Evidence to Recommendation Table 1

Questions: Can the duration of the entire course and/or the number of doses administered of current PEP regimens be reduced while maintaining immunogenicity and effectiveness?

Population: Immunocompetent rabies exposed patients (category II and III exposures)
Intervention: (a) shortened duration of the full PEP course, (b) reduced number of vaccine doses during the full PEP course
Comparison(s): (a) current duration of WHO-recommended PEP regimens, (b) WHO-recommended standard number of vaccine doses during the course of a full PEP regimen
Outcome: Adequate rabies virus neutralizing antibody titers, prevention of clinical rabies

Background:

Rabies is readily preventable through post-exposure prophylaxis (PEP) and results are best if PEP is initiated as early as possible after rabies exposure. Since 1992, WHO has promoted the use of intradermal (ID) administration of rabies vaccine, which confers up to 80% vaccine saving in rabies endemic countries, especially in high throughput clinics.

The currently approved rabies vaccine regimens require 14 to 28 days to complete. Due to the long duration of the regimen involving at least 4 clinic visits, many animal bite victims exposed to rabies do not complete the full course of PEP, which can leave them unprotected and susceptible to fatal clinical rabies. The high cost of rabies vaccines and potential loss of income due to frequent travel to the clinic are often a barrier, particularly in low- and middle-income countries. Furthermore, healthcare workers may be hesitant to fractionate vials of rabies vaccine for patients if they cannot foresee the full volume of the vaccine vial will be used before it should be discarded (after 6-8 hours), which often delays the initiation of PEP regimens. For these reasons, it would be advantageous to reduce the duration of the entire PEP course and the number of doses administered, while maintaining immunogenicity and clinical effectiveness. Abbreviating the rabies PEP regimen is expected to improve patient compliance and be potentially cost-saving. The available evidence suggests that the current PEP regimens can be reduced, including the duration and number of doses while maintaining immunogenicity and clinical protection.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFO
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	Rabies is a neglected zoonotic disease, most deaths occur in poor and marginalized communities in Asia and Africa. Prompt thorough wound washing, timely administration of the first dose of vaccine and RIG if indicated, is crucial to ensure survival of exposed victims. Millions of PEP courses are administered to rabies exposed patients every year and heavily impact the budgets of Ministries of Health. Vaccine (and RIG) stock-outs frequently occur in rabies endemic countries, particularly at decentralized levels. Reducing the number of doses of vaccine needed would contribute to mitigate the risk of stockouts.	Rabies causes approximately 59,000 deaths annually and is a public health problem in more than 150 countries worldwide. Dogs are the primary source of fatal exposure to humans, contributing up to 99% of all rabies transmissions. Moreover, children under 15 years of age are a demographic frequently exposed to rabies.

BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies by setting* ☐	Reducing the duration and/or the number of doses of a PEP course is beneficial because it will lower both direct (*i.e.* vaccine) and indirect costs (*i.e.* patient travel to clinic, loss of income). It also reduces patient pain and discomfort and increases patient compliance with PEP schedules.	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies by setting* ☐	Current rabies vaccines are safe, efficacious and highly immunogenic. There are no apparent harms for the accelerated regimens, as shown by observational data from Cambodia and published evidence on non-compliance with full course PEP .	
	Balance between benefits and harms	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies by setting* ☐	As rabies is a fatal disease, any intervention that improves chances of survival, such as increased accessibility and affordability of treatment, will outweigh undesirable outcomes or levels of uncertainty. Decades of clinical data document the safety and effectiveness of rabies vaccines (no harm).	The current PEP regimens are well-established and tolerated. A decrease in duration and number of clinic visits would be beneficial to patients.

	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☒ *High* ☐ Safety of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☐ *High* ☒	The evidence profile of Annex II of the background paper provides details on the abridged 1-week ID regimen (2-2-2-0-0) which was based on immunogenicity data and follow up of clinic patients of Pasteur Institute Cambodia bitten by confirmed rabid dogs and who did not complete the 4-visit Thai Red Cross PEP regimen. Data showed that there was no gain in immune response with a 4th vaccine administration and that the clinical outcome was not affected. Alternative ID and IM regimens, which elicited adequate antibody titers and in some cases proved clinical protection (see below) were evaluated.	

VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐	*Possibly important uncertainty or variability* ☐	*Probably no important uncertainty or variability* ☒	*No important uncertainty or variability* ☐	*No known undesirable outcomes* ☐	Rabies in a biting dog is rarely confirmed by a laboratory diagnosis. Clinical outcome data on truly rabies exposed victims would upgrade the quality of evidence. Studies reviewed have small samples sizes and limited geographic representativeness, most trials were conducted in Asia.	More studies in rabies endemic settings with larger samples sizes, and confirmed rabies exposures would improve the quality of evidence. Moreover, trials conducted on the African continent would be valuable, as the *per capita* rabies burden (deaths/exposed) is greater than in many Asian settings. There are 6 sub-Saharan Africa countries amongst the 10 highest *per capita* burden countries, but rabies vaccine trials in African countries are underrepresented in the current literature.

	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects? *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	The target population would likely prefer the intervention that is more affordable, accessible and requires fewest clinic visits. .	Individuals in low-resource communities and rural areas are likely to particularly value these interventions. For other settings, it increases the convenience for individuals in need of PEP and practicality for clinicians.
RESOURCE USE	Are the resources required small? *No* ☐ *Uncertain* ☐ *Yes* ☐ *Varies* ☒	For countries already implementing the ID Thai Red Cross PEP regimen, it would not require additional major programmatic costs as health care personnel is already familiar with this regimen (no training for ID injection technique, scheduled clinic visits for patients). For countries introducing ID regimens, this would require training of healthcare personnel. General programmatic costs for the intervention would be	

			approximately equal in both situations.	
	Cost-effectiveness	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	Savings on indirect costs (*e.g.* travel to clinic, loss of income due to absence) are expected, as only 3 instead of 4 visits to the clinic are required. Overall, the highest cost-effectiveness of all regimens was shown for the 3-visit, 2-site ID regimen (2-2-2-0-0)	

EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *Reduced* ☒ Varies ☐	Health inequities would be reduced through this recommendation. Inequities regarding affordable healthcare allow neglected tropical diseases, like rabies, to persist. Therefore, the cost-saving quality of this intervention will increase affordability and accessibility to affected populations. Bites from suspect rabid dogs are usually clustered and multiple patients would likely seek care at a clinic at the same day. Saved doses of vaccine, through shortened ID schedules, would be available for additional patients.	The baseline benefit is higher for those who live in low-resource settings, particularly marginalized communities and children under 15 years of age
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Key stakeholders in rabies endemic regions are likely to value the more affordable, dose-sparing intervention. Abridged PEP regimens will increase affordability and improve patient compliance.	

	Which option is acceptable to target group?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	The intervention is likely to be acceptable to the target population due to its increased affordability and improved accessibility. As financial and travel barriers are often the greatest for underserved populations in rabies endemic areas, the intervention will be preferable.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	This intervention is feasible, particularly compared to current PEP schedules. This intervention will increase access and affordability, particularly for marginalized communities. Training for healthcare providers is needed for both, the intervention and the comparison. Cold chain logistics are equally challenging for both.	There is no apparent risk of discrimination or variability of requirements across settings and populations.

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒
Type of recommendation	We recommend the intervention ☒	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)popul		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐

Recommendation (text)	Overview on PEP regimens and criteria for evaluation of non-inferiority to previously WHO-recommended regimens. The recommended WHO PEP regimen is the cost-and dose saving, accelerated 1-week, 2-site ID regimen. Previously WHO-recommended IM PEP regimens are still considered valid options, but may not be as cost-, dose-, or time sparing. Feasibility of either regimen is also dependent on clinical settings and patient preferences. Countries opting for other PEP regimens should consider the regimen's (a) feasibility (i.e. cost and number of doses), (b) immunogenicity and (c) clinical outcome data.

Assumptions patient throughput per month: Small clinic < 10 patients; large clinic ≥ 10 patients
Legend: ✓ Criteria fulfilled; ○ partly fulfilled; × not fulfilled
REF = Cost-effectiveness baseline reference = updated Thai Red Cross regimen (TRC)

PEP regimens	**Characteristics**	**Key evaluation criteria**					
	Number of injection sites per visit	Immuno-genicity data	Clinical outcome data	Cost-effectiveness		Feasibility	Acceptability
				small clinic	*large clinic*		
WHO recommended intradermal regimen							
1-week, 2-site ID regimen	2-2-2-0-0	✓	✓	>	>	✓	✓
WHO recommended intramuscular regimens							
2-week IM regimen	1-1-1-1-0	✓	✓	≤	<	✓	✓
3-week IM regimen	2-0-1-0-1	✓	✓	≤	<	✓	✓
Alternative immunogenic intradermal regimens evaluated							
1 month, 2-site ID regimen (Updated Thai Red Cross)	2-2-2-0-2	✓	✓	REF	REF	✓	✓
1 month, simplified 4-site ID regimen	4-0-2-0-1	✓	○	>	>	○	✓
1-week, 4-site ID regimen	4-4-4-0-0	✓	○	=	<	○	○

Implementation considerations	(a) General training of healthcare personnel especially those managing injuries/emergencies, should include management of rabies exposures risk and PEP, (b) trainings on correct ID administration of rabies vaccines, and (c) WHO to promote that quality assured rabies vaccines can safely be administered by cost-saving ID route.
Monitoring and evaluation	The use of PEP and potential and confirmed rabies exposures should be consistently monitored. National health systems should track rabies indicators and PEP use, including thorough investigation and documentation of perceived PEP failures.
Research priorities	1. Immunogenicity and clinical outcomes associated with PEP 1-week IM schedule (days 0, 3 and 7) 2. How to avoid wastage when vaccine vials are fractionated yet adhering to WHO standard of discarding open vials after 6-8 hours. 3. Development of a scientific policy paper including a statistically supported protocol describing data and sample size needed to evaluate new PEP regimens