

Epidemiology and Public Health Significance of Rabies

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SUMMARY

Rabies is one of the oldest recognized diseases affecting all warm-blooded animals and remains to be the most important zoonotic disease mainly affecting the developing countries. It is an acute, progressive and almost fatal encephalomyelitis caused by the Rabies virus and other *Lyssavirus* species of the family *Rhabdoviridae*. The disease has worldwide distribution except in some countries where there is strict quarantine system, rigorous eradication program or natural barriers like mountains and rivers. Rabies occurs in more than 150 countries and territories. Of these, most deaths from rabies occur in developing countries with inadequate public health resources and limited access to preventive treatment. This category constitutes mainly the developing countries found in the Asian and African continents. This situation occurs because dog rabies is endemic with dog-to-dog transmission of the infection, which is associated with an ongoing threat to humans due to dog bite. Rabies transmission is usually from virus laden saliva of an infected animal which comes in the contact by the bite from animal to animal or animal to man. Being rabies virus is highly neurotropic; it has high affinity for the central nervous system. The lesions produced in the central nervous system and destruction of the spinal neurons results in the clinical signs manifested by the rabid patients. All rabies infected species usually exhibit typical signs of central nervous system disturbance, with minor variations among species. The direct fluorescent antibody test is the gold standard for rabies diagnosis. An important tool to optimize public and animal health and enhance domestic animal rabies control is routine or emergency implementation of low-cost or free clinics for rabies vaccination. Being rabies is a preventable disease, some possible prevention and control components include, making responsible pet ownership, routine veterinary care and vaccination, and professionals should provide public education about the disease. To facilitate the implementation of these prevention and control components, jurisdictions should work with veterinary medical licensing boards, veterinary associations, the local veterinary community, animal control officials and animal welfare organizations.

Keywords: Dog bite; Distribution; *Lyssavirus*; Rabies; Vaccination; Zoonotic

INTRODUCTION

Rabies is an ancient and most frequent zoonotic disease caused by the Rabies virus (RABV) and other *Lyssavirus* species of the family *Rhabdovirida*¹. It results in progressive and fatal encephalomyelitis. Rabies is a life threatening zoonotic disease with world-wide occurrence and is transmitted mostly by carnivores to humans and livestock. It is known to cause significant morbidity and mortality among humans and animals each year. Rabies is responsible for estimated annual human mortalities of about 31,000 and 24,000 in Asia and Africa, respectively, with people mostly at risk of dying due to rabies being those who live in rural areas of these continents².

Although there is no accurate data on the global burden of rabies, the estimates of direct mortality due to rabies, transmitted most commonly through the bite of a rabid animal, are among the highest. The annual number of human rabies deaths globally, in 2010, is estimated to be 61,000, with the vast majority of deaths occurring in rural areas¹. The annual economic losses due to rabies were estimated to cross 8.6 billion USD. This could be attributed mostly to premature deaths of infected animals, the cost of human post-exposure prophylaxis, lost income for victims of animal bites, death of livestock, and other related costs³.

The main reason for rabies to remain as a neglected zoonotic disease in many developing countries including Asia and Africa is lack of specific diagnostic and surveillance techniques⁴.

Rabies is one of the 17 major neglected tropical diseases. Its control is more difficult because it is a neglected zoonotic disease, and is endemic in most of the world⁵. Rabies is an Office International Des Epizooties (OIE) list B disease and currently remains an ongoing threat to human populations and animals in many parts of the world. It was also rated the 11th cause of human death due to infectious diseases in 2000⁶.

As a result of growing dog and human populations, the burden of human deaths from rabies and the economic costs will continue to escalate in the absence of concerted efforts and investment for control. As countries strive to reduce the number of human deaths and improve the availability of post-exposure prophylaxis, the costs will rise; however, if dog rabies control and ultimately elimination are achieved by mass dog vaccination, both the demand for post-exposure prophylaxis and the costs decline. National vaccination programmes have widespread health benefits, particularly for the poorest communities in the world but it needs consistent and sustained commitment¹.

Despite being a preventable disease, rabies is continuing to cause immense human and animal death, claiming tens of thousands of human life and countless animal lives every year as well as significant economic loss mainly in developing countries including our country. This situation is related to the challenges in controlling rabies due to wide host range and worldwide distribution, availability of many free roaming dogs, limited access to control and lack of public and legislative awareness about the disease. With regard to the disease a limited investigations and researches are done which have no uniformity in their coverage and there is inadequate inter-sectoral collaboration on taking necessary measures to prevent and control rabies.

This review emphasizes on the epidemiology of rabies, its implications on public health, potential measures to create awareness and possible approaches to control and prevention.

LITERATURE REVIEW

Etiology

Rabies (Latin, "madness") is a highly lethal zoonotic disease caused by a neurotropic rabies virus (RABV) of the *Lyssavirus* genus, in the family of *Rhabdoviridae*, order *Mononegavirales*⁷. Rabies and the rabies-related *Lyssaviruses* have been classified into 2 phylogroups, based on how closely they are related. Phylogroup I contains the rabies virus (genotype 1), Duvenhage virus (genotype 4), European Bat *Lyssavirus*1 (genotype 5), European Bat *Lyssavirus* 2 (genotype 6) and Australian bat virus (genotype 7), while phylogroup II consists of Lagos bat virus (genotype 2) and Mokola virus (genotype 3). Four additional Eurasian bat viruses have also been tentatively classified as *Lyssaviruses*. They include Irkut virus, Aravan virus and Khujand virus, which all belong to phylogroup I, and West Caucasian bat virus. These rabies-related *Lyssaviruses* or non-rabies *Lyssaviruses*, can cause a neurological disease that is identical to rabies⁸.

Lyssaviruses have a 12-kb non-segmented RiboNucleic Acid (RNA) genome of negative polarity that encodes five viral proteins (3' to 5'): a nucleoprotein (N), a phosphoprotein (P),

a matrix protein (M), a glycoprotein (G) and an RNA-dependent RNA polymerase (or large protein, L). The *Lyssavirus* particle is a bullet shaped 100–300 nm long and 75 nm in diameter⁹. The rabies virus transmembrane glycoprotein is involved in tropism and pathogenicity. It is the main protecting antigen, inducing a complete immune response with the production of virus neutralizing antibodies¹⁰. Rabies virus is very sensitive to some environmental factors and is rapidly destroyed by direct sunlight, ultraviolet irradiation, heat at 60°C for five minutes, lipid solvent (70% alcohol and ether), sodium deoxycholate, trypsin and common detergents¹¹.

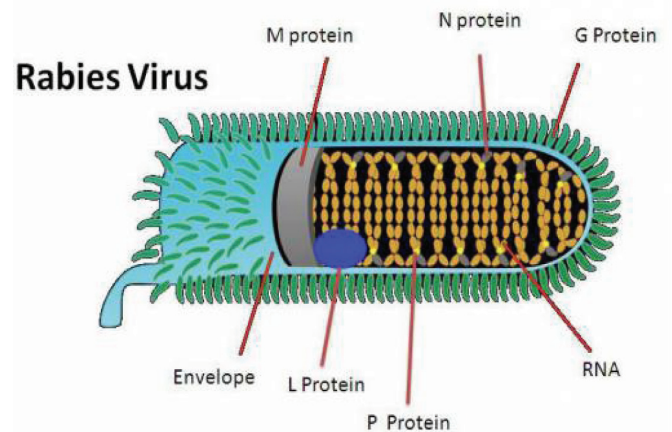


Figure1: Rabies virus; shape and its structures.

Source:

https://dokuwiki.noctrl.edu/lib/exe/fetch.php?cache=&media=bio:440:virology_wiki_10.jp

Epidemiology

Geographic distribution

Even with advances in laboratory methods and improved vaccination, Rabies still remains a fatal infection in humans and animals¹². It is found all over the world, except in some countries where there is strict quarantine system, rigorous eradication program or natural barriers like mountains and rivers¹³. Rabies remains an important public health problem in resource-limited countries, particularly in Asia and Africa. This situation occurs because dog rabies is endemic with dog-to-dog transmission of the infection, which is associated with an ongoing threat to humans due to dog bites¹⁴. The three principal global areas of rabies include countries with enzootic canine rabies (all of Asia, Latin America, and Africa); countries in which canine rabies has been brought under control and wildlife rabies predominates (Western Europe, Canada, and the United States); and rabies-free countries (mostly islands, including England, Australia, and Japan)¹⁵.

Depending on the species of animals that plays role as a major vector, three rabies cycles have been distinguished¹⁶. The first is the urban rabies cycle, in which dogs are the main reservoir host. This cycle predominates in areas of Africa, Asia, and Central and South America where the proportion of unvaccinated and semi-owned or stray dogs is high. It has been virtually eliminated in North America and Europe; although sporadic cases occur in dogs infected by wild animals, where the urban cycle is not perpetuated in the canine population⁸. The second is the sylvatic (wildlife) cycle of rabies in which wild carnivores such as jackals, foxes; skunks, mongooses, wolves etc. do play an important role as vector. This rabies cycle usually reverts to urban cycle due to frequent contact between rabid wild carnivores and stray dogs. The most common victims are dogs, cattle and man¹⁷.

The sylvatic cycle is the predominant cycle in Europe and North America. It is also present simultaneously with the urban cycle in some parts of the world. The epidemiology of this cycle is complex; factors affecting it include the virus strain, the behavior of the host species, ecology and environmental factors⁸. The third cycle is vampire rabies (paralysa). This type

cycles are Canidae (dogs, foxes, jackals, wolves etc.), Mustelidae (skunks, martens, weasels, ferrets, stoats etc.), Viverridae (mongooses, meerkat etc.), Procyonidae (raccoons), Chiroptera (>1,200 species of bats) (MoA, 2011). Although all mammals are susceptible to rabies, only a few species are important as reservoirs for the disease. Dogs remain the most important reservoirs for rabies in the developing countries of Asia and Africa and they are the primary source of infection to humans and other domestic animals^{21, 22 and 23}.

Modes of transmission of rabies

Rabies virus is usually transmitted by the bite of a rabid animal^{12, 25}. Transmission is mostly from exposure to virus laden saliva of an infected animal, either due to the bite, from animal to animal or animal to man²³. Inhalation of aerosolized rabies virus could be a potential non-bite route of exposure. This type of spread can occur among laboratory workers and spelunkers. Other contacts, such as petting a rabid animal or contact with the blood, urine, or feces of a rabid animal, does not constitute an exposure and is not an indication for prophylaxis²⁶. The contamination of open wounds or abrasions (including scratches) or mucous membranes with saliva or other potentially infectious material (e.g., neural tissue) from a rabid animal constitutes a non-bite exposure²⁷. Deposition of virus

Table1: Geographic distribution, host range and respective genotype of Rabies virus

Region	Reservoir Species	Genotype
Europe	fox , bats	European bat lyssavirus 1& 2
Asia	Dogs	Classical/Dog rabies virus
Africa	dog, mongoose, antelope	Lagos bat virus, Mokola virus
North America	foxes, skunks, raccoons, insectivorous bats	Duvenhage virus Classical rabies virus
South America	dog, vampire bats	Classical rabies virus
Australia	Insectivorous bats	Australian Bat Lyssavirus
Middle East	Wolf, dog	Classical/Dog rabies virus

Source: Adedeji *et al.*, 2010²⁴

of rabies is particularly important in Latin America and is transmitted by bite of bats. These bats usually transmit the bovine paralytic rabies and maintain the cycle in endemic areas while cattle and man are victims¹⁸. Spread of the disease is often seasonal, with high incidence in late summer and autumn because of large scale movement of wild animals at the mating time and in pursuit of food¹⁹.

Host range

Rabies virus has a wide host range, wherein all warm-blooded animals including humans can be infected by the virus^{12, 20}. The most important animal families in maintaining rabies

laden saliva into the conjunctiva, oral mucus membranes or genitalia is also incriminated as a mode of transmission²⁸.

Pathogenesis

Rabies virus is highly neurotropic and causes fatal encephalitis, when the virus gains access to the central nervous system (CNS)^{29, 30}. Transmission of *Lyssavirus* infections is mostly through the contamination of bite wounds with the saliva of an infected animal³¹. Subsequently, the virus infects local sensory and motor neurons and replicate locally in skeletal muscle cells or attach directly to nerve endings, in

particular to nicotinic acetylcholine receptors at motor-end plates^{32,33}. After peripheral nerve entry, the virus migrates in centripetal retrograde axonal transport to the CNS at the estimated speed of 5–100 mm/day¹.

When the virus reaches the central nervous system, there is massive replication on membranes within neurons. The virus then moves centrifugally from the central nervous system via slow retrograde axoplasmic flow in motor axons to the ventral roots and nerves. Then the virus moves in the peripheral sensory axons of the infected dorsal root ganglia, leading to infection of muscle spindles, skin, hair follicles and other tissues, such as salivary glands, heart muscle, lung and abdominal visceral organs via their sensory innervations³⁴.

The primary lesions are produced in the CNS and spread from the site of infection occurs only by way of the peripheral nerves. Gradually ascending paralysis of the hindquarters may be followed by severe signs of mania, which persist almost until death. Destruction of spinal neurons results in paralysis, but when the virus invades the brain, irritation of higher centers produces mania, excitement and convulsions. The clinical signs of salivation, indigestion and pica, paralysis of bladder and anus and increased libido all suggest involvement of the autonomic nervous system, including endocrine glands. Death is usually due to respiratory paralysis¹⁹.

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 system³⁵. The overall outcome of an exposure to RABV depends in part upon the rabies genotype (different strains and mutants) or variant involved, its pathogenicity (apoptogenicity, neuroinvasiveness), the dose of virus inoculated (severity of exposure), the route as well as the host species and its susceptibility to the particular pathogen together with innate and adaptive immune responses of the host³⁶.

Clinical Findings

The clinical signs of rabies are rarely definitive³⁷. In humans, initial symptoms typically appear within 30 to 60 days following exposure and can include pain and itching at the site of the virus' entrance into the body, restlessness, headache, fever, nausea, sore throat, and loss of appetite. Increased production of saliva, muscle stiffness, increased sensitivity to light or loud sounds, irrational excitement, or convulsions occurs as the infection progresses. Other symptoms may develop later, such as anxiety, confusion, agitation, delirium, and the display of abnormal behavior. Symptoms of rabies in animals can include an evident change in behavior, loss of appetite, fever, change in phonation (e.g., the sound of a dog's

bark), greater excitement, aggression, paralysis (especially in the lower jaw), and increased salivation^{12,38}.

All rabies infected species usually exhibit typical signs of CNS disturbance, with minor variations among species. The clinical course may be divided into three phases namely prodromal, excitative (furious) and paralytic or end stage³⁷. The prodromal or melancholy stage may or may not develop or it passes quickly enough that it may not even be noticed by the owners of the dogs and inexperienced Veterinarians. Signs characteristic of this stage of the disease includes disappearance from home longer than usual, hallucinations (fly-biting), changes in voice, springing at moving objects, claustrophobia, chewing at the site of infection (hyperesthesia of the bite site), fever which at this time may be moderate and usually disappears as symptoms progress. This stage lasts a few hours to 36 hours. The animals then go into either furious or dumb rabies stages or may just drop dead³⁹.

The furious stage is characterized by an increase in aggressiveness and hyperexcitability and there is a tendency to bite at inanimate objects and at other animals. Affected animal may roam over long distances. The furious form is observed more often in cats than in dogs. Foxes rarely exhibit this form of the disease². The paralytic (dumb) stage 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 starts to salivate profusely. There may be facial paralysis or the lower jaw may drop. Ataxia, incoordination and ascending spinal paresis or paralysis are also typical of this form. Death usually occurs within 2 to 6 days, as the result of respiratory failure⁸.

Public health significance of rabies

General overview of rabies in humans

Rabies infection in humans is still a major public health problem all over the world^{22, 40}. About 98% of the human rabies cases occur in developing countries that possess large number of dogs, many of which are strays⁴¹. This situation occurs because dog rabies is endemic with dog-to-dog transmission of the infection, which is associated with an ongoing threat to humans due to dog bites. Unfortunately, children share a disproportionately high burden of the disease¹⁴. Estimates of human mortality due to endemic canine rabies in Asia and Africa annually exceed 30,000 and 23,000, respectively. The annual cost of rabies in Africa and Asia was estimated at 583.5 million USD most of which is due to cost of post exposure prophylaxis (PEP)².

Source of infection and modes of transmission in humans:

Source of infection

More than 99% of human rabies cases are caused by dog bites. Although other mammals such as bats, foxes and raccoons can transmit rabies to humans, the overwhelming majority of cases are caused by dogs¹. Though the dog is moderately susceptible, it acts as a reservoir for urban rabies virus in developing countries⁴². Dogs have been the major reservoir of rabies to humans in Africa and are responsible for more than 95% of human rabies cases in China and India^{43,44}. Eshetu et al. reported that all available data indicate that dogs are responsible in maintaining as well as dissemination of rabies in Ethiopia and are primary cause for fatal human rabies cases⁴⁵. Bats are increasingly implicated as important wildlife reservoirs for variants of rabies virus transmitted to humans⁴⁶.

Modes of transmission

The most likely mode of rabies transmission is by introduction of saliva containing rabies virus into a bite wound. Rabies transmission can also occur if saliva or central nervous system tissue from a rabid animal contacts a fresh wound or mucous membrane⁴⁷. Various routes of transmission have been documented and include contamination of mucous membranes (i.e., eyes, nose, and mouth), aerosol transmission, and corneal transplantations²⁶. Post-exposure prophylaxis is recommended in rare instances of non-bite exposure, such as inhalation of aerosolized virus by spelunkers exploring caves inhabited by infected bats or by laboratory technicians homogenizing tissues infected with rabies virus without appropriate precaution⁴⁸.

Regardless of the amount of viable rabies virus that may be shed in cows' milk, the theoretical risk for transmission of rabies from this route can be eliminated if all dairy products are pasteurized before consumption. However, because rabies virus is inactivated by temperatures below those used for cooking and pasteurization, eating cooked meat or drinking pasteurized milk from a rabid animal is not an indication for 'Post-Exposure Prophylaxis' (PEP)⁴⁶. Petting a rabid animal or handling its blood, urine or feces is not considered to be an exposure. Although these incidents do not warrant PEP such contact should be avoided⁴⁸.

Pathogenesis and clinical findings in humans

Pathogenesis

Rabies virus enters the body through wounds or by direct contact with mucosal surfaces, but cannot cross intact skin. Then rabies virus replicates in the bitten muscle and gains access to motor end plates and motor axons to reach the central nervous system⁴⁹. Rabies virus binds to the nicotinic acetylcholine receptor at the neuromuscular junction⁵⁰.

The virus rapidly ascends the nervous system to the brain by entering the pre-synaptic nerve ending through

endocytosis, and may be associated with synaptic vesicles. Inside peripheral nerves, the virus is carried in a retrograde direction by fast axonal transport, centripetally to the CNS. The virus remains intra-neural throughout its passage and is inaccessible to extra-neural antibodies. On reaching the CNS, there is massive viral replication on membranes within neuron and trans-synaptic transmission of virus occurs from cell to cell⁵¹.

Neurons are the neural cell type predominantly infected by rabies virus and there are few degenerative changes in neurons. Infected neurons may contain eosinophilic inclusions in the cytoplasm called Negri bodies. Negri bodies are most prominent in large neurons (e.g., Purkinje cells) and, ultra-structurally, they are composed of large aggregates of granulo-filamentous matrix material and variable numbers of viral particles⁵². The virus then moves centrifugally from the central nervous system via slow anterograde axoplasmic flow in motor axons to the ventral roots and nerves and in peripheral sensory axons of the infected dorsal root ganglia, leading to infection of muscle spindles, skin, hair follicles and other tissues, such as salivary glands, heart muscle, lung and abdominal visceral organs via their sensory innervations³⁵.

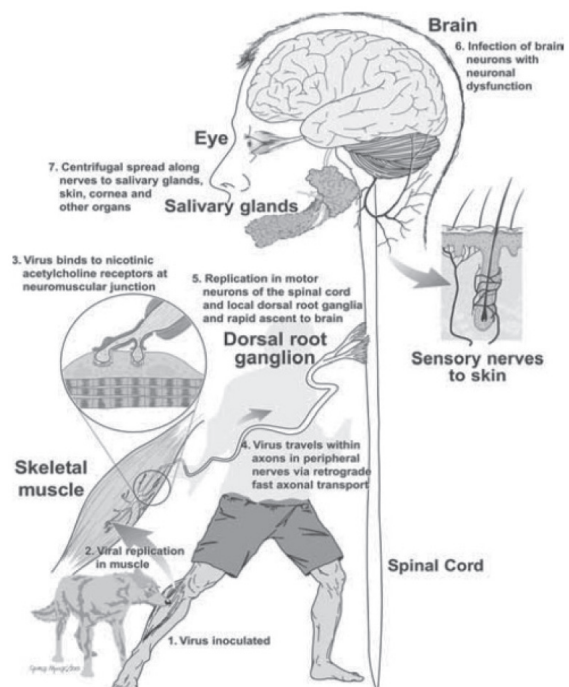


Figure 2: Schematic diagram showing the sequential steps in the pathogenesis of rabies after an animal bite/peripheral inoculation of rabies virus.

Source: (Reproduced from Jackson, 2002⁵³)

Clinical findings

Clinical rabies in humans can be divided into five stages: incubation period, prodromal stage, acute neurological phase, coma and death⁵⁴. The average incubation period of between 31 and 90 days has been reported, but it can be as short as 7 days, although it could be as long as 25 years⁵⁵. Exposures through bites on richly innervated areas of the body like the face, neck, hand and, especially, finger-tips lead more frequently to clinical infection and a shorter incubation period. Bites that occur on the trunk or proximal portions of the limbs may take longer time, unless such exposures are in direct proximity to major nerve trunks⁵⁶.

In humans, the prodromal period usually lasts for 24 to 48 hours, but rarely this may extend to one week or longer. During this time, patients present vague symptoms of a state of being unwell, often with considerable apprehension. Malaise, anorexia, low-grade fever, fatigue, headache, restlessness and tension are all possible symptoms³⁰. Classical signs of brain involvement include spasms in response to tactile, auditory, visual or olfactory stimuli (aerophobia and hydrophobia) alternating with periods of lucidity, agitation, confusion and signs of autonomic dysfunction. Spasms occur in almost all rabid patients in whom excitation is prominent⁴¹. Hydrophobia, literally the "fear of water," is a descriptive term applied to clinical rabies in man and stems from the severe, involuntary, and painful spasms provoked by attempts to drink, or sometimes the mere sight or sound of water²⁶.

Stimuli, in addition to liquids, which may triggers the spasms include foods of any type, drafts of air especially across the face (aerophobia), or touching of the inside of mouth or throat, sudden noise, and exposure to light. Even though the patients may be able to continue to swallow solid boluses of food, liquid would induce painful contractions in the throat. At this time, patients may reach extremes of agitation and terror. They may struggle frantically and attack nearby persons, although they do not bite, and generally convulsion may ensue⁵⁷. The disease then progresses to paresis or paralysis, delirium, seizures, and coma⁴⁷. Paralysis may develop progressively involving the legs, arms and trunks and may ascend resembling acute inflammatory polyneuropathy (the Guillain-Barre syndrome)⁵⁸. Without treatment, death occurs within two to six days often from paralysis of respiratory muscles⁴⁶.

Distribution of human rabies

Global distribution of rabies

Rabies occurs in more than 150 countries and territories (<http://www.who.int/mediacentre/factsheets/fs099/en>, 2016). Globally, human mortality from endemic canine rabies was estimated to be 55,000 deaths per year and 56% of the estimated deaths occur in Asia and 44% in Africa⁵⁹. Canine

rabies has been eliminated from Western Europe, Canada, the United States of America, Japan, Malaysia and few Latin American countries, while Australia is free from carnivore rabies. Bats are the source of most human deaths in United States of America, while in Australia and Western Europe it is an emerging public health threat. Asia reports the highest human rabies deaths exceeding 30,000 per annum due to endemic canine rabies. People living in rural areas are threaten more as human Post Exposure Prophylaxis (PEP) is not readily available and accessible. Average cost of rabies PEP is 40 USD in Africa and 49 USD in Asia (<http://www.who.int/mediacentre/factsheets/fs099/en>, 2016).

Most deaths from rabies occur in developing countries with inadequate public health resources and limited access to preventive treatment. These countries also have few diagnostic facilities and almost no rabies surveillance. Under reporting is a characteristic of almost every infectious disease in developing countries and increasing the estimated human mortality does not in itself increase the relative public health importance of rabies⁶⁰.

Status of rabies in Ethiopia

Rabies in Ethiopia is primarily a disease of dogs. Many people are at increased risk of being exposed to rabies since man-dog contact is very common⁴⁵. Ethiopia has been considered among the most rabies affected country in the world with an estimated annual occurrence of 10, 000 cases of human rabies which makes it to be one of the worst affected countries in the world⁶¹. Deressa et al., in their study have indicated the available data during the years 2001 to 2009 at the Ethiopian Health and Nutrition Research Institute (EHNRI) showed that 35 to 58 annual human deaths were recorded mostly in Addis Ababa, the capital city of Ethiopia⁶². Meseret and Debasu, in their three year retrospective study at Gonder Health Center indicated that a total of 261 human rabies exposure cases were reported to the Gondar Health Center from 2011 to 2013⁶³.

Dogs were noted to be the principal source of infection for humans and livestock⁶². In Ethiopia the number of dog to human ratio is approximately assumed to be 1:6 and 1:8 in urban and rural areas, respectively⁶⁴. Thus, 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 Ethiopia⁶⁵.

In Ethiopia, individuals who are exposed to rabies virus often see traditional healers for the diagnosis and treatment of the disease. These widespread traditional practices of handling rabies cases are believed to interfere with timely seeking of Post exposure prophylaxis. Rabies victims especially from rural areas seek PEP treatment after exhausting the traditional medicinal intervention and usually after a loss of life from family members⁶².

Diagnosis of rabies

Samples and sample collection

When an animal develops rabies, usually from the bite of another animal whose saliva is infected with the rabies virus, the virus moves trans-neuronally from the site of entry to the spinal cord and brain. Due to patterns of progression, a thorough histologic examination of the brain stem is critical to rabies diagnosis. The complete brain of the animal should be submitted for testing²⁶. Since, brain tissue is the preferred specimen for post-mortem diagnosis in both humans and animals⁶⁶. In addition to brain tissue other specimens, such as skin and hair follicles taken at the nape of the neck, are also highly sensitive for post-mortem diagnosis⁶⁷. The virus might also be found in other tissues such as the salivary gland, skin (tactile facial hair follicles) and corneal impression smears⁸.

Brain samples should be submitted in 50 % glycerol-saline in a leak-proof bottle. All specimens submitted to the laboratory should be marked as 'Suspected of rabies'. Accurate documentation on the correct submission form and a complete case history are extremely important for guiding laboratory interpretation, follow-up actions and control measures. People responsible for collecting specimens must be vaccinated against rabies and Protective clothing, which should include gloves, an overall, a plastic apron, gumboots and a visor, must be worn⁶⁸.

Laboratory diagnosis methods

Histopathology

Hippocampus was the tissue of choice for histologic tests for Negri bodies²⁶. Negri bodies are cytoplasmic inclusions made of rabies virus ribonucleoprotein which can be stained (Giemsa, Mann staining techniques) and observed under the light microscope⁴⁶. Infected neuronal cells reveal aggregates of viral particles "Negri bodies" when demonstrated by histological tests on smears taken from various areas of the brain. Negri bodies vary in size from as small as 30 μm to as large as 30 μm and are generally circular or oval and deeply eosinophilic with characteristic basophilic granules, often arranged in the form of a rosette, within the eosinophilic matrix⁶⁹.

Isolation and identification of rabies virus

Rabies virus isolation can be performed using neuroblastoma cells or the intracranial inoculation of mice. Virus isolation is preferably performed on saliva samples or other biological fluids such as tears and cerebrospinal fluid. The success rate depends upon the antibody status (more positive results are obtained in antibody-negative patients) and on the intermittence of viral shedding⁴¹. Identification of variant strains is performed in specialized laboratories with monoclonal antibodies, specific nucleic acid probes, or reverse transcriptase-polymerase chain reaction followed by DNA sequencing⁸.

Detection of rabies virus antigen

The characteristic size and shape of the rabies virus that accumulates in the large neurons of foliar regions of the cerebellum are easily detected and recognized by direct fluorescent antibody testing²⁶. The direct fluorescent antibody test is the gold standard for rabies diagnosis⁷⁰. This technique can identify 98-100% of cases caused by all genotypes of the rabies and rabies-related viruses, and is most effective on fresh samples⁸. A fluorescein dye conjugated to a rabies antibody is applied on a smear of the brain tissue. The fluorescence concentrates on rabies viral particles. The test is rapid and reliable in the hands of an experienced technician. During life, fluorescent antibody technique may detect viral particles in a skin biopsy (back of the neck at the hairline), corneal impression or buccal mucosal scraping can be possible⁴⁶.

Detection of rabies virus antibody

The demonstration of antibody in the serum in the absence of a history of vaccination for rabies or in cerebrospinal fluid offers indirect evidence of rabies infection⁷¹. Neutralizing antibodies in the serum or cerebrospinal fluid of non-vaccinated patients can be measured using virus neutralization tests such as the rapid fluorescent focus inhibition test or the fluorescent virus neutralization test⁷². Antibody titers against rabies glycoprotein measured by ELISA correlate well with those measured by virus neutralization and ELISA are easier to perform routinely⁷³. Rapid detection of antibodies (immunoglobulin G and M) to other viral antigens, (e.g. nucleoprotein) may also be useful, as they may appear before neutralizing antibodies⁷⁴.

The detailed information on recent developments in the diagnosis of humans and animals is available in a recent review published by Pal and others²².

Prevention and control of rabies

Prevention and control of rabies in animals

An important tool to optimize public and animal health and enhance domestic animal rabies control is routine or emergency implementation of low-cost or free clinics for rabies

vaccination. To facilitate implementation of this tool, jurisdictions should work with veterinary medical licensing boards, veterinary associations, the local veterinary community, animal control officials, and animal welfare organizations⁷⁵. In addition, 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 and owned animals are required to have identification and needed to be confined or kept on leash⁷⁶.

Rabies can be prevented in domesticated animals by vaccination and by the avoidance of contact with rabid wild animals⁸. The most practical and cost-effective way to end canine rabies is mass dog vaccination, which saves the lives of both dogs and humans. During mass campaigns, all dogs should be vaccinated, regardless of age, weight or state of health. Although the aim should be to vaccinate as many dogs as feasible, herd immunity is achieved by vaccinating at least 70% of the population¹. All dogs should be vaccinated against rabies commencing at three months of age, revaccinated with one of the three year vaccine one year later, and revaccinated every three years thereafter. And also all cats should be vaccinated at three months of age with rabies and revaccinated annually thereafter²⁵. In addition, farm livestock in endemic areas where clinical cases of rabies occur commonly should be vaccinated¹⁹.

Modern rabies vaccines are available for dogs, cats and domestic livestock species. These are broadly classified into three types: attenuated (live) virus vaccines, inactivated nervous tissue vaccines, and inactivated tissue culture vaccines. Live attenuated rabies vaccine is a weakened rabies virus to stimulate antibody production or cellular immunity against the virus upon administration. An inactivated virus vaccine used for pre- and post-exposure immunization against rabies which includes human diploid cell vaccine and purified chick embryo cell vaccine⁷⁷.

Dogs, cats, and ferrets that have never been vaccinated and are exposed to a rabid animal should be euthanized immediately. If the owner is unwilling to have this done, the animal should be placed in strict isolation for 6 months. Rabies vaccine should be administered upon entry into isolation or up to 28 days before release to comply with pre exposure vaccination recommendations⁷⁸. Regardless of rabies vaccination status, a healthy dog, cat, or ferret that exposes a

person should be confined and observed daily for 10 days from the time of the exposure⁷⁹.

Oral rabies vaccination (ORV), trap-vaccinate-release and point infection control are an evolving rabies control technologies for use in wildlife. Oral rabies vaccination involves distribution of baits containing orally immunogenic vaccines onto the landscape, thereby targeting wildlife to establish population immunity and prevent spread or eliminate specific rabies variants⁸⁰. Parenteral vaccination (trap-vaccinate-release) of wildlife rabies reservoirs may be integrated into coordinated ORV programs to enhance their effectiveness⁸¹.

Prevention and control of rabies in humans

An essential component of rabies prevention and control in human includes, making responsible pet ownership, routine veterinary care and vaccination, and professionals should provide public education. Most animal and human exposures to rabies can be prevented by raising awareness concerning rabies transmission routes, the importance of avoiding contact with wildlife, and the need for appropriate veterinary care⁷⁵.

Pre-exposure immunization should be offered to rabies researchers, certain laboratory workers and other persons in high-risk groups, such as veterinarians and their staff, and animal handlers. Pre-exposure vaccination also should be considered for persons whose activities bring them into frequent contact with rabies virus or potentially rabid bats, raccoons, skunks, cats, dogs, or other species at risk for having rabies⁸². Pre-exposure vaccination consists of two regimens: a primary vaccination regimen and a booster regimen. The primary vaccination regimen consists of three 1.0 ml injections of Human Diploid Cell Vaccine (HDCV) or Purified Chick Embryo Vaccine (PCEC) that are administered intramuscularly (IM) in the deltoid area. One injection should be given per day on days 0, 7, and 21 or 28. If a booster vaccination is recommended, a single 1.0 ml injection of HDCV or PCEC should be administered intramuscularly (IM) in the deltoid area²⁶. Rabies in humans can be prevented by avoiding exposures to rabid animals or by providing exposed persons prompt post-exposure prophylaxis consisting of local treatment of wounds in combination with appropriate administration of human rabies immunoglobulin (HRIG) and vaccine^{12,83}.

Table 2: Rabies post exposure prophylaxis (PEP) schedule.

Vaccination status	Intervention	Regimen*
Not previously vaccinated	Wound cleansing	All PEP should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent (e.g., povidine-iodine solution) should be used to irrigate the wounds.

	Human rabies immune globulin (HRIG)	Administer 20 IU/kg body weight. If anatomically feasible, the full dose should be infiltrated around and into the wound(s), and any remaining volume should be administered at an anatomical site (intramuscular [IM]) distant from vaccine administration. Also, HRIG should not be administered in the same syringe as vaccine. Because HRIG might partially suppress active production of rabies virus antibody, no more than the recommended dose should be administered.
	Vaccine	HDCV or PCECV 1.0 ml, IM (deltoid area [†]), 1 each on days 0, § 3, 7 and 14.¶
Previously vaccinated**	Wound cleansing	All PEP should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as povidine-iodine solution should be used to irrigate the wounds.
	HRIG	HRIG should not be administered.
	Vaccine	HDCV or PCECV 1.0 ml, IM (deltoid area [†]), 1 each on days 0 § and 3.
<p>* These regimens are applicable for persons in all age groups, including children.</p> <p>†The deltoid area is the only acceptable site of vaccination for adults and older children. For younger children, the outer aspect of the thigh may be used. Vaccine should never be administered in the gluteal area.</p> <p>§Day 0 is the day dose 1 of vaccine is administered.</p> <p>¶ For persons with immunosuppression, rabies PEP should be administered using all 5 doses of vaccine on days 0, 3, 7, 14, and 28.</p> <p>** Any person with a history of pre-exposure vaccination with HDCV, PCECV, or rabies vaccine adsorbed (RVA); prior PEP with HDCV, PCECV or RVA; or previous vaccination with any other type of rabies vaccine and a documented history of antibody response to the prior vaccination.</p>		

Source: ADPH, 2010

RECOMMENDATIONS

Therefore, to handle and overcome the persistence of the disease in causing economic loss, animal and public health threats extension programs and consultancy services should be widely utilized to create awareness on the distribution and health hazards of rabies to the society. The society should encourage governmental and non-governmental bodies working on rabies. Public health sectors, veterinary sectors and other stakeholders should work in collaboration to prevent and control the public health and economic impact of rabies. Mass vaccination and registration of owned pets should be conducted at regular intervals. All possible efforts have to be made by the government and other bodies to control the disease both in domestic and wild animals. There must be appropriate legislative measures to reduce the numbers of stray dogs in such a way that do not cause avoidable pain or suffering. All groups at risk of acquiring the disease should take a pre-exposure vaccination. Rabies vaccination campaigns should be available and the cost of vaccines should be affordable for the society.

CONCLUSION

Rabies is a highly fatal acute infectious meningio-

encephalitis of all warm-blooded animals. It is as old as the history of mankind having worldwide distribution. The disease is invariably fatal once clinical signs appear and is of great concern to people having frequent contact with animals especially animal owners and veterinarians. Most deaths from the rabies occur in countries with inadequate public health resources and awareness, limited access to control, vaccine, diagnostic facilities and almost no rabies surveillance. Currently, the disease is continuing to pose a series health hazard to a millions of people in developing countries. This category constitutes the poor people living in the developing countries found in Asian and African continents. As a result of growing dog and human populations, the burden of human deaths from rabies and the economic costs will continue to escalate in the absence of concerted efforts and budget allocation for control of the disease. Despite the potential of the disease to cause the loss of human and animal life as well as economic loss, there are no sufficient and tangible studies made to scale the figure in developing countries like Ethiopia. Several studies reveal that if well organized control and preventive tools are applied, the disease could significantly be reduced and even eradicated.

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