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End-user acceptability study of the nanopatch™; a microarray patch (MAP) for child immunization in low and middle-income countries

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ABSTRACT

A promising new delivery technology, the microarray patch (MAPs) consists of an array of small solid-coated or dissolvable needles, up to one mm in length, that administers a dry formulation of a vaccine or pharmaceutical. This study is not a real-life evaluation study but determines the anticipated acceptability of the Nanopatch™, a solid microarray patch device, in Benin, Nepal and Vietnam for vaccine delivery, and identifies factors that could improve the acceptability of the technology to increase measles immunization coverage.

This study combined several evaluation methods, including simulation of vaccine administration on children and in-depth interviews with key stakeholders, healthcare workers, community health volunteers, caretakers, and community representatives.

A total of 314 people participated in the study. The overall rate of total acceptability of the patch for child immunization was 92.7%. General opinions were very positive, providing clinical studies confirm that MAP administration is demonstrated to be painless, safe and effective for infectious disease prevention. The study participants were asked to consider the best strategy to introduce such vaccine delivery innovation. Firstly, delivery by skilled healthcare workers at the healthcare facilities will be preferred to establish the technology. Following this, administration by selected volunteers and outreach delivery may be possible, though under the supervision of skilled healthcare workers.

This study's protocol received approval from the World Health Organization (WHO) Ethical Research Committee (ERC0002813) and the national IRB in Benin, Nepal and Vietnam.

1. Introduction

Despite the success of global immunization programmes and mass vaccination campaigns, as well as continual research to improve existing vaccines and develop new approaches, approximately 1.5 million children under five years of age are still dying from vaccine-preventable diseases, each year [1]. The challenges associated with current needle and syringe-based immunization strategies in low and middle-income countries (LMICs) include: safety issues encountered by staff and recipients such as needle stick injuries [2] and vaccine reconstitution errors [3,4]; constrained human resources to manage complex delivery logistics and administration that can lead to lack of timely administration within the expanded programme for immunization (EPI) schedule, large volume of sharp waste [5]; unaffordable costs compared to oral administration [6] and poor acceptability by end-users [7]. To address these issues, the World Health Organization (WHO) is investigating the feasibility of promising new vaccine delivery technologies and is particularly interested in the applicability of MAP to achieve more equitable coverage of measles vaccine.

Microarray patches (MAPs) consist of an array of small solid-coated or dissolvable needles, up to 1 mm in length, that delivers a dry formulation of vaccine or pharmaceutical into the upper layers of the skin. It is anticipated that microarray patches could be used to deliver vaccines in supplementary immunization activities (SIAs) as well as routine immunization programs, to accelerate

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measles elimination [8]. Among its most promising attributes, MAP may enable vaccine to be administered by minimally trained community health volunteers (CHVs) rather than health care workers (HCWs), thereby easing resource constraints, especially during outreach [9]. Another possibility may be to use the MAP in a controlled temperature chain (CTC) or completely out of the cold chain [10]. The administration of MAP by CHVs, and/or its potentially greater thermostability would considerably ease the logistics and cost of vaccine delivery during SIAs, particularly in remote or inaccessible areas [11].

This study evaluates a prototype version of the Nanopatch™ device produced by one microarray patch developer, Vaxxas Pty Ltd. The Nanopatch™ is solid (and not dissolvable) and consists of a puck-like device containing an integrated applicator and the MAP; a square array (approximately 1 cm × 1 cm) of polymer micro-projections (up to 10,000 per MAP, 250 μm in length) (Fig. 1a). Pressure on the top of the device, actuates the spring-powered applicator which then provides the appropriate amount of force to apply the MAP to the surface of the skin and enable the micro-projections to penetrate into the epidermis and upper dermis. The Nanopatch device has been evaluated in five studies to date [12–15,18]; one with 'uncoated' MAPs to assess tolerability, reactogenicity or acceptability [12], and one where Nanopatches were used to deliver an influenza vaccine [13]. An additional phase I trial using Nanopatches to deliver influenza vaccine is in progress (ACTRN12618000112268). For the purposes of this study, the device did not contain a MAP or vaccine, but did have the spring-activated applicator, and represented the appearance and administration of the vaccine containing MAP in every other way. The simulation of the vaccination was also virtually identical to application of a vaccine-containing MAP (Fig. 1b).

A study to evaluate the perception of microneedle-patch vaccine delivery by parents in Ireland suggested that, even for those who support vaccination, there is caution regarding a novel vaccine delivery approach [14,15]. Additional acceptability studies of MAPs have been undertaken [12,16,17], including its amenability to self-administration [18], using MAPs without vaccine antigens. In general, the administration of vaccines by MAP rather than needle and syringe is much preferred and understanding of end user preferences during product development will help ensure uptake. With that in mind, the objectives of this study were to determine the anticipated end-user acceptability of the Nanopatch™ device in the context of measles containing vaccine (MCV) pediatric immunization in LMICs, specifically Benin, Nepal and Vietnam, and to identify factors that could influence the acceptability of this technology so that it may, in the future, have the potential to increase MCV immunization coverage. More broadly, these study findings help to identify barriers and improvements for acceptability of MAP technology under development, particularly for pediatric immunization in LMICs.

Fig. 1a. The MAP prototype used in the study.

2. Methods

This study combined several methods to obtain evidence-based data on the acceptability of the Nanopatch™ MAP devices in children aged 9–23 months. Opinions were collected from key stakeholders involved in the EPI and vaccine safety and management at both the central and district levels, as well as HCWs and CHVs in health facilities. Caretakers (CTs) of children aged 9–23 months and community representatives (CRs) were also included. A combination of in-depth interviews, questionnaires, administration simulations and post-simulation questionnaires were used (Fig. 2).

2.1. Study site selection

The study was conducted in three different WHO regions: Benin in the African region, Nepal in the South-East Asian region and Vietnam in the Western Pacific region. All three countries subscribe to the Global Vaccine Action Plan to eliminate measles by 2020 and participate in the Measles Rubella Initiative. Two districts were selected in each country: one rural and one urban. District selection was conducted in collaboration with the Ministry of Health (MoH) and WHO country offices; districts with MCV immunization coverage close to the national targets were selected.

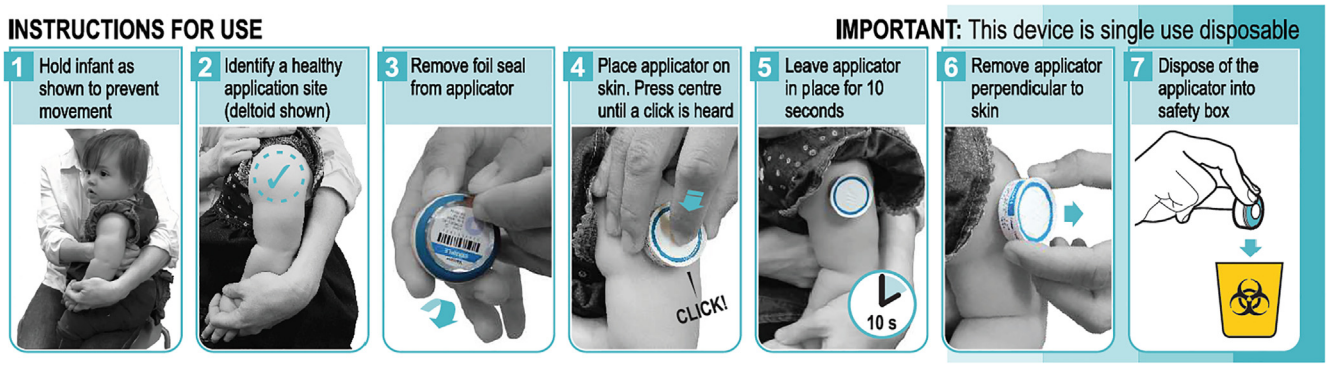

Fig. 1b. Manufacturer's Instructions for Use.

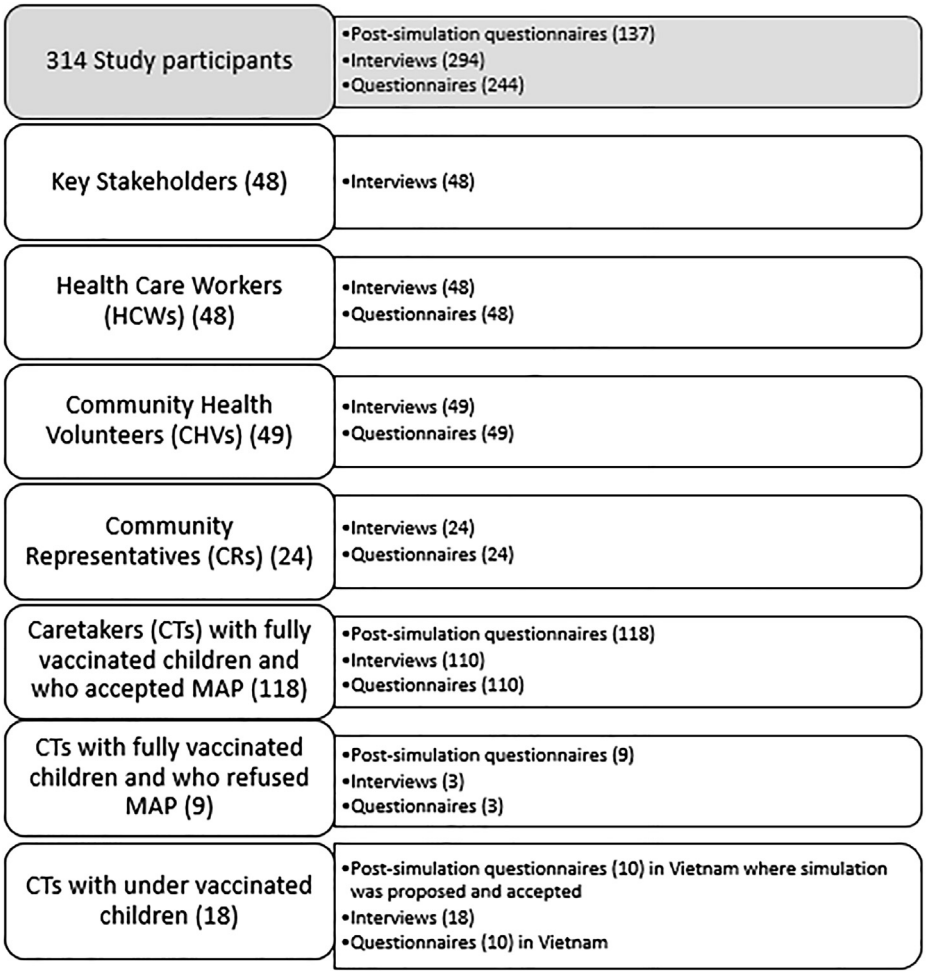

Fig. 2. Overview of study groups and Methodology used.

2.2. Participant selection

Study participants were identified mostly using purposive sampling. This type of sampling can be very useful to reach a targeted sample quickly, and it has been used in this study to facilitate identification and inclusion of participants who have the most relevant experience to participate. At the central and district levels specifically, key stakeholders who were involved in the EPI and vaccine safety and management were identified in collaboration with the MoH and WHO country offices. To document the vaccinators' perspectives at a peripheral level, HCWs were identified in health facilities when they were involved in immunization activities. CHVs were included in the study when they were involved in health promotion activities for immunization. These CHVs typically participate in oral polio vaccine (OPV) delivery and received information about Adverse Events Following Immunization (AEFI) monitoring. Community representatives were also included in the study.

The majority of caretakers were identified based on convenience at the health facility level. To assess the recipient viewpoints, caretakers of children aged 9–23 months were asked to participate in vaccination simulation when they presented at the health facility to immunize their children against measles or Japanese encephalitis. Furthermore, some CTs of under-vaccinated children aged 9–23 months were identified at the health facility based on the information contained in vaccination cards in Vietnam or on CHVs' indications in Benin at community level.

2.3. Methods for data collection

Observation grids were completed by the national research team during the simulated vaccination with the MAP device to compile the reactions of recipients and administrators at each stage of the application procedure. The MAP device simulation was performed before the needle and syringe immunization that the child was to receive that day. Briefly, the simulation involved holding the child while positioning the device onto the application site and pressing the applicator until the click was heard. The device was left in place on the skin for 10 s. Vaxxas has preclinical data (unpublished) showing that the amount of antigen delivered with a 10 s wear time is equivalent to that seen with 2 min wear time. Therefore a 10-second wear time is expected to be equivalent to 2 min in terms of immune response induction, and this is why it was selected for this study.

The device is designed to remain in place on the arm, without being held in position. In the usual configuration, this is achieved by the micro-projections penetrating the skin; because the prototypes in the study did not have projections, the devices incorporated a medical adhesive as an alternative. The device was then removed and disposed of into a safety box (Fig. 1b). Just after the

simulation, post-simulation questionnaires were conducted with CTs who accepted or refused but observed the MAP device application on another child, to document their reasons for accepting or refusing to participate in the simulation. Semi-structured in-depth interviews were conducted with all categories of participants after the device presentation or simulation. Six caretakers who refused the simulation were not available to participate in the interviews. Questionnaires included socio-economic indicators and closed-ended questions to collect data on the socio-economic characteristics of the caretakers in case this had a bearing on acceptability (tools are available upon request).

2.4. Data analysis

Observations were entered in an Microsoft Excel database for analysis. The post-simulation and closed-ended questionnaires were completed by hand and answers were entered in the SurveyGizmo software to generate descriptive quantitative reports for the central team's analysis (the team who designed and coordinated the study and did the cross-country analysis). All interviews were coded using pre-identified items listed in the interview guidelines by the country teams. In addition, to monitor and ensure the quality of analysis, and identify trends across contexts in the different countries, 20% of the most thorough interviews were purposively selected by each category of participants to assess consistency by the central team.

2.5. Ethical considerations

In order to assess ethical integrity of the methodology, the study protocol underwent review and approval by the WHO Ethics and Review Committee (ERC0002813). As part of this process, reviews by three independent expert and external peers were conducted, followed by further review by the national institutional review boards (IRB) in the three study sites. All participants were informed about the study and signed a consent form before participating in the study.

3. Results

3.1. Study participants

A total of 314 people participated in the study (Fig. 2), which included: forty-eight experts (Key stakeholders) of the EPI (30 at central and 18 at district level), 48 HCWs, 49 CHVs, 24 CRs and 145 CTs.

A total of 294 interviews were conducted across the different categories of participants, with 244 closed-ended questionnaires completed. The number of participants at the central and district levels were the same in all three countries, and consistent across the healthcare facilities and community settings for Benin and Vietnam. In Nepal, the number of study participants was lower as it was not possible to identify CTs who did not vaccinate their children. In total, 258 of the 266 (97%) study participants at the health facility level answered socio-demographic questions. Following a total of 128 vaccine administration simulations across all three sites, 137 short questionnaires were completed with caretakers who accepted (n = 128) or refused (n = 9) the device application (Fig. 2).

Overall, 76.4% of respondents were women (Table 1). Male respondents were made up 75% of the HCWs, CHVs (although in Nepal the CHVs were all female) and CRs, however males represented only 5.1% of the CTs. The gender distribution among MAP device recipients was equal, including those for whom their CTs refused simulation. CTs were mostly 18–45 years old, while in other stakeholder categories ages mostly ranged from 36 to 55 years old. The same demographic trends were observed in urban and rural contexts, as expected in the protocol.

All levels of education and the profession were represented with no clear influence on opinions. Both CTs with and those lacking formal education refused the simulation or shared concerns

Table 1
Characteristics of study participants.

	HCW (n = 48)	CHV (n = 49)	CT who accepted (n = 128)	CT who refused (n = 9)	CR (n = 24)	Total (n = 258)	Percent
Gender							
Male	18	18	7	0	18	61	23.6
BN	5	12	0	0	8	25	9.7
NL	9	0	0	0	5	14	5.4
VN	4	6	7	0	5	22	8.5
Female	30	31	121	9	6	197	76.4
BN	11	4	40	4	0	59	22.9
NL	7	17	32	2	3	61	23.6
VN	12	10	49	3	3	77	29.8
Age							
Under 18	0	0	6	0	0	6	2.3
18–25	2	3	50	2	0	57	22.1
26–35	18	9	57	5	7	96	37.2
36–45	17	20	14	2	6	59	22.9
46–55	9	10	0	0	6	25	9.7
56–65	2	5	1	0	4	12	4.6
Over 65	0	2	0	0	1	3	1.2
Rural/urban							
Rural	ND	ND	78	4	14	96	37.2
Urban	ND	ND	50	5	10	65	25.2
ND	48	49	0	0	0	97	37.6
Level of education							
Illiterate	ND	ND	21	2	0	23	8.9
Primary level	ND	ND	39	2	4	45	17.4
Secondary level	ND	Nd	44	2	9	55	21.3
Intermediate/vocational training	ND	ND	5	1	2	8	3.1
Graduate	ND	ND	19	2	7	28	10.8
ND	48	49	2	0	0	99	38.4

Table 2
Summary of perceived Advantages and Drawbacks of MAP.

MAP features	Perceived advantages	Perceived drawbacks
Perceived pain	• MAP looks painless • MAP could overcome vaccine refusal due to fear of injection with needles	"Is the MAP efficacious if the administration route is painless?"
Safety	No needle-stick injuries due to reconstitution or during administration device is prefilled and sterilized reduced risk of loss of potency if heat-stable	Risk of severe cutaneous reactions associated with intradermal administration (BCG like)
Efficacy	N/A	Asked for evidence of intradermal immunization efficacy
Period of administration (10 sec.)	Seems acceptable for most participants	• Concerns about the feasibility of holding children during 10 s if painful • Not possible for vaccinators to count during administration and provide advice to CTs simultaneously
Single dose presentation	• Would reduce the time to receive vaccination and facilitate CTs availability with no need to wait for other recipients in the case of a multi-dose vial • Would facilitate catch-up activities for hard-to-reach children	• Volume in the cold chain • Advantage of a single dose presentation would potentially be limited if children needed to receive other MDV vaccines
Heat-stability	• Would improve vaccine safety in case of equipment or power failure • Would facilitate storage at all levels of delivery system • Would reduce loss of potency and vaccine wastage • Would facilitate transport for outreach activities with no need for heavy equipment	• Need for scientific evidence of safety associated with storage out of cold chain in warm settings • Warehouses for dry storage are not well controlled
Dose delivery	N/A	• How to ensure the right dose has been delivered? • How to ensure the patch is coated with the vaccine and not reused?

about MAP or immunization in general. Religious affiliation did not appear as a socio-demographic determinant for vaccine or device acceptability.

3.2. Study participants' initial impressions

A total of 137 CTs were invited to participate in the vaccination simulation at health centres. Of these, 128 CTs accepted the simulation (93.5%) and 9 CTs refused to participate (6.5%). Seven CTs explained that they refused to apply an unknown device on their child (even though they understood that it did not contain a vaccine or MAP). Two CTs added that the time of simulation (prior to immunization) was not suitable, notably because their children were already unsettled and they did not want to extend the session. CTs who accepted the simulation were subsequently asked "Would you accept to let your child be vaccinated using the patch during routine activities at health facility level?" The overall rate of total acceptability of the patch for their child's immunization was 92.7%, with the lowest observed in Nepal (81.3%), and highest in Vietnam (98.3%).

In interviews, general opinions from study participants about MAPs device were very positive. The major perceptions regarding the advantage and disadvantages the device are listed in Table 2. This feedback is mostly through solicited responses.

A total of 10 main aspects were identified by the study participants to describe their enthusiasm or doubts about the MAP device, and these can be classified into two major themes: (i) the potential programmatic benefits which might be enabled by MAP features, and (ii) the potential impact of MAP on end-users' experiences of immunization.

3.2.1. Potential programmatic benefits

According to key informants at the central and district level, the ease of MAP delivery could mean that additional vaccinators could be available among the CHVs to facilitate outreach activities, notably house-to-house (H2H) vaccine delivery to increase vaccine coverage and equity of vaccination. However, a key pre-requisite for success of using MAP in this immunization strategy is the acceptability by end-users (both administrators and recipients) of such strategies when delivering current vaccines (Fig. 3). This is particularly important, given that countries may be reluctant to use H2H delivery because it is considered more costly and logistically difficult [19] even though some studies suggest it is an effective method for ensuring universal immunization [20]. This study aims to consider the acceptability of delivery by CHVs in a H2H setting, not the feasibility of the H2H vaccination strategy.

MAP device uses during routine activities in health facilities where vaccines are usually administrated was positively perceived by the majority of participants in all three countries (91.8% of all types of participants in all countries combined). Using MAP during outreach activities at fixed posts was also well anticipated by the majority of participants (average of 87.7%), with a preference for such a strategy in Nepal (93% approval). Using MAP at home during outreach strategies/SIAs was perceived more cautiously (average of 60.2%). CRs (average of 79%) were the most enthusiastic about MAP vaccine delivery by CHVs whereas strong concerns were expressed by approximately 50% of HCWs in each of the three countries. Even community health volunteers themselves (45%) shared doubts about the acceptability of the CHV group performing immunization using the MAP, even though they already conduct vaccination related activities.

A significant proportion of CTs (37%) were not confident in the ability of the CHV group to deliver immunizations by MAP (Fig. 4). These concerns regarding the required skills of vaccinators explains why the anticipated acceptability of MAP use during house-to-house activities was lower than for the other vaccination scenarios at 60.2% overall. This is because of the existing lack of confidence in the quality of vaccines or in the unskilled vaccinators during house-to-house activities in both settings where these activities are and are not used in practice, rather than the features of the MAP device itself. CTs and CRs in all three countries explained they would prefer trained vaccinators with the highest level of education to administer vaccines to their children.

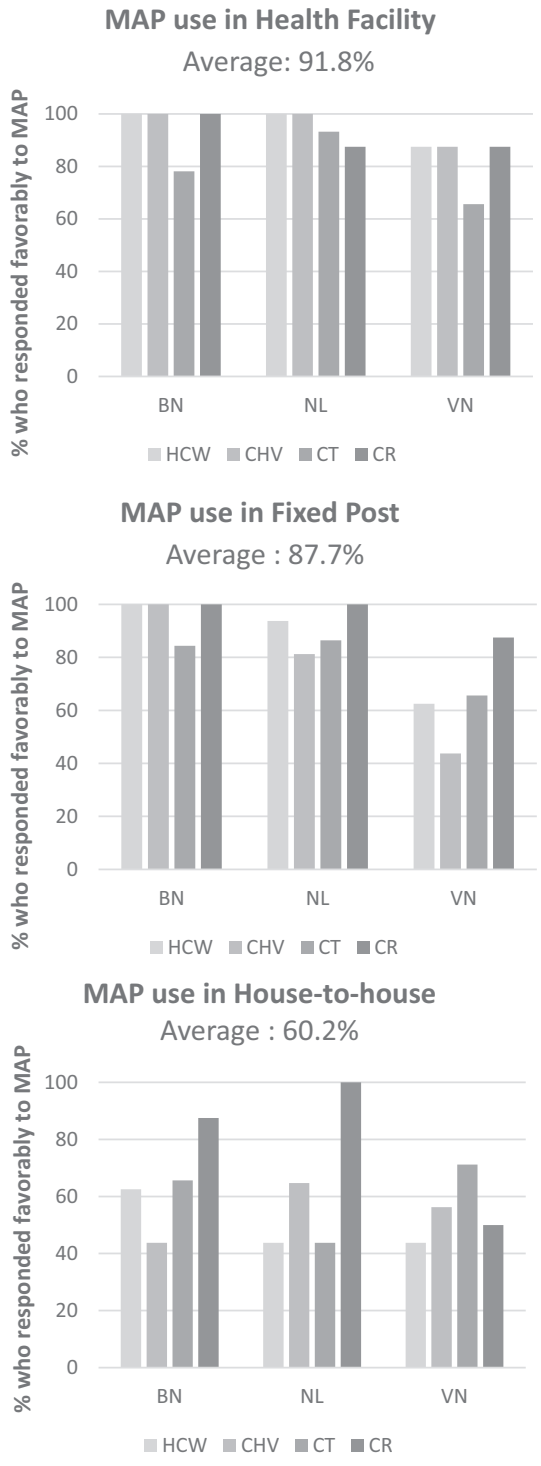

Fig. 3. Anticipated Acceptability of MAP use per delivery strategy, by stakeholder group.

According to study participants in the three countries, MAP would be a valuable tool to facilitate house-to-house catch-up activities among the most hard-to-reach and willing populations. These include people who cannot cover costs for transport to the health facility (HF) or fixed posts, people who cannot suspend their economic/household activities for a significant amount of time, and those who avoid social interactions (because of existing conflicts with other community members who may be met during public sessions or because of perceived discrimination/shame due to their visible poverty). But conditions for successful CHVs involvement for house-to-house MAP immunization would be: (1) to select and train the CHVs with the requisite skills and qualifications (2) to not allow CHVs to administer a vaccine with a MAP without healthcare worker supervision, notably to ensure AEFI prevention and management, and to verify EPI reporting, (3) to have clear communication from the Ministry of Health to the CHVs, CRs and CTs explaining why CHVs should be allowed to administer MAPs, rather than injectable vaccines, and that CHVs have received the training they need to perform this activity.

Study participants shared similar requirements when commenting on the theoretical possibility of caretaker administration on their own child.

3.2.2. The potential impact of MAP on end-users' experiences of immunization

The common perception is that MAP immunization will be painless. This impression provides interesting insights into the preference for painless delivery methods to replace injection for vaccine administration. Pain is attributed to the act of injection itself as well as to the potential AEFI. The CTs explained how children's pain and reactions can impact their household life. They described the associated expenses if reactions require medical follow-up with repeated transport to the HF, and costs for treatment and care. In such situations, the constraints on CTs' availability are compounded. MAP (both device and process of vaccine delivery) would impact very positively on the experience of immunization and contribute towards eliminating vaccine hesitancy and refusals due to fear of injections.

All study participants considered that MAP looks safer than injection. All categories of participants spontaneously perceived how infection or injuries attributed to deep intramuscular injection (such as nerve damage) and needle stick exposure would be avoided with MAP administration. In addition, some healthcare workers and some key informants described how delivery of a vaccine dose by an integrated and sterile device would avoid contamination of the vaccine and would also eliminate the errors due to vaccine reconstitution and dose preparation that occur with needle and syringe. Potential heat-stability was also perceived by key informants in Vietnam as being an advantage for maintaining vaccine quality in case of equipment failure or power outage.

Nevertheless, even if MAP looks safer, some HCWs and key informants compared the route of administration by MAP device with the intradermal administration of the Bacillus Calmette–Guérin (BCG) vaccine against tuberculosis (TB). The study participants described how a BCG scar is perceived as a sign of vaccine efficacy. However, complications which occasionally result from BCG immunization such as infection, have been described by some study participants as a reason for becoming vaccine hesitant. MAP reactogenicity, which would most probably be antigen dependent, is not expected to be a concern if the reactions are equivalent or less severe than for BCG, and if they are well anticipated before MAP administration.

Perception of efficacy is the third criterion for MAP acceptability. All categories of participants shared a common concern about the MAP efficacy over the intramuscular administration and expressed the need for scientific evidence to demonstrate equivalent or superior performance of the MAP vaccine.

4. Discussion

The potential applicability of microarray patch vaccine delivery in various immunization strategies depends on current perceptions of various stakeholders involved in immunization [21] and should be considered when determining how MAPs can best be used in increase coverage and improve equity goals [22]. Participants from

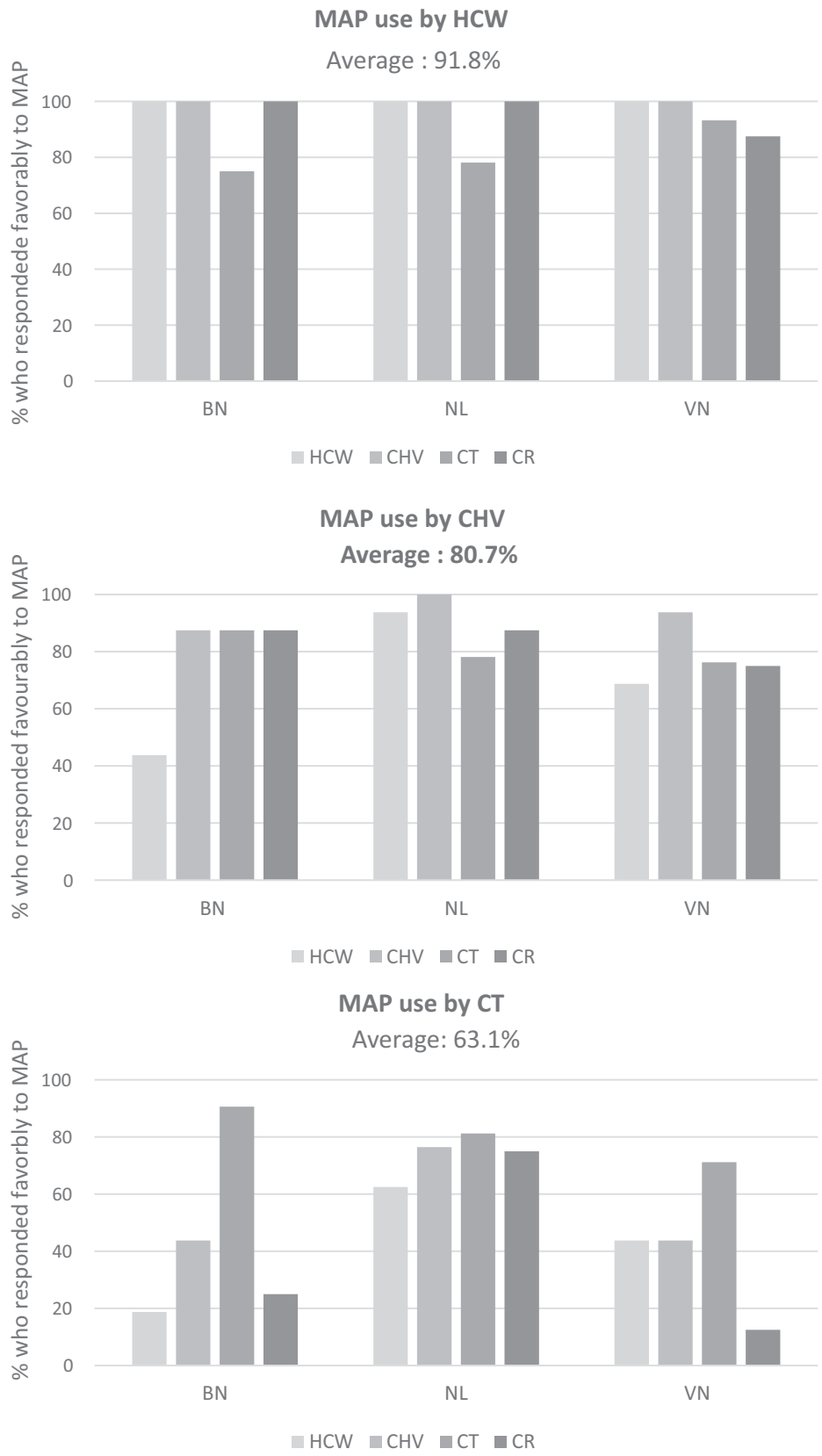

Fig. 4. Anticipated acceptability of MAP administration by vaccinators by stakeholder group.

all stakeholder categories would prefer the use of MAPs during routine activities at the health facility level – which are perceived as having the highest standards for vaccine storage and administration by skilled vaccinators. The current perception that MAP delivery by CHVs is not of interest in house-to-house activities led to suggestions that the MAP devices should initially be used

by HCWs in HFs to increase familiarity with the innovation and establish its safety and effectiveness prior to their use for outreach activities (in fixed posts or house-to-house activities). Under these conditions, CHVs could be authorized to administer MAPs at the HF, though only under supervision of healthcare workers and after clear communication about the CHVs' selection process and their limited involvement in house-to-house activities. Once the acceptability of MAP is established at the HF level, the MAPs could be implemented in outreach activities where it would lead to real improvements in vaccine coverage and equity.

This study does not allow for pain or AEFI evaluation when administering MAPs because of the use of a dummy device during simulations. Despite this limitation, it was extremely clear that the ability of MAPs to decrease the pain and anxiety associated with immunization is the major expectation of CTs and would be a significant advantage over needle and syringe. If only few CTs refuse vaccines because of the risk of AEFI and painful experiences, an alternative delivery method to needle and syringe may be accepted if reactogenicity is limited and well-described. The first clinical studies with a MAP have been performed with influenza vaccine in adults [12,13,16–18]. Applications resulted in erythema lasting several days or weeks. A qualitative assessment of the perceptions of such AEFI in LMICs when a MAP containing arrays and vaccine is applied on children will be crucial to informing key communication messages prior to microarray patch administration.

Demonstration of equivalent efficacy in comparison with the conventional sub-cutaneous injection would be imperative for accepting MAP use for MCV immunization. In most cases, syringes are transparent and enable verification that the complete vaccine dose is delivered and no liquid remains in the syringe. Participants requested a visible cue on MAP to indicate delivery of the complete dose.

The study presents some additional limitations. Study participants were recruited following the purposive or convenient sampling method. Quantitative results are not statistically representative (not randomized or stratified samples) but they give some indication about the weight of each type of response. CTs with negative attitudes towards vaccines are under-represented. Evaluation of acceptability and feasibility of MAP and outreach strategies among the hard-to-reach populations would be of interest to confirm whether the MAP strategy is able to enhance vaccine equity.

Prior to undertaking this study, the assumptions of many involved in MAP product development was that this innovative delivery technology would have the greatest public health impact in the context of house-to-house vaccination, by enabling CHVs to deliver potentially thermostable vaccines to the most remote and inaccessible areas. This acceptability study has evaluated the perceptions of end-users across several vaccination settings within three LMICs and concluded that the concept of MAP vaccination is generally very well accepted. Of note, there is broad support for its use primarily in routine immunization within health care facilities, particularly with administration by trained health care workers since MAP is a novel, unfamiliar vaccination technology. A real-life evaluation will be required also to confirm MAP usability when administrated by community health volunteers.

Considering that the cost per dose of MAP [23] is anticipated to be higher than multi-dose vials and delivery by injection, MAP vaccine delivery may not be cost effective in the routine immunization setting when first introduced [24]. However, this study suggests that the MAP will need to be implemented in this setting initially, in order to establish familiarity and credibility of the technology before its implementation in more remote areas. It will also be important to evaluate the logistical impact of introducing MAP into the healthcare system, as well as the safety and acceptability benefits of eliminating the need for vaccine reconstitution. Evaluation of the trade-off in cost per dose and cost to vaccinate a child, in addition to the reach (currently un- or under-immunized populations) that MAPs may achieve in relation to needles and syringe will be needed to demonstrate its potential value as compared to vials, needle and syringes. Cost-effectiveness and logistical impact evaluations based on the potential use cases for MAP will provide additional insight to estimate the real potential for introducing acceptable and sustainable alternatives to needle and syringe. Overall MAPs were found to be acceptable, and additional analysis of their use is warranted.

5. Contributors

EG contributed to the development of the study protocol with RD and PJ, coordinated the study implementation and data collection, conducted the analysis, was the main author and contributed substantially to writing the report and manuscript. DA coordinated the implementation of the study in Benin, provided technical input for developing the protocol, analyzed Benin's data, wrote the Benin report, and provided input on the cross-country report and article. LTPM coordinated the implementation of the study in Vietnam, provided technical input for developing the protocol, analyzed Vietnam's data, wrote the Vietnam report, and provided input on the cross-country report and article. MS coordinated the implementation of the study in Nepal, provided technical input for developing the protocol, analyzed Nepal's data, wrote the Nepal report, and provided input on the cross-country report and article. RD developed the study protocol with EG and PJ, developed the study tools, contributed to the study implementation coordination, trained the country teams, and provided input on the report and manuscript. BG provided input on protocol, report and manuscript writing. PJ oversaw the development and implementation of the project, analyzed the logistical and programmatic data, provided input on developing the protocol, data analysis, the study report, and manuscript writing. All authors agreed on the final draft.

6. Role of the funding source

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Conflict of interest

The MAP developer, Vaxxas Pty Ltd provided support during the evaluation notably by providing the dummy devices for the simulations but did not interfere in the study. EG, RD and PJ worked for the Agence de Médecine Préventive (AMP), which received

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References

[1] https://www.who.int/en/news-room/fact-sheets/detail/immunization-coverage [accessed the 18 February 2019].

[2] Prüss-Üstün A, Rapiti E, Hutin Y. Sharps injuries: global burden of disease from sharps injuries to health-care workers. Geneva, World Health Organization, 2003. WHO Environmental Burden of Disease Series, No. 3. https://www.who.int/quantifying_ehimpacts/publications/en/sharps.pdf [accessed the 18 February 2019].

[3] https://www.who.int/immunization/documents/updat34e.pdf [accessed the 18 February 2019].

[4] De Coster I, Fournie X, Faure C, et al. Assessment of preparation time with fully-liquid versus non-fully liquid paediatric hexavalent vaccines. A time and motion study. Vaccine 2015;33:3976–82. https://doi.org/10.1016/j.vaccine.2015.06.030.

[5] Agbenu E, Chartier Y, Eleeza J, et al. Use of hub cutters and the volume of sharp waste and occurrence of needle-stick injuries during 2011 mass immunization campaigns against yellow fever in Ghana: a cohort study. Int J Occup Environ Med 2014;5:9–17. , http://www.theijoem.com/ijoem/index.php/ijoem/article/view/303.

[6] Sartori AM, Vicentine MP, Gryninger LC, Soárez PC, Novaes HM. Polio inactivated vaccine costs into routine childhood immunization in Brazil. Rev Saude Publica 2015;49:8. https://doi.org/10.1590/S0034-8910.2015049005492.

[7] Farag NH, Mansour Z, Torossian L, Said R, Snider CJ, Ehrhardt D. Feasibility of jet injector use during inactivated poliovirus vaccine house-to-house vaccination campaigns. Vaccine 2018;6:36. https://doi.org/10.1016/j.vaccine.2018.06.011.

[8] Edens C, Collins ML, Ayers J, Rota PA, Prausnitz MR. Measles vaccination using a microneedle patch. Vaccine 2013;31(34):3403–9. https://doi.org/10.1016/j.vaccine.2012.09.062.

[9] Donnelly RF, Larraneta E. Mircoarrays patches: potentially useful delivery systems for long-acting nanosuspensions. Drug Discovery Today 2017. https://doi.org/10.1016/j.drudis.2017.10.013.

[10] Kahn AL, Kristensen D, Rao R. Extending supply chains and improving immunization coverage and equity through controlled temperature chain use of vaccines. Vaccine 2017;35(17):2214–6. https://doi.org/10.1016/j.vaccine.2016.10.091.

[11] Arya J, Prausnitz MR. Microneedle patches for vaccination in developing countries. J Control Release 2016;240. https://doi.org/10.1016/j.jconrel.2015.11.019.

[12] Griffin P, Elliott S, Krauer K, Davies C, Skinner SR, 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(48):6676–84. https://doi.org/10.1016/j.vaccine.2017.10.021.

[13] 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(26):3779–88. https://doi.org/10.1016/j.vaccine.2018.05.053.

[14] Marshall S, Fleming A, Moore AC, Sahm LJ. Acceptability of microneedle-patch vaccines: A qualitative analysis of the opinions of parents. Vaccine 2017;35(37):4896–904. https://doi.org/10.1016/j.vaccine.2017.07.083.

[15] Marshall S, Sahm LJ, Moore AC. Microneedle technology for immunization: perception, acceptability and suitability for pediatric use. Vaccine 2016;34(6):723–34. https://doi.org/10.1016/j.vaccine.2015.12.002.

[16] Hirobe S, Azukizawa H, Matsuo K, Quan YS, Kamiyama F, Suzuki H, et al. Development and clinical study of a self-dissolving microneedle patch for transcutaneous immunization device. Pharm Res. 2013;30(10). https://doi.org/10.1007/s11095-013-1092-6.

[17] 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. https://doi.org/10.1016/j.biomaterials.2017.02.040.

[18] 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(16):1856–62. https://doi.org/10.1016/j.vaccine.2014.01.076.

[19] Hanvoravongchai P, Mounier-Jack S, Oliveira Cruz V, Balabanova D, Biellik R, Kitaw Y, et al. Impact of measles elimination activities on immunization services and health systems: findings from six countries. J Infect Dis 2011;204(suppl_1):S82–9. https://doi.org/10.1093/infdis/jir091.

[20] Portnoy A, Jit M, Helleringer S, Verguet S. Impact of measles supplementary immunization activities on reaching children missed by routine programs. Vaccine 2017;36(1):170–8. https://doi.org/10.1016/j.vaccine.2017.10.080.

[21] Guillermet E, Dicko HM, Le Thi Phuong M, N'Diaye M, Hane F, Ba SO, et al. Acceptability and feasibility of delivering pentavalent vaccines in a compact, prefilled, autodisable device in vietnam and senegal. Plos One 2015. https://doi.org/10.1371/journal.pone.0132292.

[22] Lim J, Claypool E, Norman Bryans A, Rajgopal J. Coverage models to determine outreach vaccination center locations in low and middle-income countries. Operations Research for Health Care 2016;9. https://doi.org/10.1016/j.orhc.2016.02.003.

[23] Lee BY, Bartsch SM, Mvundura M, et al. An economic model assessing the value of microneedle patch delivery of the seasonal influenza vaccine. Vaccine 2015;33(37):4727–36. https://doi.org/10.1016/j.vaccine.2015.02.076.

[24] Wong C, Jiang M, You JH. Potential cost-effectiveness of an influenza vaccination program offering microneedle patch for vaccine delivery in children. PLoS One 2016;11(12):e0169030. https://doi.org/10.1371/journal.pone.0169030.