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Prevention and Control of Rabies in Animals and Humans in Ethiopia

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Summary

Rabies, a viral disease caused by lyssa virus of family Rhabdoviridae. It is a fatal zoonotic disease with worldwide occurrence and endemic in developing countries of Africa and Asia. The disease generally affects all warm-blooded animals, even though it is primarily a disease of dogs in Ethiopia and elsewhere in Africa. More than 95% of human rabies cases are due to bites by infected animals, predominantly from saliva of domestic dogs. Once clinical symptoms appear, it is almost 100% fatal, in which the disease is one of the major public-health burdens in Ethiopia. The country has the second most rabies related deaths in Africa. Although it is entirely preventable, nearly 3000 lives are lost every year in Ethiopia, with high economic burden and Daily Adjusted Life-Years (DALYs). Mass dog vaccination along with prompt administration of post-exposure prophylaxis (PEP) to bite victims, public awareness and 'One-Health' approach are successful elements for rabies prevention and control programmes. Low effort of animal rabies control by government and stake holders, lack of finance, limited rabies diagnostic capacity, neglect and lack of coordination and among others are the challenges holding back not to control a century long deadly disease in resource limited African countries like Ethiopia. Thus, this paper provides a brief overview of the varied measures for Rabies prevention and control in animals and humans in Ethiopia.

Keywords: Control, Ethiopia, One-Health, Prevention, Rabies and Vaccination

Abbreviations: AFROREB: Africa Rabies Expert Bureau; AREB: Asia Rabies Expert Bureau; CDC: Center for Disease control and Prevention; CNS: Central Nervous System; DALY: Daily Adjusted Life-Years; ELISA: Enzyme Linked Immunosorbent Assay; ERIG: Equine Rabies Immunoglobulin; FAT: Fluorescent Antibody Test; GARC: Global Alliance for Rabies Control; HRIG: Human Rabies Immunoglobulin; HDCV: Human Diploid Cell Vaccine; IU: International Unit; MEEREB: Middle East and Central Eastern Europe Rabies Expert Bureau; OIE: World Organization for Animal Health (Organization International des Epizootes); PEP: Post Exposure Prophylaxis; PrEP: Pre-Exposure Prophylaxis; PCECV: Purified Chick Embryo Cell Vaccine; PRP: Partners for Rabies Prevention; RABV: Rabies Virus; RIA: Rabies in Asia Foundation; RIG: Rabies Immunoglobulin; RMCV: Rhesus Monkey Kidney Cell Vaccine; RNA: Ribonucleic Acid; RT-PCR: Reverse Transcription Polymerase Chain Reaction; SEARG: Southern and Eastern Africa Rabies Group; UK: United Kingdom; USD: United States Dollar; UV: Ultra Violet; WHO: World Health Organization

Literature Overview

Introduction

Rabies is one of the oldest and the most serious zoonotic viral disease caused by the species of rabies virus which is a fatal zoonotic disease through world-wide occurrence [1]. Humans and livestock along with other mammals (almost all) get infected to the virus chiefly by carnivores. Rabies virus infection most frequently occurs when a rabid animal bites an animal or a person [2] and causes an acute viral disease of the CNS that affects humans and other mammals [3]. Infected species always die from the disease, once clinical symptoms appear. More than 95% of human rabies cases are because of dog bites and the rest associated with

cat, fox and other carnivores [4]. The virus sheds in the saliva of clinically ill animals and is transmitted through a bite of infected animals that someone might find [5]. Rabies is a most important public-health problem commonly in the parts of the developing world, where the dog plays a key role as a reservoir and transmitter of the disease to humans. It is well-known to cause huge number of deaths in humans and animals each year [6,7]. Globally, human mortality from endemic canine rabies was estimated to be 60,000 deaths per year and 56% of the estimated deaths occur in Asia and 44% in Africa and was responsible for 1.74 million DALYs [7-9]. About 98% of the human rabies cases occur in developing countries that have large number of dogs, along

with this, stray dogs bear the most [10,11]. In Ethiopia it is a significant disease that had been documented for many centuries as a “Mad Dog Disease”. and domestic dogs being the most vector of human exposure [5].

As dogs, cats, and wild life species are identified to transmit rabies virus to both humans and livestock. A feline thought to be the second most affected animal in Ethiopia next to dogs [12]. According to Ali [13], the first major outbreak in dogs were reported in many parts of Ethiopia in 1884 and documented in and around in Addis Ababa in August, 1903s, since then Ethiopia being one of the developing countries which is highly endemic for rabies [14]. Human rabies is an important public health concern in Ethiopia being a particular trouble in the outsized cities of the developing countries, with extensive, impoverished border and high densities of dogs. With high numbers of human deaths, economic loss and public health burden [15]. Even though human rabies is 100% deadly, global elimination of human deaths from canine mediated rabies is possible. Exposure to rabid animal can be eliminated at source through continued reservoir populations’ mass vaccination [16].

The objective of this seminar paper is therefore:

a.To review the continuous existence of rabies.

b.To show the effective and successful methods for prevention and control of rabies both in animals and humans.

Aetiology

Rabies is a member of genus *Lyssavirus* (Greek: *Lyssa*= ‘rage’ or ‘madness’) and a family of *Rhabdoviridae* (*Rhabdos*= ‘a rod’) that has typically bullet shaped RNA virus in which many animal, plant, fish and insect viruses are included [4]. Among this family; there are seven genotypes to date known. *Vesicular stomatitis* (a member of *Vesiculovirus*; affecting horses and cattle) and *RABV* are the two genera that affect animals. But other genera in this family affect only insects and plants [17]. *RABV* is unsegmented, single-stranded, negative sense, enveloped, helical symmetry with a length of about 180 nm and a cross-sectional diameter of about 75 nm RNA virus. Also, they are easily prone to desiccation, UV light (sunlight), heat, formalin, Phenol, and other organic solvents [18] (Table 1).

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 humans [19].

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. Rabies is reported in many countries throughout the world and has been documented in all continents except Australia (where only the bat *lyssa* viruses have been found), New Zealand, UK, Japan, Scandinavian and Caribbean countries, some Islands, and Antarctica; where the major vectors of rabies are absent. Fekadu reported saying that, rabies is endemic in Ethiopia and is well-known in domestic dog populations all over the country.

Cycles

Two epidemiologically important infectious cycles are recognized, urban rabies in dogs and sylvatic rabies in wildlife [20].

Urban rabies: More than 95% of human cases of rabies by far are recorded in cities are due to bites of rabid dog.

Wild (sylvatic) rabies: This is rabies contracted from bites of wild carnivores such as jackals, foxes; skunk, mangoes, and wolves [19]. According to Kidane [15], sylvatic rabies can become urban rabies caused by dogs and wild carnivores which enter urban areas. Also Reta [21] said few confirmed rabies cases were observed in wildlife and domestic animals other than carnivores. This makes the role of wildlife in the maintenance and transmission of rabies to be elusive under Ethiopian circumstances. This is due to the fact that most of the samples submitted to the diagnostic laboratory were from the capital city and its surroundings where the wildlife population is low. People also traditionally link rabies with dogs and rarely submit brain samples from other animal species including wildlife. In Ethiopia, rabies outbreak occurred in 2008 and 2009 in rare Ethiopian wolves (*Canis simensis*). However, outbreak was not common in a household livestock [22].

Species affected

Species susceptibility to rabies virus is important epidemiologically. All mammals are susceptible to infection by the *RABV*. Domestic animals and humans are considered to be moderately susceptible to the virus, whereas foxes, wolves, coyotes and jackals are considered to be highly susceptible [23]. Deressa and Yimer reported *asfeline* species to be the second most affected animal in Ethiopia after dogs.

Table 1: The seven genotypes of Lyssavirus.

Genotypes	Viruses	Reservoirs	Geographical Distribution
Genotype 1	Rabies virus (RABV) classical rabies	All warm-blooded animals	Worldwide
Genotype 2	Lagos bat virus (LBV)	Frugivorous bats	Africa
Genotype 3	Mokola virus (MOKV)	Unknown	Africa
Genotype 4	Duvenhage virus (DUVV)	Insectivores bats	Africa
Genotype 5	European bat Lyssaviruses (EBLV 1)	Insectivores bats	Europe
Genotype 6	European bat Lyssaviruses (EBLV 2)	Insectivores bats	Europe
Genotype 7	Australian bat Lyssavirus (ABLV)	Frugivorous bats and Insectivores bats	Australia

Transmission

Domestic carnivores were the prime animals accountable for maintenance and transmission of rabies in the area even if several animal species were involved. A study conducted in Addis Ababa by [24] indicated that most of dog biting cases on humans were occurred in Autumn season (September, October and November) than any other seasons, in which many of these bites were from stray dogs than that of owned. Also, found highest transmission of RABV on their study on the month of September but declining figures on November. This increased occurrence probably coincides with breeding season of dogs which is from June to September. The decline in November could be as a result of mass destruction of unconfined dogs in response to increased movement during mating and increased rabies cases.

Direct contact with an infected animal (bites): Fekadu and Quinn remarked that domestic and wild animals can potentially transmit the disease to humans mainly during biting. However infected animals may expel virus in their

saliva for a while before the onset of clinical signs. Although virus may be transmitted through scratching and licking, transmission usually occurs through bites. The source of infection is always an infected animal, and the method of spread is almost always by the bite of an infected animal, even though contamination of skin wounds by fresh saliva may consequence in infection. The virus may be present in the saliva for periods up to 5 days before signs are evident. Not all bites from rabid animals result in infection because the virus is not always present in the saliva; the virus may not gain entrance to the wound if the saliva is cleaned from the teeth by clothing.

Air-borne: Transmission of RABV by aerosol has been reported in a few humans working in bat caves, but alternative natural occurrence of rabies in animals in caves inhabited by infected insectivorous bats, inhalation as a route of infection came under suspicion. It is now accepted that inter-bat spread, and spread from bats to other species is predominantly by bites, but that infection by inhalation also occurs (Figure 1).

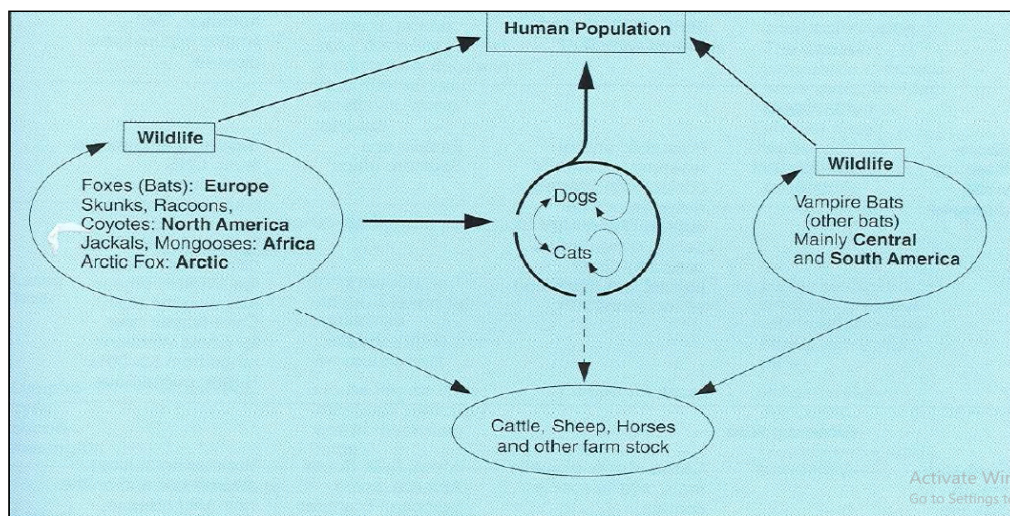


Figure 1: Transmission of rabies from wildlife reservoirs to humans and to domestic animals.

Pathogenesis

Rabies virus enters the body through wounds or by direct contact with mucosal surfaces, but cannot cross intact skin. The highly neurotropic RABV replicates in the bitten muscle tissue (local viral proliferation in non-neural tissue) and enters peripheral nervous system (viral attachment) where it remains localized for periods ranging from days to months. Bites in areas rich in nerve fibers, such as the hands and face, are especially dangerous, and the resulting incubation period tends to be short. At this stage the immune response is ineffective because the viruses are introduced into the wound in numbers too low to provoke it; also, they do not travel through the bloodstream or lymphatic system, where the immune system could best respond. Then after the virus is transported along afferent axons (centripetal spread) to reach the central nervous system [25]. The rate of centripetal progress of the virus along the axons of the peripheral nerve has been estimated experimentally in mice as 3 mm per day. Thereby the virus spreads to the spinal cord and ascends to the brain where it causes encephalitis. In people infected by aerosols, e.g. in bat-infested caves or in laboratory accidents, the virus probably reaches the CNS via nerves supplying the conjunctiva or the upper respiratory tract, including the olfactory nerves [25].

Once the virus replicates in the spinal cord and throughout the CNS, it may disseminate rapidly (centrifugal spread) along the neuronal axons of the peripheral nerves to other tissues, including the salivary glands and hair-bearing tissues. The dissemination of virus in peripheral tissues outside the CNS depends on the inoculum dose and the length of the incubation period. Large inoculums produce a short incubation period and a rapid course of illness leads to death before spread of virus throughout the brain; dogs die suddenly after a short incubation period and without showing any signs of illness. The presence of virus in saliva, especially in carnivores, is an important factor in rabies transmission. Inoculation dogs with various doses of canine street rabies virus will excrete virus in their saliva up to 14 days before signs appear.

The severity of infection and, in some measure, the location of changes depends for the most part on the inoculum dose. A small dose of virus can produce longer incubation periods and results in more pathologic changes. The degree of inflammation of the brain and, less commonly, the spinal cord is directly proportional to the length of the incubation and morbidity periods. Neuronal degeneration in the CNS ranges from minimal to severe, with satellitosis and neurophagia as evidence of early neuronal necrosis. Negri bodies can be found in the brain stem, pons, cerebral

cortex, and cervical part of the spinal cord. In general, the number of Negri bodies present is directly proportional to the severity of inflammation.

Clinical Signs

The clinical features of rabies are similar in most species, but there is great variation between individuals. After the bite of a rabid animal, such as a bat or dog, the incubation period is usually between 14 and 90 days, but it may be considerably longer. In which the incubation period depends on: dose of virus inoculum, route, location, severity of exposure, distance (from the lesion to the spinal cord or brain) and vaccination status. Dogs, cats, and wild carnivores (foxes, raccoons, and coyotes) are primarily affected. In humans, rabies is usually acquired from the bite of an infected animal, but simple licking of abraded skin may also transmit the virus; the infection has also been acquired from aerosols in bats' caves. The incubation period in humans varies from 10 days to a year or more, but on average it ranges from 1–3 months, the time depending on the above incubation period factors mentioned. The onset is usually insidious, with a 1–10-day. Cattle carrier animals transmit infective saliva to them by biting. In cattle the average incubation period is thought to be 3 weeks. The virus sheds in the saliva of clinically ill animals and is transmitted through a bite. Once clinical symptoms appear, RABV is almost 100% fatal. More than 95% of human rabies cases are due to dog bites and the rest associated with cat, fox and other carnivores.

There are three stages of clinical manifestation, these are;

(i) Prodromal period (1 to 2 days) - Clinical signs manifested are: malaise, fever, headache, and hyper salivation. Canines show nervousness, apprehension, anxiety, isolation, fever, behavioral changes (became aggressive and vice versa), friendly animals become shy (hiding), severe licking of bite site (itching), the larynx begins to spasm and a voice change may be noted initially.

(ii) Furious rabies (2 to 4 days) - The patient passes into the stage of excitement, with anxiety, violent behavior (aggression), continuous and increased salivation are mostly manifested signs. The classical sign, present in most cases, is hydrophobia; this is particularly distressing, as the patient needs to drink, but any attempt to do so, or even the sight of water, elicits violent spasms of the respiratory and other muscles, accompanied by a feeling of extreme terror. So, the patient dies in coma with generalized paralysis and cardiovascular collapse.

As Quinn wrote, behavioural change and excessive salivation to be the two main signs in cattle. He also added that hypersensitivity to sounds and bellowing (vocalization) is usual at this stage. Ferociously attack other animals or inanimate objects; these attacks are often badly directed and are impeded by the incoordination of gait, muscular tremor, restlessness then paralysis, difficulty of swallowing and stop ruminating and death. Major clinical findings in Sheep included are, muzzle and head tremors, aggressiveness, hyper-excitability, and hyperesthesia.

Outbreaks are common, sexual excitement, salivation, vocalization and recumbency, wool pulling, attacking, incoordination, and then paralysis. The furious form occurred in 80% of sheep. Goats are commonly aggressive, and continuous bleating is common. While in canine, excitability, ate objects (suffer hallucinations), dangerously aggressive with not fear to animals or humans, abundant salivation. But cats will show strange behaviour, erratic, nonstop running, attack objects and death can occur due to respiratory failure.

(iii) Paralytic ('dumb') rabies (next to 4 days) - The course is less dramatic. An illness lasting as long as a month is characterized by ascending paralysis; hydrophobia is not a prominent feature. Painful pharyngeal and muscle spasms (convulsions), progress to paralytic phase, respiratory arrest, and death, the disease in unvaccinated and untreated humans has always been considered fatal. As with furious rabies, death is inevitable.

Cattle show muscular incoordination, decreased reased sensation of hindquarters, tonic clonic contractions of head and neck musculature, drooling saliva, tenesmus, with paralysis of the anus, resulting in the sucking in and blowing out of air usually occurs late in the incoordination stages just before the animal becomes recumbent. Death usually occurs 48 hours after recumbency develops and after a total course of 4–7 days. While clinical findings in horse included are, pharyngeal paresis, ataxia or paresis, lethargy or somnolence, abnormal postures, biting, loss of anal sphincter tone and death in 4–6 days.

Diagnosis

Laboratory diagnosis of rabies in humans and animals is essential for timely post-exposure prophylaxis. In developing countries, rabies diagnoses are mostly made based on clinical signs, history of exposure and epidemiological information due to lack of facilities [26]. This is also true in Ethiopia. This may be due to lack of rabies diagnostic laboratories in all regions except Addis Ababa. Other studies also indicate that data on community's health seeking practice for

rabies in Ethiopia was limited, and a significant number of cases were managed inappropriately for the sick within 24 hours. Because of this, lack of personnel facilities for rabies surveillance and diagnosis in most developing countries means that only very limited data of questionable reliability are available.

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. Rabies virus was more frequently detected in brain samples from carnivores (94.5%) than other animal species.

Direct Fluorescent Antibody Test (dFAT)

DFAT is the 'gold-standard' and most widely used test for rabies diagnosis, recommended by both WHO and OIE. Rabies is usually diagnosed in the laboratory by detection of the viral antigen using the dFAT, which is nearly 100% sensitive and highly specific. This test can be done on samples of saliva or biopsies of certain external tissues; post-mortem samples are usually taken from the brain [26].

Cell culture and Mouse inoculation test

These tests are based on the principles of detecting the infectivity of a rabies virus tissue suspension in cell cultures or in laboratory animals (mouse) after inoculation. These tests should be used if FAT gives an uncertain result or when FAT is negative in the case of known human exposure. Both tests require longer turnaround times compared to FAT (4-days for cell culture test and 28-days for mouse inoculation test).

Direct Rapid Immunohistochemical Test (dRIT)

A direct rapid immunohistochemical test employs anti-rabies monoclonal antibodies specific for the nucleoprotein (a viral protein produced in abundance during productive infection), and can detect rabies antigen by direct staining of fresh brain impressions within 1 hour. For less-developed parts of the world, the CDC has recently developed a RIT. It requires only the use of an ordinary light microscope and has a sensitivity and specificity equivalent to the standard dFAT.

Molecular techniques and Serological tests

Various molecular diagnostic tests, e.g. detection of viral RNA by RT-PCR, PCR-ELISA, real-time PCR, hemi-nested PCR, and nested PCR are used as rapid and sensitive tests for rabies diagnosis. Serological tests are used to measure the level of virus neutralizing antibody in vaccinated individuals and to detect host response to rabies infection by measuring

antibodies in cerebrospinal fluid/serum in suspected rabid cases. However, these tests require a specialized laboratory and facilities to handle tissue culture and the virulent rabies virus, and also are too complex for large scale screening of field sera.

Differential Diagnosis

Rabies must be considered in the differential diagnosis of any suspected mammalian meningitis/ encephalitis cases. Of this, the followings are mostly misdiagnosed with rabies.

1. Equine encephalitis virus- Misdiagnosed with RABV due to the stage of paralysis, unable to swallow, weakness, recumbency and death within 2–4 days after onset. But Equine encephalitis virus causes impaired eyesight, circling and Recovery rate (60–75%); which are mostly absent in case of RABV.
2. Canine distemper virus in dogs- Misdiagnosed with RABV due to neurological signs. But this disease can cause uveitis, sudden blindness, respiratory signs such as
3. coughing and nasal discharge; puppies are mostly affected showing signs of pneumonia, diarrhoea, dehydration and vomiting.
4. Botulism in cattle- Misdiagnosed with RABV due to signs of weakness, stumbling and recumbency. But in Botulism, normal mentation, paralysis of tongue and thoracic muscles and some recovery are mostly evident.
5. Aujeszky's disease (pseudorabies)- Misdiagnosed due to signs of intense and local pruritus at site of bite, excitement, bellowing, convulsions, paralysis, and death within 2–3 days after onset. But pseudorabies mostly affects pigs and cattle and responds to magnesium sulphate early.
6. Lead poisoning (in acute and subacute) in cattle- Misdiagnosed because the clinical findings are similar to those of furious and dumb rabies. In acute lead poisoning, the common clinical findings are blindness, convulsions, death within 2 and 4 days after onset, pharyngeal paralysis, dysphagia, weakness and recumbency.
7. Vitamin A deficiency in cattle- occurs in groups of young cattle from 6 months to 18 months of age not receiving adequate carotene intake or vitamin A supplementation and is characterized by blindness in the ocular form and episodes of tremors and convulsions.

Treatment

No treatment should be attempted after clinical signs are evident; hence rabies is fatal once clinical signs are seen. Only high-risk individuals,

such as laboratory workers, animal control professionals, and veterinarians, are routinely vaccinated against rabies before known exposure. If a person is bitten, immediately the wound should be thoroughly washed with 20% soft soap, water (for about 15 minutes) and 40% to 50% alcohol solution of all bite wounds and scratches is perhaps the most effective measure for preventing rabies in people bitten by rabid animals. The proper cleaning of the wound would remove most of the virus but these simple and cheap treatment procedures are often omitted in most cases [27]. If the animal is positive for rabies, the person must undergo PEP -meaning a series of anti-rabies vaccine and immune globulin injections is recommended. "Another indication for anti-rabies treatment is any unprovoked bite by a skunk, bat, fox, coyote, bob-cat, or raccoon not available for examination. Treatment after a dog or cat bite, if the animal cannot be found, is determined by the prevalence of rabies in the area. The bite of a bat may not be perceptible and may be impossible to rule out in cases where the bat had access to sleeping person or small children. Therefore, the CDC recommends PEP after any significant encounter with a bat unless the bat can be tested and shown to be negative for rabies". Euthanasia of suspect animals must be avoided, particularly if human exposure has occurred, because the development of the disease in the animals is necessary to establish a diagnosis.

Socioeconomic and Public Health Burden of Rabies

Rabies kills an estimated 59,000-60,000 people each year in the world. Each year around 55,000 people die of rabies in Asia and Africa alone [28]. Of these countries, Ethiopia is one of the worst affected, with domestic dogs being the major sources of the infection to humans. Dog management is, however, poor and anti-rabies dog vaccination is generally limited to a small number of dogs found in urban settings. The large dog population size in combination with poor dog management contributes to a high endemicity of canine rabies in Ethiopia. According to Taame [29], out of the total exposure to RABV, 98.9% (15,008) of exposure cases and 97.1% (264) of fatal cases were from Addis Ababa, Oromia, Amhara, SNNPR, and Tigray regions. Also, the national data on rabies indicates an exposure of 2.6/100,000 people. The highest incidence is registered from Tigray (11.4/100,000), followed by Oromia (3.5/100,000), Benshangul (3.3/100,000), Amhara (1.5/100,000), SNNPR (1.2/100,000) and Addis Ababa (0.8/100,000).

Due to the endemicity of rabies in Ethiopia, with an estimated 2,871 human lives are lost and 96,657 people are exposed to rabies each year [30]. Based on these estimates, Ethiopia has the second highest annual number of human rabies

deaths on the African continent. These estimates are much higher than the actual numbers reflected in official reports; due to, poor surveillance, irregular reporting and discrepancies in official data which are critical factors contributing to the underestimated burden of rabies in Ethiopia. Annual rabies associated livestock losses in Ethiopia are estimated at >\$50 million (USD).

Rabies also represents a significant economic burden to society in rabies endemic countries. It has been estimated that globally ≥ 15 million people receive rabies prophylaxis annually, the majority of who live in China and India. In Ethiopia the annual post exposure treatment costs an amount of 2 mln USD (1.6 mln–2.5 mln). Deaths due to rabies are responsible for an estimated 1.74 and 3.7 million DALYs lost per year in Asia and Africa and globally, respectively and the corresponding health losses due to the disease in Ethiopia is estimated to be 193,748 (168,049–222,406) DALYs per year. The burden of rabies is influenced by age-related and socioeconomic factors: rabies is most commonly reported in children below 15 years of age and in poor and low-income people that have no access to treatment facilities. The cost-effectiveness studies of rabies control have demonstrated that dog rabies elimination is more economical than the intensified use of PEP in humans [31]. “The World Animal Health Organization has stated that just 10% of costs currently used to treat people bitten by potentially rabid dogs would be sufficient to eradicate dog rabies in the world and thereby prevent almost all human rabies cases”.

Prevention and Control

Prevention and control of rabies in dogs

There is no specific treatment for rabies, which is a fatal disease– that implies incurable but preventable. Almost 45–60% of dog bite injuries and human deaths occur in children under 15, who rarely understand how rabies is transmitted, and often do not know how to behave around animals, especially dogs living in the same household or community. Children who have been bitten or scratched by suspect rabid dogs may therefore not tell their parents or guardians, especially if they have been instructed not to approach animals that are not their own pets. Therefore, earlier combating of the RABV (prevention) mainly aims for children, elderly, disabilities, poor and less reached third world nations. Domestic dogs are the main reservoir of rabies in many developing countries, and account for about 99% of all human rabies cases in Asia and Africa. The principles of canine rabies control programme is described elsewhere and should consist of: public awareness education on rabies, one health approach, mass dog vaccination, dog population control and international

(global) collaboration (partnership).

As of case definition, “an animal is determined to be rabid after diagnosis by a qualified laboratory and confirmation either by a positive direct fluorescent antibody test (preferably performed on central nervous system tissue) or isolation of rabies virus in cell culture or in a laboratory animal”.

Public awareness: One of the most important points in rabies prevention is the level of awareness in both the medical profession and the general public. Novel educational methods are beginning to make progress in many countries. For example, Philippine educators have made remarkable strides by including rabies educational activities in elementary school modules. Also, this novel idea is further elaborated in Ethiopia, according to. in the last five years the University of Mekelle, college of veterinary medicine delivered awareness creation to more than 7,000 students in different schools (marking ‘World Rabies Day’ on September 28), in which the feedback from the students was encouraging. ‘World Rabies Day’ continues to provide opportunities for communities and international health organizations to get involved in improving awareness of rabies (www.worldrabiesday.org).

However, because many children are not taught in a formal classroom setting, new approaches that could reach a wider population in endemic areas would save lives. Governments must also be involved in public awareness programmes that support responsible pet ownership, routine veterinary care and vaccination, and professional continuing education. Unless otherwise: the lack of effective health education programmes results in a low degree of awareness of the disease burden and the methods necessary to prevent and control rabies [32]. Low awareness also causes poor community participation in local rabies control programmes and to save the lives of people exposed to rabid dogs [33]. Almost every human rabies death has resulted from a lack of awareness that PEP should be administered as soon possible or from failure to follow WHO recommendations for wound washing and vaccination. All effective public education programmes must consider cultural, religious, and political factors. Programmes that use imaginative information highways like schools, religious and other local organizations and meetings have had major impact in increasing awareness on the disease.

‘One Health’ approach (operational activities): Programmes aimed at bringing together professionals from human and veterinary medicine to work together, using a ‘One Health’ strategy, to begin to develop programmes to eliminate canine rabies. The most cost-effective strategy to reduce

exposure to a disease is to eliminate the source. For canine-transmitted rabies, this can only be accomplished through a 'One Health' strategy, in which officials responsible for animal and human health work together. This should be considered as a public health goal for Africa and Asia, the two continents currently bearing the brunt of the global rabies burden. No emphasis has been given to rabies in Ethiopia by the relevant veterinary, medical and public authorities in contrast to European and American countries.

Canine rabies control programmes must include experts from both the human and animal health sectors in their daily activities. In many countries, these departments are not connected, and they are often centred in separate locations, but it is essential that they work together. Although the immediate objective is to stop the circulation of rabies virus among dogs, protecting humans is the ultimate goal. Among this, surveillance activities and reports of rabies in animals and humans must therefore be shared across departmental lines. According to Pieracci [34], workshop was held in Ethiopia on 'One Health-focused Zoonotic Diseases' and to facilitate this, the workshop participants recommended the creation of a 'One Health-focused Zoonotic Disease Unit', which would include staff from

EPHI (Ethiopian Public Health Institute) and MoLFR (Ministry of Livestock and Fishery Resources) or other appropriate animal health agencies. The proposed unit would develop a national zoonotic disease strategy and coordinate efforts between the human and animal health sectors to jointly address the selected zoonotic diseases and respond to outbreaks in people and animals.

Dog Vaccination

Vaccination of dogs is the proven way of preventing human exposures and eliminating the disease at source. Research has shown that canine rabies can be eliminated by establishing a 70% level of vaccination coverage. Ecology studies, including evaluation of the location of the dog population in the region, must be conducted before beginning a mass vaccination campaign. Increased access to the utilization of PEP is therefore essential to protect exposed people, in conjunction with dog vaccination. Highest mortality rates occur in areas with limited dog vaccination, where PEP is the only lifeline for at-risk populations, yet PEP supply and distribution systems are wholly inadequate in many of these places and often very costly. Because almost all human cases result from the bite from an infected dog, the best way to reduce the global burden of canine-mediated human rabies is to eliminate canine rabies. This approach is much more cost-effective than attempting to expand the availability of PEP or to integrate rabies vaccination into

national immunization programmes.

Vaccinating dogs have multiple advantages rather than culling them. For instance,

1) It is a barrier: Dogs are the main host for human and canine rabies. Vaccinating at least 70% of dogs in an area creates 'herd immunity'. The vaccinated dogs form a barrier, slowing the spread of rabies until it dies out. By eradicating this main source of infection, rabies cases in dogs and other animal populations can be eliminated and human rabies deaths vastly reduces.

2) Its humane: Millions of dogs are saved from needless inhumane culling that is driven by a fear of rabies; millions of cases of rabies in dogs are also prevented; vaccination promotes a more responsible and less fearful attitude towards dogs within communities [35].

3) It is cost-effective: Vaccinating dogs is not only more effective than culling dogs for controlling rabies, but it is also very cost-effective [36]. However,

dog vaccinations are implemented mostly in urban areas, which are easiest to access; dog to human ratios are typically higher in rural areas; and PEP access is best in capital cities. Hence most rabies case is expected to be from rural areas. As more dogs are vaccinated, fewer people are bitten by rabid dogs and this can greatly reduce the demand

for costly human vaccines given for postexposure treatment. Beyene [37], demonstrated that canine mass rabies vaccination in Ethiopia will be a cost-effective means of combating rabies by reducing the human health burden and by saving costs compared to the status quo of 18% canine vaccination coverage in urban districts and no vaccination in rural districts.

Vaccine coverage

The WHO recommends that vaccination coverage of minimum of 70% of the dog population is necessary to eliminate dog rabies, in which it is hardly ever achieved in many developing countries where canine rabies is endemic, resulting in continuous transmission and maintenance of endemicity of the virus. It is recommended that mass dog vaccination should be carried out intensively within the shortest possible time (within a 2-to-3-week period) each year depending on the immune responses of the vaccinated population.

Vaccination centre

It is recommended that the vaccination points should be located in strategic locations chosen on the basis of dog population concentration within the community. Central-

point vaccination was found to be cost-effective in carrying out mass vaccination campaigns in some of the African nations and resulted in good vaccination coverage.

Age of dog at first vaccination

Although it is recommended not to vaccinate puppies (<3 months age) born of immunized bitches, so that vaccine induced active immunity is not affected by the presence of maternally-derived antibodies, field studies have demonstrated that puppies (<3 months age) have responded well to rabies vaccination and produced protective antibodies without any significant interference by maternally-derived antibodies. Therefore, a dog at any age vaccination is useful to combat RABV in a timely manner.

Identification marks:

It is recommended that vaccinated dogs be given identification marks by the use of coloured tags, coloured plastic collars, or paint on the body to allow for verification of vaccination status. This is more applicable in the stray dog population. Permanent marking such as ear notching has to be done under general anaesthesia and can best be performed along with an animal birth control programme.

Oral vaccination of dogs

One of the major obstacles for establishing satisfactory vaccination coverage in the dog population through parenteral vaccination is the accessibility of dogs. After a successful elimination of fox rabies in Western Europe through the use of oral bait vaccine, the WHO has encouraged several studies on the development of safer and more effective vaccines for oral vaccination of dogs (OVD) (WHO, 2010). The OVD promises a substantial increase in vaccination coverage both when applied exclusively and when used in combination with parenteral vaccination, as demonstrated in field trials in Tunisia, Turkey and Sri Lanka. However, OVD safety for non-target species, especially humans and the cost of the bait vaccine has remained the main barrier for adoption and has still not become an operational component of large dog rabies control and elimination programmes.

Dog population control

Research focusing on humane methods to reduce the fecundity of dogs in countries where an overpopulation of free-roaming animals hampers disease control would be a major step forward. There are many methods of dog population control, among those, surgical removal of reproductive organs as a means of 'Animal Birth Control (ABC)' (neutering and spaying) or (castration, hysterectomy, ovariectomy) is an effective permanent method for dog birth control, but it is costly

(although it may be more cost efficient in the long term). Nevertheless, 'ABC' programmes have been launched in a number of countries with encouraging results, one of these were in Ethiopia, in which 'ABC' approaches were employed to reduce or depopulate ownerless dogs in Mekelle city [38]. Also, hormonal contraception using progestins, androgens, or gonadotropin releasing hormone (GnRH) analogs act to either directly block reproductive hormone receptor-mediated events, or indirectly block conception via negative feedback mechanisms. In contrast to this, in Ethiopia, different anaesthetic agents, formalin, magnesium sulphate and other chemicals were used to humanely remove the ownerless dogs from the Mekelle city [38].

Mass killing is not effective, alienates the general population and often creates conflict with international organizations. It often causes dog owners to hide their dogs or move them to other areas, potentially promoting the spread of rabies. It is also inhumane to use 'strychnine' to kill dogs. Not only does poisoning, it causes unnecessary pain and suffering, it can also pose a threat to humans and other animals where the poison is distributed. Instead of mass killing, rabies control programmes should support the enforcement of international recommendations for the reduction of dog populations. Reputable animal welfare organizations are often willing to provide training and assistance for dog handling, spaying and neutering. They can be valuable partners for national governments engaged in sustainable canine rabies control programme. Due to this, government must not promote the mass killing of dogs. However, killing rabid dogs might reduce the number of rabid dogs as well as the number of human exposure.

Global partnerships in rabies prevention and control

The building of public private partnerships is proving to be one of the most effective global strategies to address the needs of disadvantaged populations living in the midst of neglected diseases such as SEARG, RIA, AREB, AFROREB, and MEEREB, all demonstrate the utility of coalitions in successful information flow and regional health promotion in bringing support to local scientific and public health communities worldwide. In the 21st century, the formation of the GARC and the PRP groups perhaps best epitomizes this shift from a regional to a global approach and the modern concept of a global health fellowship.

Prevention and control of rabies in humans

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 and immediate post-exposure prophylaxis following exposure to rabid animals.

Pre-exposure prophylaxis (PrEP)

The WHO recommends that PrEP is administered to persons such as laboratory staff working with rabies virus, veterinarians, animal handlers and wildlife officials, who are at increased risk of exposure. PrEP is also a valuable tool for protecting populations in remote, high-risk regions, where prompt PEP is not immediately available. PrEP vaccination is given as a three-dose series of intra muscular (IM) or intra dermal (ID) injection of tissue culture rabies vaccine (potency of at least 2.5 IU per dose), and is given as one dose (1ml as IM or 0.1ml as ID) each on day 0, 7, and 21 or 28 as a for active immunization. Antibodies can be administered for prior vaccinated individuals if HDCV is used. Booster doses should be offered to people at continuing risk every 3 years with one dose of 1ml IM.

The recommended PEP includes thorough cleaning of the bite wound with soap and water or detergent, administration of rabies vaccine to stimulate an active immune response, and administration of rabies immunoglobulin to provide immediate passive immunity (WHO, 2010). However, the indication for PEP depends on the type of contact with the suspected rabid animal and should follow the WHO guidelines (Tenzin, 2012) (Table 2).

Wound management

Surgical debridement should be carried out without suturing up with promotion of bleeding and it must be washed with soap and water with antiseptics and disinfectants.

Passive immunization

The RIG should be infiltrated into and around bite wounds

Table 2: Categories, exposures and recommendations of PEP for rabies source.

Categories	Exposure to suspect rabid animal	Treatment/recommendations
Category-1	Touching or feeding animals, licks on intact skin (i.e. no exposure)	None (not required if there is clear history)
Category-2	Nibbling of uncovered skin, minor scratches or abrasions without bleeding	Immediate vaccination and local treatment of the wound
Category-3	Single or multiple ID bites or scratches, licks on broken skin; contamination of mucous membrane with saliva from licks; exposure to bats	Immediate vaccination and administration of rabies immunoglobulin; local treatment of the wound

There are a number of important reasons to utilize PrEP.

- PrEP will provide protection to people with in-apparent or unrecognized exposures to rabies virus that occur due to their vocation, hobby, or due to endemicity of rabies in the region in which they live.
- It also simplifies PEP in the event of subsequent exposure to rabies by reducing the amount of vaccine required from 5 to 2 doses and by eliminating the need to administer rabies immunoglobulin, which is expensive and often unavailable.
- PrEP will prime the immune system so that an immediate anamnestic response will occur in a previously vaccinated individual.
- It may protect people whose PEP might be delayed.

Post-exposure prophylaxis (PEP)

at a dose rate of 20 IU/kg body weight for HRIG and 40 IU/kg body weight for ERIG. The entire calculated dose should be injected directly into and around the bite wound if feasible (but avoiding possible compartment syndrome) with any remainder of the dose injected intramuscularly at the site distant from the site of vaccine administration. RIG is recommended to all people with category III exposure (confirmed rabid exposure) and to those with category II exposure who are immunodeficient.

Active immunization

The different types of vaccines used to prevent RABV includes- the Fermi type RABV vaccine (nervous tissue rabies vaccine), HDC, PCECV, RMCV. The complete course of the vaccine requires 5 doses given 1ml in deltoid area intramuscularly on days 0, 3, 7, 14 and 28. If the person is vaccinated before, no HRIG is used and only two doses of vaccine is given on days 0 and 3. HDCV contains a high titre

of RABV, evokes a high immunologic response and causes less severe side effects than Fermi type rabies vaccine which has many side effects such as nervous problems, serous allergic reactions and it is not effective on severe and proximal bites to the CNS.

Major challenges and gaps in rabies prevention and control in Ethiopia

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

(II) Low effort in human rabies prevention (absence of modern tissue culture vaccine, low public awareness, limited PET service and in adequate skill on the use of PET, Weak human rabies surveillance).

(III) Limited rabies diagnostic capacity (rabies diagnoses technology, absence of trained manpower, only one laboratory facility, lack of inter-sectoral effort).

(IV) 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) [39,40].

Conclusions and Recommendations

In general, Rabies is a deadly zoonotic disease with world-wide occurrence and is transmitted mostly by carnivores to humans and livestock. Also it is one of the most disastrous and major public-health diseases for both animal and human being in most parts of the developing world, where the domestic dog plays a principal role as a reservoir and transmitter of the disease to humans. Rabies kills an estimated 59,000-60,000 people each year in the world of these countries, Ethiopia is one of the worst affected with an estimated 2,871 human lives are lost and 96,657 people are exposed to rabies each year. If a person is bitten, immediately the wound should be thoroughly washed with 20% soft soap, water (for about 15 minutes) and 40% to 50% alcohol solution of all bite wounds and scratches. The global elimination of human deaths from canine-mediated rabies is achievable by integrating effective strategies of mass dog vaccination with improved accessibility to human preventive measures (dog bite management and PEP), programmes aimed at bringing together professionals from human and veterinary medicine to work together, using a 'One Health' strategy, public awareness and dog

population control as mass killing of dogs is not advocated. Human rabies prevention should not rely only on PEP. While PEP is effective at preventing human rabies deaths, the approach is costly and can only protect individuals who have prompt access to health facilities with appropriate PEP provision. Recent successful outcomes from rabies programmes implemented in the Philippines, South Africa, the United Republic of Tanzania and Bangladesh provide proof of principle that rabies can indeed be controlled and eliminated with currently available tools.

Based on the above conclusive remarks, the following recommendations are given:

- Through 'One Health' strategy, in which officials responsible for animal and human health should work together
- Public awareness using educational curriculums and marking of world rabies day should be addressed for children and as a whole for the general public community.
- Since rabies outbreaks are frequently occurring and the disease is life threatening, mass vaccination of dog population should be carried out in the country.
- Well-designed strategy for stray dog population control should be developed and implemented.
- The government must not carry out and advocate the mass killing of dogs.
- Post exposure treatment should be given to humans immediately after exposure to bite or scratch by rabid animals.

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