Evidence to Recommendation Table 2

Question: Are there novel approaches to RIG (-sparing) injection vs current practice as part of PEP for category III exposed patients? Such as (a) discontinuation of calculation of RIG dose needed according to body weight and/or (b) RIG into or around the bite wound(s) only without additional administration of remaining RIG to other sites distant to the wound?

Population: Those eligible for RIG (Category III exposed individuals and immuno-compromised category II exposed
Intervention: Dose-sparing use of RIG:
a. RIG volume calculation based on factors other than patient body weight
b. RIG administration to wound area without remaining RIG injection at sites distant to the wound
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 dose 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), short shelf-life and correct administration of RIG are barriers to implementing the standard set by WHO for PEP. This represents a missed opportunity for PEP. There is evidence to suggest that simplifying WHO recommendations to allow for the use of less RIG could be equally effective in the prevention of rabies. RIG is often a barrier for attaining public health impact because of a hesitation to use vaccine without RIG and therefore manufacturers and clinicians often do not want to make vaccines available without RIG, which means no PEP at all. The dose sparing use of RIG based on new evidence available is important issue for consideration. 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 of rabies infection.

	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 the first dose of vaccination. Only a small percentage of severe suspect rabid animal bite victims can currently access RIG due to its high cost and low availability. Public	Rabies causes approximately 59,000 deaths annually and is a public health problem in more than 150 countries

			health authorities' budget for procurement of RIG is in most cases very limited or even absent. Worldwide, only 2% of individuals requiring RIG receive it. Conversely, in other settings there may be a tendency of overuse RIG. Paying for vaccine and RIG can cause catastrophic out of pocket expenses to individuals in rabies-endemic areas (in some settings equivalent to more than a month's salary).	worldwide. Moreover, children under 15 years of age most frequently suffer from severe rabies exposures. As rabies is a neglected 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) Improved access to and more efficient use of life-saving RIG ; (b) more equitable use of RIG, and (c) cost-savings for both individuals and public health sector. 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, 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 small?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	Due to inadequate training and non-standardized volume o administer, clinician decision is needed and adequate training will be required. Clinicians are averse to infiltrating wounds with RIG. Administration of RIG into small wound spaces (*e.g.* finger tips, toes, ears, noses) is limited and may create compartment syndrome and may not achieve a sufficient dose of virus neutralizing antibodies.	The baseline risk for harm is similar across subgroups.
	Balance between benefits and harms	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	Increased affordability, availability and accessibility of RIG in low-resource settings saves lives. Experimental studies in the animal model show that neutralization by RIG occurs at the site of infection and antibodies injected intramuscularly stay at the injection site. Theoretical 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 virus neutralizing antibody titers > 0.5 IU/ml throughout the body, but maybe provide additional safety in severe exposures or when small bite	Training of clinicians in risk assessment and correct post-exposure administration is needed.

			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 observational studies on this subject. As rabies is a fatal disease, conducting randomized controlled trials presents ethical and logistical challenges and therefore would not be feasible.	

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 experimental 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 quality of 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 clinicians often do not want to make vaccines available without RIG, which means no PEP at all.	Most rabies deaths occur in children in low-resource settings.
RESOURCE USE	Are the resources required small?	*No* *Uncertain* *Yes* *Varies*	Resources additional to the current RIG recommendations are not required for this intervention . It will decrease the costs required for RIG	The lower cost per patient may favor an increased uptake

		☐ ☐ ☒ ☐	purchase by both individuals (out of pocket expenses) or health care systems (if subsidized or free of charge to the patient).	by governments resulting in better forecasting and increased affordability.
	Cost-effectiveness	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	This intervention improves cost-effectiveness of PEP as a reduction of 60% to 80% in RIG dose volume can be obtained by the intervention compared to previous recommendations. Modelling results show savings of up to 40% of RIG volume, rapidly increasing with patient throughput as vials can be fractionated more effectively	
EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *Reduced* ☒ Varies ☐	Health inequity would be reduced through this intervention, as more people would have access to RIG and it would 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 highly cost-effective, the acceptability will be high for stakeholders in low-resource settings as it will save additional lives without increasing costs, since less RIG will be needed on average per person	
	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 care 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 individuals 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 resolve some of the 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 care systems. This intervention would be particularly feasible and beneficial in low-resource settings .
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 or F(ab')2 products at 40 IU/kg body weight. 2. After calculating the RIG dose, only the amount of RIG necessary for infiltrating into and around the wound is administered, as much as anatomically possible (*e.g.* to avoid compartment syndrome). The maximum benefits of RIG are gained when administered directly into the wound. For large and multiple wounds, the RIG dose can be diluted with physiological buffered saline to ensure greater wound coverage 3. The remainder of the calculated maximum dose of RIG does not need to be injected IM at a distance from the wound. The dose can be fractionated in smaller, individual syringes to be used for other patients, but this requires aseptic retention 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.
Implementation considerations	General training of healthcare personnel especially those managing injuries/emergencies, should include management of rabies exposures and PEP including RIG administration. 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 being implemented in India and will be in other settings. This intervention should be continued to be evaluated. 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.