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Endemic Rabies in Ethiopia in the One Health Era

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Abstract Rabies is the most lethal viral zoonosis, with bats as reservoirs, causing fatal encephalomyelitis in humans and terrestrial mammals across various categories, including pets, livestock, stray animals, and wildlife. Rabies spans natural, rural, and urban areas, primarily affecting marginalized communities in low-income countries and posing a threat to food security and livelihoods. In Ethiopia, where dog-mediated human rabies is endemic, it is considered a prioritized zoonotic disease addressed through ongoing efforts, including parental dog vaccination initiatives. These efforts are supported by various global and international organizations. The One Health approach emphasizes the need to intensify these actions to resolve the persistent issue of a large population of stray dogs possibly interacting with wild animals and bats. Urgent experimentation is essential for the development of new protective vaccines against the bat-associated rabies viruses present in Ethiopia. These viruses can infect dogs vaccinated with the currently available vaccine. Additionally, adopting Oral Rabies Vaccination for stray and guard dogs in urban and rural areas, respectively, could be crucial. Oral Rabies Vaccination, already successfully implemented in Europe for wildlife (foxes), establishes a natural barrier of vaccinated animals effectively protecting the territory from the entry of rabid wild animals, as vaccinated animals can preside over the territory without being infected.

Keywords: *One Health, zoonoses, rabies, bat-associated rabies viruses, stray dogs, Oral Rabies Vaccination, Ethiopia*

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1. Introduction

Zoonoses are infections or diseases naturally transmissible from vertebrate animals to humans [1]. They can be classified according to their etiological agents as bacterial, viral, prionic, protozoan, helminthic, fungal, and ectoparasitic zoonoses, distinguishable in infections or infestations if the etiological agent is classified in the *Eukarya* Domain. Zoonotic agents are, then, pathogens (viruses, bacteria, unicellular or pluricellular parasites and unconventional infectious agents) with an unrestricted host spectrum, and their survival in nature is ensured by one or more animal species that act as reservoirs. Their indirect horizontal transmission can involve contact with infected hosts, or fomites; ingestion of contaminated food, water or intermediate hosts of different taxa; and the bite of infected vectors [2,3]. Food-borne zoonoses (FBZ) assume particular importance since they are transmitted through food derived from asymptomatic infected animals or food that becomes contaminated during production, commercialization, and domestic manipulation. FBZ can spread through the global food trade, reaching individuals unrelated to animals or their environment. Despite their denomination, FBZ are increasingly transmitted to humans from plant-based foods, demonstrating the adaptability of zoonotic agents [4]. Zoonoses threaten human health, animal health, food safety, and food security. The protection of the environment is essential in their control as deforestation and destruction of natural habitats contribute to pushing infected wild species into new territories – including the human environment and urban areas – where promiscuity between livestock and wildlife, and closeness to humans can occur, increasing the risk of spillover. Zoonoses account for 60% of human infectious diseases and 75% of the emerging ones [5]. In controlling and eradicating zoonoses, the broad interactions between different animal species, humans, and the environment, which are interdependent, necessitate multi focused interventions and cooperative strategies to improve systems for preventing, anticipating, identifying, responding to, and recuperating from infectious diseases and associated problems (e.g.: antimicrobial resistance) that jeopardize the general public health as well as the health of humans and animals [6,7,8]. The One Health approach responds to these needs, since "*One Health is an integrated, unifying approach that aims* *to sustainably balance and optimize the health of people, animals and ecosystems. It recognizes the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and interdependent. The approach mobilizes multiple sectors, disciplines, and communities at varying levels of society to work together to foster well-being and tackle threats to health and ecosystems while addressing the collective need for clean water, energy and air, safe and nutritious food, taking action on climate change, and contributing to sustainable development"* [9]. The One Health approach has been adopted by the Food and Agricultural Organization (FAO) and the Environment Programme of the United Nations (UNEP), the World Health Organization (WHO), and the World Organisation for Animal Health (WOAH, founded as OIE), which conduct joint actions as Quadripartite since 2022; furthermore, One Health is adopted by the European Union (EU) where it aligns with the EU Green Deal, and the Centers for Disease Control and Prevention (CDC) of the United States, as well as an increasing number of countries all over the world [4,10]. The One Health approach is of utmost importance in tackling rabies, the oldest recognized and the most lethal zoonosis which can affect all mammals, including humans, causing a fatal zoonotic encephalomyelitis [11,12]. In its spreading, the displacement of reservoirs and infected susceptible hosts – threatened by deforestation, habitat alteration, or war conflicts – plays a key role and can lead to the extension of infected areas or to the reintroduction of rabies in territories that previously achieved the eradication goal. To fight rabies, WHO, FAO, WOAH, and the Global Alliance for Rabies Control (GARC) gathered as *United Against Rabies Collaboration* in the *Global Strategic Plan Zero by 30*. It adopts the One Health approach and control measures based on the vaccination of reservoirs (mainly dogs) with the aim to end human rabies deaths transmitted through dog bites by 2030 [13,14]. Rabies remains a major public health problem and causes severe economic impact in many low-income countries, including Ethiopia, where endemic human rabies is reported [15,16].

2. Etiology of Rabies

Rabies is caused by the primarily pathogenic and neurotropic *Lyssavirus rabies* virus (RABV), and by the 16 genetically and antigenically rabies-related viruses, collectively constituting the Genus *Lyssavirus*, Order *Mononegavirales*, Family *Rhabdoviridae*, Subfamily *Alpharhabdovirinae* (Table 1), [17]. The Genus *Lyssavirus* shows 321 identified genomes, and it segregates into the following groups.

- Group 1 – dog-associated rabies viruses, globally present, including the taxonomic prototypical species *Lyssavirus rabies* virus, having dogs and some mesocarnivores (medium and small-sized carnivores) as reservoirs. It is responsible for the vast majority of human cases of rabies, although all lyssaviruses can cause fatal encephalitis in humans and other mammals.
- Group 2 – bat-associated rabies viruses, present in the Americas, further distinguished as follows.
- A clade with bats as reservoirs; bat-associated *Lyssavirus* seems to have limited geographic distribution and host specificity, posing minimal risks to public and animal health (only in the Americas rabies can be transmitted by vampire bats).
- A clade with skunks/raccoons as reservoirs.
- Divergent viruses do not belong to the previous groups [17,18].

RABV is a bullet-shaped, enveloped virus having a central core containing an unsegmented, single-stranded, negative-sense RNA genome encapsidated with the nucleoprotein, an RNA-dependent RNA-polymerase, and a polymerase cofactor phosphorylated protein. The inner core is associated with the matrix protein and is surrounded by a lipid envelope, on which is anchored the G glycoprotein, which protrudes in trimeric spikes and mediates binding to cellular receptors; it induces the host production of rabies immunoglobulin. As an enveloped virus, it is rapidly inactivated by disinfectants, and it is labile in the external environment and when exposed to ultraviolet radiation, air, sunlight, and blood drying. All the lyssaviruses share many biological and physicochemical features as well as amino acid sequence characteristics that distinguish them. These include the bullet-shaped morphology of the helical nucleocapsid or ribonucleoprotein core and the structural proteins of the virion [19,20,21,22].

Table 1. The Genus *Lyssavirus* [17]

Genus	Species	Virus name	Acronym
Lyssavirus	*Lyssavirus aravan*	Aravan virus	ARAV
Lyssavirus	*Lyssavirus australis*	Australian bat lyssavirus	ABLV
Lyssavirus	*Lyssavirus bokeloh*	Bokeloh bat lyssavirus	BBLV
Lyssavirus	*Lyssavirus caucasicus*	West Caucasian bat virus	WCBV
Lyssavirus	*Lyssavirus duvenhage*	Duvenhage virus	DUVV
Lyssavirus	*Lyssavirus formosa*	Taiwan bat lyssavirus	TWBLV
Lyssavirus	*Lyssavirus gannoruwa*	Gannoruwa bat lyssavirus	GBLV
Lyssavirus	*Lyssavirus hamburg*	European bat lyssavirus 1	EBLV1
Lyssavirus	*Lyssavirus helsinki*	European bat lyssavirus 2	EBLV2
Lyssavirus	*Lyssavirus ikoma*	Ikoma lyssavirus	IKOV
Lyssavirus	*Lyssavirus irkut*	Irkut virus	IRKV
Lyssavirus	*Lyssavirus khujand*	Khujand virus	KHUV
Lyssavirus	*Lyssavirus lagos*	Lagos bat virus	LBV
Lyssavirus	*Lyssavirus lleida*	Lleida bat lyssavirus	LLEBV
Lyssavirus	*Lyssavirus mokola*	Mokola virus	MOKV
Lyssavirus	*Lyssavirus rabies*	Rabies virus	RABV
Lyssavirus	*Lyssavirus shimoni*	Shimoni bat virus	SHIBV

3. Pathogenesis

A susceptible non-immune host acquires rabies when RABV (or rabies-related viruses) directly penetrates his/its body through the saliva of an infected mammal that bites, scratches, or licks on non-intact skin or intact mucous membranes. There is a possibility of bite and scratch hazards for those who handle animals during birth control program capture events [23]. Furthermore, aerosol transmission of rabies virus is possible (but very rare) in caves with very large bat colonies coupled with extreme humidity, high temperature, and poor ventilation [24]. After it has penetrated the body of a susceptible host, RABV enters a phase of eclipse during which it can replicate in the muscle tissue at the inoculation site, moving from cell to cell (local viral proliferation in non-neural tissue). Then it gains access (viral attachment) to motor endplates (neuromuscular junction) and motor nerve axons [25,26], following the neuronal pathway that protects the virus from the host's immune surveillance, resulting in the absence of an early antibody response. Virions are carried in transport vesicles [27] and travel to the Central Nervous System (CNS) exclusively by fast retrograde transport along motor axons (Peripheral Nervous System – PNS) with no uptake by sensory or sympathetic endings [28]. In the peripheral nervous system, rabies virus receptors are present only on motor endplates and motor axons, since uptake and transneuronal transmission to the CNS occur exclusively via the motor route, while sensory and autonomic endings are not infected. Using retrograde axonal transport, the virus reaches the CNS rapidly spreading through motor and sensory neurons of the spinal ganglia and in the brain, where cytoplasmic inclusions are detectable (Negri bodies). Almost all regions of the CNS can be affected. The brain, spinal cord, and peripheral nerves show ganglion cell degeneration, perineural and perivascular mononuclear cell infiltration, and neuronophagia. Inflammation is most marked in the midbrain and medulla in furious rabies and the spinal cord in paralytic rabies. Virus is recovered from end organs only after the development of rabies because anterograde spread to end organs is likely mediated by passive diffusion, rather than active transport mechanisms. The retrograde dissemination along peripheral nerves carries the virus from the CNS to various organs and tissues, among which the salivary glands, where additional replication induces the virus release into saliva and the possibility of transmission to new hosts, also before the onset of symptoms [20,21]. Acute, widespread dysfunction of the CNS leads to the fatal outcome of the disease, which is an acute encephalomyelitis. The symptoms are related to acute neurological disorders, without pathognomonic signs, accompanied (furious form) or not (paralytic form) by behavioral changes (unusually aggressive or uncharacteristically affectionate), which can also be mild. Anorexia, lethargy, dysphagia, fearfulness, restlessness, fever, vomiting, allotryophagy, urinary difficulty, fecal incontinence, diarrhea, altered vocalization, disorientation, stupor, mydriasis, hyperreactivity to stimuli, loss of fear of humans (in wild animals), aggression are possible symptoms; neuronal dysfunction, flaccid paralysis and the subsequent respiratory and cardiac failure induce the fatal outcome of the infection. Dogs are affected by laryngeal and masseter paralysis inducing altered vocalization and sialorrhea; due to paralysis of the throat muscles, the animal may be unable to swallow (hydrophobia) [19] [29,30,31,32]. The amount of virus in the inoculum, the density of motor endplates at the wound site, and the proximity of virus entry to the CNS affect how long the incubation period takes (typically 2-3 months; rarely more than 1 year). WOAH Terrestrial Code set the duration of the incubation period, corresponding to the asymptomatic phase, is 6 months [30]. Several factors influence the overall outcome of rabies exposure: the host species and the related susceptibility to the specific pathogen, the host's immunological status, the rabies genotype (various strains and mutants) or variant involved, the pathogenicity (apoptogenic and neuroinvasiveness), the route, and the dose of virus inoculated related to the severity of exposure [26]. In the excitement (furious) phase, the prodromal stage is eventually followed by a period of severe agitation and aggressiveness. The animal often bites any material. Rabid dogs, for example, may develop the typical high barking sound during furious rabies. Death may follow convulsions even without the paralytic stage of the disease. The furious form is characterized by restlessness, wandering, howling, polypnea, drooling, and attacks on other animals, people, or inanimate objects. Affected animals often swallow foreign objects, such as sticks and stones. Wild animals frequently lose their fear of humans and may attack humans or animal species they would normally avoid (e.g., porcupines). Nocturnal animals may be visible during the day. In cattle, unusual alertness can also be a sign of this form. In the paralytic (dumb) phase, the throat and masseter muscles become paralyzed; the animal may be unable to swallow, 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. There may also be facial paralysis, or the lower jaw may drop. Ruminants may separate from the herd and can become somnolent or depressed. Rumination may stop. Ataxia, incoordination, and ascending spinal paresis or paralysis are also seen. This stage is characterized by the inability to swallow, leading to the typical sign of foaming saliva around the mouth. Some animals may develop paralysis beginning at the hind extremities. Eventually, complete paralysis is followed by death [26]. After the onset of symptoms, the clinical course is rapid and severe (about a week) with a 100% fatality rate (ratio of deaths to cases x 100, expressed as a percentage); only in 15 human cases survival from clinical rabies has been documented.

4. Reservoirs and Transmission

Bats are the primary or sole reservoir for all *Lyssavirus* except for *Lyssavirus mokola* and *Lyssavirus ikoma*, for which the reservoir species have not yet been clearly identified. The transmission of rabies from bats to a terrestrial mammal is an accidental and rare event and it is classified as spillover. Bats are the main reservoirs of RABV only in America. RABV is widely distributed and responsible for terrestrial rabies with mesocarnivore reservoirs. Rabies is distinguished in two different epizootic cycles based on the reservoirs involved:

- the wildlife cycle, which in Europe has the red fox *Vulpes vulpes* as a reservoir and in the world is maintained by foxes, wolves, jackals, raccoons, and mongoose;
- the urban cycle, which has the dog as the main reservoir and can reach cats, ruminants, and pigs; it can more easily involve humans.

In nature, *Lyssavirus* spp. is found in most parts of the world, and they are associated with specific mammalian reservoirs: carnivores and/or bats. Bats can be asymptomatic, nevertheless, cytoplasmic inclusions Negri bodies and viral antigens have been observed in histological preparations of the brain [33]. Mesocarnivore mammals, such as dogs, foxes, raccoons, and mongoose serve as primary reservoirs independently maintaining the infection cycle, which they can transmit to other mammals and humans. Globally, infected dogs (*Canis lupus familiaris*) cause up to 99% of human rabies cases [14,34]. Humans and some herbivores are dead-end hosts, unable to transmit the infection. Their infection leads to death, blocking the epidemiological chain. RABV infection in rodents is very uncommon. No human rabies cases due to bites by rodents have been reported. RABV can be found in saliva, tears, urine, and nervous tissues of human rabies cases and exposure to these body fluids and tissues carries a theoretical risk of transmission. RABV is not found in blood. Human-to-human transmission of RABV is extremely rare. The only documented cases of human-to-human transmission occurred via tissue and organ transplants from RABV-infected individuals, and a single case of possible perinatal transmission of RABV was described [19].

5. Epidemiology of Rabies in the European Union and Ethiopia

5.1. European Union

In the European Union, 6 different species of *Lyssavirus* circulate among bats. Among these, *Lyssavirus hamburg* (previously known as European bat lyssavirus 1 - EBLV-1) is widely distributed and specifically associated with the common serotine and southern serotine (*Eptesicus serotinus* and *E. isabellinus* in the Iberian Peninsula), for which a spillover case has been observed in France. A case of spillover was reported in June 2020, in a domestic cat in Arezzo (Italy), that died presenting a neurological disease caused by *Lyssavirus caucasicus* (former West Caucasian bat virus - WCBV) hosted in bats living in a neighboring tunnel where the cat used to go [34,35]. Europe hosts 53 different bat species. Rabies in bat is present in Europe and spillovers can occur in terrestrial mammals; consequently, after any contact with bats it is advisable to practice the proper prophylaxis, as bats can bite if handled and bat bites are barely visible. Due to their important role as insectivores and pollinators, European bat species are protected by regulations (Council Directive 92/43/EEC on the conservation of natural habitats and wild fauna and flora; Agreement on the Conservation of Bats in Europe *Eurobats*, 1991) and killing them is forbidden [34]. In rabies-free countries, imported rabies cases involving pets and humans can occur (as seen in Eastern Europe due to the illegal importation of pets, especially from Morocco, due to travels with pets to endemic countries) which, without further spread, do not compromise the country's health status. In 2019, countries of the European Union and the European Economic Area reported 5 human cases of *Lyssavirus* infections, including 4 cases linked to travels in Tanzania, India, Morocco, and the Philippines, reported in Italy, Latvia, Spain, and Norway respectively. While in 2019 the reported cases were the highest since 2007, in 2020 the cases of rabies were reduced to zero with global restrictive measures adopted to counter the COVID-19 pandemic. In 2022, a total of 71 cases of rabies of autochthonous origin in animals other than bats were reported in the EU Member States Poland, Romania, Hungary and Slovakia; Hungary and Slovakia, had not recorded any cases in the previous 5 and 7 years, respectively [36]. These countries border Ukraine, a European country with a high prevalence of rabies and a site of armed conflict [4]. The total number of reported indigenous rabies cases in non-flying animals in the European Union decreased in 2022 compared with 2021 (118 cases) but was higher than in 2020 (12 cases) and 2019 (5 cases). Surveillance data on *Lyssavirus* spp. in bats were reported by 16 EU MSs, with France, Germany, the Netherlands, Poland, and Spain reporting 26 positive results for *Lyssavirus* spp., mainly European bat lyssavirus 1. Switzerland reported a positive result in a bat for European bat lyssavirus 2. A case of rabies was reported in France, involving an illegally imported dog [37].

5.2. Ethiopia

One of the emerging nations with high rabies endemicity is Ethiopia, where rabies is a serious illness that has long existed. Here, nearly 95% of rabies cases are caused by infected dogs. In 1884, the first widespread dog epidemics were documented throughout Ethiopia, particularly in the former districts of Tigre, Begemder, Gojjam, and Wollo. Currently, the highest number of exposures to rabies and human fatal rabies cases were reported from Oromia Regional State, followed by Amhara Regional State. Tigray has no fatal rabies cases thanks to the prophylactic measures adopted in infected people before the onset of symptoms, even though it is the second Region in exposure [38]. The most severe cases occurred in Addis Ababa, where the illness has spread widely and is becoming endemic, as in other major cities of low-income countries. The contact between humans and animals is developing faster, broader, and more significantly. Sylvatic and urban rabies cycles occur concurrently in some regions, while the sylvatic cycle predominates in others. Rabies can be a serious concern for some rare or endangered species in Africa, threatening the Ethiopian wolf (*Canis simensis*) and African wild dogs (*Lycaon pictus*) [26].

6. Diagnosis

Detection of the virus or some of its specific components using WHO and WOAH-recommended standard laboratory tests is the only way to undertake a reliable diagnosis of rabies [34].

Laboratory diagnosis of rabies in animals can be essential for a timely Post-Exposure Prophylaxis (PEP) in humans, which consists of vaccination or vaccination and concomitant immunotherapy in the possible prodromal period started after exposure to the risk of rabies infection. Rabies diagnosis may be carried out either *in vivo* or *post* *mortem* [39], but the infection with the rabies virus can be difficult to diagnose *ante mortem*; diagnosis can only be confirmed by laboratory tests, preferably conducted *post mortem* on CNS tissue removed from the cranium [40].

Although hydrophobia is highly indicative, 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 [41,42].

6.1. Antigen Detection

Any section of the afflicted animal's brain can be used to diagnose rabies. However, tissue from the brain stem and cerebellum, or at least two different parts of the brain, must be tested to rule out rabies [40]. The predominant method employed for diagnosing rabies in animals and humans is the Fluorescent Antibody Test (FAT), a primary tool for antigen detection. Composite brain tissue samples are used for impression smears and subsequently treated with fluorescein isothiocyanate (FITC)-labeled anti-rabies immunoglobulin. The specific aggregates of rabies virus antigen are then identified through their fluorescence, utilizing a reflected light fluorescence microscope. In cases where fluorescence microscopy is unavailable, the Direct Rapid Immunohistochemistry Test (dRIT) is a viable alternative. This method involves streptavidin-biotin peroxidase staining [34].

6.2. RNA Detection

For RNA detection, the Reverse Transcriptase - Polymerase Chain Reaction (RT-PCR) is commonly employed to amplify distinct fragments of viral RNA. Real-time PCR has emerged as a more recent advancement, enhancing sensitivity and expediting results. These techniques boast the highest sensitivity levels in rabies diagnosis [34].

6.3. Antibody Detection

In the realm of antibody detection, serological testing is not utilized for *ante mortem* diagnosis due to delayed seroconversion and high mortality rates in host species. However, it proves invaluable for evaluating seroconversion post-vaccination and conducting epidemiological studies [31]. The gold standard in serological testing is the Virus Neutralization Test, with virus-neutralizing antibody titers directly correlating with protective immunity. This assay is also mandated for international trade and travel with pets, with both the Fluorescent Antibody Neutralization Test (FAVN) and Rapid Fluorescent Focus Inhibition Test (RFFIT) approved for determining virus neutralizing antibody titres. Additionally, Enzyme-Linked Immuno-Sorbent Assays (ELISAs) offer a swift serological test, eliminating the need to handle live rabies virus. These tests detect antibodies binding specifically to rabies virus antigens, primarily focusing on the glycoprotein and nucleoprotein [34].

7. Prevention and Control

Rabies is a globally prevalent and mandatorily notifiable disease, except in bats. Despite the absence of a proven therapy, supportive care remains the primary approach. However, the preventable nature of rabies is underscored by the adoption of Pre-Exposure Prophylaxis (PrEP) – involving vaccination in the absence of prior contact with a rabid or suspected animal – and or Post-Exposure Prophylaxis (PEP) involving vaccination and possibly immunoglobulin administration. They aim to prevent the virus from spreading within the CNS. Unlike many infections, rabies development can be averted through timely immunization, even post-exposure (Table 2), [19,32].

7.1. Human Rabies Prevention

7.1.1. Administering the Appropriate Rabies PrEP

PrEP for workers at higher risk, such as those handling at-risk animals (veterinary staff, other animal handlers, wildlife officers, laboratory employees, and others), involves intradermal vaccine doses on specific days: injection doses to be given on days 0, 7 and 21 or 28 in the deltoid area of the arm in adults (rabies vaccine should not be administered in the gluteal area, as the induction of an adequate immune response may be less reliable) [19,32]. Notably, in some Asian countries, where rabies can be transmitted by processing dog meat, PrEP is administered to slaughterhouse workers [43].

7.1.2. Treating Bite Wounds Locally

Prevention involves avoiding exposure to RABV and rabies-related viruses. In case of exposure, washing the wound with soap and abundant water as soon as possible and for at least 15 minutes, and disinfecting with iodine tincture are needed [19,32].

7.1.3. Reporting of Animal Bites

It is imperative that any individual or animal who has been bitten by or may have come into contact with a rabid or suspected rabid animal promptly notify the local health officer or their designated representative. This immediate reporting is crucial in ensuring the immediate and appropriate response to potential rabies exposure. Furthermore, in cases where a human is bitten by a mammal, it is mandatory to notify the local health officer or their designee without delay. This reporting initiates the assessment of potential human rabies exposures, leading to the formulation of recommendations for rabies PEP. By adhering to these reporting protocols, individuals contribute to the timely evaluation of potential rabies risks and the implementation of necessary preventive measures, emphasizing the importance of public health in the face of potential rabies exposure incidents [44,45].

7.1.4. Administering the Appropriate Rabies PEP

Swift post-exposure vaccination, coupled with proper wound management and simultaneous administration of rabies immunoglobulin (RIG), proves highly effective in preventing rabies, even after a high-risk exposure. The current rabies vaccines utilize RABV grown in embryonated eggs or cell culture, concentrated, purified, inactivated, and lyophilized. These vaccines have demonstrated safety and efficacy, inducing a rapid and robust neutralizing antibody response to the viral glycoprotein, crucial for binding to host cellular receptors [19]. The cost constraints associated with cell-culture-based rabies vaccines for intramuscular administration have led to recommendations favoring vaccine intradermal administration in regions where canine rabies is widespread. This approach serves as an equally safe and immunogenic alternative, addressing financial limitations and logistical challenges. Intradermal administration offers a more resource-efficient solution, requiring less vaccine to complete a full course of PEP. This not only reduces the overall volume of vaccine used but also directly mitigates the associated costs when compared to standard intramuscular vaccination. Importantly, this strategy has gained endorsement from national health authorities in countries facing challenges related to canine rabies. This pragmatic approach acknowledges the importance of vaccination in canine rabies-endemic regions while addressing financial considerations that might otherwise hinder widespread immunization efforts [19,46]. RIG is a crucial component for passive immunization against rabies. It is recommended for a single administration, preferably at the initiation of post-exposure vaccination or as promptly as possible thereafter. Its efficacy diminishes beyond the seventh day after the first vaccine dose, as an active antibody response is presumed to have been triggered by vaccination. Administration of all the available RIG is directed into or around the wound sites. If any residual RIG remains, it should be injected intramuscularly at a location distant from the vaccine administration site. To ensure effective and safe infiltration, the RIG may be diluted to a volume adequate for all wounds. RIG should be administered to all people with category III exposure (Table 2). However, it's noteworthy that human RIG is in limited supply and primarily accessible in industrialized nations. In regions where human RIG is either unavailable or financially burdensome, equine immune globulin preparations stand as an alternative, since they are potent, highly purified, and notably more cost-effective than their human counterparts. Originating from a different species, a slight risk of anaphylactic reactions exists (1 in 45,000 cases) [19,46]. There is serological cross-reactivity within the phylogroups, but not between different phylogroups [18]. Therefore, vaccines against the rabies virus may not provide adequate cross-protection against phylogroup 2 *Lyssavirus* and those that are genetically divergent.

7.1.5. Observing Aggressive Animals or Those That Potentially Caused Exposure to Rabies

Rabid domestic dogs, cats, and ferrets can spread RABV from three to six days before becoming symptomatic, living only a few days after the onset of clinical signs. If a domestic dog, cat, or ferret is healthy 10 days after the incident, it can be concluded that the rabies virus could not have been in its saliva at the time of the presumed exposure of the subject. The animal might still be incubating rabies but would not have transmitted the virus through bites, licking, and scratching. The discontinuation of PEP is considered if the suspect animal, after appropriate laboratory examination or a 10-day observation period starting from the date of the bite, is proven to be free of rabies or is healthy [19,32].

7.1.6. Public Health Education

The prevention and control of rabies depend heavily on regular public education, prudent pet ownership, routine veterinary care and vaccination, and ongoing professional development. By raising public awareness of rabies transmission routes, and reducing interactions with wild animals, most rabies exposures in humans and animals can be prevented. Any such exposures must be quickly identified and reported to local public health authorities and medical professionals [44].

7.2. Stray Animals

Stray animals are unowned domestic animals, especially pets like dogs and cats [47]. The proliferation of stray animals has turned into a global problem that requires immediate attention to manage their number.

Table 2. Post-Exposure Prophylaxis (PEP) by Category of Exposure

CATEGORY I EXPOSURE	CATEGORY II EXPOSURE	CATEGORY III EXPOSURE
Touching or feeding animals, animal licks on intact skin (no exposure)	Nibbling of uncovered skin, minor scratches, or abrasions without bleeding (exposure)	Transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from animal licks, exposures due to direct contact with bats (severe exposure)
Washing of the exposed skin surfaces No PEP required	Wound washing and: 2-sites Intra Dermal (deltoid and anterolateral thigh) administration on days 0, 3 and 7 or 1-site Intra Muscle (deltoid region) administration on days 0, 3, 7 and between day 14-28 or 2-sites Intra Muscle administration on days 0 and 1-site Intra Muscle administration on days 7, 21 Rabies Immuno Globulin is not indicated	Wound washing and: 2-sites Intra Dermal (deltoid and anterolateral thigh) administration on days 0, 3 and 7 or 1-site Intra Muscle (deltoid region) administration on days 0, 3, 7 and between day 14-28 or 2-sites Intra Muscle injection on days 0 and 1-site Intra Muscle administration on days 7, 21 Rabies Immuno Globulin administration is recommended

The relevant authorities must create and implement animal rights legislation to successfully manage stray animal populations and the issues they bring about in a community or environment. The management, welfare, nutrition, housing, medical attention including vaccinations and treatments, and legal rights of stray animals must all be covered by the law [48]. Surgical neutering, also referred to as sterilization, and non-surgical contraceptive methods are the most widely used methods for reducing the number of stray animals.

7.3. Suspected Cases and Infected Animals

A suspected case in domestic and wild mammals is defined by:

- a susceptible animal showing any alteration in behavior followed by death within ten days;
- an animal showing one of the following clinical symptoms: hypersalivation, paralysis, lethargy, abnormal aggressiveness, and altered vocalization [30]. Any mammal that is bitten, scratched, or comes into direct contact with a wild mammal that cannot be tested for rabies should be assumed to have been exposed to the disease. All types of livestock, including horses, cattle, sheep, goats, llamas, alpacas, and pigs are prone to contracting rabies. The livestock species where rabies is most frequently diagnosed include cattle and horses. It is recommended to euthanize unvaccinated livestock that has been bitten by - or exposed to - a rabid or possibly rabid animal [44].

7.4. Control of Rabies in Wild Animals

The key to preventing rabies is to keep wild animals out of areas where people and domestic animals live and work, as well as to avoid contact with any wild animals that could be rabid. For a disease to be effectively prevented, the large public must be educated on the risk and fatality of rabies transmission through wild animals. With varying degrees of effectiveness, rabies has been stopped from spreading to raccoons, coyotes, and foxes in other countries by immunizing wildlife through the Oral Rabies Vaccination (ORV), consisting of mass distribution of vaccine-impregnated oral baits [44]. Since 1978, in the European Union, where red foxes are the main reservoirs, ORV has been successfully conducted. It provided a new perspective on the control of wild rabies, avoiding the previous culling of foxes which led to the creation of a biological vacuum in which the entry of foxes from nearby endemic territories caused the continuous reintroduction of the infection. Instead, vaccinated foxes preside over the territory without being infected (Mazzeo A., unpublished data), [49]. For ORV, vaccines with attenuated live viruses are used and distributed twice a year, placed inside baits typically made of fishmeal, fat, and paraffin, resistant to impacts and deterioration. Baits must be placed in all potential fox habitats; aerial distribution via plane or helicopter is the most efficient method, complete with manual distribution. Vaccine baits should contain a biomarker (usually tetracycline, detectable in teeth) to monitor the bait uptake in the target species. The distribution of baits is accompanied by monitoring the vaccine's stability and intake to assess the protection of the fox population, which must be vaccinated at least 70% to end transmission [50].

7.5. PrEP in Animals

Mass vaccination of dogs is the most cost-effective intervention to control and eliminate canine rabies. However, successful rabies control also depends on measures such as managing the dog population, mainly by promoting responsible dog ownership; compulsory notification of rabies in humans and animals; ensuring the availability of reliable diagnostic procedures; conducting *post mortem* examinations to confirm the cause of death in people suspected to have been infected with rabies; and improving coordination between all public sectors involved in rabies control [44,45]. The vaccinations can be given to puppies as young as three months old. Regardless of the initial vaccine's length of immunity, all dogs and cats should receive a second immunization within 12 months after the first. After that, revaccination is required every three years. To ensure sufficient immunity to the virus, a booster shot should be given right away after coming into contact with a rabid animal. Depending on the recommendations of the vaccine producer, cattle and sheep may be immunized annually or every two to three years. Animals without obvious bite wounds should be vaccinated after an outbreak in domestic livestock [51].

7.6. PEP in Animals

An animal that was not previously infected or vaccinated and was exposed to rabies may benefit from receiving five doses of the canine rabies vaccination on days 0, 3, 14, 21, and 35, as well as a day 0 injection of murine anti-rabies antibodies. Regardless of the animal's age at the time of the first vaccine, a booster shot should be administered one year later. If the animal exhibits symptoms (paralysis, convulsions, etc.) indicative of rabies, it should be euthanized, and the skull sent for examination [52,53].

7.7. Preventing and Managing Outbreaks

Humans, domestic animals, and wildlife are all at serious risk from the creation of new rabies virus variations or the entry of foreign viruses [54]. The following actions are essential parts of a prompt and thorough reaction: virus genotyping carried out through the National Reference Laboratory; detection of the sources of viruses introduction; increased monitoring of infection in domestic and wild animals; increased vaccination coverage for pet, livestock and wild animals; limited animal movement; vector population reduction, in particularly stray dogs; large public and professionals' engagement; interagency communication and actions [12].

8. Discussion

Rabies is a neglected viral disease: it kills an estimated 59,000 people each year - with approximately half of cases in children under 15 years of age - in more than 150 countries and territories, mainly (95%) poor and marginalized communities in Africa and Asia, where costly treatments that could prevent death are limited. Due to underreporting and uncertain estimates, this number is likely a gross underestimate. In addition to human deaths, it causes excessive livestock losses annually, affecting food security and farmer livelihoods [55,56]. The lack of effective control of canine rabies in developing countries is often attributed to low prioritization, epidemiological and operational constraints, and insufficient financial resources [57]. Ethiopia has the second-highest burden of zoonotic diseases in Africa, following Nigeria. Dependence on traditional medicinal plants, poor treatment-seeking behaviour, and considering first aid as an antiviral treatment are among the key factors contributing to human rabies cases in Ethiopia, where since 2015 the Ethiopian zoonotic disease prioritization targeted rabies, anthrax, brucellosis, leptospirosis, and echinococcosis as the top five zoonoses [58]. Nevertheless, rabies knowledge is poor, health facilities do not keep bite records, there is poor recording and reporting of rabies cases, delivery of PEP is inadequate, and communication and collaboration between the public and animal health sector are poor to non-existent [59]. In 2019, *Gavi*, the Vaccine Alliance that helps vaccinate more than half the world's children against deadly and debilitating infectious diseases, included human rabies vaccines in its Vaccine Investment Strategy 2021–2025, which would support scaling up rabies PEP in *Gavi*-eligible countries. The COVID-19 pandemic meant several new *Gavi* vaccine programmes - including rabies - had to be paused, however, the *Gavi* Board decided in June 2023 to reactivate those programmes. Planning to roll out human rabies vaccines has now started [46]. In 2021, 2,771 deaths for rabies were reported [60]. Recently, Quadripartite included dog-mediated rabies in the priority areas in the group of "neglected zoonotic diseases (NZDs)", as they mainly affect poor and marginalized populations, particularly in low-income countries. Despite NZDs persistently circulating, they are rarely targeted by formal surveillance systems, so incidence and burden are greatly underestimated. This, in turn, leads to neglect by policymakers and funding agencies. *One Health Joint Plan of Action 2022-2026* builds and complements existing and ongoing initiatives, including:

- Zero by 30: the global strategic plan to eliminate human deaths from dog-mediated rabies by 2030;
- countries supported in establishing WOAH-endorsed national control programmes for identified rabies;
- advocate the use of tools, services, and guidance provided by international expert groups and networks, such as the United Against Rabies Forum working groups;
- increased the uptake and use of available educational material and resources, such as the Open WHO One Health Rabies course;
- facilitate communication between stakeholders and partners, and use of synergies (such as partnership mapping) [61].

Furthermore, the Global Alliance for Rabies Control (GARC) developed the *Stepwise Approach towards Rabies Elimination* (SARE), a practical tool useful in planning, refining, monitoring, and evaluating the national rabies control programs in a One Health perspective. In SARE, countries endemic for dog-transmitted rabies are in Stage 0, characterized by little or no data availability; adopting and refining their control programs, countries can progress up to Stage 5, characterized by freedom from dog-mediated rabies [62]. To reach the best stage, an effective intersectoral collaboration between human and animal sectors is needed: information regarding canine vaccination coverage, pet dog registration, the total number of dogs fully recognized is of utmost importance and interdependent, as reported previously [57,63]. The education of citizens plays an important role [64], as focused on the strategy that will guide stepwise reduction of rabies burden through enhanced surveillance, prevention of rabies in dogs, prevention of rabies in humans, and education/advocacy. The strategy is based on activities planned in accordance with SARE tool to move from an endemic state to a disease-free status [65]. Attempts should also be directed to develop safe, effective, and low-cost single dose vaccines that can be easily affordable by poor resource nations [66]. Furthermore, new vaccines should be developed since the existence of *Lyssavirus lagos* virus in Ethiopia, which could cause the occurrence of rabies in vaccinated dogs (current vaccination is not protective against the virus) [67]. FAO supported interventions including a series of community-level rabies awareness campaigns in different parts of the country, accompanied by pilot dog vaccination programmes, involving 357,617 dogs. Nonetheless, the overall rabies vaccination coverage is still very low, estimated to be five percent of the total dog population, far below the 70% needed to halt the transmission of canine rabies. *Awareness Social and Behavior Change Communication* materials were developed and disseminated to sub-national levels and wider communities during mass dog vaccination campaigns, but greater efforts and investments are required to scale up these pilot activities [68,69]. The cost-effective ORV in stray dogs and in guard dogs for livestock has not been experimented or planned in Ethiopia yet, although it could be highly effective considering the significant presence of stray dogs in urban areas and the entity of rabies in rural areas [70,71,72,73]. ORV could be easily monitored [74]. The concepts of biological vacuum indicate that an empty area quickly attracts wandering animals and repopulates rapidly. This phenomenon disrupts control schemes based on reducing the number of settled animals. In the absence of well-organized actions to combat canine stray, the reduction of stray dogs can lead to a precipitous influx of animals from surrounding areas. The presence of vaccinated stray dogs and guard dogs for livestock could prove useful in creating a natural protective barrier, effectively safeguarding the territory from the entry of rabid wild animals. The ethology of canids and their ability to be vigilant and intimidate predators lead them to drive away extraneous animals [75]. Vaccinated stray and guard dogs can then oversee the territory without being infected, as occurred in Europe during the Oral Rabies Vaccination (ORV) campaigns targeting *Canidae* such as foxes and wolves (Mazzeo, A., unpublished data). Furthermore, the adoption of a low coverage vaccination regimen could be useful for the conservation of species at risk of extinction [76].

9. Conclusions

The One Health era entails a new approach to zoonoses, where every possible link in the epidemiological chain enabling the transmission of zoonotic agents must be considered to outline solutions to the specific problem, in an atmosphere of close interdisciplinarity and collaboration from the local level up to the international one. The One Health approach is crucial to tackling rabies, as this zoonosis involves humans, flying, and terrestrial mammals including bats, pets, livestock, stray animals, and wildlife; furthermore, it concerns urban, rural, and natural environments, spanning from low-income to high-income countries. Prevention of rabies necessitates addressing all connection points among these categories, in accordance with the specific characteristics of the place. In Ethiopia, considering the geographical and economic features, animals, and rabies viruses present, it would be necessary to integrate current exceptional actions also experiment a new strategy that takes into account the longstanding issue of stray dogs (costly to resolve) and the potential contact between stray and wild animals or bats, leading to possible rabid infections caused by bat-associated rabies viruses (*Lyssavirus lagos*) that could affect also vaccinated dogs. Substantial economic efforts and scientific support are therefore necessary:

- to develop new vaccines for the bat-associated rabies viruses present in Ethiopia;

- to start the cost-effective ORV in stray dogs and guard dogs for livestock, and to test it correlating human and dog rabies infections with the involved genotypes (including bat-associated rabies viruses) and the intake of vaccine baits.

Since vaccination of dogs with owners covers a low percentage due to the costly PEP, the use of the less expensive ORV in stray dogs in urban areas could reduce the risk of rabies transmission in dogs with owners and humans. Furthermore, in rural areas, ORV for guard dogs - which have the attitude to repel attacks of foreign animals that could be rabid, without being infected - could save humans, livestock, and farmer livelihoods. Urban and rural inhabitants should be engaged and educated on the administration of baits.

Statement of Competing Interests

The authors have no competing interests.

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