NATIONAL GUIDELINES FOR MANAGEMENT OF RABIES AND ANTI-RABIES PROPHYLAXIS

3rd Edition 2023

Zoonotic Disease Control Unit
Public Health Emergency Program
Department of Public Health
Ministry of Health, Thimphu Bhutan

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FOREWORD

Rabies is an important zoonosis which continue to be one of the major public health problem in the country. Regular rabies outbreaks are reported annually in animals in Bhutan that pose constant risk of transmission of the deadly virus to human. The country witnessed 1 or 2 sporadic human rabies deaths every year prior to 2020 but since then, no human rabies deaths have been recorded in Bhutan.

This virtually 100% fatal nature of the disease is preventable through timely and appropriate post-exposure treatment. Modern, safe and effective anti-rabies Cell Culture Vaccines (CCVs) are being used for post-exposure prophylaxis which are provided free of costs in all health facilities across the country. However, with increasing awareness of the people on rabies and animal bite cases presenting for rabies PEP in health centers, it is important for health workers to perform conduct appropriate risk-assessment to administer appropriate prophylaxis. In order to overcome rising costs of anti-rabies PEP and to ensure wider and uninterrupted accessibility to anti-rabies vaccines, Ministry of Health recommended intra-dermal route of vaccine administration (IDRV) since 2013. The IDRV should now be the routine route of ARV administration in all health facilities as recommended in this guideline unless when it is contraindicated or in unavoidable circumstances.

This is the 3rd edition of the national guideline on human rabies case management and antirabies prophylaxis developed jointly by experts from human and animal health sectors. This national guideline was reviewed and revised in the light of new recommendations of WHO Expert Consultation on Rabies in 2018 and final consultation from Technical Advisory Group and experts in 2020, and all the relevant health workers at all level of health care settings in August 2023 to achieve and maintain zero human death from rabies. The guidelines should help to improve in making rational use of rabies vaccine and immunoglobulin. The guideline is an outcome of consensus deliberations of the expert group which is brought out for publication, wider circulation and compliance by health workers and other relevant health officials in Bhutan.

I hope this publication will be of immense use for our health workers for managing the animal bites cases and in making appropriate decision for prescribing anti-rabies prophylaxis.

Karma Jamtsho
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Abbreviations and Acronyms

CSF	Cerebrospinal Fluid
FAVN	Fluorescent Antibody Viral Neutralization
FAT	Fluorescent Antibody Test
DRIT	Direct Rapid Immunohistochemical Test
RABV	Rabies Virus
PEP	Post Exposure Prophylaxis
PrEP	Pre-Exposure prophylaxis
ID	Intra-Dermal
IM	Intra-Muscular
SC	Subcutaneous
IDR	Intra-dermal route of Vaccination
CCVs	Cell Culture Vaccines
NCAH	National Centre for Animal Health
NEWARS	National Early Warning, Alert and Response System
NASBA	Nucleic Acid Sequence–based Amplification
RCDC	Royal Centre for Disease Control
PCECV	Purified Chick Embryo Cell culture Vaccine
PVRV	Purified Vero Rabies Vaccine
RFFIT	Rapid Fluorescent Foci Inhibition Test
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
HDCV	Human Diploid Cell Vaccine
PDCV	Purified Duck Cell Vaccine
eRIG	Equine Rabies Immunoglobulin
hRIG	Human Rabies Immunoglobulin

INTRODUCTION

Rabies is a neglected zoonotic disease caused by RNA virus. It has the highest documented case-fatality rate, approaching close to 100%. The estimated number of human rabies deaths globally is 59,000 annually. The vast majority of these deaths occur in Asia (59.6%) and Africa (36.4%) and 99% are dog-mediated rabies. The overall economic costs of dog-mediated rabies were estimated to be US$ 8.6 billion. In 2015, World Health Organization (WHO) and World Organization for Animal Health (OIE), in collaboration with Food and Agriculture Organization (FAO) and the Global Alliance for Rabies Control (GARC) launched the Global framework for the elimination of dog-mediated human rabies to achieve a global goal of zero human rabies deaths by 2030. Bhutan has committed to prioritize rabies elimination in its national plans and human and animal health stakeholders are collaborating and working closely to achieve dog-mediated human rabies death elimination by 2030. In Bhutan, rabies is commonly reported in the southern districts of the country that share direct and porous border with India. However, sporadic outbreaks are reported in some interior districts (Tashigang, Tashi Yangtse, Haa) as a result of incursion of disease from the bordering areas which pose a risk of establishing endemic transmission (Figure 1). Based on Annual health Bulletin published by the Ministry of Health, annual average of 7000 dog bites (1026 bites per 100,000 people annually) occur in the country and 18 human rabies deaths had been recorded between 2006 - 2022, equivalent to a cumulative incidence of 2.38 per 100,000 population. The annual public health expenditure incurred for providing human PEP is approximately Nu. 9.3 million (USD 142,000).

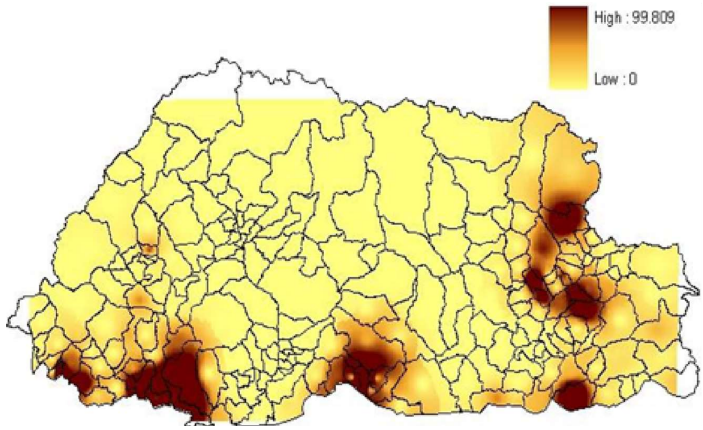

Figure 1: Map of Bhutan showing risk of rabies transmission

The virus, source, transmission and pathogenesis

Rabies virus

- The rabies virus (RABV) is a single stranded, enveloped RNA virus, and belongs to the genus Lyssavirus in the family Rhabdoviridae and order Mononegaviral
- RABV is neurotropic and it is widely distributed in the nervous systems, saliva and secretions once the clinical manifestations start in animal or human
- The highest concentration of virus occurs in the nervous system and in the salivary glands
- Rabies virus is fragile and easily inactivated by sunlight, heat and the commonly used disinfectants

Reservoirs and source of infections

- Rabies transmission is maintained by two transmission cycles: Urban cycle transmission is perpetuated by dog and sylvatic cycle by wild carnivores e.g. foxes, Jackals, wolves, mongooses
- The saliva of the rabid animals is the main source of infection for humans
- The saliva can be infective about three days before the onset of clinical symptoms and during the course of illness till the death of the rabid animal
- The dog transmitted rabies is responsible for 99% of human rabies deaths

Routes of transmission

- All warm-blooded mammals are susceptible to rabies virus infection
- Rabies is transmitted through direct contact between the virus in saliva of infected animal with bite wounds or the mucous membranes
- Human infection commonly occurs following transdermal bites and scratches from an infected animal or licks on mucus membranes
- RABV has not been isolated from the milk of rabid cows and no human cases have been attributed to consumption of raw milk but drinking raw milk from a rabid animal is not advised. As per WHO, PEP is generally not indicated in these situations

- In rare instances, rabies has been contracted by inhalation of virus-containing aerosol (caves inhabited by bats)
- Human-human transmission of rabies virus has never been confirmed, with exception of organ transplant from rabid patients

Pathogenesis

- After inoculation, RABV replicate in muscles or other local tissues and gain access to motor endplates and motor axons before reaching the central nervous system. The viruses can also enter motor axons in peripheral nerves directly during a penetrating injury.
- The incubation period is variable and varies from five days to several years (usually 2–3 months; rarely more than 1 year) depending on the amount of virus in the inoculum, the density of motor endplates at the wound site and proximity of virus entry to the central nervous system.
- By the time of clinical onset of rabies, the virus is widely disseminated throughout the central nervous system and probably to extra-neural organs.
- Without intensive care, death usually occur within 7-10 days of the manifestation of clinical symptoms.

Rabies in dogs

The incubation period of rabies in dogs range from 3−8 weeks, but may vary from 10 days to as long as 6 months. In general, rabid animals of all species commonly exhibit typical signs of central nervous system disturbances with behavioral changes. A rabid dog may show either furious or paralytic (dumb) form of rabies with signs and symptoms as described in the Table 1. Furious form of rabies is the typical mad dog syndrome characterized by change in normal behavior. The animal usually dies in about 3 -5 days after it develops clinical symptoms.

Furious rabies	Dumb Rabies
• Easy irritability • Unprovoked attacks on human and animals and biting inanimate objects, • Running aimlessly for no apparent reason • A change in voice, e.g. barking and growling in a hoarse voice or inability to make a sound • Excessive salivation or foaming at the angles of the mouth • Gasping for breath towards the later stages of illness	• The dog withdraws itself from being seen or disturbed • Hanging of jaws • Increased salivation • It lapses into a state of sleepiness • In-coordinated movement

Table 1: Signs and symptoms of furious and dumb rabies in dog

Rabies in human

The consequence of an exposure to rabies virus depends on several factors including severity of the wound, the location of the bite on the body, the inoculum of virus and time of post-exposure prophylaxis (PEP) administration after exposure. As virus spreads through the central nervous system, a progressive and acute fatal encephalomyelitis develop. Early symptoms of rabies in humans are nonspecific, consisting of fever, headache, general malaise, tingling sensation and paresthesia at the site of the bite. As the disease progresses, neurological symptoms appear and may include insomnia, anxiety, confusion, slight or partial paralysis, excitation, hallucinations, agitation, hyper salivation, difficulty swallowing, and hydrophobia (fear of water). Human rabies can manifest clinically in two forms as shown in Error! Reference source not found.

Furious rabies ~ 80%	Dumb Rabies ~ 20%
• Tingling / numbness at bite site • Non-specific symptoms (Fever, malaise, headache, etc.) • Hydrophobia, aerophobia, photophobia • Death (cardio respiratory failure) • Survival : 3 – 5 Days	• Tingling / numbness at bite site • Nonspecific symptoms (Fever, malaise, headache etc.) • Ascending Paralysis • Coma • Death (cardio respiratory failure) • Survival : 7 – 21 Days

Table 2: Clinical manifestations in furious and paralytic rabies

Clinical diagnosis

Clinical diagnosis of encephalitis can be difficult, particularly in dumb form of disease and laboratory methods should be used to confirm a diagnosis when possible. The clinical picture in rabies is often variable and may represent a continuum of signs and symptoms. The differential diagnosis to be considered are:

- Cerebral malaria
- Organophosphate poisoning
- Herpes simplex encephalitis
- Post-vaccinal encephalitis
- Scorpion and snake envenomation
- Illicit drug use
- Psychiatric disorders
- Guillain–Barré syndrome (in paralytic form)

Laboratory Diagnosis

Diagnosis of rabies is usually based on clinical features and history of exposure to suspected rabid animal. Confirmation is challenging as brain sample collection is difficult in view of sociocultural reasons. Laboratory confirmation of rabies must be done wherever feasible. Laboratory diagnosis is important to confirm or rule out rabies in suspected paralytic or encephalitis cases. Details of possible laboratory diagnosis is given in Annexure 10.

Case definitions of human rabies

Case	Definition
Suspected	• A person presenting with an acute neurological syndrome (i.e. encephalitis) dominated by form of hyperactivity (furious rabies) or a paralytic syndrome (paralytic rabies) that progress towards coma and death usually due to cardiac or respiratory failure typically within 7-10 days of the first sign if no intensive care is instituted. • The syndrome may include any of the following signs: aerophobia, hydrophobia, paresthesia or localized pain, dysphagia, localized weakness, nausea or vomiting
Probable	• A suspect case plus a reliable history of contact with a suspected, probable or confirmed rabid animal (As per definition in Annexure 7)
Confirmed	• A suspected or probable case that is confirmed by laboratory tests

Table 3: Human rabies case definitions (WHO, 2018)

Case management

There is no effective treatment to cure rabies once the clinical signs have appeared. Hospital care for patients with clinical rabies is advisable, when possible, in order to reduce their suffering and ensure that they receive adequate, respectful palliative care. The focus of the management is on comfort, with heavy sedation (barbiturates, morphine) and avoidance of intubation or life-support measures, especially once the diagnosis is certain and it should be discussed with the family as soon as possible after the diagnosis is suspected. General treatment rules include:

- Isolate the patient in a quiet room with subdued light and protect from drafts of air or stimuli likely to precipitate spasms and convulsions
- Rabies patients tend to be talkative, so avoid disturbing unnecessarily
- Sedation with diazepam, supplemented by chlorpromazine, if necessary, will help to control muscular spasms and excitability. Phenobarbitone or morphine should be considered if required.

- Feeding orally is usually impossible. Nutrition and fluids should be given intravenously or NG tubes
- Once clinical diagnosis of rabies is confirmed, referral to higher center is not recommended

Precautions during patient management

Patient with rabies does not pose a risk to health care staff if routine precautions are taken. However, the staff should be reminded of the importance of adhering to barrier nursing and wearing personal protective equipment (standard precautions, including wearing gloves, glasses and mask in case of a procedure that will generate splashes), as recommended for all infectious diseases. The procedures and precautions to be followed in management of dead bodies is provided in Annexure 9.

Prevention of human rabies

Anti-rabies vaccines (ARV)

- Rabies is almost always fatal but it is preventable by vaccination before and/or after suspected exposure to the virus
- The modern concentrated, purified cell culture and embryonated egg-based rabies vaccines have been proven to be safe and effective in preventing rabies (PCECV, PVRV, HDCV and PDCV)
- WHO recommends intradermal administration of these vaccines as a safe, immunogenic and dose-sparing alternative to intramuscular administration as only one or two vials of vaccine are required to complete a full course of PEP
- The ARV recommended for use and supplied in public health facilities in Bhutan is PVRV via ID route unless ID is not possible
- Contraindication and precautions
- There is no absolute contraindication to administration of ARV. It can be safely given to infants, pregnant women and immune-compromised individuals, including children with HIV/AIDS.
- However, a previous severe reaction to any component of a rabies vaccine is a contraindication for use of the same vaccine for PrEP or PEP, and the vaccine product should be changed.
- As for all vaccinations, recipients should be kept under medical supervision

for at least 15–20 min after vaccination.

- Storage and transportation
- The vaccines should be protected from sunlight.
- As CCEEVs are available in lyophilized (freeze dried) form, they are more tolerant to variations of temperatures, but it is recommended that these vaccines should be stored and transported at a temperature range of +2 to +8°C
- Reconstitution - The sterile diluent supplied by the manufacturer should be used for reconstitution of the vaccine.
- After reconstitution, the vaccine should be used immediately or within 6 to 8 hours, if kept at + 2 to 8 °C
- The off-label* use of anti-rabies vaccines by ID route are allowed as per new WHO recommendations.
- *Off-label use allow ID route to be used for vaccine administration even if the manufacturer leaflets mention IM route only.
- Pre-exposure prophylaxis (PrEP)
- In Bhutan, PrEP is recommended for following high risk category of people:
- Laboratory staff working with rabies virus and rabies virus infected materials
- Occupational groups working with animals - veterinarians, para-veterinarians, animal handlers, dog catchers, wildlife and quarantine workers
- Travelers to endemic countries with limited access to PEP. The pre-travel advice on precautionary measures should be provided.
- The recommended route of administration should be ID.
- The PrEP session should be arranged in a group so vaccine wastages is minimized. One dose each (0.1 ml) is given at 2 sites, on both arms (over deltoids) on D0 and D7

The recommended regimen is as below:

Regimen	Dosage per injection/ site	No. of injection sites/visit (Day 0,3,7,14/21/28)	Course duration	Injection sites
ID regimen	0.1ml	2-0-2-0-0	7 days (Day 0, 7)	Deltoids, anterolateral thighs or suprascapular areas
IM regimen (Only when ID is not possible)	0.5ml	1-0-1-0-0	7 days (Day 0,7)	Deltoid area or anterolateral thigh

Note:

1. Administration of third dose of vaccine on days 21/28 is recommended in immunodeficient patient by either ID or IM route
2. ARV should not be given in the gluteal area
3. Booster doses: as an additional precaution for people whose occupation puts them at continual or frequent risk of exposure, annual booster can be provided which is a single injection by ID/IM.

Post-exposure prophylaxis (PEP)

PEP comprise of administration of wound care and immunization after a potential exposure to the rabies virus. The indication and procedure for PEP depends on the type of contact with the suspected rabid animal and immunization status of the patient. Every animal bite should be suspected to be a potentially rabid animal bite, and treatment should be started as soon as possible, after an exposure. People exposed to animals that conform to the definitions of animals as suspected, probable or confirmed to be rabid should initiate PEP immediately (Annexure 7). However, the decision on PEP should be made after taking a rational decision based on risk assessment. The algorithm to guide PEP decision is provided in Annexure 2.

PEP always includes:

- Thorough washing and flushing of the wound for approximately 15 minutes, with soap or detergent and copious amounts of water and anti-septic application

- A complete schedule of rabies vaccine injections administered immediately after an exposure
- Administration of rabies immunoglobulin (RIG) in severe category III exposure

Risk assessment

In any person with potential exposure to rabies virus, following factors need to be considered:

- Epidemiology of rabies in the country (currently Bhutan is considered rabies endemic although risk of rabies transmission is high in the southern Bhutan)
- Types and severity of exposure (Table 4)
- Species and clinical features of the animal (Animal rabies case definition Annexure 7)
- Vaccination status of the animal (dogs and cats)
- Animal's availability for observation (only in dogs and cats)
- Results of laboratory testing in animal, if available

Category	Type of exposure to animal or animal unavailable for testing	Risk	Recommended PEP
I	• Licks on intact skin, touching or feeding of animals • Petting, bathing or coming in contact with utensils of a suspected rabid animal • Consumption of milk or milk products	None	None, if reliable case history is available
II	• Nibbling of uncovered skin • Minor scratches or abrasions without bleeding • Consumption of raw meat* • Handling meat or carcass of rabid animals	Minor	4. Wound management 5. Provide anti-rabies vaccine immediately

Category	Type of exposure to animal or animal unavailable for testing	Risk	Recommended PEP
III	• Single or multiple transdermal bites or scratches • Licks on broken skin • Contamination with mucous membrane with saliva	Severe	1. Wound management 2. Provide ARV immediately 3. Provide RIG**

Table 4. WHO recommended PEP according to the type of exposure to rabies suspected, probable or confirmed animals

*It is important to inform the public that milk or meat from rabid or suspected animals must not be consumed
**When RIG is limited, it should be prioritized for category 3 exposure to probable or confirmed rabid animals.

Management of Animal Bite Wound

- All bite wounds and scratches should be attended to as soon as possible after exposure
- Perform thorough washing and flushing of the wounds for approximately 15 minutes with soap or detergent and plenty of water
- If soap and detergent is not immediately available, wash with running water for 15 minutes.
- Wound toilet must be performed even if the patient reports late, if the wounds are not healed (Since the rabies virus can persist and even multiply at the site of bite for a long time).
- After wounds have been washed, local antiseptics like Povidone Iodine/Spirit should be applied on the wounds.
- Application of local remedies such as herbal extracts, butter and salt etc. on the wound should be strongly discouraged.
- Suturing of the wound is not recommended and if unavoidable, it should be done after infiltration with RIG.

- Suturing should be delayed by a few hours to allow diffusion of the immunoglobulin into the tissues.
- Whenever necessary tetanus prophylaxis should be provided and antibiotics as indicated

Anti-Rabies Vaccination (ARV)

The current WHO approved regimen for ID route, 1-week, 2 - sites Institute Pasteur Cambodia - IPC regimen (2-2-2-0-0) is the recommended schedule in this guideline. The ARV should be provided to all animal bite victims of category II and III exposures and irrespective of age and body weight, require the same number of injections and dose per injection as per the schedule recommended below.

Regimen	Dosage per injection/site	No. of injection	Recommended PEP	Injection sites
ID	0.1ml	2-2-2-0-0	7 days (Day 0, 3, 7)	Deltoids, anterolateral thighs or suprascapular areas
IM (Only when ID is not possible)	0.5ml	1-1-1-1-0	14 days (Day 0, 3, 7, 14)	Deltoid area or anterolateral thigh

Dose and sites of vaccine administration

- One intradermal dose is 0.1 ml of reconstituted vaccine administered per ID site while one IM dose is an entire vial of vaccine, irrespective of the vial size (0.5 ml. or 1 ml).
- Day 0 is the date of administration of the first dose vaccine.
- As far as possible, vaccination schedules should be completed in the stipulated time.

PEP in immune-compromised individual

- PEP both by ID and IM route is safe and immunogenic in such individuals

- Thorough washing of the wound should be emphasized
- Administer full course of rabies vaccine
- RIG is indicated in both Cat. II and III exposures, even if previously immunized

IMPORTANT Points to remember

- Only when ID administration is not possible, IM regimen using 0.5ml of PVRV can be administered on Day 0, 3, 7, and day 14 or 21or 28.
- For adults and children aged ≥2 years, the vaccine should always be administered in the deltoid area of the arm; for children aged <2 years, the antero-lateral area of the thigh is recommended.
- Rabies vaccine should not be administered in the gluteal area, as the induction of an adequate immune response may be less reliable.
- Health care personnel should be careful not to inject less than 0.1 mL intradermal dose due to the dead space in the syringe or needle mount (insulin syringes may be used).
- Changes in rabies vaccine product and/or the route of administration during the same PEP course are acceptable, if unavoidable, to ensure PEP course completion.
- Should a vaccine dose be delayed for any reason, the PEP regimen should be resumed (not restarted). The use can be delayed up to 7 days from the date of the first vaccine doses.
- Rabies transmission has not been documented after rats and rodents bite exposure and as such, PEP after rat/rodent is not indicated.
- In areas enzootic for (canine and wildlife) rabies, PEP should be instituted immediately unless adequate laboratory surveillance and data indicates that the species involved is not a vector of rabies.
- Routine booster vaccine doses after primary rabies vaccination are not required for the general public living in areas of risk.

Rabies Immunoglobulin (RIG)

- RIG administration when indicated is a life-saving measure. There are two types of RIGs available- equine origin RIG (ERIG) and human origin RIG

(HRIG). ERIG is much cheaper than HRIG and both have shown similar clinical outcomes in preventing rabies in humans. As ERIG products are now highly purified, skin testing before administration is not necessary and abandoned as per WHO. This guideline recommends use of ERIG in health centers in Bhutan.

Storage and dose of RIGs

- RIGs should be stored and transported at a temperature of +2 to 8ºC and should not be frozen.
- The RIG dose is calculated based on the patient body weight
- The maximum dose of ERIG is 40 IU/kg and HRIG is 20 IU/kg of body weight.
- The maximum calculated dose of RIG should not be exceeded.

Regimen	Dosage per injection/site	No. of injection sites/visit (Day 0,3,7,14/21/28)	Course duration	Injection sites
ID	0.1ml	1-1-0-0-0	3 days (Day 0, 3)	Deltoids, anterolateral thighs or suprascapular areas
IM (Only when ID is not possible)	0.5ml	1-1-0-0-0	3 days (Day 0, 3)	Deltoid area or anterolateral thigh

Precaution in RIG administration (For RIG administration procedure Annexure 4)

- RIG should be infiltrated locally at the site of exposure as priority when indicated
- RIG is administered only once, preferably at or as soon as possible after initiation of PEP
- RIG should be given with the first dose of vaccine into and around the wound site

- RIG is administered without the use of anesthesia in order to prevent AEFI and anaphylaxis. The tropical use of 2% lignocaine can reduce the pain during the procedure.
- If RIG is not available on first visit, use can be delayed by up to 7 days from the date of the first vaccine dose. It is not indicated beyond the 7th day after the first dose of rabies vaccine
- Where RIG is limited or unavailable, scrupulous wound cleaning and deep irrigation, with application of a potent antiseptic agent, and timely administration of the first vaccine dose should be performed immediately
- If a limited amount of RIG is available, RIG allocation should be prioritized based on the following criteria (Such as during outbreaks):
  - » Multiple bites
  - » Deep wounds
  - » Bites to highly innervated parts of the body, as head, neck, hands, genitals
  - » Immune-compromised patients with an unmanaged condition
  - » 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

Re-exposure cases

In person who are re-exposed with documented previous complete PrEP/PEP or who have received at least two doses of rabies vaccine, following should be applied:

- 1-site ID/IM vaccine administration on days 0 and 3 (Recommended)
- No RIG is indicated
- People who cannot document previous PEP equivalent to PrEP or complete PrEP should receive a full PEP, including RIG if indicated.
- All health centers should print and issue PrEP/PEP vaccination card to animal bites victim after vaccination (Annexure 5).
- REMEMBER, if an individual has a repeat exposure less than 3 months after a previous exposure, and has already received a complete PEP, only wound treatment is required; neither vaccine nor RIG is needed.

Management of anaphylaxis

Prompt treatment of anaphylaxis is critical. The treatment protocol for anaphylaxis management include:

- Place patient in recumbent position and elevate lower extremities.
- Monitor vital signs frequently (every two to five minutes) and stay with the patient.
- Administer epinephrine 1:1,000 (weight-based) (adults: 0.01 mL per kg, up to a maximum of 0.2 to 0.5 ml every 10 to 15 minutes as needed; children: 0.01 ml per kg, up to a maximum dose of 0.2 to 0.5 ml) by SC or IM route and, if necessary, repeat every 15 minutes, up to two doses).
- Administer oxygen, usually 8 to 10 L per minute; lower concentrations may be appropriate for patients with chronic obstructive pulmonary disease
- Treat hypotension with IV fluids or colloid replacement
- Treat bronchospasm, preferably with a salbutamol nebulization
- Give hydrocortisone, 5 mg/kg, or approximately 250 mg intravenously (prednisone, 20 mg orally, can be given in mild cases). These doses can be repeated every six hours, as required.

Surveillance of rabies

Effective control and elimination of a human dog-mediated rabies require effective surveillance system to monitor the progress of elimination and effectiveness of control measures.

Human rabies case notification

- Human rabies is one of the notifiable diseases in the National Early Warning Alert Response Surveillance (NEWARS).
- The suspected human rabies cases compatible with clinical case definition (Table 4) should be notified immediately in web-based “IMMEDATELY NOTIFIABLE REPORTING” platform in NEWARS (Refer NEWARS guideline, 3rd Edition 2019).
- The case investigation should be launched within 24 hours by the concerned health professional using case investigation form (Annexure 14).

- Contact investigation should be conducted to find out additional people who may have had contact with the case.
- If there is no case, zero reporting should be done every week in NEWARS web based reporting system.

Routine surveillance:

- All cases with animal exposures including animal bite visiting health centers should be categorized based on risk assessment and provide PEP as per risk category. The information on number and types of animal exposure cases and PEP details should be collected and maintained.
- The District Health Office should collate and submit the report to the Zoonotic Disease Control programme every quarterly as per the reporting form (Annexure 12)

Surveillance during rabies outbreak in animals

- When outbreak is confirmed in animal (single or multiple cases with epidemiological link to the first animal case in a locality), all persons exposed to animal should be listed as per the exposure categorization and PEP should be administrated (Annexure 11)
- In case, if there is another outbreak confirmed in animal in the same locality but has no epidemiological link and temporal relation, the outbreak should be documented and separate line-listing should be maintained.
- The healthcare workers should proactively ensure completion of full PEP course particularly in category II and III exposure cases.
- The line-listing form should be submitted to the Zoonotic Disease Control programme within one month from the date of outbreak in animal.
- All animal bite cases visiting health center should be provided treatment if indicted as per the category of exposure and record in the registry (Annexure 1).

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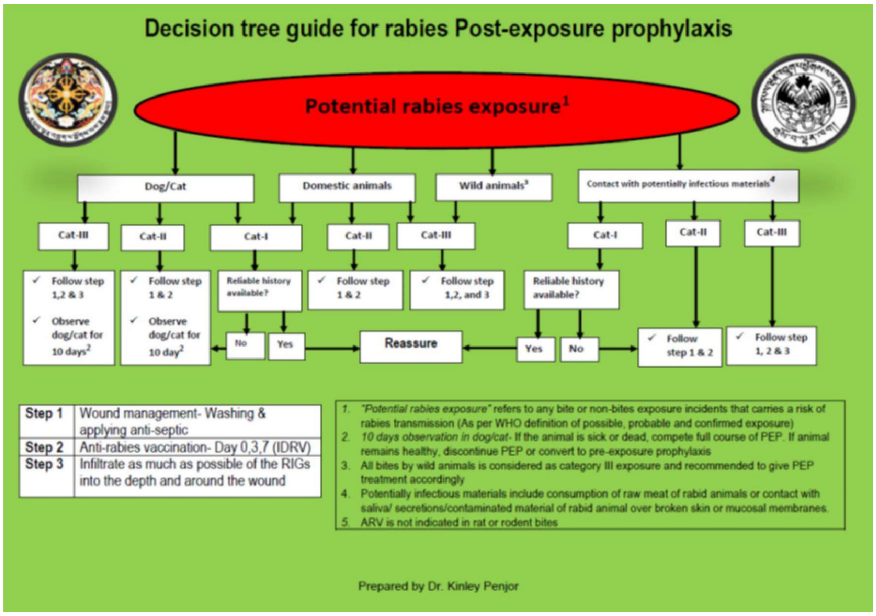
ANNEXURES

Annexure 1: Rabies PEP Register

Sl no	Reg. No	Name	Age/ sex	Occupation	Address			Exposure date	Place Where exposure occurred			Expoure type*	Animal species	Vaccination statues (dog/cat)	Site of bite	Cat of exposure**	Vaccination route	Date of ARV provided (indicate by tick mark)					Pre/ PEP	RIG (Yes/ No)	Remarks
					Dzongkhag	Geog	Village		Dzongkhag	Geog	Village							0	3	7	14	28			

Annexure 2: Rabies PEP decision algorithm



Annexure 3: Technique for ID administration of rabies vaccine

Equipment required

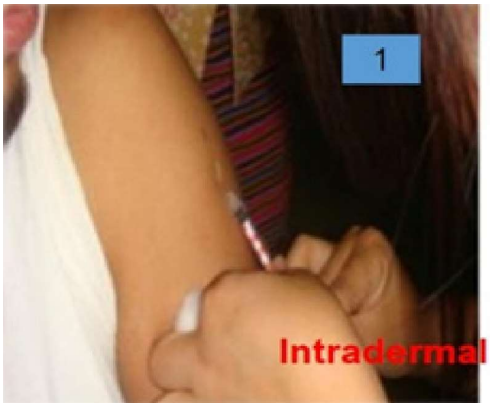
1. A vial of freeze-dried rabies vaccine and diluents
2. 2 ml. disposable syringe with needle for reconstitution of vaccine
3. Disposable 1 ml syringe. Preferably an insulin syringe with a fixed needle (28 or more gauge) should be used
4. Disinfectant swabs (e.g.70% ethanol) for cleaning the top of the vial and the patient's skin

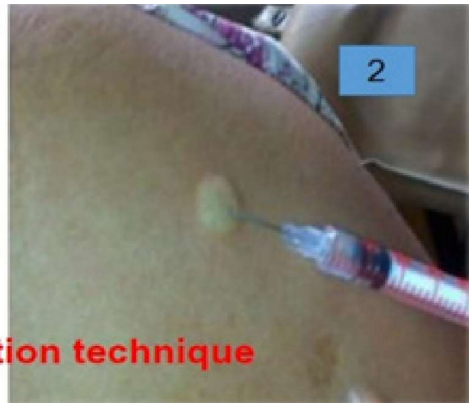
Procedure

1. Make the patient to sit comfortably and ensure adequate privacy. Patient must be reassured and their anxiety must be alleviated by briefly explaining the procedure that will be performed.
2. Both deltoids must be adequately exposed
3. Using aseptic techniques, reconstitute the vial of freeze-dried vaccine with the diluents and syringe supplied by the manufacturer.

4. Roll the reconstituted vaccine vials between the hand and not shake
5. Using 1ml syringe, draw 0.2ml of reconstituted vaccine
6. Up to 20 units if using 100u or 8units if 40u syringe)
7. For pre-exposure and re-exposure vaccination, draw only 0.1ml of reconstituted vaccine from the vial
8. Remove any air bubbles carefully from the syringe to remove any dead space
9. Clean the site and stretch the surface of the skin
10. Insert the tip of the needle with bevel upwards and keeping it almost parallel to skin, an inch above the insertion of deltoid
11. Inject 4 units (0.1ml) intradermal and form a "bleb"
12. If needle is correctly placed in the dermis, considerable resistance is felt while injecting the vaccine
13. Do not rub the site of injection
14. Inject remaining half (0.1ml) into the opposite deltoid
15. If the vaccine is injected subcutaneously, papule is not seen. Then the needle should be withdrawn and re-inject (0.1ml) at the adjacent site once more.
16. Withdraw 0.1ml (4U) of reconstituted vaccine into a new syringe and administer at another site.
17. Once all doses of vaccine have been injected into the patient discard the needle and the syringe in appropriate infectious disposal bins.

Note: Some difficulty may arise with elderly patients who have thin, inelastic skin, and with infants who are crying.





Annexure 4: Methods for RIG infiltration

Precautions

- The old practice of administering remaining immunoglobulin dose IM should not be followed but importance must be given to local infiltration of the wounds with RIG.
- If, however, there is a high likelihood that there are additional small wounds (e.g. if a child does not report all wounds) or exposure was through other than through a bite, injection of the remaining RIG volume intramuscularly as close as possible to the presumed exposure site, to the degree that is anatomically feasible, is indicated. The same applies for mucosal exposure with no wound and rinsing with RIG can be considered.
- In the case of suspected exposure to RABV in aerosols, an intramuscular injection of RIG is nevertheless recommended.
- Infected bite wounds are not a contraindication to administration of rabies immunoglobulin
- RIGs should be carefully infiltrated, without excessive pressure, in areas such as tip of fingers and toes, ear lobe, nose or around the eye, to avoid compartment syndrome.

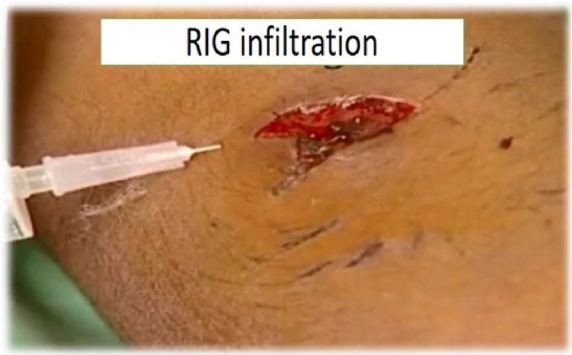
Steps

1. Rabies Immunoglobulin, which is stored in the refrigerator, should be brought to room temperature (25ºC to 30ºC), before administration to the patient.
2. There is no scientific ground for performing a skin test prior to administration of eRIG, as such tests poorly predict severe adverse events and their results should not be the basis for not giving equine immunoglobulin, if it is needed
3. RIG must not be administered in the same syringe or site as vaccine.
4. Patient should not be on an empty stomach
5. Example for calculation of dose of eRIG

A patient weighing 60 kg, with dog bite wounds on the right forearm and elbow came for treatment to the clinic.

Body weight	60kg
Dose (maximum) of eRIG to be administered	40iu/kg BW i.e. 60 x 40 = 2400 IU
Each ml. of eRIG contains	200iu
Volume of eRIG to be used for infiltration of wounds	2400/200= 12ml

6. The entre calculated immunoglobulin dose, or as much as anatomically possible, should be infiltrated carefully into or as close as possible to the wound(s) or exposure sites. Multiple needle injections into the wound/s should be avoided.
7. If the calculated dose of the rabies immunoglobulin is not sufficient to infiltrate all the wounds, the calculated volume of RIG should be diluted in sterile physiological saline to a volume sufficient to infiltrate all the wounds
8. If the rabid animal's saliva falls into the eyes, RIGs can be instilled as eye drops, after dilution (1:1) with sterile normal saline
9. The unused portion of the RIG can be used for another patient if it is aseptically stored.
10. Keep patients under observation for at least 30 minutes after RIG administration
11. While injecting into finger tips, care must be taken to avoid compartment syndrome.



Annexure 5: Anti-rabies card (To be issued to animal bite victims administered PEP)

Sl no	Day	Route of vaccination (IM/ ID)	Date of administration	Due date	Remarks
1	D0				
2	D3				
3	D7				
4	D14				
5	D28				

Annexure 6: Reporting form from health center to livestock official for potential rabies exposure

(For any patients reporting to health center with history of exposure to probable rabid animals)

Sl. no	Particulars	Details
1	Reporting Health Centre	
2	Reporting date	
3	Dzongkhag	
4	Name of reporting person	
5	Initial information by:	
	• Name	
	• Telephone number	
	• Email	
6	Patient details:	
	• Name	
	• Address	
	• Contact number	
7	Source of exposure (√):	
	• Own dog	
	• Owned cat	
	• Stray dog	
	• Stray cat	
	• Wild animal (specify)	
	• Other animal (specify)	

Annexure 7: Animal rabies case definition

Case	Definition
Suspected	A case that is compatible with a clinical case definition of animal rabies Clinical case definition: An animal that presents with any of the following signs: • hypersalivation, • paralysis, • lethargy, • unprovoked abnormal aggression (biting two or more people or animals and/or inanimate objects), • abnormal vocalization and • diurnal activity of nocturnal species
Probable	A suspected case plus a reliable history of contact with a suspected, probably or confirmed rabid animal and/or An animal with suspected rabies that is killed, died or disappears within 4–5 days of observation of illness
Confirmed	A suspected or probable animal case confirmed in a laboratory
Not a case	A suspected or probable case that is ruled out by laboratory tests or epidemiological investigation (i.e. appropriate quarantine period in eligible animals).

Annexure 8: WHO human rabies exposure definitions

Exposure type	Definitions
Possible	A Person who had close contact (usually a bite or scratch) with a rabies-susceptible animal in (or originating from) a rabies-infected area.
Probable	A person who had close contact (usually a bite or scratch) with an animal displaying clinical signs consistent with rabies at time of the exposure, or within 10 days following exposure in a rabies-infected area.
Confirmed	A person who has had close contact (usually a bite or scratch) with a laboratory-confirmed rabid animal.
Not a case	A suspected or probable case that is ruled out by laboratory tests or epidemiological investigation (i.e. appropriate quarantine period in eligible animals).

Annexure 9: Precautions in handling of dead bodies

- The body of a patient suspected to have died of rabies should be labelled as infectious but not as "contagious" (Not airborne or droplet transmission).
- The risk of transmission to others is extremely low if standard precautions are observed.
- Blood does not contain RABV, but the virus is present in many other tissues and fluids, such as those of the central nervous system and salivary glands.
- If embalming or autopsy is performed, it should be undertaken carefully, with appropriate precautions and personal protective equipment.
- Tissues and body fluids should be disposed of in the same manner as for other infectious diseases.
- The body of the deceased should be allowed to be buried or cremated, depending on their religious practice.

Annexure 10: Laboratory Diagnosis of Rabies

Antemortem diagnosis tests

The sensitivity of these tests depends on the

- Clinical presentation
- Stage of the disease
- Immunological status of the patient and
- Intermittent viral excretion

Detection of viral nucleic acid: Studies have demonstrated that testing at least 3 samples of saliva, taken at 3 to 6-hour intervals, together with a nuchal skin biopsy will help in almost 100% confirmation of an encephalitic case of Rabies. The tests done are for detection of viral nucleic acid, viz., reverse transcriptase and polymerase chain reaction (RT-PCR) or nucleic acid amplification and detection methods (NASBA). However, a negative test result does not rule out a diagnosis of Rabies.

Detection of anti-rabies antibodies: Detection of anti-rabies antibodies in serum (in unvaccinated individuals) and CSF is also useful especially when the survival is prolonged beyond a week. RFFIT (Rapid fluorescent Focus Inhibition Test) and FAVN (Fluorescent antibody virus neutralization test) are used to detect the

neutralizing antibodies and ELISA is used for detection of specific anti-rabies antibodies. A combination of tests conducted on different samples in a serial order is helpful in antemortem diagnosis of Rabies.

Postmortem diagnosis tests

When brain tissue is available for testing, the commonly used test is FAT (Direct Fluorescent Antibody Test) which detects the rabies virus nucleoprotein antigens in the brain tissue. Postmortem brain tissue can be obtained by craniotomy. However, brain biopsy is the preferred postmortem sampling technique. This can be done via the orbital or trans nasal route (samples are obtained from orbitofrontal cortex) using biopsy needles or through the occipital route through the foramen magnum (samples from cerebellum and brain stem) using lumbar puncture needles. The direct rapid immunochemistry test (DRIT) for detection of viral antigen in the brain tissue is useful for diagnosis of animal rabies and can be done in field conditions. There is no need of a fluorescent microscope for doing this test. Similarly, RDIT (Rapid Immunochromatographic diagnostic test) is available for diagnosis of animal rabies in field conditions. These tests are not adequately validated for diagnosis of human rabies. When brain tissue is not available for post mortem testing, presence of viral RNA can be tested by nucleic acid amplification techniques from samples obtained by nuchal skin biopsy. However, the sensitivity is less when compared to samples obtained from brain tissue.

Annexure 11:

Name of the health center:																					
Name of the health worker reporting:																					
	Patient information				Exposure details								Post exposure Prophylaxis (PEP)						Outbreak Response			
Sl. no.	Name	Present Address	Age	Sex	Mobile number	Date of Exposure (dd/mm/yy)	*Site of Exposure	**Exposure Type	***Animal Species	Category of exposure (as per the guideline)	Wound management (yes/no)	ARV given (yes/no)	D0	D3	D7	D14 (IM)	D28	RIG given (yes/no)	If HRIG not given, why no?	Animal health counterpart informed (yes/no)	IEC provided (yes/no)	Any other interventions taken

Note: To be submitted to the Program within one month after the confirmation of outbreak in animals

*Mention the site of the bite (leg, arm, face etc)

**Specify the Exposure type (bite by dog, cat scratch, dog lick one open wound, cared for rabies patient etc)

***Animal Species (Dog, Cat, Domestic livestock, Wild animals, Rats/Rodents)

Annexure 12: Quarterly Reporting Form

Name of the reporting district:											
Quarter (Please tick) Year.....			Q1 (Jan-Mar)		Q2 (April-June)				Q3 (July-Sept)	Q4 (Oct-Dec)	
			No. of animal exposures						Post-exposure Prophylaxis (PEP)		No. of Human Rabies Cases
			Dog bites	Other animal bites	Cat I	Cat II	Cat III	Unknown	No. of people received ARV	No. of people received RIG	
Age	<15 years	M									
		F									
	≥15 years	M									
		F									
Total											

Annexure 13: Standard Operating Procedure for disinfection and decontamination of contaminated premises and materials.

Purpose

To have standard procedure for effective disinfection and decontamination of contaminated premises and materials

Scope

The document describes procedures for disinfection and decontamination of contaminated materials and premises.

Users:

Health care workers

Materials/equipment required

Gloves; Apron; Gum boots; Buckets; Mugs/jugs; Water; bleaching powder; calcium hypochlorite

Procedure

1. Prepare 1% calcium hypochlorite solution in a bucket.
2. Utensils: Spray and wash barn utensils, tools and equipment with the above solution thoroughly.
3. Dry them for reusing.
4. Burry the beddings with carcasses if it is in small quantities, burn it in a pit if in larger quantities.
5. Contaminated premises should be disinfected thoroughly with the 1% calcium hypochlorite spray @ 1-1.5 L/m2. Allow contact time of 2-3 hrs.
6. Contaminated laboratory materials can be disinfected by immersing them in 1% calcium hypochlorite solution for at least 30 minutes.
7. Disposable items, including used PPEs must be incinerated/burnt in a pit

Annexure 14: Verbal Autopsy questionnaire (To be used for investigating

Suspected/confirmed rabies death

Name of interviewer: _____ Date of interview: – – /– – /– – – –

Name of the health facility:_____ Name of deceased: _____

Village_____ Gewog:_____ District:_____

GPS coordinate:_____/_____

I. Information about respondent

1.1 Name of main respondent_____

1.2 Contact information _____

1.3 What was your relationship to the deceased? (Tick)

- Parent
- Spouse
- Sibling
- Child
- Son-in-law or daughter-in-law
- Friend or neighbor
- Community leader
- Health care worker (facility name):
- Others (specify)

II. Information of the deceased 2. Demographics

2.1 Nationality

2.2 Sex

2.3 Age (years)

2.3.1 For infants, record the most appropriate: Month(s) __Week(s)___ Days___

2.6 Occupation

2.7 Level of education (Tick highest level of education attained)

- Illiterate
- Below primary

- Primary or middle
- Secondary or high
- Graduate
- Postgraduate
- Other (specify)

III. Exposure (during previous 12 months)

3.1 Did any family pets or livestock die during the 12 months before the patient's illness? (Tick)

- Yes (Date of death: – – / – – / – – – –)
- No
- Unknown

3.2 Did the deceased have any contact with animals (bite, scratch, lick) within the 12 months before the illness that led to death? (Tick)

- Yes
- No
- Unknown

3.3 If yes, please describe the animal contact events

3.3.1 On what date did [deceased] have contact with the animal? *(If there are more than one animal contact events, provide specific date of the event and types of animal)*	– – / – – / – – – –
3.3.2 What type of animal? (Circle)	• Dog • Cat • Bat • Livestock • Other:_____

3.3.3 Was the animal owned?	• Owned • Not owned • Wild • Unknown
3.3.4 Did the animal have any signs of disease (Describe)?	☐ Yes ☐ No ☐ Unknown • Aggression • Paralysis • Biting • Hypersalivation • Lethargy • Other:_____
3.3.5 Is the animal alive today? (If no, estimate date of death?)	☐ Yes ☐ No ☐ Unknown – – / – – / – – – –
3.3.6 Was the animal observed for at least 10 days after the exposure?	• Yes, alive after 10 days • Yes, died during observation • No • Unknown
3.3.7 Was the animal tested for rabies?	• Yes, rabies positive • Yes, rabies negative • No • Unknown

3.3.8 Was the deceased bitten by the animal?	☐ Yes ☐ No ☐ Unknown • Location of bite: • Head • Trunk • Upper limb • Hands • Lower limb • Genitalia • Other:_____
3.3.9 Did the deceased have other contact with the animal i.e. licked, scratched.	• Scratch • Saliva contact with open wound or mucous membrane • Neural tissue contact with open wound or mucous • Membrane • Other:_____
3.3.10 What treatment did the patient receive for this contact?	• Washed the wound • Sought medical care • Received rabies vaccination

Additional Notes (Use additional page if required):

IV. Rabies treatment

4.1 Did the deceased receive treatment for any of the animal exposures above?

- Yes
- No
- Don't know

4.2 Was any of this treatment received at home?

- Wound washing
- Over the counter medications
- Traditional medicines
- Other:
- None
- Unknown

4.3 Where did the deceased go for medical care for any of the exposures listed above?

	Traditional healer	**Medical practitioner**	**Other: _____**
Facility name and location			
Date(s) visited	1: – – / – – / – – – – 2: – – / – – / – – – – 3: – – / – – / – – – –	1: – – / – – / – – – – 2: – – / – – / – – – – 3: – – / – – / – – – –	1: – – / – – / – – – – 2: – – / – – / – – – – 3: – – / – – / – – – –
	• Antibiotics	• Antibiotics	• Antibiotics
	• Tetanus	• Tetanus	• Tetanus
	• Wound washing	• Wound washing	• Wound washing
	• Rabies postexposure prophylaxis or treatment	• Rabies postexposure prophylaxis or treatment	• Rabies postexposure prophylaxis or treatment
	• Traditional medicine	• Traditional medicine	• Traditional medicine
	• Other (specify)	• Other (specify)	• Other (specify)

4.4 If the patient received rabies vaccination, please record schedule of vaccine and dates received:

CCV	RIG	D0	D3	D7	D14	D28
Dose received?	• Yes • No • Unknown	• Yes • No • Unknown	• Yes • No • Unknown	• Yes • No • Unknown	• Yes • No • Unknown	• Yes • No • Unknown
Date received?						

4.5 Had the patient ever been vaccinated against rabies prior to this exposure?

- Yes: Year of vaccination: – – / – – / – – – –
- No
- Unknown

V. Signs and symptoms

5.1 Time to symptom onset and death

5.1.1 When did the illness that led to death begin?

Day_____ Month_____ Year_____ Unknown_____

5.1.2 If you don't remember the exact date, approximately how long ago did the illness begin?

Day_____ Month_____ Year_____ Unknown_____

5.1.3 How many days after illness did the deceased die? Number (estimate if needed):

5.2 During the illness did the deceased seek medical assistance?

- Yes: (Date): – – / – – / – – – –
- No
- Unknown

5.3 During the illness was the deceased admitted to a hospital?

- Yes: (Date): – – / – – / – – – –
- No
- Unknown

5.4 Characteristics of illness that led to death_____

_____

_____

5.5 Was any relevant diagnostic testing performed?

Disease	Test performed	Date	Result	Comment
Encephalitis				
Rabies				
Mosquito-borne encephalitis				
Herpes simplex virus				
Measles virus, Malaria				
Others				

5.5.1 What was the date of deceased's death? Day ____/Month _____/ Year_____

5.5.2 Where did the deceased die?

- Home
- Hospital (specify)
- Other health facility (specify)
- Other (specify)

5.5.3 Did anyone else in the community develop similar illness within the past 12 months? (If "Yes", collect contact information for other suspected cases to initiate verbal autopsy of additional cases)

- Yes
- No
- Unknown

If yes, asedescribe:_____

_____

VI. Postmortem information

6.1 Postmortem report available (if any):

- Yes
- No
- Unknown

6.2 Death certificate available?

- Yes
- No
- Unknown

6.3 Did the deceased have any evidence of recent wounds?

- Yes
- No
- Unknown

6.4 Did the deceased have any evidence of healed wounds?

- Yes
- No
- Unknown

VII. Contact investigation

- Collect the names and contact information for any family, community members or hospital workers who had contact with the suspected rabies case in the 14 days before symptom onset until death.
- Collect the names and contact information for any people who had contact with the animal suspected of transmitting rabies to the case.
- Risk assessments should be conducted with these people to rule out potential exposure.

VIII. Classification of human rabies (Please tick your inference below)

- ☐ Not a case: Does not meet the clinical definition
- ☐ Suspected: A case that is compatible with the human clinical case definition
- ☐ Probable: A suspected case with probable or confirmed exposure to rabies
- ☐ Confirmed: A suspected or probable case that is confirmed in a laboratory

Names of Investigator(s), signatures of local informants and designation

1._____ _____

2. _____ _____

3. _____ _____

4. _____ _____

Additional enclosures (description) as evidence of rabies

1. _____ (Pages_____)

2. _____ (Pages_____)