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Rabies in Ethiopia Prevention and Control Challenges: Review

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Abstract: Rabies is a zoonotic, viral disease affecting the central nervous system of all warm blood animals. Once clinical symptoms appear, rabies is virtually 100% fatal. In up to 99% of cases, domestic dogs are responsible for rabies virus transmission to humans. Worldwide, endemic canine rabies is estimated to cause 55, 000 human deaths annually. Most of these deaths occur in Asia and Africa, with rural populations and children most frequently affected. It is caused by *Lyssavirus* genus belonging to the Rhabdoviridae family in order Mongrales. Transmission usually occurs through bites of infected animals, the virus may be transmitted through scratching and licking. Rabies is maintained in two epidemiological cycles, thus urban and sylvatic. After a rabies exposure, the rabies virus has to travel to the brain before it can cause symptoms. It may last for weeks to months. Rabies does not result in any characteristic gross lesions. Clinical signs of rabies are rarely definitive. Rabid animals of all species usually exhibit typical signs of CNS disturbance, with minor variations among species. The most reliable signs, regardless of species, are acute behavioral changes and unexplained progressive paralysis. Behavioral changes may include sudden anorexia, signs of apprehension or nervousness, irritability and hyper excitability (including priapism). The diagnosis of rabies is one of the most difficult and important duties that veterinarian is called upon to perform. Rabies is diagnosis based on clinical sign and history of animal before exposure with rabid animal. It is difficult to confirm the disease in live animal. No any treatment for rabies. Dog vaccination and bite prevention is a key to stopping rabies transmission between dogs and from dogs to humans. Preventing rabies at its source is a cost–effective and sustainable way to save lives.

Key words: Rabies · Prevention · Treatment

INTRODUCTION

Rabies is a vaccine-preventable, zoonotic, viral disease affecting the central nervous system of all warm blood animals. Once clinical symptoms appear, rabies is virtually 100% fatal. In up to 99% of cases, domestic dogs are responsible for rabies virus transmission to humans. Yet, rabies can affect both domestic and wild animals. Rabies is one of the neglected tropical diseases (NTD) that predominantly affects already marginalized, poor and vulnerable populations [1].

The infection is characterized via the appearance of rigorous nervous symptoms that results in paralysis following the death of the patient. The canines especially dogs remain the primary reservoir in rising countries, while, wildlife species act as hosts in developed nations [2].

Rabies is present on all continents of the world. Worldwide, endemic canine rabies is estimated to cause 55, 000 human deaths annually. Most of these deaths occur in Asia and Africa, with rural populations and children most frequently affected. Because of this distribution, most of the burden of rabies PEP is borne by those least able to pay. Children are at higher risk of rabies because they often play with animals; bite to the face of neck; and may not report bites or scratches received during play [3].

It does not only cause economic loss due to treatment and prevention. The death of livestock is particularly detrimental to people living in rural communities in the developing world which means loss of family livelihood [4].

It is the oldest infectious disease which was known in 2000 B.C. Rabies is an important disease in Ethiopia recognized in Addis Ababa on August 1903. It is endemic throughout the country and has resulted in a significant loss of human life yearly. It is identified as the first prioritized zoonotic diseases based on its severity [4].

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Therefore the objectives of this review are:

- To familiarize with the general ideas of rabies
- To know the major gaps in rabies prevention and control measures in Ethiopia

Etiology: The Rabies virus is one of the oldest and most feared viruses in the mankind's history. It is the *Lyssavirus* genus belonging to the Rhabdoviridae family in the order Mongrales. RABV has a length of about 180 nm and a cross-sectional diameter of about 75 nm. It is a bullet-shaped virus, containing a negative sense, nonsegmented and single-stranded RNA genome. It has five structural proteins such as nucleoprotein (N protein), phosphoprotein (P protein), matrix protein (M protein), glycoprotein (G protein) and RNA dependant RNA polymerase (L protein). The lyssavirus is prone to the ultraviolet radiation. It is speedily inactivated by exposure to air; sunlight (can persist few days depending on the environmental temperature. Chemicals like quantranary ammonium compound, formaldehyde, iodine, phenol and detergent inactivate the viruses. It also inactivated by low ph (3) and high ph (11) [5].

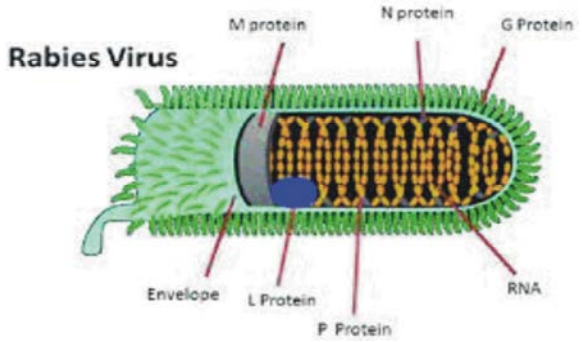

Fig. 1: Rabies virus structure
Source [6]

Transmission: Transmission usually occurs through bites of infected animals, the virus may be transmitted through scratching and licking. It may also spread to people and animals via saliva, direct contact with mucosa (e.g. eyes, mouth or open wounds). Infected animals may excrete virus in their saliva for some time before the onset of clinical signs [7].

Incubation Period: After a rabies exposure, the rabies virus has to travel to the brain before it can cause symptoms. This time between exposure and appearance of symptoms is the incubation period. It may last for weeks to months. The incubation period may vary based on the severity of the bite (scratch, superficial bite, deep bite, multiple bites, etc.;), the amount of the rabies virus introduced to the wound site; the animal responsible for the bite (e.g. bat, virus strain carried, clinically rabid animal); the immune status of the victim; and the site of the bite head and neck wounds, as well as wounds in highly innervated areas such as fingers, generally have shorter incubation periods (i.e. time from infection to clinical signs/death) due to the proximity of the viral inoculation to the nerves [8].

Epidemiology: An understanding of the epizootiology (a science that deals with character, ecology and causes of outbreaks of animal disease) of rabies is necessary in evaluating the risk of exposure and the need for rabies PEP in human [9].

Cycle and Distribution: In a particular geographical region, rabies is frequently maintained and transmitted by particular mammalian reservoir hosts. Raccoons, skunks, foxes and bats are important reservoirs of rabies virus in North America. But in continental Europe, the most important reservoir is the red fox. The vampire bat is the main reservoir of the virus in Central and South America and in the Caribbean islands [10]. Rabies is maintained in two epidemiological cycles, thus urban and sylvatic [11].

In the urban rabies cycle, dogs are the main reservoir host. This cycle predominates in areas of Africa, Asia and Central and South America where the proportion of unvaccinated and semi-owned or stray dogs is high. It has been virtually eliminated in North America and Europe; although sporadic cases occurring dogs infected by wild animals, the urban cycle is not perpetuated in the canine population [11].

The sylvatic (or wildlife) cycle is the predominant cycle in Europe and North America. It is also present simultaneously with the urban cycle in some parts of the world. The epidemiology of this cycle is complex; factors affecting it include the virus strain, the behavior of the host species, ecology and environmental factors. In any ecosystem, often one and occasionally up to 3 wildlife species are responsible for perpetuating a particular strain of rabies [11].

Species Affected: All mammals are susceptible to rabies. There are many strains of the rabies virus; each strain is maintained in particular reservoir host(s). Important maintenance hosts include members of the Canidae (dogs, jackals, coyotes, wolves, foxes and raccoon), Mustelidae (skunks, martens, weasels and stoats), Viverridae (mongooses and meerkats) and Procyonidae (raccoons) and the order Chiroptera (bats) [12].

Pathogenesis: Infection usually begins in muscle tissue following a bite from an infected animal. Rabies virus enters peripheral nerves, or may replicate in myocytes and spread to motor nerve endings. The virus then crosses neuromuscular junctions to peripheral nerves and uses retrograde axonal transport to reach the central nervous system (CNS). Evidence suggests that the virus takes multiple routes to reach the CNS (such as via motor or sensory neurons), depending on the site of inoculation and post-infection time. Whereas the initial spread of RABV is exclusively retrograde, at the end stage of infection, RABV reverses its direction of transport and migrates out of the CNS in an anterograde fashion towards the periphery. Centrifugal spread, especially to the salivary glands where the virus can easily transmit through a bite, is essential to restart the cycle. For much of its life cycle, RABV infection is asymptomatic and clinical signs of neuronal dysfunction present only at late stages of the disease. Rabies disease then rapidly deteriorates the health of the host and leads to death from respiratory or heart failure, usually within days [13].

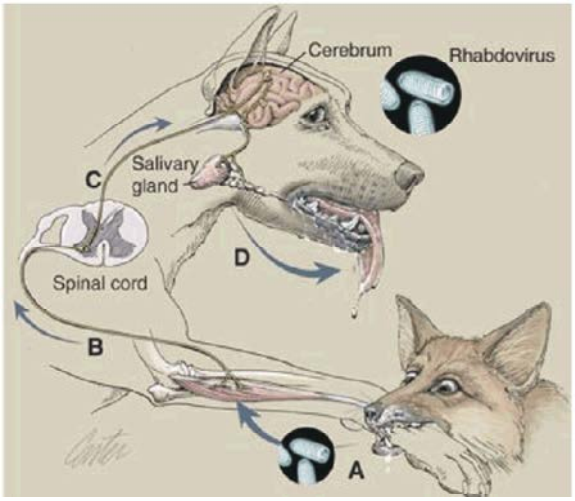

Fig. 2: Pathogenesis of rabies virus infection. *(A)* Retrograde intra-axonal (centripetal) spread to the CNS occurs in peripheral nerves *(B)* Virus replicates in spinal cord neurons and spreads rapidly throughout the nervous system, causing progressive lower motor neuron paralysis *(C)* Virus enters the brain, causing cranial nerve deficits and behavioral changes. Virus spreads centrifugally in peripheral and cranial nerves, from which it enters the salivary glands and saliva *(D)* and other tissues Source [14]

Necropsy Finding: Rabies does not result in any characteristic gross lesions, though there may occasionally be hyperemia of the meninges or hemorrhages in the spinal cord, as well as lesions resulting from trauma, aspiration pneumonia or other consequences of neurological dysfunction. The stomach sometimes contains unusual objects (e.g., rocks, sticks) that were ingested. The typical microscopic lesions are multifocal, mild polio encephalomyelitis and craniospinal ganglionitis with mononuclear perivascular infiltrates, diffuse glial proliferation, regressive changes in neuronal cells and glial nodules. Aggregates of viral material in neurons (Negri bodies) can be seen in some but not all cases [15].

Clinical Sign: Clinical signs of rabies are rarely definitive. Rabid animals of all species usually exhibit typical signs of CNS disturbance, with minor variations among species. The most reliable signs, regardless of species, are acute behavioral changes and unexplained progressive paralysis. Behavioral changes may include sudden anorexia, signs of apprehension or nervousness, irritability and hyper excitability (including priapism). The animal may seek solitude. Ataxia, altered phonation and changes in temperament are apparent. Uncharacteristic aggressiveness may develop a normally docile animal may suddenly become vicious. Commonly, rabid wild animals may lose their fear of people and normally nocturnal species may be seen wandering about during the daytime. The clinical course may be divided into three general phases prodromal, acute excitative and paralytic/end stage. However, this division is of limited practical value because of the variability of signs and the irregular lengths of the phases [16].

Prodromal Stage: Following a definite incubation phase, the beginning of clinical symptoms starts. During this first stage which typically ends within 1-3 days, slight behavioral modication may occur, i.e. anger in domestic animals, daytime tricks in nocturnal animals, no fright of humans in the wild animals or else irregularities in the appetite. Some animals die rapidly without marked clinical signs [17].

Excitement (Furious) Phase: The furious form of rabies refers to animals in which aggression (the acute neural excitative phase) is pronounced. This is the classic mad-dog syndrome, although it may be seen in all species. There is rarely evidence of paralysis during this stage. The animal becomes irritable and, with the slightest provocation, may viciously and aggressively use its teeth, claws, horns, or hooves. The posture and expression are one of alertness and anxiety, with pupils dilated.

Noise may invite an attack. Such animals lose caution and fear of people and other animals. Carnivores with the furious form of rabies frequently roam extensively, attacking other animals, including people and any moving object. They commonly swallow foreign objects, eg, feces, straw, sticks and stones. Rabid dogs may chew the wire and frame of their cages, breaking their teeth and will follow a hand moved in front of the cage, attempting to bite. Young pups can seek human companionship and are overly playful, but bite even when petted, usually becoming vicious in a few hours. Rabid skunks may seek out and attack litters of puppies or kittens. Rabid domestic cats and bobcats can attack suddenly, biting and scratching viciously. As the disease progresses, muscular incoordination and seizures are common. Death results from progressive paralysis [16].

The wild animals often drop their fright of humans and may harass humans or another surrounding animal that they would usually avoid (e.g., porcupines). On the other hand, the nocturnal animals may be observed throughout the day. In cattle, strange attentiveness can be an indication of this phase [16].

Paralytic (Dumb) Phase: The paralytic form of rabies is manifest by ataxia and paralysis of the throat and masseter muscles, often with profuse salivation and the inability to swallow. Dropping of the lower jaw is common in dogs. Owners frequently examine the mouth of dogs and livestock searching for a foreign body or administer medication with their bare hands, thereby exposing themselves to rabies. These animals may not be vicious and rarely attempt to bite. The paralysis progresses rapidly to all parts of the body and coma and death follow in a few hours.

There may be a change in the voice of infected animal due to laryngeal paralysis, including a typical bellowing in cattle and barking in dogs 16].

Species Variations of the Clinical Sign

Horses and Mules: As in other species, horses may bite or strike viciously and, because of their size and strength, become unmanageable in a few hours. The furious form is common but the animal may appear calm between bouts of aggressiveness. Dumb forms also occur and may be mistaken for colic, paresis or encephalitis from other causes. Signs may include a facial twitch, biting of wood work or self-mutilation, head-tossing, colic frequent whinnying, abnormal posture, apparent lameness, ataxia and paralysis of hindquarters. The horse may continue to eat and drink until shortly before death. The tone of voice may be altered [18].

Cattle: These animals are usually affected through having been bitten by a rabid fox or dog. The stage of excitement is short and the dumb stage most evident. Affected cattle behave in an unusual manner; they may stamp or bellow, salivate from the mouth, break loose and may do much damage. Rumination and milk production cease, muscular quivering is seen, sexual excitement is noticed and there is a great loss of condition. Exhaustion soon follows and paralysis sets in. Death occurs within 2 to 6 days or more after the commencement of the condition [19].

Sheep, Goats and Swine: The sheep and the goat are affected in a manner similar to cattle, but the stage of excitement is shorter or absent and the dumb paralytic stage is more often noticed. Pigs become excitable; they may squeal and show muscular spasms before paralysis ensues [18].

Cat: In this animal the furious form is more common than in the dog. The aggressive stage is most marked, the cat attacking other animals and man with great vigour and attempting to injure their faces with teeth or claws. Sometimes the rabid cat will at first show extra affection. The course of the disease is usually shorter than in the dog. It is worth mentioning that occasionally dogs and cats die from rabies without any observed symptoms. They may be found dead or dying. It is not unknown for a cat to be found lying in a field or garden unable to walk but still able to bite [18].

Differential Diagnosis: The diagnosis of rabies is one of the most difficult and important duties that a veterinarian is called upon to perform. Since in most cases, there is a probability of human exposure, failure to recognize the disease may place human life in jeopardy. The best policy is to handle all suspect animals with extreme care but continue to treat them for other diseases if such treatment appears to be indicated. If the animal is rabid, it will die and the diagnosis can then be confirmed by laboratory examination several diseases are characterized by signs of abnormal mental state or paralysis, or a combination both. Rabies must be differentiated from the following common diseases affecting the nervous system [20].

Cattle and Sheep: Lead poisoning, Listerosis, Grass tetany/hypomagnesaemia, Vitamin A deficiency, Choking, milk fever, botulism and anaplasmosis [21].

Horse: Grass tetany, Trauma [22].

Dog and Cat: Toxoplasmisis, CNS infection, Canine distemper, Trauma, Oral foreign body and Poisoning [23].

Diagnosis: Rabies is diagnosis based on clinical sign and history of animal before exposure with rabid animal. It is difficult to confirm the disease in live animal. Identification of the agent Clinical observation may only lead to a suspicion of rabies because signs of the disease are not characteristic and may vary greatly from one animal to another. The only way to perform a reliable diagnosis of rabies is to identify the virus or some of its specific components using laboratory tests [24]. Due to the neurotropic nature of the disease, brain tissue samples are frequently used in rabies laboratory diagnosis for the choice of specimen where the brain stem, hippocampus and cerebellum is recommended for the diagnostic sampling [25].

Routine Laboratory Tests: Laboratory diagnosis can be performed by using three kinds of procedure.

Immunochemical Identification of Rabies Virus Antigen Fluorescent Antibody Test: The most widely used test for rabies diagnosis is the FAT, which is recommended by both WHO and OIE. This test may be used directly on a smear and can also be used to confirm the presence of rabies antigen in cell culture or in brain tissue of mice that have been inoculated for diagnosis. The FAT gives reliable results on fresh specimens within a few hours in more than 95–99% of cases. The sensitivity of the FAT depends on the specimen (the degree of autolysis and how comprehensively the brain is sampled, on the type of lyssavirus and on the proficiency of the diagnostic staff. Sensitivity may be lower in samples from vaccinated animals due to localization of antigen, which is confined to the brainstem. For direct rabies diagnosis, smears prepared from a composite sample of brain tissue that includes the brain stem, are fixed in high-grade cold acetone and then stained with a drop of specific conjugate. Anti-rabies fluorescent conjugates may be prepared in the laboratory. It may be applied in glycerol preserved specimens [26].

Immunochemical Tests: The antibody may be conjugated to an enzyme such as peroxidase instead of fluorescein isothiocyanate (FITC). This conjugate may be used for direct diagnosis with the same sensitivity as FAT but attention should be paid to the risk of nonspecific false-positive results. This risk is considerably reduced by the thorough training of the technicians. It must also be emphasized that this technique needs one incubation step more than the FAT. Peroxidase conjugate may be used on sections of formalin-fixed tissue for immunohistochemical tests [27].

Detection of the Replication of Rabies Virus after Inoculation: These tests detect the infectivity of a tissue suspension in cell cultures or in laboratory animals. They should be used if the FAT gives an uncertain result or when the FAT is negative in the case of known human exposure.

- Cell culture test
- Mouse inoculation test

Five-to-ten mice, 3-4 weeks old (12-14 g), or a litter of 2-day-old newborn mice, are inoculated intracerebral and anaesthetized when inoculated. The young adult mice are observed daily for 28 days and every dead mouse is examined for rabies using the FAT [24].

Histological Identification of Characteristic Cell Lesions: Negri bodies correspond to the aggregation of viral proteins, but the classical staining techniques detect only an affinity of these structures for acidophilic stains. Immunohistochemical tests are the only histological test specific to rabies. An unfixed tissue smear may be stained by the Sellers method; diagnosis is then obtained in under 1 hour. Generally, histological tests, such as Manns test, are performed on fixed material after a paraffin-embedding step and the result of the test is obtained within 3 days. These techniques have the advantage that the laboratory equipment needed to perform them is inexpensive and any need to keep specimens cold after fixation is avoided. Whichever staining method is used, the evidence of infection is provided by intracytoplasmic acidophilic bodies. These histological methods, especially the Sellers method, can no longer be recommended because they have very low sensitivity and should be abandoned [24].

Treatment: Rabies is almost always fatal once the clinical signs develop, regardless of any attempts at treatment and rare survivors are usually left with serious neurological dysfunction. For this and other reasons (e.g., the risk to humans), no treatment is attempted and rabid animals are euthanized. Post-exposure prophylaxis of animals has not been validated and is not recommended [15].

Prevention and Control: Dog vaccination and bite prevention is a key to stopping rabies transmission between dogs and from dogs to humans. Preventing rabies at its source is a cost–effective and sustainable way to save lives [8].

In humans: hound management, reporting of bites, making public awareness, pre-exposure prophylaxis and post-exposure prophylaxis are the major measurement must be taken to prevent and control rabies in human [28].

A comprehensive domestic animal program also requires responsible pet ownership, stray animal management, leash law amendments, human population curtailment, animal importation, translocation and quarantine regulations, schedules for early pre-exposure vaccination of companion animals and rational post-exposure prophylaxis of humans which include proper wound care, administration of rabies vaccine and rabies immunoglobulin; euthanasia of exposed unvaccinated animals [29].

Rabies in Ethiopia: Rabies has probably existed in the parts of Africa for centuries as it was reported by European travelers to Ethiopia and South Africa in the eighteenth and early nineteenth centuries [30].

Each year, thousands of people are infected with rabies in Ethiopia and an estimated 2, 700 people die one of the highest rabies death rates in the world but the true number of deaths caused by rabies is unknown because the disease is underreported and rabies diagnostic laboratories are not established. Furthermore, few places in Ethiopia offer life-saving human rabies post-exposure prophylaxis (PEP) and most people don't have the means to make it to a major hospital to get treated. In addition, people's awareness about what to do if bitten by dogs is low and people often do not seek medical help when bitten [31].

The true disease burden and public health impact of rabies remain underestimated due to the lack of simple, sensitive and cost-effective laboratory methods for rabies. This may be one of the important reasons why rabies remains aneglected zoonotic disease in many developing countries in Asia and Africa [32].

The human risk for rabies is directly linked to the high rate in dogs, which is why it is important to hit the disease at its core vaccinating dogs. However, like many other countries with high human rabies death rate, the rabies vaccination coverage among dogs is very low in Ethiopia, far below the 70 percent needed to halt the transmission of canine rabies. This is partly due to lack of awareness about rabies vaccination among dog owners and high number of stray dogs in the country. The total number of animal rabies cases in Ethiopia is unknown, but with a rural and farming population of more than 80%, annual livestock losses caused by rabies place a large societal and economic burden on the country [31].

Dog-derived rabies in rural seating has also been reported as a potential problem for animal production sector. In most rural parts of the country, dogs are kept in close contact with other livestock for safeguarding purposes, which might provide an opportunity to transmit and maintain the virus in the population. The limited diagnostic facility, poor surveillance protocol, unavailability of vaccine and post-exposure treatment, an increasing stray dog population, low level of public awareness, poor attention and resource allocation by the government are major significant factors that hinder the control of rabies in Ethiopia [33].

The large dog population size in combination with poor dog management contributes to a high endemicity of canine rabies in Ethiopia. The reliability of the reported incidence data is expected to differ among the regions in Ethiopia due to geographical as well as cultural differences. For instance, in rural Ethiopia, individuals who are exposed to rabies often prefer to see traditional healers for the diagnosis and treatment of the disease because of cultural background, lack of knowledge or limited accessibility to medical treatment. These widespread traditional practices of handling rabies cases might interfere with medical treatment seeking practice, resulting in an underreporting of the actual number of rabies cases and its related health burden. To fill the disparities between officially recorded and likely occurring rabies cases, researchers have applied approaches like extensive animal bite case searching and predictive modeling [34].

Major Challenges and Gaps in Rabies Prevention and Control in Ethiopia: Rabies is an invariably fatal disease and there is no cure once clinical symptoms are present in the patient, but can be prevented by pre-exposure prophylaxis. Due to lack of rabies diagnostic laboratories in all regions except Addis Ababa surveillance and diagnosis is not done properly through the country but only very limited data are available. Major challenges for the prevention and control of the disease is listed a follow.

- Low effort of animal rabies control (no defined Legislation/guidelines, fragmented stakeholder efforts, lack of animal rabies surveillance, insufficient availability and misuse of vaccines, low vaccination coverage).

- Low effort in human rabies prevention (absence of modern tissue culture vaccine and weak human rabies surveillance).
- Limited rabies diagnostic capacity (rabies diagnoses technology, absence of trained manpower, only one laboratory facility, lack of inter-sectoral effort).
- Lack of coordination (lack of strong collaboration/ networking among concerned stakeholders, no defined role and responsibilities of stakeholders in rabies prevention and control activities, limited awareness).
- Low Awareness on Rabies Prevention and Control: There is low awareness among the public, human and animal health workers on management of dog bite wounds and pre- and post-exposure prophylaxis. Most patients who die from rabies are either misdiagnosed or do not receive timely and appropriate post-exposure treatment [35].

Economic Importance of Rabies: The economic costs of rabies in a countries are associated with pet animal vaccinations, animal bite investigations, confinement and quarantine of domestic animals which bite humans or which are suspected of exposure to rabid animals, salaries of animal control officers, laboratory diagnosis, the costs of pre-exposure and post-exposure prophylaxis and treatment and consultation, public education, staff training and clerical costs [19]

Zoonotic Implications of Rabies: The prime importance of rabies is its transmissibility to humans, with veterinarians being at special risk. Rabies is virtually always fatal in the human being and there is danger not only from being bitten by rabid animals, but also from contamination by their saliva of wounds, cut fingers, eyes, etc. Scratches may convey infection as well as bites. People have died from rabies following attacks by rabid dogs, cats, foxes, wolves, badgers, skunks, raccoons, mongooses, bats; etc. Bitten persons should seek medical advice immediately [18].

CONCLUSION AND RECOMMENDATION

Rabies is a vaccine-preventable, zoonotic, viral disease affecting the central nervous system of all warm blood animals. Once clinical symptoms appear, rabies is virtually 100% fatal. In up to 99% of cases, domestic dogs are responsible for rabies virus transmission to humans. Rabies is present on all continents of the world. Infection usually begins in muscle tissue following a bite from an infected animal. Rabies virus enters peripheral nerves, or may replicate in myocytes and spread to motor nerve endings. Rabies is almost always fatal once the clinical signs develop, regardless of any attempts at treatment. Dog vaccination and bite prevention is a key to stopping rabies transmission between dogs and from dogs to humans. Based on the above conclusion the following recommendations are forwarded

- Since the diseases is vaccine- preventable carryout mass dog vaccinating for prevention and control
- Victims rapidly wash the exposed area with soap and water for 15 minute or need first aid support
- Take post-exposure vaccine
- Rabidly send samples for conformation to the laboratory
- Give proper awareness creation to the society

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