Evidence to Recommendation Table 4

Question: Can the duration of the entire course and/or number of doses administered in the current PrEP regimens be reduced while maintaining anadequate immune response ?

Population: Persons at increased risk of rabies exposure
Intervention: (a) shorter duration (time frame, number of visits) of the PrEP course and/or (b) fewer doses of vaccine for the PrEP course
Comparison(s): (a) current duration of WHO-recommended PrEP regimen (IM or ID days 0, 7, and 21 or 28), (b) current number of doses of WHO-recommended PrEP regimen (IM or ID, 3 doses)
Outcome: Adequate antibody titres, rapid recall of immunological memory in case of PEP or (unnoticed) exposure to prevent infection with rabies virus

Background:
Individuals at high risk of rabies exposure from 1) occupation, 2) travel or 3) sub-populations in endemic settings with limited access to timely and adequate PEP, should be considered for PrEP. The aim of PrEP is to ensure sero-conversion and rapid recall of the immune response if exposed and avoiding the need for RIG in case of exposure. Reducing the time frame and number of doses required for PrEP would make it more feasible and cost-effective to implement, particularly in individuals at high risk of rabies exposure. This is also the case for individuals living in settings where control of the disease in the animal reservoir (domestic or sylvatic) is difficult. If an exposure occurs in a previously immunized patient, administration of scarce and expensive RIG is not required. Additionally, decreased duration of, or fewer visits for, completing PrEP are of high interest to professionals at high risk of rabies exposure and travellers (reduced cost and the time span between the first travel clinic consultation and the individuals' departure to a rabies endemic setting). Studies have shown that accelerated schedules are non-inferior to the currently recommended PrEP regimens.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFO
PROBLEM	Is the problem a public health priority?		PrEP is often considered less urgent than PEP, as PEP responds directly to a potential rabies exposure. Specific occupational groups of	Rabies is a public health problem in more than 150 countries

		No ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	individuals may face a higher risk of rabies exposure, both, noticed and unnoticed and national legal requirements may imply compulsory PrEP. In many rabies endemic countries such measures are not implemented due to cost and occupationally exposed individuals, such as dog vaccinators and laboratory staff are left unvaccinated. Individuals travelling to rabies endemic settings and who are involved in activities that pose an increased risk for rabies exposure are advised to seek PrEP. Timeframes needed for a full course of PrEP before departure and cost are frequently considered prohibitive by travellers. There is a lack of awareness on preventative measure, such as PrEP in areas of high incidence of animal rabies and low access to healthcare.	worldwide. Dogs are the primary source of fatal exposure to humans, contributing up to 99% of all rabies transmissions. As rabies is a neglected zoonotic disease, deaths most often occur in poor and marginalized communities in remote settings of Asia and Africa.
BENEFITS & HARMS	<u>Benefits of the intervention</u>					Decreasing the time frame and number of doses would make PrEP more feasible and more	The baseline benefit is potentially

	Are the desirable anticipated effects large?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	cost-effective to implement, particularly in sub-populations at high risk of rabies exposure. Once the PrEP schedule is completed, there is no need to consider a booster vaccination (other than PEP), unless the individual faces a continued high risk of exposure. PrEP is beneficial because it accelerates the immune response towards the rabies virus and eliminates the need for scarce and expensive RIG in case of rabies exposure. Benefits for individuals receiving PrEP are large, as rabies is fatal.	higher for individuals who live or work in low-resource and marginalized communities. For urgent deployment to endemic settings where individuals would be at high risk due to occupation or travel, the intervention would confer protection even at short notice. Since humans are not a primary source of rabies, decreasing the incidence will not result in a large benefit to the overall rabies burden.

	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies by setting* ☐	Current rabies vaccines are safe and highly immunogenic. Reducing the duration of PrEP will lower both direct (*i.e* vaccine) and indirect costs (*i.e.* patient travel to clinic), and increase compliance with PrEP schedules.	The baseline risk for harm is similar among subgroups considered for PrEP.
	Balance between benefits and harms	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies by setting* ☐	As rabies is a fatal disease, any intervention that improves chances of survival, compliance with and affordability of prevention will outweigh undesirable outcomes or levels of uncertainty.	
	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* ☐	New evidence on accelerated PrEP regimens (2-site ID or 1-site IM PrEP on day 0 and 7) indicates induction of an adequate level of neutralizing antibody titers of <u>≥</u> 0.5 IU/ml and an accelerated immune response upon boosters or PEP non-inferior to the current WHO recommended PrEP regimens. There is evidence for single day PrEP (2-site ID and 1-site IM) to induce adequate levels of antibody titers >0.5 IU/ml and an accelerated immune response	

		☐	☐	☐	☒	☐	upon booster. But the studies had limitations in terms of range of age (<50 years) and timeframes for boostability investigated (1 year). Several studies focused primarily on Asian settings, while some were conducted outside of rabies endemic settings .	
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* ☒	PrEP regimens have an established history of use and true PrEP failures are extremely rare. PrEP and PEP schedules were gradually and safely abridged in number of doses and duration of the full course, as quality of vaccines has consistently improved over the past decades.	

	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 is likely to prefer the intervention that is more affordable and requires the fewest number of clinic visits. Decreasing the duration and/or the number of doses for PrEP will be preferable and likely increase patient compliance with the vaccination schedules.	Professionals at high risk, travellers and individuals in remote, low-resource communities are likely to particularly value the intervention.
RESOURCE USE	Are the resources required small?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	Intervention costs will be reduced due to lower number of clinic visits and higher compliance rates. Training of health care staff on new PrEP regimens can be combined with general refresher trainings.	
	Cost-effectiveness	*No* ☐ *Uncertain* ☐ *Yes* ☐ *Varies* ☒	Accelerated PrEP regimens are more cost-effective as these will lower both direct (*i.e.* vaccine) and indirect costs (*i.e.* patient travel to clinic), and increase compliance with PrEP schedules. The cost savings from PEP without RIG in case of exposure reduces costs further. Modelling results suggest that PrEP as a large scale public health	Large scale implementation of PrEP has not been supported as cost-effective due to the current price of vaccine and logistic costs associated. PrEP for entire

			intervention will be substantially more expensive than other measures to prevent human rabies deaths, such as PEP provision combined with mass dog vaccination campaigns.	populations may become cost-equivalent only in settings, with extremely high annual bite incidence (>5%) and low use of RIG
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. As this intervention can potentially decrease both direct and indirect costs for those at high risk of exposure and for healthcare systems, it can increase affordability and accessibility to affected individuals, including marginalized populations.	

ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Intervention* [X] *Comparison* [ ] *Both* [ ] *Neither* [ ] *Unclear* [ ]	Key stakeholders in rabies endemic regions are likely to value the more affordable, dose- and time sparing intervention. Abridged PrEP regimens will increase affordability and improve compliance.	
	Which option is acceptable to target group?	*Intervention* [X] *Comparison* [ ] *Both* [ ] *Neither* [ ] *Unclear* [ ]	The intervention is likely acceptable to the target population due to its increased affordability and time-sparing. As financial resources, time and travel to clinics are often barriers for individuals at high occupational risk or individuals in remote, rabies endemic areas, this intervention will be preferable.	

FEASIBILITY	Is the intervention feasible to implement?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☐	*Yes* ☒	*Varies* ☐	This intervention is more feasible, compared to previously recommended PrEP regimens. This intervention will increase access, affordability and compliance, particularly for those in remote, marginalized populations. Cold chain logistics are equally challenging for both interventions.	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	We recommend the comparison	We recommend against the intervention and the comparison
	☒	☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)popul	☐	☐
Recommendation (text)	1. The following PrEP regimens are considered safe and efficacious: • A 2-site ID vaccine administration on days 0 and 7 • A 1-site IM vaccine administration on days 0 and 7 • If a high risk remains A routine pre-exposure booster vaccination, if indicated, consists of a 1-site ID vaccine administration or 1 IM vaccine administration. 2. If PrEP is required under time-constrained circumstances that do not allow for a full course, a single day vaccine administration will confer boostability up to 1 year. However, individuals who receive vaccine on only day 0, either as 2-site ID or 1-site IM administration, should receive a second vaccine administration as soon as possible. Additionally, in the event of a potential rabies exposure prior to the second vaccine administration, a full PEP course should be given, including RIG, if indicated.			
Implementation considerations	Training of health care personnel on PrEP can be integrated into immunization delivery and clinical injury management. PrEP as a large-scale implementation is only cost-effective under specific circumstances, and not recommended as a general population intervention, comparable to delivery of EPI.			
Monitoring and evaluation	M&E should include implementation of the intervention; its cost-effectiveness; and any adverse effects			

Research priorities	1. Options for PEP schedule after incomplete PrEP (e.g. following a single day PrEP) 2. Pharmacovigilance and reporting of any breakthrough events if a person has received intradermal PrEP with concurrent chloroquine or hydroxy-chloroquine treatment