## Evidence to Recommendation Table 3

**Question:** In cases of RIG shortage and constraints, can subcategories of patients be identified who should be given highest priority 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 individuals with category III exposures 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) 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 clinicians 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 individuals, a best practice statement may suggest which subcategories of individuals are objectively of the highest priority for RIG allocation and what measures should be best taken for individuals who do not receive RIG.

| | CRITERIA | JUDGEMENTS | | | | RESEARCH EVIDENCE | ADDITIONAL INFO |
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| 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.<br>Only a small percentage of severe suspect rabid animal bite victims can currently 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.<br>Worldwide, only 2% of individuals requiring RIG receive it. Conversely, in other settings there may be a tendency of overuse.<br>Paying for vaccine and RIG can cause catastrophic out of pocket expenses | Rabies causes approximately 59,000 deaths annually. Dogs are the primary source of to humans, contributing up to 99% of all transmissions. Moreover, children under 15 years of age most frequently suffer from severe rabies exposures. As rabies is a |

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| | | | to individuals in rabies-endemic areas (in some settings equivalent to more than a month's salary). | 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><br><br>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 individuals bearing the 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.<br>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, will particularly benefit the subgroups of severely rabies-exposed children and people living in marginalized and low-resource communities. |
| | <u>Harms of the intervention</u><br><br>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 prompt and thorough 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 individuals at higher risk and in low-resource settings saves lives. | Training of clinicians in risk assessment and correct post-exposure |

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| | | ☐ ☐ ☒ ☐ | | administration of RIG is needed. |
| | What is the overall quality of this evidence for the critical outcomes? | Effectiveness of the intervention<br>*No included studies* ☐ *Very low* ☐ *Low* ☒ *Moderate* ☐ *High* ☐<br>Safety of the intervention<br>*No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☒ *High* ☐ | An adequate risk assessment of rabies exposure and timely PEP (including RIG where applicable) is 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.<br>Even in the absence of RIG, field data show that thorough wound washing with immediate vaccine administration and completion of the PEP course saves 99% of patients Tanzanian data that followed up 2196 severely exposed individuals showed that even in the total absence of RIG, the risk of death after a bite by a suspect, but untested dog fell to 0%, if at least two doses of vaccine were received without delay. Similar data from Cambodia (2003-2014) confirmed no deaths among the 62 individuals severely exposed to confirmed rabid dogs and 203 individuals bitten by suspect, but untested dogs. These individuals did not receive RIG because of a worldwide shortage of RIG. | |

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| 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.<br>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 limitations in the studies. | In practice, prioritization is already happening due to shortage, cost, etc. Clinicians are confronted daily with how to allocate scarce RIG to patients at 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.<br>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. | A decision support tool for clinicians to allow for the most appropriate use of Vaccine and RIG 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 | Resources need not be allocated from other locations for implementation. |

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| | 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 patients at highest risk of infection. | |
| EQUITY | What would be the impact on health inequities? | *Increased* ☐ *Uncertain* ☐ *Reduced* ☒ Varies ☐ | Health inequality reduced 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). | |

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| 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 to where it is most needed. More prudent use of RIG might ease the overall ethical challenge of these circumstances and the budgetary burden born by RIG procurement and use. |
| | 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.<br><br>High-resource countries where RIG is available in sufficient quantity and affordable to patients have the option to maintain the original policy. | |

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| 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.<br>A decision support tool for clinicians for most appropriate use of vaccine and RIGand patient care, would also ease ethical and logistical challenges. | |

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| 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 ☐ |

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| Type of recommendation | We recommend the intervention ☒ | We suggest considering recommendation of the intervention<br>☐ Only in the context of rigorous research<br>☐ Only with targeted monitoring and evaluation<br>☒ Only in specific contexts or specific (sub)population | We recommend the comparison ☐ | We recommend against the intervention and the comparison ☐ |

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| Recommendation (text) | 1. If a limited amount of RIG is available, based on expert opinion RIG allocation should be prioritized for exposed patients based on the following criteria:<br>- Multiple bites<br>- Deep wounds<br>- Bites to highly innervated parts of the body, such as head, neck, hands, genitals<br>- Patients with severe immunodeficiency<br>- History of biting animal indicative of confirmed or probable* rabies<br>- A bite or scratch or exposure of a mucous membrane by a bat can be ascertained<br><br>* *as per definition WHO Expert Consultation on Rabies: 3rd Report (in press)* |
| Implementation considerations | General training of healthcare personnel especially those managing injuries/emergencies, should include a) management of rabies exposures and PEP and RIG administration. |
| Monitoring and evaluation | 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 | |