NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

prUPDATED HUMAN RABIES PROPHYLAXIS GUIDELINE: DRAFT

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NATIONAL HEALTH LABORATORY SERVICE
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1. Background

In April 2018, the World Health Organization (WHO) published their revised position on rabies vaccines and rabies immunoglobulins (Available from: http://www.who.int/entity/rabies/resources/who_wer9316/en/index.html).

This document summarises the current recommended regimens for post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP) for rabies in South Africa as of January 2020 (this document replaces rabies post- and pre-exposure regimens previously published).

1.1 Abbreviations

ERIG	Equine-derived rabies immunoglobulin
HRIG	Human-derived rabies immunoglobulin
IU	International units
Kg	Kilogram
mL	Millilitre
PEP	Post-exposure prophylaxis
PrEP	Pre-exposure prophylaxis
RIG	Rabies immunoglobulin

2. Post-exposure management

2.1 Wound management

All wounds have to be washed and **flushed** for approximately 15 minutes using water, or preferably soap and water. When possible, wounds should be irrigated using a syringe. Apply iodine-based topical preparations for disinfection of wounds. Apply additional measures of wound treatment (i.e. tetanus booster vaccination, antibiotic treatment, analgesia) as required on a case-to-case basis.

Suturing of wounds should be avoided or delayed, unless for urgent haemostasis; and local anaesthetic agents should not be used. This is because suturing of wounds and the use of local anaesthetic agents may serve to potentially spread the virus locally.

2.2 Post-exposure prophylaxis

Rabies PEP is considered whenever a patient has been potentially exposed to the rabies virus. A risk assessment should be done, and this should be based on the health status of the animal and its behaviour in that particular incident, the animal species, the local and provincial rates of canine rabies, and the bite wound category. The vaccination status of the animal needs to be considered, bearing in mind that this may not be accurate, and it might have been very recent; in which case the animal may not be protected. See Appendix 1.

2.2.1 Response to different severity of exposure

Figure 1 provides the algorithm for response to different types of exposure and how this relates to PEP management for the patient, who has had no previous rabies vaccines.

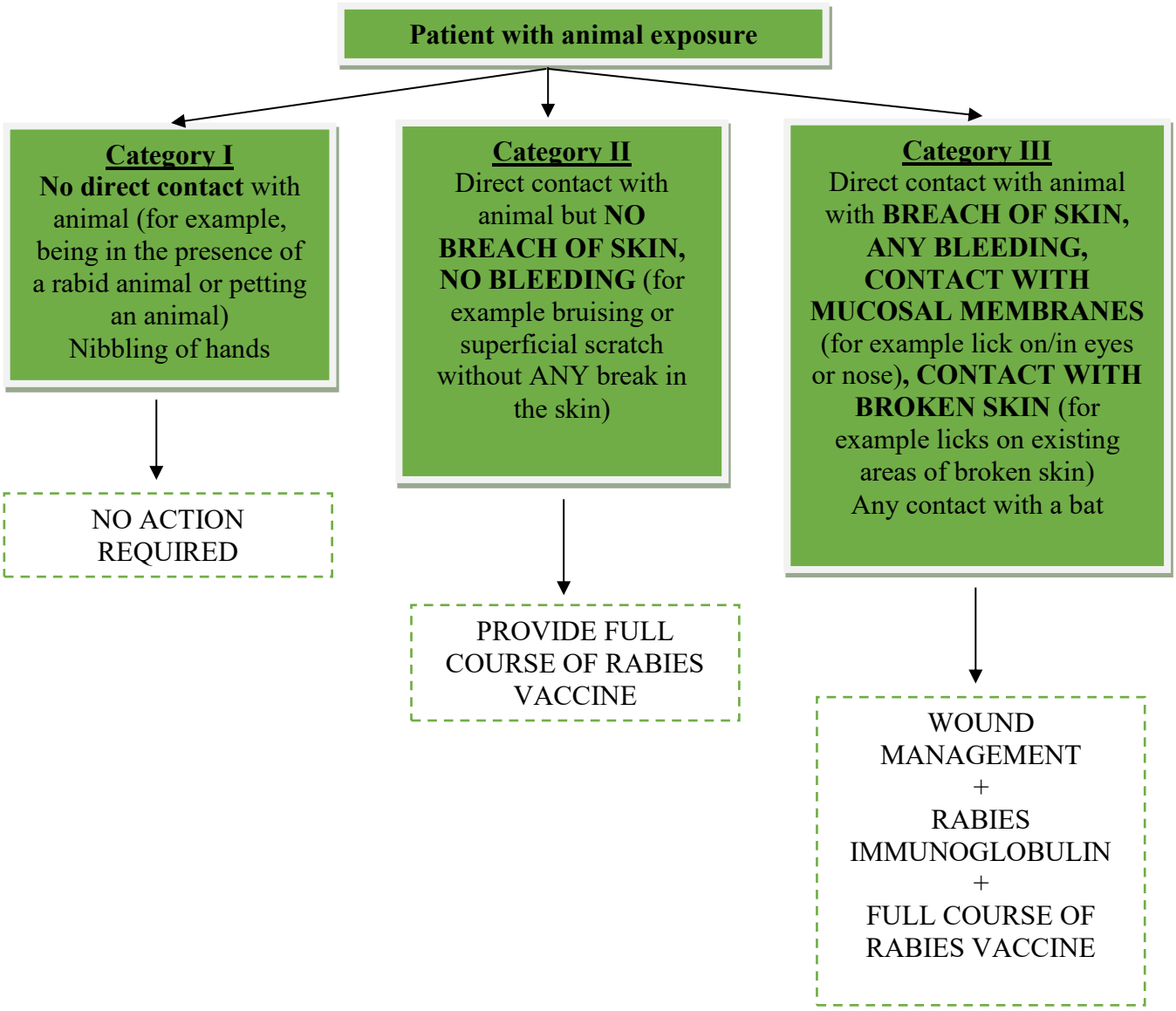

Figure 1: Algorithm for rabies PEP for patients with **no history of previous rabies PrEP or PEP.**

2.2.2 Regimen for rabies vaccine administration

The recommended regimen for rabies vaccine administration in South Africa is provided in Table 1. Four doses of vaccine should be administered intramuscularly, one on each day of days 0, 3, 7 and any day between day 14 to 28.

General considerations:

- If there is a known egg allergy, Verorab™ vaccine should preferentially be given as it is not grown in eggs;
- The dosing for both adults and children is the same (one vial per dose);

- Changes in rabies vaccine product during the same PEP course are acceptable, if unavoidable, to ensure complete PEP course;
- Should a vaccine dose be delayed for any reason, the PEP regimen should be resumed (not restarted), adhering to the minimal intervals between doses;
- The intramuscular vaccine must not be administered in the buttocks.

Table 1: Summary of PEP regimen for rabies vaccines currently available in South Africa

PRODUCT NAME	DOSAGE	SITE OF ADMINISTRATION	SCHEDULE
Verorab™	0.5 ml (one vial)	Intramuscular. Deltoid muscle in adults, anterolateral thigh in small children (aged < 2 years)*	One dose each on days **0, 3, 7 and any day between day 14 and 28

* The dosing for both adults and children is the same.
**Day 0 is the day of presentation to a health facility and when the first vaccine is administered.

2.2.3 Regimen for rabies immunoglobulin (RIG) administration

Either human-derived rabies immunoglobulin (HRIG) or equine-derived rabies immunoglobulin (ERIG) can be used (see Tables 3 and 4). Due to the potential for anaphylactic reactions with the administration of ERIG, it is recommended that ERIG only be used in facilities where cases of anaphylactic or adverse reactions can be managed. The incidence of anaphylaxis following ERIG administration is however low. Skin testing is not recommended prior to the use of ERIG.

The effect of RIG is to neutralise the virus at the wound site/site of exposure. As much as possible of the calculated dose of RIG should be infiltrated in and around the wound site/s. For smaller wounds/areas where it is not possible to infiltrate the entire calculated dose, infiltrate as much as is anatomically feasible in and around the wound site/s (Tables 2 and 3), (see Appendix 2). According to WHO, evidence has shown that maximum infiltration of RIG in and around the wound is effective and that there are no benefits from additional intramuscular administration of any remaining RIG at a site distant to the wound. For small wounds in highly innervated areas, for example on the finger or face, see appendix 2 for the maximum dose with which to infiltrate the wound.

Wounds on the face, eyelid, scalp ear and similar sensitive areas pose a challenge for local administration, especially in children. All wounds on the face are high- risk and rabies disease may present after a short incubation period. It is **CRITICAL** in these cases that RIG is infiltrated **INTO THE WOUNDS.**

2.2.3.1 Mucosal exposure

For mucosal exposures with no wound, rinse thoroughly with water, active immunisation is recommended with a vaccine course. Lavage of the area with RIG has been used but this is not an evidence- based recommendation.

2.2.3.2 Multiple wounds

RIG must be infiltrated into every wound. Dilute the RIG with normal saline to ensure sufficient volume to infiltrate all the wound areas.

NB: See Appendix 2 (Example for the dosing of RIG products) to determine the number of mls/vials to be administered

Table 2: Summary of regimen for HRIG

PRODUCT NAME	MAXIMUM DOSAGE	DESCRIPTION	SITE OF ADMINISTRATION	SCHEDULE
i. Rabigam®	20 IU/kg bodyweight	150 IU/mL Supplied in a 2 mL vial	Infiltrate up to the maximum calculated dose in and around the wound site/s. For smaller wounds/areas where it is not possible to infiltrate all of the calculated dose, infiltrate as much as is anatomically feasible in and around the wound site/s. See Appendix 2.	Ideally on day 0 (when patient presents for first time)/ as soon as possible after exposure to be effective to neutralise virus. When RIG is not available it should be sourced as a matter of urgency. When 7 days have lapsed since initial rabies vaccination, RIG is no longer indicated as the vaccine -induced immune response will be effective.
ii. KamRAB® only available on section 21 permit	20 IU/kg bodyweight	150 IU/mL Supplied in 2, 5 and 10 mL vials.		

Table 3: Summary of regimen for ERIG- <u>PRODUCT DOSAGES VARY</u>, <u>check package insert</u>

PRODUCT NAME	MAXIMUM DOSAGE	DESCRIPTION	SITE OF ADMINISTRATION	SCHEDULE
i. Equirab®	40 IU/kg bodyweight	200 IU/mL Supplied in a 5 mL vial.	Infiltrate up to the maximum calculated dose in and around the wound site/s. For smaller wounds/areas where it is not possible to infiltrate all of the calculated dose, infiltrate as much as is anatomically feasible in and around the wound site/s. See Appendix 2	Ideally on day 0 (when patient presents for first time)/ as soon as possible after exposure to be effective to neutralise virus. When RIG is not available it should be sourced as a matter of urgency. When 7 days have lapsed since initial rabies vaccination, RIG is no longer indicated as the vaccine -induced immune response will be effective.

2.3 Special considerations

2.3.1 Immunocompromised individuals

Individuals with documented immunodeficiency, such as symptomatic HIV infection, should be evaluated on a case-by-case basis and receive a complete course of PEP including RIG (see tables 1-3). Irrespective of category of exposure or previous vaccination history, RIG and four doses of rabies vaccine should be administered, one on each day of days 0, 3, 7 and any day between day 14 and 28.

2.3.2 Pregnant and lactating women

Rabies vaccine and RIG are safe and effective in pregnant and lactating women, and should be given if indicated. The dose is the same as in a non-pregnant adult (see tables 1-3).

2.3.3 Patients who have received previous PrEP or PEP

In these individuals, RIG is not indicated. For PEP, two doses of rabies vaccine should be administered on days 0 and 3. Rabies vaccination provides long-lasting immunity. Rabies PEP is not recommended in the event of repeat exposures (i.e. re-exposure within 3 months of completion of PEP or PrEP). For repeat exposures occurring >3 months after the last PEP, the PEP schedule for previously immunised individuals should be followed; which is two doses of rabies vaccine administered on days 0 and 3.

2.3.4 Delayed presentation

Rabies PEP should ideally be provided as soon after exposure as possible. When patients, present well after the exposure event, regard the first day of presentation as day 0 for vaccine and RIG administration. When wounds have healed, the RIG can be infiltrated in and around previous wound site.

2.3.5 Consumption of raw meat and milk from a rabid animal

No case of human rabies resulting from consumption of raw meat from a rabid animal has been documented. The rabies virus has never been isolated from milk of rabid cows and no documented human rabies case has been attributed to consumption of raw milk.

3. Pre-exposure management

Rabies PrEP is recommended especially for individuals at high or continual risk of exposure to the rabies virus. This may include individuals with predisposition for exposure i) due to their occupation such as veterinarians, other veterinary health professionals or laboratory workers, or ii) due to their hobbies such as bat enthusiasts.

Travellers to rabies endemic areas, where rabies PEP may not be easily accessible should also be considered for rabies PrEP.

The 2018 WHO position paper on rabies recommend the reduction of PrEP schedule to a two day regimen (i.e. days 0 and 7). Long–term follow up immunogenicity data for this regimen for boosterability is limited. Until this data is available, those at high or continual risk for rabies exposure (e.g. veterinarians) should receive the previously recommended 3 day regimen (i.e. days 0, 7 and 21/28). Individuals with documented immunodeficiency should receive one dose on days 0, 7 and 21 or 28. See Table 4.

The WHO recommends intradermal vaccination as a safe and effective alternative to intramuscular vaccine administration. See Table 4. In order **to realise the cost benefit due to dose- sparing** associated with intradermal vaccination, **it is recommended for PrEP administration** where groups of individuals (for example a team of veterinarians or a travel group) will receive PrEP simultaneously.

For example, 1 vial containing 1.0 ml (0.5 ml) dose of vaccine, could ideally be used for up to 10 (5) intradermal doses of vaccine.

3.1 Regimen for rabies vaccine administration

Table 4: Summary of PrEP regimen for rabies vaccines available in South Africa

PRODUCT NAME	DOSAGE	SITE OF ADMINISTRATION	SCHEDULE
i. Verorab™	0.5 ml (per vial) For intramuscular, full vial. For intradermal, 0.1 ml per dose	Intramuscular. 1-site IM vaccine. Deltoid muscle in adults. **OR** Intradermal*. 2-site ID vaccine. Usual site is the deltoid area. Discard open vial within 6-8 hours of opening.	**Intramuscular:** One dose on days 0 and 7. Individuals with documented immunodeficiency should receive one dose on days 0, 7 and 21/28 **Intradermal:** Two doses (at two different sites) on days 0 and 7. Individuals with documented immunodeficiency should receive two doses (at two different sites) on days 0, 7 and 21/28

*The intradermal schedule is recommended when PrEP is applied to groups of individuals and a cost benefit would apply (i.e. a single vial represents multiple doses).

3.2 Special considerations

3.2.1 Immunocompromised individuals

Individuals with documented immunodeficiency, such as symptomatic HIV infection, should be evaluated on a case-by-case basis and receive a complete course of PrEP course as in 3.1. In the event of possible exposures, full PEP should be provided as described in 2.3.1.

3.2.2 Pre-exposure vaccination boosting

Testing for antibodies is preferable, but for patients who cannot access rabies antibody titer testing (see 3.3), pre-exposure boosting is recommended every 2 years for those at high risk of exposure, e.g. veterinarians.

3.3 Laboratory testing of antibody titers

Laboratory testing for post-vaccinal rabies antibody titers is available from the National Institute for Communicable Diseases.

Testing of antibody titers are recommended in order to determine if pre-exposure boosting is required to maintain an adequate level of immunological memory to support PEP responses in the event of an exposure. **PEP is required in the event of exposure to the rabies virus, regardless of the antibody titer induced by PrEP.**

3.4 Administering vaccine at same time as other vaccines/medicines

Rabies vaccines can be administered at the same time as other vaccines, but at different sites**.** A tetanus containing vaccine should also be given for a rabies exposure, if appropriate.

Mefloquine (for malaria prophylaxis) should not be administered at the same time as intradermal rabies doses, if possible administer the rabies vaccine one to two months before starting malaria prophylaxis. Alternatively use the rabies vaccine intramuscularly.

Appendix 1: Guidelines for risk assessment for possible rabies virus exposure

Important factors that assist decisions on PEP management include details of the nature of the contact and the implicated animal's behaviour.

Do not delay! It is imperative that prophylaxis be instituted as soon as possible after exposure to rabies virus, even before there is laboratory confirmation of rabies in the animal.

Judgement on whether to initiate PEP is assisted by an estimation of risk based on the following criteria, with a high risk of exposure necessitating PEP:

- **Animal involved in the contact.** Domestic dogs and cats are important vectors of rabies virus to humans. All mammalian species may potentially be infected with the virus, however, small rodents e.g. mice and rats commonly found in and around dwellings are not typically associated with rabies. Human rabies in association with mongoose bites is well documented. Rabies in vervet monkeys has not been confirmed to date in South Africa. Rabies has very rarely been reported in baboons. Rabies in livestock including cattle and goats is well-documented. Snakes and reptiles pose no risk for rabies. Bats are an uncommon source of human rabies, and only associated with rabies-related viruses in South Africa. Bat bites may be very small and not obvious – direct contact with a bat (such as bite or scratch) requires full PEP.
- **Animal's behaviour and health.** Animals that may transmit the virus will themselves be affected with the disease. Any abnormal behaviour or signs of ill- health in the animal could indicate rabies.
- **The geographical location** of the exposure. Rabies is endemic in South Africa, but the risk of rabies transmission is not equal in all locations. Rabies is relatively more common in domestic dogs in KwaZulu-Natal, Eastern Cape, Mpumalanga, Free State and Limpopo provinces. Human rabies associated with wild animals dominates in the western, central or northern portions of the country.
- **The rabies vaccination status of the animal.** The vaccination status of the animal needs to be considered, bearing in mind that this may not be accurate, and it might have been very recent; in which case the animal may not be protected. Consider the validity of the vaccination certificate and the timing of vaccination (i.e. if vaccinated in the two weeks preceding the exposure event, may not be immune yet and may have been incubating rabies already at the time of vaccination).

Appendix 2: Example for the dosing of RIG products

Scenario:
It is determined that patient A requires rabies PEP following a category III exposure. The patient weighs 50kg and:

A) the product available is HRIG A (available in vials containing 150 IU/ml at 2ml per vial). In the scenario, patient A has suffered a) multiple bite wounds; or b) a small transdermal scratch on the ear pinna.
B) The product available is ERIG (available in vials containing 200IU/ml in a 5 ml vial)

A) Solution:
Calculate the number of maximum dose of RIG in IU required for patient A.

We require a maximum dose of 20 IU/kg for HRIG product and the patient weighs 50kg, thus:

20 IU X patient's weight

= 20 IU X 50kg
= 1000 IU required for maximum dose

We know that 1 vial of 2mL contains 300 IU (1 mL = 150 IU), so how many vials do we need to fulfil the maximum dosage?

1 vial of 2mL contains 300 IU
Y vials of 2mL contain 1000 IU

= 1000/300
= 3.33 vials required for maximum dose

So, a total of 3.33 vials are required to treat patient A with the maximum dosage of RIG. This will equate to a total volume of RIG of 6.66 ml (i.e. 3.33 X 2 ml/vial).

B) Solution:
The patient needs 40IU/kg of ERIG. He weighs 50kg and therefore needs 2000 IU. Each vial contains 1000IU. He therefore needs 2 X 5ml vials.

For scenario a (i.e. multiple bite wounds), infiltrate the product in ALL wounds (the product may be further diluted with normal saline to ensure that ALL wounds are reached).

For scenario b (i.e. a small transdermal scratch on ear pinna), it may not be possible to infiltrate the maximum volume of RIG calculated due to the size and location of the wound without risk for compartmentalisation. **It is important to infiltrate as much RIG, up to the maximum dose, even in small wounds.**

Anatomic location and indication of volume of RIG – a Guide

Anatomic location	Minimum volume of RIG /wound	Maximum volume of RIG /wound
Finger/toe	2	2
Hand/foot	2	4
Knee/ankle/wrist/elbow	2	6
Under arm/leg	4	10
Upper arm/leg/torso	4	10
Face/head	2	10

For small wounds, it is suggested that one vial be opened at a time (up to the maximum number of vials calculated) and wound infiltrated as much as possible without compromising blood supply. It is important to avoid the compartment syndrome.