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Tracking lethal threat: in-depth review of rabies

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Abstract
An infectious disease known as rabies (family Rhabdoviridae, genus *Lyssavirus*) causes severe damage to mammals' central nervous systems (CNS). This illness has been around for a very long time. The majority of human cases of rabies take place in underdeveloped regions of Africa and Asia. Following viral transmission, the Rhabdovirus enters the peripheral nervous system and proceeds to the CNS, where it targets the encephalon and produces encephalomyelitis. Postbite prophylaxis requires laboratory confirmation of rabies in both people and animals. All warm-blooded animals can transmit the *Lyssavirus* infection, while the virus can also develop in the cells of cold-blooded animals. In the 21st century, more than 3 billion people are in danger of contracting the rabies virus in more than 100 different nations, resulting in an annual death toll of 50,000–59,000. There are three important elements in handling rabies disease in post exposure prophylaxis (PEP), namely wound care, administration of anti-rabies serum, and anti-rabies vaccine. Social costs include death, lost productivity as a result of early death, illness as a result of vaccination side effects, and the psychological toll that exposure to these deadly diseases has on people. Humans are most frequently exposed to canine rabies, especially youngsters and the poor, and there are few resources available to treat or prevent exposure, making prevention of human rabies challenging.
Keywords: Rabies, Infectious disease, Bite, Virus, Public health.

Introduction

The rabies virus (RABV) (family Rhabdoviridae, genus *Lyssavirus*) is an infectious disease that infects the central nervous system (CNS) of humans and animals (Farihah *et al.*, 2022). This zoonotic illness results in deadly encephalitis in mammals (Soler-Rangel *et al.*, 2020). During an infection, severe neurological symptoms that can cause paralysis and even death appear (Gajurel *et al.*, 2022). The infection can only be prevented, not treated, in cases of rabies, which are frequently fatal (Amoako *et al.*, 2021). The primary source of transmission for this disease, which primarily affects underdeveloped nations, is the bite of an animal with rabies, but in industrialized nations, the infection is brought on by the bite of a variety of wild animal species (Kavoosian *et al.*, 2023). Dogs, monkeys, cats, wolves, goats, rabbits, horses, and cows are among the species that are categorized as being at risk of contracting rabies (Rahman *et al.*, 2020). The main sources of rabies infection in humans are dogs and cats because these two animals are the closest to humans and the environment, as well as house pets (Crozet *et al.*, 2020).

Injuries caused by bites of animals or wild animals with rabies must be vaccinated immediately, while pets should be treated by a local veterinarian to prevent rabies

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from occurring in these pets (Li *et al.*, 2021). Human rabies cases are caused by bites from infected animals, particularly dogs (91.5%), which catch the virus from other dogs or wild animals (Audu *et al.*, 2019). The risk of contracting rabies has been determined by bites from 5% to 80% of infected animals and licks from 0.1% to 1% of infected animals (Singh *et al.*, 2017). The severity of the illness depends on the location of the bite and the amount of the virus contained in the animal's saliva (Setiawan *et al.*, 2018). During the incubation stage of the sickness, the virus is shed in the saliva, which results in the process of transmission between hosts, primarily via the bite of an infected animal, though the virus can also be transferred through contact with mucous membranes (Scott and Nel, 2021). A bite from a rabid animal can be fatal, even though not all bite instances cause clinical signs (Hampson *et al.*, 2015). The presence of this disease can cause anxiety and fear for people who have been bitten by animals, even though the animal does not necessarily have rabies (Penjor *et al.*, 2019).

One or more of these symptoms, including uncontrollable movements, dread of water, restlessness, light sensitivity, inability to move certain body parts, confusion, and loss of consciousness, are present after the rabies symptoms (Cai *et al.*, 2021). The outcome is almost usually death once these symptoms arise (Burgos-Cáceres, 2011). This illness spreads from animals to animals and from animals to people (Fisher *et al.*, 2018). The local and national economies suffer economic losses as a result of this, both directly and indirectly (Premashthira *et al.*, 2021). Since 2010, rabies has spread more widely over the world, with the majority of rabies-related fatalities occurring on the continents of Africa, Southeast Asia, and the West Pacific (Fahrion *et al.*, 2017). According to information from the World Health Organization (WHO), 59,000 people worldwide pass away from rabies each year, with Asia accounting for 60% of those deaths (Pieracci *et al.*, 2019). This indicates that a rabies-related fatality occurs every 20 minutes and the majority of those affected are children (Tierradentro-García *et al.*, 2022). Since ancient times, people have been extremely scared of rabies (Gold *et al.*, 2020). This is due to the fact that the illness causes the patient to suffer from agonizing symptoms of thirst, aerophobia, and hydrophobia and is potentially the deadliest of all infectious diseases (Warrell *et al.*, 2017). In humans, the healing process rarely takes place in the clinical state of rabies patients, but extensive therapy is required, even though it does not always lead to full recovery (Subramaniam, 2016). The development of rabies can be prevented if the bite marks from animals are handled in a timely manner (Monje *et al.*, 2020). Given that there is no treatment for rabies, only prevention and postbite postexposure prophylaxis (PEP) which includes thorough wound wash with soap and water, administration of anti-rabies vaccine, anti-rabies immunoglobulin, and anti-rabies serum to people who have been bitten by animals that are known to transmit rabies, is crucial (Sarbazi *et al.*, 2020). To prevent the spread of the virus to the CNS, it is crucial that the anti-rabies vaccine is accessible, in addition to good washing facilities, in primary healthcare centers (Sahu *et al.*, 2021).

The first effective rabies vaccinations for human use were created in the 19th century, and both animal and human rabies are fully avoidable with vaccination (Hicks *et al.*, 2012). Human rabies continues to be one of the most severe and problematic diseases as well as a significant threat to public health in the twenty-first century, despite the fact that the virus is still enzootic in many parts of the world (Wunner and Briggs, 2010). The majority of individuals frequently lack knowledge about this disease and react to it incorrectly (Rehman *et al.*, 2021). The purpose of writing this review is to explain everything about etiology, history, reservoir, epidemiology, pathogenesis, diagnosis, clinical symptoms, transmission, risk factors, public health importance, economic impact, treatment, vaccination, prevention, and control of rabies. The information gathered through this review is to provide scientific literature that is very important to the public in the study of rabies.

Etiology

One of the seven genera of the family Rhabdoviridae of the order *Mononegavirales* is *Lyssavirus* (Dietzgen *et al.*, 2017). It consists of the classic RABV, *Mokola* virus, *Duvenhage* virus, *Lagos bat* virus, *Australian bat Lyssavirus*, *European bat Lyssavirus* 1, and *European bat Lyssavirus* 2 (Aiyedun *et al.*, 2017). Irkut virus, Aravan virus, *West Caucasian bat* virus, and Khujand virus are four more viruses that were identified from insectivorous bats and have recently been proposed as new members of the *Lyssavirus* genus (Rather *et al.*, 2023).

The RABV has a bullet-like structure and measures around 75 × 200 nm (Itakura *et al.*, 2023). It has a viral envelope and a ribonucleocapside core, which may be generally separated into structural and functional parts (Kiriwan and Choowongkomon, 2021). A total of five monocistronic genes that correspond to five viral proteins may be found in the N gene, which also codes for the nucleoprotein that protects the virus and unsegmented negative-strand RNA (Vagheshwari *et al.*, 2017). The P gene creates phosphoproteins, which are crucial for axoplasmic transport connections with cellular protein constituents as well as transcription and replication (Piccinotti and Whelan, 2016). M genes encode for matrix proteins and G genes create solitary transmembrane glycoproteins that assemble into trimeric spikes (Kim *et al.*, 2017). While the L gene encodes the polymerase for RNA synthesis, this glycoprotein is crucial for initial binding during infection of susceptible cells and is the exclusive target of virus-neutralizing antibodies (Sasaki *et al.*, 2018).

History

Both people and animals are afraid of the infectious disease rabies (Fooks *et al.*, 2014). This illness has been

around for a very long time (Tarantola, 2017). Around 2,300 BC, rabies was first identified in Egypt, and Aristotle provided a thorough description of the illness in ancient Greece (Bihon *et al.*, 2020). Descriptions of rabies dogs can be found in the Avesta (Persia) from the sixth century BC and the Susrutasamhita (India) from the first century BC (Radhakrishnan *et al.*, 2020). In 1,804, it was discovered that diseased dogs could transmit the disease through their saliva (Dalfardi *et al.*, 2014). Before Pasteur's discovery in 1885, there were no efficient preventive or therapeutic measures for diseased animals (Gomes, 2021). In 1881, Pasteur proved the neurotropism of viruses (Kumar *et al.*, 2023). In 1885, Pasteur invented the innovation of giving rabies vaccine, before the structure and properties of the RABV were known (Natesan *et al.*, 2023). Joseph Meister, who had been attacked by a rabid animal more violently, received the rabies vaccine for the first time that year (Rappuoli, 2014). The age of infectious illnesses, which focuses on disease control and prevention, marks the beginning of contemporary science (Baghi and Rupprecht, 2021). The RABV's structure was discovered by Remlinger and Riffat-Bay in 1903 (Burrell *et al.*, 2017). The RABV in wild animals first arose in red foxes (*Vulpes vulpes*) in the Kaliningrad region during the 1940s, and within a few decades, it spread to Western and Central Europe (Kumar *et al.*, 2023). The first oral rabies vaccine campaign for wildlife was launched in 1978, in Switzerland, followed by other European countries (Nokireki *et al.*, 2016). In outbreak areas, field tests of three oral vaccination campaigns for dogs using the SAD B19 vaccine began in 1988, and Finland was once more proclaimed a rabies-free nation in 1991 (Nokireki *et al.*, 2017).

Reservoir

All mammals are capable of contracting rabies, but only a small subset of these, known as rabies-transmitting animals, are capable of actually spreading the disease (Wei *et al.*, 2023). The type of animal that transmits rabies varies depending on various geographical locations, for example, the animal that transmits rabies in North America is the fox, skunk, raccoon, and insect-eating bats; in South America, those are vampire dogs and bats; in Europe, they are foxes and bats; in Africa, they are dogs, mongooses, and antelopes; in the Middle East, they are wolves and dogs; and in Asia, they are dogs (Sararat *et al.*, 2022). In general, bats (suborder Microchiroptera) and meat-eating animals (order Carnivora) serve as the primary global reservoirs for the RABV (Worsley-Tonks *et al.*, 2020). Dogs, cats, monkeys, and other similar animals (including primates and members of the group Carnivora) are designated as rabies-transmitting animals in Indonesia (Dibia *et al.*, 2015).

Epidemiology

Rabies can be found in 150 countries and all continents except Antarctica (Kavoosian *et al.*, 2023). In numerous regions of Asia and Africa, stray dogs are a major cause of human infection (Knobel *et al.*, 2005). The majority of human cases of rabies take place in underdeveloped regions of Africa and Asia (Nyasulu *et al.*, 2021; Ling *et al.*, 2023). Dog bites are a common cause of rabies, and there are frequently insufficient facilities for providing intensive medical care (Alam *et al.*, 2020). There have been no cases of rabies in the dog population in a number of rural locations, including Western Europe, Canada, Australia, Japan, the United States, and island nations (Uzunović *et al.*, 2019). Several nations, including the UK, Australia, Japan, Papua New Guinea, Singapore, New Zealand, and the Pacific islands, are rabies-free despite the presence of dogs in these regions (Leung and Davis, 2017).

An estimated 59,000 people worldwide die from dog rabies each year, with the majority of these deaths happening in Asia, Africa, and Latin America (60% of which are reported in Asia and Africa) (Bonaparte *et al.*, 2023). The majority of rabies-related deaths in humans occur in India, where they reach 18,000 to 20,000 per year (Baxter, 2012). In Asia, rabies causes around 30,000 fatalities each year (Pantha *et al.*, 2020). Children under the age of 15 account for 4 out of every 10 deaths from rabies (Al-Mustapha *et al.*, 2022). Only five of the 36 rabies patients survived the disease despite having symptoms and receiving intensive care (Nadeem and Panda, 2020). Since 2008, there has been a significant rabies outbreak on the Indonesian island of Bali, which as of the end of September 2010 had also claimed the lives of about 78 people (Putra *et al.*, 2013). Approximately 583.5 million USD is spent annually on rabies prevention (Wolelaw *et al.*, 2022). Rabies causes around 24,000 to 60,000 deaths worldwide per year and also causes an economic loss of 8.6 billion USD annually (Beyene *et al.*, 2018).

Pathogenesis

Following viral transmission, the Rhabdovirus enters the peripheral nervous system and proceeds to the CNS, where it targets the encephalon and produces encephalomyelitis (Potratz *et al.*, 2020). The initial signs and symptoms of nonspecific viral syndromes in humans are fever, discomfort, and headache (Mahadevan *et al.*, 2016). These initial symptoms can then progress into anxiety, agitation, and actual delirium (Burgos-Cáceres, 2011). A tingling feeling at the location of the bite within the first few days after a rabies bite is one fairly typical symptom (Chacko *et al.*, 2017). The virus then spreads back into the peripheral nervous system, specifically targeting highly innervated areas (such as salivary glands), before moving from peripheral nerves to the CNS (Farihah *et al.*, 2022). Hypersalivation, which results in tongue foaming in rabies patients, can also lead them to have hydrophobia, which is characterized by severe pharyngeal spasms at the mere sight, taste, or sound of water (Cárdenas-Canales *et al.*, 2020). The infection eventually progresses to cause an immediate death due to the total collapse of the nerve system (Jamalkandi *et al.*, 2016). Animals typically pass away

within 10 days, but the incubation period that follows vaccination might range anywhere from 2 weeks to 6 years on average (Crozet *et al.*, 2020). Factors that determine incubation time are viral load, bite site, and wound severity (Abdulmajid and Hassan, 2021). The virus ultimately damages the brainstem more severely than the rest of the CNS (Feige *et al.*, 2021). Through an inflammatory reaction, the harmful effects take place, and there are unrecognized functional changes (Zhang *et al.*, 2022). The virus then affects neurotransmission, and both viral- and cell-dependent pathways can lead to apoptosis (Kim *et al.*, 2021). Rabies is always lethal once clinical symptoms arise (Warrell and Warrell, 2015).

Diagnosis

Postbite prophylaxis requires laboratory confirmation of rabies in both people and animals (Mani and Madhusudana, 2013). Rabies can be diagnosed *in vivo* or posthumously (David, 2012). Ante-mortem diagnosis of RABV infection is challenging (Goravey *et al.*, 2020). Despite the fact that hydrophobia is quite suggestive, none of the clinical symptoms are pathognomonic for rabies (Mahadevan *et al.*, 2016). Alternative laboratory-based methods have been developed to confirm rabies infection because the diagnosis of rabies by the identification of Negribodi accumulations is no longer regarded as being adequate for diagnostic evaluation due to its low sensitivity (Mani and Madhusudana, 2013).

The majority of animal RABV diagnostic tests require brain tissue for detection, making them frequently only possible after death (Fooks *et al.*, 2014). Taking a sample of the affected area of the brain can be used to diagnose rabies in animals (Iamamoto *et al.*, 2011). However, to identify rabies, the test needs to use brain tissue from at least two distinct regions, namely the cerebellum and brainstem (Beck *et al.*, 2017). Animals can be diagnosed with rabies using a variety of diagnostic techniques, including mouse inoculation, tissue culture infection, polymerase chain reaction, and direct fluorescent antibody (Yang *et al.*, 2012). The easiest way to collect brain samples is to pierce the skull and take the sample immediately (Iamamoto *et al.*, 2011). Fluorescent antibody tests are utilized for both human and animal sample types to detect viral antigens early using brain swabs or touch impressions (Mani and Madhusudana, 2013). The suggested diagnostic technique for animals is the direct fluorescent antibody test (dFAT) (Rodrigues *et al.*, 2022). This examination looks for the rabies antigen in brain tissue (Prabhu *et al.*, 2018). Other diagnostic techniques include direct rapid neurologic immunohistochemistry test (dRIT), reverse transcription polymerase chain reaction (RT-PCR), and serological tests (Fluorescent antibody neutralization test and rapid fluorescent focus inhibition test) (Mani and Madhusudana, 2013). The suggested rabies test for people is dFAT on brain tissue (Okoh *et al.*, 2018). RT-PCR and dRIT have also been employed as additional diagnostic techniques (Dibia *et al.*, 2014).

There are three stages in the clinical diagnosis of rabies in humans: prodromal, excitation, and paralysis (Madhusudana and Sukumaran, 2008). The first clinical manifestation is neuropathic pain brought on by viral replication at the site of the damage or infection (Mahadevan *et al.*, 2016). Some species may exhibit either or both forms of excitation or paralysis in the disease's later clinical phases (Consales and Bolzan, 2007). It is thought that cats are more susceptible than dogs to contracting virulent rabies (de Lima *et al.*, 2023). In certain situations, the RABV has been detected as a case of sudden death even if there are no outward indications of the disease (Mahardika *et al.*, 2014). Only a laboratory examination can determine the diagnosis, ideally after a postmortem on the CNS tissue that has been taken from the skull (Clavijo *et al.*, 2017).

Any suspicion of meningitis, distemper, encephalitis, canine infectious hepatitis, spontaneous bovine encephalomyelitis (*Chlamydia psittaci*), cerebral cysticercosis (*Taenia solium*), water heart in sheep and cattle, or canine infectious hepatitis should be evaluated for rabies (Amor, 2009). It is important to take into account additional conditions including mineral, pesticide, and plant poisoning from plants such as monkey cord (*Cynanchum spp*) in sheep and kikuyu grass (*Pennisetum clandestinum*) in cattle (Oyda and Megersa, 2017).

Clinical symptoms

Clinical symptoms can vary widely between different species, individuals of the same species, and even in the course of the disease in certain individuals. Rabid animals may behave strangely as the condition worsens (Burgos-Cáceres, 2011). Testing in the laboratory is required to validate clinical suspicion of rabies (Mani and Madhusudana, 2013).

Early clinical symptoms are frequently nonspecific and can include anxiety, agitation, anorexia or increased hunger, nausea, vomiting, diarrhea, low-grade fever, dilated pupils, hypersensitivity to stimuli, and excessive salivation (Susilawathi *et al.*, 2012). The paralysis of the vaccinated leg is frequently the initial symptom of postvaccination rabies (Surve *et al.*, 2021). Animals frequently go through behavioral and temperamental changes and can exhibit unusually aggressive behavior (Brookes *et al.*, 2019).

Prodromal stage

The incubation phase is frequently followed by the onset of clinical symptoms. Minor behavioral changes, such as aggression in domestic animals, daytime activity in nocturnal animals, a lack of fear of people and other animals, or loss of hunger, may take place during this first stage, which typically lasts between 1 and 3 days (Thiptara *et al.*, 2011).

Excitement (furious) phase

There are periods of intense agitation and aggression after the prodromal stage. Animals often bite everything in their vicinity (Masthi and Pruthvi, 2018). During

rabies attacks that are violent, rabies dogs may make a distinctive high barking noise (Burgos-Cáceres, 2011). Even without the paralysis stage, an animal's death can happen after a seizure (Warrell and Warrell, 2015).

The growl form is characterized by attacks on other animals, people, or inanimate objects, howling, restlessness, wandering, polypnea, and drooling and drooling (Oyda and Megersa, 2017). Animals with the condition frequently ingest foreign things such as sticks and stones (Tarantola, 2017). Wild animals regularly lose their fear of humans, and as a result, they could engage in attacks against humans or other animals that they would normally avoid (Acharya *et al.*, 2020). Nocturnal animals can be seen active during the day (Lembo *et al.*, 2008). Unusual alertness in cattle may also be a symptom of this illness (Sharif *et al.*, 2021).

Paralytic (dumb) phase

Progressive paralysis is a defining characteristic of the "dump" phase of rabies (Singh *et al.*, 2017). The masseter and neck muscles are paralyzed in this form, making it possible for the animal to have trouble swallowing and to salivate a lot (Hu *et al.*, 2008). Paralysis of the larynx can cause vocalization changes, including abnormal moaning in cattle or hoarse howling in dogs (Warrell and Warrell, 2015). Face paralysis or a drooping lower jaw are possible symptoms (Ghosh *et al.*, 2009). Symptoms in ruminants typically include being cut off from the herd, being frequently sleepy, and being depressed (Sharif *et al.*, 2021). There are additional signs of spinal paresis or paralysis, ataxia, and poor coordination (Lackay *et al.*, 2008). This stage is distinguished by an inability to swallow, which results in the recognizable foamy saliva around the mouth (Wertheim *et al.*, 2009). Some animals can get paralysis starting with their rear extremities and progressing to total paralysis, which is followed by death (Shuangshoti *et al.*, 2013).

Hydrophobia

The word "fear of water" (hydrophobia) is a defining characteristic of rabies symptoms (Amoako *et al.*, 2021). This condition is a group of warning signals that appear when the illness is progressed and the patient is afraid to swallow and drink water. Any virus-infected mammal may develop hydrophobia (Tongavelona *et al.*, 2018). In this condition, the animal produces a lot of saliva, has trouble drinking, and may have severe vocal cords and throat spasms (Wertheim *et al.*, 2009). Viral particles in saliva can be transmitted through bites (Jackson, 2011).

Symptoms in humans

The RABV takes time to reach the brain or nervous system and starts infecting (Hooper *et al.*, 2009). After being bitten by an animal with the RABV, symptoms usually start to show between 30 and 90 days later (Mahardika *et al.*, 2014). Some of the first signs and symptoms include hallucinations, tingling in the bite wound, fever, headache, and muscular cramps (Susilawathi *et al.*, 2012). The RABV may also potentially result in paralysis (Ghosh *et al.*, 2009). Therefore, it is important to see a doctor immediately as soon as mild symptoms appear or after experiencing a bite from an animal suspected of being infected.

Transmission

All warm-blooded animals can transmit the *Lyssavirus* infection, while the virus can also develop in the cells of cold-blooded animals (Bano *et al.*, 2017). This disease spreads by way of an infected animal's saliva, which allows the virus to enter, and then through an open bite wound on the skin or mucous membranes (Zhu *et al.*, 2015). Animals infected with the highly contagious disease rabies typically die from the disease (Mancy *et al.*, 2022). According to US investigations on infected canines, all rabid dogs passed away after just 8 days of contracting the disease (Brunt *et al.*, 2021). Rabies is primarily spread through bites (Rehman *et al.*, 2021). The disease is rarely spread by scratches that are contaminated with saliva, despite the fact that the virus is released in saliva; in these cases, the disease transmission rate is lower than through bites (Ghasemzadeh and Namazi, 2015). Although it is highly uncommon for the virus to spread from one person to another, transplant procedures have been linked to a very limited number of instances (Zhu *et al.*, 2015).

Risk factor

There are several factors that can increase a person's risk of contracting rabies, namely working in a laboratory that researches the RABV, working as a veterinarian, having many pets such as dogs or cats, living in an environment with lots of wild animals, living in areas with poor sanitation or far from being vaccinated, traveling or living in developing countries where rabies is more common, engaging in activities where there is a risk of contact with wild animals, such as camping, hiking or exploring caves (Ling *et al.*, 2023). Other things that are risk factors for the transmission of rabies are means of transportation, especially unofficial ports, pets that are not vaccinated in infected areas, and wild animals in infected areas that have never received vaccines (Chikanya *et al.*, 2021). Some individuals who are susceptible to rabies include dog catchers, hunters, visitors, and transplant recipients, particularly cornea (Lu *et al.*, 2018). In addition, the RABV may spread more quickly to the brain if the bite site is on the head, neck, or hand (Jackson, 2011). Scratches/abrasions have also been identified as possible risk factors in the transmission of rabies, especially if left untreated for a long time (Bharti *et al.*, 2017a, 2017b). A previous study reported that five rabies deaths were due to scratches and abrasions without bleeding, especially as no PEP was sought by the patients. In addition, a rabies death review of 1,839 patients showed that all the deaths were linked to dog-related injuries including bites and scratches (Dimaano *et al.*, 2011). In another study, four people who had no history of bites but only had scratches on their hands died due to rabies after

becoming infected with the saliva of rabid animals (Simani *et al.*, 2012). Deaths caused by scratches or abrasions further show the ability of the RABV to enter nerves through the dermis due to broken skin and its potential to cause rabies.

Public health importance

In the 21st century, more than 3 billion people are in danger of catching the RABV in more than 100 different nations, resulting in an annual death toll of 50,000–59,000 from rabies, with 25,000–30,000 deaths happening in India (Wunner and Briggs, 2010). These findings are shocking, particularly given that they pertain to people, mostly children, who have been or may be attacked by rabid dogs, which are the primary cause of RABV infection that has not yet been treated (Bharti *et al.*, 2019). This many people continue to die from rabies, with nearly all cases being brought on by dog bites from rabid animals, with more than 60% of rabies deaths reported in Asia and Africa (McCarthy, 2015). Rabies is a severe threat to public health on every continent, has been a part of society for many millennia, and has its origins in enzootic (animal hosts) habitats (Wunner and Briggs, 2010). It is difficult to ignore the symptoms of rabies it causes, but the danger of this disease is still not given much attention in several countries around the world, especially in Africa and Asia, where the spread of rabies in dogs is still not under control and efforts to eradicate it are still far from being eradicated (Gan *et al.*, 2023). In affluent nations where canine rabies has been eradicated, there are management methods to be followed and lessons to be gained that will present a challenge for future epidemiologists and molecular virologists when they apply new approaches to attain a rabies-free society.

Economic impact

There are several aspects to the RABV's negative economic effects. Social costs include death, lost productivity as a result of early death, illness as a result of vaccination side effects, and the psychological toll that exposure to these deadly diseases has on people (Subedi *et al.*, 2022). The amount of rabies immunoglobulin used, the type of rabies vaccination administered, and the location of delivery, such as intramuscular or intradermal administration, all affect subsequent treatment expenses (Haradanhalli *et al.*, 2022). The rabies victims are responsible for paying for other expenses including travel, lodging, and hospitalization, but in the veterinary field, the community often pays for dog vaccinations (Suijkerbuijk *et al.*, 2020). The veterinary and medical sectors are equally responsible for the costs of rabies control and prevention (Subedi *et al.*, 2022). Losses in the livestock sector depend on the size of the livestock population at risk and the precautions taken, as well as the impact on the national and household economy (Jibat *et al.*, 2016). The emergence of a rabies outbreak in a certain area can reduce the number of tourists who usually visit that area, which can reduce the country's foreign exchange earnings (Gautret *et al.*, 2015).

Treatment

There are three important elements in handling rabies disease in PEP, namely wound care, administration of anti-rabies serum, and anti-rabies vaccine (Changalucha *et al.*, 2019). Treatment of bite wounds following an animal suspected of having rabies is crucial for preventing the spread of rabies (Savu *et al.*, 2021). The spread of rabies can be almost completely avoided through wound care given during the first 3 hours after exposure to the virus (Liu *et al.*, 2017).

The first thing that needs to be done is to clean the wound of any RABV-containing saliva (Pounder, 2005). The wound is immediately cleaned by brushing with soap and water (preferably running water) for 10–15 minutes then dried and given an antiseptic (mercurochrome, 70% alcohol, povidone-iodine, 1%–4% benzalkonium chloride or 1% centrimonium bromide) (El-Sayed, 2018). The wound is as much as possible not sewn up but if it is absolutely necessary, then stitches are done and given serum anti-rabies (SAR) which is injected by infiltration around the wound. If the calculated SAR dose is likely too high for the local wound infiltration, it could be fractionated into smaller syringes; and if properly stored and handled aseptically, the unused residual doses can be used within the same day for other patients and thereafter, discarded at the end of the day, based on the latest WHO 2018 guidelines (World Health Organization, 2018; Bhaumik *et al.*, 2019). In addition, it is vital to think about supplying painkillers, anti-tetanus serum, vaccinations, and antibiotics to avoid infection (Consales and Bolzan, 2007).

Treatment is typically supportive if symptoms of rabies occur (Mahadevan *et al.*, 2016). Rabies patients are anesthetized to overcome their fear and pain (Warrell *et al.*, 2017). The fundamental method of treatment entails providing intensive care, managing paralysis, giving sedatives, and providing breathing ventilation (Zhu and Guo, 2016). Ketamine administration is recommended as an effective mediator for this illness (Jackson *et al.*, 2008). *Lyssavirus* can only be inactivated by sunlight, soap, and aeration (Fisher *et al.*, 2020). Administering a dose of human rabies immunoglobulin that must be injected intramuscularly at a site different than the vaccine site, in the bite area (Bharti *et al.*, 2017a, 2017b).

Vaccination

According to the circumstances surrounding the exposure, the findings of animal observations, the findings of laboratory testing on animal brain specimens, and the state of the wounds created, the administration of anti-rabies vaccination and anti-rabies serum needs to be modified (Estima *et al.*, 2022). At the time of administering the anti-rabies vaccine, it is necessary to investigate whether the bite wound patient has previously received a complete anti-rabies vaccine (Briggs and Moore, 2021). The tendency for

the spread of rabies in several developing countries is due to insufficient vaccination coverage or due to a lack of public awareness of vaccination, or limited access to obtaining rabies vaccinations (Haradanahalli *et al.*, 2021). The main issues faced by poorer nations are inadequate vaccination systems, constrained vaccination attempts, and subpar postbite animal management (Acharya *et al.*, 2019).

The current method of vaccination is intramuscular (Briggs and Moore, 2021). Vaccination with anti-rabies vaccine induces an active immune response by producing neutralizing antibodies approximately 7–10 days after vaccination (Overduin *et al.*, 2019). It is said to be protective against rabies disease when the level of anti-rabies antibodies in the serum reaches a minimum of 0.5 IU/ml (Rahimi *et al.*, 2015). In addition, intradermal administration of the rabies vaccine is an option (Gongal and Sampath, 2019). The justification for providing intradermal vaccine injections is to attain increased immunization coverage at a lower cost, although intradermal vaccination has not yet been widely used (Kong *et al.*, 2018). Numerous investigations on the administration of the anti-rabies vaccine intradermally at doses less than half of those administered intramuscularly have been conducted in a number of nations (Brown, 2011; Sudarshan *et al.*, 2012). There was no difference in the production of antibodies following rabies vaccination when administered intradermally or intramuscularly (Wangmo *et al.*, 2019).

Prevention and control

Humans are most frequently exposed to canine rabies, especially the poor and youngsters, and there are few resources available to treat or prevent exposure, making prevention of human rabies challenging (Gossner *et al.*, 2020). PEP programs frequently receive their funding mostly from governments and other organizations (Changalucha *et al.*, 2019).

Over 50,000 people die from dog-borne rabies every year, and the disease has direct and indirect expenses of $5.5 billion (animal testing, PEP, cattle losses, and dog vaccination) (Borse *et al.*, 2018). Rabies also poses a hazard to the existence of endangered wildlife species (Stuchin *et al.*, 2018). Controlling rabies is essential for avoiding human fatalities, making it easier to handle animals in danger, and maintaining the economy.

Pre-exposure vaccination and management

To prevent animals from contracting rabies, rabies vaccinations must be administered according to a regular schedule (Wolelaw *et al.*, 2022). Animals must receive the rabies vaccine under the close observation of a veterinarian practice with a license (Kang *et al.*, 2018). In addition, the rabies vaccine can be administered by veterinarians for animals held in animal shelters before being released (Tizard, 2021). Veterinarians who sign the certificate and administer the vaccine must have a certificate of competence and be trained in the storage, handling, and administration of vaccines, as well as dealing with unforeseen events (Dodds *et al.*, 2020). The purpose of this is to ensure that a knowledgeable individual may be held accountable for properly vaccinating animals (Taylor *et al.*, 2017).

Pre-exposure vaccination can be given to high-risk groups such as laboratory staff handling viruses and infected materials, doctors and people handling rabies cases in humans, veterinarians, hunters, animal catchers, quarantine officers, wildlife rangers, and travelers from free areas rabies to rabies endemic areas (Rao *et al.*, 2022). Pre-exposure immunization is delivered on days 0, 7, 21, or 28 as a single complete dose or 2 doses intramuscularly or as 0.1 ml intradermally (Kessels *et al.*, 2017; WHO, 2018).

Domestic animal vaccination

A number of vaccines have permission to be used on pet species (Dodds, 2021). There are a variety of minimum age requirements for vaccination, live attenuated or modified viral vector products, intramuscular and subcutaneous products, and vaccinations with immunological durations of 1–3 years (Natesan *et al.*, 2023). The antibody titer for the RABV is anticipated to peak within 28 days of the initial vaccination, at which point the animal can be regarded as having received the vaccine (Overduin *et al.*, 2020). Due to their frequent interaction with people, livestock must be vaccinated (Liu *et al.*, 2016). In addition, other animals in zoos, exhibits, and other public displays also need to have rabies vaccinations (Yang *et al.*, 2013). However, this is challenging due to the lack of herbivore vaccinations in underdeveloped nations (Haselbeck *et al.*, 2021).

Awareness and education

The cornerstones of preventing and controlling rabies are constant professional growth, appropriate pet ownership, regular animal care, and vaccinations (Chen, 2021). Raising knowledge of the risks of rabies transmission, the significance of avoiding contact with wild animals, and the necessity of receiving the necessary veterinary care can help to prevent the majority of exposure to rabies in animals and humans (Di Quinzio and McCarthy, 2008). Reporting to medical professionals and nearby veterinarians as well as to local public health authorities is extremely important when finding animals that indicate exposure to rabies (Grill, 2009).

World rabies day (WRD)

WRD is an important international day which is held on 28 September every year. The goal of WRD is to raise public awareness of the threat posed by rabies and the significance of its eradication. In 2007, WRD was established. In general, the implementation of WRD is carried out by socializing the community and vaccinating animals against rabies, especially dogs. The purpose of this campaign is to help those who require postexposure prophylaxis, make sure that dogs

are vaccinated, and eradicate rabies from the earth by the year 2030.

Conclusion

Rabies is a deadly infectious disease for animals and humans. This disease attacks the CNS, especially the brain. Dog bites are the main source of transmission of this disease. Treatment of bite wounds following an animal suspected of having rabies is crucial for preventing the spread of rabies. In addition, appropriate administration of anti-rabies vaccines, such as SAR and rabies immune globulin, is very important to inhibit transmission of the virus to the brain.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Author's contributions

ARK and SCK drafted the manuscript. IBM and MHE revise and edit the manuscripts. SCR, AW, and KHPR took part in preparing and critically checking this manuscript. AH, SMY, and OSMS edits the references. All authors read and approved the final manuscript.

Data availability

All data are available in the manuscript.

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