

Review

Potential use of microarray patches for vaccine delivery in low- and middle- income countries



Nicolas Peyraud^{a,b}, Darin Zehrung^c, Courtney Jarrahan^c, Collrane Frivold^c, Toritse Orubu^d, Birgitte Giersing^{a,*}

^a Initiative for Vaccine Research, World Health Organization, CH-1211 Geneva 27, Switzerland

^b Médecins sans Frontières, rue de Lausanne 78, 2012 Geneva, Switzerland

^c PATH, Seattle, WA 98121, USA

^d Department of Global Health, University of Washington, Seattle, WA 98195, USA

ARTICLE INFO

Article history:

Received 9 January 2019

Received in revised form 13 March 2019

Accepted 19 March 2019

Available online 28 June 2019

Keywords:

Microarray patches

Microneedle patches

Vaccine

Delivery

Product development

ABSTRACT

Microarray patches (MAPs), also referred to as microneedle patches, are a novel methodology that have the potential to overcome barriers to vaccine delivery in low- and middle-income countries (LMICs), and transform the way that vaccines are delivered within immunization programs. The World Health Organization's Initiative for Vaccine Research and its partners are working to understand how MAPs could ease vaccine delivery and increase equitable access to vaccines in LMICs. Global stakeholders have been engaged to evaluate technical, economic, and programmatic challenges; to validate assumptions where possible; and to propose areas of focus to facilitate future vaccine-MAP product development. This report summarizes those learnings.

© 2019 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Contents

1. The public health need for vaccine delivery by microarray patches (MAPs)	4428
2. MAP product development status and attributes for vaccine delivery	4429
2.1. Vaccine MAPs under development	4429
2.2. The potential benefits of MAP product attributes for vaccination in low-resource settings	4429
3. Potential use cases for vaccine delivery in LMICs	4430
3.1. Inactivated polio vaccine	4430
3.2. Rabies vaccine	4430
3.3. Measles-rubella vaccine	4430
3.4. Hepatitis B birth dose	4430
3.5. Maternal tetanus toxoid-containing vaccine	4430
4. Microarray patch end-user acceptability studies in LMICs	4431
5. Manufacturing considerations	4431
6. Regulatory pathways	4431
7. Value proposition of MAPs for vaccine delivery	4432
8. Summary	4432
Acknowledgements	4433
Conflict of interest	4433
References	4433

* Corresponding author.

E-mail address: giersingb@who.int (B. Giersing).

1. The public health need for vaccine delivery by microarray patches (MAPs)

In line with the 2011–2020 Global Vaccine Action Plan (GVAP) strategic goals and the 2030 Sustainable Development Goals (SDG), the World Health Organization (WHO) aims to increase vaccine coverage, so that the benefits of immunization are provided equitably to all people [1]. WHO also works to accelerate development and approval of new vaccines and delivery technologies, as well as to assist low- and middle- income countries (LMICs) in implementing their immunization programs [2–4]. Microarray patches (MAPs), also referred to as microneedle patches, are a novel methodology that have the potential to transform the way that vaccines are delivered within immunization programs in LMICs, where vaccine delivery faces several challenges [5]. These include the requirement for an uninterrupted cold chain from manufacturer to point of delivery and the need for appropriate reconstitution and safe sharps disposal. Another barrier to higher vaccine coverage in these settings is the common multi-dose vial presentation, which can result in missed opportunities because of reluctance to “waste” vaccine by opening a vial to vaccinate only one or two infants. MAPs have features that can potentially address many of these difficulties.

A MAP consists of a cluster of tens to thousands of projections less than one millimeter in length attached to a backing that can be applied to the skin with finger pressure or an applicator. When applied, the projections pierce the stratum corneum to deliver vaccines to the epidermis or dermis, depending on the length of the microprojections (Fig. 1). There they encounter a high density of antigen-presenting cells (e.g., dermal dendritic cells), where vaccine delivery can evoke a strong immune response. In this review we will focus on two types of MAPs: coated and dissolving [6–8]. Coated MAPs are solid projections coated with vaccine that is then dried. After a patch is applied to the skin, vaccine diffuses into the dermis and epidermis and the projections remain attached to the backing when the MAP is removed, typically several seconds or a few minutes later. For dissolvable MAPs, the projections are formed from a polymer/vaccine-antigen blend and are designed to dissolve into the skin after penetration [7–10].

Other types of technologies also fall under the umbrella term of microneedles, including hollow microneedles that facilitate active

injection of a liquid formulation and patches that use the “poke-and-patch” approach, wherein the skin is pierced with microneedles before application of a transdermal patch or topical gel/cream containing the active ingredient. However, these have substantially different characteristics from coated and dissolvable MAPs and will not be examined here [8–12].

WHO's Initiative for Vaccine Research is working to understand how MAPs can facilitate vaccine delivery and increase equitable access to vaccines in LMICs. To this end, in 2015 WHO held a consultation to evaluate technical, economic, and programmatic challenges; to validate assumptions where possible; and to propose areas of focus to facilitate future vaccine-MAP product development [1]. Among topics discussed at the meeting were preferred product characteristics, as well as the manufacturing, clinical development, regulatory and commercialization considerations since vaccine-MAPs are considered novel vaccine combination products [13,14]. The potential commercial value for vaccine-MAPs in LMIC vs. high-income country (HIC) markets may differ with respect to assessment of need, willingness to pay and acceptability of vaccine-MAPs by end-users, including vaccine recipients, their caregivers, and health care providers. This uncertainty of perceived value of vaccine-MAPs (known as the value proposition), results in complexity for developers as they contemplate investment in the product development of this innovative technology. This is particularly the case for vaccine-MAPs where there is a clear public health need for the technology in LMICs, but for which it is challenging to identify the market for a vaccine that is likely to cost more than the existing product [15]. Therefore, in cases where MAPs might be used to deliver existing vaccines, their product attributes must offer significant advantages over the existing presentations to rationalise the costs that will be required for product development and use in immunization programs.

MAPs have the potential to offer many benefits to immunization programs and patients that are of particular relevance to LMICs. These include being less costly to transport and distribute (thermostable, small footprint), easier and safer to administer (no need for reconstitution), and greater acceptability and potentially less hesitancy by end-users (needle-free) because of the perception of being less painful than administration by needle and syringe [16–25]. Below we discuss the issues outlined above and the benefits and challenges associated with MAP vaccine delivery.

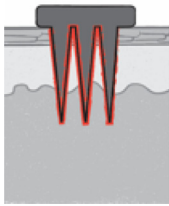
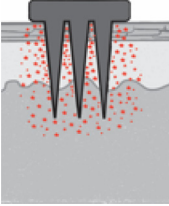
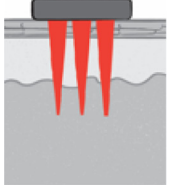
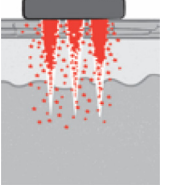
Type of MAP	MAP upon application into the skin	Release of vaccine from MAP into the skin
SOLID COATED Solid coated MAPs are made of non-biodegradable materials and coated with liquid formulation that is then dried. Upon contact with the skin's interstitial fluid, the dry formulation dissolves to release vaccine into the skin. After delivery, the intact solid projections are removed and discarded.		
DISSOLVING Dissolving MAPs are made of biocompatible, biodegradable micro-projections that encapsulate the vaccine and are designed to dissolve upon contact with the skin's interstitial fluid to release vaccine into the skin. Once dissolved, the MAP backing is removed and discarded.		

Fig. 1. Solid coated and dissolving MAPs.

2. MAP product development status and attributes for vaccine delivery

2.1. Vaccine MAPs under development

Vaccine MAPs are in clinical development for influenza and preclinical development for several vaccines. Additional vaccines have also been identified as viable MAP candidates that may be pursued in the future (Table 1). Several MAP developers have focused on seasonal influenza vaccine for the first clinical trials because of the well-accepted correlate of protection—the hemagglutination inhibition titer—that enables early demonstration of clinical proof of concept (POC), as well as the large and potentially lucrative market in HICs. The first clinical trials using three different MAP products to deliver vaccines have now been completed, with each using a form of influenza vaccine [19,25,26]. The trials demonstrated safety and similar immunogenicity for MAP administration compared with intramuscular injection using inactivated trivalent seasonal influenza vaccine (H1N1, H3N2 strain, and B strain) [19,26] or monovalent (H1N1) influenza vaccine [25].

MAPs are in preclinical development for several other existing vaccines, including measles and rubella (MR), inactivated poliovirus vaccine (IPV), tetanus toxoid, Bacille Calmette-Guérin, diphtheria, hepatitis B, human papillomavirus, and anthrax [27–34]. Researchers are also working on MAPs for vaccine candidates in early stage development, such as next generation rotavirus and dengue vaccines, malaria, hepatitis C, herpes simplex virus 2, West Nile virus, Chikungunya, HIV-1, and plague [35–42].

IPV- and MR-MAPs are the most advanced preclinical MAP candidates and non-human primate studies have been conducted with promising results [27,28]. Several MAP developers are working to develop MAPs for delivery of IPV and some have initiated manufacturing process development [28,56]. In addition, three developers, are working to advance an MR-MAP to the stage of

readiness for phase 1 clinical trials [57–59]. For both applications, partnerships and strategies for product development and commercialization between vaccine manufacturers and the MAP developers will be needed to advance them beyond early phase clinical testing.

2.2. The potential benefits of MAP product attributes for vaccination in low-resource settings

Vaccine delivery strategies in low-income contexts must contend with challenges that are less of a barrier to vaccine uptake in high-income countries. Among the novel packaging and delivery technologies in the pipeline—including jet injection, sublingual formulations, and dual-chamber devices—MAPs have emerged as potentially offering clear advantages for vaccine delivery over needle and syringe in routine immunization programs, particularly in LMICs [60]. These features include better vaccine thermostability, ease of delivery, and safer administration and disposal—possibly enabling delivery via minimally trained volunteers [5,61]. Such attributes could significantly ease the logistics and reduce the cost of vaccine delivery, which would increase the equitable coverage of vaccines that are highly effective and could be particularly advantageous in outbreak scenarios but are difficult to deliver [62]. The potentially favorable product attributes of MAPs could ultimately increase equitable coverage and facilitate administration in inaccessible areas, rendering MAPs of considerable interest for delivery of several vaccine antigens. However, in the case of MAP delivery for existing vaccines in LMICs, the vaccine-MAP would be competing with the existing, established presentation, so the vaccine-MAP would need to offer considerable benefits. The minimal and preferred attributes are being developed by WHO and an expert working group in the case of MAP delivery for MR vaccine, in the development of a target product profile (TPP). The MR-MAP TPP will be made publicly available in 2019. Some general benefits that MAPs could offer to improve programmatic vaccine delivery in LMICs are summarized in Table 2.

Table 1
Vaccine microarray patch product development status.

Antigen status	Microarray patch development status		
	Conceptual applications	Preclinical	Clinical
	Approved antigen		
Antigen status	Pertussis Yellow fever Japanese encephalitis	Anthrax [34] BCG [30] Hepatitis B [32,43] HPV [33] Measles-rubella [27] Diphtheria [31,44] IPV [28,45,46] Tetanus toxoid [29,31] Rabies [47]	Seasonal influenza [19,25,26]
	Cholera (conjugate) MERS Lassa fever Enterotoxigenic Escherichia coli	Chikungunya [40] Hepatitis C [38] Herpes simplex virus 2 [39] West Nile virus [40] HIV-1 [41] Ebola [48] Rotavirus vaccine (IRV) [35,49] RSV [50,51] Zika [52] Pandemic influenza [53] Dengue [36] Malaria [31,37,54] Plague [67]	

Table 2

General considerations for programmatic vaccine delivery by MAPs.

MAP Attribute	General considerations
Ease of use	Since vaccine-MAP delivery removes the need for reconstitution, and is needle-free, MAPs may enable immunization via minimally-trained volunteers and community health volunteers. This approach may facilitate delivery to communities with weak health systems, through “house-to-house” campaigns and temporary or fixed post sites. MAPs are thus ideally suited to Supplementary Immunization Activities and outbreak response as well as routine immunization.
Safety in reconstitution/ administration	Risks related to operational errors and reconstitution using wrong diluents will be removed. The risk of contamination would be reduced.
Single-dose presentation	Risks of needle-stick injuries would be removed. The single-dose presentation will reduce hesitancy to open a vial related to missed opportunities for vaccination compared to the multi-dose presentation that is available for most vaccines in the EPI setting.
Thermostability	Stability profiles might offer enhanced thermostability and improvement upon current vaccine storage requirements, allowing the removal of the cold chain equipment at health posts and stocking of vaccines at unequipped facilities.
Pain-free/reduced pain of vaccine delivery	A decrease in pain upon administration would reduce vaccine hesitancy and increase vaccine (and MAP) acceptability over vaccines currently administered by needle and syringe.
Disposal	In response to a stakeholder survey, including members of WHO’s Immunization Practices Advisory Committee, the assumption is that MAPs will be considered biohazard waste that can be disposed of within the clinical waste system [63].

3. Potential use cases for vaccine delivery in LMICs

MAPs could overcome some of the major bottlenecks facing the delivery of several currently available vaccines in LMICs, including IPV, rabies, MR, hepatitis B birth dose (HepB-BD), and maternal tetanus toxoid-containing vaccine, as well as investigational candidates such as inactivated rotavirus and malaria, providing technical hurdles in MAP development specific to each of these antigens can be overcome. Some vaccines, such as those delivered outside routine immunization during infant Expanded Programme on Immunization (EPI) visits—including yellow fever, human papillomavirus, and vaccines against outbreak pathogens such as Ebola—might be suitable for MAP delivery and would benefit from increased ease of delivery and potential task shifting to minimally-trained volunteers.

3.1. Inactivated polio vaccine

As part of the polio eradication strategy, countries are transitioning from use of oral poliovirus vaccine to IPV, which is more challenging to deliver as it is parenteral and therefore requires trained health care workers to give the injection and safely dispose of sharps waste. From a public health perspective, an IPV-MAP could help to maintain high population immunity against polio as oral poliovirus is phased out and would contribute to efficient stockpiling and deployment for outbreaks [61,64].

3.2. Rabies vaccine

For rabies vaccine, adherence with the full post-exposure prophylaxis regimen is challenging due to the number of injections and stringent schedule [65]. Intradermal delivery reduces the length of the full course; however, multiple injections are required during each visit, which can decrease acceptability. Delivery of post-exposure rabies vaccine by a thermostable MAP that is easy to administer, possibly by a community health volunteer, and relatively painless could improve acceptability by eliminating multiple injections, and could allow the vaccine to be stored locally, increasing accessibility and compliance. In addition, a MAP may be applicable to pre-exposure prophylaxis for individuals who are at risk of exposure in highly endemic rabies settings.

3.3. Measles-rubella vaccine

Delivery of MR vaccine by MAP would confront a clear and urgent public health need, with approximately 90,000 deaths from measles and 100,000 cases of congenital rubella syndrome occurring annually despite the availability of a safe, effective, and afford-

able vaccine [66,67]. The reasons for the immunization gap may include reluctance to open multi-dose vials for one or two infants, loss of vaccine potency due to stringent cold chain requirements, and the need for use within six hours following reconstitution. For these reasons, house-to-house campaigns to deliver MR by needle and syringe are not feasible, and a methodology that overcomes these issues, such as MAPs, is needed. The predicted thermostability and ease of use of MR-MAPs would offer significant benefits in outbreak scenarios as well as routine immunization at the community level, especially in rural areas where the infrastructure for vaccination is often poor and vaccines shortages might occur more frequently [27]. In fact, it has been argued that without the availability of an MR MAP for delivery to the most remote populations and during outbreaks, regional elimination goals for these diseases will not be met [68].

3.4. Hepatitis B birth dose

To prevent perinatal or early postnatal transmission, the most important source of chronic hepatitis B infection, WHO’s Strategic Advisory Group of Experts (SAGE) on immunization recommends a birth dose of hepatitis B vaccine (HepB-BD) as soon as possible after birth [69]. Although HepB-BD is considered a cost-effective or cost-saving intervention, coverage worldwide is persistently low, estimated at only 39% in 2015 [69–71]. Transport and cold chain storage limitations, as well as the lack of trained health staff represent the main obstacles to administering HepB-BD in low-resource settings [69]. A thermostable vaccine that could be stored at the community-level and administered by a community health volunteer or birth attendant could improve coverage and equity [32]. These attributes would enable—and hopefully, encourage—the home delivery of HepB-BD through innovative outreach strategies to newborns born outside of health facilities in LMICs.

3.5. Maternal tetanus toxoid-containing vaccine

Neonatal tetanus is an often fatal infection typically occurring when contaminated material is used to cut or cover the umbilical cord in neonates born to women with incomplete vaccination against tetanus [72]. Despite the significant improvement in the use of tetanus toxoid-containing vaccines for maternal immunization resulting from the Maternal and Neonatal Tetanus (MNT) Elimination Initiative and a 96% reduction in tetanus cases since 1988, it was estimated in 2015 that neonatal tetanus deaths worldwide range from 19,937 to 34,019 [73,74]. The uncertainty in these estimates reflects the poor vital registration and tetanus disease surveillance systems in most countries, where many neonatal deaths are not reported. A tetanus-MAP could improve complete

coverage with the challenging five-dose schedule required for full immunisation of women of reproductive age and pregnant women by improving access to the vaccine at the community level, where thermostable vaccine might be kept for several weeks. Vaccination campaigns might also be simplified, as health care workers will not need safe injection training.

4. Microarray patch end-user acceptability studies in LMICs

In a systematic review of factors affecting vaccine uptake in young children in developed countries, there was a strong association between uptake and the perception that vaccines are safe [75]. In regard to discomfort experienced with vaccination, the lower pain level observed with MAP administration may reduce vaccine hesitancy in children, compared with conventional needle and syringe injections [17,76]. The success of the MAP platform in pediatric vaccination will depend on its acceptance among stakeholders such as healthcare workers, caretakers, and children. Endorsement by community leaders may also encourage use of this new technology. Barriers to the acceptance of MAPs in pediatric populations must be identified and reduced by providing information and education to stakeholders [17,76].

As vaccine MAPs are still in early development, most studies of acceptability used either projection-only MAPs (without vaccine) or backing-only MAPs (without vaccine or projections) [10,16–18,20,24]. Two such studies have been conducted recently to assess the anticipated end-user acceptability of vaccine-MAPs in low-resource settings. In one study conducted in Ghana, the usability, acceptability, and programmatic fit of a dissolving MAP was assessed [77]. The MAPs consisted of prototype packaging and patches with no projections. An applicator was not required for delivery, but an audible feedback indicator was incorporated into the patch backings to provide users with assurance of correct application pressure. These mock MAPs were incorporated into standard EPI and antenatal clinic visits and were applied by health care workers to children aged 9 months to 3 years and adult women. All health care workers were able to apply MAPs correctly, and in focus group discussions, community-based surveillance volunteers also felt confident they could successfully apply MAPs in campaign settings. MAP application was acceptable to the recipients, and health care workers also appreciated the potential for thermostability, which they felt could enable vaccines to be provided without refrigeration during the periods between resupply visits. Monitoring the time that the MAP must be worn for complete immunization was identified as a logistical challenge.

A second study performed in Benin, Nepal, and Vietnam assessed the perception of MR-MAP acceptability among EPI managers and national stakeholders (i.e., district and central levels), healthcare workers, community health volunteers, community representatives, and caretakers/parents of children aged 9–23 months (Guillermot et al., accepted for publication in this issue). A simulation was performed with a mock prototype solid-coated MAP (without projections) with an integrated, single-use, spring-powered applicator, used on the upper arm and left in place for 10 s. The device was accepted with enthusiasm by most stakeholders interviewed in the study. While the device was found to be easy to use, respondents felt vaccination would be more acceptable if supervised by a HCW even for a house-to-house strategy. A concern for the need to set up a separate supply chain for maintaining vaccine potency was also raised if the MR-MAP were to be used out of the cold chain due to an improved thermostability profile.

In addition to the studies in LMICs, acceptability information was collected during projection-only MAP studies in human volunteers as well as clinical trials of an inactivated influenza vaccine MAP. These were all performed in developed countries, involving

only healthy adults and using either coated or dissolvable projections. Both types of projection-only MAPs provoked mild erythema, sometimes associated with tenderness and pruritus at the application site [18,20,22]. However, the presence of influenza vaccine on MAPs increased the incidence and duration of reactogenicity, and while found to be acceptable to participants in these clinical trials, reactogenicity and acceptance may vary by antigen and recipient population [19,25,26].

In general, MAP acceptability studies to date have shown the devices to be well accepted by end-users both recipients and caregivers—and MAP administration was the preferred delivery device compared with the needle and syringe injection route [16–18,20,24]. However, the acceptability of a MR-MAP by the EPI, the community, and health workers is likely to be a major factor in the success of its implementation. The factors that support a change in current behavioral practices must be identified and considered in the product development and implementation strategy.

5. Manufacturing considerations

Currently, regardless of their format, vaccine MAPs can be produced on a small scale (up to hundreds of devices per batch) in conditions suitable for use in early-stage clinical trials. The processes and equipment required to manufacture MAPs at large scale will vary, depending on the design of the device; e.g., solid-coated or dissolving projections, with or without an applicator, or aseptic vs low bio-burden Good Manufacturing Practice (GMP) conditions [78]. Once manufacturing facility plans are in place, the timeframe from breaking ground to a fully validated, operational pilot plant is anticipated to be 2–3 years [1]. A development strategy in which a large-scale GMP manufacturing process and facility are established in parallel with phase 2 clinical testing of the first vaccine MAPs would shorten the timeline to start phase 3 trials and, ultimately, the time to licensure of the first product. However, this would require significant capital investment to be made at risk.

Key considerations for MAP manufacturing for vaccines used in low-resource settings include the scalability of production processes and costs per unit when produced at large scale. Depending on the vaccine antigens used, antigen costs could be a large driver of manufacturing costs, so production yield at each step (including the concentrating of antigen, if required) will directly impact the cost of manufacturing a MAP in relation to other presentations. Facilities, equipment, and labor associated with aseptic production are also important cost factors. There has been much debate regarding the need to aseptically manufacture MAPs since the patches are exposed to a non-sterile environment upon administration and applied to non-sterile skin, which poses a low potential-risk of infection [79]. To date, regulators have accepted early stage clinical studies to be performed with low-bioburden clinical material in which general safety and endotoxin levels of the MAPs have been tested and shown to be acceptable [19,25,26]. Whether non-aseptic manufacturing would also be acceptable for a commercial product remains unclear and would be dependent on the generation of supporting data for regulatory review as well as the risk tolerance of the manufacturer. The more conservative approach would be to use an aseptic manufacturing process, even if it is not required by the regulatory authorities.

6. Regulatory pathways

From a regulatory perspective, a vaccine-MAP will most likely be considered a new combination product since it integrates a medical device with a biologic, and both form a single product designed to be used exclusively in the given combination and which are not re-usable or refillable, and therefore similar to pre-

filled syringes used for vaccine administration in high-income countries [13]. The formulations of licensed vaccines would, in most cases, need to be modified to enable production of solid-coated and dissolvable MAPs. In addition, some national regulatory authorities (NRAs) may require an extension of Marketing Authorization or a new application for Marketing Authorization or license if there is a change in the route of administration [80,81]. Therefore, safety and efficacy data comparing the approved vaccine to the new product—including its formulation and/or its new route of administration—will be required by NRAs [81].

In the case of a MAP for an existing vaccine, supporting data from bridging studies will be needed for comparison of the new product with the already licensed product, to decrease the complexity of the regulatory process. Immunological bridging studies to demonstrate non-inferiority between the MAP and an approved product might be sufficient if a correlate of protection exists, otherwise efficacy against relevant clinical outcomes in appropriate populations would likely be required to support licensure [81]. For some vaccines, it may be possible to demonstrate immunogenicity/efficacy in some age and population sub-groups and extrapolate to others based on immune response data.

An important potential concern is that the manufacturing and characterization processes of some licensed vaccines that have been approved for decades may not adhere to the current-day quality and characterization requirements. For example, the production process may include an obsolete filtration/purification process and/or unmet qualification of the cell bank or seed lot according to guidelines considered currently acceptable by the NRA for new licensure. This represents a risk for manufacturers who may have to update their bulk antigen production process for licensing a new MAP-based product [80–82].

For the purposes of pharmacovigilance, it is likely that the FDA's Biological Licensing Application or European Medicines Agency's (EMA's) Marketing Authorization Application for the vaccine-MAP will be submitted by the vaccine manufacturer who has a license to manufacture and commercialize the combination product [83]. The optimal regulatory pathway will depend on whether the vaccine-MAP is intended for use in LMICs only or will also be marketed in HIC. The WHO Vaccines Pre-Qualification (PQ) Programme is a service provided to UN purchasing agencies and member states, ensuring that candidate vaccines are suitable (quality, safety and efficacy) for the target population and the programme. As a prerequisite to the PQ application, the vaccine must be licensed by an NRA, such as FDA or EMA, or by an NRA that has been recognized as performing essential regulatory functions according to WHO indicators [84,85]. Therefore, vaccine-MAPs intended for delivery of Gavi-supported vaccines and most other vaccines included in LMIC immunization programs must be WHO-prequalified.

If the vaccine is to be used exclusively in LMICs, the EMA's Article 58 procedure may be appropriate. This is a mechanism that facilitates prequalification of the vaccine by WHO and the registration in the specific country outside the European Union [86]. The scientific review capabilities of the EMA's Committee for Medicinal Products for Human Use, in collaboration with the local epidemiology and disease expertise of WHO and national regulators in the target countries, provide a unique development and assessment pathway for human vaccines to prevent diseases of major public health interest, intended exclusively for markets outside of the European Union. This pathway targets innovative vaccines and new developments of already authorized vaccines [87,88]. Since vaccine-MAPs are considered new products, MAP developers, in collaboration with the vaccine manufacturers, are strongly recommended to discuss their development plans with NRAs, EMA/FDA, and the WHO PQ group from the very early stages of clinical development [1].

7. Value proposition of MAPs for vaccine delivery

The attributes of MAPs render them attractive for improved vaccine delivery and coverage in both HICs and LMICs, although the priority antigens for MAP delivery may differ. In HICs, a technology that can offer the possibility of minimal pain and self-administration (for adult immunizations, such as influenza vaccine) may increase uptake. However, this may be less important than attributes such as ease-of-use, cold chain footprint, and thermostability which are critical for LMIC contexts. The value proposition for vaccine-MAPs in LMICs will need to clearly articulate the public health benefit that MAPs will offer, as well as a clear market, or willingness to pay, once the product is made available. With an unclear return on investment for the MAP product, there is little incentive to invest in product development and commercialization. More specifically, there is currently a lack of enthusiasm to invest in the scale-up of pilot facility infrastructure that is needed for late-stage clinical trials and commercial manufacturing of vaccine-MAPs. Unless this investment can be made at risk or based on small-scale clinical trial data and an understanding of the demand and business case for a specific vaccine-MAP product, this step could be a barrier to technology advancement. The technology platform-based approach could support the value proposition if, for example, learnings from the development of vaccine-MAPs for one indication could be transferred to another and if one facility could be used to manufacture multiple MAP products. The timeline to commercialization will be significantly extended if the investment in manufacturing infrastructure is delayed until clinical POC data are available or if data from development of individual vaccine-MAPs cannot be leveraged to accelerate the technology platform, as a whole.

8. Summary

For several years, academic and industry groups have invested in research and development of MAPs, focusing on various vaccines that target high- and/or low-income markets. While developers are currently focusing on seasonal influenza vaccine with emphasis on HIC markets, MAPs are perceived to have significant potential to improve vaccination coverage of several other vaccines in LMICs as discussed above, thus decreasing the burden of these often-fatal diseases. Advantages such as needle-free, reconstitution-free, single-dose presentation, and minimal pain combined with enhanced thermostability and potential for dose-sparing render this new delivery technology attractive for many vaccines, potentially transforming their reach in LMICs by enabling novel vaccine delivery scenarios. However, articulation of the use case and potential demand for vaccine-MAP products is needed to define their potential value and encourage investment through to commercialization, introduction, and impact.

One approach to accelerate product development and avoid duplication of efforts, is to facilitate sharing of lessons learned among developers. PATH's Center of Excellence for Microarray Patch Technology promises to advance development of the MAP technology platform for priority global health needs by generating and disseminating information on product development, manufacturing, regulatory pathways, and commercial viability [89]. Furthermore, a new initiative has been formed between Gavi, WHO, the Bill & Melinda Gates Foundation, PATH, and UNICEF to prioritize innovative vaccine delivery technologies, such as MAPs, that will best meet programmatic needs and improve coverage and equity in LMICs. This effort is known as the Vaccination Innovation Prioritization Strategy (VIPS) [90].

Acknowledgements

The authors thank Alan Fauconnier (WHO) and Pieter Neels (independent consultant) for their support with reviewing the regulatory pathways section. We would also like to thank Julian Hickling (independent consultant) for his review of this manuscript, and Marge Murray (PATH) for editing. PATH's contribution to this paper was supported by funding from the Bill & Melinda Gates Foundation and DFID.

Conflict of interest

None declared.

References

- [1] World Health Organization. WHO Microarray Patch (MAP) Product Development Workshop; Geneva, Switzerland, 8 December 2015. Executive Summary. 2016. https://www.who.int/immunization/sage/meetings/2016/april/6_WHO_Microarray_Patch_final.pdf?ua=1.
- [2] Global Vaccine Action Plan 2011–2020. https://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/.
- [3] World Health Organization. WHO's vision and mission in immunization and vaccines 2015–2030. https://www.who.int/immunization/documents/general/WHO_Mission_Vision_Immunization_Vaccines_2015_2030.pdf?ua=1.
- [4] World Health Organization. Transforming our world: the 2030 Agenda for Sustainable Development: Resolution adopted by the General Assembly on 25 September 2015. http://www.un.org/en/development/desa/population/migration/generalassembly/docs/globalcompact/A_RES_70_1_E.pdf.
- [5] Arya J, Prausnitz MR. Microneedle patches for vaccination in developing countries. *J Controlled Release* 2016;240:135–41. <https://doi.org/10.1016/j.jconrel.2015.11.019>.
- [6] Suh H, Shin J, Kim Y-C. Microneedle patches for vaccine delivery. *Clin Exp Vaccine Res* 2014;3:42. <https://doi.org/10.7774/cevr.2014.3.1.42>.
- [7] Prausnitz MR. Engineering microneedle patches for vaccination and drug delivery to skin. *Annu Rev Chem Biomol Eng* 2017;8:177–200. <https://doi.org/10.1146/annurev-chembioeng-060816-101514>.
- [8] Chandrasekhar S, Iyer LK, Panchal JP, Topp EM, Cannon JB, Ranade VV. Microarrays and microneedle arrays for delivery of peptides, proteins, vaccines and other applications. *Expert Opin Drug Deliv* 2013;10:1155–70. <https://doi.org/10.1517/17425247.2013.797405>.
- [9] Prausnitz MR, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery. *Nat Rev Drug Discov* 2004;3:115–24. <https://doi.org/10.1038/nrd1304>.
- [10] Prausnitz MR, Langer R. Transdermal drug delivery. *Nat Biotechnol* 2008;26:1261–8. <https://doi.org/10.1038/nbt.1504>.
- [11] Burton SA, Ng C-Y, Simmers R, Moockly C, Brandwein D, Gilbert T, et al. Rapid intradermal delivery of liquid formulations using a hollow microstructured array. *Pharm Res* 2011;28:31–40. <https://doi.org/10.1007/s11095-010-0177-8>.
- [12] McAllister DV, Wang PM, Davis SP, Park J-H, Canatella PJ, Allen MG, et al. Microfabricated needles for transdermal delivery of macromolecules and nanoparticles: fabrication methods and transport studies. *Proc Natl Acad Sci USA* 2003;100:13755–60. <https://doi.org/10.1073/pnas.2331316100>.
- [13] U.S. Food & Drug Administration. Combination product definition and combination product types. US Food Drug Adm 2018 (accessed November 7, 2018). <https://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm118332.htm>.
- [14] Frequently Asked Questions About Combination Products. Available online: <https://www.fda.gov/combinationproducts/aboutcombinationproducts/ucm101496.htm> (accessed on 8 August 2018). n.d.
- [15] World Health Organization. Full Public Health Value Propositions for Vaccines: Executive summary. Geneva, Switzerland: 2018. https://www.who.int/immunization/sage/meetings/2018/april/presentations_background_docs/en/index1.html.
- [16] Norman JJ, Arya JM, McClain MA, Frew PM, Meltzer MI, Prausnitz MR. Microneedle patches: usability and acceptability for self-vaccination against influenza. *Vaccine* 2014;32:1856–62. <https://doi.org/10.1016/j.vaccine.2014.01.076>.
- [17] Marshall S, Sahm LJ, Moore AC. Microneedle technology for immunisation: Perception, acceptability and suitability for paediatric use. *Vaccine* 2016;34:723–34. <https://doi.org/10.1016/j.vaccine.2015.12.002>.
- [18] Griffin P, Elliott S, Krauer K, Davies C, Rachel Skinner S, Anderson CD, et al. Safety, acceptability and tolerability of uncoated and excipient-coated high density silicon micro-projection array patches in human subjects. *Vaccine* 2017;35:6676–84. <https://doi.org/10.1016/j.vaccine.2017.10.021>.
- [19] Roupel NG, Paine M, Mosley R, Henry S, McAllister DV, Kalluri H, et al. 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 Lond Engl* 2017;390:649–58. [https://doi.org/10.1016/S0140-6736\(17\)30575-5](https://doi.org/10.1016/S0140-6736(17)30575-5).
- [20] Arya J, Henry S, Kalluri H, McAllister DV, Pewin WP, Prausnitz MR. Tolerability, usability and acceptability of dissolving microneedle patch administration in human subjects. *Biomaterials* 2017;128:1–7. <https://doi.org/10.1016/j.biomaterials.2017.02.040>.
- [21] Haq MI, Smith E, John DN, Kalavala M, Edwards C, Anstey A, et al. Clinical administration of microneedles: skin puncture, pain and sensation. *Biomed Microdevices* 2009;11:35–47. <https://doi.org/10.1007/s10544-008-9208-1>.
- [22] Bal SM, Caussin J, Pavel S, Bouwstra JA. In vivo assessment of safety of microneedle arrays in human skin. *Eur J Pharm Sci Off J Eur Fed Pharm Sci* 2008;35:193–202. <https://doi.org/10.1016/j.ejps.2008.06.016>.
- [23] Gill HS, Denson DD, Burris BA, Prausnitz MR. Effect of microneedle design on pain in human volunteers. *Clin J Pain* 2008;24:585–94. <https://doi.org/10.1097/AJP.0b013e31816778f9>.
- [24] Kaushik S, Hord AH, Denson DD, McAllister DV, Smitra S, Allen MG, et al. Lack of pain associated with microfabricated microneedles. *Anesth Analg* 2001;92:502–4.
- [25] Fernando GJP, Hickling J, Jayashi Flores CM, Griffin P, Anderson CD, Skinner SR, et al. Safety, tolerability, acceptability and immunogenicity of an influenza vaccine delivered to human skin by a novel high-density microprojection array patch (Nanopatch). *Vaccine* 2018;36:3779–88. <https://doi.org/10.1016/j.vaccine.2018.05.053>.
- [26] Hirobe S, Azukizawa H, Hanafusa T, Matsuo K, Quan Y-S, Kamiyama F, et al. Clinical study and stability assessment of a novel transcutaneous influenza vaccination using a dissolving microneedle patch. *Biomaterials* 2015;57:50–8. <https://doi.org/10.1016/j.biomaterials.2015.04.007>.
- [27] Joyce JC, Carroll TD, Collins ML, Chen M-H, Fritts L, Dutra JC, et al. A microneedle patch for measles and rubella vaccination is immunogenic and protective in infant rhesus macaques. *J Infect Dis* 2018;218:124–32. <https://doi.org/10.1093/infdis/jiy139>.
- [28] Muller DA, Fernando GJP, Owens NS, Agyei-Yeboah C, Wei JC, Depelenaire ACI, et al. High-density microprojection array delivery to rat skin of low doses of trivalent inactivated poliovirus vaccine elicits potent neutralising antibody responses. *Sci Rep* 2017;7:12644. <https://doi.org/10.1038/s41598-017-13011-0>.
- [29] Esser ES, Romanyuk A, Vassilieva EV, Jacob J, Prausnitz MR, Compans RW, et al. Tetanus vaccination with a dissolving microneedle patch confers protective immune responses in pregnancy. *J Controlled Release* 2016;236:47–56. <https://doi.org/10.1016/j.jconrel.2016.06.026>.
- [30] Hiraishi Y, Nandakumar S, Choi S-O, Lee JW, Kim Y-C, Posey JE, et al. Bacillus Calmette-Guérin vaccination using a microneedle patch. *Vaccine* 2011;29:2626–36. <https://doi.org/10.1016/j.vaccine.2011.01.042>.
- [31] Matsuo K, Hirobe S, Yokota Y, Ayabe Y, Seto M, Quan Y-S, et al. Transcutaneous immunization using a dissolving microneedle array protects against tetanus, diphtheria, malaria, and influenza. *J Control Release Off J Control Release Soc* 2012;160:495–501. <https://doi.org/10.1016/j.jconrel.2012.04.001>.
- [32] Poirier D, Renaud F, Dewar V, Strodiot L, Wauters F, Janimak J, et al. Hepatitis B surface antigen incorporated in dissolvable microneedle array patch is antigenic and thermostable. *Biomaterials* 2017;145:256–65. <https://doi.org/10.1016/j.biomaterials.2017.08.038>.
- [33] Corbett HJ, Fernando GJP, Chen X, Frazer IH, Kendall MAF. Skin vaccination against cervical cancer associated human papillomavirus with a novel micro-projection array in a mouse model. *PLoS One* 2010;5:e13460. <https://doi.org/10.1371/journal.pone.0013460>.
- [34] Mikszta JA, Dekker JP, Harvey NG, Dean CH, Brittingham JM, Huang J, et al. Microneedle-based intradermal delivery of the anthrax recombinant protective antigen vaccine. *Infect Immun* 2006;74:6806–10. <https://doi.org/10.1128/IAI.01210-06>.
- [35] Wang Y, Vlasova A, Velasquez DE, Saif LJ, Kandasamy S, Kochba E, et al. Skin vaccination against rotavirus using microneedles: proof of concept in gnotobiotic piglets. *PLoS One* 2016;11:e0166038. <https://doi.org/10.1371/journal.pone.0166038>.
- [36] Li Jintao, Ye Nan, Guo Hongxia, Yu Tiantian, Ma Yuling, Lin Hui, Luo Xue. Novel dengue fever microneedle vaccine and preparation method thereof. Available online: CN105496986A, 2016. <https://patents.google.com/patent/CN105496986A/en>. [accessed on 8 August 2018].
- [37] Pearson FE, O'Mahony C, Moore AC, Hill AVS. Induction of CD8(+) T cell responses and protective efficacy following microneedle-mediated delivery of a live adenovirus-vectored malaria vaccine. *Vaccine* 2015;33:3248–55. <https://doi.org/10.1016/j.vaccine.2015.03.039>.
- [38] Gill HS, Söderholm J, Prausnitz MR, Sällberg M. Cutaneous vaccination using microneedles coated with hepatitis C DNA vaccine. *Gene Ther* 2010;17:811–4. <https://doi.org/10.1038/gt.2010.22>.
- [39] Kask AS, Chen X, Marshak JO, Dong L, Saracino M, Chen D, et al. DNA vaccine delivery by densely-packed and short microprojection arrays to skin protects against vaginal HSV-2 challenge. *Vaccine* 2010;28:7483–91. <https://doi.org/10.1016/j.vaccine.2010.09.014>.
- [40] Prow TW, Chen X, Prow NA, Fernando GJP, Tan CSE, Raphael AP, et al. Nanopatch-targeted skin vaccination against West Nile Virus and Chikungunya virus in mice. *Small Weinhe Bergstr Ger* 2010;6:1776–84. <https://doi.org/10.1002/smll.201000331>.
- [41] Pattani A, McKay PF, Garland MJ, Curran RM, Migalska K, Cassidy CM, et al. Microneedle mediated intradermal delivery of adjuvanted recombinant HIV-1 CN54gp140 effectively primes mucosal boost inoculations. *J Control Release Off J Control Release Soc* 2012;162:529–37. <https://doi.org/10.1016/j.jconrel.2012.07.039>.

- [42] Huang J, D'Souza AJ, Alarcon JB, Mikszta JA, Ford BM, Ferriter MS, et al. Protective immunity in mice achieved with dry powder formulation and alternative delivery of plague F1-V vaccine. *Clin Vaccine Immunol* CVI 2009;16:719–25. <https://doi.org/10.1128/CLVI.00447-08>.
- [43] Qiu Y, Guo L, Zhang S, Xu B, Gao Y, Hu Y, et al. DNA-based vaccination against hepatitis B virus using dissolving microneedle arrays adjuvanted by cationic liposomes and CpG ODN. *Drug Deliv* 2016;23:2391–8. <https://doi.org/10.3109/10717544.2014.992497>.
- [44] Ding Z, Bal SM, Romeijn S, Kersten GFA, Jiskoot W, Bouwstra JA. Transcutaneous immunization studies in mice using diphtheria toxoid-loaded vesicle formulations and a microneedle array. *Pharm Res* 2011;28:145–58. <https://doi.org/10.1007/s11095-010-0093-y>.
- [45] Leone M, Mönkäre J, Bouwstra JA, Kersten G. Dissolving microneedle patches for dermal vaccination. *Pharm Res* 2017;34:2223–40. <https://doi.org/10.1007/s11095-017-2223-2>.
- [46] Van der Maaden K, Sekerdag E, Schipper P, Kersten G, Jiskoot W, Bouwstra J. Layer-by-layer assembly of inactivated poliovirus and N-trimethyl Chitosan on pH-sensitive microneedles for dermal vaccination. *Langmuir ACS J Surf Colloids* 2015;31:8654–60. <https://doi.org/10.1021/acs.langmuir.5b01262>.
- [47] Arya JM, Dewitt K, Scott-Garrard M, Chiang Y-W, Prausnitz MR. Rabies vaccination in dogs using a dissolving microneedle patch. *J Control Release Off J Control Release Soc* 2016;239:19–26. <https://doi.org/10.1016/j.jconrel.2016.08.012>.
- [48] Liu Y, Ye L, Lin F, Gomaa Y, Flyer D, Carrion R, et al. Intradermal immunization by Ebola virus GP subunit vaccines using microneedle patches protects mice against lethal EBOV challenge. *Sci Rep* 2018;8:11193. <https://doi.org/10.1038/s41598-018-29135-w>.
- [49] Moon S, Wang Y, Edens C, Gentsch JR, Prausnitz MR, Jiang B. Dose sparing and enhanced immunogenicity of inactivated rotavirus vaccine administered by skin vaccination using a microneedle patch. *Vaccine* 2013;31:3396–402. <https://doi.org/10.1016/j.vaccine.2012.11.027>.
- [50] Kines RC, Zarnitsyn V, Johnson TR, Pang Y-YS, Corbett KS, Nicewonger JD, et al. Vaccination with human papillomavirus pseudovirus-encapsidated plasmids targeted to skin using microneedles. *PLoS One* 2015;10:e0120797. <https://doi.org/10.1371/journal.pone.0120797>.
- [51] Park S, Lee Y, Kwon Y-M, Lee Y-T, Kim K-H, Ko E-J, et al. Vaccination by microneedle patch with inactivated respiratory syncytial virus and monophosphoryl lipid A enhances the protective efficacy and diminishes inflammatory disease after challenge. *PLoS One* 2018;13:e0205071. <https://doi.org/10.1371/journal.pone.0205071>.
- [52] Kim E, Erdos G, Huang S, Kenniston T, Falo LD, Gambotto A. Preventative vaccines for Zika virus outbreak: preliminary evaluation. *EBioMedicine* 2016;13:315–20. <https://doi.org/10.1016/j.ebiom.2016.09.028>.
- [53] Wang B-Z, Gill HS, He C, Ou C, Wang L, Wang Y-C, et al. Microneedle delivery of an M2e-TLR5 ligand fusion protein to skin confers broadly cross-protective influenza immunity. *J Control Release Off J Control Release Soc* 2014;178:1–7. <https://doi.org/10.1016/j.jconrel.2014.01.002>.
- [54] Carey JB, Vrdoljak A, O'Mahony C, Hill AVS, Draper SJ, Moore AC. Microneedle-mediated immunization of an adenovirus-based malaria vaccine enhances antigen-specific antibody immunity and reduces anti-vector responses compared to the intradermal route. *Sci Rep* 2014;4:6154. <https://doi.org/10.1038/srep06154>.
- [55] Fernando GJP, Chen X, Prow TW, Crichton ML, Fairmaid EJ, Roberts MS, et al. Potent immunity to low doses of influenza vaccine by probabilistic guided micro-targeted skin delivery in a mouse model. *PLoS One* 2010;5:e10266. <https://doi.org/10.1371/journal.pone.0010266>.
- [56] Edens C, Dybdahl-Sissoko NC, Weldon WC, Oberste MS, Prausnitz MR. Inactivated polio vaccination using a microneedle patch is immunogenic in the rhesus macaque. *Vaccine* 2015;33:4683–90. <https://doi.org/10.1016/j.vaccine.2015.01.089>.
- [57] Grants Database: Vaxxas Pty Ltd. Bill Melinda Gates Found 2016. <https://www.gatesfoundation.org/How-We-Work/Quick-Links/Grants-Database/Grants/2016/11/OPP1157576> [accessed November 7, 2018].
- [58] Grants Database: Vaxess Technologies Inc. Bill Melinda Gates Found 2016. <https://www.gatesfoundation.org/How-We-Work/Quick-Links/Grants-Database/Grants/2016/11/OPP1164296> [accessed November 11, 2018].
- [59] Grants Database: Georgia Institute of Technology. Bill Melinda Gates Found 2017. <https://www.gatesfoundation.org/How-We-Work/Quick-Links/Grants-Database/Grants/2017/06/OPP1164271> [accessed November 11, 2018].
- [60] Zehrung D, Jarrahan C, Giersing B, Kristensen D. Exploring new packaging and delivery options for the immunization supply chain. *Vaccine* 2017;35:2265–71. <https://doi.org/10.1016/j.vaccine.2016.11.095>.
- [61] Giersing BK, Kahn A-L, Jarrahan C, Mvundura M, Rodriguez C, Okayasu H, et al. Challenges of vaccine presentation and delivery: How can we design vaccines to have optimal programmatic impact? *Vaccine* 2017;35:6793–7. <https://doi.org/10.1016/j.vaccine.2017.04.063>.
- [62] Jacoby E, Jarrahan C, Hull HF, Zehrung D. Opportunities and challenges in delivering influenza vaccine by microneedle patch. *Vaccine* 2015;33:4699–704. <https://doi.org/10.1016/j.vaccine.2015.03.062>.
- [63] Immunization Practices Advisory Committee (IPAC) 12th Meeting 10–11 July 2018. https://www.who.int/immunization/programmes_systems/policies_strategies/IPAC_Report_2018-07.pdf?ua=1 [accessed February 11, 2019].
- [64] Bandyopadhyay AS, Garon J, Seib K, Orenstein WA. Polio vaccination: past, present and future. *Future Microbiol* 2015;10:791–808. <https://doi.org/10.2217/fmb.15.19>.
- [65] World Health Organization null. Rabies vaccines: WHO position paper, April 2018 – recommendations. *Vaccine* 2018;36:5500–3. <https://doi.org/10.1016/j.vaccine.2018.06.061>.
- [66] Moss WJ. Measles. *Lancet* 2017;390:2490–502. [https://doi.org/10.1016/S0140-6736\(17\)31463-0](https://doi.org/10.1016/S0140-6736(17)31463-0).
- [67] Lambert N, Strebel P, Orenstein W, Icenogle J, Poland GA. Rubella. *Lancet* 2015;385:2297–307. [https://doi.org/10.1016/S0140-6736\(14\)60539-0](https://doi.org/10.1016/S0140-6736(14)60539-0).
- [68] Durrheim DN, Goodson JL. Time for an immunization paradigm shift. *Trans R Soc Trop Med Hyg* 2017;111:41–2.
- [69] Hepatitis B vaccines: WHO position paper – July 2017. *Releve Epidemiol Hebdomadaire* 2017; 92:369–92. <https://www.who.int/immunization/documents/positionpapers/en/> [accessed on 8 August 2018]. n.d.
- [70] Chaiyakunapruk N et al. Hepatitis B vaccination: An updated systematic review of economic evaluations in low and middle income countries. n.d.
- [71] Margolis HS, Coleman PJ, Brown RE, Mast EE, Sheingold SH, Arevalo JA. Prevention of hepatitis B virus transmission by immunization. *An economic analysis of current recommendations*. *JAMA* 1995;274:1201–8.
- [72] Tetanus vaccines: WHO position paper – February 2017. *Releve Epidemiol Hebdomadaire* 2017; 92:53–76.
- [73] Kyu Hmwe H, Mumford John Everett, Stanaway Jeffrey D, Barber Ryan M, Hancock Jamie R, Vos Theo, Murray Christopher JL, Naghavi Mohsen. Mortality from tetanus between 1990 and 2015: findings from the global burden of disease study 2015. *BMC Public Health* 2017;17(1). <https://doi.org/10.1186/s12889-017-4111-4>.
- [74] Tetanus vaccines WHO position paper. *Weekly Epidemiol Rec* No 6, 2017; 92, 53–76. <https://www.who.int/immunization/documents/positionpapers/en/> [accessed on 8 August 2018]. n.d.
- [75] Smith LE, Amlot R, Weinman J, Yiend J, Rubin GJ. A systematic review of factors affecting vaccine uptake in young children. *Vaccine* 2017;35:6059–69. <https://doi.org/10.1016/j.vaccine.2017.09.046>.
- [76] Marshall S, Fleming A, Moore AC, Sahn LJ. Acceptability of microneedle-patch vaccines: a qualitative analysis of the opinions of parents. *Vaccine* 2017;35:4896–904. <https://doi.org/10.1016/j.vaccine.2017.07.083>.
- [77] PATH. Evaluation of Microarray Patches for Human Factors—Considerations and Program Feasibility. Seattle, WA: 2017. <https://www.path.org/resources/evaluation-of-microarray-patches-for-human-factors-considerations-and-program-feasibility/> [accessed on 25 February 2019].
- [78] Lutton REM, Moore J, Larraneta E, Ligett S, Woolfson AD, Donnelly RF. Microneedle characterisation: the need for universal acceptance criteria and GMP specifications when moving towards commercialisation. *Drug Deliv Transl Res* 2015;5:313–31. <https://doi.org/10.1007/s13346-015-0237-z>.
- [79] McCrudden MTC, Alkilani AZ, Courtenay AJ, McCrudden CM, McCloskey B, Walker C, et al. Considerations in the sterile manufacture of polymeric microneedle arrays. *Drug Deliv Transl Res* 2015;5:3–14. <https://doi.org/10.1007/s13346-014-0211-1>.
- [80] World Health Organization. Annex 9. Guidelines on clinical evaluation of vaccines: regulatory expectations. Replacement of Annex 1 of WHO Technical Report Series, No. 924. WHO Expert Committee on Biological Standardization: sixty-seventh report. Geneva, Switzerland, 2017.
- [81] World Health Organization. Annex 4: Guidelines on procedures and data requirements for changes to approved vaccines. WHO Expert Committee on Biological Standardization: sixty-fifth report. Geneva, Switzerland, 2015.
- [82] Plotkin S, Robinson JM, Cunningham G, Iqbal R, Larsen S. The complexity and cost of vaccine manufacturing – an overview. *Vaccine* 2017;35:4064–71. <https://doi.org/10.1016/j.vaccine.2017.06.003>.
- [83] Watkins John, Ryder Clare. Marketing applications for biopharmaceuticals: Considerations for different jurisdictions – Part 1. *Regulat Rapporteur* October 2017;14(10). n.d.
- [84] Dellepiane N, Wood D. Twenty-five years of the WHO vaccines prequalification programme (1987–2012): Lessons learned and future perspectives. *Vaccine* 2015;33:52–61. <https://doi.org/10.1016/j.vaccine.2013.11.066>.
- [85] World Health Organization. WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems. World Health Organization; 2018 [accessed November 26, 2018].
- [86] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Text with EEA relevance). vol. 13; 2004.
- [87] European Commission, Bill & Melinda Gates Foundation. Article 58 Strategic Review – Summary 2015. https://www.ema.europa.eu/documents/other/article-58-strategic-review-summary_en.pdf [accessed November 13, 2018].
- [88] European Medicines Agency. Medicines for use outside the European Union n.d. <https://www.ema.europa.eu/human-regulatory/marketing-authorisation/medicines-use-outside-european-union> [accessed August 8, 2018].
- [89] PATH. The PATH Center of Excellence for Microarray Patch Technology. Seattle, WA: 2019. Accessed 19 February 2019. <https://www.path.org/resources/path-center-excellence-microarray-patch-technology/>.
- [90] Gavi. VIPS – Vaccine Innovation Prioritisation Strategy (focusing on vaccine product attributes). Geneva, Switzerland, June 2018. Accessed 19 February 2019. https://www.who.int/immunization/research/meetings_workshops/30_MenoziA_VIPS.pdf.