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Review of Available Articles on General Aspects of Rabies

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Abstract: Rabies, one of the oldest and deadliest diseases known to human, is incurable and neglected viral zoonosis which causes encephalitis in many warm-blooded animals and humans. The disease is caused by rabies virus which belongs to the order Mononegavirales, family Rhabdoviridae and genus *Lyssavirus*. This virus has a negative single-stranded RNA genome and the virions are bullet-shaped. The virus is present in the saliva of affected animals and transmitted among mammals through close contact with saliva from infected animals. The most frequent method of transmission to humans is by bites, scratches or licks to broken skin or mucous membranes. Classical rabies virus occurs worldwide, with the exception of Antarctica, Australia and some Island peninsulas nations being historically free of the disease or having succeeded in eradicating it. The most important reason why rabies is still endemic is the huge global reservoirs, in both domestic and wildlife animals, all mammals are thought to be susceptible to infection, but reservoirs important to the maintenance and transmission of rabies virus are limited to the Carnivora and Chiroptera orders. The first clinical symptom is neuropathic pain at the site of infection or wound due to viral replication. To date, rabies is an important disease in Ethiopia both in human and animals. Rabies is a central nervous system (CNS) disease that is almost invariably fatal except for few rare reported cases. Although hydrophobia is highly suggestive, no clinical signs of disease are pathognomonic for rabies diagnosis. Essential components of rabies prevention and control include on-going public education, responsible pet ownership, routine veterinary care and vaccination and professional continuing education. The majority of animal and human exposures to rabies can be prevented by raising awareness concerning rabies transmission routes and avoiding contact with wildlife. Prompt recognition and reporting of possible exposures to medical professionals and local public health authorities is critical. To control this fatal zoonotic disease the collaborative effort of government authority, medical and veterinary professionals should be encouraged.

Key words: Control · Epidemiology · Prevention · Rabies · Zoonotic

INTRODUCTION

Rabies is a fatal zoonotic central nervous system disease that is characterized by an acute encephalitis illness caused by rabies virus which is genus *Lyssavirus* in the family of Rhabdoviridae that affects virtually all mammals. Infected species invariably die from the disease once clinical signs are manifested [1]. This disease affects all warm-blooded mammals including human and has been threatening the lives of mankind for more than 4, 000 years [2, 3]. Globally, it is estimated that at least 60, 000 people die of rabies each year [4, 5]. This virus has a negative single-stranded RNA genome and the virions are bullet-shaped [2].

Dogs remain the primary reservoir in developing countries, whereas wildlife species serve as hosts in developed nations [6]. Dog rabies potentially threatens over three billion people in Africa and Asia and people most at risk live in rural areas, where vaccines and immunoglobulin are not readily available or accessible. The WHO considers rabies as neglected disease and declares it to be primarily a problem in areas troubled with

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a lack of economic resources [7] with over several deaths per year [8] and signs of it re-emerging [9]. In Ethiopia rabies has been known for centuries in society as Mad Dog Disease [10] and has been recorded scientifically since 1903 [11].

To date, rabies is an important disease in Ethiopia both in human and animals [12-15]. In Four-Years Retrospective Study by Teklu *et al*. [13] in North western Tigray the incidence of human rabies exposure cases calculated per 100, 000 populations was 35.8, 63.0, 89.8 and 73.1 in 2012, 2013, 2014 and 2015, respectively. The proximity of the site of the virus entry to the CNS increases the likelihood of a short incubation period [16]. Following the bite of rabid animal the incubation period varies from 5 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 the proximity of the virus entry to the central nervous system [7].

In animal the initial clinical signs are often nonspecific and may include fearfulness, restlessness, anorexia or an increased appetite, vomiting, a slight fever, dilation of the pupils, hyper reactivity to stimuli and excessive salivation. The first sign of post-vaccinal rabies is usually lameness in the vaccinated leg. Animals often have behavioural and temperament changes and may become either unusually aggressive or uncharacteristically affectionate [17].

Laboratory diagnosis of rabies in humans and animals is essential for timely post-exposure prophylaxis. Rabies diagnosis may be carried out either in vivo or post-mortem especially by diagnostic methods like direct fluorescent antibody, mouse inoculation technique, tissue culture infection technique and PCR [18]. There is no certain cure for rabies except supportive care. Rabies can be prevented before the latent symptoms can develop, which consists of giving a person an injection of rabies immune globulin and another injection of rabies vaccine as soon as possible after the bite or exposure to saliva from an infected animal [18].

Essential components of rabies prevention and control include on-going public education, responsible pet ownership, routine veterinary care and vaccination and professional continuing education. The majority of animal and human exposures to rabies can be prevented by raising awareness concerning: rabies transmission routes and avoiding contact with wildlife. Prompt recognition and reporting of possible exposures to medical professionals and local public health authorities is critical [19]. Even though rabies is the most fatal disease for both human and veterinary public significance there is scarcity of information mostly in developing countries. Therefore, the main objective of this seminar is to review available articles on general aspect of rabies.

Literature Review

Aetiology and Taxonomy: The word rabies is derived from the Sanskrit word rabhas, which means to range or from the Latin word rabere, which means to rave´ [20]. Rabies virus (RABV) is the prototype virus of the genus *Lyssavirus* (From the Greek lyssa meaning 'rage') in the family Rhabdoviridae (From the Greek rhabdos meaning 'rod').The prototype RABV is a genotype 1 virus (Formerly recognized as serotype 1). Lagos bat virus (LBV, genotype 2/serotype 2), Mokola virus (MOKV, genotype 3/serotype 3), Duvenhage virus (DUVV, genotype 4/serotype 4), European bat lyssa virus type 1 (EBL-1, genotype 5), European bat *Lyssavirus* type 2 (EBL-2, genotype 6) and Australian bat *Lyssavirus* (ABLV, genotype 7) are rabies-related *Lyssaviruses* that reflect the genotypic diversity of the genus *Lyssavirus* [21]. It is a disease of mammals, but the sensitivity to the virus can vary between different mammal hosts [22].

Rabies is a fatal neurological infectious disease caused by of rabies virus (RABV) [23, 24]. This disease has been threatening the lives of mankind for more than 4, 000 years [2, 3]. The virions or virus particles have a bullet-shaped structure (75 nm diameter and 100-300 nm length), a single-stranded and negative-sense RNA genome of about 12 kb nucleotide [3, 25]. Rabies virus encodes five sub genomic mRNAs that encodes five structural proteins. The viral proteins include (i) the nucleoprotein (N), which encapsulates the genomic and antigenomic RNA to form the ribonucleoprotein (RNP) complex; (ii) the phospoprotein (P), which is the non-catalytic subunit of the RNA polymerase complex; (iii) the viral polymerase protein (L), which transcribes and replicates the RNA genome; (iv) the trans membrane glycoprotein (G), which is the surface spike protein involved in attachment to host cell and (v) the matrix protein (M), which is the major structural protein involved in virion assembly and egress [3, 26].

All rhabdoviruses have two major structural components i.e., a helical riboneucleoprotein core (RNP) and a surrounding envelope. The capsid is surrounded by the host cell-derived membrane that interacts with two viral proteins, the matrix protein and glycoprotein. The N, P and L together with the genomic RNA form the riboneucleoprotein complex (RNP) [26, 27]. Among these, the rabies virus glycoprotein (G) is the only one that is

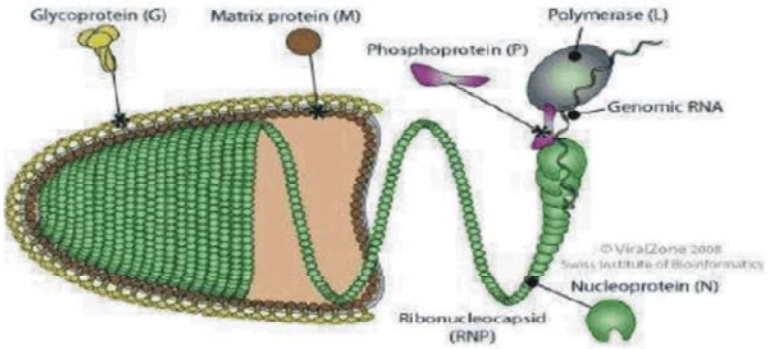

Fig. 1: Schematic representation of rhabdovirusvirion
Source: Bela-Ong *et al.* [30].

exposed on the viral particle surface and can mediate viral entry into the host cell [24]. The G protein is a key protein for both virus infectivity and eliciting protective immunity as an antigen. Nevertheless, the nucleoprotein (N) is also a significant rabies virus antigen [28].

Rabies caused by rabies virus (RABV) genotype 1st one of the most common fatal infections worldwide. However, the existence of *Lyssaviruses* that are closely related to rabies virus and that can also causes clinical diseases has been known for several decades [29].

The virus is susceptible to ultraviolet radiation. It is rapidly inactivated by sunlight and drying and (In dried blood and secretions) it does not survive for long periods in the environment [31]. Fundamentally, viruses are infectious nucleic acids that have evolved efficient mechanisms for shuttling their genomes between the host cells that they depend upon for replication [32].

The sequence of events in the RABV life cycle, i.e. replication in vitro and in vivo (In cell culture or animal) can be divided into three phases. The first or early phase includes virus attachment to receptors on susceptible host cells, entry via direct virus fusion externally with the plasma membrane and internally with endosomal membranes of the cell and uncoating of virus particles and liberation of the helical RNP in the cytoplasm. The second, or middle, phase includes transcription and replication of the viral genome and viral protein synthesis. The third, or late, phase includes virus assembly and egress from the infected cell. The early phase of the RABV life cycle, often regarded as the most difficult of the events in RABV infection to understand fully, has been studied in many different cell culture systems. These include neuronal and non-neuronal cell lines and primary, dissociated cell cultures derived from dissected pieces of nervous tissue [33].

Epidemiology

Occurrence and Distribution: Classical RABV occurs worldwide, with the exception of Antarctica, Australia and some Island peninsulas nations being historically free of the disease or having succeeded in eradicating it [34]. Lack of reporting and under reporting by some countries undermines knowledge of the true impact of the disease. In Africa, five *Lyssavirus* species in addition to RABV have been documented; these include Lagos bat virus (LBV) and Mokola virus (MOKV), which circulate widely across the continent, Duvenhage virus (DUVV), isolated from bats in southern Africa, Shimoni bat virus (SHIBV) and Ikoma virus (IKOV). To date, only single isolates of the last two species have been recovered, so their range is unknown [35].

Rabies is a classic example of a multi-host pathogen for which the identification of reservoirs has proven challenging [36-38]. In Africa and Asia, domestic dog rabies predominates among reported and confirmed cases and domestic dogs are the reported source of infection for over 90% of human cases [39] however, it has been argued that this may reflect surveillance bias and that the role of wildlife is poorly understood [40]. An outbreak of the disease in dogs was first confirmed in the Eastern Cape Province of South Africa in 1893 by inoculation of rabbits. In the developed world, rabies in dogs has been controlled, but the disease has established itself in the wildlife. In North America, various species of wildlife are involved including the fox, raccoon dogs and skunks, while in much of Europe; the fox is the principal reservoir [41]. In spite of rabies been confirmed in a variety of wildlife species in Africa, the domestic dog still remains the most dangerous reservoir of the disease because of its close association with man [42].

In Kenya, rabies has been confirmed in a variety of wildlife species including the jackal, honey badger, civet rat, mongoose, hyena, ground squirrel and in livestock (Cattle, sheep, goats, donkeys) [43].

Host Range and Excretion of Rabies Virus: The most important reason why rabies is still endemic is the huge global reservoirs, in both domestic and wildlife animals, all mammals are thought to be susceptible to infection, but reservoirs important to the maintenance and transmission of rabies virus are limited to the Carnivora and Chiroptera orders [6]. The excretion of rabies virus and the levels of virus excreted are the most important factors for transmission. Rabies virus can be excreted in saliva of infected animals for many days after the onset of clinical signs of disease. Rabies virus has also been found in dog saliva up to seven days before signs of rabies were observed. The carrier state, a chronic infection with or without a period of clinical signs during which animals can transmit disease by excreting virus in saliva, can be found in dogs. Rabies virus has been isolated from the saliva of clinically normal dogs and dogs with transient paralysis.

Fekadu *et al*. [44] found that saliva collected on day 42 and 169 from a dog that had recovered from experimental Ethiopian strain rabies inoculation produced fatal rabies in mice inoculated intracerebrally. Fekaduet *et al*. [44] also reported that viable virus could be isolated from the palatine tonsil of an experimentally infected dog up to 305 days after its recovery. Rabies virus can be excreted from the saliva of cats for one to three days and cattle for one to two days prior to onset of signs. The virus may be detectable earlier in wildlife than in dogs, in skunk up to four days prior to clinical disease onset, one to two days in foxes and 12 days in insectivorous bats. Virus can be excreted in urine and this may lead to transmission by aerosol in foxes and bats [41]. Excretion in milk also occurs but is considered to not represent a major hazard because viral particles will be destroyed by enzymes present in the milk [45].

All mammals are susceptible to rabies, but only a limited number of species also act as reservoir hosts. The most predominant rabies reservoirs are listed in table 1 below. They include members of the families Canidae (Dogs, jackals, coyotes, wolves, foxes and raccoon dogs), Mustelidae (e.g., skunks), Viverridae (e.g., mongooses) and Procyonidae (Raccoons) and the order Chiroptera (Bats) [46]. Rabies reservoirs are generally grouped into terrestrial (i.e., land-dwelling) species and bat species. Rabies can occur sporadically in individuals or can exist in an enzootic or epizootic state in animal populations. In enzootic state rabies is indigenous to a reservoir species in a locality and occurs with a relatively stable incidence rate. An epizootic occurs when the incidence of disease increases markedly in the reservoir species. Rabies that is transmitted sporadically from reservoir to non-reservoir species is said to be spillover. These reservoir species are: raccoon (Procyonlotor), striped skunk (Mephitis mephitis), coyote (Canislatrans; infected with the dog variant), gray fox (Urocyoncinereoargenteus) and Arctic fox (Alopexlagopus) and red fox (Vulpes vulpes) [47].

Table 1: Predominant global rabies reservoirs

Dog	Major susceptible host of rabies throughout the world, particularly Asia, Latin America and Africa
Foxes	Europe, Arctic and North America.
Raccoons	Eastern United States.
Skunks	Midwestern United States, Western Canada.
Coyotes	Asia, Africa and North America.
Mongooses	Yellow mongoose in Asia and Africa; Indian mongoose in the Caribbean Islands.
Bats	Vampire bats from Northern Mexico to Argentina, insectivorous bats in North America and Europe

Mode of Transmission: The commonest mode of transmission in man is by the bite of a rabid animal or the contamination of scratch wounds by virus- infected saliva. However, other routes have been implicated in the past, such as through mucous membranes of the mouth, conjunctiva, anus and genitalia. Infection by aerosol transmission had been demonstrated in experimental animals and has been implicated in human infection in rabies-infected bat caverns and in several laboratory accidents [48]. Transmission of rabies virus usually begins when infected saliva of a host is passed to an uninfected animal.

Pathogenesis: Rabies is a central nervous system (CNS) disease that is almost invariably fatal [49] except for few rare reported cases [50]. Rabies-infected animals have high titres of the rabies virus in their salivary glands, which can be even greater than in the brain. There are marked differences between the different strains of virus and their ability to infect, spread within the body and produce disease [49]. It has been suggested that the attenuated rabies viruses activate the host's innate immune and antiviral responses, while these responses are evaded by the pathogenic rabies viruses [51].

After the bite, the virus particles travel to the nearby nerves and then along the nerve fibres to the brain at a speed of a few millimetres per day [52]. It was suggested that the virus is propagated from the entry point to the CNS due to the interaction between the P protein of the rabies virus and the dynein light chain LC8 [53]. A bite on the head or neck will usually cause symptoms more quickly than a bite on the hind leg. However, when the virus has entered the nerve endings, it advances relentlessly up the nerve bodies until it reaches the spinal cord and eventually the brain. From the brain, the virus can spread to other tissues - the salivary glands, respiratory system and the digestive tract [54].

The proximity of the site of the virus entry to the CNS increases the likelihood of a short incubation period [55]. Viruses can also enter motor axons in peripheral nerves directly during a penetrating injury. The incubation period varies from 5 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 the proximity of virus entry to the central nervous system [56]. The incubation period is less than 50 days if the patient is bitten on the head or neck or if a heavy inoculum is transferred through multiple bites, deep wounds, or large wounds.

A person with a scratch on the hand may take longer to develop symptoms of rabies than a person who receives a bite to the head. In dogs and cats, the incubation period is 10 days to 6 months; most cases become apparent between 2 weeks and 3 months. In cattle, an incubation period from 25 days to more than 5 months has been reported in vampire bat- transmitted rabies. In humans, the incubation period can be a few days to several years. Most cases become apparent after 1-3 months [17].

Clinical Signs: The clinical picture can be highly variable between different species, individuals of the same species and even within the course of the disease in a particular individual. As the disease progresses, animals with rabies may show strange behaviour. Any clinical suspicion of rabies must be confirmed by laboratory examination [57]. The initial clinical signs are often nonspecific and may include fearfulness, restlessness, anorexia or an increased appetite, vomiting, diarrhoea, a slight fever, dilation of the pupils, hyper reactivity to stimuli and excessive salivation. The first sign of post-vaccinal rabies is usually lameness in the vaccinated leg.

Animals often have behavioural and temperament changes and may become either unusually aggressive or uncharacteristically affectionate [17]. In bats, the clinical signs of a *Lyssavirus* infection include loss of body mass, lack of coordination, muscular spasms, agitation, increased vocalization and overt aggression [58, 59] but in many cases, rabies in bats can be clinically silent and left unnoticed before dead animals are found and laboratory tests are performed [60]. When bats were found alive, the clinical signs were generally described as paralysis, unprovoked vocalization and aggression (Biting) during handling [61]. However, almost all bats will bite when handled [62].

Prodromal Stage: After a certain incubation period, the onset of clinical symptoms follows. During this first stage which usually lasts for about 1-3 days minor behavioural changes might occur, i.e. aggressiveness in tame animals, daytime activities in nocturnal animals, no fear of humans in wild animals or abnormalities in appetite [7].

Excitement (Furious) Phase: Eventually, the prodromal stage is followed by a period of severe agitation and aggressiveness. The animal often bites any material. Rabid dogs, for example, may develop a typical high barking sound during furious phase. Death may follow convulsions even without the paralytic stage of the disease. The furious form is characterized by restlessness, wandering, howling, polypnea, drooling and attacks on other animals, people or inanimate objects. Affected animals often swallow foreign objects such as sticks and stones. Wild animals frequently lose their fear of humans and may attack humans or animal species they would normally avoid (e.g., porcupines). Nocturnal animals may be visible during the day. In cattle, unusual alertness can also be a sign of this form [17]. The furious form of rabies is characterized by hydrophobia: terror and excitation with spasm of aspiratory muscles, larynx and pharynx precipitated by attempts to drink and episodes of hallucinations and excitement are common [29].

Paralytic (Dumb) Phase: The dumb form of rabies is characterized by progressive paralysis. In this form, the throat and masseter muscles become paralyzed; the animal may be unable to swallow and it can salivate profusely. Laryngeal paralysis can cause a change in vocalization, including an abnormal bellow in cattle or a hoarse howling in dogs. There may also be facial paralysis or the lower jaw may drop. Ruminants may separate from the herd and can become somnolent or depressed. Rumination may stop. Ataxia, incoordination and ascending spinal paresis or paralysis are also seen [17]. This stage is characterized

by the inability to swallow, leading to a typical sign of foaming saliva around the mouth. Some animals may develop paralysis beginning at the hind extremities. Eventually, complete paralysis is followed by death [7].

Diagnosis: Laboratory diagnosis of rabies in humans and animals is essential for timely post-exposure prophylaxis. Rabies diagnosis may be carried out either *in vivo* or post mortem [63]. Infection with rabies virus can be difficult to diagnose ante-mortem. Although hydrophobia is highly suggestive, no clinical signs of disease are pathognomonic for rabies. Historical reliance on the detection of accumulations of Negri-bodies is no longer regarded as suitable for diagnostic assessment because of low sensitivity and alternative laboratory based tests have been developed to conclusively confirm infection [64].

Most diagnostic tests for rabies virus in animals need brain material for diagnosis and as such are often only possible post mortem [65]. The diagnosis of rabies in animals can be made by taking any part from the affected brain. But in order to rule out rabies, the test must include tissues from at least two locations in brain, from the brain stem and cerebellum. There are many diagnosis methods for detection of rabies in animals like direct fluorescent antibody, mouse inoculation technique, tissue culture infection technique and polymerase chain reaction [18].

Brain samples are most readily taken by breaching the skull and sampling directly. Brain smears or touch impressions are used for the detection of virus antigen with the fluorescent antibody test (FAT) for both human and animal samples. In animals the direct fluorescent antibody test (dFAT) is the recommended diagnostic test. This test detects the presence of rabies antigens in brain tissue. Other diagnostic techniques include reverse transcription polymerase chain reaction (RT-PCR), direct rapid immunohistochemistry test (dRIT) and serological tests (Fluorescent antibody neutralization test, rapid fluorescent focus inhibition test). In humans, the rabies recommended test is dFAT on brain tissue. Other diagnostic tests that have been used are RT-PCR and dRIT [64].

Clinical diagnosis of rabies divided upon three stages in human; prodromal, excitement (Furious) and paralytic (Dumb). But all these stages cannot be observed in an individual. The very first clinical symptom is neuropathic pain at the site of infection or wound due to viral replication. Following by the prodromal phase either or both the excitement or paralytic forms of the disease may be observed in the particular species. It is also documented that cats are more likely to develop furious rabies than dogs [18]. In some cases, no signs are observed and rabies virus has been identified as the case of sudden death [66].

Diagnosis can only be confirmed by laboratory tests preferably conducted post mortem on central nervous system tissue removed from cranium [67]. Rabies must be considered in the differential diagnosis of any suspected mammalian meningitis/ encephalitis, distemper, infectious canine hepatitis and cerebral cysticercosis (Taenia solium,) in dogs, sporadic bovine encephalomyelitis (Chlamydia psittaci), heart water in cattle and sheep. Other conditions like mineral/ pesticide poisoning and Plant poisoning From *Pennisetum clandestinum* (Kikuyu grass) in cattle, Cynanchum spp (Monkey rope) in sheep should be considered [68].

Prevention and Control: There is no certain cure for rabies except supportive care. Rabies can be prevented before the latent symptoms can develop, consists of giving a person an injection of rabies immune globulin and another injection of rabies vaccine as soon as possible after the bite or exposure to saliva from an infected animal [18]. Essential components of rabies prevention and control include on-going public education, responsible pet ownership, routine veterinary care and vaccination and professional continuing education. The majority of animal and human exposures to rabies can be prevented by raising awareness concerning: rabies transmission routes and avoiding contact with wildlife. Prompt recognition and reporting of possible exposures to medical professionals and local public health authorities is critical [19].

Human rabies can be prevented by a) eliminating exposure to rabies virus, b) providing appropriate rabies pre-exposure prophylaxis and c) prompt local treatment of bite wounds combined with appropriate rabies post-exposure prophylaxis [31]. Inactivated human vaccines are available for at risk veterinary staff, other animal handlers, wildlife officers, laboratory workers and others at high risk of exposure [69].

Domestic Animal Rabies Control: The primary components of a rabies control program for companion animals are: immunization and licensing, stray animal control, reporting, investigation and isolation of animals involved in bite incidents; and public education. Multiple vaccines are licensed for use in domestic animal species. Vaccines available include: inactivated or modified live virus vectored products, products for

intramuscular and subcutaneous administration, products with durations of immunity from one to 4 years; and products with varying minimum age of vaccination [31].

Animal Bites Reporting: The local health officer or designee shall be immediately notified of any person or animal bitten by or potentially exposed to a rabid or suspected rabid animal. In addition, the local health officer or designee shall be notified when any person is bitten by a mammal. Potential human rabies exposures are then evaluated and rabies post-exposure prophylaxis (PEP) recommendations made [19, 31].

Stray Animals: Stray dogs, cats and ferrets should be removed from the community. Local health departments and animal control officials can enforce the removal of strays more effectively if owned animals are required to have identification and are confined or kept on leash. Strays should be impounded for at least 3 business days to determine if human exposure has occurred and to give owners sufficient time to reclaim animals [70].

Isolation of Animals Exposed to Rabies: Any animal bitten by, scratched by, or having direct contact with a wild mammal that is not available for rabies testing should be regarded as having been exposed to rabies. All livestock species (Horses, cattle, sheep, goats, llamas/alpacas and swine) are susceptible to rabies infection. Cattle and horses are the livestock species most frequently diagnosed with rabies. Unvaccinated livestock bitten by or exposed to a rabid or suspect rabid animal should be euthanized [19].

Wild Animal Rabies Control: Principles of rabies prevention should focus on excluding wild animals from areas of human and domestic animal habitation and activity and avoidance of contact with possibly rabid wild animals. Public education on the risks of rabies transmission from wild animals is paramount to effective disease prevention. Immunization of wildlife by widespread distribution of vaccine-impregnated oral baits has shown variable success toward arresting the propagation of rabies in raccoons and coyotes in other states. The use of oral rabies vaccines for the mass vaccination of free-ranging wildlife should be considered in selected situations [19, 71].

Animal Pre-Exposure Vaccination: A number of recently developed, highly-effective, thermo stable, inactivated vaccines are available for veterinary use. The duration of immunity conferred varies from one to three years. Most veterinary vaccines are only registered for use in specific species, for example dogs. All rabies vaccines registered for human and animal use must conform to established potency standards. A minimum antigenic potency of 2.5 IU per dose is mandatory [72]. The vaccines may be used in young pups, but they must be boosted at three months of age and again within the following year. Revaccination must be carried out every three years thereafter. Cattle and sheep may be vaccinated annually or every two to three years, depending on the vaccine manufacturer's instructions. Following an outbreak in domestic livestock, vaccination of animals without visible bite wounds is strongly recommended [73].

Post-Exposure Treatment (PET): Rabies has a 100% case fatality rate; meaning that once clinical signs are manifested treatment will be futile and death will inevitably occur. Thus, it is very important that treatment be initiated immediately a person has been exposed to a suspect rabid animal. The World Health Consultation on Rabies [74] drew up guidelines on the management of patients exposed to rabies suspect animals. Post-exposure treatment (PET) consists of local treatment of the wound, initiated as soon as possible after an exposure, followed by the administration of passive immunization, if indicated and a potent and effective rabies vaccine that meets WHO criteria. The PET may be discontinued if the animal involved is a dog or cat that remains healthy for an observation period of 10 days after the exposure occurred; or if the animal is humanely killed and proven to be negative for rabies by a reliable diagnostic laboratory using a prescribed test. If the animal inflicting the wound is not apprehended, PET should be instituted immediately.

The World Health Organization [39] and Centres for Disease Control [75] have guidelines for post exposure treatment and assessment of each category of exposure and level of risk. Two kinds of rabies immunoglobulin's, human rabies immunoglobulin (HRIG) and equine rabies immunoglobulin (ERIG), are currently effective forms of passive immunization used in serious or high risk exposure cases except for the exposed person who has been vaccinated previously. The HRIG is given at 20 IU/kg and ERIG at 40 IU/kg by infiltrating one half around the wound and one half intramuscularly followed by five doses of cell culture vaccine one each on day 0, 3, 7, 14 and 28 [76]. Findings from a study conducted by Hanlon *et al*. [77] suggested that 5 doses of canine rabies vaccine administered on days 0, 3, 14, 21 and 35 along

with murine anti-rabies antibody on day 0 may be effective in protecting a previously unvaccinated animal exposed to rabies. Regardless of the age of the animal at initial vaccination, a booster vaccination should be administered 1 year later [57]. If signs suggestive of rabies develop (e.g., paralysis, seizures, etc.), the animal should be euthanized and the head shipped for testing [77].

Vaccine Strains and Anti-rabies Vaccines: Since the first rabies vaccination in 1885 by Louis Pasteur, significant progress has been made in improving the pre- and post-exposure treatment of human rabies [49]. There are several types of vaccines: live attenuated, inactivated (killed), DNA-based and vector vaccines. For the production of anti-rabies vaccines, a number of attenuated vaccine strains are employed: the Pasteur Virus (PV), Evelyn Rokitniki Abelseth (ERA), Street-Alabama-Dufferin (SAD), 3aG, Fuenzalida S-51 and S-91, Ni-Ce, SRV9, PM, Nishigahara, RC-HL, Kelev, Flury, Shelkovo-51, O-73 Uz-VGNKI, RV-71, Krasnopresnenskii-85 and the RV-97 strain [78, 79]. The PV is one of the first vaccine strains; it was isolated from a rabid cow in 1882 and attenuated by multiple passages in rabbits. The SAD strain was isolated from a rabid dog in Alabama (USA) in 1935 and adapted for cultivation in the mouse brain and in the baby hamster kidney cell culture. It has two main derivates: ERA and Vnukovo-32.

Several variants of the SAD strain exist: SAD-Berne, SAD B19, SADP5/88 etc. and also non-virulent mutants SAG-1 and SAG-2. The vaccine strains belonging to the SAD group are widely used throughout the world. One of the most widely used oral anti-rabies vaccines is prepared from the SAD B19 strain, the high immunogenicity and relative safety of this strain has been demonstrated experimentally [80, 81].

Live Attenuated Vaccines: Live attenuated vaccines are still in use in some developing countries for parenteral vaccination of animals and humans. These contain live attenuated rabies virus which has been developed in cell cultures or in live animals such as sheep. In the developed world, live attenuated vaccines are only used for the oral immunization of wild animals. Oral vaccines are widely used and several vaccine strains are used for the production of such vaccines: the SAD B19 and other SAD-strains, SAG1 and SAG2 pathogenic deletion mutants, Vnukovo-32 and the VRG strain [80]. The vaccine strain RV-97 is used in Russia for producing the oral anti-rabies vaccine Sinrab. This strain was obtained in the FGI, Federal Centre for Animal Health (Vladimir, Russia) from strain RB-71. The ancestor to these .two strains is the strain Sheep, derived from the PV strain. The strain Moscow is also believed to be a derivate of the PV strain [78] and was used in the former USSR for producing anti-rabies vaccine. The strain RV-97 is adapted for cultivation in cell culture BHK-21 [79].

Inactivated Vaccines: Complete inactivated rabies virus particles are highly immunogenic. The vaccines based on this principle are used for the pre- and post-exposure immunization of humans and domestic animals [49]. The inactivated chicken embryo vaccines and vaccines based on virus cultivated in cell cultures are used for veterinary and medical purposes [82]. Modern medical vaccines can be administered by the intradermal route.

DNA Vaccines: DNA vaccines are based on plasmid vectors expressing rabies virus glycoprotein. These vaccines have been tested for their efficiency in several animal species (Mice, dogs and nonhuman primates) and it has been found that the DNA vaccine develops VNA levels and offers protection comparable with those obtained with the inactivated vaccines [83]. On the basis of the results of the study conducted in mice, a single administration of the rabies DNA vaccine may be as effective as at least five injections of the cell-culture derived vaccine [84].

Vector Vaccines: Vector vaccines are based on recombinant viruses and several viruses have been tested for these purposes. The VRG vaccine was designed on the basis of poxvirus (Vaccinia virus) expressing SAD strain glycoprotein and used for oral immunization of wildlife [85]. The Adrab.gp - vaccine is based on the adenovirus expressing the ERA strain glycoprotein and was found capable of inducing an immune response in dogs [86]. The canine herpesvirus (CHV) expressing the glycoprotein of rabies virus has also been used successfully as an anti-rabies vaccine [87]. A raccoon poxvirus (RCNV) recombinant vaccine for the immunization against feline panleukopenia and rabies has been developed and tested in cats [88]. A recombinant rabies virus vaccine carrying two identical glycoprotein (G) genes (SPBNGA-GA) has also been constructed [89]. The rabies virus vaccine strain based on vectors have shown great promise as vaccines against other viral diseases such as human immunodeficiency virus type 1 (HIV-1) infection and hepatitis C, but a low residual pathogenicity remains a concern for their usage [90].

Plant-derived antigens can also be used for the immunization against rabies. The coat protein of alfalfa mosaic virus has been used as a carrier molecule to express the antigenic peptides from rabies virus. The in vitro transcripts of the recombinant virus with sequences encoding the antigenic peptides have been synthesized from DNA constructs and used to inoculate tobacco plants. The plant-produced protein (Virus particles) has been purified and used for the immunization of mice and specific anti-rabies virus neutralizing antibodies in immunized mice has been found. The transgenic maize expressing the G protein of the Vnukovo strain has also been obtained and tested in mice. It was shown that the mice developed virus neutralizing antibodies which were able to provide protection of 100% against the challenge of a vampire bat strain [91].

Oral Vaccination of Wildlife Against Rabies: Before the era of oral vaccines, the only feasible measure for controlling rabies in wildlife was the depopulation of reservoir species [92] but currently rabies is the only zoonosis that can be controlled by the oral vaccination of wildlife. The idea of conducting active immunization of wildlife appeared in the last century but many difficulties, such as the form of the vaccine, methods of distribution and uptake control and possible residual pathogenicity have to be surpassed. Since then, several laboratory and field trials have been conducted and different delivery methods including vaccine traps and wool getters were designed [93].

Initially, plastic vessels containing the vaccine were attached to chicken heads, but recently different types of modern vaccine baits and different meal mixtures for producing these were developed and tested. The vaccine based on the strain SAD B19 is one of the most widely used in Europe: 70 million vaccine baits were used between 1983 and 1988 [80]. Studies on the immunogenicity and efficacy of the SAD B19 attenuated rabies virus vaccine in foxes were conducted under laboratory conditions [81]. Vos *et al*. [94] studied the safety of the SAD B19 vaccine in 16 animal species by different administration routes; a low residual pathogenicity was observed only for certain rodent species, but transmission of the vaccine virus to control animals was not demonstrable, since no vaccine virus was detected in the saliva of the six mammal species examined. Furthermore, the genetic stability of the SAD B19 vaccine was shown through passage in neural tissue of dogs, foxes and mice. From those results presented here on the innocuity and stability, it can be concluded that the SAD B19 rabies vaccine is suitable for the oral vaccination campaigns of carnivores against rabies [94]. Nevertheless, several rabies cases have been caused by live attenuated viruses [95] so the development of new, safer vaccine strains is a very important issue.

Two mutant vaccine strains were obtained by directed mutagenesis of the strain SAD. The SAG-1 contains one nucleotide substitution, while the SAG-2 has two substitutions at amino acid position 333 of the rabies virus glycoprotein [96]. These vaccine strains are apathogenic for adult mice inoculated by the intracerebral route [97]. The SAG-2 based vaccine was demonstrated as a safe and effective vaccine for the oral immunization of canines [98-100].

The vector-based VRG vaccine is another candidate for the oral application to immunize wild carnivores. The pathogenicity of a vaccinia recombinant virus expressing the rabies glycoprotein was tested with the red fox, wild boar, Eurasian badger, different species of mice and voles, common buzzard, kestrel, carrion crow, magpie and jay. During the observation period, the 107 animals given the vaccine orally did not show any clinical signs

[101]. Experiments have demonstrated the efficacy of a vaccinia-rabies recombinant virus administered by the oral route in foxes. Because of its safety and heat-stability, this recombinant virus could be an excellent alternative to the attenuated strains of rabies virus currently used in the field [100].

The high thermo stability of the commercially produced Raboral VRG bait allows its use during the summer for emergency vaccination campaigns [102] and is being used for the vaccination of wild raccoons in the USA [103].

There are two ways of distributing vaccine baits in nature: manually and by air (Helicopters, airplanes). Presently, aerial distribution is widely used and special computer models have been developed to plan the distribution of vaccine baits taking into account many factors including landscape and terrain details [104].

Status of Rabies in Ethiopia: In Ethiopia, rabies is an important disease that has been recognized for many centuries. The first major outbreak of rabies in Ethiopia in dogs in many parts of Ethiopia (Tigrie, Begemder, Gojjam and Wollo) was recorded in 1884. The first case of an epidemic of rabies was reported in August 1903 and had a high prevalence in Addis Ababa. According to Ethiopian public health Institute rabies in Ethiopia is primarily a disease of domestic animals, particularly dogs; however, the involvement of other domestic animals like

cats, cattle, sheep, goats and equines were reported. Moreover, the occurrence of rabies in wild animals was evidenced by laboratory confirmed rabies cases by direct fluorescent antibody test (FAT) in hyenas, jackals, foxes, mongoose, monkeys, rabbits, leopards, Cervical cat and cheetah at Pasteur Institute of Ethiopia [105].

The number of dog to human ratio is approximately assumed 1:6 and 1:8 in urban and rural parts of Ethiopia, respectively. The total population of dogs in Addis Ababa is estimated between 150, 000 and 200, 000, of which 50% are stray dogs [105]. Although it is presumed that rabies is very much widespread throughout Ethiopia, the actual figure of the incidence of the disease is not well known throughout the country. In 1998 Ethiopia reported the highest number of human rabies deaths [106] in Africa and in 2012 it was assumed that approximately 10, 000 persons/annum die of rabies which makes one of the highest rabies deaths in Africa [107].

According to Ethiopia p ublic health institute, annual number of brain tissue samples examined between 1990 and 2010 ranges from 89 to 1, 298 of which rabies positive samples ranged from 50.8% to 85.3%. Based on the above data, the highest number of rabies cases was reported in cold season (June to September) though animal rabies occurred throughout the year. This is most probably due to mass gathering and highest reproduction of dogs during the period which increases the contact between rabid and health dogs [105].

An increasing number of stray dogs in Ethiopia and the absence of legislation to determine and certify the status of vaccinated and non-vaccinated dogs create difficulty to control the disease. Moreover, lack of utilization of modern anti-rabies vaccines, low level of public awareness, lack of nationwide animal rabies surveillance and poor attention and resource allocation by government are major important problems that hinder the control of rabies in Ethiopia [108].

CONCLUSION AND RECOMMENDATIONS

Rabies is a fatal viral zoonosis that can affect all mammals, including humans, cats, dogs and wildlife and farm animals. The virus is present in the saliva of affected animals and the most frequent method of transmission to humans is by bites, scratches or licks to broken skin or mucous membranes. There is no certain cure for rabies except supportive care. Essential components of rabies prevention and control include on-going public education, responsible pet ownership, routine veterinary care and vaccination for dogs and professional continuing education. The majority of animal and human exposures to rabies can be prevented by raising awareness.

Based on the above conclusion the following recommendations are forwarded:

- The cost of Pre exposure prophylaxis should be decreased or free, especially in rural areas.
- Raising awareness of the community on the mode of transmission, prevention and control of rabies is of paramount importance.
- Stray dog management should be adopted and strict control of free-ranging dogs and mandatory rabies vaccination should be enforced.

REFERENCES

1. Jackson, A.C. and W.H. Wunner, 2007. Rabies. Scientific Basis of the D isease and its Management, Second edition, San Diego, Academic Press, pp: 680.
2. Schnell, M.J., J.P. McGettigan, C. Wirblich and A. Papaneri, 2010. The cell biology of rabies virus: using stealth to reach the brain. Nature Reviews Microbiology, 8: 51-61.
3. Liu W., Y. Liu, J. Liu, J. Zhai and Y. Xie, 2011. Evidence for inter- and intraclade recombinations in rabies virus. Infection, Genetics and Evolution, 11: 1906- 912
4. Zhao, X.L., J. Yin, W.Q. Chen, M. Jiang, G. Yang and Z.H. Yang, 2008. Generation and
5. Characterization of human monoclonal antibodies to G5, a linear neutralization epitope on glycoprotein of rabies virus, by phage display technology. Microbiology Immunology, 52: 89-93.
6. Blanton, J.D., C.A. Hanlon and C.E. Rupprecht, 2007. Rabies surveillance in the United States during 2006. Journal of the American Veterinary Medical Association, 231(4): 540-556.
7. World Health Organization, 2013. WHO expert consultation on rabies: second report (Vol. 982). World Health Organization.
8. Nilsson, M., 2014. Effect of rabies education programs on rabies awareness, attitudes towards dogs and animal welfare among children in Lilongwe, Malawi.
9. Depani, S., M. Mallewa, N. Kennedy and E. Molyneux, 2012. World Rabies Day: evidence of rise in paediatric rabies cases in Malawi. The Lancet, 380(9848): 1148.

10. Warner, C.K., S.G. Whitfield, M. Fekadu and H. Ho, 1997. Procedures for reproducible detection of rabies virus antigen mRNA and genome in situ in formalin-fixed tissues. .Journal of Virological Methods, 67(1): 5-12.
11. Abdela, N., B. Midekso, J. Jabir and W. Abdela, 2017. Knowledge, attitudes and practices towards rabies in Dedo district of Jimma zone, southwestern Ethiopia: A community based cross-sectional study. International Journal of Medicine and Medical Sciences, 9(5): 61-71.
12. Deressa, A., A. Ali, M. Bayene, B.N. Selassie, E. Yimer and K. Hussen, 2010. The status of rabies in Ethiopia: A retrospective record review. Ethiopian Journal of Health Development, 24(2).
13. Teklu, G.G., T.G. Hailu and G.R. Eshetu, 2017. High incidence of human rabies exposure in northwestern tigray, Ethiopia: A four-year retrospective study. PLoS Neglected Tropical Diseases, 11(1): e0005271.
14. Tschopp, R., S. Bekele and A. Aseffa, 2016. Dog demography, animal bite management and rabies knowledge-attitude and practices in the Awash Basin, Eastern Ethiopia. PLoS neglected tropical diseases, 10(2): e0004471.
15. Yimer, E., B. Newayeselassie, G. Teferra, Y. Mekonnen, Y. Bogale, B. Zewde, M. Beyene and A. Bekele, 2002. Situation of rabies in Ethiopia: a retrospective study 1990-2000. Ethiopian Journal of Health Development, 16(1): 105-112.
16. Yin, C.P., H. Zhou, H. Wu, X.Y. Tao, S. Rayner, S.M. Wang, Q. Tang and G.D. Liang, 2012. Analysis on factors related to rabies epidemic in China from 2007-2011. Virologica Sinica, 27(2): 132-143.
17. Banyard, A.C., D.L. Horton, C. Freuling, T. Müller and A.R. Fooks, 2013. Control and prevention of canine rabies: the need for building laboratory-based surveillance capacity. Antiviral Rese., 98(3): 357-364.
18. Yousaf, M.Z., M. Qasim, S. Zia, U.A. Ashfaq and S. Khan, 2012. Rabies molecular virology, diagnosis, prevention and treatment. Virology Journal, 9(1): 1-5.
19. Roth, J.A. and A.R. Spickler, 2010. Duration of immunity induced by companion animal vaccines. Animal Health Research Reviews, 11(2): 165-190.
20. Hankins, D.G. and J.A. Rosekrans, 2004. May. Overview, prevention and treatment of rabies. In Mayo Clinic Proceedings, 79(5): 671-676. Elsevier.
21. Hanlon, C.A., I.V. Kuzmin, J.D. Blanton, W.C. Weldon, J.S. Manangan and C.E. Rupprecht, 2005. Efficacy of rabies biologics against new lyssaviruses from Eurasia. Virus Res., 111(1): 44-54.
22. Quinn, J.H. and D.A. Whisson, 2005. The effects of anthropogenic food on the spatial behaviour of small Indian mongooses (Herpestes javanicus) in a subtropical rainforest. Journal of Zoology, 267(4): 339-350.
23. Kaku, Y., A. Noguchi, K. Hotta, A. Yamada and S. Inoue, 2011. Inhibition of rabies virus propagation in mouse neuroblastoma cells by an intrabody against the viral phosphoprotein. Antiviral Research, 91(1): 64-71.
24. Haines, D.E., 2012. Fundamental Neuroscience for Basic and Clinical Applications E-Book: with STUDENT CONSULT Online Access. Elsevier Health Sciences.
25. Houimel, M. and K. Dellagi, 2009. Peptide mimotopes of rabies virus glycoprotein with immunogenic activity. Vaccine, 27(34): 4648-4655.
26. Okumura A. and R.N. Harty, 2011. Rabies virus assembly and budding. Advance in Virus Research, 79: 23-32.
27. Ando, T., T. Yamashiro, Y. Takita-Sonoda, K. Mannen and A. Nishizono, 2005. Construction of human Fab library and isolation of monoclonal Fabs with rabies virus-neutralizing ability. Microbiology and Immunology, 49(4): 311-322.
28. Zhou, M., G. Zhang, G. Ren, C.W. Gnanadurai, Z. Li, Q. Chai, Y. Yang, C.M. Leyson, W. Wu, M. Cui and Z.F. Fu, 2013. Recombinant rabies viruses expressing GM-CSF or flagellin are effective vaccines for both intramuscular and oral immunizations. PloS one, 8(5): e63384.
29. Both, L., A.C. Banyard, C. Van Dolleweerd, D.L. Horton, J.K. Ma and A.R. Fooks, 2012. Passive immunity in the prevention of rabies. The Lancet Infectious Diseases, 12(5): 397-407.
30. Bela-Ong, D., B.D. Schyth and N. Lorenzen, 2014. Rhabdovirus-induced microribonucleic acids in rainbow trout (Oncorhynchus mykiss Walbaum).
31. Garg, S.R., 2014. Rabies in man and animals. Springer India.
32. Bhella, D., 2015. The role of cellular adhesion molecules in virus attachment and entry. Phil.Trans. R. Soc. B, 370(1661): 20140035.
33. Frederick, A., 2007. Murphy Department of Pathology. University of Texas Medical Branch Galveston, Texas, USA, Rabies 2nd Edition.
34. Sabeta, C.T., J. Bingham and L.H. Nel, 2003. Molecular epidemiology of canid rabies in Zimbabwe and South Africa. Virus Research, 91(2): 203-211.

35. Hanke, D., C.M. Freuling, S. Fischer, K. Hueffer, K. Hundertmark, S. Nadin-Davis, D. Marston, A.R. Fooks, A. Bøtner, T.C. Mettenleiter and M. Beer, 2016. Spatio-temporal analysis of the genetic diversity of arctic rabies viruses and their reservoir hosts in Greenland. PLoS Neglected Tropical Diseases, 10(7): e0004779.
36. Bingham, G.M., C.M. Budke and M.R. Slater, 2010. Knowledge and perceptions of dog-associated zoonoses. Brazos County, Texas, USA. Preventive Veterinary Medicine, 93(2): 211-221.
37. Johnson, N., A.R. Fooks, S.M. Brookes, L.M. Mcelhinney and A.M. Hutson, 2003. European bat lyssaviruses: an emerging zoonosis. Epidemiology and Infection, 131(03): 1029-1039.
38. Bernardi, F., S.A. Nadin-Davies, A.I. Wandeler, J. Amstrong, A.A.B. Gomes, F.S.R. Lima, F.R.B. Noguera and F.H. Ito, 2005. Antigenic and Genetic Characterization of rabies virus isolated from domestic wild animals of Brazil identifies the hoary fox as a rabies reservoir. Journal of General Virology, 86(11): 3153-3162.
39. WHO, 2012. Working to overcome the global impact of NTD, first WHO Report on Neglected Tropical Diseases.
40. Wandeler, A., 1994. Epidemiology and Ecology of Fox Rabies in Europe. In: Historical perspectives of rabies in Europe and the Mediterranean Basin. (Eds), A.A. King, A.R. Fooks. Germany, pp: 297-324.
41. Finnegan, C.J., S.M. Brookes and N. Johnson, 2002. Rabies in North America and Europe Journal of the Royal Society of Medicine, 95: 9-13.
42. Taylor, L.H., S.M. Latham and M.E.J. Woolhouse, 2001. Risk factors for human disease emergence. Philosophical Transactions B of the Royal Society, London, 356: 983-989.
43. Chong, W.K., 1993. Rabies in Kenya. In Proceedings of the Southern and Eastern African Rabies Group International Symposium, Pietermarizburg, South Africa, pp: 57-67.
44. Fekadu, M., F.W. Chandler and A.K. Harrison, 1982. Pathogenesis of rabies in dogs inoculated with Ethiopian rabies virus strain. Immunofluorescence, histological and ultrastructural studies of central nervous system. Archive of Virology, 71: 109-126.
45. Beran, G.W. and J.H. Steele, 1994. Rabies and infections by rabies related virus. Beran GW, ed. Handbook of Zoonoses. Section B, 2nd ed. Boca Raton, Ann Arbor: CRC Press, Inc., pp: 307-357.
46. OIE, 2008. Manual of diagnostic tests and vaccines for terrestrial animals. OIE. Rabies.
47. Bruce C. and A.W. Margaret, 2001. Biological Resource Management Division, Fort Collins, CO., pp: 15-27.
48. Andrews, L.R., 2015. A survey of animal-bite injuries in humans and the economic burden of rabies in machakos county, Kenya , MSc thesis, University of Nairobi.
49. Dietzschold, B., M. Schnell and H. Koprowski, 2005. Pathogenesis of rabies. Curr. Top. Microbiol. Immunol., 292: 45-56.
50. Suartha, I.N., M.S. Anthara, I.G.N.N. Putra, N.M.R.K. Dewi and I.G.N.K. Mahardika, 2012. Pengetahuan Masyarakat Tentang Rabies dalam Upaya Bali Bebas Rabies. Buletin Veteriner Udayana.
51. Wang, Y., Z. Xiang, S. Pasquini and H.C. Ertl, 1998. Effect of passive immunization or maternally transferred immunity on the antibody response to a genetic vaccine to rabies virus. J. Virol., 72: 1790-1796.
52. Jackson, A.C., 1991. Biological basis of rabies virus neurovirulence in mice: comparative pathogenesis study using the immunoperoxidase technique. J. Virol., 65: 537-540.
53. Poisson, N., E. Real, Y. Gaudin, M. Vaney, S. King, Y. Jacob, N. Tordo and D. Blondel, 2001. Molecular basis for the interaction between rabies virus phosphoprotein P and the dynein light chain LC8: dissociation of dyneinbinding properties and transcriptional functionality of P. J. Gen. Virol, 82: 2691-2696.
54. Belotto, A., L.F. Leanes, M.C. Schneider, H. Tamayo and E. Correa, 2005. Overview of rabies in the Americas. Virus research, 111(1): 5-12.
55. Lang, S.L., X.Y. Tao, Z.Y. Guo, Q. Tang, H. Li, C.P. Yin, Y. Li and G.D. Liang, 2012. Molecular characterization of Viral G gene I emerging and re - emerging areas of rabies in China, 2007 to 2011. Virologica Sinica, 27(3): 194-203.
56. Ugolini, G., 2011. Rabies virus as a transneuronal tracer of neuronal connections. In Advances in virus research, 79: 165-202). Academic Press.
57. Blackmore, C., 2014. Rabies Prevention and Control in Florida, Division of Disease Control and Health Protection, pp: 122.
58. Whitby, J.E., P.R. Heaton, E.M. Black, M. Wooldridge, L.M. Mcelhinney and P. Johnstone, 2000. First isolation of a rabies-related virus from a Daubenton's bat in the United Kingdom. Vet. Rec., 147: 385-388.

59. Shankar, V., R.A. Bowen, A.D. Davis, C.E. Rupprecht and T.J. O'Shea, 2004. Rabies in a colony of big brown bats (*Eptesicus fuscus*). J. Wildlife Dis., 40: 403-413.
60. Ronsholt, L., K.J. Sorensen, C.J.M. Bruschke, G.J. Wellenberg, J.T. Oirschot, J.E. Whitby and H. Bourhy, 1998. Clinically silent rabies infection in (zoo) bats. Vet. Rec., 142: 519-520.
61. Picard-Meyer, E., J. Barrat, M. Wasniewski, A. Wandeler, S. Nadin-Davis, J.P. Lowings, A.R. Fooks, L. McElhinney, V. Bruyere and F. Cliquet, 2004. Epidemiology of rabid bats in France, 1989 to. The Veterinary Record, 155: 774-777.
62. Vos, A., I. Kaipf, A. Denzinger, A.R. Fooks, N. Johnson and T. Muller, 2007. European bat lyssaviruses, an ecological enigma. Acta Chiropterologica, 9: 283-296.
63. Consales, C. A. and V. L. Bolzan, 2007. Rabies review: immunopathology, clinical aspects and treatment. Journal of Venomous Animals and Toxins including Tropical Diseases, 13(1): 5-38.
64. Abera, E., A. Assefa, S. Belete and N. Mekonen, 2015. Review on Rabies, with Emphasis on Disease Control and Eradication Measures. International Journal of Basic and Applied Virology, 4(2): 60-70.
65. Fooks, A.R., L.M. McElhinney, D. Horton, D.L. Knobel, S. Cleaveland, P.G.C. Coleman, N. Tordo and T. Müller, 2012. Molecular tools for rabies diagnosis in animals. In: Fooks AR, Müller T, eds. OIE, Compendium of the OIE Global Conference on Rabies Control, pp: 75-87.
66. Bronnert, J., H. Wilde, V. Tepsumethanon, B. Lumlertdacha and T. Hemachudha, 2007. Organ transplantations and rabies transmission. Journal of Travel Medicine, 14(3): 177-180.
67. McElhinney, M., A.R. Fooks and A.D. Radford, 2008. Diagnostic tools for the detection of rabies virus. EJCAP., 23; 18:03.
68. Bishop, G.C., D.N. Durrheim, P.E. Kloeck, J.D. Godlonton, J. Bingham, R. Speare and the Rabies Advisory Group, 2003. Rabies, Guide For The Medical, Veterinary and Allied Professions 2nd ed. ISBN: 1-86871-119-6 : Government Printer, Pretoria, pp: 26.
69. Carrara, P., P. Parola, P. Brouqui and P. Gautret, 2013. Imported human rabies cases worldwide, 1990-2012. PLoS Neglected Tropical Diseases, 7(5): E2209.
70. National Association of State Public Health Veterinarians, Compendium of Animal Rabies Prevention and Control Committee, Brown, C.M., Slavinski, S., Ettestad, P., Sidwa, T.J. and F.E. Sorhage, 2016. Compendium of animal rabies prevention and control, 2016. Journal of the American Veterinary Medical Association, 248(5): 505-517.
71. Ayscue, P., K. Van Haren, H. Sheriff, E. Waubant, P. Waldron, S. Yagi, C. Yen, A. Clayton, T. Padilla, C. Pan and J. Reichel, 2014. Acute flaccid paralysis with anterior myelitis-California, June 2012-June 2014. MMWR. Morbidity and Mortality Weekly Report, 63(40): 903.
72. Cliquet, F., M. Aubert and L. Sagne, 1998. Development of a fluorescent antibody virus neutralisation test (FAVN test) for the quantitation of rabies-neutralising antibody. Journal of Immunological Methods, 212(1): 79-87.
73. Murray, K.O., K.C. Holmes and C.A. Hanlon, 2009. Rabies in vaccinated dogs and cats in the United States, 1997-2001. JAVMA, 235: 691-95.
74. Morters, M.K., O. Restif, K. Hampson, S. Cleaveland, J.L. Wood and A.J. Conlan, 2013. Evidence-based control of canine rabies: a critical review of population density reduction. Journal of Animal Ecology, 82(1): 6-14.
75. Dyer, J.L., R. Wallace, L. Orciari, D. Hightower, P. Yager and J.D. Blanton, 2013. Rabies surveillance in the United States during 2012. Journal of the American Veterinary Medical Association, 243(6): 805-815.
76. Dreesen, D.W., W.G. Winkler and R.L. Parker, 1996. Epidemiology of antirabies treatment in Georgia, 1967-71. JAMA, 1983; 250: 1990-1996.
77. Hanlon, C.A., M. Niezgoda and C.E. Rupprecht, 2002. Post exposure prophylaxis for prevention of rabies in dogs. Am. J. Vet. Res., 63: 1096-110.
78. Gruzdev, K.N. and V.V. Nedosekov, 2001. Rabies of animals. Moscow, Akvarium, pp: 57.
79. Borisov, A.V., A.C. Toloknov, A.E. Metlin, V.V. Mikhalishin and S.S. Rybakov, 2002. Efficacy and safety testing of the viral vaccine Sinrab on the targeted species. Scientific notes of Vitebsk State Academy of Veterinary Medicine. Vitebsk, Belarus, 38: 15-18.
80. Vos, A., T. Muller, P. Schuster, H. Shluter and A. Neubert, 2000. Oral vaccination of foxes against rabies with SAD B19 in Europe, 1983-1998: A Review Vet. Bull., 70: 1-6.

81. Neubert, A., P. Shuster, T. Muller, A. Vos and E. Pommerening, 2001. Immunogenicity and efficacy of the oral rabies vaccine SAD B19 in foxes. J. Vet. Med., 48: 179-183.
82. Benjavongkulchai, M., C. Kositprapa, K. Limsuwun, P. Khawplod, P. Thipkong, P. Chomchey, C. Yountong, N. Naraporn, A.B. Ayuthya, S. Raksakate, P. Samranwetaya, T. Oka, K. Ohkuma, T. Hamasaki and H. Wilde, 1997. An immunogenicity and efficacy study of purified chick embryo cell culture rabies vaccine manufactured in Japan. Vaccine, 15: 1816-1819.
83. Lodmell, D.L., M.J. Parnell, J.R. Bailey, L.C. Ewalt and C.A. Hanlon, 2002. Rabies DNA vaccination of non-human primates: post-exposure studies using gene gun methodology that accelerates induction of neutralizing antibody and enhances neutralizing antibody titers. Vaccine, 20: 2221-2228.
84. Bahloul, C., S.B. Ahmed, B.I. B'chir, H. Kharmachi, A. Hayouni and K. Dellagi, 2003. Post-exposure therapy in mice against experimental rabies: a single injection of DNA vaccine is as effective as five injections of cell culture-derived vaccine. Vaccine, 22: 177-184.
85. Meslin, F.X., D.B. Fishbein and H.C. Matter, 1994. Rationale and prospects for rabies elimination in developing countries. In: Lyssaviruses. Rupprecht, C.E., Dietzchold, B., Koprowski, H. (Eds.) Springer, NY, USA, pp: 1-26.
86. Tims, T., D.J. Briggs, R.D. Davis, S.M. Moore, Z. Xiang, H.C. Ertl and Z.F. Fu, 2000. Adult dogs receiving a rabies booster dose with a recombinant adenovirus expressing rabies virus glycoprotein develop high titers of neutralizing antibodies. Vaccine, 18: 2804-2807.
87. Xuan, X., K. Tuchiya, I. Sato, Y. Nishikawa, Y. Onoderaz, Y. Takashima, A. Yamamoto, A. Katsumata, A. Iwata, S. Ueda, T. Mikami and H. Otsuka, 1998. Biological and immunogenic properties of rabies virus glycoprotein expressed by canine herpesvirus vector. Vaccine, 16: 969-976.
88. Hu, L., C. Ngichabe, C.V. Trimarchi, J.J. Esposito and F.W. Scott, 1997. Raccoon poxvirus live recombinant feline panleukopenia virus VP2 and rabies virus glycoprotein bivalent vaccine. Vaccine, 15: 1466-1472.
89. Faber, M., R. Pulmanausahakul, S.S. Hodawadekar, S. Spitsin, J.P. McGettigan, M.J. Schnell and B. Dietzschold, 2002. Overexpression of the rabies virus glycoprotein results in enhancement of apoptosis and antiviral immune response. J. Virol., 76: 3374-3381.
90. McGettigan, J.P., R.J. Pomerantz, C.A. Siler, P.M. McKenna, H.D. Foley, B. Dietzschold and M.J. Schnell, 2003. Second-generation rabies virus-based vaccine vectors expressing human immunodeficiency virus type 1 gag have greatly reduced pathogenicity but are highly immunogenic. J. Virol., 77: 237- 44.
91. Loza-Rubio, E., E. Rojas-Anaya, L. Gomez Nieto, M.T.J. Olivera Flores and M.A. Gomez, 2007. Development of an edible rabies vaccine in maize, using Vnukovo strain. Towards the elimination of Rabies in Eurasia. Joint OIE/WHO/EU International Conference. Paris, 27-30 May. Abstract Book, pp: 71.
92. Aubert, M., 1994. Control of rabies in foxes: what are the appropriate measures? Vet Record, 134: 55-59.
93. Matter, H.C., C.L. Schumacher, H. Kharmachi, S. Hammami, A. Tlatli, J. Jemli, L. Mrabet, F.X. Meslin, M.F. Aubert, B.E. Neuenschwander and K.E. Hicheri, 1998. Field evaluation of two bait delivery systems for the oral immunization of dogs against rabies in Tunisia. Vaccine, 16: 657-665.
94. Vos, A., A. Neubert, O. Aylan, P. Schuster, E. Pommerening, T. Muller and D. Chai Chivatsi, 1999. An update on safety studies of SAD B19 rabies virus vaccine in target and non target species. Epidemiol. Infect, 123: 165-175.
95. Wandeler, A.I., 2000. Oral immunization against rabies: afterthoughts and fore sight. Swiss Arch. Vet. Med., 142: 455-462.
96. Ballard, W.B., E.H. Follmann, D.G. Ritter, M.D. Robards and M.A. Cronin, 2001. Rabies and canine distemper in an arctic fox population in Alaska. Journal of Wildlife Diseases, 37(1): 133-137.
97. Flamand, A., H. Raux, Y. Gaudin and R.W. Ruigrok, 1993. Mechanisms of rabies virus neutralization. Virology, 194(1): 302-313.
98. Fekadu, M., S.L. Nesby, J.H. Shaddock, C.L. Schumacher, S.B. Linhart, D.W. Sanderlin, 1996. Immunogenicity, efficacy and safety of an oral rabies vaccine (SAG2) in dogs. Vaccine, 14: 465-468.
99. Takayama-Ito, M., N. Ito, K. Yamada, M. Sugiyama and N. Minamoto, 2006. Multiple amino acids in the glycoprotein of rabies virus are responsible for pathogenicity in adult mice. Virus Research, 115(2): 169-175.
100. Woldehiwet, Z., 2002. Rabies: recent developments. Research in Veterinary Science, 73(1): 17-25.

101. Brochier, B., J. Blancou, I. Thomas, B. Languet, M. Artois, M.P. Kieny, J.P. Lecocq, F. Costy, P. Desmettre, G. Chappuis and P.P. Pastoret, 1989. Use of recombinant vaccinia-rabies glycoprotein virus for oral vaccination of wildlife against rabies: innocuity to several non-target bait consuming species. Journal of Wildlife Diseases, 25(4): 540-547.
102. Vos, A., 2003. Oral vaccination against rabies and the behavioural ecology of the red fox (Vulpes vulpes). Journal of Veterinary Medicine, Series B., 50(10): 477-483.
103. Olson, C.A., K.D. Mitchell and P.A. Werner, 2000. Bait ingestion by free-ranging raccoons and non target species in an oral rabies vaccine field trial in Florida. Journal of Wildlife Disease, 36(4): 734-743.
104. Thulke, H.H., T. Selhorst, T. Muller, T. Wyszomirski, U. Muller and U. Breitenmoser, 2004. Assessing anti-rabies baiting - what happens on the ground? BMC Infect. Dis., 4: 9.
105. Ethiopian health Institute (EPHI), 2011. Rabies Case Report 1990-2010: EPHI, Addis Ababa, Ethiopia.
106. Wunner, W.H. and D.J. Briggs, 2010. Rabies in the 21st century. Plos Neglected Tropical Diseases, 4(3): e591.
107. Ethiopian Veterinary Association (EVA), 2012. Striving for enhanced animal health, welfare and production. Ethiopian Veterinary Bulletin, 3: 1-38.
108. Pritchard, J. and Z. Dagnatchew, 2010. Animal Welfare Policy and Legislative Gap Analysis. Addis Ababa, Ethiopia.