Rabies vaccine microarray patch: Target product profile

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This version of the TPP serves as the first draft broadly distributed for public consultation. Please send any feedback or comments on the document to maps@path.org. The TPP will serve as a living document that will evolve over time as new data are generated.

Abbreviations

CCEEV	cell culture or embryonated egg–based vaccine
EPI	Expanded Programme on Immunization
ID	intradermal
IM	intramuscular
LMIC	low- and middle-income country
MAP	microarray patch
PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
RIG	rabies immunoglobulin
TPP	target product profile
WHO	World Health Organization

Background

Objective

The objective of this target product profile (TPP) is to describe key attributes—minimally acceptable and optimal targets—for microarray patch (MAP) delivery of rabies vaccines. MAPs, also known as microneedle patches, consist of hundreds of microscopic projections that deliver dry vaccine or drug into the skin. They are applied to the body and projections penetrate the top layer of the skin. Some platforms require an applicator for delivery (integrated or separate). Administration may be perceived as less painful than an injection since microprojections are shorter than a needle and often do not reach dermal pain receptors. Wear times range from a few seconds to hours to release their payload, depending on their design.

Product development of a dissolving rabies MAP is currently in early-stage preclinical development. This TPP includes considerations for dissolving and solid-coated MAP subtypes. The document is intended to guide and inform those efforts for both pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) regimens with a focus on use cases in low-resource settings.

Critical parameters for the success of using a MAP to deliver rabies vaccine include efficacy, the intended use case, dosage, and schedule. This TPP outlines the expectations of PATH's Center of Excellence for Microarray Patch Technology for a product that would be clinically and programmatically suitable for use in low- and middle-income countries (LMICs). Additional context related to India is also provided since rabies is a key public health issue in India and several vaccine manufacturers and MAP developers are based there. The TPP will serve as a living document that will benefit from stakeholder input and evolve over time as new data are generated.

Rabies overview

The World Health Organization (WHO) estimates that rabies causes 59,000 deaths annually, of which 95% occur in Africa and Asia.[1] Although prompt PEP is highly effective at preventing rabies disease after rabies virus exposure, access to PEP is limited in many countries; access is also more limited at district-level health facilities compared to national-level hospitals.[2] Moreover, many rabies exposures occur in rural areas without access to any medical services. Since PrEP is expensive compared to other interventions to prevent human rabies (i.e., vaccination of dogs), it is currently only recommended for populations at high risk of exposure, such as veterinarians and laboratory workers.[3] Therefore, most individuals in low-resource settings at high risk of exposure do not have access to PrEP; they rely on PEP after suspected rabies exposure (i.e., animal bite).

Every year, more than 15 million people, mostly children, receive PEP due to dog bites, but many do not complete the full vaccination series since at least three clinic visits are required and some regimens require multiple injections per visit.[1] Cost is considered a key barrier to rabies control, with an estimated global economic rabies burden of US$8.6 billion per year.[4] A disproportionate amount of this burden falls on the world's poorest and most disadvantaged communities.[4]

Current presentation

Modern rabies vaccines are made from inactivated virus purified from cell culture or embryonated eggs (CCEEVs). Nerve tissue–based rabies vaccines can cause severe adverse reactions and are no longer recommended by WHO.[3] Therefore, nerve tissue–based rabies vaccines will not be covered in this TPP.

Rabies vaccines are currently available in a lyophilized presentation that requires reconstitution with diluent at the time of use. Vaccines are delivered with a needle and syringe by intramuscular (IM) or intradermal (ID) injection. Although autodisable syringes are commonly required in EPI immunization settings, syringes used for rabies vaccines are often procured separately. ID rabies vaccine injections are often delivered with insulin syringes, which do not have an autodisable feature. One ID dose is 0.1 mL of vaccine (two ID doses are typically given at different body sites on each day of the regimen); one IM dose is 0.5 mL or 1.0 mL, depending on the product.

There are over 15 vaccine manufacturers of rabies vaccines. Four products are WHO prequalified: VERORAB® (Sanofi Pasteur SA), Rabipur® (Chiron Behring Vaccines Pvt. Ltd.), VaxiRab N (Cadila Healthcare Ltd.), and RABIVAX-S (Serum Institute of India Pvt. Ltd.). However, Rabipur is no longer being manufactured in India. RABIVAX-S is the only rabies vaccine available through UNICEF in 2020.

Many other vaccines are licensed domestically, such as Indian Immunologicals Ltd.'s Abhayrab®, or targeted at high-income country markets. Rabies vaccine products contain a single IM dose, 0.5 mL or 1.0 mL, and range from separate vaccine and diluent components to co-packaged products where the vaccine and diluent are stored in a kit with a delivery device.

Scenarios for use

PrEP: Prophylactic vaccination to protect individuals at high risk of rabies exposure, such as laboratory staff handling the virus, animal health care workers, or travelers who may be at risk of exposure.

Most vaccine manufacturers currently recommend a one-site, three-dose regimen (days 0, 7, and 21 or 28) delivered by IM route for PrEP. Regimens commonly recommended by vaccine manufacturers and WHO are summarized in Table 1.

Table 1. Recommended regimens for pre-exposure prophylaxis.

Route	Site	Clinic visits (days)	Notes
IM	1 site	3 (0, 7, 21 or 28)	Recommended by most vaccine manufacturers
ID	1 site	3 (0, 7, 21 or 28)	Recommended by some manufacturers
IM	1 site	2 (0, 7)	Recommended by WHO
ID	2 sites	2 (0, 7)	Recommended by WHO

Abbreviations: ID, intradermal; IM, intramuscular; WHO, World Health Organization.

PEP: Vaccination after potential exposure to rabies virus (e.g., animal bite) accompanied by wound washing at the rabies virus–exposure site and rabies immunoglobulin (RIG) administration, if indicated.

For PEP, most vaccine manufacturers currently recommend a one-site IM, five-dose regimen (days 0, 3, 7, 14, and 28) or four-dose Zagreb regimen (two-site IM on day 0 and one-site IM on days 7 and 21). Some manufacturers additionally include the two-site ID Thai Red Cross regimen, with four clinic visits on days 0, 3, 7, and 28.[3]

WHO-recommended PEP vaccine schedules are based on the following categories of exposure:

- **Category I:** Touching or feeding animals, animal licks on intact skin; no PEP is required.
- **Category II:** Nibbling of uncovered skin, minor scratches or abrasions without bleeding; immediate vaccination is recommended; RIG is not indicated.
- **Category III:** Single or multiple transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from animal licks, exposures due to direct contact with bats; immediate vaccination is recommended, and RIG administration is recommended.

On-label, manufacturers generally recommend a five- or four-dose PEP schedule. WHO also recommends alternative schedules that reduce the duration of the vaccine regimen and the number of doses administered while maintaining immunogenicity and clinical effectiveness (see Table 2). These schedule reductions were endorsed by WHO's Strategic Advisory Group of Experts (SAGE) on Immunization in 2018 and summarized in the updated WHO position paper on rabies vaccines.[3] A reduced PEP schedule also has the potential to increase programmatic suitability by reducing costs, the number of vaccine doses delivered, and the time required to complete the PEP regimen.

The vaccine schedule used in practice may depend on the delivery setting and patients' preferences. WHO encourages all rabies vaccine manufacturers to submit a license variation application to national regulatory authorities for inclusion of ID administration and WHO-recommended schedules as approved uses on the label.[3] However, manufacturers expect that regulators would require them to generate data with the new schedule to approve the reduced schedules, which is a barrier to changing the on-label indications.

Recommended PEP schedules by category of exposure in immunologically naïve individuals[a] are summarized in Table 2.

Table 2. Recommended regimens for post-exposure prophylaxis.

Route	Site	Clinic visits (days)	Notes
IM	1 site	5 (0, 3, 7, 14, 28)	Recommended by most manufacturers; RIG, if indicated
IM	2 sites (day 0); 1 site (days 7 and 21)	3 (0, 7, 21)	Recommended by most manufacturers; recommended by WHO; RIG, if indicated
ID	2 sites	4 (0, 3, 7, 28)	Recommended by some manufacturers; RIG, if indicated
IM	1 site	4 (0, 3, 7, 14–28)	Recommended by WHO; RIG, if indicated
ID	2 sites	3 (0, 3, 7)	Recommended by WHO; recommended in Gavi rabies investment case; RIG, if indicated

Abbreviations: ID, intradermal; IM, intramuscular; RIG, rabies immunoglobulin; WHO, World Health Organization.

a. Alternative schedules are recommended for previously immunized individuals. Schedules for immunologically naïve individuals are included in the table for simplicity. For further information on rabies schedules, see World Health Organization position on rabies vaccine.[3]

Delivery settings

Currently, rabies vaccines for PrEP and PEP are provided in two general types of settings*:*

- *Health facility providing immunization services:* Vaccination at a health facility where vaccinations are provided along with other health services. These facilities are available at different levels in the health care delivery system, ranging from national-level hospitals to district-level health centers.
- *Rabies clinic/center:* Specialized health facility where health care providers are trained to evaluate and manage potential rabies cases.

Due to the increased ease of use of the MAP presentation, community-based immunization is being considered in this TPP as an alternative delivery scenario to increase access to rabies vaccines, especially in remote areas, where rabies vaccine is typically not stocked. However, the feasibility and logistics of this scenario require further investigation. A key implementation requirement of this delivery scenario will be proper wound management and identification of when vaccines are required and when not:

- *Community-based immunization:* Delivery at the community level could be carried out by a lesser-trained health care worker, trained volunteer, or caregiver, or through self-administration. If PEP is indicated and initiated at the community level, MAP administration should be accompanied by extensive wound washing and an assessment of whether a visit to a health facility for RIG is indicated. Alternatively, after seeking treatment at a clinic or health facility, the vaccine regimen could be completed at home or through community-level care with a MAP product to reduce the number of clinic visits required to complete the rabies vaccine regimen.

Delivery of a rabies MAP at the community level is considered a priority for PEP since PEP should be initiated as soon as possible after potential rabies exposure. There is expected to be a limited scope for PrEP delivery at the community level, and it will likely continue at health facilities since the visits can be planned and prepared for to minimize disruption and cost and to save time. For PrEP, there is also greater flexibility in the timing of completing the vaccine regimen.

Rabies immunization programs in low- and middle-income countries

Interviews with country stakeholders conducted as part of Gavi's Vaccine Investment Strategy emphasized that most countries have weak, fragmented rabies immunization programs.[5] Moreover, rabies programs in LMICs require coordination between the immunization program, primary health care, and animal health, which increases complexity compared to vaccines delivered through routine immunization programs. Not all health facilities stock rabies vaccines, and availability may be more limited in the public sector as well as lower-level health facilities. The high cost of the vaccine to governments and subsequently patients is considered a key barrier to access. The high cost of the vaccine to patients is also associated with a lack of funding for rabies prevention and control at the government level. As a result, patients often must seek vaccination in the private sector and self-purchase the vaccine. In addition, rabies vaccine is sometimes distributed and stored separately (at both central and health facility levels) from routine childhood vaccines, which further complicates delivery.[2]

As part of Gavi's Vaccine Investment Strategy for the 2021–2025 strategic period (VIS 2018), it was recommended that Gavi provide support for human rabies vaccine for PEP using the two-site ID regimen on days 0, 3, and 7. In November 2018, the Gavi Board approved support for PEP, beginning in 2021.[6] Since Gavi investment in PEP will likely shift the landscape of rabies immunization programs in LMICs, some of the current barriers to rabies vaccine uptake related to financing and demand forecasting challenges may be addressed by the time a rabies MAP could come to market in the next decade. More countries utilizing PEP could increase the potential market size for a rabies MAP. A MAP presentation could also eliminate the need for skilled health workers and comprehensive training for ID injection technique. Through the Vaccine Investment Strategy Phase III country survey, 41% of countries interviewed reported that they thought it would be challenging to implement the WHO-recommended two-site ID PEP regimen that Gavi plans to support compared to the five-dose IM regimen due to costs of retraining.[5]

Rabies MAP value proposition

The research priorities for rabies vaccines outlined in the 2018 WHO position paper on rabies vaccines include identifying options that can simplify vaccine delivery at the community level, including improved thermostability, prolonged shelf life, and reduced packaging volume. A rabies MAP has the potential to address these challenges.[3] Moreover, development of a rabies MAP aligns with aims of the Global Strategic Plan to End Human Deaths from Dog-Mediated Rabies by 2030 (Zero by 30).[4] Due to increased ease of use, a rabies MAP could also enable delivery by a lesser-trained health care worker, trained volunteer, or caregiver, or through self-administration.

Although the price per dose of a MAP presentation may be more expensive than the current lyophilized vaccine, a rabies MAP could reduce the required number of clinic visits, which could increase the portion of patients that complete PEP regimens and subsequently reduce the global burden of rabies. Moreover, facilitating community-based immunization could reduce the indirect costs associated with traveling to a health facility for multiple clinic visits and lost wages, especially for patients traveling long distances to access care. A rabies MAP could also improve safety since it eliminates reconstitution and reduces the risk of needlestick injuries.

Since MAPs deliver vaccine to the skin, which is rich in antigen-presenting cells, they also have the potential to enable dose-sparing, which could reduce the amount of vaccine antigen required compared to IM delivery and could therefore contribute to cost savings. Dose-sparing ID delivery with needle and syringe has been demonstrated and used programmatically for pre- and post-exposure vaccination. Compared to an ID injection, a MAP could simplify administration and ensure completion of the PEP regimen. As a single-dose presentation, a MAP could also reduce open-vial wastage which could reduce the total cost of delivery for a rabies vaccine regimen compared to ID delivery of the lyophilized vaccine.

Target product profile

The following section describes minimally acceptable and optimal targets for a rabies MAP (dissolving and solid-coated). The baseline presentation for comparison (as defined in many of the minimally acceptable targets) is the current lyophilized rabies vaccine. The TPP describes a rabies MAP product that would be clinically and programmatically suitable for use in LMICs and is informed by the current development status and understanding of this early-stage technology. Unless otherwise specified, the targets apply to both PrEP and PEP.

1. Indication

Attribute	Minimally acceptable target	Optimal target	Rationale/notes

1.1 Indication	PEP only.	PrEP and PEP.	• WHO recommends two main immunization strategies for the prevention of human rabies:
			  ○ PrEP, which is the administration of a series of rabies vaccine doses before exposure to rabies virus.
			  ○ PEP, which includes extensive and thorough wound washing at the rabies virus–exposure site, together with RIG administration if indicated, and the administration of a series of rabies vaccine doses.
			• PEP is considered the primary indication for a rabies MAP since that is where there is the greatest unmet need in LMICs and there is an established correlate of protection for rabies.
			• However, since rabies is a fatal disease, some stakeholders have suggested that it may be more suitable to first introduce a rabies MAP for PrEP to generate sufficient post-licensure data to demonstrate that the rabies MAP is safe and immunogenic. Afterwards, the indication could be expanded to PEP.

1.2 Target population	*PrEP:* At-risk individuals, irrespective of age, including rabies research or production laboratory workers, rabies diagnostic laboratory workers, veterinarians, animal handlers, and travelers visiting enzootic areas.	*PrEP:* Same as minimally acceptable target and expanded to include subpopulations in highly endemic settings with limited access to timely and adequate PEP, especially children.	• Individuals of all ages are susceptible to rabies exposure. However, children are most likely to be exposed. Most cases occur in Africa and Asia, with approximately 40% of cases in children aged less than 15 years.[1] • Expanding PrEP to children in remote areas could significantly reduce the rabies disease burden. • In the vast majority of cases (up to 99%), bites from domestic dogs are responsible for rabies virus transmission to humans. However, rabies is also transmitted from other animals, including bats.[1] • In the Americas, bats are a major source of human rabies deaths. Bat rabies is also an emerging public health threat in Australia and Western Europe.[1]

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
	PEP: Suspected or confirmed exposure to rabies based on WHO categories of exposure, irrespective of age.	*PEP:* Same as minimally acceptable target.	• Human deaths following exposure to foxes, raccoons, skunks, jackals, mongooses, and other wild carnivore host species are very rare, and bites from rodents are not known to transmit rabies.[1] • In Mongolia, wolves are considered another major source of human rabies.[7]

1.3 Intended use case	Facility-based immunization by a trained health care provider.	Facility- or community-based immunization. The MAP could be delivered by a trained HCW, community health worker, trained volunteer, or caregiver, or through self-administration.	• Use of a rabies MAP should integrate into the service delivery structure established for rabies treatment/prevention, which may vary by country.
			• The WHO position paper[3] on rabies vaccination suggests that MAPs may be able to ease delivery at the community level (i.e., home delivery, health post, community gathering place). MAPs are potentially well suited for alternative delivery scenarios due to improved ease of use, including rural/remote areas where trained HCWs may not be available. Increasing access is particularly important for a rabies vaccine since PEP should be initiated as soon as possible after exposure.
			• MAPs could enable the following community-based delivery scenarios. However, there is disagreement among key stakeholders, including public health professionals and clinicians, about whether this would be acceptable from an ethical and regulatory standpoint:
			  ○ The PEP regimen could be initiated in the community setting through delivery by a community health worker, trained volunteer, or caregiver, or through self-administration prior to seeking medical care. The vaccine regimen could also be completed at home or through community-level care with a MAP presentation if initiated at a health facility to reduce the number of clinic visits required to complete the rabies vaccine regimen. A single dose of RIG, if indicated, should be administered by a trained HCW as soon as possible after exposure.
			  ○ Although PrEP could also be delivered at the community level, community-based PEP delivery is considered the priority among global health stakeholders.
			• Whether delivery of a rabies MAP at the community level reduces the likelihood of patients receiving RIG requires further evaluation and risk assessment.
			• However, there are often shortages of RIG in endemic countries due to insufficient demand and supply forecasting. It is estimated that less than 2% of category III exposed patients receive RIG globally.[3] In an evaluation of PEP and RIG distribution and access in Africa and Asia, only 35% of countries (8/23) reported that RIG was consistently available. Approximately half of the countries interviewed (12/23) reported having RIG on a limited

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
			basis with frequent stockouts, primarily due to its high cost and limited global availability.[2] • During stakeholder interviews in India, several respondents commented that RIG is not widely available at health facilities, which was reported as a barrier to effective rabies treatment that a rabies MAP could not address.
1.4 Target countries	Countries with a large rabies burden and potential market size such as India.	Availability and use of rabies MAP in all countries.	• WHO and its partners have endorsed a target of zero human rabies deaths from dog-transmitted rabies by 2030 (Zero by 30).[4] • This is aligned with Goal 3 of the Sustainable Development Goals—to end epidemics of communicable diseases including neglected tropical diseases by 2030.[8] • One of the outcomes of Zero by 30 that a rabies MAP could address is that "human deaths from rabies exposures are prevented by ensuring equitable, affordable and timely access to health care, medicines and vaccines."[4] • Another goal is to "integrate last mile strategies to increase access of poor and rural populations to PEP into the global movement towards achieving universal health coverage, and support countries to evaluate and amend current practices for PEP procurement to ensure availability and access for all."[4] • Development of a rabies MAP also aligns with priorities of WHO's Immunization Agenda 2030 (IA2030), such as reducing inequity, providing vaccines throughout the life-course, and accelerating innovation.[9] • Rabies cannot be eradicated since there are natural reservoirs of rabies virus in the environment, so control efforts must be continued even if the rabies disease burden is reduced. • Since rabies is a major public health problem in India, accounting for 36% of the world's rabies deaths, India will be an important target country for a rabies MAP.[10] Many rabies vaccine manufacturers are also based in India.
1.5 Product registration path	Approval by any functional NRA, as defined by WHO, followed by WHO prequalification.	Same as minimally acceptable target.	• A rabies MAP would be regulated and approved as a novel device/biologic combination. PATH recommends engaging regulatory authorities early to discuss the potential regulatory pathway, thereby streamlining the approval process of a novel combination product. • In India, where several rabies vaccine manufacturers serving LMIC markets are located, the DCGI within the Central Drugs Standard Control Organisation regulates pharmaceutical and medical devices under the purview of the Ministry of Health and Family Welfare. DCGI would be the regulatory authority for a future rabies MAP product. As a combination product, the Ministry of Science and Technology's Department of Biotechnology may also have a role in determining the appropriate regulatory pathway.

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
			• The EMA's Article 58[11] is another potential regulatory pathway for products used outside of the EU; it promotes the development of drugs and vaccines for LMICs. This regulatory pathway includes assessment by the EMA's Committee for Medicinal Products for Human Use in collaboration with WHO, experts, and national regulators, which could facilitate and potentially accelerate the WHO prequalification process. • WHO prequalification would be needed for UNICEF procurement of rabies MAPs after the product is approved by a functional NRA. This process involves review of general product process and quality control procedures, testing of consistency lots, and WHO site audit to manufacturing facilities with observers from the responsible NRA.[12] • The MAP product should be programmatically suitable for low-resource settings, which is part of the WHO prequalification process to ensure the "suitability of the vaccine for the immunization services where it is intended to be used."[13] • Experience with similar technologies—such as transdermal patches, ID injection devices, or MAPs for other vaccine and drug applications—may be useful for drafting initial regulatory strategies, such as the NDA Zosano Pharma submitted to the FDA in December 2019 for migraine treatment delivered by MAP (Qtrypta™).[14]
Abbreviations: DCGI, Drug Controller General of India; EMA, European Medicines Agency; EU, European Union; FDA, US Food and Drug Administration; HCW, health care worker; ID, intradermal; LMIC, low- and middle-income country, MAP, microarray patch; NDA, New Drug Application; NRA, national regulatory authority; PEP, post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; RIG, rabies immunoglobulin; UNICEF, United Nations Children's Fund; WHO, World Health Organization.			

2. Dosage and administration

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
2.1 Formulation	Formulation containing inactivated rabies virus antigen as the active ingredient. Necessary excipients and/or additives (e.g., stabilizers, polymer, other inactive ingredients) may be	Same as minimally acceptable target.	• Currently, the lyophilized vaccine formulation contains inactivated rabies virus that is purified from cell culture or embryonated eggs as the active ingredient. • The rabies MAP formulation should be optimized to improve thermostability and light sensitivity compared to the current lyophilized presentation. ○ The WHO position paper[3] on rabies vaccination recommends protecting the current lyophilized vaccine from sunlight, and some package inserts recommend storing the vaccine in its "original outer package protected from light." • The necessary excipients/additives will depend on the MAP format (solid-coated or dissolving), particularly to improve stability and release.

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
	added that are currently used clinically and generally regarded as safe (GRAS) by the FDA.		• Concentration of the antigen will be important for both dissolving and solid-coated microprojections. MAP delivery will require a higher antigen concentration than the current formulation.
2.2 Dose presentation	A single-dose, single-use presentation, composed of an integrated rabies vaccine delivery device in which rabies vaccine is presented as a solid-coated or dissolving microarray format.	Same as minimally acceptable target.	• As a combination product, MAPs would integrate both the vaccine antigen and delivery device; this would be incorporated into solid-coated or dissolving microarray projections. • The size of the rabies MAP should be driven by the minimal surface required to achieve the optimal antigen dose.

2.3 Vaccine schedule (duration, clinic visits)	*PrEP:*
	The rabies MAP follows an abbreviated vaccine schedule currently recommended for ID injection, with no more than two clinic visits (days 0, 7) for naïve individuals.
	
	PEP:
	The rabies MAP follows an abbreviated vaccine schedule currently recommended for ID injection, with no more than three clinic visits (days 0, 3, 7) for naïve individuals.
		The rabies MAP requires fewer doses for PrEP and PEP or a single application to fully immunize the patient.
		
		Rabies MAP may be used interchangeably with currently available rabies vaccines administered by IM or ID route.
			• The recommended MAP vaccine schedule will depend on the schedule that generates a comparable immune response to an ID injection.
			• The following schedules are suggested as guidelines based on current WHO recommendations for ID delivery. See Tables 1 and 2 in the Background Section for more details on currently recommended vaccine schedules.
			• ID regimens currently recommended by WHO that may be suitable for MAP delivery:
			  ○ PrEP: one clinic visits (days 0, 7).
			  ○ PEP: three clinic visits (days 0, 3, 7).
			• Although not currently considered a complete course, a one-visit PrEP (2 x 0.1 mL ID) regimen is also being considered and may be suitable for a MAP. Studies from Thailand, Netherlands, and Belgium demonstrated that a single-visit vaccine administration followed by simulated PEP resulted in antibody titers > 0.5 IU/mL in 99.5%–100.0% of subjects.[15,16,17]
			• A vaccine schedule with fewer clinic visits and a shorter duration would improve patient compliance and reduce the burden of returning to a health facility if facility-based vaccination is required.
			• There is an opportunity that application of a single rabies MAP could deliver the complete vaccine regimen through controlled release technology. Some MAP technologies can slowly release vaccine for prolonged antigen presentation, which can simulate prime and boost vaccine doses in a single administration.
			• The IM and ID routes can be used interchangeably to complete a course of PEP or PrEP for current lyophilized vaccine products.[18,19]

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
	Rabies MAP may be used interchangeably with currently available rabies vaccines administered by IM or ID route.		
2.4 Application sites per clinic visit	Rabies MAP is delivered at two application sites, similar to the recommended ID injection regimens.	Rabies MAP is delivered at a single application site.	• Currently, when delivered by ID route, rabies vaccines typically follow a two-site ID regimen. • Similar to an ID injection, a rabies MAP may require two-site application to generate a robust immune response through targeting two different lymphatic drainage sites, which would need to be assessed in clinical studies. • Some vaccine manufacturers recommend a one-site ID regimen for PrEP. • The number of application sites required will have a significant impact on the cost of the MAP vaccine regimen.
2.5 Dosage	The antigen content of a full vaccination course with the rabies MAP should be the same as the quantity of antigen contained in a full ID vaccination course.	The antigen content of a full vaccination course with the rabies MAP should be reduced compared to the quantity of antigen contained in a full ID vaccination course.	• Although the rabies MAP will likely require the same antigen content as an ID injection, the optimal target dosage for the rabies MAP should be the minimum required to give a non-inferior immune response to the currently available injectable vaccine delivered by IM or ID injection, as the antigen content will have a significant impact on MAP cost and production capacity. • Current rabies vaccines have a recommended potency of at least 2.5 IU per dose for IM injection (0.5 mL or 1.0 mL volume after reconstitution, depending on the type of vaccine).[2] For the ID route, one dose is 0.1 mL of CCEEV (irrespective of the vaccine brand). • A systematic review of vaccine potency has shown that current vaccines (> 2.5 IU/IM dose), when administered by the ID route for either PEP or PrEP, have efficacy equivalent to or higher than that of the same vaccine administered by the IM route.[20] • For MAP delivery, there is the potential that a reduced dose of antigen may be required due to the immune-enhancing benefits of MAP delivery, which could enable further dose reduction compared to an ID injection. It should be noted, however, that to date, there are no data from studies in preclinical or clinical studies to suggest that MAP delivery of rabies vaccine enables a reduced antigen content compared to ID injection.
2.6 Route of administration	Product should be suitable for delivery to dermis at an anatomic site that is acceptable to users and	Same as minimally acceptable target.	• Some MAP designs might deliver primarily by ID route, but others might deliver to both the epidermis and dermis. There are insufficient data to specify the optimal depth or target tissue within the skin. • For rabies vaccination, topical delivery following skin abrasion has been found to be less effective than ID delivery. ID delivery of a reduced dose (2 x 0.1 mL per dose) is comparable to an IM injection.[21]

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
	immunization programs.		
2.7 Application site	Application site should be accessible and acceptable to the majority of intended recipients.	Application site should be the same as those currently recommended for rabies vaccines.	• The deltoid region is typically the preferred application site for ID delivery of rabies vaccine and would likely be suitable for delivery of a rabies MAP. • Other sites recommended by vaccine manufacturers and WHO for the injectable vaccine include the anterolateral thigh or suprascapular regions. • MAPs in development are being tested on various anatomical sites, such as the deltoid, wrist, forearm, shoulder, and thigh. • Multiple application sites may be evaluated in clinical studies to ensure that different anatomical sites do not have an impact on vaccine efficacy. • Premature removal of the MAP has been suggested as a potential concern, especially for infants and toddlers. Therefore, an option to use an application site such as the scapular region, where a MAP is less likely to be disturbed and/or removed, may be preferable for those age groups, assuming the site has comparable immunogenicity.
Abbreviations: CCEEV, cell culture or embryonated egg–based vaccine; FDA, US Food and Drug Administration; ID, intradermal; IM, intramuscular; MAP, microarray patch; PEP, post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; WHO, World Health Organization.			

3. Safety and efficacy

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
3.1 Systemic reactions	Systemic adverse events should be no more serious or frequent than those for current injectable vaccines.	Systemic adverse events should be less frequent and less serious than those for current injectable vaccines.	• CCEEVs have been shown to be safe and cause mild systemic reactions. • The safety of rabies MAPs would need to be established in pre-licensure safety studies in the target population for whom this product is indicated. With the current rabies vaccine, adverse reactions following vaccination are generally mild and transient. • Mild systemic adverse events following immunization—such as transient fever, headache, dizziness, and gastrointestinal symptoms—have been observed in 5%–15% of vaccinees. Serious adverse events following immunization seldom occur, and no causality has been established in cases of neurological symptoms.[22] • No serious adverse events considered related to the treatment have been recorded with any vaccine MAP delivery to date, but few vaccine MAP clinical studies have been conducted. Risks related to reconstitution with wrong, or incorrect use of, diluents will be eliminated, and risks related to other types of operational errors should be reduced. Recent clinical

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
			reactogenicity data with seasonal influenza MAPs are summarized below in the 'Local reactions' attribute.

3.2 Local reactions	The severity and/or frequency of local reactogenicity at the application site may increase with MAP delivery due to the route of administration compared to IM/ID rabies vaccination.	Local reactogenicity is similar to ID injection.	• For injectable rabies vaccines, in 35%–45% of vaccinees, minor and transient erythema, pain, and/or swelling may occur at the site of injection, particularly following ID administration in the case of repeat vaccination.[22]
			• Delivery of rabies vaccine via MAPs to the dermal layer of the skin has the potential to increase reactogenicity compared to an injection.
			• Minor local reactions lasting several days to weeks have been observed after MAP application in clinical studies with seasonal influenza vaccine. However, these were generally found to be acceptable.
			  ○ In a recent phase 1 study for a dissolving seasonal influenza MAP, application resulted in a mild and transient reactogenicity, mostly reported as tenderness (66% of recipients), erythema (40% of recipients), and pruritus (82% of recipients), lasting on average between 2 and 3 days. Of MAP recipients, 20% reported pain after vaccination compared to 44% of IM injection recipients.[23]
			  ○ In a recent phase 1 study of a solid-coated seasonal influenza MAP, the skin response following vaccination peaked at 3 days and faded between days 7 and 28. All application site reactions were mild or moderate, with the exception of a single subject with "severe" coloration at 10 minutes after application. Erythema and edema were reported.[24]
			• Similar local reactions (i.e., visible erythema) are expected to occur post vaccination with a rabies MAP and may take weeks to fully resolve. However, since reactogenicity is likely to be antigen-dependent, local reactions observed for a rabies MAP may differ from those observed following vaccination with a seasonal influenza MAP.
			• The frequency and severity of such reactions should be assessed in pre-licensure clinical safety trials and prior to introduction to assess vaccine acceptability, taking into consideration other benefits of the rabies MAP vaccine compared to the injectable presentation.
			• A visible local reaction, if highly reliable, may be a desirable feature as an indicator of successful vaccination.

3.3 Immunogenicity	Neutralizing antibody levels should be non-inferior to a currently licensed IM/ID rabies vaccine, indicated by a GMC ratio >0.5 on day 14 of the regimen.	*PrEP:* Same as minimally acceptable target. *PEP:* Same as minimally acceptable target and antibody responses	• Modern CCEEVs are among the most immunogenic vaccines and are highly effective in preventing rabies.[25] Direct assessment of CCEEV-induced antibody levels is a surrogate for the effectiveness of PEP. Animal models have been used to demonstrate the efficacy of CCEEVs after experimental infection.[26] • All CCEEVs induce a prompt and robust vaccine-induced neutralizing antibody response to the G protein of the rabies virus. The WHO-specified minimum serum antibody concentration of 0.5 IU/mL is widely used as a

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
		are induced more rapidly.	measure of adequate seroconversion after vaccination.[25] In most individuals, irrespective of age or nutritional status, this level is reached by day 7–14 of a PEP regimen, with or without simultaneous administration of RIG. • Previous lyophilized rabies vaccine non-inferiority studies have used the day 14 GMC ratio measured by RFFIT as the primary endpoint to demonstrate non-inferiority. This endpoint was also recently used to license SIIPL's RABIVAX-S vaccine. In the clinical study, a simulated PEP regimen was administered to non-exposed study participants.[27] It is expected that a similar study design could be suitable for a rabies MAP. • It would be advantageous if the MAP induced a protective immune response more rapidly, since the timeliness of PEP impacts effectiveness.[3] • Three preclinical challenge studies have recently been conducted to evaluate a rabies MAP compared to IM and ID delivery. In all three studies, the rabies MAP was found to generate a protective immune response in mice demonstrated by neutralizing antibody titers in serum. The immune response and survival in the MAP study group were comparable to ID delivery, according to a personal communication from Nitin Saigal in April 2020.
Abbreviations: CCEEV, cell culture or embryonated egg–based vaccine; GMC, geometric mean concentration; ID, intradermal; IM, intramuscular; MAP, microarray patch; PEP, post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; RFFIT, rapid fluorescent foci inhibition test; RIG, rabies immunoglobulin; SIIPL, Serum Institute of India Pvt. Ltd.; WHO, World Health Organization.			

4. MAP application and delivery

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
4.1 Human factors and usability	A summative usability evaluation must demonstrate that safety-related use errors related to the device, applicator (if needed), labeling, and training have been identified and mitigated (or that the residual risk is acceptable).	Same as minimally acceptable target.	• For intended users and the scenarios of use for a rabies MAP (see Section 1. Indication), usability/human factors of the device must be assessed in the relevant target population (children and adults) and geography. • If self-administration is an intended use case for the MAP, a usability/human factors evaluation should be conducted with this user group. • To guide user-centered product development efforts, it is recommended that formative usability testing be conducted iteratively throughout the development process to ensure the "suitability of the vaccine for the immunization services where it is intended to be used," which is part of the WHO prequalification process.[13] • The usability engineering process in *IEC 62366-1:2015 Medical devices – Part 1: Application of usability engineering to medical devices* should be followed to verify and validate the final rabies MAP design and applicator (if required for use). This includes establishing a usability engineering file.

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
			• Human factors principles outlined in ANSI/AAMI HE75 *Human factors engineering – Design of medical devices* should be followed. • Key components of usability for a rabies MAP are described in other sections of this TPP, including labeling, packaging, user training requirements, application site, delivery time, wear time, applicator, indication of successful vaccination, and disposal.
4.2 Applicator	If an applicator is required, MAP is delivered using a simple, single-use, disposable applicator (integrated or separate) while maintaining compliance with packaging requirements. If an applicator is not required, MAP is applied similar to standard transdermal patches.	Use of an applicator is not required. Similar to standard transdermal patches, the MAP is a stand-alone patch that can be successfully administered manually.	• Some MAP platforms may require an applicator, either a separate component or integrated with the MAP, for successful delivery. • Ideally, the MAP could be successfully applied to the skin by manual pressure without the use of an applicator, since an integrated applicator could increase the packaging volume in the cold chain. However, a simple, single-use disposable applicator may be required to ensure the MAP is applied consistently and correctly (dependent on MAP design). • If self-administration is an intended use case for the MAP, the applicator should be suitable for self-administration and evaluated through usability studies with the intended user group(s). • The geometry and design of the MAP and its projections will inform the need for an applicator. • Regardless of the need for an applicator, usability studies will be required to ensure that the MAP can be successfully applied by intended users. • If an applicator is required, an integrated applicator would be preferable from a usability and logistics perspective, provided this has no unacceptable negative impact on cost or cold chain storage volume. • If an applicator is required, it should maintain compliance with packaging requirements.
4.3 Delivery time	Total time for delivery of one rabies MAP should be comparable to two ID injections with N&S, including time for reconstitution from a vial.	Total time for delivery of one rabies MAP should be less than two ID injections with N&S, including time for reconstitution.	• The MAP delivery time should be acceptable to the health care system in question (informed by usability testing). • In the public sector, the two-site ID regimen is typically used where vaccine shortages and access are of greater concern. These settings may benefit the most from saving HCW time compared to community-based delivery scenarios. • Decreasing the time required to deliver each dose could be beneficial to overall program logistics and capacity. However, delivery time will be less critical for rabies vaccines since it is not delivered in a high-throughput setting (i.e., campaign).
4.4 Wear time	Up to 5 minutes, under observation, before removal of MAP by HCW, trained lay	Less than 1 minute, under observation, before removal of MAP by HCW, trained	• Required wear times for vaccines are expected to range from seconds to minutes depending on the MAP design. The wear time is dependent on the time required to release the required antigen dose from the MAP into the skin (i.e., dissolution time).

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
	health worker, caregiver, or patient.	lay health worker, caregiver, or patient.	• Stakeholders interviewed in India commented that wearing a MAP for several minutes would be acceptable given the current delivery setting for rabies vaccine administered by N&S. Stakeholders did not express concern that the wear time would impact programmatic fit. • Wear time must be evaluated in preclinical and clinical studies to ensure successful delivery of the required antigen dose. • Acceptable wear time will be evaluated by end users in stakeholder interviews and usability studies; end-user feedback should be considered and incorporated during product development to help ensure future product uptake. Based on initial stakeholder interviews in India, wear time was not considered to be as critical for rabies vaccine delivery compared to outbreak response settings and campaign delivery. • In general, reducing the wear time is recommended to reduce the risk of removal by infants and toddlers. • There should be minimal safety concerns associated with leaving the patch on for longer periods.
4.5 Indication of successful vaccination	The design should include at least one functional auditory, visual, or tactile cue during or after application of a single dose as an indicator of successful vaccine delivery. This cue would provide the user feedback that the patch was properly applied to the skin. The indicator should be intuitive and easily understood by intended users.	The design should include more than one functional auditory, visual, or tactile cue during or after application of a single dose as an indicator of successful MAP application.	• There is likely a need for an auditory or visual (color-based) indicator to confirm that appropriate pressure has been applied over the entire surface area during patch application to ensure that the MAP projections have been inserted into the skin correctly. • The current guidance on successful ID delivery of rabies vaccine recommends that the formation of a bleb is a confirmation of successful vaccine delivery. If a bleb is not present, revaccination is recommended. Stakeholders interviewed in India suggested that providers will expect an equivalent indicator of successful vaccination for a rabies MAP. • The success rate of delivery (penetration of the skin by a sufficient percentage of the microarray projections) by typical users in target countries should be validated under ideal and non-ideal conditions (e.g., with minimal or no prior training and instructions). • Future usability studies may be required to ensure that intended users can successfully understand and confirm indication of successful MAP application. • Effectiveness of skin-based visual cues (i.e., red projection pattern at the application site) may be dependent on skin tone/texture, and end-user acceptability of this method should be assessed. • Failure to activate the indicator will inform the user that the MAP has already been used or the application process was faulty.

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
4.6 Autodisable feature	The MAP should be designed to prevent reuse. The indicator and/or applicator, if required, should have an autodisable feature to prevent reuse.	Same as minimally acceptable target.	• For WHO prequalification, vaccine delivery devices are required to be autodisable. • The indicator or integrated applicator should have an autodisable mechanism (i.e., once used, it is automatically disabled without any additional action from the user, and cannot be intentionally or accidentally reused).
4.7 User training requirements	Minimal training required (e.g., 15 minutes). MAP can be correctly administered by a health care provider or lay health worker with printed instructions after minimal training. Printed, written instructions must be made available in at least one of the recognized languages of the destination country, pre-tested for comprehension, and revised as needed. Training materials should also include simple pictorial instructions.	No in-person device training required. Similar to currently available transdermal patches, MAP can be correctly administered by a health care provider, patient (self-administration), or caregiver after reading simple product instructions or package insert.	• Some studies have shown that people with minimal training can apply MAPs.[28,29] • Patches are designed to be easy to apply and have been shown to facilitate consistent, reproducible application by non–medically trained volunteers. • The MAP should be suitable for clinic and community settings since it is expected that MAPs will be used in remote areas with limited access to trained HCWs.
4.8 Co-administration	Co-administration with other vaccines is possible, similar to the lyophilized presentation. RIG, if indicated, can also be administered	Same as minimally acceptable target.	• The rabies MAP should be suitable for co-administration with the same vaccines as the current lyophilized presentation. • It is safe and effective to co-administer lyophilized rabies vaccines with other inactivated vaccines, such as DTP-containing vaccines, Japanese encephalitis vaccine, and IPV, and with live vaccines such as MMR vaccine.[3]

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
	at the same time as PEP initiation.		

Abbreviations: AAMI, Association for the Advancement of Medical Instrumentation; ANSI, American National Standards Institute; DTP, diphtheria-tetanus-pertussis; HCW, health care worker; ID, intradermal; IEC, International Electrotechnical Commission; IPV, inactivated polio vaccine; MAP, microarray patch; MMR, measles-mumps-rubella; N&S, needle and syringe; PEP, post-exposure prophylaxis; RIG, rabies immunoglobulin; TPP, target product profile; WHO; World Health Organization.

5. Storage, handling, and distribution

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
5.1 Primary packaging	Primary packaging (in direct contact with MAP) should protect the projections to prevent damage and/or contamination of projections during shipping and storage. Primary packaging should include a moisture-impermeable barrier.	Same as minimally acceptable target.	• Packaging components and design must follow regulatory guidance, such as FDA (or applicable NRA) guidance and ISO standards.[30,31] • A moisture-impermeable barrier, such as a foil pouch, will prevent water loss during storage. • A rabies MAP may also need to be packaged with a desiccant. • Stability studies according to regulatory guidance of the rabies MAP will be required to ensure safety and efficacy of the product throughout the duration of labeled shelf life and required storage conditions.[32] • An integrated applicator could potentially serve as the MAP's primary packaging, depending on the design. • The environmental impact of primary packaging should be minimized. • If the rabies MAP is sensitive to light, similar to the current presentation, the packaging should protect the vaccine from light. However, efforts should be made to optimize the formulation so that the rabies MAP is not light sensitive (see 'Formulation' attribute).
5.2 Secondary packaging	Secondary packaging should group MAPs (within their primary packaging) to facilitate transport and storage.	Same as minimally acceptable target.	• Secondary packaging, such as cardboard boxes, should facilitate transport, storage, and handling within the public-sector health system and distribution channels.
5.3 Storage volume	The storage volume per day should be no greater than that of one IM dose of lyophilized rabies vaccine (~17.6 cm^3) where the vaccine and diluent are stored	The storage volume per day should be less than that of two ID doses (0.1 mL per dose) of the lyophilized rabies vaccine (mean volume: 10.2 cm^3).[33]	• Storage volume (e.g., second packaging volume) should be efficient and minimized as much as possible. • Current cold chain volume estimates of MAP prototypes range from 5 cm^3 to > 25 cm^3. Designs with integrated applicators increase the cold chain footprint. • Secondary packaging that allows the vaccinator to visualize the number of remaining doses should be considered.

<table>
<tr><th>Attribute</th><th>Minimally acceptable target</th><th>Optimal target</th><th>Rationale/notes</th></tr>
<tr><td></td><td>separately (i.e., not co-packaged).[33]</td><td></td><td>

The environmental impact of secondary packaging should be minimized and include recycled and recyclable or biodegradable materials.
A future packaging assessment should be conducted to optimize packaging configuration from a technical, programmatic, and usability standpoint.

Current secondary packing volumes per one IM and two ID doses for WHO-prequalified rabies vaccines are summarized below.[34]
<table>
<tr><th>Rabies vaccine product</th><th>IM delivered dose volume (mL)</th><th>Cold chain volume per IM dose (cm^3)</th><th>Cold chain volume per two ID doses (cm^3)</th><th>Diluent dry storage volume per IM dose (cm^3)</th></tr>
<tr><td>VERORAB</td><td>1.0</td><td>50.5</td><td>10.1</td><td>0</td></tr>
<tr><td>Rabipur</td><td>0.5</td><td>48.0</td><td>19.2</td><td>0</td></tr>
<tr><td>VaxiRab N</td><td>1.0</td><td>40.5</td><td>8.1</td><td>9.15</td></tr>
<tr><td>RABIVAX-S</td><td>1.0</td><td>17.6</td><td>3.5</td><td>12.53</td></tr>
<tr><td>Average</td><td></td><td>39.2</td><td>10.2</td><td>5.42</td></tr>
</table>

Diluent and delivery syringe are stored in the cold chain for some rabies vaccine products. Reported volumes also vary by the number of doses stored in a carton.
For patches that do not require cold storage, comparator volume for total packaging comprises the vaccine vial, diluent, reconstitution syringe (43 cm^3), and delivery syringe (ID N&S 36 cm^3). Based on the VaxiRab N product, this is ~54.6 cm^3 for two-site ID delivery.

</td></tr>
<tr><td>5.4 Tertiary packaging</td><td>Product should be contained within suitable tertiary packaging that is compatible with the existing immunization supply chain.</td><td>Same as minimally acceptable target.</td><td>

Suitable tertiary packaging is defined as that which complies with the VPPAG's gPPP recommendation to "minimise volume and weight of tertiary packaging and limit the need for repackaging for in-country supply chain distribution."[35]

</td></tr>
<tr><td>5.5 Labeling</td><td>Labels should comply with regulatory guidance and include required sections and formatting.[36]</td><td>Same as minimally acceptable target.</td><td>

MAPs should be clearly labeled on both the primary and secondary packaging with simple language to explain pertinent information—such as product title, indication and usage, dosage forms and strength, and contraindications—that enables consistently successful use by the intended end user.
If more detail is required, a package insert with instructions for use may be added and a job aid developed. Simple pictorial instructions may be included.

</td></tr>
</table>

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
			• If CTC is indicated, additional labeling is required (see 'Temperature indicator' attribute below).
5.6 Temperature indicator	Rabies MAPs should include an appropriate VVM on the primary packaging. For CTC use, a separate threshold indicator should be included.	Same as minimally acceptable target or a combined indicator with an integrated threshold indicator known as a VVM-TI could be used, which is identical to a standard VVM.	• Current lyophilized rabies vaccines are labeled with "VVM30," meaning they are stable at 37°C for up to 30 days. • The creation of a new VVM type may be needed to fit the thermostability characteristics of the product if thermostability exceeds 30 days at 40°C. • A separate threshold indicator could accompany the vaccine or be placed on the primary or secondary packaging depending on the delivery strategy and microplanning.
5.7 Heat stability	Vaccine potency stability profiles should be superior to current lyophilized rabies vaccine stability and must be qualified for use in a CTC at ≥40°C for 1 week.	Stability profiles should have enhanced thermostability compared to current lyophilized rabies (i.e., use under CTC conditions for at least 2 months).[37,38]	• A rabies MAP should offer improved storage conditions over current rabies vaccine requirements. • Current lyophilized rabies vaccines have a VVM30 and a shelf life of ≥ 3 years when stored at 2°C–8°C. • Stakeholders interviewed in India recommended that, at a minimum, a MAP should be able to be stored at ambient temperatures for 4–5 days to improve delivery of rabies vaccine. • For self-administration, the vaccine would need to be qualified for use in a CTC for the duration of the regimen (i.e., up to 28 days). Research would be needed to confirm whether intended users have the ability to maintain CTC conditions at home, identify temperature excursions (i.e., using a VVM-TI), and respond appropriately by seeking replacement doses. • Based on a WHO assessment of common supply chain structures, up to 2 months under CTC conditions would remove reliance on cold chain equipment and logistics at health posts and stocking of vaccines at unequipped facilities. This target was proposed by immunization program experts, including IPAC members. This stability profile would be particularly beneficial to community-based delivery.[39]
5.8 Freeze stability	The rabies MAP should not be freeze sensitive similar to the current lyophilized vaccine.	Same as minimally acceptable target.	• Lyophilized rabies vaccines are not damaged by freezing and a rabies MAP is expected to have a similar freeze stability profile. • Formulating vaccines to prevent risk of damage from freezing can reduce vaccine ineffectiveness and wastage due to freeze exposure.
5.9 Product shelf life	Shelf life should be the same as the current presentation (i.e., 2°C–8°C for 36 months).	Shelf life should be ≥ 36 months at 2°C–8°C.	• Product shelf life (i.e., long-term storage) of the rabies MAP should be comparable or improved compared to the current lyophilized presentation. • The shelf life may depend on the duration of CTC use that would add programmatic value since by WHO's current definition of CTC, the vaccine must be sufficiently heat stable at the end of its shelf life.

<table>
<tr><th>Attribute</th><th>Minimally acceptable target</th><th>Optimal target</th><th>Rationale/notes</th></tr>
<tr><td></td><td></td><td></td><td>This means that the vaccine is tested at the threshold CTC exposure temperature at the end of its shelf life.
<table><tr><th>Rabies vaccine product</th><th>Shelf life (2°C–8°C)</th></tr><tr><td>VERORAB</td><td>36 months</td></tr><tr><td>Rabipur</td><td>48 months</td></tr><tr><td>VaxiRab N</td><td>36 months</td></tr><tr><td>RABIVAX-S</td><td>36 months</td></tr></table></td></tr>
<tr><td>5.10 Disposal</td><td>The MAP should be able to be disposed of as non-sharps biohazard waste. MAP and packaging materials should be safe to dispose of in typical health care waste management practices (i.e., burning, burial).

The MAP should have a similar disposal volume compared with the lyophilized vaccine, which requires delivery with N&S and reconstitution with N&S.</td><td>The MAP should be safe to dispose of at home and in the community.

The MAP should have a reduced disposal volume compared with the lyophilized vaccine, which requires delivery with N&S and reconstitution with N&S.</td><td>• After application, the rabies MAP will need to be disposed of, either at the immunization setting itself or in the community in the context of caregiver administration or self-administration.
• For dissolving MAPs, after removal of the patch, the MAP projections are dissolved and no longer able to penetrate skin, thereby precluding the potential for reuse or needlestick injury.
• For solid-coated MAPs, if the projections cannot penetrate the skin without an applicator, they could be considered non-sharps waste.
• MAP technology has the potential to reduce the environmental impact of providing medical services by reducing the volume of biohazardous waste to be disposed of and eliminating the need for injections that generate sharps waste that can be an infectious disease hazard to communities if disposed of improperly.
• For delivery at the community level, MAP design features should mitigate risks to community, household members, and environment associated with exposure to residual vaccine on the MAP backing or surface of the skin after MAP use.
• A MAP is likely to have a similar volume to a single-dose vial, which would be biohazard waste when empty, but would eliminate the need for disposal of N&S for delivery, reconstitution syringe, and diluent vial/ampoule.
• MAPs should be made of biodegradable materials that limit environmental impact; future assessments should review the MAP life cycle from manufacture to disposal to identify and address potential areas for reducing waste and minimizing environmental impact.</td></tr>
<tr><td colspan="4">Abbreviations: CTC, controlled temperature chain; FDA, US Food and Drug Administration; gPPP, generic preferred product profile; ID, intradermal; IM, intramuscular; IPAC, Immunization Practices Advisory Committee; ISO, International Organization for Standardization; MAP, microarray patch; N&S, needle and syringe; NRA, national regulatory authority; TI, threshold indicator; VPPAG, Vaccine Presentation and Packaging Advisory Group; VVM, vaccine vial monitor; VVM-TI, vaccine vial monitor–threshold indicator; WHO, World Health Organization.</td></tr>
</table>

6. Cost and cost-effectiveness

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
6.1 Cost and cost-effectiveness	The rabies MAP can be slightly more expensive than current rabies vaccine presentations but should be cost-effective compared to current rabies vaccine presentations.	The rabies MAP price should be less than or equal to the current ID vaccine in the applicable market segment.	• The 2020 UNICEF price for a rabies vaccine in a single-dose vial for IM delivery is US$8 per IM dose.[40] • Trade-offs between potential increases in the price per regimen of a rabies MAP versus the programmatic benefits compared to standard ID injection delivery will be considered by decision-makers and purchasers when making product decisions. Cost-effectiveness will be impacted by scenarios of use. • Future Gavi support for PEP will likely impact cost considerations for a rabies MAP product and willingness to pay among key stakeholders. • As a novel delivery device, a MAP is likely to be more expensive than the current presentation. Several MAP developers have suggested their technologies could be similar in price to a prefilled syringe (~US$1) plus the cost of antigen. The actual cost of a rabies MAP will depend on factors such as antigen content, device design, production yield, and manufacturing volume. • The manufacturing conditions (e.g., manufacturing in an aseptic versus low-bioburden environment) will also impact cost. Manufacturing under aseptic conditions compared to low-bioburden could at least double the cost of goods. It is unclear whether regulators would approve a low-bioburden product. • There are opportunities to reduce the delivery/programmatic costs with the MAP presentation, which could reduce the total cost of delivery for health systems and households. • A rabies MAP could increase vaccine coverage of PEP and expand the target population of PrEP. • As a single-dose presentation, a rabies MAP could reduce open-vial wastage compared to rabies vaccine delivered by ID injection (a single-dose IM vial contains five to ten 0.1-mL ID doses depending on the product). • If PrEP availability were to increase, this would reduce the need for RIG, which is expensive and often in short supply in endemic areas. • If a MAP could result in a vaccine schedule with fewer clinic visits and/or a shorter duration of treatment, that would reduce the treatment costs per patient, which would be a benefit to rabies programs as well as patients who often have to self-finance rabies vaccine and incur costs associated with travel to the health facility. • When using current presentations and schedules, literature shows:

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
			○ The United Against Rabies collaboration reported that the average cost of rabies PEP (i.e., treatment cost) per patient is US$108.07 (US$7.48–US$597.36).[4] ○ WHO reports that the average cost of treating rabies through PEP is US$40 in Africa and US$49 in Asia. These costs can be a significant economic burden in low-resource settings.[1] • In India, rabies vaccine is provided free in the public sector through government hospitals. In private clinics/hospitals, patients pay for the vaccine. The vaccine is often purchased by the patient/caregiver at the pharmacy and then taken to a health care provider for administration. ○ In an assessment of PEP in India, the total median cost paid by the patient for seeking PEP (i.e., treatment cost) at a government facility was INR 1,400 (US$22).[41] ○ For IM delivery, the cost to the health facility to provide vaccine and RIG for category III exposures free of charge to patients was INR 1,188 (US$19). The cost to the health facility to provide rabies vaccine only for category II exposures was INR 640 (US$10).[41] ○ For ID delivery, the cost to the health facility for vaccine and RIG for category III exposures was INR 676 (US$10). The cost to the health facility to provide rabies vaccine only for category II exposures was INR 128 (US$2).[41] ○ In a private health facility, the total median PEP cost paid by the patient was INR 3,685 (US$58) for category III exposures and INR 3,034 (US$48) for category II exposures.[41] • In 2017–2018, an evaluation of the procurement and distribution of rabies PEP in Africa and Asia reported that in 43% of the countries interviewed, all or some patients in the public sector were required to pay for the vaccine, which ranged from US$6.60–US$20.00 per dose. Countries also considered the indirect costs associated with travel to the health facility for multiple clinic visits and lost wages to be key barriers to accessing PEP, especially for patients traveling long distances to access care.[2] • A rabies MAP that enabled self-administration or community-based vaccination could reduce the economic burden on patients and increase patient compliance with PEP regimens. • Completion of the vaccine regimen in the community after consultation with a trained health care provider would also reduce the economic burden. • A modeling study focused on 67 Gavi-supported countries evaluated the potential impact of improved investments in ID rabies vaccines. It found that PEP would be cost-effective but PrEP as a large-scale public health intervention would be substantially more expensive than other measures to

Attribute	Minimally acceptable target	Optimal target	Rationale/notes
			prevent human rabies deaths, such as PEP provision combined with mass dog vaccination campaigns.[42] ○ This study estimated that 73.5 million vials would be used over a 15-year period (2020–2035) for these 67 Gavi-supported countries or approximately 4.5 million vials per year.
Abbreviations: ID, intradermal; IM, intramuscular; INR, Indian rupee; MAP, microarray patch; PEP, post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; RIG, rabies immunoglobulin; UNICEF, United Nations Children's Fund; WHO, World Health Organization.			

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