APPENDIX III: Evidence to Recommendation Tables

More supporting evidence on the use of rabies vaccines can be found in the background paper on the WHO website.

These Evidence to Recommendation tables are based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel). http://www.decide-collaboration.eu/WP5/Strategies/Framework

Questions 3 & 4: Can the duration of the entire course and/or number of doses administered in the current PrEP regimens be reduced while maintaining immunogenicity?

Population: Persons at increased risk of rabies exposure
Intervention: (a) shorter duration (time frame, number of visits) of the PrEP course, (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)
Outcome: Adequate antibody titers, protective and rapid recall of immunological memory in case of PEP or (unnoticed) exposure to prevent infection with rabies virus. No requirement of RIG for PEP

Background:
PrEP plays an important role in protecting those at high risk of rabies exposures. The aim of PrEP is to ensure sero-conversion and rapid recall of the immune response if exposed and avoid the necessity 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 sub-populations at the highest risk of rabies exposure. This is especially the case for people living in areas where control of disease in the animal reservoir (domestic or sylvatic) is difficult and where timely access to PEP and RIG is highly unreliable or non-existent. Should an exposure occur in a fully immunized patients do not need a costly administration of scarce and expensive RIG in case of a rabies exposure. Additionally, shortened duration of, or fewer visits for, completing PrEP are also of high interest to professionals at high risk of rabies exposure and travel medicine (reduced cost and the time span between the first travel clinic consultation and the patients' departure to a rabies endemic region). Studies have shown that abbreviated schedules may be non-inferior to the currently recommended regimens.

See Table 1b in evidence profile for this question for a more detailed description of different risk groups

	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. There is a lack of awareness on the importance of	Rabies is a public health problem in more than 150 countries

		No ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	PrEP as a preventative measure in areas of high incidence of animal rabies and low access to healthcare. Specific groups of professionals may face a higher risk of rabies exposure, both noticed and unnoticed and national legal requirements imply compulsory PrEP. In many rabies endemic countries this is not implemented due to cost and professionals such as dog vaccinators and laboratory staff are left unprotected. People travelling to rabies endemic settings and involved in specific activities posing an increased risk for rabies exposure are currently advised to seek PrEP. Timeframe needed for full priming before departure and cost are frequently considered prohibitive by such travelers.	worldwide. Dogs are the primary source of fatal exposure to humans, contributing up to 99% of all rabies transmissions. As rabies is a neglected tropical zoonotic disease, deaths most often occur in poor and marginalized communities in remote settings of Asia and Africa.
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 time frame and number of doses would make PrEP more feasible and more cost-effective to implement, particularly in sub-populations at highest risk of rabies exposure. Once the PrEP schedule completed, there is no need to consider a booster vaccination	The baseline benefit is potentially higher for those who live in low-resource and marginalized communities and children

			(other than PEP), unless the person 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.	under 15 years of age. For urgent deployment to endemic settings where individuals would be at high risk, the intervention would protect. Benefits on incidence of rabies in the human or animal population are low, because humans are not the primary source of rabies infection to other humans.
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies by setting* ☐	Current rabies vaccines are known to be safe and highly immunogenic. Reducing the duration of PrEP is beneficial because it will lower both direct (*i.e* vaccine) and indirect (*i.e.* patient travel to clinic) costs, lower patient pain and discomfort and increase compliance with PrEP schedules.	The baseline risk for harm is similar among subgroups.

	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 modified PrEP regimens indicates induction of a protective level of neutralizing antibody titres of $\geq$ 0.5 I.U. and an accelerated immune response upon boosters or PEP non-inferior to the current WHO recommended PrEP regimens. Several studies were conducted outside of rabies endemic settings or focus primarily on South and South East Asia. Rabies vaccines are highly immunogenic and safe. The interventional regimen elicited adequate antibody titers.	
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 anecdotal. PrEP and PEP schedules were gradually and safely reduced in number and duration, as quality of vaccines has improved consistently over 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 will prefer the intervention that is more affordable, accessible and requires the fewest number of clinic visits. Shortening the duration and/or decreasing the number of doses for PrEP will be preferable and likely increase patient compliance with the vaccination schedules. The cost savings from PEP without RIG in case of exposure have a positive impact on marginalized populations.	Professionals at high risk, travelers and people in low-resource communities and remote rural areas 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* ☒	Reducing the duration of the PrEP regimen is cost-effective as it will lower both direct (*i.e* vaccine) and indirect (*i.e.* patient travel to clinic) costs, lower patient pain and discomfort, and increase compliance with PrEP schedules. The cost savings from PEP without RIG in case of exposure reduces costs.	Large scale implementation of PrEP has not been supported as cost-effective due to the current price of vaccine and logistic costs associated.

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 are what allow neglected tropical diseases, like rabies, to persist. As this intervention can potentially decrease both direct and indirect costs for those at highest risk of exposure and healthcare systems, it can increase affordability and accessibility to affected populations.	
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 and accessible intervention. Shorter duration and fewer doses for PrEP will increase affordability and improve patient compliance.	
	Which option is acceptable to target group?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	The intervention is acceptable to the target population due to its increased affordability and accessibility. As financial, time and travel barriers are often the greatest for those in 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 feasible, particularly compared to current PrEP schedules. This intervention will increase access, affordability and compliance, particularly for those in disadvantaged populations. 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)	1. The following PrEP schedules for healthy individuals of all ages are recommended: a. two ID doses on days 0 and 7 b. one IM dose on days 0 and 7 2. Although a 1-day course of PrEP likely confers some protection, it is not recommended. However, if it is impossible to complete a full course of PrEP, those who have received PrEP only on day 0 should receive a second dose as soon as possible, and be given full PEP in the event of potential rabies exposure. 3. Those who are immunocompromised should receive a 3-visit, 7-day course of PrEP (days 0, 3, 7) either ID or IM, as they may have a decreased immune response to vaccine. Moreover, a 2-day/visit course of PrEP (days 0, 7) in immunocompromised individuals has not been studied. Where possible, serology can be used to assess seroconversion, and additional doses can be administered if needed.
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 considerations, see Table 1b in the evidence profile of Question 2 and not recommended as a general population intervention, comparable to EPI.
Monitoring and evaluation	M&E should include implementation of the intervention; its cost-effectiveness; and any adverse effects
Research priorities	1. Options of PEP schedule after incomplete PrEP (e.g. emergency 1-day PrEP) 2. Pharmacovigilance and reporting of any breakthrough events if a person has received intradermal PrEP with concurrent chloroquine treatment

Questions 6 & 7

Questions 6 & 7: Can the duration of the entire course and/or number of doses administered in current PEP schedules be reduced while maintaining efficacy, effectiveness and immunogenicity in immunocompetent patents with WHO category II and III rabies exposure?

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

Background:
Rabies is readily preventable through post-exposure prophylaxis (PEP). PEP should be initiated as early as possible following a potential rabies exposure. Since 1992, WHO has promoted the use of ID administration, which confers 60-80% vaccine saving in rabies endemic countries, especially in high throughput clinics.

The currently approved rabies vaccine regimens require approximately a month to complete. Due to the long duration of the regimen, many animal bite victims exposed to rabies do not complete the full course of vaccination, which can leave them unprotected and susceptible to fatal clinical rabies. The high cost of rabies PEP 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 guarantee the full volume will be used before it should be discarded (6 to 8 hours), which often delays the initiation of PEP schedules. 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 protection. 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 efficacy, effectiveness and immunogenicity.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFO
PROBLEM	Is the problem a public health priority?	*No*	*Uncertain*	*Yes*	*Varies by setting*	Timely PEP is of high priority because it is the only way to ensure survival of exposed victim. Millions of PEP treatments are	Rabies causes approximately 59,000 deaths annually and is a public health problem in

		☐	☐	☒	☐		administered to rabies exposed patients every year and heavily affect the budgets of ministries for public health. Biologics stock-outs frequently occur in rabies endemic countries, particularly at decentralized levels. As rabies is a neglected tropical zoonotic disease, most deaths occur in poor and marginalized communities in Asia and Africa.	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 number of doses of PEP is beneficial because it will lower both direct (*i.e* vaccine) and indirect (*i.e.* patient travel to clinic) costs, lower patient pain and discomfort and increase patient compliance with PEP schedules.	The baseline benefit is higher for those who live in low-resource and marginalized communities and children under 15 years of age.
	<u>Harms of the intervention</u> Are the undesirable	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐		Current rabies vaccines are safe, efficacious and immunogenic. There are no apparent harms for the shortened schedules.	

	anticipated effects small?			
	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. There is decades of data documenting the safety and efficacy of rabies vaccines (no harm).	The current PEP regimens are well-established and tolerated. A reduction in duration and number of clinic visits is in favor of 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 provides details on the shortened ID regimen (2-2-2) and other alternatives elicited adequate antibody titers and showed protection in clinical 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* ☐	Rabies in a biting dog is rarely confirmed. Outcome data on truly exposed victims would upgrade the quality of evidence. Data reviewed have small samples sizes and limited geographic representativeness, as most trials are conducted in (South East) Asia. More studies in rabies endemic settings with larger samples sizes could improve the quality of evidence. Trials conducted on the African continent would also be valuable, as the *per capita* rabies burden (deaths/exposed) is larger 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 will prefer the intervention that is more affordable, accessible and requires fewest clinic visits. Shortening the duration and/or decreasing the number of doses for PEP will be preferable and likely increase patient compliance with the vaccination schedules, and thus save lives.	Those in low-resource communities and rural areas are likely to particularly value these interventions. For other settings, it increases the convenience for PEP patients and practicability for clinicians.
RESOURCE USE	Are the resources required small? *No* ☐ *Uncertain* ☐ *Yes* ☐ *Varies* ☒	For countries already implementing the ID TRC regimen, it would not imply additional major programmatic costs. For countries introducing ID regimens, this implies training of healthcare personnel. General programmatic costs for the intervention would be approximately equal in both situations.	
	Cost-effectiveness *No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	Major saving on indirect costs (*e.g.* travel to clinic) is 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) and the 3-visit modified 4-site ID regimen (4-0-2-0-1).	
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 are what allow neglected tropical diseases, like rabies, to persist. Therefore, the cost-saving quality of this intervention will increase affordability and accessibility to affected populations. Suspect rabies bites are usually clustered and multiple patients would seek care at a clinic at the same time. Saved doses of vaccine, through shortened ID schedules, would be available for additional patients.	
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 and accessible intervention. Shorter duration and fewer doses for PEP will increase affordability and improve patient compliance.	

	Which option is acceptable to target group?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	The intervention is 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 those in disadvantaged populations. 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)

WHO-approved and shortened PEP regimens which are described in the overview below. Countries considering new or alternate regimens should take into account (a) feasibility (i.e. cost and number of doses), (b) immunogenicity and (c) clinical protection of the schedule.

Overview existing approved and investigational PEP regimens and criteria for evaluation of non-inferiority to WHO recommended regimens

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 on days 0, 3, 7, 14, 21 or 28	Immuno-genicity data	Clinical outcome data	Cost-effectiveness		Feasibility	Acceptability
				small clinic	*large clinic*		
WHO recommended intradermal regimen							
IPC regimen, 1 week	2-2-2-0-0	✓	✓	>	>	✓	✓
WHO recommended intramuscular regimens							
Essen regimen, 14 to 28 days	1-1-1-1-0	✓	✓	≤	<	✓	✓
Zagreb regimen, 21 days	2-0-1-0-1	✓	✓	≤	<	✓	✓
Alternate immunogenic intradermal regimens							
Updated Thai Red Cross regimen, 1 month	2-2-2-0-2	✓	✓	REF	REF	✓	✓
Simplified 4-site regimen, 1 month	4-0-2-0-1	✓	○	>	>	○	✓
4-site regimen, 1-week	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 WHO pre-qualified 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 through investigation and documentation of perceived PEP failures.
Research priorities	1. Efficacy and clinical outcomes associated with PEP 2-visit ID (Day 0 and 7) schedule 2. Efficacy and clinical outcomes associated with PEP 1-week IM schedule (day 0, 3 and 7) 3. How to avoid wastage due to WHO standard on holding of open vials for 6-8 hours before discard, when vaccine vials are fractionated 4. Development of a policy paper or a protocol describing data and sample size needed to recommend a new regimen, that is statistically supported

Question 10

Question 10: Is there evidence to simplify recommendations on the administration of RIG as a part of PEP for category III exposed patients? Such as (a) discontinuation of calculation of RIG dose needed according to body weight and (b) RIG into or around the bite wound(s) only with or without additional administration of remaining RIG to other sites?

Population: Category III exposed patients and specific subsets of category II exposed patients receiving PEP
Intervention: Simplification of recommendations, for example:
a. RIG volume calculation based on factors other than patient body weight
b. RIG administration to wound area without remaining RIG injected at distant site
Comparison(s): Current recommendations:
a. RIG volume calculation based on body weight: 20 IU/kg body weight for hRIG and 40 IU/kg body weight for eRIG
b. RIG administration into or around the wound sites with remaining RIG injected intramuscularly at a site distant from the site of vaccine administration
Outcome: Sustained or increased patient survival; more efficient use of RIG; improved cost-effectiveness

Background:
The high cost (hRIG 40$, eRIG 30$ per vial, for an adult 3-4 vials of eRIG are needed for PEP), low availability and supply, batch to batch variation affecting efficacy, uncertain quality (no WHO prequalification process) and short shelf life of RIG are barriers to implementing the gold standard set by WHO for PEP in category III bites. RIG is often a barrier for attaining public health impact because of a hesitation to use vaccine without RIG and therefore manufacturers and countries often do not want to make vaccines available without RIG, which means no PEP at all. The simplification of WHO's recommendations on RIG based on new evidence available is important considering the aspects above. The individuals in rabies-endemic settings most often affected are those who can least access and afford PEP. Additionally, RIG is in scarce availability, compared to the other components of the PEP regimen, so its efficient use is important for ensuring maximal availability to the patients bearing the highest risk. Remining RIG would then be available for other patients. If new evidence shows that RIG dose and volume for administration can be adjusted for factor(s) other than body weight, then recommendations can be made to determine RIG-saving administration practices that are non-inferior than current recommendations.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFO
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☐	*Varies by setting* ☒	RIG is life-saving particularly in severe rabies exposures when administered within 7 days following first dose of vaccination. Only a small percentage of severe suspect rabid animal bite victims can access RIG due to its high cost and low availability. Public health authorities' budget for procurement of RIG is in most cases very limited or even absent. Only 2% of patients	Rabies causes approximately 59,000 deaths annually and is a public health problem in more than 150 countries worldwide. Moreover, children under 15

			requiring RIG receive it. Conversely, in other settings there may be a tendency of overuse. Paying for vaccine and RIG can cause catastrophic out of pocket expenses to those in rabies-endemic areas (in some settings equivalent to more than a month's salary).	years of age are most frequently suffer from severe rabies exposures. As rabies is a neglected tropical zoonotic disease, most deaths occur in poor and marginalized communities in Asia and Africa.
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies by setting* ☐	The beneficial effects of this intervention include (a) Access to and more efficient use of RIG which is life-saving; (b) more equitable use of RIG, (c) cost-saving for both individuals and public health sector, and (d) simplification of practices for care providers. The beneficial effects of this intervention are large per individual. As rabies is invariably fatal, RIG corresponds directly to lives saved, particularly in case of severe exposures. Moreover, as rabies PEP is only administered to those potentially exposed to the rabies virus, there is a high impact.	Offering this intervention as an alternative option, it will particularly benefit the subgroups of rabies-exposed children and people living in marginalized and low-resource communities.
	<u>Harms of the intervention</u> Are the undesirable anticipated effects	*No* *Uncertain* *Yes* *Varies by setting*	Administration of RIG only into the wound would rely on the decision of the clinician rather than a standardized of volume administered and adequate training will be required. Administration of	The baseline risk for harm is similar across subgroups.

	small?	☐	☐	☒	☐	RIG into small wound spaces (*e.g.* fingers, toes, ears, noses) is limited and may create compartment syndrome and may not provide a sufficient dose of RIG. Clinicians are averse to administering RIG into wounds.	
	Balance between benefits and harms	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	Increased affordability, availability and accessibility of RIG in low-resource settings saves lives. Training of clinicians in risk assessment and correct post-exposure administration is needed. Preliminary calculations carried on patient data from Cambodia show that the remaining RIG dose (maximum dose based on body weight) injected distant from the wound site is unlikely to produce adequate levels of circulating antibody titers, but maybe provide additional safety in severe exposures or when small bite wounds are overlooked.	

	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* ☐	There are only a few studies with observational data on this subject. As rabies is a fatal disease, conducting randomized controlled trials present ethical and logistical challenges; and for example, placebo controlled superiority trials are not appropriate.	
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* ☐	There are a limited number of studies on the intervention and large-scale experience has been collected mainly from one country or in the animal model. Not all field studies consider the confirmation of the rabies status of the biting animal to determine the certainty of rabies exposure. As rabies is a fatal disease, any intervention improving accessibility and affordability of RIG will outweigh undesirable outcomes or levels of uncertainty due to the studies.	

	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 value of this intervention lies in life-, dose and cost-saving use of RIG for both the public health sector and the individual. Saved doses of RIG would be available for additional patients. RIG is often a barrier for attaining public health impact because of a hesitation to use vaccine without RIG and therefore manufacturers and countries often do not want to make vaccines available without RIG, which means no post-exposure prophylaxis (PEP) at all.	Most rabies deaths occur in low-resource settings. This is the reason for offering the intervention.
RESOURCE USE	Are the resources required small?	*No* ☐ *Uncertain* ☐ *Yes* ☒ | *Varies* ☐	Resources additional to the current RIG recommendations are not required for this implementation. Indeed, this intervention will decrease the costs required for RIG purchase by both individuals (out of pocket expenses) or health systems (if subsidized or free of charge to the patient).	The lower cost per patient may favor an increased uptake by governments resulting in better forecasting and increased affordability.
	Cost-effectiveness	*No* ☐ *Uncertain* ☐ *Yes* ☒ | *Varies* ☐	This intervention improves cost-effectiveness of PEP.	

EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *Reduced* ☒ Varies ☐	Health equity would improve through this recommendation, as more people would have access to RIG and be a feasible intervention at decentralized healthcare facilities (in many countries rabies biologics are only available at central level or the capital)	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Intervention* ☐ *Comparison* ☐ *Both* ☒ *Neither* ☐ *Unclear* ☐	As the intervention is more cost-effective, the acceptability will be high for stakeholders in low-resource settings as it will save additional lives	
	Which option is acceptable to target group?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	The majority of the target group consists of rural or marginalized populations who have limited access to health systems and often face resource constraints to pay for RIG and vaccines. High-resource countries where RIG is available in sufficient quantity and affordable to patients have the option to maintain the original policy.	

FEASIBILITY	Is the intervention feasible to implement?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☐	*Yes* ☒	*Varies* ☐	Data show that continued education of healthcare providers is needed to improve correct RIG administration, regardless of the intervention or comparator chosen. Cold-chain and delivery mechanisms are equally challenging for both options. Shortages in supply are very frequent, at both central and decentralized levels. Thus, the intervention is likely to reduce costs and supply issues resulting in timely and affordable care to patients.			This intervention would improve accessibility to RIG and would be cost-saving to individuals and health systems. This intervention would be particularly feasible and beneficial towards low-resource 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 populations				We recommend the comparison ☐			We recommend against the intervention and the comparison ☐

Recommendation (text)	1. The RIG dose is calculated by weight, for hRIG at 20 IU/kg, and for purified eRIG F(ab')2 products at 40 IU/kg body weight. 2. After calculating the RIG dose, as much as anatomically possible (*e.g.* to avoid compartment syndrome) should be administered carefully and thoroughly into and around the wound. The maximum benefits of RIG are gained when administered directly into the wound. When the calculated volume is too small to fully infiltrate the wound (*e.g.* in large or multiple wounds), the RIG may be diluted with sterile normal saline to a volume sufficient for complete infiltration of all wounds. 3. It is current practice that, after full infiltration of the wounds, the remaining RIG (if any) be administered IM at a site distant from the wound. However, updated evidence suggests that this may be of limited benefit. In settings where RIG is of low availability, the relative benefits of IM RIG injection distant to the wound should be weighed against the possibility of providing the remaining RIG to other patients, to confer maximum public health benefit. This requires aseptic retention of the RIG (*e.g.* in smaller, individual syringes).
Implementation considerations	General training of healthcare personnel especially those managing injuries/emergencies, should include management of rabies exposures and PEP, (b) trainings on correct administration of RIG. Additionally, there should be training on safe fractionating of RIG vials to avoid contamination of open vials shared between several patients.
Monitoring and evaluation	The intervention is already implemented at large scale in a State of India and punctually in other settings. This intervention should be promoted in other settings in India and elsewhere. Due to varying quality of available RIG products and no pre-qualification process rigorous M&E of RIG use and any adverse effects should be conducted.
Research priorities	1. Can RIG be administered intravenously 2. Effect of analgesics on PEP and RIG, if used as a component of wound care

Questions 11 & 12

Questions 11 & 12: Is there updated evidence on the safe use and efficacy of eRIG compared to hRIG in rabies exposed patients?

Population: Category III exposed patients and specific subsets of category II exposed patients
Intervention: The use of eRIG products as a safe and efficacious alternative to hRIG
Comparison(s): The use of hRIG as the preferred product, as data from 2010 Rabies Vaccination Position Paper suggest that eRIG carries a small risk (1/45000) of anaphylactic reaction
Outcome: Safety of PEP process (e.g. severe adverse effects); efficacy of PEP (e.g. patient survival); cost-effectiveness

Background:
Updated data regarding the safety and efficacy of eRIG and hRIG are important because eRIG is less expensive and more available option than hRIG. However, in some places there is still a belief that hRIG is superior to eRIG. However, eRIG is a safe and efficacious alternative and clinically non-inferior to hRIG. Since the introduction of eRIG, manufacturing processes have improved and led to a more purified and safe product. Already in the 2010 position paper, the skin sensitivity test for eRIG was deemed unnecessary. There is still widespread practice of skin testing due to discrepancies between WHO policy and national regulatory requirements.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFO
PROBLEM	Is the problem a public health priority?	No ☐	Uncertain ☐	Yes ☐	Varies by setting ☒	RIG is life-saving particularly in severe rabies exposures when administered within 7 days following first dose of vaccination. Only a small percentage of severe suspect rabid animal bite victims can access RIG due to its high cost and low availability. Public health authorities' budget for procurement of RIG is in most cases very limited or even absent. Only 2% of patients requiring RIG receive it. Conversely, in other settings there may be a tendency of overuse. There is limited in supply for both products.	Rabies causes approximately 59,000 deaths annually and is a public health problem in more than 150 countries worldwide. Moreover, children under 15 years of age are a demographic frequently exposed to rabies. As rabies is a neglected tropical zoonotic disease, most deaths

				occur in poor and marginalized communities in Asia and Africa.
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	No ☐ Uncertain ☐ Yes ☒ Varies by setting ☐	The beneficial effects of this intervention include (a) Improve access to and more efficient use of RIG is life-saving; (b) cost-saving for both individuals and public health sector, and (c) simplification of practices by removal of skin testing. eRIG is a safe and efficacious alternative and clinically non-inferior to hRIG. Since the introduction of eRIG, manufacturing processes have improved and led to a more purified and safe product. Although eRIG fragments have a shorter half-life than hRIG, neutralization is completed well before this critical period. Moreover, eRIG F(ab')2 fragments have higher specificity, thus preserving efficacy. eRIG shows high success rates in clinical practice. Deaths despite the administration of eRIG have been attributed to deviations from the PEP guidelines or causes unrelated to rabies exposure or treatment.	This intervention will particularly benefit the subgroups of children and those living in marginalized and low-resource communities. In some cases eRIG is not used due to believed inferiority of the product even if no alternative is available.
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	No ☐ Uncertain ☐ Yes ☒ Varies by setting ☐	Severe adverse effects from eRIG are infrequent; modern techniques allow eRIG to be highly purified. Other adverse reactions tend to be mild, not life-threatening, and easily resolved (e.g. local pain, redness, induration, fever and itching).	Baseline risk is similar across groups. Adverse reaction rates for eRIG are similar to that of penicillin and

				nowadays only minimally higher than observed in hRIG.
	Balance between benefits and harms	No ☐ Uncertain ☐ Yes ☒ Varies by setting ☐	Increased affordability and availability of RIG to patients in low-resource settings saves lives. As rabies is a fatal disease, very low rates of severe adverse effects are acceptable.	
	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 ☒	Solid evidence was already available for the 2010 position paper. Most newer studies are non-randomized observational and have some limitations in design and sample size.	

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 ☒	As rabies is a fatal disease, any intervention improving accessibility and affordability of RIG will outweigh undesirable outcomes or levels of uncertainty due to the studies.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☐ | Yes ☒ | Varies ☐	Increased affordability, availability and accessibility of RIG in low-resource settings saves lives. Training of clinicians in correct RIG administration is needed. Currently, in the worst cases, due to hesitation of using eRIG, care providers falsely do not administer any rabies vaccines if hRIG is not available. This issue can be palliated by the promotion of eRIG as non-inferior and clinically equivalent to hRIG.	
RESOURCE USE	Are the resources required small?	No ☐ | Uncertain ☐ | Yes ☐ | Varies ☒	No additional resources are required for the implementation.	The lower cost of eRIG may favor an increased uptake by governments, resulting in better forecasting and increased affordability.
	Cost-effectiveness	No ☐ | Uncertain ☐ | Yes ☒ | Varies ☐	This intervention improves cost-effectiveness of PEP.	RIG products are still very expensive compared to the

				other PEP components.
EQUITY	What would be the impact on health inequities?	Increased ☐ Uncertain ☐ Reduced ☒ Varies ☐	Health equity would improve through this recommendation, as more people would have improved access to RIG	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	Intervention ☐ Comparison ☐ Both ☒ Neither ☐ Unclear ☐	Due to the lower cost of eRIG compared to hRIG, the acceptability will be high for stakeholders in most settings.	
	Which option is acceptable to target group?	Intervention ☒ Comparison ☐ Both ☐ Neither ☐ Unclear ☐	Paying for RIG is one of the largest resource constraints for bite victims in rabies-endemic areas. Therefore, the increased affordability of eRIG will be preferable to the target group.	
FEASIBILITY	Is the intervention feasible to implement?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	Data show that continued education of healthcare providers is needed to improve correct RIG administration, regardless of its human or equine origin. Programs to educate care providers about the safety and efficacy of eRIG would be beneficial. Cold-chain and delivery mechanisms are equally challenging for both eRIG and hRIG.	

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)population		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	1. Equine immunoglobulins (eRIG) are clinically equivalent to human rabies immunoglobulins (hRIG) and are considered safe and efficacious life- and cost-saving biologics. Both, eRIG and hRIG neutralize the virus at the wound site within a few hours. For all RIG products meeting quality standards, the safety and efficacy profiles result in no product preference between eRIG and hRIG. 2. Considering the increase in product purity and safety, skin testing before eRIG administration is unnecessary. Thus, skin testing is not recommended and should be abandoned. 3. Severe adverse events or perceived lower efficacy of RIG (*e.g.* batches of insufficient potency or lower purification degree) should be monitored, recorded and reported, so that biological producers receive immediate feedback and can respond accordingly. A classification of adverse events is available in Annex 1 of the evidence profile. Post-marketing surveillance is recommended.				
Implementation considerations	Dissemination of recommendations to health authorities so that they can be implemented in practice. Continued education of healthcare providers will be needed to ensure correct RIG administration. Post-marketing surveillance and general pharmacovigilance should be strengthened.				

Monitoring and evaluation	Potential and confirmed rabies exposures, PEP treatments and use of eRIG and hRIG should be monitored. National health authorities should track rabies indicators and RIG use and report back to manufacturers and regional or global health organizations. These figures will contribute to an accurate and comprehensive understanding of RIG need and uptake.
Research priorities	Alternatives to RIG, such as monoclonal antibodies

Question 13

Question 13: Is there enough evidence for a recommendation on the safety and efficacy of monoclonal antibodies in preventing rabies in category III exposed patients compared to standard RIG?

Population: Patients with rabies exposures requiring RIG (general category III exposures in some circumstances category II exposures)
Intervention: Anti-rabies monoclonal antibody (mAbs), either alone or in a cocktail of 2+ mabs
Comparison(s): Rabies immunoglobulin (RIG) from either human (hRIG) or equine (eRIG) origin
Outcome: Rabies virus neutralisation at the wound site, patient survival

Background:
RIG, derived from hyperimmunized humans or horses, is currently used as a component of rabies PEP as a method of passive immunization. RIG neutralizes the rabies virus in the time before the immune system responds to the vaccine, which prevents the rabies virus from infiltrating the central nervous system. While RIG is an effective and life-saving product, the barriers of high cost, low availability, limited access and short shelf-life suggest the need for a supplement or alternative to RIG. Moreover, concerns with interference with rabies vaccine, and to a lesser extent the variable degree of RIG purification and weakened efficacy against non-rabies virus Lyssaviruses, further support the need for a RIG alternative. A prospective alternative to RIG is an anti-rabies mAb. An efficacious and safe anti-rabies mAb would increase access and affordability of PEP and subsequently decrease rabies deaths. A review of the licensed, novel SII mAb (RAB1/17C7) was conducted and the assessment was included in the deliberations for the recommendations (see annex 2 evidence profile on mAbs)

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFO
PROBLEM	Is the problem a public health priority?	No ☐	Uncertain ☐	Yes ☒	Varies by setting ☐	RIG is a particularly expensive and scare component of rabies PEP. Only a small percentage (global average is 2% for rabies endemic countries) of severe suspect rabid dog bite victims receive RIG due to these limitations. In some cases, even life-saving vaccine is withheld because of lack of RIG. Therefore, promoting mAbs as an affordable and accessible alternative or supplement to RIG is of high priority.	Rabies causes approximately 59,000 deaths annually and is a public health problem in more than 150 countries worldwide.
BENEFITS & HARMS OF	<u>Benefits of the intervention</u> Are the desirable	No	Uncertain	Yes	Varies by setting	mAbs show the potential for a large positive impact. They can display non-inferiority to RIG when they are comprised of mAbs cocktails with multiple, non-	The baseline benefit is similar across

	anticipated effects large?	☐	☐	☒	☐	overlapping target antigens. Furthermore, mAbs have not been shown to impact the immune responses elicited by vaccination, as is suggested with RIG of human or equine origin. mAbs have similar adverse effect rates to standard RIG. As production technologies for mAbs evolve, yields are likely to improve with production costs decrease. A reduced cost to the patient and governments would further increase access to and availability of mAb to save lives.	groups.
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	No ☐	Uncertain ☒	Yes ☐	Varies by setting ☐	There are potential harms, limitations and uncertainties associated with rabies mAbs. First, as the rabies RNA-polymerase is not capable of genetic proofreading and repair, treatment with a mAb that targets a single epitope may provide sufficient selection pressure for the development of escape mutants to occur. However, these mutants are unlikely to spread beyond the affected patient, as transmission between humans is rare. True PEP failure is uncommon and resistance has not been reported in the medical use of other antiviral mAbs, such as those for respiratory syncytial virus (RSV). Second, the cost of production of mAbs is of concern. While only a small amount of mAb is needed for treatment, it is still an expensive biological to produce. However, as this technology improves and the demand increases, cost of goods should drop.	The baseline risk is similar across all subgroups.
	Balance between benefits and harms	No	Uncertain	Yes	Varies by setting	There are uncertainties and limitations regarding the currently available mAbs, as discussed above. However, as rabies is a fatal disease, any intervention improving	Only a small percentage of severe suspect rabid

		☐ ☐ ☒ ☐	accessibility and affordability of PEP will outweigh undesirable outcomes or levels of uncertainty.	animal bite victims can access RIG due to its high cost and low availability. Public health authorities' budget for procurement of RIG is in most cases very limited or even absent. Only 2% of patients requiring RIG receive it. The use of mAb would save lives.
	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 ☐	Most attempts to evaluate safety and efficacy of mAbs as an alternative to RIG stopped at the pre-clinical phase and never made it to phase III. There are now phase III clinical trial data available from one single product which has been licensed in India in 2016. In most settings a single mAb is effective, however in settings like Latin America (particularly for wildlife rabies) a mAb cocktail would be able to neutralize a larger spectrum of virus variants. Cost-effectiveness will have to be investigated over a longer timeframe and will depend on demand and improvements in technology.	

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 ☐	There are current clinical trials for mAbs and mAb cocktails that are in early preclinical, late preclinical, phase I, phase II, and phase III stages. The first anti-rabies mAb has recently only been licensed in India.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☐ | Yes ☒ | Varies ☐	Due to better availability and affordability, an increased uptake of PEP by these populations is expected with the introduction of mAbs.	
RESOURCE USE	Are the resources required small?	No ☐ | Uncertain ☐ | Yes ☒ | Varies ☐	The mAb administration to patients will require training of healthcare personnel. The dosage and administration volumes are different from classical RIG. The cold chain and logistical aspects may improve as the product is highly concentrated (smaller vials). However, training of clinicians in risk assessment and correct post-exposure administration is needed for both, the intervention and the comparison.	
	Cost-effectiveness	No ☐ | Uncertain ☒ | Yes ☐ | Varies ☐	While mAbs are currently expensive per unit compared to eRIG and hRIG. Costs may come down depending on demand, production capacity and likely on sub-licensing for geographic production site spread.	

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 are what allow neglected tropical diseases, like rabies, to persist. Therefore, the potentially cost-saving quality of this intervention will increase affordability and accessibility to affected populations.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	Intervention ☒ Comparison ☐ Both ☐ Neither ☐ Unclear ☐	As the intervention shows the possibility for increased efficacy, safety and affordability, it would likely be preferable alternative to RIG by stakeholders in rabies-endemic areas.	
	Which option is acceptable to target group?	Intervention ☒ Comparison ☐ Both ☐ Neither ☐ Unclear ☐	Access to life-saving RIG and out of pocket expenses associated with RIG use are two of the largest constraints for bite victims in rabies-endemic areas. Therefore, any increased accessibility or affordability of classical RIG or mAbs through this intervention will be better than the current situation for the target group.	

FEASIBILITY	Is the intervention feasible to implement?	No ☐	Probably No ☐	Uncertain ☐	Probably Yes ☒	Yes ☐	Varies ☐	This intervention would improve accessibility to rabies PEP and would potentially be cost-saving to individuals and health systems. This intervention would be particularly feasible and beneficial towards underserved, low-resource populations. Shortages in RIG supply are very frequent, both at central and decentralized levels. Thus, this intervention is likely to reduce costs and supply issues, resulting in timely and affordable care to patients.	

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)populations	We recommend the comparison ☐	We recommend against the intervention and the comparison ☐

Recommendation (text)	1. Monoclonal antibodies (mAbs) **#** have demonstrated safety and efficacy in clinical trials when used as a component of PEP, and offer a potential solution to the limited availability of RIG. 2. Cocktails using two or more mAbs working synergistically show higher efficacy and increased breadth of neutralization. Ideally, the production of mAbs for supplementation of RIG should aim to be affordable and include two or more mAbs with nonoverlapping epitopes. We recommend that a registry be maintained to monitor clinical use and outcomes of mAb products. *# based on clinical trial data evaluation of one recently licensed product*
Implementation considerations	If recommended SAGE, this intervention will be communicated to healthcare providers in rabies-endemic areas. Continued education of healthcare providers will be needed to ensure appropriate use of mAbs. Community education programmes on rabies, PEP and mAbs also have the potential to improve outcomes and increase appropriate uptake of PEP. WHO has included mAbs for consideration in Gavi VIS
Monitoring and evaluation	PEP treatments in conjunction with use of mAbs should be consistently monitored (Post marketing surveillance). National health systems should track rabies indicators and mAb use; these figures will contribute to an accurate and comprehensive understanding of mAb need, cost-effectiveness and uptake. As is the case for classical RIG, it is recommended to improve pharmacovigilance for adverse effects and promote thorough recording and investigation of PEP failures.
Research priorities	1. Pharmacovigiliance for mAbs including development of a register to monitor use and outcomes 2. Further innovation improving current product into a cocktail of antibodies

Question 14

Question 14: In cases of RIG shortage and constraints, can subcategories of patients be identified who should be in the highest priority group for RIG administration?

Population: Category III exposed patients receiving PEP (focus on dog-mediated exposures)
Intervention: PEP without RIG administration for clearly specified subcategories of patients in case of RIG shortage
Comparison(s): Current recommendations: PEP with RIG under all category III circumstances
Outcome: Sustained or increased patient survival; more efficient use of RIG; improved cost-effectiveness

Background:
The current WHO recommendation states that "rabies immunoglobulin should be administered in all people with category III exposure and to those with category II exposure who are immunodeficient" (2010). The high cost, low availability and supply, batch to batch variation affecting efficacy, uncertain quality (no WHO prequalification), short shelf life and correct administration of RIG are barriers to implementing the gold standard set by WHO for PEP in category III bites. RIG is often a barrier for attaining public health impact because of a hesitation to use vaccine without RIG and therefore manufacturers and countries often do not want to make vaccines available without RIG, which means no PEP at all. The individuals in rabies-endemic settings most often affected are those who can least access and afford PEP. Additionally, RIG is in scarce availability, compared to the other components of the PEP regimen, so its efficient use is important for ensuring maximal availability to the patients bearing the highest risk. In cases where there is not enough RIG to be administered to all category III exposed patients, a best practice statement may suggest which subcategories of patients are objectively of the highest priority for RIG administration and what measures should be taken for those who do not receive RIG.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFO
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	RIG is life-saving particularly in severe rabies exposures when administered within 7 days following first dose of vaccination. Only a small percentage of severe suspect rabid animal bite victims can access RIG due to its high cost and low availability. Public health authorities' budget for procurement of RIG is in most cases very limited or even absent. Only 2% of patients requiring RIG receive it. Conversely, in other settings there may be a tendency of overuse. Paying for vaccine and RIG can cause catastrophic out of pocket expenses to those in rabies-endemic areas (in	Rabies causes approximately 59,000 deaths annually. Dogs are the primary source of to humans, contributing up to 99% of all transmissions. As rabies is a neglected tropical zoonotic disease, most deaths occur in poor and marginalized communities in

			some settings equivalent to more than a month's salary).	Asia and Africa.
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies by setting* ☐	The beneficial effects of this intervention include (a) Access to and more efficient use of RIG in patients at highest risk; (b) more equitable use of RIG, (c) cost-saving for both individuals and public health sector, and (d) improved guidance for care providers. The beneficial effects of this intervention are large per individual. As rabies is fatal, RIG corresponds directly to lives saved. Moreover, as rabies PEP is only administered to those potentially exposed to the rabies virus, so there is a high specific impact.	Offering this intervention as an alternative option, it will particularly benefit the subgroups of rabies-exposed children and people living in marginalized and low-resource communities.
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies by setting* ☐	The limitation of subjectively assessed risk versus actual risk could potentially contribute to undesirable effects. PEP without RIG may be safe and acceptable under some conditions, due to the efficacy of wound washing and the high immunogenicity of the vaccine.	For healthcare personnel withholding RIG from a patient may constitute psychological stress.
	Balance between benefits and harms	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies by setting* ☐	Increased affordability, availability and accessibility of RIG for patients at higher risk and in low-resource settings saves lives. Training of clinicians in risk assessment and correct post-exposure administration of RIG is needed.	
	What is the overall quality of this evidence for the	Effectiveness of the intervention	An adequate risk assessment of rabies exposure and timely PEP (including RIG where applicable) is	

	critical outcomes?	Safety of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☒ *Moderate* ☐ *High* ☐ *No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☒ *High* ☐	supported as highly effective over decades. However, there are only a few studies with observational data on this subject. As rabies is a fatal disease, conducting randomized controlled trials with placebos present ethical and logistical challenges.	
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* ☐	Out-of-stock situations or even complete absence of RIG in the entire country are a reality in many rabies endemic countries. As rabies is a fatal disease, any intervention improving accessibility and affordability of RIG to those at highest risk will outweigh undesirable outcomes or levels of uncertainty due to the studies.	In practice, prioritization is already happening due to shortage, cost, etc. Clinicians are confronted daily on how to allocate scarce RIG to patients at highest risk of rabies infection; this recommendation will allow for evidence-based guidance on these decisions.

	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 value of this intervention lies in life- and cost-saving use of RIG in case of shortage or other constraints. RIG is often a barrier for attaining public health impact because of a hesitation to use vaccine without RIG and therefore manufacturers and countries often do not want to make vaccines available without RIG, which means no post-exposure prophylaxis (PEP) at all.	A decision support for clinicians for most appropriate use of biologicals and patient care would also ease ethical and logistical challenges.
RESOURCE USE	Are the resources required small?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	Resources additional to the current RIG recommendations are not required for this implementation. Indeed, this intervention will decrease the costs required for RIG purchase by both individuals (out of pocket expenses) or health systems (if subsidized or free of charge to the patient).	Resources need not be allocated from other locations for implementation.
	Cost-effectiveness	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	The prudent use of RIG will improve cost-effectiveness of PEP, as the intervention allocates expensive RIG to the target patients at highest risk of infection.	

EQUITY	What would be the impact on health inequities?	*Increased* ☒ *Uncertain* ☐ *Reduced* ☐ Varies ☐	Health equity improves through this recommendation. It could be argued that prioritization of RIG confers unequal treatment to victims of rabies exposure. However, while the administrations of RIG to individuals may be perceived unequal, health equity is still preserved, as the product is allocated in a manner most likely to confer equal health outcomes (*i.e.* survival).	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	As the intervention is more cost-effective, the acceptability will be high for stakeholders in low-resource settings as it will save additional lives	Many ministries of health in rabies endemic countries face challenges to assure supply (if any) and distribution of RIG where it is most needed. More prudent use of RIG might ease the overall ethical challenge of this situation and the budgetary burden born by RIG.

	Which option is acceptable to target group?	*Intervention* ☐	*Comparison* ☐	*Both* ☒	*Neither* ☐	*Unclear* ☐			The majority of the target group consists of rural or marginalized populations who have limited access to health systems and often face resource constraints to pay for RIG and vaccines. High-resource countries where RIG is available in sufficient quantity and affordable to patients have the option to maintain the original policy.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☐	*Yes* ☒	*Varies* ☐		Data show that continued education of healthcare providers is needed to improve correct RIG administration, regardless of the intervention or comparator chosen. Cold-chain and delivery mechanisms are equally challenging for both options. A decision support for clinicians for most appropriate use of biologicals and patient care, would also ease ethical and logistical challenges.	
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 ☐	

<table>
<tr><td>Type of recommendation</td><td>We recommend the intervention

☒</td><td>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)population</td><td>We recommend the comparison

☐</td><td>We recommend against the intervention and the comparison

☐</td></tr>
<tr><td>Recommendation (text)</td><td colspan="4">1. Even if RIG is not available or affordable, prompt local treatment of all bite wounds or scratches, and for category II and III exposures a full course of rabies vaccine is indicated.
2. For patients who can reliably document previous PEP that is equivalent to a PrEP regimen, RIG is not indicated.
3. In cases of shortage or unaffordability, the following groups should be prioritized for RIG allocation:
- Multiple bites
- Deep wounds
- Highly innervated parts of the body, as head, neck, hands, genitals
- Immunocompromised patients
- History of biting animal indicative of confirmed or probable* rabies
- A bite or scratch or exposure of a mucous membrane by a bat can be ascertained

* as per definition WHO Expert Consultation on Rabies: 3rd Report (in press)
Animal Case Definition
The clinical signs of rabies in animals vary widely. An animal rabies case is defined as an animal that presents with any of the following signs:
- Hypersalivation
- Paralysis
- Lethargy
- Unprovoked abnormal aggression (biting 2 or more people or animals, and/or inanimate objects)
- Abnormal vocalization
- Diurnal activity of nocturnal species
Cases of animal rabies are classified as follows:
▪ suspected: a case that is compatible with a clinical case definition of animal rabies
▪ probable: a suspected case plus a reliable history of contact with a suspected, probable, or confirmed rabid animal, and/or a suspect animal that is killed, died, or disappears within 4-5 days of observing illness
▪ confirmed: a suspected or probable case that is laboratory-confirmed
▪ not a case: a suspected or probable case that is ruled-out by laboratory confirmation</td></tr>
<tr><td>Implementation considerations</td><td colspan="4">General training of healthcare personnel especially those managing injuries/emergencies, should include a) management of rabies exposures and PEP, (b) trainings on correct administration of RIG.
Cold-chain and delivery mechanisms are equally challenging for both options.</td></tr>
<tr><td>Monitoring and evaluation</td><td colspan="4">Due to varying quality of available RIG products and no pre-qualification process, rigorous M&E of RIG use and any adverse effects should be conducted.</td></tr>
</table>

Research priorities	

Potency of Intradermal Vaccines

Evidence to recommendation table

Benefits	The immunogenicity of current rabies vaccines administered by ID route for PEP appears as least as good as that of IM vaccination regimens. While ID PrEP seems associated with lower antibody titers than IM PrEP, the observation has not been associated with any clinical relevance. Individual studies included in the present review may be of moderate size and quality, but the large number of reports available helps provide a good level of strength to the conclusions.
Harms	Very limited information available regarding the immunogenicity of ID doses of 0.25 to 0.5 IU ; analysis of efficacy according to vaccine potency not feasible.
Summary of the quality of evidence	MODERATE

Values and preferences	
In favor	(no change to current practices recommended)
Against	-
Uncertainty or variability?	no

Feasibility (including resource use considerations)	-
Uncertainty or variability?	-

Recommendation

There is currently no evidence of a need to revise the WHO recommendation of a potency 2.5 IU/IM dose.
Nevertheless, in view of the limitations of the scientific evidence supporting this recommendation, a regular re-assessment of available information supporting the immunogenicity and efficacy of rabies vaccines administered by ID route is recommended in future years.

Rationale : the current recommendations, including both ≥ 2.5 IU/mL per IM dose and a volume of 0.1 mL per ID dose correspond to a recommendation of ≥ 0.25 IU per dose. Available data do not indicate that vaccines meeting this requirement lack efficacy.