Guidelines for human Rabies Prophylaxis

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Epidemiology

- Rabies is a vaccine-preventable viral zoonotic disease
- Rabies is an almost 100% fatal disease
- Estimated **59, 000** human rabies deaths every year in the world
- Transmission by dogs is responsible for up to 99% of human rabies cases
- In Nepal about 100 human rabies cases are estimated to occur every year

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Rabies situation in the world

- Neglected Tropical disease
- Most Rabies cases are reported from Africa & Asia
- 80% cases are from rural areas
- 40% are in children <15 years of age
- Global economic burden is US $ 8.6 billion
- 3.7 million disability-adjusted life years (DALYs) lost every year

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Status of reported dog bites and rabies cases in Nepal

Fiscal year	No of cases of dog bites	No. of cases of other animal bites	No. of cases of animal bites (dog + other animal)	No. of ARV vials consumed	Deaths
2008/09	24,005	2,571	26,576	145,978	97
2009/10	23,517	2,145	25,662	168,194	89
2010/11	24,269	2,197	26,466	167,663	83
2011/12	29,102	2,211	31,313	229,851	76
2012/13	31,937	2,996	34,933	219,651	68
2013/14	31,976	2,540	34,516	195,868	10
2014/15	17,320	3,290	20,610	273,000	13
2015/16	20,133	2,494	22,627	320,139	6
2016/17	23,726	2, 518	39,774	217,639	8
2017/18	26,312	2,202	28,514	281,718	32

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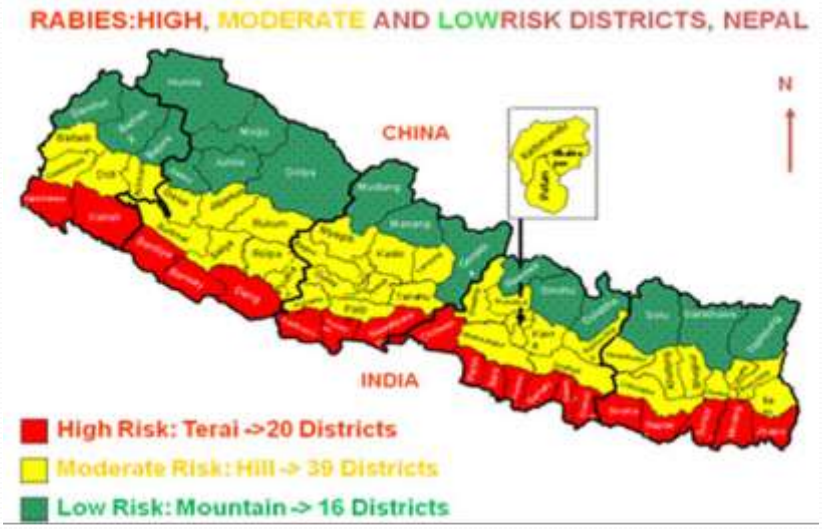
Rabies risk zones in Nepal



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WHO Recommendations

Aim of WHO

"Global elimination of dog mediated human Rabies by 2030"

WHO has published in 2018

- Position Paper
- Technical Report Series

focusing on programmatic feasibility, simplification of vaccination schedules and improved cost-effectiveness.

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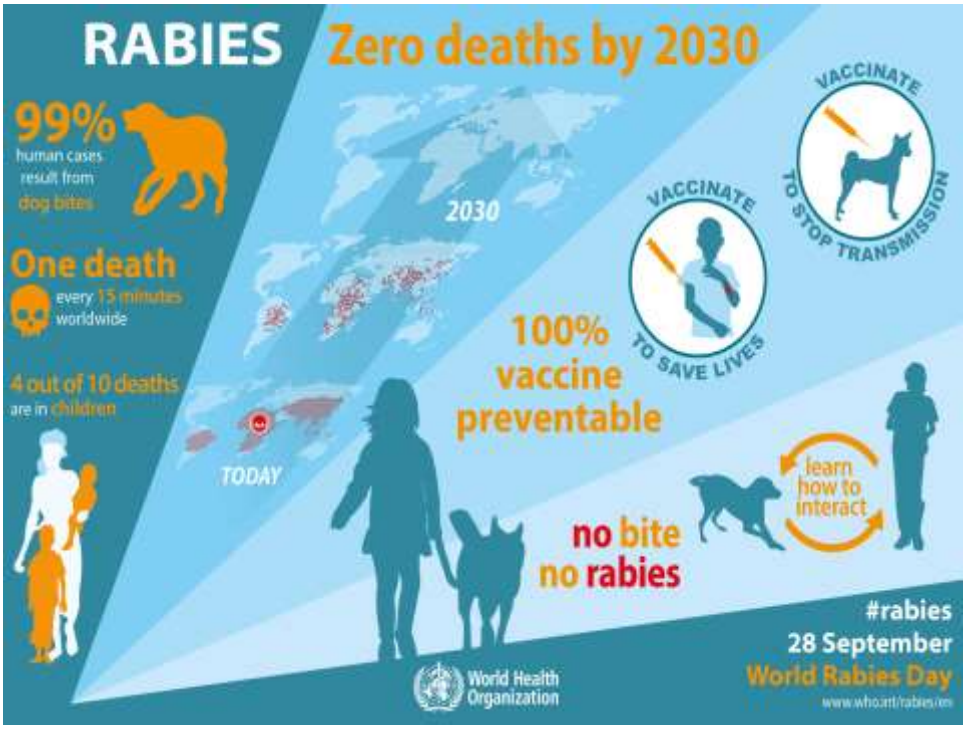

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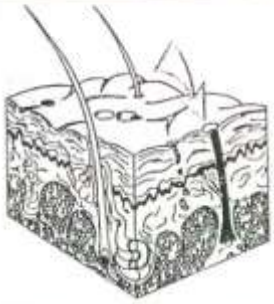
Transmission of Virus



⊕ Through broken skin

⊕ Organ transplants

⊕ Through intact mucosa

⊕ Inhaled as an aerosol in Bat caves

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Animals transmitting Rabies

- All mammals are susceptible to infection by the rabies virus (RABV) and can transmit Rabies to other animals and human beings
- Exposure to domestic rodents, squirrel, hare and rabbits do not routinely require PEP.

  No human rabies cases due to bites by rodents have been reported

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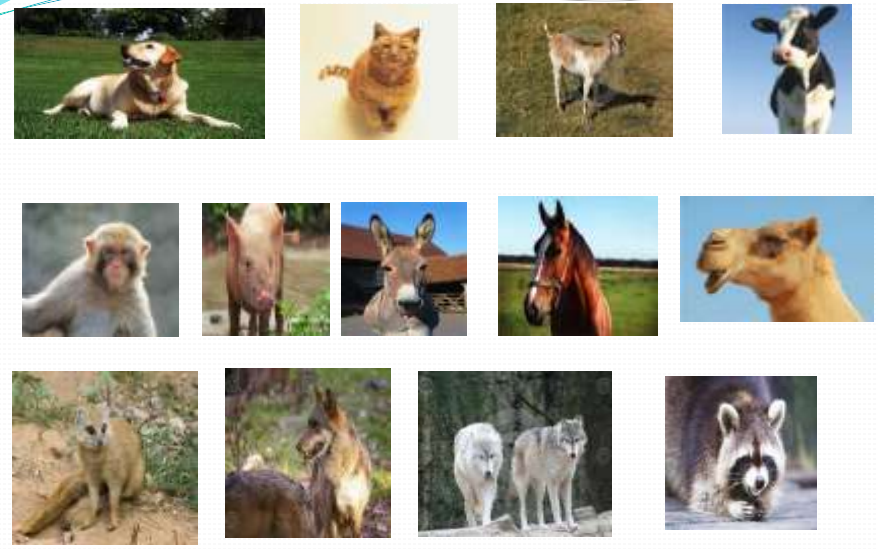

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Incubation Period of human Rabies

- 1 month to 3 months commonly
  May vary from one week to one year

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Clinical Presentation

Classical rabies (Encephalitic form) (80% of cases)

- Hydrophobia
- Aerophobia and photophobia
- Spasms, convulsions
- Excitation, confusion, excessive sweating, salivation and dehydration
- Respiratory paralysis, cardiac arrest and death in 2-5 days

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Clinical Presentation

Paralytic Rabies

- Gradual ascending paralysis
- Hydrophobia not seen
- May resemble G-B syndrome
- Myoedema and piloerection
- Stupor, coma and death in 1-2 weeks

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WHO Classification of Exposures

Category I

- Touching or feeding an animal
- Animal licks on intact skin

(No exposure)

Treatment
None

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WHO Classification of Exposures

Category II

- Nibbling of uncovered skin
- Minor scratches or abrasions *without bleeding*

(Exposure)

Treatment

Administer Vaccine immediately

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WHO Classification of Exposures

Category **III**

- Single or multiple trans-dermal bites or scratches
- Contamination of mucous membrane or broken skin with saliva from animal licks

(Severe Exposure)

Treatment

Administer Rabies Vaccine immediately and Immunoglobulins asap

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Post Exposure Prophylaxis (PEP)

Comprises three components

- Local wound treatment
- Passive Immunization (RIGs)
- Active immunization (Vaccine)

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Local wound treatment

- To be done immediately or as soon as possible after exposure (Cat. II & III)
- Wash and flush the wounds thoroughly with soap/detergent and copious amounts of water for 15 minutes

(This **reduces risk of infection by 50%)**

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Local wound treatment

- Apply Povidone Iodine / Spirit (70%) (virucidal agents) over the wound
- Tetanus prophylaxis
- Antibiotics and analgesics , if needed

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Practices to be avoided

- **Suturing of the wounds should be avoided**
  - It **increases** local trauma and helps in large area of tissues to come in contact with the virus
- If suturing is unavoidable
  - First infiltrate the wounds with RIGs
  - Postpone suturing for a few hours
  - Minimum sutures to be applied

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PASSIVE IMMUNITY-Importance

- Vaccine stimulates antibody production in the recipient by 7 to 14 days
- Protective titers in all vaccine recipients by day 14
- Patients are vulnerable during this window period of up to 14 days, especially when bites are on highly innervated areas
- Timely and proper administration of RIGs can neutralize the virus at the site of exposure

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RABIES IMMUNOGLOBULINS(RIGs)
WHO RECOMMENDATIONS

Recommended in all Category III Exposures

To be administered as soon as possible after exposure

RIGs should be preferably given along with the first dose of vaccine

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RABIES IMMUNOGLOBULINS

- Can be given irrespective of the interval between exposure and starting treatment (i.e., if treatment is delayed)
- Not recommended beyond day 7, after administration of first dose of vaccine

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RABIES IMMUNOGLOBULINS

- RIGs : As much as possible should be infiltrated into and around the wounds
- *All the wounds should be infiltrated with RIGs*
- RIGs should be given as a single dose (not to be repeated)

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Types and dose of RIGs

- Human RIGs
  dose : 20 IU/kg body wt
- Equine RIGs (purified Fab2 fragments)
  dose : 40 IU/kg body wt
- Recommended dose of RIGs should *not* be exceeded

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Multiple wounds

- the calculated volume of RIG should be diluted in sterile physiological saline to a volume sufficient to infiltrate all the wounds

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RIGs- use in immune compromised

- Are life saving in immunecompromised individuals and patients on immune suppresants
- Very useful in A.I.D.S./HIV positive patients with animal exposures
- Recommended even in Class II Exposures in these patients

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ERIG administration

Keep patient under observation for at least half–an–hour after ERIG administration

Following medicines should be kept ready

- Inj.Hydrocortisone
- Inj.Pheniramine maleate
- IV Fluids, Oxygen
- Inj.Adrenaline-1 in 1000 ,1mg/ml
  (dose: Adults-0.5 ml ; Children-0.01ml/kg)
- Deriphyllin, Dopamine, Ranitidine

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If RIGs are not available

- Thorough wound cleaning and application of a potent antiseptic (virucidal) agent
- and administration of the first dose of vaccine

should be performed immediately, when the patient presents

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RABIES VACCINE

Chronology

- 1880s: **Louis Pasteur** develops Vaccine derived from spinal cord of Rabbit
- 1911: **Sir David Semple** develops sheep brain derived Vaccine
- 1965: 1st Cell culture vaccine (HDCV)
- 1984: WHO recommends use of CCVs
- 1992: WHO recommends phasing out NTV

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RABIES VACCINE

- CCEEVs : Cell culture and embryonated egg-based rabies vaccines
- highly immunogenic and safe
- After growth in cell culture (or embryonic egg), the viral harvest is concentrated, purified, inactivated and *lyophilized* (freeze dried)
- Rabies Vaccine should be stored between 2° to 8° C
- *The diluent supplied by the manufacturer should be used for reconstitution of the vaccine*

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Routes of administration

- Intramuscular (IM) or
- Intradermal (ID)
- Rabies vaccines are manufactured as individual vials for IM use (no separate ID vials)
- Potency should be ≥ 2.5 IU per IM dose
- One IM dose is entire content of vial (diluent may be 0.5 ml or 1.0 ml)
- One ID dose is 0.1 ml of reconstituted vaccine
- Day O is the date of administration of the first dose of vaccine (ID or IM)

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IDRV
(Intra dermal Rabies Vaccination)

- Introduced in Nepal in 2017
- With same quantity of vaccine vials, more patients can be given vaccine when compared with Intramuscular route
- Reduces cost of vaccine used by 60 to 80%
- Safety and efficacy of IDRV has been proven

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IDRV-Precautions

- Vaccine has to be approved for ID use
- Staff should be adequately trained
- Cold chain to be maintained
- Once reconstituted and used for one patient , the vaccine should be stored between 2° to 8° C and used for other patients within 6- 8 hours
- Disposable Insulin syringes with fixed needles (not detachable needles) should be used for IDRV

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Intra Dermal Route -Scientific Basis

- Dermis is rich in antigen presenting cells
- Compared to I-M or S-C route, delivery of vaccine through I-D route induces protective immune response with <u>smaller doses of vaccine</u>

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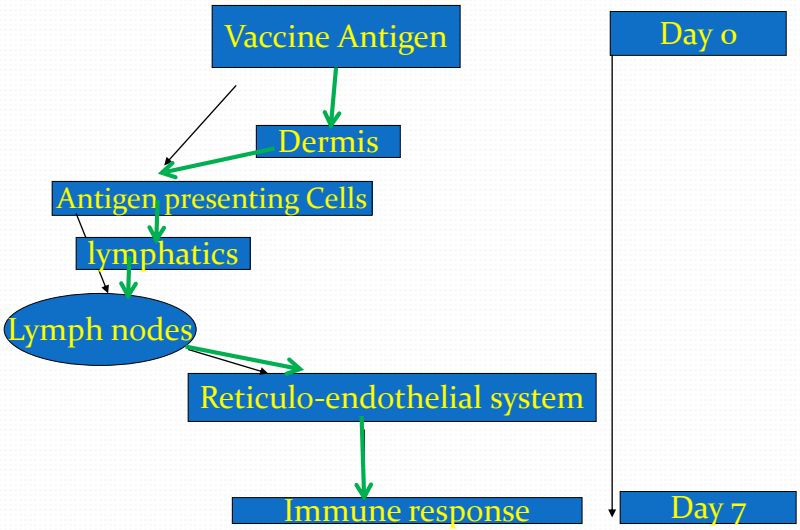
Mechanism of action of IDRV



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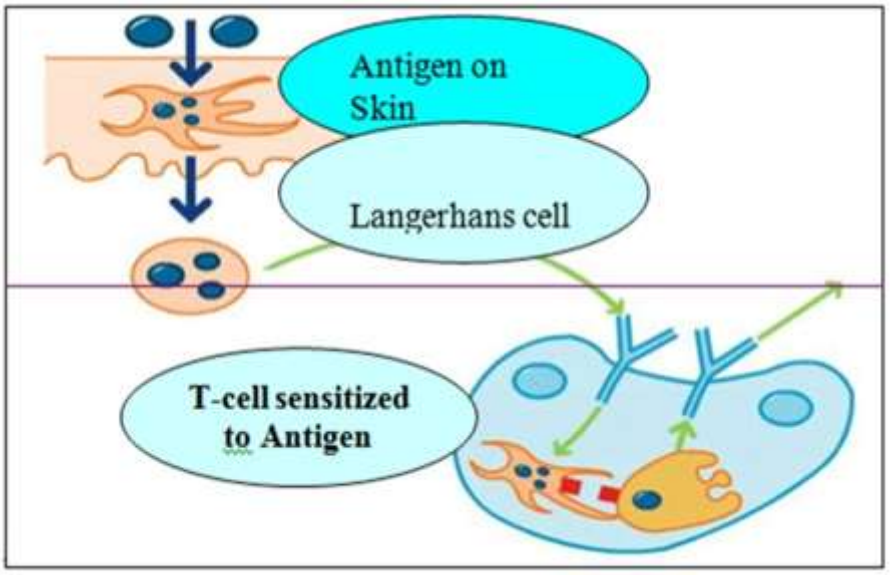

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IDRV –dose and site

- 0.1 ml of reconstituted vaccine is administered per ID site
- common site of injection is the deltoid (upper arm).
- Other sites are
  antero- lateral part of the thigh (in children) and
  supra scapular region (in adults).

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IDRV Regimen

Regimen	Visit days	Number of injections per clinic visit	Duration
1 week 2 sites	days 0,3 &7	2-2-2	7 days

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Intramuscular Regimens for PEP

Regimen	Duration	Number of injections per clinic visit
2 weeks (modified Essen)	14 -28 days	1-1-1-1-0 (days 0,3,7 & 14 to 28)
3 weeks (Zagreb)	21 days	2-0-1-0-1 (days 0,7 & 21)

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Infants and Children

- Dosage and schedule of CCEEVs is same as in adults (both IM and ID)
- CCEEVs can be administered in antero-lateral aspect of thigh (in children < 2years of age) or deltoid

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Exposure of Pregnant / Lactating Women

- Pregnancy – is NEVER a contraindication to post - exposure rabies prophylaxis
- Lactating patients can be given PEP
- RIGs and Rabies Vaccine can be safely administered to pregnant or lactating women

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PEP in Immunecompromised

- Persons on Immunesuppresants or HIV +ve patients:
  Following PEP is recommended-

1] thorough wound wash

2] RIG in both Category II and III exposures

3] full course of Rabies Vaccine

If facilities are available: RVNA to be estimated 14 days after the last dose of vaccine to assess need of additional doses of vaccine

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PEP

- In view of the almost invariably fatal outcome of rabies,
  there is no contraindication to PEP
- No case of human rabies resulting from consumption of raw meat or milk from a rabid animal has been documented

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Is it advisable to start PEP several days after exposure to the animal ?

Due to wide variation in the incubation period, treatment should not be withheld, irrespective of the lapsed time interval.

Such patients should be carefully evaluated and treated

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Adverse Events after vaccination

- CCEEVs are safe and well tolerated
- In 35–45% of vaccinated people minor, transient erythema, pain or swelling occurs at the site of injection
- in 5–15% of vaccinated people mild systemic adverse events : transient fever, headache, dizziness and gastrointestinal symptoms
- Serious adverse events are rare

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Treatment failures

- Delay in seeking treatment
- Improper wound care
- unnoticed wounds
- direct inoculation of the virus into nerve
- lack of or improper administration of rabies immunoglobulin (failure to inject all bite sites)

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Vaccine failures

True vaccine failures are extremely rare

- lack of patient compliance with vaccination schedules
- Improper cold chain
- Use of vaccines that do not have their stated efficacy

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Pre-Exposure Prophylaxis (PrEP)

Recommended for

- ✓ Persons at high risk of exposure to Rabies:
  - ➢ Medical professionals attending on rabies patients
  - ➢ Animal health care workers
  - ➢ Research and lab. personnel handling rabies virus
  - ➢ Travellers to rabies endemic areas
- Sub-populations in remote rabies-endemic settings where the incidence of dog bite is >5 %

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PrEP Regimens

Regimen	Duration	Number of injection sites per visit
WHO Recommended ID regimen		
Two visits	7 days	2-0-2-0-0
WHO Recommended IM regimen		
Two visits	7 days	1-0-1-0-0

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PEP in case of Re-exposure

Administration of **2 booster doses** after Primary course of vaccination (PEP or PrEP) results in good anamnestic response in *normal, healthy* individuals

This response will occur whether:

-the initial vaccine regimen was administered IM or ID

-the booster dose is given by IM or ID route

Persons who cannot document previous PEP or PrEP and those who have taken NTV previously, should be treated as a fresh case and given complete PEP

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PEP in Re-Exposure

	Category I Exposure	Category II Exposure	Category III Exposure
Previously immunized individuals of all age groups	No PEP required	1)Wound washing 2) Immediate vaccination: 1-site ID on days 0 and 3 or 1-site IM on days 0 and 3 RIG is not indicated	1)Wound washing 2) Immediate vaccination: 1-site ID on days 0 and 3 or 1-site IM on days 0 and 3 RIG is not indicated

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Prevention of human rabies

The Important Things

Traditional Practices
DO NOT HELP

Do not cover or
Suture the wound

Wash the wounds thoroughly with water and soap at the earliest

Apply povidone iodine or alcohol

Start Vaccination asap
Administer RIGs, when needed

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THANK YOU

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