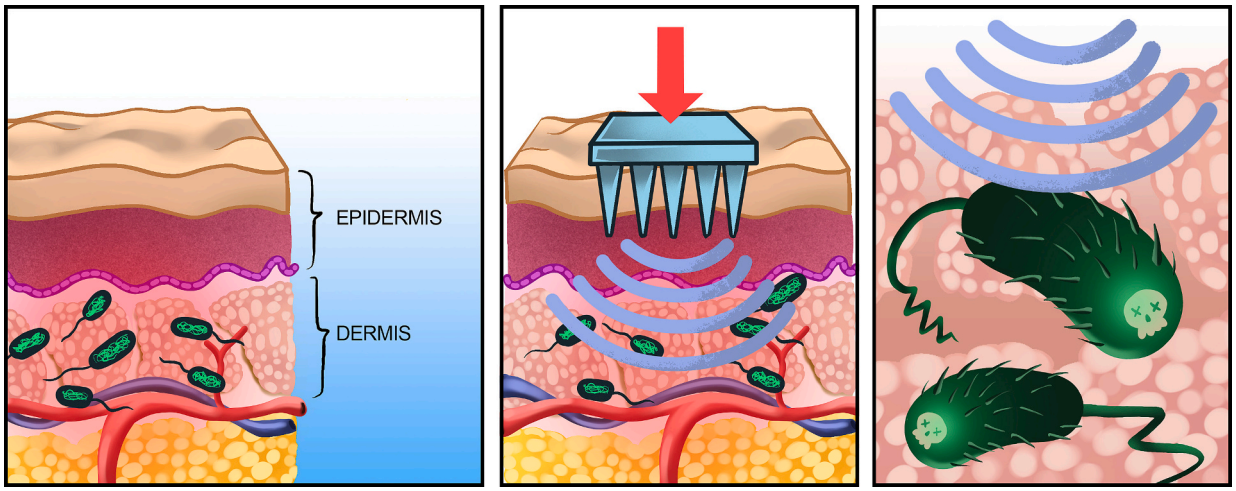


**Fig. 5.** Illustration of MAPs loaded with antimicrobial agents used in the management of skin and soft tissue infections.

There was a paradigm shift towards utilising other MAP systems for the treatment of skin and soft tissue infections. For instance, González-Vazquez *et al.* fabricated dissolving MAPs that contained gentamicin. Through the use of *in vitro* Franz cell diffusion experiments and an *in vivo* rat model, it was shown that the dissolving polymeric MAP system was able to release gentamicin into and across the skin within a matter of 5 minutes [100]. Although the MAP system developed was designed for the treatment of sepsis, the overall formulation could be refined and tailored to treat more localised skin infections. In order to do so, gentamicin, which is indicated for systemic infections [101], could be swapped for other antimicrobial agents which are more suited for localised cutaneous infections such as neomycin, mupirocin and polymyxins [102]. Indeed, the use of dissolving MAPs provides an improvement with regard to drug loading, as the researchers showed that high antibiotic loading was achievable with dissolving MAPs [103]. However, in doing so, they also showed that such high antibiotic loading may in some instances be incompatible with several pharmaceutical polymers resulting in the formation of brittle MAPs that fractured on the skin surface during application.

In order to circumvent this issue while still provide a solution to improve drug loading, several researchers within the field have moved toward the use of hydrogel-forming MAPs as a drug delivery vehicle to deliver high doses of antibiotic agents into the skin. Hydrogel-forming MAPs are a class of microneedles that were developed by Donnelly *et al.* through thermal crosslinking of polymers. When inserted into the skin, this class of MAPs absorb interstitial fluid from vicinal dermal tissue leading to hydrogel swelling [104]. This leads to the formation of continuous, unblocked hydrogel channels which can be used by

molecules to diffuse into and across the skin. Additionally, the rate of drug delivery can be tuned by the density of crosslinking within the hydrogel network permitting controlled drug delivery release. Recently, Sabri & Anjani *et al.* confirmed that using a composite pharmaceutical system consisting of a dry antibiotic reservoir in combination with hydrogel-forming MAPs is a viable approach in delivering high doses of antibiotic into the skin [105]. In this work, it was shown that by modulating the chemistry of the hydrogel-forming MAPs *via* the use of commonly approved pharmaceutical polymers, the researchers were capable of developing MAPs that swells rapidly when placed in an aqueous rich environment such as the dermis. However, for such system to be effective in delivering the antibiotic agent, judicious and meticulous selection of excipients used in the dry drug reservoir is also crucial. The researchers showed that the system developed was capable of delivering cephalosporin and cefazolin into and across the skin. More importantly, the dermatokinetic study conducted showed that the duration of microneedle application in tandem with the type of dry reservoir (wafer *vs* tablets) played a pivotal factor on the localisation of the antibiotic within the epidermis and dermis.

Recent evidence has emerged to suggest that some bacteria such as *S. aureus* can reside within phagolysosomes of skin cells such as keratinocytes and phagocytic cells. This provides the cells with a protective environment which enable the bacteria to evade both the immune systems and antimicrobial agents [106]. Studies have shown that one promising strategy to target these evasive bacteria is *via* the use of nanogels. A nanogel is a type of nanoparticle which is formed from a crosslinked hydrophilic polymer network that swells in an aqueous environment, leading to hydrogel formation [106]. Using hyaluronan based nanogels, Montanari *et al.* showed that hyaluronic acid based nanogels can be easily taken up by keratinocytes and dermal phagocytic cells leading to intracellular co-localisation between the nanocarrier and the bacteria. Nevertheless, one downside of this approach is the poor penetration profile of the nanogels into intact skin [107]. Moving forward, future work could involve loading these intracellular targeting nanogels into dissolving microneedles to bypass the *stratum corneum* in order for these nanogels to be delivered intradermally where it can be taken up keratinocytes and dermal phagocytic cells to actively target evasive bacteria. Therefore, it can be viewed that composite microneedle systems such as dissolving MAPs loaded with antibiotic nanocarriers [108] or hydrogel-forming MAPs used in tandem with antibiotic loaded dry reservoirs are emerging strategies that are employed or being researched to treat cutaneous and deep-seated skin infections.

The promising potential for MAPs to be utilised as a drug delivery system to treat skin and soft tissue infections has led to several patents being filed for such purposes [109,110]. Based on promising results and if future research in this area continues to prove the value of MAPs in managing localised skin infection, it is envisioned that antibiotic-loaded MAPs may emerge as a promising formulation for the treatment of skin infections. However, much work is still necessary before this system could be translated into clinical practice. Table 1 summarises some of the studies that have focussed on the development of antimicrobial MAPs for the treatment of skin and soft tissue infections. One of the translational and clinical hurdles that ought to be considered in the development of MAPs for the management of skin infections is the possibility for the disease to manifest on random anatomical locations with varying sizes. For instance, furuncles, carbuncles, erythrasma and impetigo typically manifest as a localised skin infection while folliculitis and erysipelas affect a larger surface area of the body [111]. In some instances, these infections may become exacerbated and lead to a more systemic effect which can manifest as septicaemia or sepsis. Due to the miniature size of MAPs, these patches may be well suited to manage and treat localised skin infections. Nevertheless, some work within the field has explored the possibility of developing and applying larger MAPs [112]. These larger patches could be explored as a platform to treat skin infections over a larger surface. In addition, the ability to incorporate a flexible backing layer in the overall MAP design should also be explored for the purpose of treating skin infections [113]. These MAPs with a flexible backing offer the possibility to contour and apply the patch on more curved skin surfaces. In the instance where the skin infection has progressed to septicaemia, MAPs could still be used to manage these infections by delivering antibiotics and therapeutic agents systemically rather than intradermally as evidenced by the work by González-Vazquez *et al.* [100]. Nevertheless, the use of MAPs may be limited should the infection become too widespread or even cover the whole body. Another translational hurdle that could be observed in the area of antimicrobial MAPs is that most of MAPs efficacy studies have largely been limited to *in vitro* agar plating assays. There are limited studies that use an *in vivo* model of skin infection to evaluate the full efficacy of antimicrobial MAPs. The development of such antimicrobial MAPs accompanied with careful evaluation of efficacy using a suitable *ex vivo* and *in vivo* model is paramount in order to move the field forward. (See Table 2.)

Considerable strides have been made in order to develop a suitable skin infection model to evaluate MAPs that are loaded with antimicrobial agents. For instance, Permana *et al.* recently developed an *ex vivo* fungal infection model in porcine skin, as a method to evaluate the efficacy of dissolving MAPs loaded with itraconazole nanocrystals. Using the *ex vivo* fungal infection model, the researcher showed that dissolving MAPs resulted in 100% decline in *Candida albican* viability 48 h post-administration [108]. Although such methodology does not fully mimic *in vivo* cutaneous candidiasis, such a model may be viewed as an improvement to the classic agar plating assay, as the drug is released into actual skin tissues compare to the microbial growth in agar [108]. However, it was not until recently that researchers within the microneedle field have begun using relevant animal models for skin infection in an effort to evaluate and demonstrate the efficacy of antibiotic loaded MAPs [124,126]. Within the field of dermatological research, there are several well-established murine models for skin infections that range from subcutaneous models [127], intradermal models [128], epicutaneous models [129] and even wound models [130]. To this end, murine skin infection models have enabled researchers to examine host immunity by investigating the timing, inoculum, route of infection and the causative bacterial species for skin infections [131]. However, these models have yet to be fully utilised in evaluating the efficacy of MAPs loaded with antimicrobial agents. Evaluating the efficacy of MAPs using these *in vivo* models would not only enable researchers to gauge the efficacy of the formulation developed but would provide fundamental insight on additional immunologic mechanisms that are involved against skin infections. Such models would be of heuristic value in developing and refining antimicrobial MAPs for the treatment of skin and soft tissue infections. Therefore, it is postulated that judicious candidate antibiotic selection in combination with meticulous microneedle formulation design that is subsequently evaluated in clinically relevant *in vivo* model would be pivotal in the development of an effective and clinically relevant antimicrobial MAP.

### 2.4. *Methicillin-resistant Staphylococcus aureus infections*

Due to their capacity to penetrate into the different skin layers, MAPs can be used to treat skin infections at a local or systemic level. Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are classified as one of the most harmful diseases, killing nearly 50,000 in the USA and Europe [132,133]. Hence, effective drug delivery in both local and systemic fashions is required to better target these diseases and MAPs could become advantageous for this purpose. On the one hand, direct penetration of the needles into wound infections and necrotic tissues could allow the direct delivery of antimicrobial agents towards the biofilm formed and locally treat the disease, as illustrated in Fig. 6. Moreover, as outlined in previous sections, transdermal delivery of compounds is also possible *via* their absorption within the skin microcirculation.

In order to investigate the utilization of MAPs for wound healing, Mir

**Table 1**
Summary of MAP design and material for antimicrobial delivery of skin infection treatment.

A

| Microneedle Design | Material | Microneedle type | Antimicrobial agent | Outcome | Ref |
|---|---|---|---|---|---|
| 5 x 5 microneedle arrays with a length of 500 μm | Polyethylene glycol 600 diacrylate | Dissolving | Gentamicin sulphate | MAP exhibited antibacterial effect against *S. aureus* when evaluated using agar plating assay. | [95] |
| Acrylate-based microneedle with our different geometries. Height ranged from 1000-1250 μm. | Acrylate polymer (eShell 200) | Coated | Silver and zinc oxide | MAP exhibited antibacterial effect against *Staphylococcus epidermidis* and *Staphylococcus aureus* but not for *Escherichia coli.* When evaluated using agar plating assay. | [96] |
| 14 x 14 microneedle with height ~600 μm. | Gantrez® AN-139 | Dissolving | Methylene blue | MAP showed an antibacterial effect of >96%when tested against *S. aureus*, *E. coli* and C. *albicans*. | [114] |
| 1 x 5 array with microneedle height of ~ 800 μm. | Gantrez ® AN 169 BF | Dissolving | none | The MAP dissolved when placed in the agar plating assay while resulting in a large zone of inhibition for *E. coli, S. aureus, E. faecalis* and *B. subtilis*. However, no antimicrobial effects were found when tested against *P. aeruginosa* and *C. albicans*. | [115] |
| 19 x 19 arrays of polymeric microneedles with height of ~ 500 μm | Sodium hyaluronate and polyvinylpyrrolidone. | Dissolving | Gentamicin sulfate | MAP was shown to dissolve and deliver gentamicin transdermally resulting in a maximum plasma level in the range of 2-5μg/ml within 1-6 hours after microneedle application. | [100] |
| 120 x 120 array microneedles with height of ~ 500 μm | Hyaluronic acid | Dissolving | Green tea extract | MAP inhibited the growth *E. coli, B. subtilis, P. putida, S. aureus,* and *S. typhimurium* when evaluated using agar plating assay. | [116] |
| 1 x 4 array microneedles with height of ~750 μm. | Polyglycolic acid | Coated | Voriconazole | Voriconazole coated MAPs displayed antifungal activity against *Candida albicans* but were ineffective against *Escherichia coli, Pseudomonas aeruginosa* and *Staphylococcus aureus.* | [97] |
| 1 x 5 array of microneedles with height of ~ 900 μm | Gantrez 169 BF | Coated | Amphotericin B | Amphotericin B coated MAPs exhibited efficacy against *Candida parapsilosis* when evaluated using agar plating assay. | [117] |

B

| Microneedle Design | Material | Microneedle type | Antimicrobial agent | Outcome | Ref |
|---|---|---|---|---|---|
| 1 × 4 array of microneedle with height of either ~ 900 μm or 1500 μm. | Polyglycolic acid | Coated | Amphotericin B | MAP exhibited antifungal activity against *Candida albican* when evaluated using agar plating assay. | [98] |
| 1 x 5 microneedle array with height of ~ 900 μm | Gantrez® AN 169 | Coated | Miconazole | MAP exhibited antifungal activity against *Candida albican* when evaluated using agar plating assay. | [118] |
| 1 x 4 microneedle arrays with height of ~ 640 μm | Polyglycolic acid coated with poly (methyl vinyl ether–co-maleic anhydride) | Coated | Itraconazole | MAP exhibited antifungal activity against *Candida albican* but was void of any inhibitory effect on the growth of E. coli and S. aureus when evaluated using agar plating assay. | [99] |
| 15 x 15 arrays with height of 700 μm | carboxymethyl cellulose | Dissolving | Nanosilver | MAP exhibited antibacterial activity against Gram positive bacteria such as *S. aureus* and *S. epidermidis* as well as Gram-negative bacteria such *E. coli* and *P. aeruginosa*. | [119] |
| 10 x 10 arrays with microneedle height of 650 μm | gold-coated polystyrene | Coated | Zinc oxide nano-bushes | MAP exhibited antibacterial activity against Gram positive *S. aureus* and *S. epidermidis* and Gram-negative *Salmonella.* | [120] |
| 10 x 10 arrays microneedles with height of 600 μm. | hyaluronic acid | Hydrogel forming | Clindamycin | MAP displayed antibacterial properties against *P. acnes* while *in vivo* study in mice showed 90% reduction in skin inflammation. | [121] |
| 11 × 11 conical needle holes, each measuring a height of 600 μm | Gantrez S-97, PEG and sodium carbonate | Hydrogel forming | Vancomycin | Hydrogel-forming MAP delivered 46 % of the vancomycin dose across *ex vivo* neonatal porcine skin when evaluated using Franz diffusion cell set up. *In vivo* studies, showed that the area under the plasma concentration time curve from time zero to infinity (AUC0−∞) was 162.04 μg h/mL following the application of hydrogel forming MAPs which was significantly greater than that of the oral and dissolving MAP administration control group. | [122] |

C

| Microneedle Design | Material | Microneedle type | Antimicrobial agent | Outcome | Ref |
|---|---|---|---|---|---|
| 11 × 11 conical needle holes, each measuring a height of 600 μm | Gantrez® S-97, PEG 10 000 & Carbopol® 974P NF | Hydrogel forming | Cefazolin | *In vitro* permeation studies, using full thickness *ex vivo* neonatal porcine skin demonstrated the dry reservoir combination consisting of directly compressed tablet with hydrogel-forming MAPs was capable of delivering cefazolin into the epidermis within 2 hours of application. In addition, the composite pharmaceutical system was capable of delivering up to 1.8 mg cefazolin into and across the skin at 24 hours. | [105] |

(*continued on next page*)

**Table 1** (*continued*)

C

| Microneedle Design | Material | Microneedle type | Antimicrobial agent | Outcome | Ref |
|---|---|---|---|---|---|
| 16 × 16 pyramidal needles with a height of 850 μm. | Polyvinylpyrrolidone & polyvinyl alcohol | Dissolving | Itraconazole | Dissolving MAP containing itraconazole nanocrystal exhibited better dermatokinetic profiles, compared to needle-free patches and conventional creams. Importantly, the antifungal activity in an *ex vivo* candidiasis infection model showed that the MAP resulted in 100% decline in *Candida albican* viability after 48 h of administration. | [108] |
| 16 × 16 needles with 850 μm needle height | Polyvinylpyrrolidone & polyvinyl alcohol | Dissolving | Amphotericin B | MAP inhibited Candida albicans growth and resulted in 100% eradication within 24 h. Pharmacokinetic and biodistribution studies in rats showed that Amphotericin B concentration in plasma, kidney, liver, and spleen in the MAP group was significantly lower than that in the IV group indicating that the MAP resulted in enhanced intradermal delivery with less systemic exposure to the drug. | [123] |
| 10 × 10 needles with 1000 μm needle height | Chitosan–polyethylenimine | Dissolving | Amphotericin B | MAP efficacy was evaluated using fungal infection mouse model. It was shown that the MAP that was fabricated from chitosan–polyethylenimine and loaded with amphotericin B offered higher efficacy relative to the control over the course of 6 days. Such enhancement in efficacy was attributed to the high bioavailability of Amphotericin B and the synergistic actions of the antifungal polymer and drug. | [124] |

D

| Microneedle Design | Material | Microneedle type | Antimicrobial agent | Outcome | Ref |
|---|---|---|---|---|---|
| 16 × 16 needles with 850 μm needle height | Polyvinylpyrrolidone & polyvinyl alcohol | Dissolving | Doxycycline | The incorporation of these doxycycline nanoparticles into dissolving MAP significantly enhanced the dermatokinetic profiles of the antibiotic, indicated by higher retention time com-pared to needle-free patches. Importantly, the antibiofilm activity in *ex vivo* biofilm model showed that after 48 h, the bacterial bioburdens decreased up to 99.99% following the application of this approach. | [125] |

*et al.* fabricated dissolving MAPs loaded with polycaprolactone nanoparticles containing the antimicrobial agent carvacrol [134]. *Ex vivo* drug deposition studies in porcine skin showed that over 80% of the drug was retained in the skin layers after 24 hours when nanoparticle-loaded MAPs were used, whereas only 7% of the drug was present with free-drug loaded microneedles. An *ex-vivo* porcine skin wound model was developed by making burn wounds and culturing different bacterial strains, including the MRSA strains ATCC® 33593 and ATCC® BAA-1707. MAPs were applied into the *ex vivo* wound model for 24 hours, achieving over 90% of bacteria killed in both strains, proving that MAPs do indeed have potential in the treatment of infected MRSA wounds.

In regards of systemic infection, Ramadon *et al.* developed MAPs for the transdermal delivery of vancomycin, the first-line antibiotic therapy for MRSA-derived infections [135]. The drug was loaded in dissolving MAPs and also, compressed tablets which were then coupled with hydrogel-forming MAPs. *Ex vivo* permeation studies using neonatal porcine skin mounted on Franz diffusion cells showed that, after 24 hours, approximately 35 mg and 4 mg of drug permeated when using hydrogel-forming and dissolving MAPs, respectively. Pharmacokinetic studies in female Sprague Dawley rats were also conducted, testing both MAP-based devices. Here, it was seen that MAPs coupled with compressed tablets of vancomycin led to a higher drug deposition in the skin whereas dissolving MAPs led to a higher drug accumulation in the lymph nodes after 24 h. Moreover, the $t_{(1/2)}$ and mean residence time was significantly higher when hydrogel-forming MAPs were applied (in comparison to oral and IV drug administration). In addition, plasma concentrations after application of the same device were kept between 2-4 μg/mL from 12 h to approximately 50 h, which is within the range of the minimum inhibitor concentration (MIC) of VCL for treatment of MRSA-derived infection (1−2 μg/mL) but also within the plasma concentration recommended to prevent bacterial resistance. Similarly, Ziesmer *et al.* explored vancomycin MAPs aiming at the retention of the drug in the skin, which could be useful for the local treatment of MRSA-caused skin infections while minimizing adverse effects of systemic administration. To achieve this, dissolving MAPs were fabricated using PVA needle tips (where the drug was included) combined with a water-insoluble PMMA baseplate layer. *Ex vivo* permeation studies using neonatal porcine skin showed that the amount of drug on and within the skin was two times higher in comparison to the amount permeated. Importantly, although only 48% of the drug was delivered from the MAP, the concentrations reached were over 500-fold higher to those reported when vancomycin is administered intravenously. In addition to peptide-related work, Su *et al.* developed a MAP device that included: 1) a database-designed antimicrobial peptide called W379, which targets the cell membrane of both Gram-positive and Gram-negative bacteria and 2) a electrospinning-made nanofiber mat containing the same peptide [136]. The compound was included in dissolving MAPs and the nanofiber mat was placed on top, as a baseplate. In doing so, the peptide could be delivered both inside and outside of biofilms. *Ex vivo* studies in a wound infection model instilled with MRSA showed that the microneedle device system significantly decreased the colony forming units (CFU) counting in comparison to nanofiber mat alone, showcasing the enhance effect of MAPs on directly delivering the drug inside the biofilms. In addition, an MRSA chronic wound model based on type II diabetic mice was treated with peptide-loaded nanofibers and the MAP system describe above. In both cases, the CFU counting decreased significantly after the application of the systems (changed every 24 hours for three times), with this decrease more marked in the case of the MAP device.

With regards systemic delivery of antibiotics, McAlister *et al.* explored the feasibility of using hydrogel-forming MAP in order to deliver and achieve therapeutic plasma levels of amoxicillin and levofloxacin *in vivo* [137]. From their work McAlister and co-workers discovered that therapeutical relevant plasma concentration of

**Table 2**
Summary of MAP design and material for antimicrobial delivery of methicillin-resistant *Staphylococcus aureus* infections.

A

| Microneedle design | Material | Microneedle type | Antimicrobial agent | Outcome | Ref |
|---|---|---|---|---|---|
| 16 × 16 needle density, cuboidal in shape, 850 μm in height with base width of 300 μm and interspacing of 100 μm)<br>19 × 19 needle density, conical in shape, 600 μm in height with base width of 300 μm and interspacing of 50 μm | PVP (29–32 K)<br>PVA (31–50 K) | Dissolving | Carvacrol | Carvacrol-loaded polycaprolactone nanoparticles were loaded in dissolving MAPs to pierce the necrotic tissue barrier, which limits the diffusion of drugs into the wound bed. An *ex vivo* wound model infected with different bacterial strains showed the antimicrobial effect of the system and its potential for the treatment of infected wounds. | [134] |
| 11 × 11 conical needle holes, each measuring a height of 600 μm, base widths of 300 μm, and an interspacing of 250 μm<br>19 × 19 conical needle, 600 μm height, 300 μm base widths, and 50 μm interspacing). | PMVE/MA cross-linked by esterification with 7.5% w/w PEG 10,000 and 3% w/w sodium carbonate<br>PVP K-30 and sodium hyaluronate | Hydrogel-forming Dissolving | Vancomycin | Vancomycin was loaded in dissolving MAPs and reservoirs to be used with hydrogel-forming MAPs. The later led to higher drug deposition in the skin as well as sustained plasma concentrations for a period of 50 hours. | [135] |
| 10x10 pyramidal needles, 600 μm height and 200 μm base widths. | PVA (87–89% hydroxylation), MW 12–23k<br>Polym-ethylmethacrylate | Dissolving | Vancomycin | Vancomycin-loaded MAP were fabricated with a water-insoluble base plate layer to maximize drug delivery into the skin. *Ex vivo* permeation studies showed that 10 min were enough to reach the maximum in-skin drug deposition. Moreover, porcine skin infected with MRSA and treated with MAPs twice led to significant bacterial killing. | [139] |

B

| Microneedle design | Material | Microneedle type | Antimicrobial agent | Outcome | Ref |
|---|---|---|---|---|---|
| 11 × 11 conical needles with 600 μm height, 300 μm base diameter, and 5 μm tip radius | Manuka honey | Dissolving | Manuka honey | MAPs were successfully fabricated using Manuka honey exposed to high temperature and vacuum while bacterial assay showed that honey extracts can effectively kill MRSA. | [138] |
| 100 or 150 conical needles per patch. 300 μm in a round-base diameter and 300 μm in height. | PVP | Dissolving | W379 peptide | A dissolving MAP containing an antimicrobial peptide and a nanofiber membrane as baseplate was fabricated. Tests in an *ex vivo* wound infection and a diabetic mouse wound infection model showed that the system was able to eradicate MRSA biofilms. | [136] |

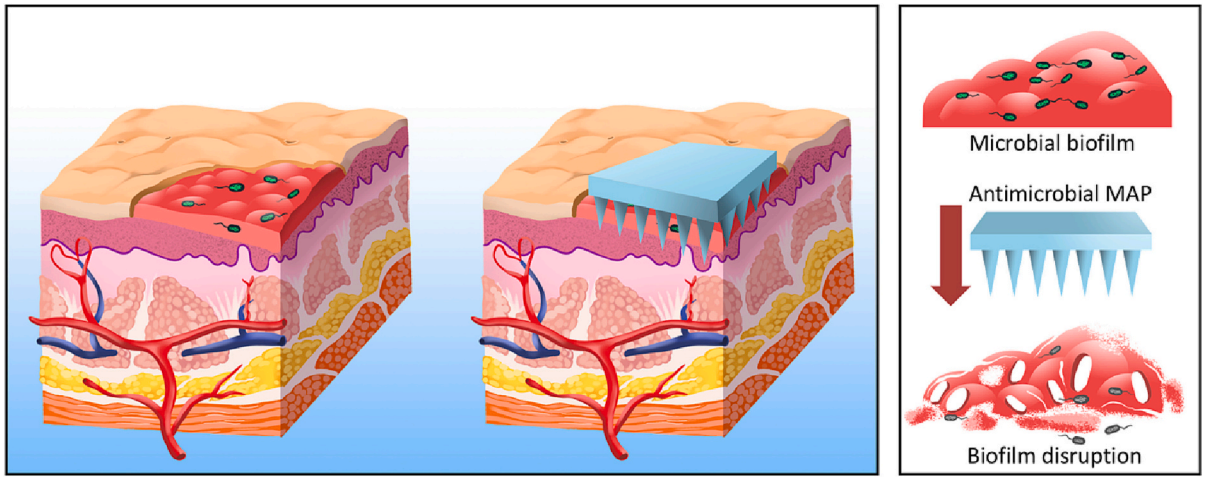


**Fig. 6.** Biofilms are formed to protect bacteria underneath and mostly observed in breached skin wounds, which prevent the access of antimicrobial *via* topical application. The microbial biofilm can be penetrated by MAP transdermally. When the MAP loaded with antimicrobial compound is inserted into the skin, the MAP subsequently releases the loading and disrupt the integrity of the biofilm structure.

amoxicillin and levofloxacin were achieved within the 1 hour following the application of hydrogel-forming MAP in tandem with drug loaded compressed table. The plasma levels achieved were above the MIC breakpoint for AMX and LVX for nonspecific bacterial species which are 2 and 0.5 μg $mL^{-1}$, respectively. Thus, this proof-of-concept study highlighted that the utility of MAP as a promising and effective drug delivery platform to deliver antibiotic systemically which may be of great therapeutic benefits in the treatment of systemic MRSA infections.

Moving forward to natural products, Frydman *et al.* investigated the use of Manuka honey (which is obtained in Australia and New Zealand) for the fabrication of MAPs [138]. Honeys have natural antimicrobial properties and Manuka honey in particular shows a higher

concentration of methylglyoxal, a major antibacterial compound. Hence, studies were initially performed to evaluate the most suitable technique to fabricate MAPs purely of honey by dehydrating it and so achieving a "hard-to-crack" material that could form the needles. Dehydrating the honey *via* vacuum and heating combined with increased pressures was tested, achieving in both cases the formation of MAPs. Bacterial killing assays were performed by co-culturing MRSA with honey solutions, which were previously exposed to the same conditions as for the fabrication of the MAPs. Here, it was seen that 10% of honey concentration is the minimum amount required to observe a bactericidal effect on MRSA strains, where the bactericidal effect of vacuumed honey might be more potent. Nonetheless, the studies confirmed that honey could be used as primary or adjunct material for the fabrication of MAPs against MRSA infections.

### 2.5. COVID-19

Coronavirus infectious disease (COVID-19) took the world by surprise in 2019 resulting in a profound and detrimental effect on healthcare systems worldwide. Many countries were unprepared to fight severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), forcing them to introduce strict measures to contain the virus. This included mass testing and immunisation programmes, both of which are widely understood to be the only methods of battling a pandemic such as COVID-19. For instance, early diagnosis through regular testing plays an important role in controlling COVID-19 as it identifies those required to undergo a period of isolation to prevent the further spread to uninfected individuals. Nevertheless, this approach of public mass testing resulted in substantial backlog in both accurate disease diagnosis as well as the provision of adequate treatment to patients. To date, this has been achieved using viral nucleic acid testing from oropharyngeal swabs [140]. However, this has been associated with low efficiency due to ineffective sample collection, limited physical absorption from mucosal tissues and contamination from food or drink [141–143]. According to several reports, this can result in up to 30% of tests appearing as 'false-negatives' and thus enabling further viral spread [143–146]. To improve the current sampling efficiency, Chen *et al.* developed a MAP swab that is inserted into the oral cavity, contacting the posterior pharynx and tonsillar areas. This MAP was fabricated using alginate polymers, with the antibody targeting spike protein of SARs-CoV-2 incorporated into the polymeric matrix [147]. This dual function MAP consisted of a highly crosslinked region for mucosal insertion and a low-crosslinked region to facilitate viral infiltration and release into virus preservation solution (Fig. 7). The authors reported a higher amount of collected virus when compared to a conventional swab, improving the distinction of positive and negative patients. This has demonstrated that MAP devices can greatly improve the early diagnosis of COVID-19 or indeed other oral and respiratory tract infections.

In addition to COVID-19 detection and diagnosis, MAPs have also been developed for COVID-19 vaccine delivery. Kim *et al.* have manufactured a carboxymethyl cellulose (CMC) dissolving MAP incorporated with SARS-CoV-2 S1 subunit vaccine. S1 is an important target in COVID-19 vaccine development as it plays a crucial role in viral transmission and infection, determining the tropism of the virus and host cell entry [148]. In this instance, dissolving MAPs were fabricated using a two-step spin drying strategy that has been previously upscaled for Phase 1 clinical trials. The authors demonstrated that this MAP could elicit a potent SARS-CoV-2-specific antibody response that was evident as early as 2 weeks after immunisation in BABL/c mice [147]. Furthermore, gamma irradiation (25 kGy) sterilisation of the SARS-CoV-2 S1 loaded MAPs had no adverse effect on immunogenicity in this study. This was a key finding and now provides a viable method to assure sterility of MAPs for up-coming clinical investigation. To this end, this research group at the University of Pittsburgh have named this vaccine delivery platform "PittCoVacc" and are currently preparing for a Phase 1 clinical trial. Kuwentrai *et al.* have also developed a hyaluronic acid (HA) dissolving MAP loaded with an S1 receptor-binding domain. Specifically, the S1 protein was loaded into the needle tips alongside an aluminium hydroxide gel adjuvant [149]. After dosing in BABL/c mice, specific B-cell antibodies and IFN-γ T-cell responses were detected. When compared to the CMC dissolving MAP vaccine delivery platform developed by Kim *et al.*, HA dissolving MAPs obtained similar antibody responses, albeit for a longer period of up to 97 days after administration. Encouragingly both studies showed comparable outcomes to the conventional injection. In addition, a separable MAP loaded with nanovaccines has been developed to trigger immune responses for blocking the infection of SARS-CoV-2 virus [150]. Notably, these separable MAPs efficiently induced an immune response in C57BL/6 mice after storage at room temperature for two weeks. This indicates that MAPs can maintain vaccine stability during transport without the need for cold chain storage. This is a key advantage when improving vaccine coverage and could enable direct transport to point-of-care use.

Vaxxas, a spin out company from the Australian Institute of Bioengineering and Nanotechnology at the University of Queensland, secured a $22 million grant from the Biomedical Advanced Research and Development Authority (BARDA), the U.S. Government Agency leading

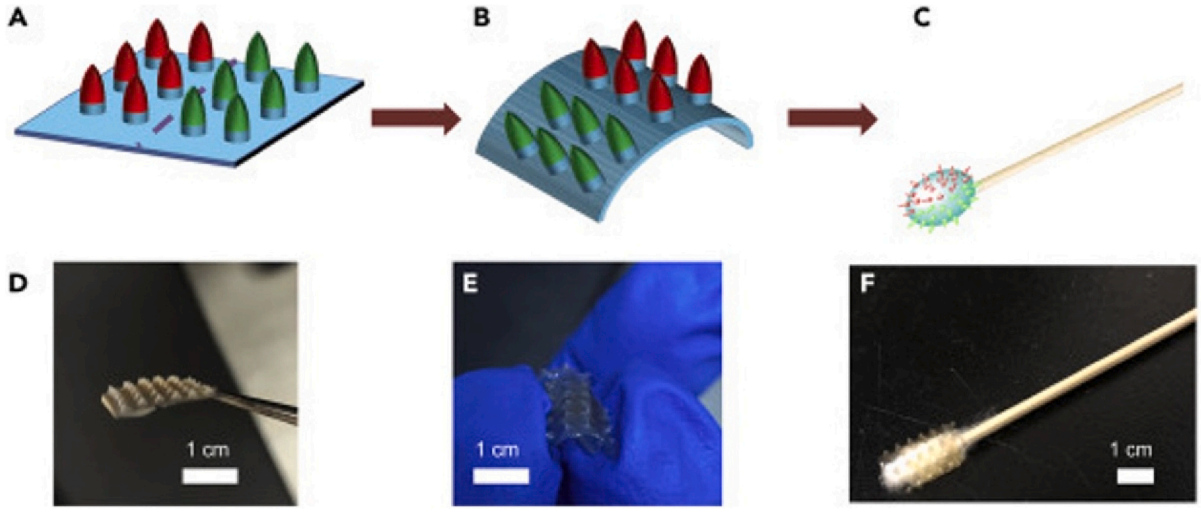


**Fig. 7.** A-C) Schematic representation of a dually functionalised MAP swab. Red and green needles indicate high and low crosslinking levels, respectively. D-F) Images of a dually functionalised MAP and attachment onto a regular swab. Adapted with permission from [147].

the pandemic response, to develop MAPs for vaccination, including COVID-19 [151]. In this instance, SARS-CoV-2 spike subunit vaccine was dry-coated onto a high-density (HD) MAP composed of 5000 needles, 250 μm in length and a tip diameter of 25 μm [152]. In a preclinical study, the HD-MAP displayed an enhanced T-cell and SARS-CoV-2 spike-specific antibody responses when compared to conventional needle and syringe delivery. Furthermore, the authors stated that post-vaccine serum antibody levels demonstrate the potential to neutralise emerging isolates as the pandemic progresses [153]. Vaxxas are not the only company exploring the use of MAPs for COVID-19 vaccination. Vaxess Technologies and Medigen Vaccine Biologics Corp. (MVC), a Taiwanese pharmaceutical company, have formed a partnership to develop a combined COVID-19 and quadrivalent seasonal influenza vaccine (QIV) using a MIMIXTM MAP platform. This involved incorporating SARS-CoV-2 spike subunit vaccine and a QIV into a dissolving MAP fabricated from silk fibroin proteins [154,155]. This has been designed to offer a seasonal protection vaccine via single-dose that is easy to use, pain-free and is associated with greater patient acceptance when compared to a conventional needle and syringe. By securing a $2.85 million grant through the Commercialization Readiness Program (CRP), a Phase 1 proof-of-concept trial is expected to commence in Q1 of 2022.

From a healthcare perspective, the COVID-19 pandemic magnifies the issue of staff shortages in several healthcare systems globally [156]. In these instances, the provision of adequate healthcare to treat patients suffering from other health related issues is compromised as a large proportion of the healthcare workforce are relocated to treat and manage COVID-19 patients. This issue is further exacerbated as most routine injectable drugs still necessitate the attendance at a healthcare setting. Furthermore, the boom of biotechnology has led to an ever-increasing prevalence of biotherapeutics such as peptides, antibodies and oligonucleotides with astounding therapeutic potential. However, these macromolecules possess high molecular weights, extreme physicochemical properties along with poor oral bioavailability which necessitate injection thus requiring the intervention of a healthcare professional. Therefore, there is a need to explore alternative drug delivery systems which can offer the possibility of at-home administration. Such systems would not only free up healthcare providers but also mitigate the risk of COVID-19 transmission. In this instance, the use of MAP technology may provide a solution to deliver these therapeutics transdermally in a minimally invasive fashion. As these compounds typically require milligram dosing, delivering therapeutic levels may prove challenging with dissolving MAPs due to their limited drug loading. Instead, hydrogel-forming MAPs which are designed with a separate drug containing reservoir may provide a suitable alternative [157]. Nevertheless, administrating these therapeutics using MAP obviates the need for healthcare worker interventions and would mitigate unnecessary attendance at a healthcare setting.

## 3. Clinical considerations and future perspectives

In more recent times, the necessity for alternative methods of drug administration has come to the forefront of disease management. For instance, the stresses and strains on healthcare systems across the globe as a result of the COVID-19 pandemic have highlighted the need for more efficient vaccine delivery strategies. With this in mind, dissolving MAPs offer a potential immunisation strategy to prevent future infections. Not only are they pain-free, self-disabling, easy to use and enable self-administration, but the elimination of cold-chain storage could greatly improve global access to vaccines. Indeed, the future appears promising for MAPs-based technologies. This is evidenced by their inclusion as one of the top 10 emerging technologies of 2020 by the World Economic Forum [33]. This has certainly put MAPs in the spotlight, creating an attractive prospect for further investments.

Despite the benefits conferred by MAP technologies along with the advancements made in the field, there is no MAP-based drug product to date that has gained US Food and Drug Administration (FDA) approval. Currently, there is a lack of standard and universal methods for quality control of MAPs, however, it seems likely that regulators will view MAPs, particularly coated, dissolving and hydrogel-forming MAPs, as a new drug delivery system rather than as a CE marked medical device or an adjunct to existing transdermal patches. For example, the FDA has stated that "regulation of combination products must take into account the safety and effectiveness questions associated with each constituent and the product as a whole" [158]. As a result, key regulatory questions likely to be considered include sterility of the MAP dosage forms, dosing accuracy, assurance of delivery, potential for reuse and packaging. While this is not an exhaustive list, it certainly covers the critical attributes to ensure reliable clinical translation of the MAP technology. Recent collaborations between academic institutions and pharmaceutical manufacturers are addressing such regulatory questions. In addition, LTS Lohmann Therapy Systems (LTS), a German company based in Andernach that focusses on the development of transdermal therapeutic systems, has recently gained GMP status for the production of MAPs for clinical trials [159]. Such approval would not only encourage more MAP-based clinical trials but could also help accelerating the transition of MAP-based systems into clinical practice [160].

From a commercial standpoint, the choice of the sterilisation method will be critical as this will ultimately impact the cost of the final product. McCrudden *et al.* were the first to explore methods of sterilisation for MAPs. They discovered that using terminal sterilisation techniques, such as steam autoclaving and dry sterilisation, resulted in substantial irreversible damage to dissolving and hydrogel-forming MAP systems [161]. This is attributed to the hygroscopic nature of the hydrophilic polymers used in fabricating these type of microneedle systems. Furthering this, Swathi *et al.* explored the effect of gamma irradiation on dissolving MAPs. Four different dissolving MAP systems fabricated from sodium carboxymethyl cellulose (CMC), polyvinylpyrrolidone (PVP) K30, PVP K90 and sodium hyaluronate (HU) were explored. Upon exposure to gamma irradiation, it was discovered that CMC and PVP K30 microneedles were affected by this mode of sterilisation, resulting in poor mechanical properties and disruption of needles architecture. However, the appearance, properties and release profile of PVP K90 and HU were unaffected by the dose of gamma irradiation used [162]. With respect to MAPs production, gamma sterilisation will not be compatible with all polymers, as shown by Swathi and co-workers, but may also result in unwanted irreversible changes to drugs, particularly biologics [163–166]. In order to overcome this issue, self-sterilising MAPs could be a viable alternative. For instance, Garcia *et al.* have developed self-sterilising dissolving nanosilver-loaded MAPs fabricated from CMC. Nanosilver is a potent antimicrobial with activity against both Gram-negative and Gram-positive bacteria [149]. This concept has been shown to be capable of supressing microbial pathogen growth at the site of MAPs application [150]. That being said, further work to maximise API loading is necessary with this design to ensure that therapeutically relevant doses could be administered. Therefore, at present, it is postulated that dissolving and coated microneedles would probably be made under aseptic conditions, or sterilised with more milder methods, such as UV or ion beam, rather than gamma sterilisation [165]. In contrast, hydrogel-forming MAP could still undergo gamma sterilisation as the drug loaded reservoir may be added separately and aseptically down the production line [165].

The dosage accuracy and assurance of delivery are closely linked. To achieve complete MAPs skin insertion, the user must be confident that the correct force has been applied. In doing so, the dose administered across the skin can be not only controlled but also reproducible. Through feedback questionnaires, users and healthcare professionals had expressed a preference towards an indicator device to confirm correct MAPs in-skin insertion [167]. Several concepts have been developed to address this request. This has included the use of a pressure indicator sensor film [168], snap-based device that closed shut at a certain force [169] and more recently, Hutton *et al.* developed a reservoir-based

feedback mechanism for hydrogel-forming MAPs that ruptured upon application of the required insertion force [170]. Although all these concepts have demonstrated considerable success, a true cost-effective product has yet to be developed. Another key method to achieve precise dosing is to optimise the MAP design. As a "one-size-fits-all" approach cannot be used for the 5 different MAP types, considering parameters such as needle height, geometry, sharpness and density is vitally important. Such considerations have been discussed in detail in previous reviews [171–174], however, studies are still ongoing to preempt queries from regulatory bodies.

Financial investment from pharmaceutical companies would also play a pivotal factor in translating MAPs from bench to bedside. However, before pharmaceutical industries invest more in the development of MAP technologies, they ought to have reassurance that their commercialisation would provide a lucrative return on revenue. From a healthcare perspective, oral antibiotics and anti-infective agents are inexpensive, as are needle-and-syringe based vaccines [175]. Therefore, there is a possibility that healthcare providers would be somewhat reluctant to pay for MAP-based formulations should the final market price of commercialised MAP products be too expensive compared to conventional oral antibiotics and hypodermic injections, unless there is a very clear benefit. For example, the use of MAPs in delivering conventional injectable therapeutics may provide a solution in circumventing COVID-19 backlog in healthcare provision. This could result in less people ending up in hospitals that would otherwise impose substantial financial burden to the overall healthcare system. Additionally, the involvement of charities also plays a critical role in funding the research involved in translating MAP systems which are targeted for the treatment of infectious disease in LMICs. This is evidenced from the fact that support from charities, such as Bill & Melinda Gates Foundation has helped to accelerate the development of vaccine-loaded MAPs targeted for the eradication of measles and rubella [176]. Moving forward, the involvement of charities such as UNICEF, Malaria No More, TB Alert and Giving What We Can with academic institutions could help accelerate MAP research for the treatment and management of tuberculosis and malaria.

As we have discussed in the review, the delivery of antibiotics using MAPs may offer a solution to prevent the development of antimicrobial resistance. This may be achieved by delivering antibiotics transdermally into the systemic circulation thus obviating the potential damaging effect of oral antibiotic delivery that could result in gut dysbiosis as well as a reduction in taxonomic richness [177]. It has been shown that by delivering antibiotics transdermally or *via* IV injection, there will still be some level of dysbiosis occurring within the gut microbiome to a level that is comparable to oral administration. Nevertheless, the period of dysbiosis induced by delivering antibiotics directly into the systemic circulation is far shorter relative to oral administration of antibiotics [178]. Thus, it is postulated that by reducing the period of dysbiosis induced by changing the route of antibiotic administration, this will shorten the time that the gut microbiome is placed under a selective evolutionary pressure thus, mitigating the likelihood of antibiotic resistance arising. Furthermore, with respect to more localised infections such as SSTI, the delivery of antibiotics using MAPs offers an elegant solution to achieve a more localised delivery of drug substances to the site of infection. In doing so, it is possible to reduce the unnecessary exposure of bacteria located within other parts of the body to the antibiotics thus, reducing the likelihood of antibiotic resistance arising. It is worth noting that circumventing unnecessary antibiotic exposure for non-targeted bacteria is expected to be a very minor and indirect factor, as the development of antimicrobial resistance mainly occurs in the targeted microbes. To avoid this issue, formulators must design MAPs in a manner that ensures sufficient quantities of antibiotics are loaded into the patch. In addition, the patch should also be capable of delivering sufficient doses of the antibiotic above the minimum bactericidal concentration until the causative microorganism is fully eradicated. This formulation could be further refined by utilising ligand decorated nanotechnology to ensure a more selective and effective delivery of the antibiotic to the causative organism.

Once a final product has been developed, it is vitally important that MAPs maintain their functionality and that the API remains stable over the product lifetime. Many studies have investigated API stability in MAPs using accelerated storage conditions. For instance, Zhan *et al.* exposed dissolving MAPs loaded with lidocaine hydrochloride to 40 ± 2°C, 75 ± 5% RH for 84 days. The authors reported no significant changes with the MAP throughout the 84-day study period [179]. Additionally, dissolving MAPs have been shown to maintain the stability of vaccines following exposure to 60°C for 4 months [180]. This is because these patches hold their payload in the dry state, similar to a lyophilised vaccine before dissolving upon contact with the skin's interstitial fluid. For hydrogel-forming MAPs, the high temperatures used during esterification can lead to degradation of therapeutic proteins and peptides. To overcome this issue, hydrogel-forming MAPs are devoid of drug themselves, rather they contain a separate API containing reservoir. Currently, this can be either a drug film, directly compressed tablet, 3D printed construct or a lyophilised wafer [70,105,135]. As demonstrated by Courtenay *et al.*, freeze dried lyophilised wafers can be used to maintain the stability of high valued biomolecules such as monoclonal antibodies [181]. However, the hydroscopic nature of lyophilised wafers or the loaded API itself can result in instability following an ingress of moisture. This was observed by McAllister *et al.*, in which amoxicillin sodium was incorporated into a hydrogel-forming MAP system using a directly compressed tablet. In this instance, the MAP system was incorporated into two different types of packaging and exposed to 40 ± 2 °C, 75 ± 5% RH for 168 days [180]. Notably, colour changes and distorted needle shape was observed for both MAPs unpackaged and those packaged in poly(ester) foil. Additionally, the percentage of recovery of amoxicillin sodium remaining was 0.15 ± 0.06% at day 168. In contrast, Protect™ 470 MIL-PRF-131 K Class 1 foil provided suitable moisture and heat protection, as evidenced by no visible changes in MAP shape or insertion. Furthermore, the percentage recovery of amoxicillin sodium did not substantially reduce after 168 days. Consequently, this study proves that the choice of primary packaging must be another consideration in the end-product. Evidently in recent years, the research conducted within academia has gone someway to addressing the key regulatory questions that are likely to be associated with MAP technology. Therefore, ongoing collaboration between academia and industry will undoubtedly advance the commercialisation of MAP-based technologies.

## 4. Conclusion

The spread of infectious disease along with the emergence of new ones is fuelled by the evolutionary conflicts between rapidly adapting infectious microbes and their slowly evolving human hosts. It is of great importance that broadly based preventative measures, as well as new and improved strategies (e.g., surveillance tools, diagnostics, therapeutics and vaccines), are continually developed, tested, refined and improved, in order to mitigate and prevent antibiotic resistance microbes from spreading. Such efforts necessitate a strengthened relationship between public health and clinical sciences. It can be seen that MAPs may serve as a potential platform to help improve and refine these strategies in both the treatment and diagnosis of infectious diseases. MAPs have been investigated for a variety of biomedical applications ranging from biodiagnostics to drug delivery. Since the first paper on MAP-mediated drug delivery was published in 1998, the field has gained considerable momentum. This has opened new avenues for the delivery of a wide array of antibiotics and prophylactic agents of varying physiochemical properties into and across the skin for the treatment and prevention of different infectious diseases. From a diagnostic point of view, the ability for MAP to be applied in a minimally invasive fashion at an infection site opens the possibility to extract and detect potential biomarkers that may help expedite decision making for patient

management.

Indeed, the application of MAP for diagnosing and treating infectious diseases are still in the early stages of development with most studies being associated with preclinical research only. Nevertheless, there is plenty of room for future clinical research within the field, considering the rapid rise of multidrug-resistant microorganism. Furthermore, advancement in polymer chemistry has recently led to unprecedented control over polymer physicochemical properties with some even displaying bactericidal properties. The utilisation of such polymers in fabricating MAPs may be utilised as antimicrobial adjuvants to help boost the efficacy of current antibiotics. In addition, with the rapid advancement within the field of nanotherapeutics it can be envisioned that future generations of MAPs may be fabricated with the inclusion of antimicrobial nanoparticles accessorized with bacteria targeting ligands which may offer improved antimicrobial efficacy with minimal side effects. However, in order for these systems to transition into clinical practice some translation challenges would need to be considered and addressed. Such translational hurdles include dosage accuracy, sterility, stability and scale-up production. In addition, engagement with potential end-users during the development of future MAP product would also be critical as this will also help researchers identify and resolved any additional hurdles in bringing antimicrobial MAPs into clinical practice.

In addition, another key challenge that ought to be acknowledged towards the commercialisation and widespread use of MAPs is the lack of efficacy and practicality data in humans. At the time of writing this review, there are indeed several clinical trials that are currently underway or have been completed that look into the utility of MAPs as potential drug delivery and biodiagnostic platforms [182–184]. Nevertheless, these are early phase clinical trials that place emphasis on side effects and safety with some focus on efficacy within a small group of healthy participants. More late phase clinical trials conducted within target patient groups will provide key information on the efficacy and side effects of using MAP based technology in real world scenarios. It is also worth noting, more GMP approved manufacturing facilities ought to be established in order to mass manufacture MAPs for these late phase clinical trials due to the multicentred nature and large patient numbers recruited in these studies. Clinicians ought to be involved in the planning of these clinical trials as this may provide an avenue to introduce MAP technology to clinicians as well enabling the design of a more robust study design. Besides that, these clinical trials ought to be complemented with the implementation of human factor studies that investigate the development of MAP designs which are ergonomic and end-user friendly to enable the safe and effective use of the technology. The data obtained from these human factor studies and late phase clinical trials would be critical in propelling the transition of MAP for true clinical application.

Despite the impact and potential benefit that MAP may bring in the combat against infectious diseases, considerable effort should still be made in discovering new anti-infective agents. However, the ability and flexibility offered by MAP technology in delivering a wide array of agents of varying physiochemical properties may help mitigate the attrition rate of bringing new drug entities such as potential antibiotic into the market. Given the widespread nature of infectious diseases in our society, there is a growing need to improve the way we treat and manage them. MAPs are slowly making an impact in this area as evidenced by the growing number of research and publications. However, it is apparent that some infections are gaining more attention than others (such as HIV and skin infections) due to the severity and prevalence of these diseases. For MAPs to have a true impact in managing severe infections, clinicians need to be made aware of the potential benefit of MAP technology. In addition, establishing a research partnership between clinicians, academia, and industry is paramount in promoting and translating MAP research into clinical practice.

## Declaration of Competing Interest

The authors declare no conflict of interest.

## Data availability

Data will be made available on request.

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## References

[1] P.N. Fonkwo, The economic and health implications of infectious diseases, EMBO Rep. 9 (2008) 3–7, https://doi.org/10.1038/embor.2008.110 ©2008.
[2] A.A. Cerda, L.Y. García, Willingness to Pay for a COVID - 19 Vaccine, Appl. Health Econ. Health Policy 19 (3) (2021) 343–351, https://doi.org/10.1007/s40258-021-00644-6.
[3] D.M. Morens, G.K. Folkers, A.S. Fauci, The challenge of emerging and re-emerging infectious diseases, Nature. 430 (July) (2004), https://doi.org/10.1038/nature02759.
[4] R. Antia, R.R. Regoes, J.C. Koella, C.T. Bergstrom, The role of evolution in the emergence of infectious diseases, Lett. Nat. 426 (December) (2003) 8–11, https://doi.org/10.1038/nature02177.1.
[5] R.P. Wenzel, The antibiotic pipeline — challenges, costs, and values, N. Engl. J. Med. 351 (6) (2004) 523–526, https://doi.org/10.1056/nejmp048093.
[6] L.B. Rice, Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE, J. Infect. Dis. 197 (8) (2008) 1079–1081, https://doi.org/10.1086/533452.
[7] C. Nathan, F. Goldberg, The profit problem in antibiotic R&D, Nat. Rev. Drug Discov. 4 (2005) 887–891, https://doi.org/10.1038/nrd1878.
[8] C.G. Buffie, I. Jarchum, M. Equinda, L. Lipuma, A. Gobourne, A. Viale, C. Ubeda, Profound alterations of intestinal microbiota following a single dose of clindamycin results in sustained susceptibility to *Clostridium difficile* -induced colitis, Infect. Immun. 80 (1) (2012), https://doi.org/10.1128/IAI.05496-11.
[9] C. Ubeda, Y. Taur, R.R. Jenq, M.J. Equinda, T. Son, M. Samstein, A. Viale, N. D. Socci, Brink M.R.M. Van Den, microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans Vancomycin-resistant Enterococcus domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans, J. Clin. Invest. 120 (12) (2010) 4332–4341, https://doi.org/10.1172/JCI43918.4332.
[10] J. Rolain, Food and human gut as reservoirs of transferable antibiotic resistance encoding genes PATHOGENS ANTIBIOTIC RESISTANCE IN FOOD ANIMALS THE USE OF ANTIBIOTICS IN FOOD ANIMALS AND AQUACULTURE AND THE SUBSEQUENT EMERGENCE, Front. Microbiol. 4 (June) (2013) 1–10, https://doi.org/10.3389/fmicb.2013.00173.
[11] A. Zumla, J. Chakaya, R. Centis, L.D. Ambrosio, P. Mwaba, M. Bates, N. Kapata, T. Nyirenda, D. Chanda, S. Mfi, M. Hoelscher, M. Maeurer, G.B. Migliori, Tuberculosis treatment and management — an update on treatment regimens, trials, new drugs, and adjunct therapies, Lancet Respiratory 3 (March) (2015), https://doi.org/10.1016/S2213-2600(15)00063-6.
[12] P.N. Davies, H.E.C. Worthington, F. Podczeck, J.M. Newton, The determination of the mechanical strength of tablets of different shapes, Eur. J. Pharm. Biopharm. 67 (1) (2007) 268–276, https://doi.org/10.1016/j.ejpb.2007.01.014.
[13] Q.K. Anjani, A.D. Permana, Á. Cárcamo-Martínez, J. Domínguez-Robles, I. A. Tekko, E. Larrañeta, L.K. Vora, D. Ramadon, R.F. Donnelly, Versatility of hydrogel-forming microneedles in in vitro transdermal delivery of tuberculosis drugs, Eur. J. Pharm. Biopharm. 158 (December) (2021) 294–312, https://doi.org/10.1016/j.ejpb.2020.12.003.
[14] A.R.J. Hutton, M.T.C. McCrudden, E. Larrañeta, R.F. Donnelly, Influence of molecular weight on transdermal delivery of model macromolecules using hydrogel-forming microneedles: Potential to enhance the administration of novel low molecular weight biotherapeutics, J. Mater. Chem. B 8 (19) (2020) 4202–4209, https://doi.org/10.1039/d0tb00021c.
[15] S. Martin, V.A.P. Gerstel, United States Paten. PatentimagesStorageGoogleapis …, Published online, 1972, pp. 1–4.
[16] Y.C. Kim, J.H. Park, M.R. Prausnitz, Microneedles for drug and vaccine delivery, Adv. Drug Deliv. Rev. 64 (14) (2012) 1547–1568, https://doi.org/10.1016/j.addr.2012.04.005.
[17] S. Kaushik, A.H. Hord, D.D. Denson, D.V. Mcallister, S. Smitra, M.G. Allen, M. R. Prausnitz, Lack of Pain Associated with Microfabricated Microneedles, Published online, 2001, pp. 2000–2002.
[18] Global Transdermal Drug Delivery Market Worth USD 95.57 Billion by 2025 - Analysis, Technologies & Forecasts Report 2016-2025 - Vendors: 3M Company, 4P Therapeutics, Biogel Technology - Research and Markets, Published. Accessed September 20, 2001, https://www.businesswire.com/news/home/20161111005701/en/Global-Transdermal-Drug-Delivery-Market-Worth-USD, 2016.
[19] E. Larrañeta, R.E.M. Lutton, A.D. Woolfson, R.F. Donnelly, Microneedle arrays as transdermal and intradermal drug delivery systems: materials science,

manufacture and commercial development, Mater. Sci. Eng. R. Rep. 104 (2016) 1–32, https://doi.org/10.1016/J.MSER.2016.03.001.
[20] U. Detamornrat, E. Mcalister, A.R.J. Hutton, E. Larrañeta, R.F. Donnelly, U. Detamornrat, E. Mcalister, A.R.J. Hutton, E. Larrañeta, R.F. Donnelly, The role of 3D printing technology in microengineering of microneedles, Small. 18 (18) (2022) 2106392, https://doi.org/10.1002/SMLL.202106392.
[21] T. Waghule, G. Singhvi, S.K. Dubey, M.M. Pandey, G. Gupta, M. Singh, K. Dua, Microneedles: a smart approach and increasing potential for transdermal drug delivery system, Biomed. Pharmacother. 109 (2019) 1249–1258, https://doi.org/10.1016/J.BIOPHA.2018.10.078.
[22] E. Larrañeta, M.T.C. McCrudden, A.J. Courtenay, R.F. Donnelly, Microneedles: a new frontier in nanomedicine delivery, Pharm. Res. 33 (5) (2016) 1055–1073, https://doi.org/10.1007/S11095-016-1885-5.
[23] R. Nagarkar, M. Singh, H.X. Nguyen, S. Jonnalagadda, A review of recent advances in microneedle technology for transdermal drug delivery, J. Drug Deliv. Sci. Technol. 59 (2020), 101923, https://doi.org/10.1016/J.JDDST.2020.101923.
[24] Á. Cárcamo-Martínez, B. Mallon, J. Domínguez-Robles, L.K. Vora, Q.K. Anjani, R. F. Donnelly, Hollow microneedles: A perspective in biomedical applications, Int. J. Pharm. 599 (2021), 120455, https://doi.org/10.1016/j.ijpharm.2021.120455.
[25] V.S. Moorthy, M.F. Good, A.V.S. Hill, Malaria vaccine developments, Lancet 363 (9403) (2004) 150–156, https://doi.org/10.1016/S0140-6736(03)15267-1.
[26] L.K. Schrager, J. Vekemens, N. Drager, D.M. Lewinsohn, Olesen OF, The status of tuberculosis vaccine development, Lancet Infect. Dis. 20 (3) (2020) e28–e37, https://doi.org/10.1016/S1473-3099(19)30625-5.
[27] J.L. Excler, M. Saville, S. Berkley, J.H. Kim, Vaccine development for emerging infectious diseases, Nat. Med. 27 (4) (2021) 591–600, https://doi.org/10.1038/s41591-021-01301-0.
[28] P.M. Frew, M.B. Paine, N. Rouphael, J. Schamel, Y. Chung, M.J. Mulligan, M. R. Prausnitz, Acceptability of an inactivated influenza vaccine delivered by microneedle patch: Results from a phase I clinical trial of safety, reactogenicity, and immunogenicity, Vaccine. 38 (45) (2020) 7175–7181, https://doi.org/10.1016/J.VACCINE.2020.07.064.
[29] A.C. Müller, F.P. Breitwieser, H. Fischer, C. Schuster, O. Brandt, J. Colinge, G. Superti-Furga, G. Stingl, A. Elbe-Bürger, K.L. Bennett, A comparative proteomic study of human skin suction blister fluid from healthy individuals using immunodepletion and iTRAQ labeling, J. Proteome Res. 11 (7) (2012) 3715–3727, https://doi.org/10.1021/PR3002035.
[30] R.V. Dixon, E. Skaria, W.M. Lau, P. Manning, M.A. Birch-Machin, S.M. Moghimi, K.W. Ng, Microneedle-based devices for point-of-care infectious disease diagnostics, Acta Pharm. Sin. B 11 (8) (2021) 2344–2361, https://doi.org/10.1016/J.APSB.2021.02.010.
[31] A.A. Gebru, T. Birhanu, E. Wendimu, A.F. Ayalew, S. Mulat, H.Z. Abasimel, A. Kazemi, B.A. Tadesse, B.A. Gebru, B.S. Deriba, N.S. Zeleke, A.G. Girma, B. Munkhbat, Q.K. Yusuf, A.O. Luke, D. Hailu, Global burden of COVID-19: Situational analysis and review, Hum. Antibodies 29 (2) (2021) 139–148, https://doi.org/10.3233/HAB-200420.
[32] Burden of Disease - Our World in Data, Accessed January 25, https://ourworldindata.org/burden-of-disease, 2023.
[33] These are the top 10 emerging technologies of 2020 | World Economic Forum, 2023. Accessed January 27, 2023. https://www.weforum.org/agenda/2020/11/2020-top-10-emerging-technologies/.
[34] R. Skov, K. Christiansen, S.J. Dancer, R.S. Daum, M. Dryden, Y.C. Huang, F. D. Lowy, Update on the prevention and control of community-acquired meticillin-resistant Staphylococcus aureus (CA-MRSA), Int. J. Antimicrob. Agents 39 (3) (2012) 193–200, https://doi.org/10.1016/J.IJANTIMICAG.2011.09.029.
[35] A.J. Paredes, I.K. Ramöller, P.E. Mckenna, M.T.A. Abbate, F. Volpe-zanutto, L. K. Vora, M. Kilbourne-brook, C. Jarrahian, K. Moffatt, C. Zhang, I.A. Tekko, R. F. Donnelly, Microarray patches : Breaking down the barriers to contraceptive care and HIV prevention for women across the globe, Adv. Drug Deliv. Rev. 173 (2021) 331–348, https://doi.org/10.1016/j.addr.2021.04.002.
[36] M. Pai, M.A. Behr, D. Dowdy, K. Dheda, M. Divangahi, C.C. Boehme, A. Ginsberg, S. Swaminathan, M. Spigelman, H. Getahun, D. Menzies, M. Raviglione, Tuberculosis, Nat. Rev. Dis. Primers 2 (16076) (2016) 1–23.
[37] WHO, WHO | Global Tuberculosis Report 2019, 2020.
[38] B.J. Marais, R.P. Gie, H.S. Schaaf, A.C. Hesseling, C.C. Obihara, L.J. Nelson, D. A. Enarson, P.R. Donald, N. Beyers, The clinical epidemiology of childhood pulmonary tuberculosis: A critical review of literature from the pre-chemotherapy era, Int. J. Tubercul. Lung Dis. 8 (3) (2004) 278–285.
[39] T.R. Lerner, S. Borel, M.G. Gutierrez, The innate immune response in human tuberculosis, Cell. Microbiol. 17 (9) (2015) 1277–1285, https://doi.org/10.1111/cmi.12480.
[40] S. Luca, T. Mihaescu, History of BCG vaccine, Maedica (Bucur) 8 (1) (2013) 53–58.
[41] J.P. Cegielski, D.N. McMurray, The relationship between malnutrition and tuberculosis: Evidence from studies in humans and experimental animals, Int. J. Tubercul. Lung Dis. 8 (3) (2004) 286–298.
[42] A. Pawlowski, M. Jansson, M. Sköld, M.E. Rottenberg, G. Källenius, Tuberculosis and HIV co-infection, PLoS Pathog. 8 (2) (2012) 1–7, https://doi.org/10.1371/journal.ppat.1002464.
[43] WHO, Global tuberculosis report, World Health Organization, 2019. Published online.
[44] K.E. Dooley, R.E. Chaisson, Tuberculosis and diabetes mellitus: convergence of two epidemics, Lancet Infect. Dis. 9 (12) (2009) 737–746, https://doi.org/10.1016/S1473-3099(09)70282-8.
[45] P. Narasimhan, J. Wood, C.R. Macintyre, D. Mathai, Risk factors for tuberculosis, Pulm Med. 2013 (828939) (2013) 1–11, https://doi.org/10.1155/2013/828939.
[46] T. Sen, S.R. Joshi, Z.F. Udwadia, Tuberculosis and diabetes mellitus: Merging epidemics, J. Assoc. Physicians India 57 (1) (2009) 399–404.
[47] A.K. Niazi, S. Kalra, Diabetes and tuberculosis: A review of the role of optimal glycemic control, J. Diabetes Metab. Disord. 11 (28) (2012) 1–4, https://doi.org/10.1186/2251-6581-11-28.
[48] Y. Liu, L. Bi, Y. Chen, Y. Wang, J. Fleming, Y. Yu, Y. Gu, C. Liu, L. Fan, X. Wang, M. Cheng, Active or Latent Tuberculosis Increases Susceptibility to COVID-19 and Disease Severity, 2020, https://doi.org/10.1101/2020.03.10.20033795.
[49] Y. Marimuthu, B. Nagappa, N. Sharma, S. Basu, K.K. Chopra, COVID-19 and tuberculosis: A mathematical model based forecasting in Delhi, India, Indian J. Tuberc. 67 (2) (2020) 177–181, https://doi.org/10.1016/j.ijtb.2020.05.006.
[50] R. Rappuoli, A. Aderem, A 2020 vision for vaccines against HIV, tuberculosis and malaria, Nature. 473 (7348) (2011) 463–469, https://doi.org/10.1038/nature10124.
[51] I.G. Sia, M.L. Wieland, Current concepts in the management of tuberculosis, in: Mayo Clinic Proceedings vol. 86, 2011, pp. 348–361, https://doi.org/10.4065/mcp.2010.0820.
[52] N.A. Knechel, Tuberculosis: Pathophysiology, clinical features, and diagnosis, Crit. Care Nurse 29 (2) (2009) 34–43, https://doi.org/10.4037/ccn2009968.
[53] E.A. Nardell, Transmission and institutional infection control of tuberculosis, Cold Spring Harb. Perspect. Med. 6 (2) (2016) 1–12, https://doi.org/10.1101/cshperspect.a018192.
[54] G. Delogu, M. Sali, G. Fadda, The biology of Mycobacterium tuberculosis infection, Mediterr J. Hematol. Infect. Dis. 5 (1) (2013) 1–8, https://doi.org/10.4084/mjhid.2013.070.
[55] A. Zumla, J. Chakaya, R. Centis, L. D'Ambrosio, P. Mwaba, M. Bates, N. Kapata, T. Nyirenda, D. Chanda, S. Mfinanga, M. Hoelscher, M. Maeurer, G.B. Migliori, Tuberculosis treatment and management-an update on treatment regimens, trials, new drugs, and adjunct therapies, Lancet Respir. Med. 3 (3) (2015) 220–234, https://doi.org/10.1016/S2213-2600(15)00063-6.
[56] WHO, Latent Tuberculosis Infection: Updated and Consolidated Guidelines for Programmatic Management, 2018, https://doi.org/10.1055/s-2004-829504.
[57] J.G. Douglas, M.J. McLeod, Pharmacokinetic factors in the modern drug treatment of tuberculosis, Clin. Pharmacokinet. 37 (2) (1999) 127–146, https://doi.org/10.2165/00003088-199937020-00003.
[58] S. Ahmad, E. Mokaddas, Current status and future trends in the diagnosis and treatment of drug-susceptible and multidrug-resistant tuberculosis, J. Infect. Public Health 7 (2) (2014) 75–91, https://doi.org/10.1016/j.jiph.2013.09.001.
[59] WHO, The Shorter MDR-TB Regimen, 2016.
[60] C. Araújo-Mariz, E.P. Lopes, B. Acioli-Santos, M. Maruza, U.R. Montarroyos, R.A. A. De Ximenes, H.R. Lacerda, D.D.B. Miranda-Filho, De Militão De Albuquerque, MFP., Hepatotoxicity during treatment for tuberculosis in people living with HIV/AIDS, PLoS One 11 (6) (2016) 1–15, https://doi.org/10.1371/journal.pone.0157725.
[61] A. Tostmann, M.J. Boeree, R.E. Aarnoutse, W.C.M. De Lange, A.J.A.M. Van Der Ven, R. Dekhuijzen, Antituberculosis drug-induced hepatotoxicity: Concise up-to-date review, J. Gastroenterol. Hepatol. (Australia) 23 (1) (2008) 192–202, https://doi.org/10.1111/j.1440-1746.2007.05207.x.
[62] S.A. Zargar, B.R. Thapa, A. Sahni, S. Mehta, Rifampicin - Induced upper gastrointestinal bleeding, Postgrad. Med. J. 66 (1) (1990) 310–311, https://doi.org/10.1136/pgmj.66.774.310.
[63] J.J. Saukkonen, D.L. Cohn, R.M. Jasmer, S. Schenker, J.A. Jereb, C.M. Nolan, C. A. Peloquin, F.M. Gordin, D. Nunes, D.B. Strader, J. Bernardo, R. Venkataramanan, T.R. Sterling, An official ATS statement: Hepatotoxicity of antituberculosis therapy, Am. J. Respir. Crit. Care Med. 174 (1) (2006) 935–952, https://doi.org/10.1164/rccm.200510-1666ST.
[64] L. Zhang, Y. Huang, Y. Zhou, T. Buckley, H.H. Wang, Antibiotic administration routes significantly influence the levels of antibiotic resistance in gut microbiota, Antimicrob. Agents Chemother. 57 (8) (2013) 3659–3666, https://doi.org/10.1128/AAC.00670-13.
[65] T. Caon, C.E.M. Campos, C.M.O. Simões, M.A.S. Silva, Novel perspectives in the tuberculosis treatment: Administration of isoniazid through the skin, Int. J. Pharm. 494 (1) (2015) 463–470, https://doi.org/10.1016/j.ijpharm.2015.08.067.
[66] A. Hussain, M.A. Altamimi, S. Alshehri, S.S. Imam, F. Shakeel, S.K. Singh, Novel approach for transdermal delivery of rifampicin to induce synergistic antimycobacterial effects against cutaneous and systemic tuberculosis using a cationic nanoemulsion gel, Int. J. Nanomedicine 15 (1) (2020) 1073–1094, https://doi.org/10.2147/IJN.S236277.
[67] S. Chen, Y. Han, D. Yu, F. Huo, F. Wang, Y. Li, L. Dong, Z. Liu, H. Huang, Transdermal delivery of isoniazid and rifampin in guinea pigs by electro-phonophoresis, Drug Deliv. 24 (1) (2017) 467–470, https://doi.org/10.1080/10717544.2016.1267275.
[68] S. Chen, M. Qin, Y. Han, L. Zhao, Y. Fu, Y. Shang, Z. Liu, H. Huang, Assessment of the efficacy of drug transdermal delivery by electro-phonophoresis in treating tuberculous lymphadenitis, Drug Deliv. 23 (5) (2016) 1588–1593, https://doi.org/10.3109/10717544.2015.1124474.
[69] J. Yi, A.J. Barrow, N. Yu, B.E. O'Neill, Efficient electroporation of liposomes doped with pore stabilizing nisin, J. Liposome Res. 23 (3) (2013) 197–202, https://doi.org/10.3109/08982104.2013.788024.
[70] Q.K. Anjani, A.D. Permana, Á. Cárcamo-Martínez, J. Domínguez-Robles, I. A. Tekko, E. Larrañeta, L.K. Vora, D. Ramadon, R.F. Donnelly, Versatility of hydrogel-forming microneedles in in vitro transdermal delivery of tuberculosis

drugs, Eur. J. Pharm. Biopharm. 294-312 (2021) 294–312, https://doi.org/10.1016/j.ejpb.2020.12.003.
[71] F. Chen, Q. Yan, Y. Yu, M.X. Wu, BCG vaccine powder-laden and dissolvable microneedle arrays for lesion-free vaccination, J. Control. Release 255 (April) (2017) 36–44, https://doi.org/10.1016/j.jconrel.2017.03.397.
[72] Q. Yan, H. Liu, Z. Cheng, Y. Xue, Z. Cheng, X. Dai, W. Shan, F. Chen, Immunotherapeutic effect of BCG-polysaccharide nucleic acid powder on mycobacterium tuberculosis-infected mice using microneedle patches, Drug Deliv. 24 (1) (2017) 1648–1653, https://doi.org/10.1080/10717544.2017.1391892.
[73] Q. Yan, Z. Cheng, H. Liu, W. Shan, Z. Cheng, X. Dai, Y. Xue, F. Chen, Enhancement of Ag85B DNA vaccine immunogenicity against tuberculosis by dissolving microneedles in mice, Vaccine. 36 (30) (2018) 4471–4476, https://doi.org/10.1016/j.vaccine.2018.06.025.
[74] J. Jin, V. Reese, R. Coler, D. Carter, M. Rolandi, Chitin microneedles for an easy-to-use tuberculosis skin test, Adv. Healthc. Mater. 3 (3) (2013) 349–353.
[75] W. Wang, H.M. Liu, J. Zhou, Y.G. Wang, X. Feng, H. Tang, Q. Yan, R.S. Zhu, Y. W. Wu, X.G. Wang, D. He, F. Chen, Skin test of tuberculin purified protein derivatives with a dissolving microneedle-array patch, Drug Deliv. Transl. Res. 9 (4) (2019) 795–801, https://doi.org/10.1007/s13346-019-00629-y.
[76] World Health Organization, World Malaria Report 2021, 2021.
[77] G. Kokwaro, Ongoing challenges in the management of malaria, Malar. J. 8 (Suppl. 1) (2009), https://doi.org/10.1186/1475-2875-8-S1-S2.
[78] L. Yenkoidiok-Douti, C. Barillas-Mury, C.M. Jewell, Design of dissolvable microneedles for delivery of a PFS47-based malaria transmission-blocking vaccine, ACS Biomater. Sci. Eng. 7 (5) (2021) 1854–1862, https://doi.org/10.1021/acsbiomaterials.0c01363.
[79] D.A. Milner Jr., Malaria pathogenesis, Cold Spring Harb. Perspect. Med. 8 (1) (2018), https://doi.org/10.1101/CSHPERSPECT.A025569.
[80] N. Sarma, E. Patouillard, R.E. Cibulskis, J.L. Arcand, The economic burden of Malaria: revisiting the evidence, Am. J. Trop. Med. Hyg. 101 (6) (2019) 1405–1415, https://doi.org/10.4269/ajtmh.19-0386.
[81] C.J.M. Whitty, C. Chandler, E. Ansah, T. Leslie, S.G. Staedke, Deployment of ACT antimalarials for treatment of malaria: Challenges and opportunities, Malar. J. 7 (Suppl. 1) (2008), https://doi.org/10.1186/1475-2875-7-S1-S7.
[82] J.N. Burrows, S. Duparc, W.E. Gutteridge, R. Hooft Van Huijsduijnen, W. Kaszubska, F. Macintyre, S. Mazzuri, J.J. Möhrle, T.N.C. Wells, New developments in anti-malarial target candidate and product profiles, Malar. J. 16 (1) (2017) 1–29, https://doi.org/10.1186/S12936-016-1675-X.
[83] L.S. Vestergaard, P. Ringwald, Responding to the Challenge of Antimalarial Drug Resistance by Routine Monitoring to Update National Malaria Treatment Policies, Published online, 2007.
[84] CDC: Artesunate Now First-Line Treatment for Severe Malaria in the United States | CDC Online Newsroom | CDC, Accessed January 28, https://www.cdc.gov/media/releases/2019/s0328-artesunate-first-line-treatment.html, 2023.
[85] M. Eisenhut, A.A. Omari, Group CID, Intrarectal quinine versus intravenous or intramuscular quinine for treating Plasmodium falciparum malaria, Cochrane Database Syst. Rev. 2009 (1) (2009), https://doi.org/10.1002/14651858.CD004009.PUB3.
[86] S. Pawar, P. Shende, 22 factorial design-based biocompatible microneedle arrays containing artemether co-loaded with lumefantrine nanoparticles for transepidermal delivery, Biomed. Microdevices 22 (1) (2020), https://doi.org/10.1007/s10544-020-0476-8.
[87] F. Volpe-Zanutto, L.T. Ferreira, A.D. Permana, M. Kirkby, A.J. Paredes, L.K. Vora, A. Bonfanti, I. Charlie-Silva, C. Raposo, M.C. Figueiredo, I.M.O. Sousa, A. Brisibe, F.T.M. Costa, R.F. Donnelly, M.A. Foglio, Artemether and lumefantrine dissolving microneedle patches with improved pharmacokinetic performance and antimalarial efficacy in mice infected with Plasmodium yoelii, J. Control. Release 333 (2021) 298–315, https://doi.org/10.1016/j.jconrel.2021.03.036.
[88] L. Yenkoidiok-Douti, C. Barillas-Mury, C.M. Jewell, Design of dissolvable microneedles for delivery of a PFS47-based malaria transmission-blocking vaccine, ACS Biomater. Sci. Eng. 7 (5) (2021) 1854–1862, https://doi.org/10.1021/ACSBIOMATERIALS.0C01363/ASSET/IMAGES/LARGE/AB0C01363_0005.JPEG.
[89] X. Jiang, P.B. Lillehoj, Microneedle-based skin patch for blood-free rapid diagnostic testing, Microsyst. Nanoeng. 6 (1) (2020) 1–11, https://doi.org/10.1038/s41378-020-00206-1.
[90] J. Edelsberg, C. Taneja, M. Zervos, N. Haque, C. Moore, K. Reyes, J. Spalding, J. Jiang, G. Oster, Trends in US hospital admissions for skin and soft tissue infections, Emerg. Infect. Dis. 15 (9) (2009) 1516–1518, https://doi.org/10.3201/eid1509.081228.
[91] S. Rajan, Skin and soft-tissue infections: Classifying and treating a spectrum, Cleve. Clin. J. Med. 79 (1) (2012) 57–66, https://doi.org/10.3949/ccjm.79a.11044.
[92] A.L. Byrd, Y. Belkaid, J.A. Segre, The human skin microbiome, Nat. Rev. Microbiol. 16 (3) (2018) 143–155, https://doi.org/10.1038/nrmicro.2017.157.
[93] C. Gimblet, J.S. Meisel, M.A. Loesche, S.D. Cole, J. Horwinski, F.O. Novais, A. M. Misic, C.W. Bradley, D.P. Beiting, S.C. Rankin, L.P. Carvalho, E.M. Carvalho, P. Scott, E.A. Grice, Cutaneous Leishmaniasis Induces a Transmissible Dysbiotic Skin Microbiota that Promotes Skin Inflammation, Cell Host Microbe 22 (1) (2017) 13–24.e4, https://doi.org/10.1016/j.chom.2017.06.006.
[94] H.S. Lawrence, A.J. Nopper, Superficial Bacterial Skin Infections and Cellulitis, Fifth ed., Elsevier Inc., 2012 https://doi.org/10.1016/B978-1-4377-2702-9.00070-2.
[95] S.D. Gittard, A. Ovsianikov, H. Akar, B. Chichkov, N.A. Monteiro-Riviere, S. Stafslien, B. Chisholm, C.C. Shin, C.M. Shih, S.J. Lin, Y.Y. Su, R.J. Narayan, Two photon polymerization-micromolding of polyethylene glycol-gentamicin sulfate microneedles, Adv. Eng. Mater. 12 (4) (2010) 77–82, https://doi.org/10.1002/adem.200980012.
[96] S.D. Gittard, P.R. Miller, C. Jin, T.N. Martin, R.D. Boehm, B.J. Chisholm, S. J. Stafslien, J.W. Daniels, N. Cilz, N.A. Monteiro-Riviere, A. Nasir, R.J. Narayan, Deposition of antimicrobial coatings on microstereolithography-fabricated microneedles, J. Miner. Met. Mater. Soc. 63 (6) (2011) 59–68, https://doi.org/10.1007/s11837-011-0093-3.
[97] R.D. Boehm, J. Daniels, S. Stafslien, A. Nasir, J. Lefebvre, R.J. Narayan, Polyglycolic acid microneedles modified with inkjet-deposited antifungal coatings, Biointerphases. 10 (2015), 011004, https://doi.org/10.1116/1.4913378.
[98] R. Sachan, P. Jaipan, J.Y. Zhang, S. Degan, D. Erdmann, L. Vanderwal, S. J. Stafslien, I. Negut, A. Visan, G. Dorcioman, G. Socol, R. Cristescu, D.B. Chrisey, R.J. Narayan, Printing amphotericin B on microneedles using matrix- assisted pulsed laser evaporation, Int. J. Bioprint. 3 (2) (2017) 147–157. https://doi.org/10.18063/IJB.2017.02.004.
[99] R.D. Boehm, P. Jaipan, S.A. Skoog, S. Stafslien, L. VanderWal, R.J. Narayan, Inkjet deposition of itraconazole onto poly(glycolic acid) microneedle arrays, Biointerphases. 11 (1) (2016), 011008, https://doi.org/10.1116/1.4941448.
[100] P. González-vázquez, E. Larrañeta, M.T.C. Mccrudden, C. Jarrahian, A. Rein-weston, M. Quintanar-solares, D. Zehrung, H. Mccarthy, A.J. Courtenay, R. F. Donnelly, Transdermal delivery of gentamicin using dissolving microneedle arrays for potential treatment of neonatal sepsis, J. Control. Release (May) (2017) 0–1, https://doi.org/10.1016/j.jconrel.2017.07.032.
[101] M. Cobussen, Kort J.M.L. De, R.M. Dennert, S.H. Lowe, P.M. Stassen, M. Cobussen, Kort J.M.L. De, R.M. Dennert, S.H. Lowe, No increased risk of acute kidney injury after a single dose of gentamicin in patients with sepsis patients with sepsis, Infect. Dis. Ther. 48 (4) (2015) 274–280, https://doi.org/10.3109/23744235.2015.1109136.
[102] F. Bath-Hextall, A.J. Birnie, J.C. Ravenscroft, H.C. Williams, Interventions to reduce Staphylococcus aureus in the management of atopic eczema: an updated Cochrane review, Br. J. Dermatol. 163 (2010) 12–26, https://doi.org/10.1111/j.1365-2133.2010.09743.x.
[103] Q.K. Anjani, A.H. Sabri, J. Domínguez-Robles, N. Moreno-Castellanos, E. Utomo, L.A.H. Wardoyo, E. Larrañeta, R.F. Donnelly, Metronidazole nanosuspension loaded dissolving microarray patches: An engineered composite pharmaceutical system for the treatment of skin and soft tissue infection, Biomater. Adv. 140 (2022), 213073, https://doi.org/10.1016/J.BIOADV.2022.213073.
[104] R.F. Donnelly, T.R.R. Singh, M.J. Garland, K. Migalska, R. Majithiya, C. M. McCrudden, P.L. Kole, T.M.T. Mahmood, H.O. McCarthy, A.D. Woolfson, Hydrogel-forming microneedle arrays for enhanced transdermal drug delivery, Adv. Funct. Mater. 22 (23) (2012) 4879–4890, https://doi.org/10.1002/adfm.201200864.
[105] A.H. Sabri, Q.K. Anjani, E. Utomo, A. Ripolin, R.F. Donnelly, Development and characterization of a dry reservoir-hydrogel-forming microneedles composite for minimally invasive delivery of cefazolin, Int. J. Pharm. 617 (2022), 121593, https://doi.org/10.1016/J.IJPHARM.2022.121593.
[106] N. Leimer, C. Rachmühl, M. Palheiros Marques, A.S. Bahlmann, A. Furrer, F. Eichenseher, K. Seidl, U. Matt, M.J. Loessner, R.A. Schuepbach, A. S. Zinkernagel, Nonstable staphylococcus aureus small-colony variants are induced by low pH and sensitized to antimicrobial therapy by phagolysosomal alkalinization, J. Infect. Dis. 213 (2) (2016) 305–313, https://doi.org/10.1093/infdis/jiv388.
[107] E. Montanari, P. Mancini, F. Galli, M. Varani, I. Santino, T. Coviello, L. Mosca, P. Matricardi, F. Rancan, C. Di Meo, Biodistribution and intracellular localization of hyaluronan and its nanogels. A strategy to target intracellular S. aureus in persistent skin infections, J. Control. Release 326 (April) (2020) 1–12, https://doi.org/10.1016/j.jconrel.2020.06.007.
[108] A.D. Permana, A.J. Paredes, F. Volpe-Zanutto, Q.K. Anjani, E. Utomo, R. F. Donnelly, Dissolving microneedle-mediated dermal delivery of itraconazole nanocrystals for improved treatment of cutaneous candidiasis, Eur. J. Pharm. Biopharm. 154 (April) (2020) 50–61, https://doi.org/10.1016/j.ejpb.2020.06.025.
[109] William W. Lee, Q. Zhao, Y. Rao, Z. Shen, Disposable self-powered drug delivery device, Published online November 24, 2009.
[110] Kim Kabseog, Jeong-Bong Lee, Tapered hollow metallic microneedle array assembly and method of making and using the same, Published online December 8, 2009.
[111] P.D. Wortman, Bacterial infections of the skin, Curr. Probl. Dermatol. 5 (6) (1993) 197–224, https://doi.org/10.1016/1040-0486(93)90020-V.
[112] A. Ripolin, J. Quinn, E. Larrañeta, E.M. Vicente-Perez, J. Barry, R.F. Donnelly, Successful application of large microneedle patches by human volunteers, Int. J. Pharm. 521 (1–2) (2017) 92, https://doi.org/10.1016/J.IJPHARM.2017.02.011.
[113] P. Xue, X. Zhang, Y.J. Chuah, Y. Wu, Y. Kang, Flexible PEGDA-based microneedle patches with detachable PVP–CD arrowheads for transdermal drug delivery, RSC Adv. 5 (92) (2015) 75204–75209, https://doi.org/10.1039/C5RA09329E.
[114] E. Caffarel-Salvador, M.C. Kearney, R. Mairs, L. Gallo, S.A. Stewart, A.J. Brady, R. F. Donnelly, Methylene blue-loaded dissolving microneedles: Potential use in photodynamic antimicrobial chemotherapy of infected wounds, Pharmaceutics. 7 (4) (2015) 397–412, https://doi.org/10.3390/pharmaceutics7040397.
[115] R.D. Boehm, P.R. Miller, R. Singh, A. Shah, S. Stafslien, J. Daniels, R.J. Narayan, Indirect rapid prototyping of antibacterial acid anhydride copolymer microneedles, Biofabrication. 4 (1) (2012), 011002, https://doi.org/10.1088/1758-5082/4/1/011002.

[116] S.Y. Park, H.U. Lee, Y.C. Lee, G.H. Kim, E.C. Park, S.H. Han, J.G. Lee, S. Choi, N. S. Heo, D.L. Kim, Y.S. Huh, J. Lee, Wound healing potential of antibacterial microneedles loaded with green tea extracts, Mater. Sci. Eng. C 42 (2014) 757–762, https://doi.org/10.1016/j.msec.2014.06.021.
[117] R.D. Boehm, P.R. Miller, W.A. Schell, J.R. Perfect, R.J. Narayan, Inkjet printing of amphotericin B onto biodegradable microneedles using piezoelectric inkjet printing, Jom. 65 (4) (2013) 525–533, https://doi.org/10.1007/s11837-013-0574-7.
[118] R.D. Boehm, P.R. Miller, J. Daniels, S. Stafslien, R.J. Narayan, Inkjet printing for pharmaceutical applications, Mater. Today 17 (5) (2014) 247–252, https://doi.org/10.1016/j.mattod.2014.04.027.
[119] L. Garcia, M. MacGregor, R. Visalakshan, N. Ninan, A. Cavallaro, A. Trinidad, Y. Zhao, J. Hayball, K. Vasilev, Self-sterilizing antibacterial silver-loaded microneedles, Chem. Commun. 55 (2019) 171–174, https://doi.org/10.1039/c8cc06035e.
[120] S.W.T. Chew, Y. Zeng, M. Cui, H. Chang, M. Zheng, S. Wei, W. Zhao, C. Xu, In situ generation of zinc oxide nanobushes on microneedles as antibacterial coating, in: SLAS TECHNOLOGY: Translating Life Sciences Innovation, 2018, pp. 1–7, https://doi.org/10.1177/2472630318812350. Published online.
[121] Y. Zhang, P. Feng, J. Yu, J. Yang, J. Zhao, J. Wang, ROS-responsive microneedle patch for acne vulgaris treatment, Adv. Ther. (Weinh) 1 (3) (2018) 1800035, https://doi.org/10.1002/adtp.201800035.
[122] D. Ramadon, A.D. Permana, A.J. Courtenay, M.T.C. McCrudden, I.A. Tekko, E. McAlister, Q.K. Anjani, E. Utomo, H.O. McCarthy, R.F. Donnelly, Development, evaluation, and pharmacokinetic assessment of polymeric microarray patches for transdermal delivery of vancomycin hydrochloride, Mol. Pharm. 17 (9) (2020) 3353–3368, https://doi.org/10.1021/acs.molpharmaceut.0c00431.
[123] K. Peng, L.K. Vora, I.A. Tekko, A. Dian, J. Domínguez-, D. Ramadon, P. Chambers, H.O. Mccarthy, E. Larra, F. Donnelly, Dissolving microneedle patches loaded with amphotericin B microparticles for localised and sustained intradermal delivery: Potential for enhanced treatment of cutaneous fungal infections, J. Control. Release 339 (October) (2021) 361–380, https://doi.org/10.1016/j.jconrel.2021.10.001.
[124] P. Zan, A. Than, P.K. Duong, J. Song, C. Xu, P. Chen, Antimicrobial microneedle patch for treating deep cutaneous fungal infection, Adv. Ther. (Weinh) 2 (10) (2019) 1900064, https://doi.org/10.1002/adtp.201900064.
[125] A.D. Permana, M. Mir, E. Utomo, R.F. Donnelly, Bacterially sensitive nanoparticle-based dissolving microneedles of doxycycline for enhanced treatment of bacterial biofilm skin infection: A proof of concept study, Int. J. Pharm X 2 (December) (2020), 100047, https://doi.org/10.1016/j.ijpx.2020.100047.
[126] T. Zhang, B. Sun, J. Guo, M. Wang, H. Cui, H. Mao, B. Wang, F. Yan, Active pharmaceutical ingredient poly(ionic liquid)-based microneedles for the treatment of skin acne infection, Acta Biomater. 115 (2020) 136–147, https://doi.org/10.1016/j.actbio.2020.08.023.
[127] B.J. Berube, G.R. Sampedro, M. Otto, B. Wardenburg, The psm _ Locus Regulates Production of Staphylococcus aureus Alpha-Toxin during Infection, Infect. Immun. 82 (8) (2014) 3350–3358, https://doi.org/10.1128/IAI.00089-14.
[128] C.A. Dillen, E. Maverakis, L.S. Miller, C.A. Dillen, B.L. Pinsker, A.I. Marusina, A. A. Merleev, O.N. Farber, H. Liu, N.K. Archer, D.B. Lee, Y. Wang, R.V. Ortines, S. K. Lee, M.C. Marchitto, S.S. Cai, A.G. Ashbaugh, L.S. May, S.M. Holland, A. F. Freeman, L.G. Miller, M.R. Yeaman, S.I. Simon, J.D. Milner, Clonally expanded γδ T cells protect against Staphylococcus aureus skin reinfection Clonally expanded γδ T cells protect against Staphylococcus aureus skin reinfection, J. Clin. Invest. 128 (3) (2018) 1026–1042, https://doi.org/10.1172/JCI96481.
[129] M.R. Williams, S.K. Costa, L.S. Zaramela, S. Khalil, D.A. Todd, H.L. Winter, J. A. Sanford, A.M.O. Neill, M.C. Liggins, T. Nakatsuji, N.B. Cech, A.L. Cheung, K. Zengler, A.R. Horswill, R.L. Gallo, Quorum sensing between bacterial species on the skin protects against epidermal injury in atopic dermatitis, Sci. Transl. Med. 11 (2019) 1–11, https://doi.org/10.1126/scitranslmed.aat8329.
[130] R.V. Ortines, H. Liu, L.I. Cheng, T.S. Cohen, H. Lawlor, A. Gami, Y. Wang, C. A. Dillen, N.K. Archer, R.J. Miller, A.G. Ashbaugh, B.L. Pinsker, M.C. Marchitto, C. Tkaczyk, C.K. Stover, B.R. Sellman, S. Miller, Neutralizing alpha-toxin accelerates healing of Staphylococcus aureus-infected wounds in nondiabetic and diabetic mice roger, Antimicrob. Agents Chemother. 62 (3) (2018), https://doi.org/10.1128/AAC.02288-17 e02288-17.
[131] C. Youn, N.K. Archer, L.S. Miller, Research techniques made simple: mouse bacterial skin infection models for immunity research, J. Investig. Dermatol. 140 (8) (2020) 1488–1497, e1, https://doi.org/10.1016/j.jid.2020.04.012. e1.
[132] A. Chokshi, Z. Sifri, D. Cennimo, H. Horng, Global contributors to antibiotic resistance, J. Global Infect. Dis. 11 (1) (2019) 36, https://doi.org/10.4103/JGID.JGID_110_18.
[133] B.N. Green, C.D. Johnson, J.T. Egan, M. Rosenthal, E.A. Griffith, M.W. Evans, Methicillin-resistant Staphylococcus aureus: an overview for manual therapists, J. Chiropr. Med. 11 (1) (2012) 64–76, https://doi.org/10.1016/J.JCM.2011.12.001.
[134] M. Mir, A.D. Permana, N. Ahmed, G.M. Khan, A. Rehman, R.F. Donnelly, Enhancement in site-specific delivery of carvacrol for potential treatment of infected wounds using infection responsive nanoparticles loaded into dissolving microneedles: A proof of concept study, Eur. J. Pharm. Biopharm. 147 (2020) 57–68, https://doi.org/10.1016/J.EJPB.2019.12.008.
[135] D. Ramadon, A.D. Permana, A.J. Courtenay, M.T.C. McCrudden, I.A. Tekko, E. McAlister, Q.K. Anjani, E. Utomo, H.O. McCarthy, R.F. Donnelly, Development, evaluation and pharmacokinetic assessment of polymeric microarray patches for transdermal delivery of vancomycin hydrochloride, Mol. Pharm. (2020), https://doi.org/10.1021/acs.molpharmaceut.0c00431. Published online.
[136] Y. Su, V.L. Mainardi, H. Wang, A. McCarthy, Y.S. Zhang, S. Chen, J. John, S. L. Wong, R.R. Hollins, G. Wang, J. Xie, Dissolvable microneedles coupled with nanofiber dressings eradicate biofilms via effectively delivering a database-designed antimicrobial peptide, ACS Nano 14 (9) (2020) 11775–11786, https://doi.org/10.1021/ACSNANO.0C04527/SUPPL_FILE/NN0C04527_SI_013.MP4.
[137] E. McAlister, B. Dutton, L.K. Vora, L. Zhao, A. Ripolin, D.S.Z.B.P.H. Zahari, H. L. Quinn, I.A. Tekko, A.J. Courtenay, S.A. Kelly, A.M. Rodgers, L. Steiner, G. Levin, E. Levy-Nissenbaum, N. Shterman, H.O. McCarthy, R.F. Donnelly, Directly compressed tablets: a novel drug-containing reservoir combined with hydrogel-forming microneedle arrays for transdermal drug delivery, Adv. Healthc. Mater. 10 (3) (2021) 2001256, https://doi.org/10.1002/ADHM.202001256.
[138] G.H. Frydman, D. Olaleye, D. Annamalai, K. Layne, I. Yang, H.M.A. Kaafarani, J. G. Fox, Manuka honey microneedles for enhanced wound healing and the prevention and/or treatment of Methicillin-resistant Staphylococcus aureus (MRSA) surgical site infection, Sci. Rep. 10 (1) (2020) 1–11, https://doi.org/10.1038/s41598-020-70186-9.
[139] J. Ziesmer, P. Tajpara, N.J. Hempel, M. Ehrström, K. Melican, L. Eidsmo, G. A. Sotiriou, Vancomycin-loaded microneedle arrays against methicillin-resistant Staphylococcus aureus skin infections, Adv. Mater. Technol. 6 (7) (2021) 2001307, https://doi.org/10.1002/ADMT.202001307.
[140] F. Wang, Y. Chen, Y. Cheng, H.C. Min, Transdermal drug delivery systems for fighting common viral infectious diseases, 2021 (0123456789).
[141] Y.W. Tang, J.E. Schmitz, D.H. Persing, C.W. Stratton, Laboratory diagnosis of COVID-19: current issues and challenges. McAdam AJ, ed, J. Clin. Microbiol. 58 (6) (2020), https://doi.org/10.1128/JCM.00512-20.
[142] N. Panpradist, B.J. Toley, X. Zhang, S. Byrnes, J.R. Buser, J.A. Englund, B.R. Lutz, Swab sample transfer for point-of-care diagnostics: characterization of swab types and manual agitation methods. Schuch R, ed, PLoS One 9 (9) (2014), e105786, https://doi.org/10.1371/journal.pone.0105786.
[143] P. Winichakoon, R. Chaiwarith, C. Liwsrisakun, P. Salee, A. Goonna, A. Limsukon, Q. Kaewpoowat, Negative nasopharyngeal and oropharyngeal swabs do not rule out COVID-19. McAdam AJ, ed, J. Clin. Microbiol. 58 (5) (2020), https://doi.org/10.1128/JCM.00297-20.
[144] X. Xie, Z. Zhong, W. Zhao, C. Zheng, F. Wang, J. Liu, Chest CT for typical coronavirus disease 2019 (COVID-19) pneumonia: relationship to negative RT-PCR testing, Radiology. 296 (2) (2020) E41–E45, https://doi.org/10.1148/radiol.2020200343.
[145] Y. Fang, H. Zhang, J. Xie, M. Lin, L. Ying, P. Pang, W. Ji, Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR, Radiology. 296 (2) (2020) E115–E117, https://doi.org/10.1148/radiol.2020200432.
[146] R. Hase, T. Kurita, E. Muranaka, H. Sasazawa, H. Mito, Y. Yano, A case of imported COVID-19 diagnosed by PCR-positive lower respiratory specimen but with PCR-negative throat swabs, Infect. Dis. Ther. 52 (6) (2020) 423–426, https://doi.org/10.1080/23744235.2020.1744711.
[147] W. Chen, B. Cai, Z. Geng, F. Chen, Z. Wang, L. Wang, X. Chen, Reducing false negatives in COVID-19 testing by using microneedle-based oropharyngeal swabs, Matter. 3 (5) (2020) 1589–1600, https://doi.org/10.1016/j.matt.2020.09.021.
[148] Y. Li, D. Lai, Q. Lei, Z. Xu, F. Wang, H. Hou, L. Chen, J. Wu, Y. Ren, M. Ma, B. Zhang, H. Chen, C. Yu, J. Xue, Y. Zheng, X. Wang, H. Jiang, H. Zhang, H. Qi, S. Guo, Y. Zhang, X. Lin, Z. Yao, P. Pang, D. Shi, W. Wang, X. Yang, J. Zhou, H. Sheng, Z. Sun, H. Shan, X. Fan, S. Tao, Systematic evaluation of IgG responses to SARS-CoV-2 spike protein-derived peptides for monitoring COVID-19 patients, Cell. Mol. Immunol. 18 (3) (2021) 621–631, https://doi.org/10.1038/s41423-020-00612-5.
[149] C. Kuwentrai, J. Yu, L. Rong, B.Z. Zhang, Y.F. Hu, H.R. Gong, Y. Dou, J. Deng, J. D. Huang, C. Xu, Intradermal delivery of receptor-binding domain of SARS-CoV-2 spike protein with dissolvable microneedles to induce humoral and cellular responses in mice, Bioeng. Transl. Med. 6 (1) (2021), https://doi.org/10.1002/BTM2.10202.
[150] Y. Yin, W. Su, J. Zhang, W. Huang, X. Li, H. Ma, M. Tan, H. Song, G. Cao, S. Yu, D. Yu, J.H. Jeong, X. Zhao, H. Li, G. Nie, H. Wang, Separable microneedle patch to protect and deliver DNA nanovaccines against COVID-19, ACS Nano (2021), https://doi.org/10.1021/ACSNANO.1C03252/ASSET/IMAGES/LARGE/NN1C03252_0006.JPEG. Published online.
[151] A. Philippidis, A 'Patch'-Work Solution to Vaccine Delivery 2(1), 2020, pp. 284–289, https://doi.org/10.1089/GENEDGE.2.1.49. https://home.liebertpub.com/genedge.
[152] C.L.D. McMillan, J.J.Y. Choo, A. Idris, A. Supramaniam, N. Modhiran, A. A. Amarilla, A. Isaacs, S.T.M. Cheung, B. Liang, H. Bielefeldt-Ohmann, A. Azuar, D. Acharya, G. Kelly, G.J.P. Fernando, M.J. Landsberg, A.A. Khromykh, D. Watterson, P.R. Young, N.A.J. McMillan, D.A. Muller, Complete protection by a single-dose skin patch–delivered SARS-CoV-2 spike vaccine, Sci. Adv. 7 (44) (2021), https://doi.org/10.1126/sciadv.abj8065.
[153] C.L.D. McMillan, A.A. Amarilla, N. Modhiran, J.J.Y. Choo, A. Azuar, K. E. Honeyman, A.A. Khromykh, P.R. Young, D. Watterson, D.A. Muller, Skin-patch delivered subunit vaccine induces broadly neutralising antibodies against SARS-CoV-2 variants of concern, Vaccine. 40 (34) (2022) 4929–4932, https://doi.org/10.1016/J.VACCINE.2022.07.013.
[154] Trial VTANG of up to 2. 85 M to DMSRVPI a 2022 P 1 HTTANG of up to 2. 85 M to DMSRVPI a 2, 2023. Accessible on, https://www.businesswire.com/news/home/20210422005269/en/Vaxess-Technologies-Awarded-NIH-Grant-of-up-to-2.85-Million-to-Drive-MIMIX™-Sustained-Release-Vaccine-Patch-Into-a-2022-Phase-1-Human-Trial.
[155] J.A. Stinson, A.V. Boopathy, B.M. Cieslewicz, Y. Zhang, N.W. Hartman, D. P. Miller, M. Dirckx, B.L. Hurst, E.B. Tarbet, J.A. Kluge, K.M. Kosuda, Enhancing

influenza vaccine immunogenicity and efficacy through infection mimicry using silk microneedles, Vaccine. 39 (38) (2021) 5410–5421, https://doi.org/10.1016/j.vaccine.2021.07.064.
[156] B. Gohar, M. Larivière, B. Nowrouzi-Kia, Sickness absence in healthcare workers during the COVID-19 pandemic, Occup. Med. (Chic Ill) 70 (5) (2020) 338–342, https://doi.org/10.1093/OCCMED/KQAA093.
[157] A.J. Courtenay, M.T.C. McCrudden, K.J. McAvoy, H.O. McCarthy, R.F. Donnelly, Microneedle-mediated transdermal delivery of bevacizumab, Mol. Pharm. 15 (8) (2018) 3545–3556, https://doi.org/10.1021/ACS.MOLPHARMACEUT.8B00544/ASSET/IMAGES/MEDIUM/MP-2018-00544C_M004.GIF.
[158] FDA, FDA Guidance. Use of International Standards. ISO 10993-1. Biological Evaluation of Medical Devices—Part 1:Evaluation and Testing within a Risk Management Process, 2016.
[159] First-ever Clinical Trial of Microarray Patches for Psoriasis Treatment, Accessed January 25, https://www.ltslohmann.com/en/press-releases/leo-pharma-a-s-and-lts-lohmann-therapie-systeme-ag-initiate-first-ever-clinical-trial-of-microarray-patches-for-psoriasis-treatment/, 2023.
[160] LEO Pharma and LTS Lohmann Therapie Systeme AG Initiate First Ever Clinical Trial | LEO Pharma, Accessed April 5, https://www.leo-pharma.com/media-center/news/leo-pharma-and-lts-lohmann-therapie-systeme-ag-initiate-first-ever-clinical-trial, 2022.
[161] M.T.C. McCrudden, A.Z. Alkilani, A.J. Courtenay, C.M. McCrudden, B. McCloskey, C. Walker, N. Alshraiedeh, R.E.M. Lutton, B.F. Gilmore, A. D. Woolfson, R.F. Donnelly, Considerations in the sterile manufacture of polymeric microneedle arrays, Drug Deliv. Transl. Res. 5 (1) (2014) 3–14.
[162] H.P. Swathi, V. Anusha Matadh, J. Paul Guin, S. Narasimha Murthy, P. Kanni, L. Varshney, S. Suresh, H.N. Shivakumar, Effect of gamma sterilization on the properties of microneedle array transdermal patch system, Drug Dev. Ind. Pharm. 46 (4) (2020) 606–620, https://doi.org/10.1080/03639045.2020.1742144.
[163] A. Singh, R. Singh, γ-ray irradiation-induced chemical and structural changes in CVD monolayer MoS2, ECS J. Solid State Sci. Technol. 9 (9) (2020), 093011, https://doi.org/10.1149/2162-8777/ABB583.
[164] Y. Blanco, G. de Diego-Castilla, D. Viúdez-Moreiras, E. Cavalcante-Silva, J. A. Rodríguez-Manfredi, A.F. Davila, C.P. McKay, V. Parro, Effects of gamma and electron radiation on the structural integrity of organic molecules and macromolecular biomarkers measured by microarray immunoassays and their astrobiological implications, Astrobiology. 18 (12) (2018) 1497–1516, https://doi.org/10.1089/AST.2016.1645/ASSET/IMAGES/LARGE/FIGURE6.JPEG.
[165] M.T.C. McCrudden, A.Z. Alkilani, A.J. Courtenay, C.M. McCrudden, B. McCloskey, C. Walker, N. Alshraiedeh, R.E.M. Lutton, B.F. Gilmore, A. D. Woolfson, R.F. Donnelly, Considerations in the sterile manufacture of polymeric microneedle arrays, Drug Deliv. Transl. Res. 5 (1) (2015) 3–14, https://doi.org/10.1007/S13346-014-0211-1/FIGURES/4.
[166] C.R. Harrell, V. Djonov, C. Fellabaum, V. Volarevic, Risks of using sterilization by gamma radiation: the other side of the coin, Int. J. Med. Sci. 15 (3) (2018) 274, https://doi.org/10.7150/IJMS.22644.
[167] J.C. Birchall, R. Clemo, A. Anstey, D.N. John, Microneedles in clinical practice - an exploratory study into the opinions of healthcare professionals and the public, Pharm. Res. 28 (2011) 95–106, https://doi.org/10.1007/s11095-010-0101-2.
[168] E.M. Vicente-Pérez, H.L. Quinn, E. McAlister, S. O'Neill, L.A. Hanna, J.G. Barry, R.F. Donnelly, The use of a pressure-indicating sensor film to provide feedback upon hydrogel-forming microneedle array self-application in vivo, Pharm. Res. 33 (12) (2016) 3072–3080, https://doi.org/10.1007/s11095-016-2032-z.
[169] J.J. Norman, J.M. Arya, M.A. McClain, P.M. Frew, M.I. Meltzer, M.R. Prausnitz, Microneedle patches: Usability and acceptability for self-vaccination against influenza, Vaccine. 32 (16) (2014) 1856–1862.
[170] A.R.J. Hutton, M. Kirkby, E. Larrañeta, R.F. Donnelly, Designing a unique feedback mechanism for hydrogel-forming microneedle array patches: a concept study, Drug Deliv. Transl. Res. (2021), https://doi.org/10.1007/s13346-021-01033-1. Published online July 31.
[171] M. Avcil, A. Çelik, Microneedles in drug delivery: progress and challenges, Micromachines (Basel) 12 (11) (2021) 1321, https://doi.org/10.3390/mi12111321.
[172] J. Halder, S. Gupta, R. Kumari, Gupta G. Das, V.K. Rai, Microneedle array: applications, recent advances, and clinical pertinence in transdermal drug delivery, J. Pharm. Innov. 16 (3) (2021) 558–565, https://doi.org/10.1007/s12247-020-09460-2.
[173] J.G. Turner, L.R. White, P. Estrela, H.S. Leese, Hydrogel-forming microneedles: current advancements and future trends, Macromol. Biosci. 21 (2) (2021) 2000307, https://doi.org/10.1002/mabi.202000307.
[174] E. Larrañeta, R.E.M. Lutton, A.D. Woolfson, R.F. Donnelly, Microneedle arrays as transdermal and intradermal drug delivery systems: Materials science, manufacture and commercial development, Mater. Sci. Eng. R 104 (2016) 1–32, https://doi.org/10.1016/j.mser.2016.03.001.
[175] K. McCarthy, M. Avent, Oral or intravenous antibiotics? Aust. Prescr. 43 (2) (2020) 45–48, https://doi.org/10.18773/AUSTPRESCR.2020.008.
[176] Micron Biomedical, Inc, Bill & Melinda Gates Foundation, Accessed April 5, https://www.gatesfoundation.org/about/committed-grants/2019/11/inv002311, 2022.
[177] K. Parkin, C.T. Christophersen, V. Verhasselt, M.N. Cooper, D. Martino, Risk factors for gut dysbiosis in early life, Microorganisms. 9 (10) (2021), https://doi.org/10.3390/MICROORGANISMS9102066.
[178] S.A. Kelly, J. Nzakizwanayo, A.M. Rodgers, L. Zhao, R. Weiser, I.A. Tekko, H. O. McCarthy, R.J. Ingram, B. Jones, v., Donnelly RF, Gilmore BF., Antibiotic therapy and the gut microbiome: investigating the effect of delivery route on gut pathogens, ACS Infect. Dis. 7 (5) (2021) 1283–1296, https://doi.org/10.1021/ACSINFECDIS.1C00081/ASSET/IMAGES/LARGE/ID1C00081_0008.JPEG.
[179] H. Zhan, F. Ma, Y. Huang, J. Zhang, X. Jiang, Y. Qian, Application of composite dissolving microneedles with high drug loading ratio for rapid local anesthesia, Eur. J. Pharm. Sci. 121 (2018) 330–337, https://doi.org/10.1016/j.ejps.2018.06.014.
[180] M.J. Mistilis, J.C. Joyce, E.S. Esser, I. Skountzou, R.W. Compans, A.S. Bommarius, M.R. Prausnitz, Long-term stability of influenza vaccine in a dissolving microneedle patch, Drug Deliv. Transl. Res. 7 (2) (2017) 195–205, https://doi.org/10.1007/s13346-016-0282-2.
[181] A.J. Courtenay, M.T.C. McCrudden, K.J. McAvoy, H.O. McCarthy, R.F. Donnelly, Microneedle-mediated transdermal delivery of bevacizumab, Mol. Pharm. 15 (8) (2018) 3545–3556, https://doi.org/10.1021/acs.molpharmaceut.8b00544.
[182] N.G. Rouphael, M. Paine, R. Mosley, S. Henry, McAllister DV, H. Kalluri, W. Pewin, P.M. Frew, T. Yu, N.J. Thornburg, S. Kabbani, L. Lai, E.V. Vassilieva, I. Skountzou, R.W. Compans, M.J. Mulligan, M.R. Prausnitz, A. Beck, S. Edupuganti, S. Heeke, C. Kelley, W. Nesheim, The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered by microneedle patch (TIV-MNP 2015): a randomised, partly blinded, placebo-controlled, phase 1 trial, Lancet 390 (10095) (2017) 649–658, https://doi.org/10.1016/S0140-6736(17)30575-5.
[183] H. Iwata, K. Kakita, K. Imafuku, S. Takashima, N. Haga, Y. Yamaguchi, K. Taguchi, T. Oyamada, Safety and dose-sparing effect of Japanese encephalitis vaccine administered by microneedle patch in uninfected, healthy adults (MNA-J): a randomised, partly blinded, active-controlled, phase 1 trial, Lancet Microbe 3 (2) (2022) e96–e104, https://doi.org/10.1016/S2666-5247(21)00269-X.
[184] T.M. Rawson, S.A.N. Gowers, D.M.E. Freeman, R.C. Wilson, S. Sharma, M. Gilchrist, A. MacGowan, A. Lovering, M. Bayliss, M. Kyriakides, P. Georgiou, A.E.G. Cass, D. O'Hare, A.H. Holmes, Microneedle biosensors for real-time, minimally invasive drug monitoring of phenoxymethylpenicillin: a first-in-human evaluation in healthy volunteers, Lancet Digit. Health 1 (7) (2019) e335–e343, https://doi.org/10.1016/S2589-7500(19)30131-1.