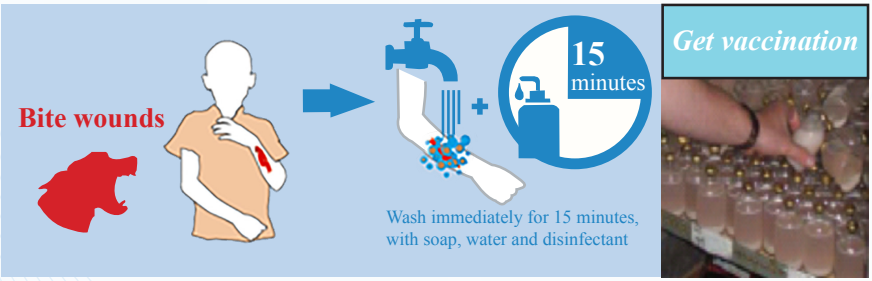
Guideline on Rabies Exposure Assessment for Nerve Tissue Vaccine Administration



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Abbreviations

CBRS	Community-Based Rabies Surveillance
CCV	Cell Culture Vaccine
CDC	Center for Disease Control and Prevention
DALYs	Disability-Adjusted Life Years
EPHI	Ethiopian Public Health Institute
IBCM	Integrated Bite Case Management
IU	International Unit
IPC	Infection Prevention and Control
NTV	Nerve Tissue Vaccine
PEP	Post-Exposure Prophylaxis
RABV	Rabies Virus
RIG	Rabies Immunoglobulin
VNA	Virus Neutralizing Antibody
WHO	World Health Organization

Terms and Definitions

Abrasion: Is a wound caused by rubbing or scraping the skin or a mucous membrane.

Bite: Wound from a tooth that penetrates the skin.

Confirmed Rabies Case: Animal that has been tested positive for the rabies virus by fluorescent antibody test technique.

Exposure: Defined as any bite, scratch or other situation in which saliva or nervous tissues from a potentially rabid animal enters an open or fresh wound, abrasion or break in the skin, or comes in contact with a mucous membrane by entering the eye, nose or mouth.

Incubation Period: The time from exposure to a disease until the development of clinical signs or symptoms. The incubation period of rabies is longer and more variable among different species and individuals than in other viral diseases. The incubation period of rabies may depend on the virus variant, susceptibility of the exposed species, the location and amount of inoculum, and post exposure management.

Minor bite: Nibbles on exposed skin, small wound, without bleeding and not enough to damage internal; Bite wound at 'minor end scale' of severity can be a simple abrasion or superficial penetration of the skin layer including contusions (without break in the skin) in covered areas of arms, trunks and legs.

Non-bite: Contact with saliva, brain tissue, or cerebral spinal fluid from a potentially rabid animal into an open wound or in the eyes, nose, or mouth, or via a scratch.

Quarantine: Confinement of an animal to a limited, enclosed area in order to restrict exposure of that animal to other animals and to humans, and to facilitate observation of the animal for signs of rabies.

Rabies Virus Shedding Period (infectious stage): The time that an animal excretes rabies virus in its saliva. During this period, an animal can transmit rabies to another animal or human. Viral shedding tends to occur only during the late stage of the disease, after rabies has affected the brain (just before death).

Scratch: A superficial wound that do not penetrate the deeper layers of the skin. It is the commonest type of injury we often get due to animals.

Quarantine/Observation Period: The maximum infectious stage of rabies in dogs and cats is ten days. If a dog or cat remains healthy for 10 days after biting a person, it is safe to assume that rabies was not transmitted. Rabies shedding period in wild animals is not known, and they should be tested for rabies rather than quarantined if they expose a person.

Foreword

Rabies is a viral infectious disease that affects the central nervous system. The disease is almost 100% fatal once the symptom develops. Globally, human mortality from rabies is estimated to be 60,000 annually. Death due to rabies in Ethiopia is the highest from African continent. According to CDC report, it is estimated that 2,700 people died each year and domestic dogs are the major sources of infection.

Rabies is 100% preventable disease through applying strategic intervention like mass vaccination of dogs, vaccination of exposed peoples, effective dog management and through establishing strong and sensitive surveillance system within the country. Cognizant of the real situation in the country leads in prioritizing and targeting to eliminate the disease by 2030.

To ensure the availability of effective rabies post exposure prophylaxis, the Ethiopian Public Health Institute (EPHI) is producing and distributing Nerve Tissue Vaccine (NTV) (Fermi-type) throughout the country since 1944. The vaccine produced with its standard preventive efficacy and reaching the community with very low price.

Even though Ethiopia is using NTV for extended decades, there was no standard vaccine administration guideline to be used by the health professionals. Therefore, developing the guideline will fill the gap to utilize the vaccine effectively and efficiently.

Hence, by the mandate given from the Federal Ministry of Health to prepare health and health related guidelines and standard, this NTV administration guideline is prepared by EPHI.

In this guideline, major emphasis is given for rabies exposure risk assessment, nerve tissue vaccine administration and vaccine cold chain management. To assure the effective vaccine utilization, this guideline will be the standard guiding tool which support the respective users of this guideline.

Finally, I would like to thank the technical working group members who have been actively engaged on the preparation of such an important guideline.

Getachew Tollera (Dr.)
Deputy Director General

1. Introduction

Rabies is a viral zoonotic disease responsible for an estimated 60, 000 human deaths and over 3.7 million Disability-Adjusted Life Years (DALYs) lost every year worldwide. It is almost invariably fatal once clinical signs appear, as a result of acute progressive encephalitis. The disease mainly occurs in poor and vulnerable populations; both rural and urban areas, and has been documented for more than 4000 years.

Most cases occur in Africa and Asia, with approximately 40% of cases in children aged <15 years. All mammals are susceptible to infection by the Rabies Virus (RABV). Transmission of RABV by dogs is responsible for up to 99% of human rabies exposure in rabies-endemic regions, with a small proportion transmitted via wildlife (such as foxes, wolves, jackals, bats, raccoons, skunks or mongoose). Over 95% of rabies deaths in humans result from virus transmission through the exposure to infected dogs.

Rabies is a 100% preventable disease with effective preventive measures. Post exposure prophylaxis soon after exposure to rabies is mandatory, which shall be implemented based on the exposure risk assessment category. Rabies elimination can be realized if government, community and relevant stakeholders' coordination, collaboration and attention is given. Effective rabies prevention and control strategies shall be prioritized and implemented based on the country context. Mass vaccination of dogs is the major intervention strategy to prevent rabies. Furthermore, dog population management, community awareness and cooperation of all stakeholders improve the cost-effectiveness of the strategic interventions.

Once symptoms of the disease develop, rabies is 100% fatal. Rabies differs from any other infections in that the development of the clinical disease can be prevented through timely immunization even after exposure. There are two types of vaccines globally available to protect against rabies in humans; which are Nerve Tissue Vaccine

(NTV) and Cell Culture Vaccine (CCV).

Even though, WHO has been strongly recommending to discontinue NTV and replace with the modern cell culture derived vaccine, few low-income countries including Ethiopia are still using the vaccine as PEP following rabies exposure. Because of the affordability and accessibility problems related to modern cell culture vaccine, the vaccine has been predominantly used in the country since 1944.

Even though the vaccine has been used for long period of time in the country, there was no standard national guideline for exposure assessment and proper vaccine administration.

Therefore, developing this guideline is fundamental and shall be used as standard national working tool for respective health and veterinary professionals. It will be used during rabies exposure risk assessment and NTV administration. For further information, the 1984 recommendation by WHO should be considered.

2. Purpose of the guideline

The purpose of this guideline is to set effective rabies exposure risk assessment for post exposure prophylaxis using Nerve Tissue Vaccine (NTV). It emphasizes on exposure risk assessment based on WHO 1984 recommendation, NTV vaccine administration, Vaccine cold chain management and vaccination related challenges with recommended solutions.

In this guideline, the only anti-rabies vaccine considered is NTV. In case of CCV, separately available guideline should be considered.

3. Intended guideline users

This guideline will be used by:

- Public health professionals
- Veterinary professionals

- Environmental health professionals
- Public health institutes (national and regional)
- Academic institutions

4. General considerations

Proper vaccine administration is a critical component of a successful immunization. It is a key part of ensuring that vaccination is as safe and effective as possible. This document provides best practice guidance for rabies exposure risk assessment/screening and NTV administration. The guidance application shall be used in conjunction with laboratory results, detailed exposure risk assessment, clinical diagnosis of exposing animals, professional qualification for vaccine administration and guidance from the vaccine manufacturer. For every bite or scratch, the health professional should consider exposure ascertainment. The victim shall fall in either of the following WHO's exposure definition:

4.1 Human exposure to rabies

Possible exposure: 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 exposure: 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.

Exposed: A person who has had close contact (usually a bite or scratch) with a laboratory-confirmed rabid animal

General considerations for NTV administration:

- NTV prepared from brain tissue of adult sheep which has a neuro-paralytic factor like myelin; so that it has neurological

adverse effect (The vaccine might have minor, moderate or severe adverse reactions).

- NTV is less immunogenic than modern rabies cell culture vaccines; however, it is being used for a longer time in Ethiopia and practically proven that it has potential to protect or immunize exposed peoples against rabies or used as post exposure prophylaxis; if appropriately used.
- NTV shall only be used for post-exposure immunization.
- Adverse effects should be strictly considered up on administration of NTV and risk communications between the victim and/or her/his parents is important. Special consideration shall be given to groups like children, Immuno-compromised, pregnant and others.
- Administration of NTV shall be guided and followed by in-depth risk assessment, animal clinical examination and laboratory diagnosis with IBCM concept.
- Even though Ethiopia is one of rabies endemic country, epidemiological endemicity of the disease in the area and type of exposing animals should be considered up on administration of NTV.
- If NTV is not initiated immediately due to waiting for the result of clinical observation of dog or cat and/or in order to discontinue the initiated vaccine as per the guidance; the status of the animals should be either followed and confirmed by IBCM or the victim itself.
- Strict adherence of the full dose of NTV administration shall be considered during prescription and providing vaccination services.
- Up on application of this guideline, continuous knowledge and skill shall be shared among professionals with in their facility.

4.2 Integrated Bite Case Management (IBCM)

Concept: To join animal data investigations with human bite victim information.

IBCM – assisting the individual by following up with the suspect animal which will ultimately aid for discontinuation of PEP for those who don't need PEP based on quarantine or laboratory results, (Detailed description of the two components attached on Annex 3).

One Investigation, Two Components:

1st Component: Animal rabies investigation (completed by animal health workers)

2nd Component: Human exposure investigation (completed by human healthcare workers)

Practicing active surveillance is essential to controlling and eliminating rabies.

IBCM is integral in an effective and active surveillance system

- Helps to identify new cases
- Identifies suspected animals
- Ensures more cases are detected and reported
- Ensuring exposed individuals receive adequate PEP
- Facilitates investigations and follow-up
- Improves suspected sample submission
- Will result in proper PEP utilization

IBCM relies on reports collected from the communities on the ground about suspected animals and bite incidents. These reports trigger a cascade of responses:

- Ideally, every bite individual is identified
- Risk assessment undertaken to determine risk of rabies and

need for PEP

- Veterinary investigations to identify suspect animal and act accordingly
- Improves the number of samples collected and taken for laboratory confirmation
- Potential for rapid vaccination responses to area where positive cases identified to stem further spread of the disease

The idea of the Community-Based Rabies Surveillance (CBRS) system is:

For animals:

- Rapidly identify suspected animals in communities
- Undertake an immediate risk-assessment for each suspected animal
- Trigger a rapid veterinary investigation response in that area
- Quarantine or sample the animal for lab testing
- Track sample to the laboratory with diagnostic outcome being available immediately

For humans:

- Identify potentially exposed individuals in the area
- Link these individuals to the suspect animal
- Base PEP on laboratory result (negative result, individual can stop PEP)
- Identified suspect animals can be linked to potentially exposed individuals
- Outcomes of veterinary quarantine or lab diagnosis can influence exposed individuals' PEP requirements
- Samples received at the laboratory can be linked with other exposed individuals

5. Exposure risk assessment for PEP initiation

Prevention of rabies in humans exposed to rabies virus should include prompt and thorough wound cleansing followed by passive vaccination with rabies immunoglobulin (RIG), if available and indicated, and vaccination with rabies vaccines. The decision for administration of rabies PEP shall not be delayed.

The algorithm for evaluation of animal bites and other rabies exposures for appropriate use of rabies PEP should be used to determine if vaccination is required. The algorithm shall be posted on a visible area in the health facilities where the treatment service is given.

Health care providers must individually evaluate each human exposure to a potentially rabid animal. These exposures are rarely clear-cut issues, and treatment decisions must take into account a variety of factors. The following factors should always be evaluated and communicated with the individual before specific rabies post-exposure treatment is initiated. These are also described in more depth below.

- Type of exposure
- Extent or severity of the exposure
- Type of animal species involved
- Vaccination status of the animal
- Circumstances (i.e., provoked vs. unprovoked) leading to the bite or other exposure
- Availability of the animal for confinement (Quarantine) and observation or testing
- Epidemiology of rabies in the region

5.1 Type of Exposure

Rabies is transmitted to humans only by directly introducing the virus into open cuts or wounds in the skin, or by introducing the virus onto mucous membranes. If exposure has not occurred, post-exposure prophylaxis shall not be indicated. The likelihood that rabies infection will result from exposure varies with the nature and extent of exposure.

a) Bite Exposure

Any penetration of the skin by teeth constitutes a bite exposure. All bites represent a potential risk of rabies transmission. The risk for transmission varies in part with the species of biting animal, the anatomic site of the bite, and the severity of the wound.

b) Non-Bite Exposure

The contamination of open wounds or abrasions (including scratches) or mucous membranes with saliva or other potentially infectious material (e.g., neural tissue) from a rabid animal is considered a non-bite exposure. Non-bite exposures from terrestrial animals rarely causes rabies. Indirect contact and activities (e.g., petting or handling an animal, contact with blood, urine, feces or skunk spray, and contact of saliva with intact skin) do not constitute exposures; therefore, rabies PEP shall not be administered in these situations.

5.2 Extent or Severity of Exposure

In exposures involving multiple severe bites or bites to the face, head, neck, hands and genitals immediate PEP shall be considered. Discontinuation might be possible depending on results of quarantine period or laboratory test result.

5.3 Type of Animal Species Involved

a) Dogs and Cats

Bites inflicted by dogs and cats pose a potential risk of rabies transmission. The driving strategy for managing bite incidents involving these animals is to locate the animal for observation or testing. An apparently healthy domestic dog or cat, that bites a person may be confined and observed for 10 days under the supervision of the animal health officer in the place where the animal resides. PEP shall be initiated while the animal is being confined and observed. In most cases, the confinement and observation can be managed at the owner's home. Cats are more commonly involved in exposures than dogs because cats interact more with wildlife, and cat control and rabies immunization regulations are more difficult to enforce.

If the biting dog or cat is unavailable for testing or observation, the recommendation for rabies PEP is determined on a case-by-case basis. Every effort should be made to locate and apprehend the animal for confinement/observation or testing. If the biting animal is not in custody and could not be located, the victim shall take full course of PEP.

b) Livestock and other Domesticated Animals

Livestock such as donkeys, horses, cows, sheep, goats, camels, pigs, etc.; and other domesticated wild animals such as monkeys could be infected with rabies but are considered less likely to be involved in the transmission of rabies. In almost all potential rabies exposure events involving these animals, the animal must be confined and readily available for investigation and rabies risk assessment. Efforts shall be made to take any helpful history that might help for decision. Initiate PEP immediately, if history is unreliable and these animals are not available for testing PEP should be given in full regimen.

C) Rodents

Rodents (mouse, rat, squirrel), Lagomorph (rabbit, hare) or opossum exposure rarely need PEP for rabies if they bite. If the animal was exhibiting signs consistent with rabies or there were unusual circumstances, test the animal; if the animal is not available for testing, rabies PEP shall be considered. The period of rabies virus shedding in these animals is unknown.

d) Human to human transmission

Although it can occur, human-to-human rabies transmission is rare. There are documented cases of human rabies as a result of exposure through organ transplantation. People could have the chance to get rabies from the bite of rabid patients. It is also possible, but quite rare, that people may get rabies if infectious material from a patient such as saliva, gets directly into their eyes, nose, mouth, or a wound.

The cases of rabies caused by human-to-human transmission occurred among eight recipients of transplanted corneas, and recently among three recipients of solid organs. Casual contact, such as touching a person with rabies or contact with non-infectious fluid or tissue (urine, blood, and feces) does not constitute an exposure and does not require post exposure prophylaxis.

Practically, there is no risk to other humans from a patient with rabies unless it is by mucous exposure to saliva or a bite. In addition, contact with someone who is receiving rabies vaccination could not be a risk of rabies exposure for others. Human rabies patients do not pose any infection risk to health-care personnel if appropriate infection prevention and control measures (IPC) are properly applied.

5.4 Vaccination Status of the Animal

Vaccinated dog or cat is unlikely to become infected with rabies. However, healthy domesticated dogs or cats that expose humans or

other domesticated animals to rabies must be confined and observed for 10 days (if available for confinement) regardless of vaccination status. Thus, such exposures will be managed based on the WHO rabies exposure category and rabies PEP algorithm mentioned in (Table 1 and Figure 1).

5.5 Circumstances (Provoked vs Unprovoked)

An unprovoked attack is more likely than a provoked attack to indicate that the animal is rabid. A provoked incident occurs when a person creates a situation that makes an animal feel threatened and causes them to react by biting or scratching. Provocation is judged from the animal's perspective. An animal will be provoked by infringement on its territory, menacing gestures, handling its young, or fear of injure. Bites inflicted on a person attempting to feed or handle an apparently healthy animal should generally be regarded as provoked. In such circumstances, PEP shall not be initiated unless the risk level is identified to be very high as indicated on the algorithm.

5.6 Availability of the Animal for Quarantine or Testing

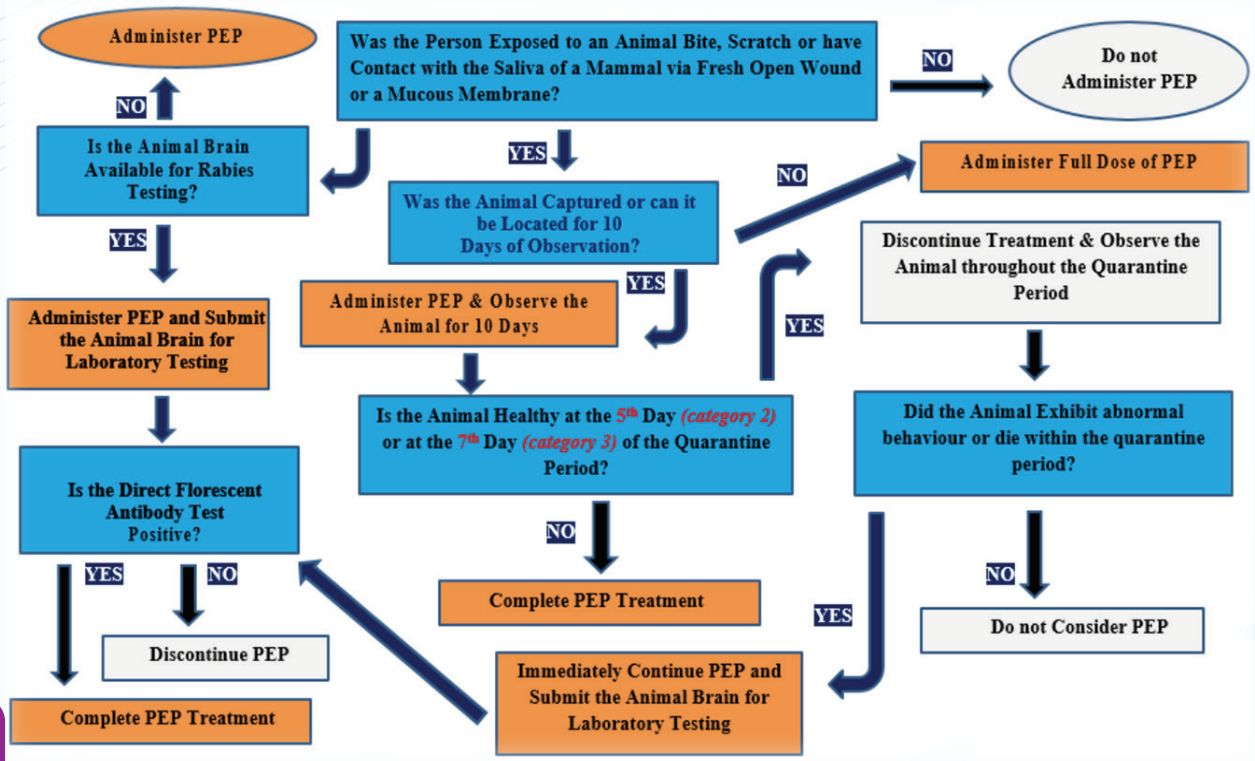
A healthy dog or cat that bites human or another domesticated animal shall be confined and observed for 10 days (if the animal can be located); if the observed animal remains alive and healthy for 10 days would not have been shedding rabies virus in its saliva at the time of the exposure. However, PEP could be initiated if the animal was suspected of rabies at the time of exposure and discontinued at the fifth day if the status of the animal was confirmed to be healthy (Note that only NTV is considered).

Table 1. WHO rabies exposure category (1984)

Categories	*Nature of exposure*	*At time of exposure*	*During 10 days*	*Recommended treatment (PEP)*
I	Touching or feeding animals, licks on intact skin (no exposure);	Healthy	Healthy	None
		Suspected as rabid	Rabid	
II	Scratches or abrasions	Healthy	Rabid	Start vaccination
	Minor bites (on covered areas arms, trunk and legs)	Healthy	Rabid	Start vaccination
		Suspected as rabid	Healthy	Start vaccination; discontinue treatment if animals remain healthy for 5 days
		Rabid Wild animal or unavailable for observation	-	Give complete course of vaccine
III	Single or multiple transdermal bites or scratches, contaminatio n of mucous membrane or broken skin with saliva from animal licks, exposures due to direct contact with bats (severe exposure).	Suspected or confirmed rabid domestic or wild animals, or animal unavailable for observation	Suspected	Administer rabies vaccine i mmediately, and rabies immunoglobulin, preferably as soon as possible after initiation of PEP. Rabies immunoglobulin can be injected up to 7 days after administration of first vaccine dose.
			Healthy	Stop treatment if animal (only for dogs and cats) remains healthy throughout an observation period of 7 days or is proven to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques.

Minor bites: - Nibbles on exposed skin, small wound without bleeding at 'minor end scale' of severity can be a simple abrasion or superficial penetration of the skin layer including contusions (without break in the skin) in covered areas of arms, trunks and legs.

Figure 1. Rabies Exposure Risk Assessment Algorithm for Nerve Tissue Vaccine Administration



6. Considerations for PEP

Rabies PEP is a medical urgency, NOT an emergency. The severity and location of a wound (severe wounds or obvious wounds near the head and neck should be given highest priority), and the expected interval between the time of the bite and receipt of rabies test results should be considered when making a decision to begin PEP while awaiting test results.

Unprovoked exposures are rare compared to provoked and typically require an animal to cross neutral space and attack. Provoked exposures may include: attempting to feed an animal, having contact with an injured animal, entering an animal's territory, petting or playing with an animal, handling an animal, breaking up a fight between animals, walking, running, or riding a bicycle past an animal and etc.

This algorithm only addresses rabies post-exposure prophylaxis. Other treatment such as wound care, antibiotics, and tetanus immunization may be indicated.

7. Vaccination

7.1 Vaccine dosage and administration

For individuals who are exposed and unvaccinated, wound treatment, administration of vaccine and rabies immune globulin (if available) are the essential components for post exposure management. In the case of nerve tissue rabies vaccine (Fermi-type), only post exposure treatment considered to minimize vaccine associated complications. The schedule for post-exposure prophylaxis using nerve tissue anti-rabies vaccine shall follow the following schedule:

- Infants up to 2 years of age, 2 mL daily subcutaneous injections around the umbilicus for 14 consecutive days. Booster doses on the 10^{th}, 20^{th} and 30^{th} days following the last injection.

- For children 3 years of age, 3 mL daily subcutaneous injections for 14 consecutive days. Booster doses on the 10th, 20th and 30th days following the last injection.
- For children 4 years of age, 4 mL daily subcutaneous injections for 14 consecutive days. Booster doses on the 10th, 20th and 30th days following the last injection.
- For 5 years of age and above, 5 mL daily subcutaneous injections for 14 consecutive days. Booster doses on the 10th, 20th and 30th days following the last injection.

Table 2. Summary for age-based dosage

Age group/Years	Vaccine volume	Schedule
≤ 2 Yrs.	2 mL	Daily 1 injection for 14 days, and 3 injections with 10 days interval
3 Yrs.	3 mL	Daily 1 injection for 14 days, and 3 injections with 10 days interval
4 Yrs.	4 mL	Daily 1 injection for 14 days, and 3 injections with 10 days interval
≥ 5 Yrs.	5 mL	Daily 1 injection for 14 days, and 3 injections with 10 days interval

Storage and shelf life:- *The shelf life for this vaccine is five months from the date of issuance provided that the vaccine is kept at a temperature between 2 °C and 8 °C.*

N.B: -

- *Do not freeze! Freezing destroys the antigenicity of phenolized vaccine and the vaccine shall not be used if frozen.*
- *Do not use nerve tissue anti-rabies vaccine for pre-exposure prophylaxis*

- *Health facilities shall prepare and provide vaccination certificate for individuals who had taken full dose of vaccination.*

7.2 Vaccine immunogenicity

Based on WHO guidance, the adequate protective virus neutralizing antibody (VNA) titer for anti-rabies vaccine is 0.5 IU/mL. In healthy individuals, this adequate concentration is regularly achieved by day 14 of post-exposure immunization. The three injections in 10 days interval are taken as booster doses.

7.3 Duration of immunity

For previously immunized individuals, virus neutralizing antibody titer test shall be performed to decide further booster doses or full course of vaccination (provided that VNA test is available). If there is detectable antibody with less than 0.5 IU/mL, individual should receive the three booster doses at 10 days interval. For undetectable virus neutralizing antibody, full vaccination course shall be initiated.

If VNA titer test is not available, individuals who re-exposed to rabies within 3 months following completion of full course of vaccination, no re-vaccination is required and it's expected that, individual will have protective antibody titer ($\geq$ 0.5 IU/mL). For individuals re-exposed within 3-6 months following completion of full course of vaccination, only the three booster doses with 10 days interval shall be given to boost immune response. Individuals re-exposed after 6 months following complete vaccination, a full course of vaccination (17 injections) shall be recommended considering the presence of protective antibody titer not guaranteed.

Table 3. Summary for vaccination after re-exposure

Re-exposure with history of vaccination/in months	Decision	Number of doses
1-3 months	No vaccine required	-
3-6 months	Give booster dose	3 booster doses, 10 days interval
> 6 months	Give full dose of vaccination	Full course of vaccination (17 injections)

7.4 Interruptions in the schedule

Once vaccination is initiated, every attempt should be made to adhere to the recommended vaccination schedules strictly. In some conditions, interruptions in the vaccine schedule do not require re-initiation of the entire series. For some minor deviations from the schedule, vaccination can be resumed as the individual was on schedule. When interruption of schedule occurs, the following possible corrections are recommended. For example, if individual misses the dose schedule due to an unexpected reason for 2 days after receiving 1-6 injections and presents for next vaccination, the next dose should be administered as a resume, maintaining the same interval between doses. In this scenario, the remaining dose would be rescheduled based on the days missed. In case individuals have received 7 injections from 17 full course of vaccination and missed injection for more than 2 days, vaccination schedule shall be re-initiated as a new course of vaccination starting from 1 injection. In case an exposed individual received more than 7 injections and missed next vaccination for 5 days, the next dose shall be administered as a resume, maintaining the same interval between doses. For the three booster doses; if the individual misses next injection for days or

weeks, next booster dose/s shall be resumed as in 10 days interval from the day of last injection. When substantial deviations from the schedule occur, health professionals shall consult vaccine manufacturer as necessary.

Table 4. Decision for interruption in vaccination schedule

Number of injections received	Interruption/in days	Decision
1-6	≤ 2	Resume injection
≤ 7	> 2	Re-initiate injection (full course of the vaccine)
>7	≤ 5	Resume injection
≥ 14	≤ 30	Resume booster injection
≥ 14	31 - 60	Re-initiate booster doses
≥ 14	> 60	Re-initiate injection (full course of the vaccine)

7.6 Shift in the vaccine type

For individuals receiving NTV and get access to cell culture anti-rabies vaccine, and want to shift from NTV to cell culture vaccine, full dose of cell culture vaccine shall be given and specific vaccination schedule for cell culture anti-rabies vaccine shall be followed. In such conditions, amount of NTV doses received shall not be considered and full course of vaccination using cell culture anti-rabies vaccine shall be provided.

7.6 Adverse effects

Nerve tissue anti-rabies vaccine contains a phenolized 5% homogenate of rabies virus-infected sheep brain suspension.

7.6.1 Local adverse events

Nerve tissue anti-rabies vaccine contains myelin basic protein. The vaccination may cause pain, swelling, tenderness and itching, erythematous patches after the beginning of the anti-rabies treatment, fading in 6-8 hours and reappearing after the next dose.

7.6.2 Severe adverse events

Severe adverse events may occur with nerve tissue anti-rabies vaccines. Severe adverse events have been mainly neurological and resulted from an immune response to the myelin basic protein contained in the vaccine. The incidence of these reactions varies widely ranging from 0.14 per 1,000 to 7 per 1,000 cases per treatments.

N.B: - *When neuro-paralytic signs are observed, the following shall be done:*

1. If the dose has not been completed or if further immunization is indicated, the vaccine shall be replaced by an alternative modern vaccine (cell culture vaccine).

2. Individual with severe adverse effects shall be referred for further investigation and treatment.

7.7 Recommendation for special groups

7.7.1 Immunocompromised people

The number of doses recommended will not be changed for persons with altered immune status; but in the case of such individuals, it is recommended to receive cell culture anti-rabies vaccine based on availability. If cell culture anti-rabies vaccine is not available, nerve tissue anti-rabies vaccine shall be given following the same general dose schedule stated previously.

7.7.2 Pregnancy and infancy

For infants and pregnant women, it is recommended to receive cell culture anti-rabies vaccine so as to minimize vaccine associated complications. Because of the potential consequences of inadequately treated rabies exposure, pregnancy shall not be considered as a contraindication to rabies PEP. In addition, there is no indication that fetal abnormalities have been associated with rabies vaccination. Rabies exposure or the diagnosis of rabies in the mother shall not be regarded as reasons to terminate the pregnancy.

7.8 Cold chain management

To retain potency and effectiveness, this vaccine must be kept refrigerated between +2 ^{0}C and +8 ^{0}C throughout its shelf life. Maintaining accurate and up-to-date documentation of refrigerator temperatures is necessary to maintain vaccine potency. Maximum, minimum and current temperatures shall be checked twice daily and documented (at the beginning and end of each day) using temperature recording Log Book. This will ensure that vaccines have been stored at the right temperature, and have not been exposed to temperatures out of the range indicated.

Take vaccines out of the refrigerator only when ready to administer and protect vaccines from exposure to direct sunlight and environmental temperature. As NTV is multi-dose format vaccine, return unused vaccine to the refrigerator immediately after the required dose has been drawn up for injection.

7.8.1 Considerations for vaccine storage management

- Vaccine storage refrigerator shall be optimally placed in an area that is well ventilated, out of direct sunlight and away from external walls.
- Vaccine must be secured away from public access and refrigerators shall be equipped with a lockable door.

- Ensure that the electrical outlet and refrigerator plug are secured to prevent the refrigerator from accidentally being unplugged or turned off.
- Always ensure that the refrigerator door is closed tightly.
- Perform refrigerator preventive maintenance regularly, including cleaning and dusting the back (including coils, top and sides).
- Minimize the number of times the refrigerator door is opened.
- Keep icepacks in the freezer compartment in the case of a refrigerator malfunction or electricity disruption.

7.8.2 Vaccine Transportation

The vaccine shall be transported with the appropriate temperature indicated in the cold chain management part (between +2 ^{0}C and +8 ^{0}C); this can be applied using cold box and icepacks. Its temperature shall be maintained during the middle of transportation by changing the melted icepacks with the dried pack as required. The vaccine shall be managed and transported only by health professionals.

7.9 Vaccine call backing and feedback system

All health facilities providing NTV vaccine in their facility shall report and call back the number of vaccine doses to the manufacturer before 44 days of its shelf life or the expiry date as stated on the labeling of the bottle. Note that, 44 days is the period that will take to complete full dose of vaccine to a single exposed individual. Any adverse event including vaccine administration errors shall be reported to the manufacturer; this will enable the health professional to get a clear guidance.

8. General recommendations

For further detail rabies related information, refer the main comprehensive training manual on human and animal rabies (2019) prepared by Ethiopian Public Health Institute.

Regarding rabies post exposure prophylaxis using nerve tissue anti-rabies vaccine, this guideline shall be used as an updated version over the previous manual published in 2019.

Generally, for any rabies exposure;

- Wounds must be washed/flushed immediately with water for 15 minutes and disinfected in addition to vaccination.
- PEP must be applied using vaccine regimen and administration route that has been proven to be safe and effective.
- PEP should be administered even if the suspected animal is not available for testing or observation.
- As rabies incubation period is extremely variable, exposed individual presenting for rabies PEP even months or years after having been bitten/exposed to rabies shall be treated immediately as his/her presence to the health facility.
- Any patient with sign and symptom of rabies, and present for treatment shall not be eligible for PEP; however, he/she should be referred to the appropriate palliative care center/hospital.
- NTV will not restrict any type of foods except alcohol consumption during taking the course of vaccination.

9. References

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10. Annex

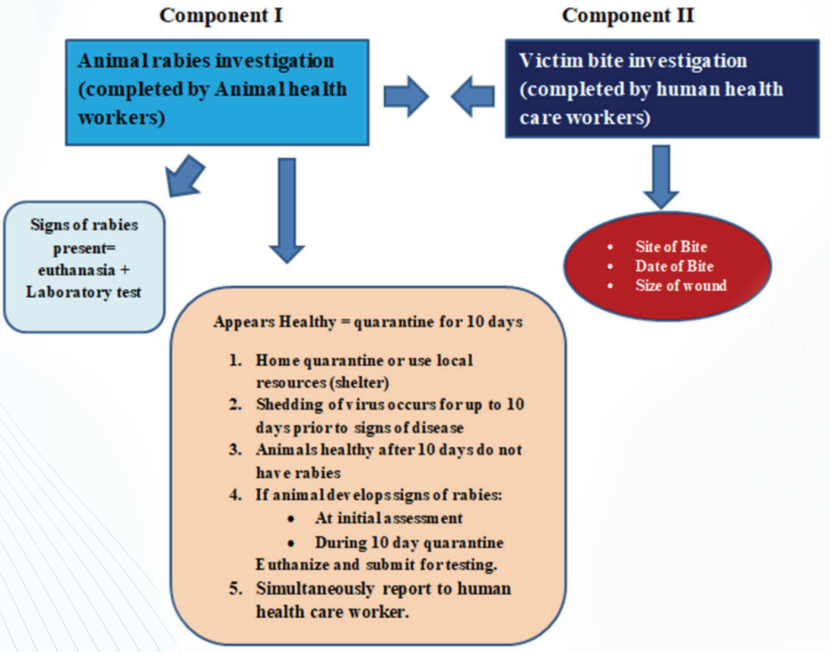
10.1 Integrated Bite Case Management (IBCM)

Animal Bite Surveillance

One health system requires reporting of bites from health centers and reporting of bites from community health workers to animal rabies surveillance officers.

Bite Investigation (One Investigation: Two Components) General rule for bite investigation

Communication between animal health workers and human health care workers at each step of bite investigation via in person, telephone, email or any other appropriate medium is mandatory for better PEP decision.



10.2 Feedback form for Integrated Bite Case Management/IBCM

Individual Information

Name _____Age_____Sex____

Phone number _____

Date of bite/exposure _____ Type of exposing animal _____

Veterinarian section

Animal code, if any: _____

Exposing animal status: Owned ☐ Stray ☐ Unknown ☐

Is exposing animal alive? Yes ☐ No ☐

If yes, does it show sign of rabies after 10 days? Yes ☐ No ☐

If no, date of death _____

If dead, is the sample sent to lab? Yes ☐ No ☐

If yes, date: _____

Laboratory section

Result: Positive ☐ Negative ☐ Inconclusive ☐

Decision for discontinuation of PEP by health care provider

Is individual safe to discontinue vaccine? Yes ☐ No ☐

Health care provider's name _____

Signature_____

Date_____

N.B. *All results should have a stamp of the health facility.*

10.3 Vaccination follow up format

Ethiopian Public Health Institute

Vaccinations follow up format for Nerve Tissue rabies Vaccine (NTV)

- *Date of vaccination started*_____
- *Region*_____
- *Zone*_____
- *Woreda*_____
- *Name of Health Facility*_____
- *Professional name and signature*_____

S.No	*Name*	*Age*	*Sex*	*Days of vaccination (tick at each vaccination date) Vaccine volume/dose _____mL*															
1.				*1.* ___	*2.* ___	*3.* ___	*4.* ___	*5.* ___	*6.* ___	*7.* ___	*8.* ___	*9.* ___	*10.* ___	*11.* ___	*12.* ___	*13.* ___	*14.* ___	*24.* ___	*34.* ___	*44.* ___
Vaccine associated complications observed (circle applicable number and indicate vaccination dates of complication)				*1. Local reaction (pain, swelling, edema, erythema)* *2. Systemic complication (burning, muscle pain, paralytic reaction)* *3. Other, please specify* _____															

10.4 Vaccination certificate

The form should be filled and stamped at the end of full vaccination using NTV by health facilities providing the vaccine. This certificate should be kept carefully by the vaccinee under personal health documents. Vaccinees should avail this certificate up on re-exposure to rabies to support next decision.

Rabies vaccination certificate for Nerve Tissue Vaccine (NTV)

	Date ----------
Full Name	----------
Age	----------
Sex	----------
Individual ID	----------
Name and Address of Health Facility	----------
Date of Complete Full Vaccination	----------
Name of health care provider	----------
Signature and Stamp	----------