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Microneedle patches for vaccination in developing countries

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Abstract

Millions of people die of infectious diseases each year, mostly in developing countries, which could largely be prevented by the use of vaccines. While immunization rates have risen since the introduction of the Expanded Program on Immunization (EPI), there remain major challenges to more effective vaccination in developing countries. As a possible solution, microneedle patches containing an array of micron-sized needles on an adhesive backing have been developed to be used for vaccine delivery to the skin. These microneedle patches can be easily and painlessly applied by pressing against the skin and, in some designs, do not leave behind sharps waste. The patches are single-dose, do not require reconstitution, are easy to administer, have reduced size to simplify storage, transportation and waste disposal, and offer the possibility of improved vaccine immunogenicity, dose sparing and thermostability. This review summarizes vaccination challenges in developing countries and discusses advantages that microneedle patches offer for vaccination to address these challenges. We conclude that microneedle patches offer a powerful new technology that can enable more effective vaccination in developing countries.

Graphical abstract

Microneedle patches for vaccination in developing countries: *100 microneedle patches placed next to 100 needle and syringes, 10 ten-dose vials, a biohazardous sharps waste container and a refrigerator for cold-chain storage*

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1. Barriers to vaccination in developing countries

According to 2014 WHO estimates, 1.5 million children die each year from vaccine-preventable diseases for which there are vaccines recommended by the WHO and 29% of deaths among children 1–59 months old are vaccine preventable [1]. For example, measles vaccine is 97% effective after two doses [2], yet, as of 2010, more than 100,000 children under the age of five died each year from measles, most of whom were unvaccinated children [3].

Vaccines are currently administered in developing countries primarily in two scenarios: routine vaccination and mass vaccination campaigns. Routine vaccination is used to achieve high immunization coverage on an on-going basis, but can fall short by itself due to infrastructural challenges in developing countries. Instead, or in addition, mass vaccination campaigns are employed to target large populations in specific regions more effectively [4, 5]. Mass vaccination campaigns can be performed at fixed-post clinics, which is typically required for injectable vaccines, or can be carried out door-to-door, usually by minimally trained personnel administering non-injectable vaccines [6].

While immunization rates have risen since the introduction of the Expanded Program on Immunization (EPI), there remain significant barriers to more effective vaccination in developing countries (Table 1). We summarize these barriers in the rest of this section.

1.1 Need for increased vaccine effectiveness

While many vaccines are extremely effective and offer life-long protection, other vaccines provide only moderate protection rates, especially in developing countries where nutrition levels may be low and individuals may have a compromised immune system due to presence of other infections [9, 10]. Most vaccines need booster doses in order to mount an appropriate immune response; this requires vaccinating the same people multiple times, which can be difficult to execute in places with poor healthcare infrastructure and recordkeeping.

For example, the efficacy of oral polio vaccine (OPV) is known to be sub-optimal in densely populated tropical countries [9] and the immunogenicity of rotavirus vaccine has been shown to be much worse in resource-poor countries in Africa and Asia [11–13]. Measles vaccine can be less efficacious in the presence of vitamin A deficiency in developing countries and vitamin A supplementation along with measles vaccination is often recommended [10].

1.2 Need for trained healthcare providers

Most vaccines are administered by hypodermic needle and syringe injection. A trained healthcare provider is needed to safely administer these injections as well as to safely dispose of the resulting sharps waste. The lack of trained healthcare providers in developing countries can be a significant barrier to attaining high vaccination rates, especially in the case of vaccination campaigns [14].

Smallpox eradication was achieved in part due to the ability to achieve high vaccination coverage using minimally trained personnel administering the vaccine using the scarification technique with a bifurcated needle [15]. Similarly, OPV is being administered orally by minimally trained personnel as part of polio eradication efforts [14], and the anticipated switch to inactivated polio vaccine (IPV) that is given by injection is of great concern to public health officials due to its increased cost and complexity [16].

1.3 Need for effective supply chain

Vaccines must be maintained at the correct temperature (i.e., usually refrigerated) during storage and distribution as well as during use after reconstitution. Heat and freezing temperatures are both detrimental to most vaccines. The resulting need for a cold chain during storage and distribution can be difficult to maintain due to limited infrastructure in developing countries, leading to vaccine wastage [17, 18]. Size and volume of vaccine vials and syringes are thus also important considerations to utilize the supply chain most effectively [19, 20].

The cost of the cold chain is estimated to be $200 to $300 million per year [18] and can even experience failures in industrialized countries with established cold chain systems [17], indicating that developing countries with less-established cold chain systems can be especially susceptible to losses in the cold chain.. As an example of the variation in cold-chain space occupied by a given vaccine presentation, estimates suggest that one dose of a given vaccine in a 10-dose vial occupies 3 cm^3 of cold-chain volume, where as one dose of vaccine in a single-dose vial presentation occupies 12.9 cm^3 of cold-chain volume [21].

1.4 Risk of sharps

Hypodermic needles need to be handled carefully to prevent needle-stick injuries to healthcare providers and others. Hypodermic needles also create biohazardous sharps waste after use that needs to be disposed of safely to ensure that the needles are not reused intentionally or accidentally. During vaccination campaigns it may be more difficult to safely collect and dispose of needles in developing countries [22, 23]

Both healthcare workers and patients are at risk due to unsafe injection practices. A study estimated that up to 33,800 HIV infections, 1.7 million hepatitis B infections and 315,000 hepatitis C infections are caused every year due to unsafe injection practices [24].

1.5 Vaccine wastage due to multi-dose vials

Many vaccines are available in multi-dose (e.g., ten-dose) vials for injection. On a per-dose basis, multi-dose vials are less expensive than single dose vials, take up less space during transportation and in the cold-chain and create less waste. However, the actual cost savings can be difficult to evaluate based on the amount of vaccine that gets wasted because opened vials need to be used quickly to prevent microbial growth and, if not used in time, must be discarded. Vaccine wastage can be very high in developing countries for some vaccines [25–27].

In general vaccine wastage rates increase as the number of vaccine doses per vial increases and an estimate suggests wastage rates for 10 dose vials could be as high as 25% for liquid vaccines and 40% for lyophilized vaccines [21]. The WHO Vaccine Presentation and Packaging Advisory Group's guidelines recommend vaccines to be presented in formats to minimize the number of steps and potential for error during administration when possible [20].

1.6 Need for vaccine reconstitution

Some vaccines are lyophilized and need to be reconstituted with a diluent at the time of use for injection, which adds additional challenges in developing countries [28]. Reconstitution adds another step that requires additional reconstitution needles, syringes and vials that also need to be stored and transported in part in the cold chain, further complicating the supply chain. Time and expertise is needed to reconstitute the vaccine since there is room for error if an incorrect diluent is used or mixing is not carried out using sterile devices. Reconstitution errors lead to vaccine wastage, ineffective vaccination or, in some cases, injury to patients.

As an example, measles vaccine contamination by *Staphylococcus Aureus* from non-sterile diluent has been documented in many countries and accidental injection of other drugs stored in the diluent's container have resulted in infant deaths [28]. In a recent case in Syria, the use of an incorrect diluent for the reconstitution of measles vaccine caused the death of 15 children [24].

1.7 Cost of vaccine/vaccination

The cost of vaccination is the cost of vaccine plus the logistical costs associated with making the vaccine available for use. Healthcare provider, waste disposal, vaccine transportation, cold-chain and vaccine wastage all contribute to the cost of vaccination [29, 30]. While vaccine manufacturers often sell vaccine at significantly reduced cost for use in developing countries, the logistical costs to vaccinate can remain a significant barrier.

As evidence of the significance of vaccination costs other than the cost of the vaccine itself, a study of the average cost to administer vaccines in Senegal found that logistics comprise approximately 50% of the total average cost of each dose delivered [29]. As another example, the 2015 UNICEF price for measles/rubella vaccine is US$0.578 per dose [31], but the cost to administer a dose of measles and rubella vaccine is estimated at approximately US$1.50 per dose [32].

2. Microneedle patches address challenges to vaccination in developing countries

2.1 Overview of microneedles for vaccination

Microneedle patches (MNPs) have been proposed to improve vaccination in developing countries and are the subject of increasing research in academia and industry (Figure 1). Microneedles are less than one millimeter long and deliver vaccines to the skin's epidermis and dermis, as compared to conventional injection into deeper tissues in the muscle or

subcutaneous space by hypodermic needle and syringe. In a MNP, an array of microneedles is attached to a backing such that it can be applied to the skin by hand like a bandage [33, 34].

MNPs are typically designed either as solid metal, silicon or polymer microneedles coated with vaccine that releases the vaccine upon dissolution of the coating in the skin or as solid, dissolving microneedles made of water-soluble materials that encapsulate vaccine and releases the vaccine when the microneedles dissolve in the skin. While this review focuses on MNP, microneedles have also been employed for vaccination as solid microneedles used for skin pretreatment followed by application of a topical vaccine formulation for delivery through residual holes in the skin and as hollow microneedles for liquid vaccine formulation delivery into the skin.

In contrast to hypodermic needles that deliver vaccine in a liquid form, MNPs contain the vaccine in a dried solid form which dissolves within the skin upon administration. Each MNP contains a single dose of the vaccine and can be easily applied by pressing down against the skin with the thumb or with the use of an applicator. Upon application of a MNP to the skin, the microneedles penetrate the skin and the patch is left on the skin for a few minutes to allow for dissolution to deliver the payload contained in it. In the case of coated MNP, the coating dissolves but not the microneedles themselves. In the case of dissolving MNPs, the microneedles dissolve within the skin, thus leaving behind only the backing and no biohazardous sharps waste.

MNPs inherently target vaccine delivery to the skin, which is the largest immunological organ in the body and is densely populated by antigen-presenting cells, which play a crucial role in induction of immune responses. As a result, skin vaccination has been shown to be beneficial for many vaccines [35]. However, conventional intradermal injection using a hypodermic needle by the Mantoux technique can be difficult to perform reproducibly [36]. MNPs offer a simple and reliable way to target the skin and have been studied for delivery of many vaccines [33, 34, 37, 38]. Table 2 summarizes the vaccines that have been studied using microneedles; although not otherwise part of this review, hollow microneedles have been included in the table for completeness.

2.2 Potential impact of microneedle patches for vaccination in developing countries

In addition to effectively targeting the skin, MNPs offer many other advantages for vaccination, including addressing logistical challenges to vaccine delivery, which are extremely important for vaccination in developing countries. Table 3 summarizes the main advantages that MNPs offer to vaccination in developing countries.

2.3 Increased vaccine effectiveness

2.3.1 Skin vaccination enables dose sparing—Delivering vaccines in the epidermis or dermis puts the antigen in close contact with the skin’s rich population of antigen-presenting cells and can result in lower doses of antigens being used. For example, dose-sparing using the intradermal route has been demonstrated in clinical studies for IPV, seasonal influenza and rabies vaccines [36, 103]. Since MNPs also target the skin for

delivery, they could offer improved protection in terms of vaccine dose sparing or a wider range of immune response. In support of that hypothesis, vaccination using MNPs has demonstrated dose-sparing in pre-clinical studies with influenza [63, 78], rotavirus [101] and herpes simplex virus [92], among other vaccines.

2.3.2 Skin vaccination offers improved protection—MNP vaccination has been shown to provide superior immunological responses by other measures as well. Vaccination at the same dose has been shown to produce stronger antibody and/or cellular responses when performed using MNPs compared to hypodermic injection [83, 104, 105], including improved immune responses in very young animals [104]. As a measure of protection, animals vaccinated against influenza using MNPs have been shown to clear virus from the lungs after challenge with live influenza virus better than those vaccinated intramuscularly [67, 105, 106]. Immune response and protection after vaccination have also been shown to last longer after MNP vaccination compared to intramuscular injection [107].

While the mechanisms responsible for the increased immunogenicity of vaccination using MNPs is still under study, evidence suggests that it may be due to vaccine delivery targeted to the unique collection of antigen-presenting cells found in the skin (e.g., Langerhans cells) [75, 76, 94, 108], transport of antigen and antigen-presenting cells from the skin to draining lymph nodes [73], adjuvanted immune response due to cell death caused by the trauma of microneedle insertion into skin [64, 109], and other factors.

2.4 Reduced need for trained healthcare providers

The simple and minimally invasive approach of MNP delivery could allow administration by personnel with minimal training and also offer the possibility of self-administration – with or without the presence of a healthcare provider. This could enable vaccines that currently must be injected by trained healthcare personnel at fixed-post clinics to instead be administered by minimally trained personnel in house-to-house campaigns.

In focus group studies of the public as well as healthcare professionals, MNPs were generally viewed favorably as compared to hypodermic needle injections, suggesting good acceptance of MNPs [110, 111]. In human studies with placebo MNPs, naïve subjects with no prior experience with microneedles were able to successfully administer MNPs when provided with only a brief set of instructions [112, 113]. MNPs for drug delivery have been taken home and used repeatedly by patients without supervision with excellent outcomes [114]. Additional analysis showed that the use of self-administered MNPs could improve vaccination coverage [113] and their use was shown to be cost effective in the majority of scenarios considered in an analysis of influenza vaccination in the United States [111].

2.5 Simplified supply chain

2.5.1 Simplified storage, distribution and disposal—MNPs are much smaller in size than a vaccine vial and needle-syringe system, which could allow MNPs to be stored in a smaller volume and enable simpler storage and distribution [115]. For example, microneedle arrays are typically on the order of 1 cm^2 in area and, once assembled onto a patch, could have a representative volume on the order of 1 cm^3 [33, 37]. Although packaging, possibly

in multi-dose presentations, would increase the product size, it is clear that MNPs have the potential to dramatically reduce the size of vaccines during storage, distribution and disposal.

2.5.2 Reduction or elimination of cold chain—MNPs contain vaccines in a dried form, and suitable excipients can be used in the formulation to make vaccines thermostable. If sufficiently stabilized, MNP could be stored at ambient temperature, eliminating the cold chain completely. If only partial thermostability is achieved, MNPs could be refrigerated during storage at major distribution hubs, but then removed from the cold chain during transportation, storage at village clinics or mass vaccination campaigns.

Influenza vaccine MNPs have been studied extensively for stability at elevated temperatures. A recent study identified formulations stable for at least 6 months at 25 °C and for at least a few weeks at 40 °C [116]. Thermostability has also been studied for MNPs with adenovirus-based vaccines [40] and measles vaccine, which was shown to be stable for at least 4 months at 25 °C and lost less than 10-fold potency after 4 months at 40 °C [97].

2.6 Reduced risk of sharps

MNPs contain microneedles that are a few hundred microns tall and are assembled on a patch backing that is applied to the skin either with thumb pressure or the use of a high-velocity applicator. Casual contact with a MNP is unlikely to result in accidental penetration of microneedles into the skin of an unintended subject, because the MNP needs to be placed flat against the surface of the skin and a significant force needs to be applied for a successful insertion [113]. MNPs could in this way reduce the risks associated with accidental needle stick injury to healthcare providers.

After use, MNPs may offer additional safety advantages. Dissolving MNPs contain microneedles made of water-soluble, biocompatible materials that dissolve in the skin after administration. Thus, they do not leave behind biohazardous sharps waste; only an adhesive backing that can be discarded as non-sharps waste (e.g., similar to a used bandage). This eliminates the risk of injury and disease transmission from used needles. Coated MNPs do not completely eliminate sharps waste. However, used MNPs cannot be reloaded with vaccine absent special coating equipment, making reuse unlikely. Accidental exposure to used MNPs is also expected to be safer than for hypodermic needles because, as mentioned above, it is difficult to get microneedles to penetrate the skin without an intentional, forceful application.

2.7 Reduced vaccine wastage

Each MNP contains a single dose of vaccine and is intended as a single-use product. In comparison to multi-dose vials, single-dose MNPs avoid the problem of vaccine wastage because vaccine in a multi-dose vial must be discarded before all of the doses are used. The single-dose format also avoids patients being turned away without vaccination, as sometimes occurs when an insufficient number of patients need a vaccine on a given day and the vaccinator does not want to open a new vial, knowing that much of the vaccine will be wasted [26].

2.8 No need for vaccine reconstitution

Vaccines are often lyophilized to increase vaccine stability, but this requires vaccine reconstitution before use. MNPs contain vaccine that is administered in a dried form without reconstitution that rapidly dissolves in the skin upon administration. In this way, MNPs can have the increased stability of a dry formulation without the time of clinical personnel and risk of errors associated with reconstitution.

2.9 Reduced cost of vaccine/vaccination

2.9.1 Low-cost manufacturing—In developing countries, a critical concern is the cost of vaccination. Part of that cost is the cost the vaccine itself. The cost-of-goods for a vaccine manufactured in a MNP may be similar to that of conventional vaccine vials or pre-filled syringes, depending in part on the type of MNP technology used. The cost of MNP manufacturing can be low in part because the materials are generally low-cost medical-grade polymers, metals and other excipients that are used in very small amounts, e.g., a representative microneedle array (not including the backing, adhesive and packaging) weighs less than 1 g, and the backing, adhesive and packaging are typically made of conventional pharmaceutical materials used in transdermal patches and other products.

Manufacturing of coated MNPs typically involves a metal, polymer or silicon microneedle structure than can be mass-produced at low cost (e.g., < US$ 0.10), upon which a vaccine is coated by dipping or spraying, allowed to dry and packaged. Manufacturing of dissolving MNPs typically involves a polymer microneedle mold that can be mass produced at low cost (e.g., < US$ 0.10), onto which a vaccine is cast, allowed to dry and packaged. Dipping, spraying, coating and drying are all commonly performed in the pharmaceutical industry, which suggests that MNP manufacturing methods can be compatible with conventional pharmaceutical manufacturing environments and equipment. Much of the cost of MNP manufacturing is the need to perform it under aseptic conditions, which is similar to the cost structure of manufacturing vaccines in vials and syringes.

Terminal sterilization after manufacturing of microneedle patches may be possible, but the sterilization method will need to maintain stability of the vaccine as well as be compatible with the materials that microneedle patches are made of. Although terminal sterilization of vaccine patches has not been studied yet, electron beam and gamma irradiation of a microneedle patch containing a peptide therapeutic was found to unacceptably alter the product [117].

While companies have not released detailed information about their manufacturing methods and costs, 3M offers a solid microneedle device (sMTS) that has undergone FDA-approval and is available for purchase as a stand-alone device with no vaccine or other active. Their proprietary GMP manufacturing and aseptic coating technology has a capacity of up to 10,000 patches per day [118].

2.9.2 Reduced cost of vaccination—In addition to the cost of the vaccine, the complete cost of vaccination should be considered, by accounting for the logistical costs of getting a vaccine delivered to a patient. Thus, even if the cost of a MNP vaccine is greater

than a conventional one, those increased costs may be more than offset by reduced logistical costs, including direct costs of vaccine delivery and indirect costs of reduced vaccine safety, efficacy and coverage.

As discussed throughout this section, the costs of vaccination could be reduced through the use of MNPs to increase vaccine effectiveness, reduce the need for trained healthcare providers, simplify the supply chain, reduce the risk of sharps, reduce vaccine wastage and eliminate the need for vaccine reconstitution.

3. Directions for future research and development

MNPs have great potential to improve vaccination in developing countries, but more work needs to be done to realize this potential. Overall, translation of preclinical studies into clinical trials of MNP vaccination is strongly needed, as is commercial manufacturing that can mass produce MNPs at suitable cost. Additional considerations follow.

- Increased vaccine effectiveness has been shown for a number of vaccines in animal models, but has not yet been established in human subjects, and the mechanisms associated with improved immunogenicity need further elucidation.
- Initial studies suggest that MNPs can be reliably used by minimally trained personnel, including patients themselves, but more widespread assessment and possible improved MNP designs are needed to assure reliable vaccine delivery.
- Reduced product size and increased vaccine thermostability are expected to simplify the supply chain, but the true extent of thermostability and the actual impact on healthcare systems have not yet been determined.
- Reduced risk of sharps is expected, especially for dissolving MNPs. While MNPs reduce this risk associated with hypodermic needles, MNPs may introduce new, unanticipated risks that may only become apparent once they are placed in the hands of diverse users in diverse scenarios and cultures.
- Reduced vaccine waste and elimination of vaccine reconstitution appear to be inherent capabilities of MNP vaccines, but, again, unintended consequences of these changes may present new challenges.
- The cost of MNP manufacturing remains a significant uncertainty and an opportunity for advances that bring down costs. Modeling can predict the possible cost savings associated with MNP vaccination balancing cost of goods and costs of vaccine delivery, but commercial and clinical implementation will be needed to determine the true cost, which will vary based on vaccine and use scenario. Identification of terminal sterilization methods that avoid the need for costly aseptic manufacturing could significantly reduce the costs of MNP products.

4. Conclusions

Many lives could be saved by improved vaccination in developing countries. MNPs offer advantages that could improve vaccination through increased vaccine effectiveness, reduced need for trained healthcare providers, simplified supply chain, reduced risk of sharps, reduced vaccine wastage, no need for vaccine reconstitution and reduced cost of vaccine/vaccination. With continued development, especially translation into clinical trials and advanced manufacturing, MNPs have great potential to address the limitations of current vaccination methods and thereby improve vaccination in developing countries.

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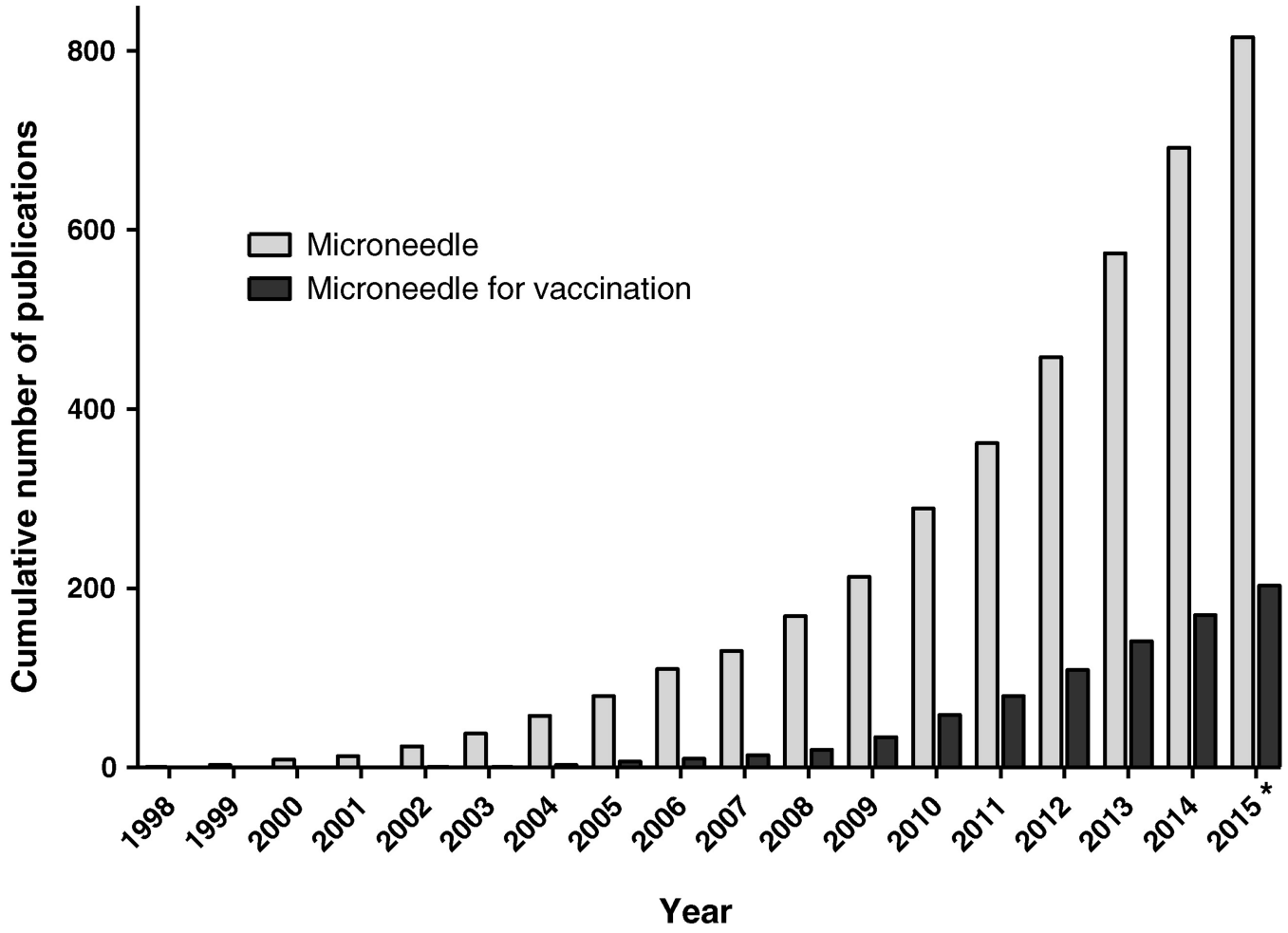

Figure 1.

Cumulative number of publications on microneedles and on microneedles for vaccination. The total number of microneedle publications was determined by searching the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/) on 2nd August 2015 using the search terms "microneedle", "microfabricated needle", or "nanopatch". The subset of microneedle publications with focus on vaccination was determined by adding "vaccin*" or "immuniz*" terms to the previous search. Conference proceedings were excluded. *Publications from 2015 only represent those posted on PubMed by 2nd August 2015.

Table 1

Barriers to more effective vaccination in developing countries [7, 8]

Need for increased vaccine effectiveness
Need for trained healthcare providers
Need for effective supply chain
Risk of sharps
Vaccine wastage due to multi-dose vials
Need for vaccine reconstitution
Cost of vaccine/vaccination

Table 2

Vaccines studied with microneedles

Microneedle type		
Coated	**Dissolving**	**Hollow**
Adenovirus [39–42]	Adenovirus [39–42]	Anthrax [43–46]
BCG [47, 48]	Amyloid β peptide [49]	Botulism [45, 50]
Chikungunya virus [51]	Diphtheria [52–56]	Influenza [55, 57–83]
Hepatitis B [84–87]	HIV [88]	Japanese encephalitis [89]
Hepatitis C [90]	Influenza [55, 57–83]	Poliovirus [91]
Herpes simplex virus [92, 93]	Malaria [41, 52, 94]	Rabies virus [95]
HPV [96]	Measles [97]	Staphylococcus aureus [43, 45]
Influenza [55, 57–83]	Poliovirus [98]	Yersinia pestis [45, 99]
Measles [100]	Tetanus [52]	
Modified Vaccinia Ankara [39, 94]		
Rotavirus [101]		
Small Pox [102]		
West Nile virus [51]		

Table 3

Advantages of microneedle patches for vaccination in developing countries

Increased vaccine effectiveness
Reduced need for trained healthcare providers
Simplified supply chain
Reduced risk of sharps
Reduced vaccine wastage
No need for vaccine reconstitution
Reduced cost of vaccine/vaccination