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Rabies Diagnostic, Prevention and Control Method, A Review

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Abstract: Rabies, a viral disease caused by lyssa virus of the family Rhabdoviridae, is a fatal zoonotic disease with worldwide occurrence and endemic in developing countries of Africa and Asia. Warm blooded animals are susceptible to infection with the rabies virus and are therefore possible reservoirs. Dogs are the main reservoir of rabies virus in developing countries. Even though developed countries have been able to contain recent outbreaks of zoonotic diseases, many resource-limited and transitioning countries have not been able to react adequately. The virus is present in the saliva of affected animals and the most frequent method of transmission to humans is by bites, scratches or licks to broken skin or mucous membranes. The disease has a long incubation period (six months) and symptoms may take several weeks to appear after infection. The first clinical symptom is neuropathic pain at the site of infection or wound due to viral replication. Diagnosis can only be confirmed by laboratory tests preferably conducted post-mortem on central nervous system tissue removed from the cranium. Dog-mediated rabies diagnosis in humans and animals has greatly benefited from technical advances in the laboratory setting Approaches to diagnosis now include the detection of rabies virus (RABV), of RABV RNA or RABV antigens. 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.

Key words: Diagnosis · Lyssa virus · Prevention · Rabies · Vaccine · Zoonotic

INTRODUCTION

Rabies is derived from the Latin rabere, “to rage or to rave”, rabid; rabere possibly may have earlier origin in the Sanskrit *rabhas*, for “violence” [1] The Greeks adopted their word, Lyssa meaning “madness”, for rabies;” [2] and also according to Chernet and Nejash [3], the name Rhabdo comes from the Greek and identifies the characteristic bullet or rod-shape of the virus. Rabies is an acute viral infection of the central nervous system, caused by a Lyssavirus in the family *Rhabdoviridae* [4, 5].

Rabies is a viral disease that affects the central nervous system of all warm-blooded animals, including humans [6-8] is widespread in many regions of the world and it is a zoonotic viral disease that produces almost invariably fatal encephalitis in humans and most other mammals [9]. The disease is characterized by the development of severe nervous symptoms that lead to paralysis and death [10]. Once symptoms of the disease develop, it is invariably almost 100% fatal [11] and this deadly viral disease can only be prevented but not cured [12]. Dogs remain the primary reservoir in developing countries, whereas wildlife species serve as hosts in developed nations [13].

Like all zoonotic diseases, rabies is maintained in an animal reservoir [14]. Each rabies virus (RABV) variant has a unique geographical range and ecology, requiring different control and intervention strategies. In developed countries, where canine rabies has been eliminated, the virus may continue to circulate in wildlife, whereas in most developing countries, the principal reservoir is domestic dogs (*Canis lupus familiaris*) [15].

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Canine rabies is an economically unique zoonosis, as most of its associated costs do not result from illness in the infected individual, but rather are the consequences of human deaths and efforts to prevent the disease in humans, livestock and companion animals [16, 17]. This pattern of costs reflects two basic facts: the case fatality rate of rabies in humans is nearly 100% and the disease is preventable through timely post-exposure prophylaxis (PEP) with rabies immune globulin (RIG) and multiple doses of rabies vaccine [18]. Unfortunately, in most developing countries, RIG is often unavailable [19].

Laboratory diagnosis and surveillance for animal and human rabies are severely constrained in much of the developing world where rabies is endemic [20]. The true disease burden and public health impact due to rabies remain underestimated due to the lack of simple, sensitive and cost-effective laboratory methods for rabies diagnosis [21]. This may be one of the important reasons why rabies remains a neglected zoonotic disease in many developing countries in Asia and Africa [22].

Public awareness and an increase in knowledge about rabies disease, first aid measures after dog bites, increased knowledge about dog behaviour and how to avoid getting bitten by dogs are suggested methods to prevent rabies in humans [5, 23]. Generally, the objective of this paper is to highlight a review of rabies, with current diagnostic prevention and control methods.

Rabies

Aetiology: 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 Mononega virales [7, 24]. The name Rhabdo comes from Greek and identifies the characteristic bullet or rod-shaped of the viruses containing a single-stranded RNA genome [5]. The Lyssavirus is prone to ultraviolet radiation. It is speedily inactivated by exposure to air, sunlight and in dried blood with secretions [24, 25].

Epidemiology

Geographical Distribution: Three principal global areas of rabies have been defined. These areas are: (1) countries with enzootic canine rabies (all of Asia, Latin America and Africa); (2) countries in which canine rabies has been brought under control and wildlife rabies predominates (Western Europe, Canada and the United States); and (3) rabies-free countries (mostly islands, including England, Australia and Japan) [26].

Depending on the species of animals that play a role as a major vector, three rabies cycles have been distinguished [27].

- 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 [27].
- 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 men [28, 29]. The sylvatic cycle is the predominant cycle in Europe and North America. The epidemiology of this cycle is complex; factors affecting it include the virus strain, the behavior of the host species, ecology and environmental factors [27].
- Vampire rabies (paralysa). This type of rabies is particularly important in Latin America and is transmitted by the bite of bats. These bats usually transmit the bovine paralytic rabies and maintain the cycle in endemic areas while cattle and man are victims [30]. The Spread of the disease is often seasonal, with high incidence in late summer and autumn because of the large-scale movement of wild animals at the mating time and in pursuit of food [31].

Host Range: Rabies virus has a wide host range, all mammals are susceptible to rabies, but only a limited number of species also act as reservoir hosts [32]. They include members of the family Canidae (dogs, jackals, coyotes, wolves, foxes and raccoon dogs) [3]. 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 [33]. The most common hosts are domestic dogs, cattle and man in Ethiopia [7].

Transmission Route: From CNS RABV reaches the salivary glands via cranial nerves (facial and glossopharyngeal nerves) and then it is excreted in saliva, which is ready to be transmitted to a new host [34]. The most common way of transmission for rabies (90%) is a bite of infected animals like dogs and cats, because of their intimate association with human beings [35, 36].

Deposition of virus-laden, 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 exposure [27] saliva into the conjunctiva, oral mucus membranes or genitalia is also incriminated as a mode of transmission [37].

Table 1: 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*. [38]

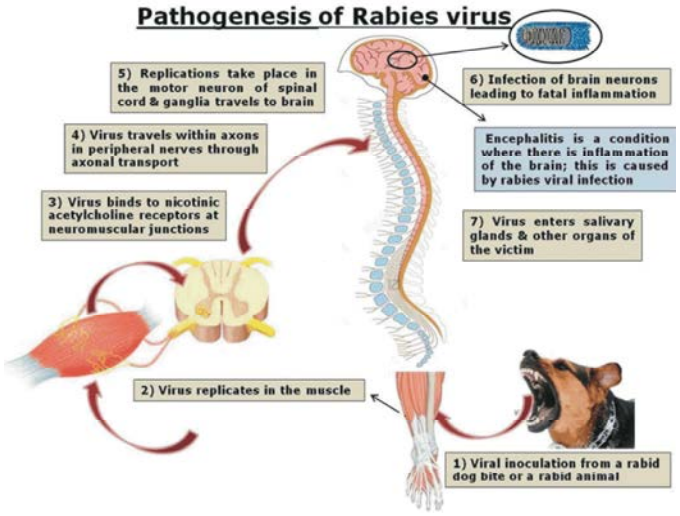

Fig. 1: Typical representation of the pathogenesis of rabies virus, where the virus infects the brain and leads to encephalitis, the virus also moves out and infects most other organs especially salivary glands, skin, mucosal surfaces and gut [40]

Pathogenesis: Rabies virus enters the body through wounds or by direct contact with mucosal surfaces. It cannot cross intact skin. Rabies virus replicates in the bitten muscle (local viral proliferation in non-neural tissue) and gains access (viral attachment) to motor endplates and motor axons to reach the central nervous system (Ugolini, 2008). Virions are carried in transport vesicles [39] and travel to the central nervous system (CNS) exclusively by fast retrograde transport along motor axons, with no uptake by sensory or sympathetic endings [37].

Clinical Sign: The incubation period has been said to depend on the size of the viral inoculums, the proximity of the wound to large nerves and the length of the neural path from the wound to the brain [41]. The incubation period in animals can vary considerably. In dogs and cats, it is between 2 to 12 weeks [4]. In humans, the incubation period for rabies is typically 1-3 months, but may vary from below 1 week to more than 1 year [42].

All rabies-infected species usually exhibit typical signs of CNS disturbance, with minor variations among species [43 The clinical course may be divided into three phases namely: The prodromal stage, the Excitative (furious) stage and the paralytic or end stage [44].

Prodromal Stage: Following a definite incubation phase, the beginning of clinical symptoms starts [3]. During this first stage which typically ends within 1-3 days, slight behavioural modification may occur, i.e. anger in domestic animals, daytime tricks in nocturnal animals, no fright of humans in the wild animals or else irregularities in the appetite [2, 9, 45].

Excitement (Furious) Phase: The furious phase is the classic mad dog syndrome characterized by an increase in aggressiveness and hyperexitability and there is a tendency to bite at inanimate objects and at other animals [37]. Affected animals may roam over long distances [7] and are characterized by restlessness, aggressiveness,

wandering (aimless movement with speed), howling, polypnea, swallow foreign objects such as sticks and stones [46]. Nocturnal animals may be visible during the day [43]. The furious form is observed more often in cats than in 3dogs. Foxes rarely exhibit this form of the disease [47, 48].

Paralytic (Dumb) Phase: The "dumb" form of rabies is characterized by progressive paralysis [46 It is first manifested by paralysis of the throat and masseter muscles often with profuse salivation and in the ability to swallow, Hydrophobia [2] and it can salivate profusely. Laryngeal paralysis can cause a change in vocalization, including an abnormal bellow in cattle or a hoarse howling in dogs, facial paralysis or the lower jaw may drop [27]. Ruminants may separate from the herd and can become somnolent or depressed, rumination may stop [7]. Ataxia, incoordination and ascending spinal paresis, dropping of foamy salivary secretion and paralysis of hind limbs eventually leading complete paralysis followed by death [41, 45].

Diagnostic Method of Rabies: Laboratory diagnosis of rabies in humans and animals is essential for timely post-exposure prophylaxis. Rabies diagnosis may be carried out either in vivo or postmortem [49]. Infection with rabies virus can be difficult to diagnose ante-mortem. Although hydrophobia is highly suggestive, no clinical signs of disease are pathognomonic for rabies. Historical reliance on the detection of accumulations of Negri bodies is no longer regarded as suitable for diagnostic assessment because of low sensitivity and alternative laboratory-based tests have been developed to conclusively confirm infection [10].

Most diagnostic tests for rabies virus in animals need brain material for diagnosis and as such are often only possible post mortem [9]. There are many diagnosis methods for the detection of rabies in animals like; direct fluorescent antibody, mouse inoculation technique, tissue culture infection technique and polymerase chain reaction [50].

Histopathology: Hippocampus was the tissue of choice for histologic tests for Negri bodies. Negri bodies are cytoplasmic inclusions made of rabies virus ribonucleoprotein which can be stained (Giemsa, Mann staining techniques) and observed under the light microscope [27]. 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 from as small as 3μm to as large as 30μm and are generally circular or oval and deeply eosinophilic with characteristic basophilic granules, often arranged in the form of a rosette, within the eosinophilic matrix [51].

Demonstration of Viral Antigen

Direct Fluorescent Antibody Testing (DFAT): DFAT is the main assay used worldwide as it is recommended by WHO and OIE as gold standard for the diagnosis of rabies in fresh or frozen brain samples [52]. It is based on attaching fluorescein isothiocyanate to polyclonal antibodies targeting the RABV ribonucleocapsid or monoclonal antibodies targeting the RABV nucleoprotein (N) [53]. If the targeted RABV antigen is present in the sample fixed on a slide, antibodies attach to it, remain attached despite lavage and can be observed using a fluorescence microscope [51] results are available within 1-2 hours and results are expressed as positive or negative. The sensitivity and specificity of DFAT nears 99% in an experienced laboratory but is extremely observer-dependent [54].

Rapid Rabies Enzyme Immunodiagnosis (RREID): The RREID test is an Enzyme Linked Immunosorbent Assay (ELISA) test performed on the supernatant of brain wer55or salivary gland suspensions. This test is based on the immune capture of the rabies nucleocapsid antigen by an antinucleocapsid polyclonal globulin coated to the ELISA plates, followed by the addition of the same globulin conjugated to horse radish peroxidase enzyme. The results are obtained within three hours [55]. These techniques, however, are less sensitive than DFAT (96% agreement between DFAT and RREID test results [51].

Rapid Immunodiagnostic Test (RIDT): The Antigen Rapid Rabies Ag Test is based on a qualitative chromatographic immunoassay, developed for the detection of RABV antigen in fresh animal brain tissue [56]. It is performant (specificity and sensibility) in brain samples from any animal and is highly dependent on the antibodies (polyclonal or monoclonal) used. This test has a sensitivity ranging from 91.7 to 96.9% and a specificity varying from 98.9 to 100% when compared to a fluorescent antibody test [41]. Furthermore, a result can be obtained within 15-20 minutes including preparation time. This test appears to be very accurate in detecting RABV antigen [57].

Direct Rapid Immunohistochemical Test (dRIT): It is based on the detection of rabies N protein in brain smears fixed in formalin, using highly concentrated monoclonal antibodies monoclonal antibodies in the presence of streptavidin peroxidase and a substrate coloring agent. Test results are available within 1 hour, can be implemented in the field and no fluorescent microscope is required. The estimated sensitivity and specificity nears 100% when compared to a fluorescent antibody test [20]. This method can also be used for samples frozen or preserved in glycerol. Cost-effective, indirect immunochemistry assays have been developed which can also provide indications on the RABV variant [58]. A major concern, however, is the access to uninterrupted supplies of controlled batches of monoclonal antibodies which are only available through few laboratories specialized in rabies diagnosis [51].

Detecting Viral RNA in Samples

Reverse Transcriptase-PCR (RT- PCR):

Principle: Transcribes viral RNA to cDNA and amplifies it using specific primers with further detection of PCR products in agarose gel [59]. Reverse-transcriptase polymerase chain reaction (RT-PCR) is the method most often used to detect RABV RNA for intravitam diagnosis of rabies in humans. Saliva samples or skin biopsies taken at the nape of the neck (being careful to include hair follicles) can be tested using this technique [60]. The test reaches 100% sensitivity when at least three successive saliva samples are collected at 3 to 6-hour intervals (due to irregular viral shedding) and tested [61]. Positive results can be obtained as soon as the patient is admitted. Human and animal brain samples collected by various methods can also be tested by this technique, even when they have been kept at relatively high ambient temperatures or when they have become degraded [62, 63]. RT-PCR is highly susceptible to cross-contamination in the operational setting, unless standardization and procedures are stringent, both for the PCR itself as well as the sample extraction and reverse transcription of the RNA [64].

Real-time PCR (RT-qPCR): These assays are based on the transcription of viral RNA to cDNA before amplification RT [59].This phase is followed by PCR which uses specific primers and probes or a dye to provide real time quantification of DNA. These assays reduce the risk of cross-contamination due to its closed tubes and show an improved sensitivity compared to conventional RT-PCR protocols [64]. As the probes used are highly specific of known sequences, however, sequence mismatch between the primer/probe sequences and the target viral sequence may adversely affect the sensitivity of the test, leading to false negative results. Because the PCR fragments generated are usually very short, the sequencing of the amplicons may provide diagnostic confirmation but cannot be used for in-depth molecular phylogenetic analyses [65].

Detecting Virus

Mouse Inoculation Test: Principle: Intra cerebral inoculation into young mice for virus amplification [66]. 3-4 weeks old (12–14 g), or a litter of 2-day-old newborn mice, are inoculated intra cerebrally with the clarified supernatant of a 10–20% (w/v) homogenate of brain material in an isotonic buffered solution containing antibiotics. The inoculated mice are observed daily for 28 days; they develop typical signs and symptoms of rabies any time after 5–7 days depending on the incubation period. Paralysis occurs within 5-10 days in newborn mice, 8-15 days in adult mice. Diagnosis is confirmed using the FAT if available, otherwise by detection of Negri bodies and by virus neutralization index test [51].

Rapid Tissue Culture Infection Test (RTCT): Virus isolation by in-vitro technique (RTCIT) is done by using highly susceptible neuroblastoma cell line and it can be used for testing saliva and cerebrospinal fluid samples from living individuals as well as for testing brain and salivary gland tissues from post mortem. Virus isolation in cell culture can be used in cases where immunofluorescence is inconclusive. After incubation of 18hr at 37°C in 5%CO2, the cells are fixed, stained with an anti-nucleocapsid antibody conjugated to FITC and observed under the fluorescent microscope [66]. RTCIT has progressively replaced MIT because it is less expensive as it avoids the use of live animals, is relatively sensitive, is easy to undertake and can substantially reduce the time required to obtain results from 30 days in MIT to 4 days [67].

Detecting Antibodies: The detection of antibodies in the serum in the absence of a history of rabies vaccination or cerebrospinal fluid (CSF) provides indirect evidence of rabies infection. However, interpretation of test results may be difficult since the host immune response may vary among individuals: the sensitivity and negative predictive

value of antibody detection methods in rabies patients is very poor [64] as suspect rabies deaths overwhelmingly occur before patients can mount an antibody response. Antibody response is only detectable in the blood or CSF after 8-10 days [52], while the majority of human rabies deaths occur around six days after the onset of clinical signs [45].

Prevention and Control: Rabies can be prevented before the latent symptoms can develop, consists of giving a person an injection of rabies immune globulin and another injection of rabies vaccine as soon as possible after the bite or exposure to saliva from an infected animal [50].

Vaccination

Animal Post-Exposure Vaccination: A number of recently developed, highly-effective, thermo stable, inactivated vaccines are available for veterinary use. All rabies vaccines registered for human and animal use must conform to established potency standards [32].

All dogs and cats should be revaccinated 12 months after initial vaccination regardless of the length of immunity period of the initial vaccine. Obtaining a booster vaccination immediately following an exposure to a rabid animal is important to ensure adequate protection against the virus. Revaccination must be carried out every three years thereafter. Following an outbreak in domestic livestock, vaccination of animals without visible bite wounds is strongly recommended [68].

Animal Post Exposure Vaccination: Findings from a study conducted by Hanlon *et al*. [69] suggested that 5 doses of canine rabies vaccine administered on days 0, 3, 14, 21 and 35 along with murine anti-rabies antibody on day 0 may be effective in protecting a previously unvaccinated animal exposed to rabies. Regardless of the age of the animal at initial vaccination, a booster vaccination should be administered 1 year later. If signs suggestive of rabies develop (e.g., paralysis, seizures, etc.), the animal should be euthanized and the head shipped for testing [69].

Human Pre-Exposure Prophylaxis: The people who are considered as high risk group need pre-exposure prophylaxis. These groups includes; veterinarian, animal handlers and laboratory workers; the people whose activities bring them in contact with rabies virus or rabid animals; international travelers likely to come in contact of the animals in the rabies threaten areas. All these groups should be treated with rabies vaccines to avoid the chances of sudden infection [70].

Pre-exposure vaccination consists of two regimens: a primary vaccination regimen and a booster regiment. The primary vaccination regiment 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. 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 [71].

Post-Exposure Prophylaxis: If a person is bitten by an animal, the wound and scratches should be washed thoroughly with soap and water to decrease the chances of infection. Post-exposure prophylaxis involved one dose of rabies immune globulin and five doses of rabies vaccine within the 28 days period. The rabies vaccine works by stimulating a person's immune system to produce antibodies that neutralize the virus [50]. Wound washing, passive immunization with rabies immune globulin and a series of rabies vaccine doses are included in PEP [20]. There is no specific treatment for rabies. Therapy of rabies has been unsuccessful except, in four reported cases in which rabies vaccination was completed prior to the onset of disease [72].

Public Health Education: Essential components of rabies prevention and control include ongoing public education, responsible pet ownership, routine veterinary care and vaccination and professional continuing education. The majority of animal and human exposures to rabies can be prevented by raising awareness concerning: rabies transmission routes and avoiding contact with wildlife. Prompt recognition and reporting of possible exposures to medical professionals and local public health authorities is critical [73].

September 28 is World Rabies Day, a global health observance that seeks to raise awareness about rabies and enhance prevention and control efforts. World Rabies Day is an excellent time to take steps that can help prevent and control rabies, such as vaccinating pets including dogs and cats and providing education on how to avoid the animals that typically transmit rabies: raccoons, bats, skunks and foxes [74].

Table 2: Decision aid for post-exposure prophylaxis according to type of exposure. Adapted from World Health Organization

Category of exposure	Type of exposure to domestic or wild* animal suspected or confirmed to be rabid, or animal unavailable for testing	Recommended post-exposure prophylaxis
I	Touching or feeding animals; licks on intact skin; contact of intact skin with secretions or excretions of rabid animal or human case	None, if reliable case history is available
II	Nibbling of uncovered skin; minor scratches or abrasions without bleeding	Administer vaccine immediately†' stop treatment if animal remains healthy throughout an observation period of 10 days‡ or is proved to be negative for rabies by reliable laboratory using appropriate diagnostic techniques
III	Single or multiple transdermal bites§ or scratches, licks on broken skin; contamination of mucous membrane with saliva (that is, licks) exposure to bats	Administer rabies vaccine immediately and rabies immunoglobulin, preferably as soon as possible after initiation of post-exposure prophylaxis. Rabies immunoglobulin can be injected up to seven days after first vaccine dose has been administered. Stop treatment if animal remains healthy throughout an observation period of 10 days (does not apply to bats) or is proved to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques

Source: WHO [45]

Dog Population Control: The main cause for an increase in the number of dog bites is its high breeding rates. Controlling the stray dogs is one of the challenging criteria. The main cause for an increase in the number of dog bites is its high breeding rates. Controlling stray dogs is one of the challenging criteria. Sterilization is one of the methods for controlling the population of dogs; it is widely implemented by three effective methods: surgical sterilization, chemical sterilization or constipation and nonsurgical sterilization [75].

Stray Animals: Having a large population of stray dogs in a community is considered to be a risk factor for the spreading of zoonotic diseases such as rabies [76]. Stray dogs, cats and ferrets should be removed from the community. Local health departments and animal control officials can enforce the removal of strays more effectively if owned animals are required to have identification and are confined or kept on. Strays should be impounded for at least 3 business days to determine if human exposure has occurred and to give owners sufficient time to reclaim animals [77].

Isolation of Animals Exposed to Rabies: Any animal bitten by, scratched by, or having direct contact with a wild mammal that is not available for rabies testing should be regarded as having been exposed to rabies. All livestock species-horses, cattle, sheep, goats, llamas/alpacas and swine are susceptible to rabies infection. Cattle and horses are the livestock species most frequently diagnosed with rabies. Unvaccinated livestock bitten by or exposed to a rabid or suspect rabid animal should be euthanized [9].

Wild Animal Rabies Control: Principles of rabies prevention should focus on excluding wild animals from areas of human and domestic animal habitation and activity and avoidance of contact with possibly rabid wild animals. Public education on the risks of rabies transmission from wild animals is paramount to effective disease prevention. Immunization of wildlife by widespread distribution of vaccine-impregnated oral baits has shown variable success toward arresting the propagation of rabies in raccoons and coyotes in other states. The use of oral rabies vaccines (ORV) for the mass vaccination of free-ranging wildlife should be considered in selected situations [9].

Outbreak Prevention and Control: The emergence of new rabies virus variants or the introduction of non-indigenous viruses poses a significant risk to humans, domestic animals and wildlife. A rapid and comprehensive response includes: Characterize the virus at the national reference laboratory, Identify and control the source of the introduction, Enhance laboratory-based surveillance in wild and domestic animals, Increase animal rabies vaccination rates, Restrict the movement of animals [71].

Rabies in Ethiopia: In Ethiopia rabies is an important disease that has been recognized for many centuries. According to the Ethiopian Health and Nutrition Research Institute (EHNRI), rabies has been endemic in Ethiopia since the early 17th century. For the first major outbreaks of rabies, one must consider multiple facets of the impact of rabies in Ethiopia in dogs in many parts of Ethiopia [78].

The first major outbreaks of dogs were reported in many parts of Ethiopia in 1884, especially in the former provinces of Tigre, Begemder, Gojjam and Wollo [79]. Like other big cities in developing countries, the rabies problem has been greatest in Addis Ababa where the disease had been well established and become endemic. The reviewed rabies situation in Ethiopia revealed that 2172 cases of animal rabies had been confirmed in and around Addis Ababa during 1990-2000, where dogs constituted 89.83 % with an incidence rate of 73.2 %. Deressa *et al*. [80] 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 Ethiopia. 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 2013 [81].

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 in controlling the disease. Moreover, lack of utilization of modern anti rabies vaccines, low level of public awareness lack of nationwide animal rabies surveillance and poor attention and resource allocation by government are major important problems that hinder the control of rabies in Ethiopia [82].

CONCLUSION AND RECOMMENDATION

Rabies is an ancient disease that remains a modern problem in much of the developing world. Rabies is a highly fatal acute infectious meningoencephalitis 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 animal's especially animal owners and veterinarians. It is important in developing countries like Ethiopia. This is because of the widespread occurrence of a large number of stray dogs. Most deaths from rabies occur in countries with inadequate public health resources and awareness, limited access to control, vaccines, diagnostic facilities and almost no rabies surveillance.

Laboratory diagnosis of rabies is imperative to guide public health measures in non-endemic settings, document protection (intravitam serology on vaccines' blood samples) or conduct research (seroprevalence studies, death despite timely PEP). Although laboratory testing is desirable, it is extremely limited in resource-poor settings and/or rural areas of endemic countries, where most cases occur worldwide. A growing body of knowledge about the rabies virus has not resulted in effective treatment, so prevention remains the key. Vaccination and control of rabies in domestic animals has reduced human rabies to almost negligible levels in developed countries. The primary measures to prevent and control rabies are controlling domestic animals and wild animals, health education and awareness creation in public (community) to not access to wild animals. Generally, based on this review, the following recommendations are forwarded the following recommendations are forwarded:

- Since rabies outbreaks frequently occur the disease is life-threatening and affects all warm-blooded mammals, so mass vaccination of dogs of the population should be carried out in the country.
- The stray dogs and cats should be removed from the community because most are carriers and reservoirs.
- Post-exposure treatment should be given immediately after exposure to bite or scratches by rabid animals.
- Raising awareness in the community on the mode of transmission, prevention and control of rabies is of paramount importance.
- All local jurisdictions should incorporate rabies control and animal and human bite prevention.

REFERENSES

1. Drew, W.L., 2004. "Chapter 41: Rabies". In: Ryan, K.J. and Ray, C.G. (Editors).
2. Shite, A., T. Guadu and B. Admassu, 2015.Challenge of Rabies. International Journal of Basic and Applied Virology, 4(2): 41-52.
3. Abera, E., A. Assefa, S. Belete and N. Mekonen, 2015. Review on rabies, with emphasis on disease control and eradication measures.
4. Chernet, B. and A. Nejash, 2016. Review of Rabies Control and Prevention Journal of Medicine, Physiology and Biophysics, 23: 45-53.
5. Nilsson, M., 2014. Effect of rabies education programs on rabies awareness, attitudes towards dogs and animal welfare among children in Lilongwe, Malawi.
6. Windsor, R., 2004. "Chapter 70: Rabies". In: Andrew, A. H. and Blowey. W., Eddy, R. G. (Editors). Bovine Medicine Diseases and Husbandry of Cattle, 2nd edn Black Well. 1164-1170.

7. Moges, N., 2015. Epidemiology, prevention and control methods of rabies in domestic animals. European Journal of Biological Science, 7(2): 85-90.
8. Otolorin, G.R., A.J. Olaniyi, M.P. Paul, A.V. Odinya, D.A. Adamu, D.M. Atinuke and D.F. Audu, 2015. A review on human deaths associated with rabies in Nigeria.
9. Balcha, C. and N. Abdela, 2017. Review of rabies preventions and control. International Journal of Public Health Science, 6(4): 343-350.
10. Aga, M.A., B. Hurisa and K. Urga, 2015. Current Situation of Rabies Prevention and Control In Developing Countries: Ethiopia Perspective. Vaccination and Diagnostic Production, Journal of Ancient Disease and Preventive Remedies, 4(1): 1-6.
11. Admasu, P. and Y. Mekonnen, 2014. Rabies and its folk drugs remedies in Ethiopia: a review. International Journal of Basic and Applied Virology, 3(2): 22-27.
12. Blackmore, C., 2014. Rabies Prevention and Control in Florida, Division of Disease Control and Heal the Protection.
13. Rupprecht, C.E., J. Barrett, D. Briggs, F. Cliquet, A.R. Fooks, B. Lumlertdacha, F.X. Meslin, T. Müler, L.H. Nel, C. Schneider and N. Tordo, 2008. Can rabies be eradicated? Developments in Biologicals, 131: 95-121.
14. Narrod, C., J. Zinsstag and M. Tiongco, 2012. A one health framework for estimating the economic costs of zoonotic diseases on society. Economic Health, 9(2): 150-162.
15. Zinsstag, J., S. Dürr, M.A. Penny, R. Mindekem, F. Roth, S.M. Gonzalez, S.Naissengar and J. Hattendorf, 2009. Transmission dynamics and economics of rabies control in dogs and humans in an African city. Proceedings of the National Academy of Sciences, 106(35): 14996-15001.
16. Shwiff, S.A., R.T. Sterner, M.T. Jay, S. Parikh, A. Bellomy, M.I. Meltzer, C.E. Rupprecht and D. Slate, 2007. Direct and indirect costs of rabies exposure: a retrospective study in southern California (1998–2002). Journal of Wildlife Diseases, 43(2): 251-257.
17. Yang, D.K., E.K. Shin, Y.I. Oh, K.W. Lee, C.S. Lee, S.Y. Kim, J.A. Lee and J.Y. Song, 2012. Comparison of four diagnostic methods for detecting rabies viruses circulating in Korea. Journal of Veterinary Science, 13(1): 43-48.
18. Khazaei, S., M. Karami, Y. Veisani, M. Solgi and S. Goodarzi, 2018. Epidemiology of animal bites and associated factors with delay in post-exposure prophylaxis; a cross-sectional study. Bulletin of Emergency & Trauma, 6(3): 239.
19. Elser, J.L., B.G. Hatch, L.H. Taylor, L.H. Nel and S.A. Shwiff, 2018. Towards canine rabies elimination: Economic comparisons of three project sites. Transboundary and Emerging Diseases, 65(1): 135-145.
20. Lembo, T., M. Niezgoda, A. Velasco-Villa, S. Cleaveland, E. Ernest and C.E. Rupprecht, 2006. Evaluation of a direct, rapid immunehistochemical test for rabies diagnosis. Emerging Infectious Diseases, 12(2): 310.
21. Lankester, F., K. Hampson, T. Lembo, G. Palmer, L.Taylor and S. Cleaveland, 2014. Implementing Pasteur's vision for rabies elimination. Science, 345(6204): 1562-1564.
22. Coleman, P.G., E.M. Fèvre and S. Cleave land, 2004. Estimating the public health impact of rabies. Emerging Infectious Diseases, 10(1): 140.
23. Depani, S.J., N. Kennedy, M. Mallewa and E.M. Molyneux, 2012. Evidence of rise in rabies cases in Southern Malawi–better preventative measures are urgently required. Malawi Medical Journal, 24(3): 61-64.
24. Albertini, A.A., R.W. Ruigrok and D. Blondel, 2011. Rabies virus transcription and replication. Advances in Virus Research, 79: 1-22.
25. Tojinbara , K., K. Sugiura, A. Yamada, I. Kakitani and N.C. Kwan, 2016. Estimating the probability distribution of the incubation period for rabies using data from the 1948–1954 rabies, 2014:26.
26. De Serres, G., F. Dallaire, M. Côte and D.M. Skowronski, 2008. Bat rabies in the United States and Canada from 1950 through 2007: human cases with and without bat contact. Clinical Infectious Diseases, 46(9): 1329-1337.
27. Barecha, C.B., F. Girzaw, R.V. Kandi and M. Pal, 2017. Epidemiology and public health significance of rabies. Perspect Clinical Research, 5: 55-67.
28. Quinn, P.J., B.K. Markey, M.E. Carter, W.J. Donnely and F.C. Leonard, 2002. Rabies. In: Veterinary Microbiology and Microbial diseases, 1st ed., Black well science Ltd, United Kingdom, pp: 390-395.

29. Kuzmin, I.V., B. Bozick, S.A. Guagliardo, R. Kunkel, J.R. Shak, S. Tong and C.E. Rupprecht, 2011. Bats, emerging infectious diseases and the rabies paradigm revisited. Emerging Health Threats Journal, 4(1): 7159.
30. Muhammad, K., 2021. Awareness of Rabies in Kafin-Hausa Local Government Area of Jigawa State. American Journal of Zoology, 4(3): 45-49. Health Threats Journal, 4(1): 7159.
31. Lackay, S.N., Y. Kuang and Z.F. Fu, 2008. Rabies in small animals. Veterinary Clinics of North America: Small Animal Practice, 38(4): 851-861.
32. Sudarshan, M.K., S.N. Madhusudana, B.J. Mahendra, N.S.N. Rao, D.A. Narayana, S.A. Rahman, F.X. Meslin, D.Lobo and K. Ravikumar, 2007. Assessing the burden of human rabies in India: results of a national multi-center epidemiological survey. International Journal of Infectious Diseases, 11(1): 29-35.
33. Pal, M., A. Hailu, R.K. Agarwal and P. Dave, 2013. Recent developments in the diagnosis of rabies in humans and animals. Journal of Veterinary Public Health, 11: 77-82.
34. Blanton, J.D., D. Palmer and C.E. Rupprecht, 2010. Rabies surveillance in the United States during 2009. Journal of the American Veterinary Medical Association, 237(6): 646-657.
35. Chhabra , M. and R.L. Ichhpujani, 2003. Animal bites: the current management guidelines. Indian J. Pediatr., 70(1): 11-16.
36. Hemachudha, T., J. Laothamatas and C.E. Rupprecht, 2002. Human rabies: a disease of complex neuropathogenetic mechanisms and diagnostic challenges. The Lancet Neurology, 1(2): 101-109.
37. Pal, M., 2007. Zoonoses. 2nd Ed. Satyam Publishers, Jaipur, India
38. Adedeji, A.O., I.O. Okonko, O.D. Eyarefe, O.B. Adedeji, E.T. Babalola, M.O. Ojezele, J.C. Nwanze and T.A. Amusan, 2010. An overview of rabies-History, epidemiology, control and possible elimination. African Journal of Microbiology Research, 4(22): 2327-2338.
39. Klingen, Y., K.K. Conzelmann and S. Finke, 2008.Double labeled rabies virus: live tracking of enveloped virus transport. J. Vir., 82: 237-245.
40. Ugolini, G., 2008. Use of rabies virus as a transneuronal tracer of neuronal connections: implications for the understanding of rabies pathogenesis. Developments in Biologicals, 131: 493-506.
41. Yang, J., Q. Li, Y. GAO and J. Wu, 2013. Temporal Dependency of Multisensory Audiovisual Integration. Biomedical Engineering and Cognitive Neuroscience for Healthcare: Interdisciplinary Applications, pp: 320-326.
42. Shankar, S.K., A. Mahadevan, S.D. Sapico, M.S.G. Ghodkirekar, R.G.W. Pinto and S.N. Madhusudana, 2012. Rabies viral encephalitis with proable 25 year incubation period! Annals of Indian Academy of Neurology, 15:3, 221.
43. Banyard, A.C., D.L. Horton, C. Freuling, T. Müller and A.R. Fooks, 2013.Control and prevention of canine rabies: the need for building laboratory-based surveillance capacity. Antivir. Res., 98(3): 357-364.
44. Slate, D., T.P. Algeo, K.M. Nelson, R.B. Chipman, D. Donovan, J.D. Blanton, M. Niezgoda and C.E. Rupprecht, 2009. Oral rabies vaccination in North America: opportunities, complexities and challenges. PLoS Neglected Tropical Diseases, 3(12): 549.
45. WHO, 2013. World Health Organization Expert consultation on rabies, 2nd Report (No. 982).
46. Madhusudana, S.N., S. Subha, U. Thankappan and Y.B. Ashwin, 2012. Evaluation of a direct rapid immunohistochemical test (dRIT) for rapid diagnosis of rabies in animals and humans. Virologica Sinica, 27(5): 299-302.
47. Knobel, D.L., S. Cleaveland, P.G. Coleman, E.M. Fèvre, M.I. Meltzer, M.E.G. Miranda, A. Shaw, J. Zinsstag and F.X. Meslin, 2005. Re-evaluating the burden of rabies in Africa and Asia. Bulletin of the World health Organization, 83: 360-368.
48. OIE, A., 2008. Manual of diagnostic tests and vaccines for terrestrial animals. Office international des epizooties, Paris, France, pp: 1092-1106.
49. Consales, C.A. and V.L. Bolzan, 2007. Rabies review: immunopathology, clinical aspects and treatment. Journal of Venomous Animals and Toxins including Tropical Diseases, 13(1): 5-38.
50. Yousaf, M.Z., M. Qasim, S. Zia, U.A. Ashfaq and S. Khan, 2012. Rabies molecular virology, diagnosis, prevention and treatment. Virology Journal, 9(1): 1-5.
51. Mani, R.S. and S.N. Madhusudana, 2013. Laboratory diagnosis of human rabies: recent advances. The Scientific World Journal.
52. Weyer, J. and L.H. Blumberg, 2017. Emerging Zoonotic and Vector-Borne Viral Diseases. In Viral Infections in Children, 1:125-150.

53. Duong, V., A. Tarantola, S. Ong, C. Mey, R. Choeung, S. Ly, H. Bourhy, P.Dussart and P. Buchy, 2016. Laboratory diagnostics in dog-mediated rabies: an overview of performance and a proposed strategy for various settings. International journal of infectious diseases, 46: 107-114.
54. Robardet, E., S. Andrieu, T.B. Rasmussen, M. Dobrostana, D.L. Horton, P. Hostnik, I. Jaceviciene, T. Juhasz, T. Müller, F. Mutinelli and A. Servat, 2013. Comparative assay of fluorescent antibody test results among twelve European National Reference Laboratories using various anti-rabies conjugates. Journal of Virological Methods, 191(1): 88-94.
55. Jayakumar, R., K. Nachimuthu and V.D. Padmanaban, 1994. A comparison between avidin-biotin peroxidase complex (ABC) and unlabeled antibody (PAP) procedures in rabies diagnosis. Indian Veterinary Journal, 71(9): 866-869.
56. Kang, B., J. Oh, C.Lee, B.K. Park, Y. Park, K. Hong, K. Lee, B. Cho and D. Song, 2007. Evaluation of a rapid immunodiagnostic test kit for rabies virus. Journal of Virological Methods, 145(1): 30-36.
57. Voehl, K.M. and G.A. Saturday, 2014. Evaluation of a rapid immunodiagnostic rabies field surveillance test on samples collected from military operations in Africa, Europe and the Middle East. US Army Medical Department Journal, 1: 27-32.
58. Dyer, J.L., M. Niezgoda, L.A. Orciari, P.A. Yager, J.A. Ellison and C.E. Rupprecht, 2013. Evaluation of an indirect rapid immunohistochemistry test for the differentiation of rabies virus variants. Journal of Virological Methods, 190(1-2): 29-33.
59. Hayman, D.T., A.C. Banyard, P.R. Wakeley, G. Harkess, D. Marston, J.L.Wood, A.A. Cunningham and A.R. Fooks, 2011. A universal real-time assay for the detection of Lyssaviruses. Journal of Virological Methods, 177(1): 87-93.
60. Rojas, A.E., E. Loza-Rubio, R.V.M. Banda and B.E. Hernández, 2006. Use of reverse transcription-polymerase chain reaction to determine the stability of rabies virus genome in brains kept at room temperature. Journal of Veterinary Diagnostic Investigation, 18(1): 98-101.
61. Dacheux, L., J.M. Reynes, P. Buchy, O. Sivuth, B.M. Diop, D. Rousset, C. Rathat, N. Jolly, J.B. Dufourcq, C. Nareth and S. Diop, 2008. A reliable diagnosis of human rabies based on analysis of skin biopsy specimens. Clinical Infectious Diseases, 47(11) : 1410-1417.
62. Araújo, D.B., H. Langoni, M.F. Almeida and J. Megid, 2008. Heminested reverse-transcriptase polymerase chain reaction (hnRT-PCR) as a tool for rabies virus detection in stored and decomposed samples. BMC Research Notes, 1(1): 1-6.
63. Beltrán, F.J., F.G. Dohmen, H. Del Pietro and D.M. Cisterna, 2014. Diagnosis and molecular typing of rabies virus in samples stored in inadequate conditions. The Journal of Infection in Developing Countries, 8(08): 1016-1021.
64. Fooks, A.R. and A.C. Jackson, 2020. Rabies: Scientific Basis of the Disease and Its Management. Academic Press.
65. Mey, C., A. Metlin, V. Duong, S. Ong, S. In, P.F. Horwood, J.M. Reynes, H. Bourhy, A. Tarantola and P. Buchy, 2016. Evidence of two distinct phylogenetic lineages of dog rabies virus circulating in Cambodia. Infection, Genetics and Evolution, 38: 55-61.
66. Singathia, R., P. Dutta, R. Yadav, S.R. Gupta, R. Gangil and A. Gattani, 2012. Current update on rabies diagnosis. International Journal for Agro Veterinary and Medical, 6(4): 229-240.
67. Dacheux, L. and H. Bourhy, 2015. Virus isolation in cell culture: the rabies tissue culture infection test. In Current Laboratory Techniques in Rabies Diagnosis, Research and Prevention, 2: 25-31.
68. Murray, K.O., K.C. Holmes and C.A. Hanlon, 2009. Rabies in vaccinated dogs and cats in the United States, 1997–2001. Journal of the American Veterinary Medical Association, 235(6): 691-695.
69. Hanlon, C.A., M. Niezgoda and C.E. Rupprecht, 2002. Postexposure prophylaxis for prevention of rabies in dogs. American Journal of Veterinary Research, 63(8): 1096-1100.
70. Manning, S.E., C.E. Rupprecht, D. Fishbein, C.A. Hanlon, B. Lumlertdacha, M.Guerra, M.I. Meltzer, P. Dhankhar, S.A. Vaidya, S.R. Jenkins and B. Sun, 2008. Human rabies prevention—United States, 2008: recommendations of the advisory committee on immunization practices. Morbidity and Mortality Report Recommendation and Report, 57(3): 1-28.
71. Rupprecht, C.E., D. Briggs, C.M. Brown, R. Franka, S.L. Katz, H.D. Kerr, S.M. Lett, R. Levis, M.I. Meltzer, W. Schaffner and P.R. Cieslak, 2010. Centers for Disease Control and Prevention (CDC) Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies: recommendations of the advisory committee on immunization practices. Morbidity and Mortality Weekly Report. Recommendation Report, 59(2): 1-9.

72. Jackson, A.C., 2002. Update on rabies. Current Opinion in Neurology, 15(3): 327-331.
73. Brightman, C., 2012. Rabies: an acute viral infection. Trends in Urology & Men's Health, 3(5): 31-33.
74. Anderson, A., S. Shwiff, K. Gebhardt, A.J. Ramírez, S. Shwiff, D. Kohler and L. Lecuona, 2014. Economic Evaluation of Vampire Bat (D esmodus rotundus) Rabies Prevention in Mexico. Transboundary and Emerging Diseases, 61(2): 140-146.
75. Purswell, B.J. and K.A. Kolster, 2006 Immunocontraception in companion animals. Theriogenology, 66: 510-3
76. OIE, 2010. Stray Dog Population Control. Chapter. 7.7.
77. Roebling, A.D., D. Johnson, J.D. Blanton, M. Levin, D. Slate, G. Fenwick and C.E. Rupprecht, 2014. Rabies prevention and management of cats in the context of trap–neuter–vaccinate–release programmes. Zoonoses and Public Health, 61(4): 290-296.
78. Tulu, A.M. and P.R. Koya, 2017. The impact of infective immigrants on the spread of dog rabies. American Journal of Applied Mathematics, 5(3): 68.
79. Ali, A., F. Mengistu, K. Hussein, G. Getahun, A. Deressa, E. Yimer and K. Tafesse, 2010. Overview of Rabies in and around Addis Ababa, In Animal Examined In Ehnri Zoonosis Laboratory Between, 2003 and 2009. Ethiopian veterinary Journal 14(2): 91-101.
80. Deressa, A., A. Abraham, B. Mekoro, N. Bethelehem, Y. Eshetu and H. Kedir, 2010. The status of rabies in Ethiopia: Retrospective record review from 2001-2009. Ethiopian Journal of Health Development, 24: 127-132
81. Meseret, Y. and D. Debasu, 2015. Incidence of human rabies exposure and associated factors at the Gondar Health Center, Ethiopia: a three-year retrospective study Infectious Disease Poverty, 4: 3.
82. Pritchard, J. and Z. Dagnatchew, 2010. Animal Welfare Policy and Legislative Gap Analysis. Addis Ababa, Ethiopia.