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Review Article

Rabies: A neglected zoonotic disease and its public health concern in Ethiopia

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Summary
Rabies is a deadly neglected zoonotic disease that affects the central nervous system of all warm-blooded animals and is widespread in many regions of the world. It is caused by rabies virus belongs to genus *Lyssavirus* ("*lyssa"* meaning "madness"), family *Rhabdoviridae*, and order *Mononegavirales*. Rabies is a devastating disease endemic in developing countries that is responsible for the death of thousands of lives every year; more than 95% of them are from Africa and Asia. Ethiopia is one of the highest human deaths due to rabies from Africa, even though the cases are under-reported. Rabies is almost fatal once clinical signs and symptoms are developed for both animals and humans. There are different modes of rabies transmission; the most common one is by being bitten by infected hosts and transferring rabies virus contained saliva through the exposure of wound or scratched skin. Domestic dogs serve as a major reservoir of the rabies virus in many developing countries and play a great role in virus transmission. Several countries that apply successful rabies elimination programs perform free post-exposure prophylaxis (PEP) for bite victims and mass dog vaccination, establish a strong national rabies surveillance system, and encourage the capacity of medical staff through sustainable training. Implementing these best experiences toward rabies elimination and dealing with great emphasis in Ethiopia is essential to avoid dog-mediated rabies deaths. In developing countries like Ethiopia, where dog-mediated rabies is endemic, execute dog vaccination policies at regional and municipal levels to break the transmission chains of rabies due to dog bites. Therefore, the government points up sustainable strong inter-sectoral collaboration and community engagement, as well as it provides safe, effective, and affordable modern anti-rabies vaccine to be used for post-exposure prophylaxis to eliminate this public health important disease.
***Keywords**:* Elimination, Ethiopia, Rabies, Vaccination, Zoonotic disease

Introduction

Zoonotic diseases are infectious diseases caused by pathogen agents such as viruses, bacteria, fungi, and parasites that can be transmitted from animals to humans directly by bite or via different vectors (Venkatesh et al., 2016). Rabies is a neglected zoonotic disease caused by rabies virus belonging to genus *Lyssavirus ('lyssa' meaning 'madness'),* family *Rhabdoviridae, and* order *Mononegavirales*. It is a neurological disease that infects all mammals including humans. In developing countries, humans and animals often live close together that increases the transmission rate of zoonotic diseases. The main feature of neglected zoonotic disease is commonly associated with poverty that affects primarily developing countries and excessively affects neglected or marginalized populations. Rabies has two importance because it can be devastating to both public and animals' health (WHO, 2011; FAO, 2018). It is present in more than 150 countries of the world and infects a wide range of mammalian species. Throughout the world, rabies cause more than 60,000 human deaths annually, which is approximately one person every nine minutes of

every day, and most of them are children living in Asia and Africa (WHO, 2018).

Rabies incidence and prevalence are high in African countries with limited surveillance systems and reliable available documented data since it is under-reported (Noel et al., 2021). Based on the situation of rabies, countries are categorized into three such as countries with enzootic canine rabies, those countries with mainly wildlife rabies, and countries that controlled both canine and other wildlife rabies, which is considered rabies-free countries by the World Health Organization guideline (OIE, 2018; Beyene et al., 2020). Rabies is fatal if timely and appropriate medical treatment is not applied for infected patients before the appearance of symptoms. However, after the onset of symptoms, rabies is 100% lethal. Dogs are the principal reservoirs of the rabies virus in developing countries and are responsible for the majority (97%) of disease transmission. In many countries, rabies cases are significantly underreported. Therefore, a proper rabies case report should be applied to support its public health priorities and economic impact, to monitor the use of a vaccine and cost-effectiveness of interventions, as well as to allocate resources for disease prevention and control (Tajunnisa et al., 2021). Many people are infected with rabies in Ethiopia each year; for instance, according to the center for disease control and prevention, an estimated 2,700 people die of rabies annually that makes the country the highest death rate in the world, even though the disease is underreported and rabies diagnostic facilities are not established to get the real figure of rabies cases (Teklu et al., 2017; Mulugeta et al., 2020). Therefore, this review aims to search available information on the status of rabies disease, its public health impact, and designate the appropriate control and prevention interventions toward rabies elimination in Ethiopia.

The economic impact of rabies

Rabies affects the economy through the losses in productivity due to premature death, the cost of post-exposure prophylaxis (PEP) that includes costs to the medical treatment (wound care and tetanus anti-toxin administration), and anti-rabies vaccine (Sambo et al., 2013). According to WHO report, the costs required for PEP are twenty times higher than the amount spent on dog vaccination in impacted countries, and the current estimated average cost of rabies PEP is US$ 108, which is a ruinous financial burden on exposed families whose average daily income may be as low as US$ 1-2 per person. Annually, more than 29 million people worldwide receive a PEP vaccination to prevent hundreds of thousands of rabies deaths. Globally, the economic burden of dog-mediated rabies is estimated at US$8.6 billion per year. The average annual economic losses in affected herds, due to rabies for mixed-crop livestock system and pastoral system, were 288 USD and 477 USD, respectively (Jibat et al., 2016). In Ethiopia, there is no exact economic burden of rabies due to under-reported cases, limited diagnosis facilities, and insufficient surveillance.

Rabies transmission in Ethiopia

Rabies is a neglected zoonotic disease but preventable; that highly affects public health. The transmission of the rabies virus usually starts immediately when the infected saliva of a host is transferred to the healthy individual through a bite or wound contact (Aiyedun et al., 2017; Taylor, 2017). Rabies is transmitted by the bite or exposure of broken skin with a lick from rabid dogs, which is the principal vector of rabies in Ethiopia. There is various mode of rabies transmission; the most common one is through a bite of infected hosts and transfers rabies virus contained saliva exposure of wound or scratched skin (Beyene et al., 2018). Domestic dogs serve as a major reservoir of rabies virus in many developing countries and they play a great role in virus transmission to other domestic animals involved in as secondary transmission. Rabies transmission through consumption/feeding of rabid animals' meat or milk has not been reported, but ingestion of raw meat or milk from an exposed animal is firmly discouraged and should be avoided. Mortality in rabies exposure depends on the severity of infection, location of the bite, and

amount of rabies viruses found in the saliva of a rabid animal. Different rabies virus isolates have different virulence based on the route of inoculation; for instance, virus isolates from bats are more virulent when injected on the surface into the epidermis since viruses replicate quickly in non-neuronal cells at lower temperatures than dog rabies virus isolates. In the last half-century, there was few non-bite exposures of rabies have been documented in humans. Other than bite, there are also other routes of rabies that include inhalation of concentrated aerosolized rabies viruses, organ and cornea transplants, and contamination of broken skin with rabies antigen in saliva or brain tissues of a rabid animal (Deressa et al., 2015). Therefore, it was suggested that donors, mainly those with nervous signs, must be tested for rabies before transplantation (Pieracci et al., 2016). To break the pattern of the disease, robust surveillance is needed to obtain the precise data requisite to raise the perception of the community on the severity of rabies, to create the political will and joint efforts needed to initiate changes in rabies policies (Kabeta et al., 2015; Broban et al., 2018).

Sign and symptoms of rabies

The early symptoms of rabies in people are similar to that of many other diseases that include fever, headache, and general weakness or discomfort. As the disease progresses, more specific symptoms appear, such as insomnia, cranial nerve dysfunction, difficulty breathing and swallowing, aggression, aerophobia, photophobia, hyper-salivation, and hydrophobia. After the viruses are replicated in the nervous system, rabies-infected animals release viruses into salivary glands for two weeks before the onset of clinical signs based on strains virulence and host species. The suspected animals' isolation and observation for ten days are usually recommended. Death usually proceeds within days after the onset of these symptoms (Taylor et al., 2017). The incubation period depends on the type of exposure, the severity of the bite, the concentration of rabies virus introduced, the animal responsible for the bite, the immune status of the patient, and site of the bite (Ogun et al., 2010). The bite of highly innervated areas, such as fingers-tips and face has shorter incubation periods. When the virus has moved into the salivary glands, the saliva contains rabies viruses ready to infect another host (WHO, 1987). The virus first replicates at the site of inoculation and then travels through peripheral nerves from this site to the spinal cord and brain, where it causes disease (Brown et al., 2016). Clinically rabies has two forms; those include furious rabies, which is characterized by hyperactivity, and paralytic rabies, which is characterized by paralysis. It is often misdiagnosed and causes the under-reporting of rabies cases. Death from rabies usually occurs due to cardiac or respiratory failure (Hemachudha et al., 2005).

Management of rabies suspected animals

The management of suspected animals requires alerted veterinary services following any animal biting. The suspected animal should quarantine for observation (for ten days) or the animal may be euthanized for immediate laboratory diagnosis. The bitted person continues PEP during the ten days observation period, or until laboratory results conformation. If a suspected animal is euthanized and found to be negative/confirmed to be free of rabies by laboratory test or remain healthy after ten days period observation, vaccination may be discontinued. In another case, if a suspected animal cannot be captured for observation and not confirmed by laboratory diagnosis, then, a full course of PEP should be completed (Haselbeck *et al.,* 2021).

Mass dog vaccination effort in Ethiopia

Controlling zoonotic diseases is so complex; however, different experiences indicated that dog-mediated rabies virus elimination is feasible and cost-effective. Mass dog vaccination is the most cost-effective technique of preventing and stopping the transmission of rabies. Most high-income countries have been eliminated dog-mediated rabies through the implementation of mass vaccination and dog population management programs to break rabies transmission chains. To

perform an effective mass dog vaccination campaign that covers a large number of dog population, the vaccine should be delivered free of charge for dogs or with reasonable cost (Durr et al., 2009).

The current experience of large-scale dog vaccination and applications of rabies elimination strategies in those countries are unusual due to funding scarcity. Dogs are the principal host and dog-mediated rabies is common in developing countries like Ethiopia. Oral rabies vaccination is an alternative and successful vaccination method to cover a large number of dog population within a limited time to reach adequate (vaccinate 70% of dog population) to get herd immunity where high dog accessibility (Minghui et al., 2018). Developed countries implement oral rabies vaccination to control and eliminate rabies in wildlife; however, there is hesitancy to apply this for mass dog vaccination. Therefore, to avoid such hesitancy situation evaluation of vaccine safety for target and non-target animal species, virus dissemination potential, genetic stability, environmental safety, and mode of distribution are essential (Cliquet et al., 2018; Wallace et al., 2020). There is a limited effort for dog mass vaccination campaigns to eliminate dog-mediated rabies in Ethiopia. The estimated dog population of Mekelle city is about 20,000, which includes both owned and ownerless dogs (Habtamu et al., 2017). In Addis Ababa, the estimated dog population was 250,000 to 350,000, out of this, half of them are owned dogs, and the remains are free-roaming (Reta et al., 2014). Anti-rabies vaccination services are offered for dogs at government veterinary clinics and laboratories in some parts of the country, but these services are usually not affordable for most people to use (Moges, 2015). A recent study carried out in two sub-cities of Addis Ababa dog owners' residents showed that dogs' vaccination status is increasing and more than half of dog owners were attained regular vaccination of their dogs previously. This is a very important practice that should be extended to other parts of the country to tackle the transmission of the disease. However, some dog owners have no awareness about vaccination and allow free roaming that intensifies the imparting of rabies. The cases are high in and around Addis Ababa due to the poor management of owned dogs and the presence of high unvaccinated dogs population (Yoak et al., 2021).

Rabies Diagnosis

Rabies can be difficult to diagnose clinically, because in the early stages, it is easily confused with other diseases. Therefore, suspected and probable clinical cases of rabies should be confirmed by laboratory tests. Rabies diagnosis is primary analytical antemortem and postmortem testing of samples collected from suspect animals and humans (WHO, 2018). It is used to detect rabies virus infection both before rabies specific signs (hydrophobia or aerophobia) are present or post mortem through detecting the whole viruses, viral antigens, or nucleic acids in infected tissues. The best sample for diagnosis of human rabies is the skin biopsy from a richly innervated zone. Saliva is the second-best sample for rabies diagnosis. Secretions and biological fluids, such as saliva, spinal fluids, and tears are used to test rabies while the animal is alive (WHO, 2005). In Ethiopia, the experience of sending the suspected and dead animal's brain for examination was very low due to the limited available diagnostic center in the country (Deressa et al., 2010). There are different rabies diagnosis methods, including virus isolation, virus and its antigens detection, detection of anti-rabies antibodies, and detection of viral nucleic acid (Melo et al., 2020).

Fluorescent Antibody Test (FAT)

The fluorescent antibody test (FAT) is the recommended gold standard for rabies diagnosis. In this method, rabies virus is detected by binding fluorescein isothiocyanate with rabies specific antibody to form conjugate, and rabies antigen is observed under fluorescent microscopy. The fresh brain tissue sample is preferable for diagnostic of rabies to get result within 3 hours (Rupprecht et al., 2018). Based on the result, there is no need for PEP treatment when FAT results with a sensitivity of 100% are negative (Ehizibolo et al., 2009).

Rapid Immunodiagnostic Test (RIDT)

Rapid Immunodiagnostic Test (RIDT) is the method of antigen detection in fresh animal brain tissue. It is important for the field and frontline laboratories. The result of all positive RIDT tests requires to be confirmed employing direct fluorescent anti-body testing at a qualified laboratory (Brown et al., 2016).

Microscopic analysis of samples

This method is the direct diagnostic approach used for the identification of rabies virus-specific antigen in a short time with limited cost, disregarding geographical origin. It has to be considered as the first step in diagnostic procedures for all laboratories. The sample used for this technique can be taken from saliva, urine, and cerebrospinal fluids, but less sensitive and reliable than brain samples (Brown et al., 2016).

Rabies control and prevention

Control of neglected zoonotic diseases requires integrated interventions among humans, animals' health, and other relevant sectors to reduce the associated impact on public health. Through the implementation of public policies to improve epidemiological surveillance actions, the eradication of dog-mediated human rabies transmission can be controlled (Suu-ire et al., 2021; Viana et al., 2021). Several reports indicated that more than 95% of human rabies cases are due to dog bites, particularly in developing countries in Asia and Africa *(*Beyene et al., 2018). Mass vaccination of dogs is the method of choice, since it is the only key technique to break up the infection cycle between animals and humans. The efficacy of the vaccine used for this purpose should be tested with local rabies virus isolates to ensure cross-protection with fixed virus strains. The regular intervention targeted at vaccinating stray dogs with standardized anti-rabies vaccine evaluated in terms of local rabies virus isolate is strongly recommended for effective disease prevention and control (Mohammad et al., 2015; Aga et al., 2016). The large dog population size in combination with poor dog management contributes to a high endemic of dog-mediated rabies in Ethiopia. These vaccines were developed two decades before, but nerve tissue vaccines are still in use by a million people every year in some Asia and African countries. In Ethiopia, the NTV is an anti-rabies vaccine for post-exposure immunization for humans that is currently used by the vast community, which is produced from sheep brain tissue attenuated with 5% of phenol. Due to the unaffordability of imported modern cell culture-based anti-rabies vaccines to the large community, outdated NTV is still in use. WHO firmly recommends the discontinuation of this vaccine due to the high rate of adverse reactions and low immunogenicity; however, some countries, including Ethiopia is still producing and administering for humans (WHO, 2018). In the 1940s, these NTV were replaced with more immunogenic and safer cell culture-derived vaccines. Cell culture-based anti-rabies vaccine for human use from fixed rabies virus strains is in progress through propagation on Vero cell lines in Ethiopia, which needs great attention of the government to meet the objective of replacing outdated NTV and to provide WHO-recommended vaccine for rabies victims (Hurisa et al., 2013).

Pre-exposure prophylaxis vaccination

Pre-exposure vaccination is recommended to people at high risk of exposure to rabies, such as those working in rabies diagnostic and anti-rabies vaccine production facilities, veterinarians, animal handlers, animal rehabilitators, wildlife officers, and other people living in or traveling to high-risk areas where dog rabies is endemic. The individuals at frequent risk of exposure such as people working with the live rabies virus should have their antibody titer (amount of antibody present in their blood) checked every six months, and for other professions at permanent risk of exposure to rabies this should be performed every year. If the quantity of the anti-body present in their blood falls less than 0.5 IU/mL, one additional routine booster is recommended (WHO, 1996).

The pre-exposure vaccination allowed for humans consists of three doses of full intramuscular administration of cell culture-based or embryonated egg-based vaccine given based on producers' instruction. If the immune status of a patient is questionable at the time of vaccination, the patient immune response to the vaccine should be assessed after the three-dose pre-exposure series has been administered (WHO, 2013). A person who was previously immunized and who has had a potential rabies exposure should receive two intramuscular doses of vaccine; the first dose as soon as possible after exposure and the other one three days later (Singh et al., 2017). Anti-rabies vaccines that are used for this purpose are not accessible and affordable to a large community in Ethiopia (Hurisa et al., 2013).

Post-exposure prophylaxis vaccination

Post-exposure vaccination consists of the combination of local wound cleansing, anti-rabies vaccine administration, and human rabies immunoglobulin to infected persons based on the category of exposure (Figure 1). In Ethiopia, recently, the vaccine used for PEP is NTV, produced from sheep brain infected with rabies virus. A full post-exposure dose of NTV consists of 17 doses of vaccine administered consecutively for the first 14 days, and the remaining three doses at intervals of 10 days, at days 24, 34, and 44. The PEP vaccination is allowed for individuals exposed to a rabid or suspected animal (Adedeji et al., 2010). The NTV is locally produced at Ethiopian Public Health Institute (EPHI). It is the most common anti-rabies vaccine in Ethiopia that holds 88% of domestic demands of vaccines used for PEP in and around the capital Addis Ababa (Deressa et al., 2010). This number may vary in the regions of the country due to the inaccessibility and unaffordability of imported cell culture-based vaccines. The WHO recommends immediate washing of the wound with soap and water, application of human anti-rabies immunoglobulin, and administration of cell culture rabies vaccine at 0, 3, 7, 14, 30, and 90 days after exposure (Rajeev et al., 2021). Through the administration of the anti-rabies vaccine, the body takes from 7 to 14 days to produce its own antibodies after rabies vaccination. If a repeat exposure occurs within three months of completion of effective PEP vaccination, only first aid wound treatment is required; neither vaccine nor RIG is needed (WHO,2018).

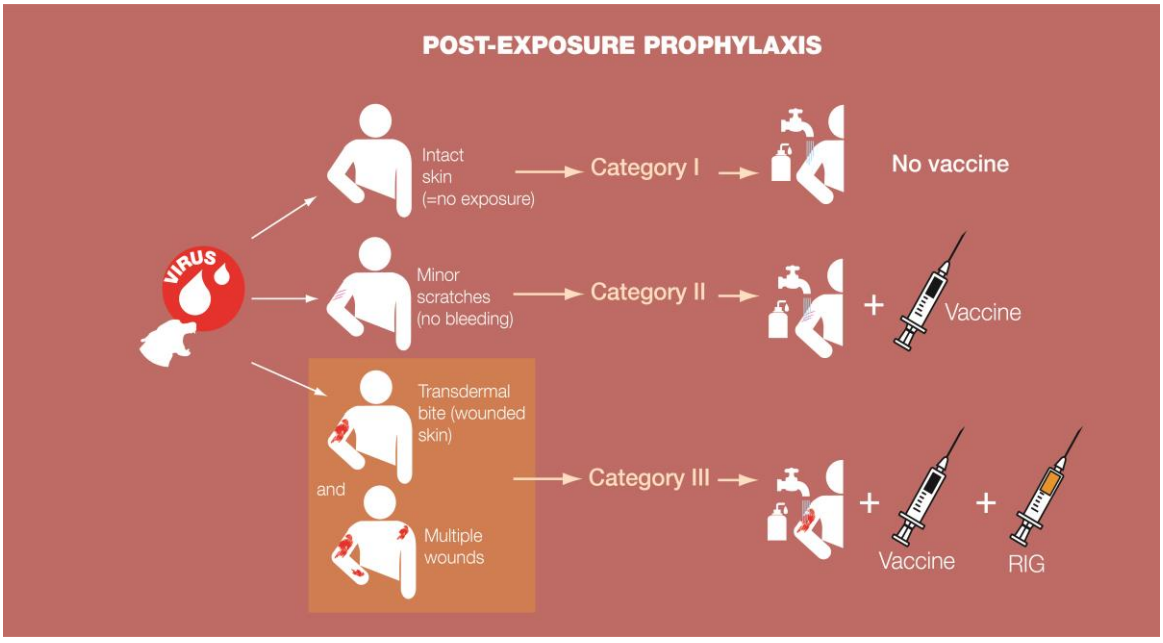

Fig. 1. Categories of rabies exposure (Source: First annual progress report: global strategic plan to end human deaths from dog-mediated rabies by 2030).

Challenges of rabies control and prevention in Ethiopia

The principal reasons for rabies remain a neglected zoonotic disease in many developing countries is the lack of specific diagnostic methods and surveillance techniques. The dog ownership policy of the government of Ethiopia is not defined to prevent and control rabies in the country. According to a retrospective study carried out, among suspected dog brain samples collected to EPHI for diagnosis, 96.67% of unknown owners (ownerless) dogs were confirmed rabies positive.

Table 1- Examples of successful rabies elimination programs

Countries	Activities	Outcomes
Bangladesh 2010-present	▶ Increase the government investment five times for rabies control activities. ▶ Capacity building training for dogs vaccinators ▶ Switch from dog population control to mass dog vaccination campaigns ▶ Free PEP for bite victims	▶ >90% reduction in human rabies cases
Mexico 1990–2000	▶ Media and community engagement ▶ Mass dog vaccination campaigns ▶ Decentralized national rabies alert ▶ surveillance system	▶ Zero human rabies deaths
Philippines (Visayas) 2010–present	▶ Rabies prevention, education, and awareness creation ▶ Establish a national rabies database ▶ Mass dog vaccination campaigns ▶ Establish dog vaccine banks ▶ Free PEP for bite victims	▶ >80% decrease in human rabies cases ▶ Two provinces, five island municipalities, and five smaller islands declared rabies-free
South Africa (KwaZululu-Natal) 2007–2014	▶ Public awareness and medical staff training ▶ Establish dog vaccine bank and dogs vaccination in a high-risk area ▶ Free PEP for bite victims ▶ Rabies stimulus packages to support the expansion of control activities	▶ Elimination of human rabies in KwaZulu-Natal ▶ Expansion of control activities to neighboring areas such as Eastern Cape, Lesotho, and Swaziland
Sri Lanka 1990–2014	▶ National notification of human and animal rabies cases ▶ Mass dog vaccination and sterilization campaigns ▶ Free PEP for bite victims	▶ >85% reduction in human rabies cases
United Republic of Tanzania (south-east) 2010–2015	▶ Novel mobile phone surveillance system ▶ Mass dog vaccination campaigns ▶ Cost-saving switch from intramuscular to intra-dermal PEP	▶ >75% reduction in animal bite cases (a proxy for rabies exposure) across project sites ▶ Local elimination of human cases on Pemba Island by 2014

(Source: Zero By 30)

This indicates that free-roaming dogs play a great role in the transmission of disease and the management status of the principal vector of the disease is very poor in the country. Among the vaccinated and unvaccinated dogs, those suspected and confirmed rabies positive were 50% and 73.43%, respectively (Deressa et al., 2010). The detection of rabies virus in brain samples collected from vaccinated dogs may be due to several various reasons, such as passing a long time after vaccination that needs boosting, lack of proper cold chain during transportation of vaccines, and lack of

storage facilities at health centers (vaccine failure due to frequent power disruption) are other challenges in the country. Therefore, such a vaccine cannot induce an immune response against the virus and disease develops in vaccinated dogs. Another reason may be the presence of the Lagos bat virus in dogs, as the vaccine that exists in the country may not protect against this genotype. Besides these, it is under-reported and lack of multi-sectoral preparedness with defied role and responsibility, gaps in the state policies against rabies, the limited effort of dog mass vaccination campaign, as well as copiously free-roaming dogs make control and prevention of rabies difficult (Mableson et al., 2014). Inadequate awareness of the disease and its transmission, in addition to limited access to vaccines, impede control efforts. Rabies is a neglected zoonotic disease, and as the country did not identify rabies as a top priority, political dedication and allocating resources for control of rabies remain insufficient *(*Hasen et al., 2021).

Rabies is a neglected zoonotic viral disease that affects all warm-blooded animals. The disease is lethal once clinical signs appear. In developing countries, the main means of rabies virus transmission is the bite of exposed dogs to healthy people or animals. The control and prevention of rabies were achieved successfully in some parts of the world, mostly in developed countries. However, the disease is still endemic and killing thousands of people every year in Africa and Asia. Rabies significantly affects both public and animal health; therefore, it seeks regional and national priorities to control the transmission. As dogs are the principal host in rabies transmission, mass vaccination of dogs is the key strategy to eliminate the disease and to minimize the cost of vaccination in humans. Low rabies surveillance system, the absence of clear policy targeting the elimination of rabies that focused on vaccinating of dogs, unavailability, and inaccessibility of affordable and effective modern anti-rabies vaccines for humans increase the severity of disease to public health in Ethiopia. Therefore, engaging sophisticated practical training for health professionals on PEP administration, bite management, and establishing palliative care for clinical rabies cases to improve the delivery of life-saving PEP activities are needed. Providing cost-free PEP treatments, including anti-rabies vaccines for exposed individuals is also a key strategy to eliminate rabies in Ethiopia. Besides, to prevent and control of rabies disease in Ethiopia, setting as a public health priority, allocating resources for disease prevention, assessing the impact, and focusing on dog-mediated rabies as the major cause of human rabies with considering the best experiences implemented are crucial. Establishing more rabies diagnosis centers at regional levels with sensitive diagnostic methods and ensuring the capacity of the staff, who conducts the laboratory tests are extremely important to eliminate rabies disease. Generally, to eliminate rabies, Ethiopia should encourage studies of the rabies burden, its surveillance with appropriate infrastructure to collect and transport samples for rabies testing and generating reliable national data for effective decision making, accompanied with providing safe, effective, and affordable modern anti-rabies vaccine for bite victims.

Experiences toward rabies eliminations strategies

Rabies is a preventable disease that needs the joint effort of the animal, human, and wildlife sectors. Different countries (Table 1) implement rabies elimination approaches and reduce rabies cases or have zero human death due to rabies. Rabies free Africa initiative was established to eliminate rabies in Africa. The rabies-free Africa team that is currently working in Kenya and Tanzania should be expanded to other rabies endemic African countries. As part of dog mediated rabies elimination strategy, Chad has implemented the mass dog vaccination campaign for two years and reduced the rabies cases by 90% within two years (Léchenne et al., 2016).

Conclusion

Acknowledgements

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Ethics approval

Not applicable.

Conflict of interest statement

The authors declare no conflicts of interest.

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