1 Executive Summary

As micro-array patches (MAPs, also known as microneedle patches) continue to be developed, their potential advantages of thermal stability and improved ease-of-use, and immunogenicity make them a candidate for use with measles-rubella (MR) vaccines. They have particular advantages that could facilitate delivery and increase coverage for these two vaccines in both low and middle-income countries (LMICs) and high income countries. The following is a Target Product Profile (TPP) for a generic microarray patch (MAP) presentation) with a solid vaccine formulation of a live-attenuated measles-rubella (MR) vaccine (including both coated and dissolvable MAP formats, but not hollow microneedle arrays intended to deliver liquid or reconstituted vaccines). The process of deriving this MR MAP TPP is intended to help focus stakeholders to define acceptable and optimal product attributes, to guide product developers.

2 General considerations for a MR vaccine delivered by MAPs

Attribute	MR MAP	Notes
Indication	Prophylactic vaccination against both Measles and Rubella infection of at-risk infants, children, adolescents and young adults.	Indications for use of MR MAPs would be both routine immunisation and supplementary immunisation efforts, including large campaigns in response to disease outbreaks. Possible concurrent vaccinations for simultaneous delivery are pentavalent (DTP-Hib-HepB), DT, TT, Td, BCG, poliovirus vaccines (OPV and IPV), PCV and yellow fever (YF) and Japanese encephalitis (JE) vaccines.[1] Thus MAPs may be incorporated into the supply chain of a larger expanded program on immunisation (EPI) and as such coordinating logistical requirements will reduce total programmatic impact.

Attribute	MR MAP	Notes
Use-case scenarios	Routine immunisation efforts and supplementary immunisation activities including "catch-up", "speed-up", and outbreak response campaigns.	The World Health Organization (WHO) has an initial goal of reaching >90% immunisation coverage with routine vaccination efforts by supplementary immunisation efforts for both first and second round doses of MR to attain >95% coverage for MR vaccines.[2] To reach this goal, both supplementary and campaign immunisation efforts will be utilized. Large volume "campaign" immunisation activities may be needed either for "speed-up/catch-up campaigns"[3] or in response to situations that create the potential for large outbreaks (for example in refugee camps, post-disaster communities without health support, previously unvaccinated communities). These may be implemented via 'house-to-house' efforts, temporary or fixed post sites, and/or permanent clinic settings. The unknown scale of future mass MR vaccination campaigns may also make stockpiling MAP MR vaccines desirable.
Dose Regimen and schedule	**First dose (MCV1)**: Typically delivered at ages 9 to 15 months, or in accordance with WHO recommended schedules. **Second dose (MCV2)**: Ideally delivered at ages 15 to 18 months, or in accordance with WHO recommended schedules.	For countries that achieve >80% national coverage of one dose of measles containing vaccines (MCV1) for three consecutive years, a second dose (MCV2) is to be added to the routine immunisation schedule. This second MCV should be delivered a minimum of 1 month after the first dose. Depending on the situation, the delivery of MCV2 at the age of school entry can be an effective strategy.[4]
Formulation	Formulation contains MR vaccine as the active ingredient, with necessary excipients/additives depending on MAP format (coated or dissolvable).	It will be important from the perspective of programmatic suitability, safety, efficacy, and regulation that MR MAPs are within the specified threshold in dose, content, identity, stability, purity, and sterility/endotoxins. Patches may need to be produced aseptically in accordance with current good manufacturing practices and will need to be tested for potency. Because of the possible dose-sparing advantages of MAPs for ID delivery[5], there may be the potential for a reduced dose of virus antigen compared to current MR doses. Doses should be formulated to prevent risk of damage from freezing if stored at 2 – 8^{o}C and stability to higher temperatures would be highly desirable.[6]

3 Generic product characteristics for a MR vaccine on MAPs

Two targets (minimally acceptable and optimal) have been assigned for each of the following MR MAP attributes according to the current understanding and development status of this technology.

Minimally Acceptable Target: This case represents the "shall meet" requirements necessary for effective acceptance of the MAP technology into current MR use settings.

Optimal Target: This case represents the "should aim for" guidelines. They represent a potential scenario that would be a significant improvement over the current situation of subcutaneous (SC) injection delivery of MR vaccine.

Characteristic	Minimally Acceptable Target	Optimal Target	Notes
Target Population	**Routine Immunisation**: Infants aged 9 to 12 months for the first dose, and at least 1 month later for the second dose (between ages 15 months to 6 years). **Campaigns**: Children aged 9 months to young adults.	Same as minimum, with the addition of Infants aged 6 to 9 months.	The WHO recommends the initial dose of MCV vaccine to be delivered between ages 9 and 12 months but any unvaccinated child aged over 12 months should be offered a MCV vaccination at the soonest available opportunity.[7] Current SPHERE guidelines[8] suggest campaign vaccinations for children aged 6 to 59 months when the population vaccination coverage is <90%.
Target Countries	All LMICs currently providing measles or MR vaccines in EPI efforts.	All countries. Note: MMR (measles, mumps, rubella) or MMRV (V - varicella) are typically delivered as measles containing vaccines for high income countries, but these vaccine combinations are unlikely to be a target for low income countries.	According to the Global Measles and Rubella Strategic Plan: 2012-2020[9], all six WHO regions (Africa, the Americas, South-East Asia, Europe, the Eastern Mediterranean, and the Western Pacific) have committed to measles elimination.

<table>
<tr><th>Characteristic</th><th>Minimally Acceptable Target</th><th>Optimal Target</th><th>Notes</th></tr>
<tr><td>Safety</td><td>MR MAP related adverse events shall be comparable to those of the current SC MR vaccination method.</td><td>MR MAP related adverse events should be significantly lower than those for the current SC MR vaccination method.</td><td>Ideally, MR MAPs will have similar or lower rates of adverse events than full-dose. It is also possible that a MR MAPs containing a lower dosage could trigger less allergic or anaphylactic responses.[10]</td></tr>
<tr><td>Immunogenicity</td><td>Seroconversion rates shall be non-inferior to a currently qualified SC MR vaccination.</td><td>Seroconversion rates should be superior to currently qualified SC MR vaccination.</td><td>The median seroconversion rate of infants vaccinated at ages 8 to 9 months with their first dose of MCV is 89.6% (interquartile range, 82 to 95%), and for first vaccinations at ages 11 to 12 months was 99% (interquartile range, 93-100%).[11] Rubella vaccinations induced a seroconversion rate of >95% after a single dose in susceptible individuals aged 12 months and older.[12]</td></tr>
<tr><td>Stability</td><td>Stability profiles shall be comparable to current MR vaccine stability (i.e. VVM14) stored at 2 - 8 °C for 2 years.</td><td>Stability profiles should have enhanced thermostability, i.e. applicability to controlled temperature chain (CTC). Shelf life longer than 2 years at 2—8°C. MR MAP offers significant improvement upon current MR vaccine cold-chain requirements.</td><td>Stability condition definitions:
<table>
<tr><th>Condition</th><th>Temperature</th><th>Stability timeline minimum</th></tr>
<tr><td>Full cold chain (“shelf life”)</td><td>2°C – 8°C (< 0°C acceptable)</td><td>2 years</td></tr>
<tr><td>CTC</td><td>Up to 40°C</td><td>3 days</td></tr>
</table>
Source: Internal PATH report[13], WHO CTC Website[14]

Testing and validation of stability characteristics of MR MAP should be implemented according to the WHO’s guidance on Extended Controlled Temperature Conditions (ECTC).[15]</td></tr>
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Characteristic	Minimally Acceptable Target	Optimal Target	Notes
Vaccine Vial Monitors	All MR MAPs shall be labeled with a VVM.	MAPs designated for CTC use shall be labeled with a VVM and peak temperature threshold indicator (PTTI).	CTC applies to vaccines capable of tolerating at least 40°C for a minimum of three days prior to use, designated for use in campaign or special strategy settings, labeled with specific use conditions, and licensed for this use by the relevant regulatory authorities.[16]
Dosage	MR MAPs shall contain similar quantity (i.e. virus potency on product release) of active biologic as contained in 0.5 mL of injectable MR vaccine (>1000 $CCID_{50}$ for both M and R) without reduction in induced immunogenicity and potency throughout projected shelf life of product.	MR MAP should require a reduced quantity (potency on product release) of active biologic ingredient compared with amount of active biologic ingredient contained in 0.5 mL of injectable MR vaccine without reduction in induced immunogenicity and potency throughout projected shelf life of MR MAP product.	An advantage of MAPs is the potential for antigen dose sparing and several preclinical studies suggests dose sparing may be feasible.[17] It is yet to be determined whether will be the case for MR in the field.

4 Generic product characteristics for MAPs for delivery of MR vaccines

Characteristic	Minimally Acceptable Target	Optimal Target	Notes

Characteristic	Minimally Acceptable Target	Optimal Target	Notes
Product Registration Path	MR MAPs shall be eligible for prequalification by the WHO; and comply with its Programmatic Suitability for Prequalification (PSPQ) guidelines.	MR MAPs should be appropriate for worldwide regulatory approval.	MR MAPs would be a novel vaccine-delivery system and will need to be evaluated for eligibility of prequalification by the PSPQ Standing Committee.[18] Experience with some analogous technologies (such as transdermal patches with small or large molecule non-vaccine medicines) may be useful for drafting initial regulatory guidelines.
Dose Presentation	Product shall be provided in a single dose, single-use (disposable) MAP format.	Same.	Relevant MAP formats are either dissolvable or vaccine coated onto a solid substrate such as steel, titanium, silicon or polymer.

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<tr><th>Characteristic</th><th>Minimally Acceptable Target</th><th>Optimal Target</th><th>Notes</th></tr>
<tr><td>Secondary Packaging</td><td>Product shall be contained within suitable secondary packaging compatible with the immunisation supply chain and has a cold-chain storage volume per dose no greater than a single dose vial of injectable MR vaccine (26 cm^3), if the MR MAP product requires cold-chain storage.</td><td>Product should be contained within suitable secondary packaging that is compatible with the immunisation supply chain and requires less cold-chain storage volume per dose than a 10-dose vial of injectable MR vaccine (3 cm^3), if product requires cold-chain storage.

Secondary packaging that allows the vaccinator to visualize the number of remaining doses should be considered.</td><td>Suitable secondary packaging for MR MAPs will protect them against damage, moisture transfer, and sunlight exposure if deemed necessary.[19] The patches may require an applicator (single use or re-usable), which could be shipped with, or separately, from the patches.

Secondary packaging configuration should minimize volume, weight and the need of repackaging for in-country distribution, as defined by Vaccine Presentation and Packaging Advisory Group’s (VPPAG) gPPP for vaccines.[20]

Current packing vial volumes per dose:

<table><tr><th>Storage volume of vaccine, (diluent)</th><th>Comparison MR product</th></tr><tr><td>3 cm^3, (3 cm^3)</td><td>10-dose glass vial</td></tr><tr><td>5 cm^3, (5 cm^3)</td><td>5-dose glass vial</td></tr><tr><td>26 cm^3, (26 cm^3)</td><td>1-dose glass vial</td></tr></table>
Note: Diluent is not stored in the cold chain but is to be kept cool. Currently, 1-, 2-, 5-, and 10-dose vials of MR vaccine are prequalified but only 10-dose vials are supplied through UNICEF due to manufacturers’ fill-finish capacity limitations. 5-dose vials have been requested by countries to decrease wastage rates.[21]</td></tr>
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Characteristic	Minimally Acceptable Target	Optimal Target	Notes
Tertiary Packaging	Product shall be contained within suitable tertiary packaging that is compatible with the existing immunisation supply chain.	Same.	Tertiary packaging shall comply with the VPPAG's gPPP recommendations. Compatible packaging is defined as that which will "minimize weight and volume and limit the need for repackaging for in-country supply chain distribution".[20]
Labeling	Primary container labeling shall meet recommendations outlined by the VPPAG's gPPP for vaccines and WHO's PSPQ guidelines.	Same.	The VPPAG's gPPP for vaccines outlines recommendations for minimum labeling content, conventions and font. If Controlled Temperature Chain (CTC) is indicated, additional labeling is required (see: Vaccine Vial Monitors).
Route of Administration	Product shall be delivered to dermis and/or epidermis in an anatomic site that is acceptable to immunisation systems and optimises efficacy of immunisation.	Same.	The term ID has been used for the delivery route and target tissue for MR MAPs. Some patches might deliver ID but others might deliver to the epidermis only. There are insufficient data to indicate the optimum depth or target tissue within the skin.
Human Factors (HF)	Applicator/MAP interface and procedure shall be designed in accordance with the general principles laid out in IEC 62366 and AAMI HE75.	Same.	For any application method, human factors of the device must be assessed in the relevant target population (children and adults) and geography. Human factors guidance documents such as ANSI/AAMI HE75 Human factors engineering—Design of medical devices and IEC 62366 Medical devices—Application of usability engineering to medical devices should be followed in order to verify and validate the final MR MAP design and applicator (if required for use).

Characteristic	Minimally Acceptable Target	Optimal Target	Notes
Applicator	MAP delivery requires a single-use or reusable applicator (while maintaining compliance with packaging requirements).	MAP should be able to be successfully delivered without applicator.	A standalone MR MAP that does not require an applicator for delivery would be advantageous from a packaging perspective. If required, packaging the applicator(s) and MAPs together would be preferable from a usability and logistics perspective, providing this did not have an unacceptable negative impact on cost or cold-chain storage volume. Note: Any patient-contact surfaces of a reusable applicator shall be disposable to prevent cross-contamination between vaccinees.
Skill Level	Minimal device-training shall be required; HCW or non-medical volunteer with printed instructions shall be able to administer MAP correctly after training.	No device-training required; HCW, non-medical volunteer or care giver should be able to administer MR MAP correctly using printed instructions.	MR MAPs should be designed to be easy to use without extensive training. Some studies have shown that people with minimal training can apply MAPs.[22,23] Ideally, MR MAPs could be used by minimally trained HCWs in routine vaccination settings or by non-medical volunteer with printed instructions in campaign settings after training. The MR MAP should be simple, intuitive, and easy enough to use in clinic-based or outreach vaccination settings since it is expected that MAPs will likely be used in both rural and urban settings (particularly in low-resource settings).

Characteristic	Minimally Acceptable Target	Optimal Target	Notes
Delivery Time	For campaign settings, total time for delivery shall be comparable to that of SC MR injection delivery methods, For routine settings, delivery time shall be acceptable to the immunisation system in question (informed by usability evidence).	For campaign settings and some routine settings, total delivery time should be less than that of SC MR injection delivery methods.	"Total delivery time" consists of preparation, administration, and wear time of the MAP. Because MR MAPs are to be used in both routine and campaign settings, decreasing the time required per dose delivered could have a significant impact on overall program logistics. Preparation and application of MAP should be compared to the estimated time required for reconstitution and delivery of a lyophilized vaccine from a 10-dose vial in campaign settings (approximately 70 seconds for reconstitution and delivery of the first dose and 20 seconds for each subsequent dose; following the assessment of the vaccinee and paperwork).[24] Specifying and monitoring acceptable "wear time" of the patch is likely to be critical for ensuring effective immunisation as some of the MAP technologies might require extended (and monitored) wear time after 'patch application' for reliable antigen delivery - from seconds to several minutes. The actual timings are not yet known from clinical studies in the appropriate target groups. It is also unknown how acceptable this would be to immunisation systems in LMICs, especially in campaign settings. Wear time of MAPs should be compared to the observation period (15 to 20 min) for monitoring for adverse reactions suggested by the Center for Disease Control.[25] Routine immunisation is, however, often performed alongside other vaccinations and health interventions and so an extended wear-time for the MR MAP, might not extend the total time per vaccinee. Reduction of MAP wear time should be prioritized by developers to further reduce the risk of removal by

Characteristic	Minimally Acceptable Target	Optimal Target	Notes
Delivery: Indication of appropriate application	The design shall include at least one functional, auditory, or visual cue during or after application as a correlate of successful vaccine-delivery.	Same as minimum.	The specific delivery indicator for successful use depends on the tolerance of the system for over- or under-application pressure and the subsequent effect on immunogenicity and adverse events. Some delivery systems might include a visual (such as patch color change, dye transfer or intrinsic change in skin color) or auditory or pressure cue (such as a click) for delivery confirmation. Effectiveness of visual cues maybe dependent on skin tone and there may be end user acceptability concerns with this method that would need to be assessed.
Delivery: Application Site	Site of application shall not impede efficacy of vaccination	Same.	Whether the MR MAP would be dislodged during application by the vaccinee (or carer) is also unknown and resistance to this should be designed into the device. Ideally, the patch and applicator should be of minimal visual interest, particularly for pediatric vaccines. For MR MAPs that require extended wear, device systems that allow un-monitored wear with safe disposal outside the immunisation setting are likely to be more favourable. All patches are anticipated to be applied to a location on infants and toddlers that is less likely to be disturbed and/or removed (such as the scapular region), and the upper arm in older children[26]. Some MAPs in development are being tested on other anatomical sites such as the wrist, forearm, shoulder and thigh.
Reactogencity	Reactogenicity and pain perception shall be similar to that associated with SC MR vaccination.	Reactogenicity and pain perception should be less than that associated with SC MR vaccination.	Erythema is expected to occur post vaccination and be highly visible, but resolves with days to week.

Characteristic	Minimally Acceptable Target	Optimal Target	Notes
Cost of Goods Sold (COGS)	Incremental increase (TBD) to COGS shall be acceptable if MAPs offer other programmatic benefits that translate into reduced total systems cost.	Product COGS should be comparable with the COGS of current MR vaccine needle and syringe.	Higher COGS maybe tolerable if other, additional features that improve total systems costs, such as applicability to CTC or administration by minimally trained volunteers can be demonstrated.
Total cost per dose delivered	Total cost shall be comparable to SC injection-delivery methods. The price per dose is not expected to be greater than "to be determined (TBD)".	Total cost should be lower than standard SC injection delivery methods. The price per dose could be less than "TBD".	Total cost—a combination of cost of good (COGs), distribution, administration, wastage, and disposal costs)—is a key attribute to the suitability of MR MAPs for LMIC settings. Thus, even if the COGs for patches is greater than for other delivery methods, the programmatic advantages of MAPs might still lead to a lower total health costs. For example, the costs associated with administering typical injections (requiring trained HCWs) may prove to be higher than those for a non-needle and syringe method. This can be seen in the comparison of related OPV and IPV campaigns.[27] Additionally, if MR MAPs are able to attain CTC approval they may be able to realize similar distribution cost savings as demonstrated in recent MenAfriVac CTC campaigns.[28] Note: Current MR vaccine and syringe price per dose (from 10-dose vial with RUP syringe for reconstitution and AD syringe for delivery) is about $0.64 per dose.[29] Wastage rates for this presentation are estimated to be ~50% in routine immunisation and <10% in SIAs.[30]

Characteristic	Minimally Acceptable Target	Optimal Target	Notes
Disposal	Product shall allow for safe clinical disposal as biohazard waste, at healthcare facility, with less sharps waste volume compared with needle and syringe delivery and reconstitution.	Product should not be sharps waste and thus acceptable to dispose of just as biohazard waste. It should also have lower clinical waste volumes compared with needle and syringe delivery and reconstitution.	After application the MR MAP will need to be disposed of, either at the immunisation setting itself or perhaps after extended wear in a community setting. After administration, dissolvable patches loose the distinct micro-projection structures, thereby preventing reuse and eliminating the need for sharps disposal. For coated patches, the micro-projections would still be present after delivery and as such may still be considered sharps waste, however, the degree of risk to the vaccinator and community is likely to be much less than for traditional needle and syringe application (and previous reconstitution). In the case of a dissolvable patch, a MR MAP would carry live attenuated virus and have been in contact with human skin—it is likely that the device, after application, would be considered biohazard waste and need to be disposed of within the clinical waste system, even if not considered a sharps waste. Per the VPPAG's gPPP, materials used in delivery devices, primary containers, and secondary and tertiary packaging should be chosen to minimize the environmental impact of waste disposal for resource-limited systems.

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