**Title: Study of pathological, etiological, epidemiological, control, prevention, and treatment findings in rabies: A systematic review with a policy approach**

**Running Title: An update on our understanding of rabies**

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## Abstract

Rabies, a fatal viral disease of the central nervous system (CNS) that is transmitted to humans through the saliva of infected animals, primarily through dog bites, has always been a significant public health challenge in many countries, especially in developing regions. In this study, we aimed to comprehensively review the pathological, etiological, and epidemiological findings and ways to control, prevent, and treat rabies. In this regard, an extensive search was conducted across reputable international databases, including Google Scholar, PubMed, Scopus, and Web of Science, using keywords related to rabies from January 2020 to December 2024. The inclusion criteria included original studies that examined different aspects of rabies. Finally, of the 1257 articles identified by keywords, 159 were selected for full-text analysis based on titles and abstracts, and 37 eligible studies were selected for comprehensive analysis. The findings showed that the rabies virus is a Lyssavirus, and its pathogenesis mechanism involves targeting neurons and causing acute encephalomyelitis. Epidemiologically, more than 95% of human rabies deaths occur in Asia and Africa, and dogs are responsible for transmitting 99% of human rabies cases. In the control and prevention section, vaccination of domestic and stray dogs was identified as the most effective method. In the field of post-exposure prevention, immediate wound washing with soap and water for 15 minutes, and the use of rabies serum and vaccine are essential. Consequently, despite significant advances in vaccination and post-exposure prophylaxis protocols, rabies remains a serious threat, and implementing integrated control programs in dog populations, increasing public awareness, and equitable access to prevention services, especially in underserved areas, are key to eliminating this disease.

**Keywords:** Control, Epidemiology, Lyssavirus, Pathology, Rabies

## 1. Context

Rabies is one of the deadliest zoonotic diseases and is a serious threat to public health worldwide. This viral disease targets the CNS and is fatal in almost 100% of cases if clinical symptoms occur. Although rabies is a preventable disease, tens of thousands of people die from the disease every year, mainly in poor and rural communities in developing countries [1, 2].

The causative agent is a virus of the genus Lyssavirus, family Rhabdoviridae. This virus has a negative-sense single-stranded RNA genome and can infect a wide range of warm-blooded mammals, including humans (Figure 1). The virus is transmitted to a new host through the saliva of an infected animal, mainly through a bite. After entry, the virus travels through peripheral nerve endings to the CNS, ultimately causing acute encephalomyelitis [3, 4].

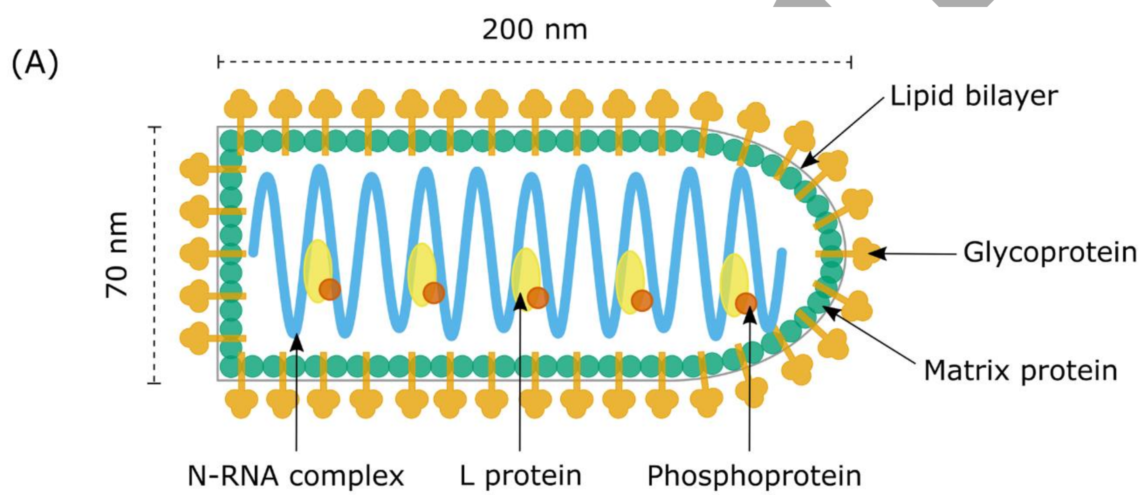


**Figure 1.** Rhabdovirus structure and genome organization (MDPI Copyright, 2023) [5].

Epidemiologically, the disease's main burden lies in Asia and Africa. According to the World Health Organization estimates, more than 59,000 human deaths from rabies occur annually, of which about 99% are due to bites by rabid dogs. Children under 15 years of age are disproportionately affected by the disease, as they are more susceptible to dog bites and often suffer more severe injuries [6, 7].

The approach to controlling the disease is multifaceted. It includes control of the animal reservoir, pre-exposure prophylaxis for high-risk groups, and, most importantly, post-exposure prophylaxis

(PEP) for individuals exposed to animals suspected of having rabies. Immediate and thorough washing of the wound with soap and water, along with timely administration of the vaccine and, in cases of severe exposure, rabies-specific immunoglobulin, constitute the basis of post-exposure prophylaxis [8, 9].

Despite the availability of practical prevention tools, there are significant challenges on the path to eliminating human rabies transmitted by dogs. These challenges include a lack of public awareness, inadequate access to health services, especially in remote areas, the high cost of required biologicals, and weak surveillance systems to control dog populations. Therefore, a comprehensive and up-to-date understanding of all aspects of this disease is essential for designing effective control and elimination strategies. Hence, the current study aims to review and integrate the most comprehensive and latest scientific evidence on the pathological, etiological, epidemiological aspects, as well as control, prevention, and treatment strategies of rabies, to provide a clear and complete picture and serve as a reference for researchers and policymakers in the field of health to formulate and implement effective strategies to reduce the economic, psychological, stress, and risk factors caused by this disease.

## 2. Data Acquisition

The present work is a systematic review conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol to ensure comprehensiveness and transparency throughout the review process [10, 11]. An initial and extensive search was conducted to identify relevant articles published between January 2020 and December 2024 in reputable international databases, including PubMed, Scopus, Web of Science, and Google Scholar, using key English-language keywords. The main keywords used were: "Rabies", "Lyssavirus", "Epidemiology", "Pathogenesis", "Prevention", "Control", "Vaccination", and "Post-Exposure Prophylaxis". These keywords were used alone or in combination with Boolean operators (AND, OR) to maximize search sensitivity. Finally, of the 1257 articles identified by keywords, 159 were selected for full-text analysis based on titles and abstracts, and 37 eligible studies were selected for comprehensive analysis.

After the initial collection of articles, the screening process was carried out in two stages: title-abstract and then full text, considering predefined inclusion and exclusion criteria. Inclusion criteria were studies published in English that investigated the pathological, etiological, epidemiological, control, prevention, or treatment aspects of rabies in humans or animals. This range included observational studies, clinical trials, case reports, and case series. In contrast, articles that were available only in abstract form, duplicate articles, studies that did not provide sufficient data for extraction, or texts that were not relevant to the objectives of this review were excluded from the review process.

Finally, key data, including author, year of publication, country of study, study type, objectives, methodology, study population, main findings related to pathology, epidemiology, control and prevention strategies, and treatment outcomes, were extracted from each of the selected articles and recorded in a pre-designed data collection form. The extracted data were then analyzed qualitatively and by narrative synthesis. At this stage, the findings were categorized into main and sub-themes to provide a comprehensive, structured view of the latest evidence across all aspects of rabies. This systematic approach provided a solid basis for conclusions and practical recommendations grounded in evidence.

## 3. Results

### 3.1.Pathological

Reviewed studies have conclusively shown that the rabies virus, with its strong affinity for cells of the nervous system, causes an acute and almost always fatal encephalomyelitis [12-19]. After entry through a wound, the virus remains at the wound site for a variable period, then ascends through neural pathways to the CNS via retrograde axonal transport. Virus replication occurs primarily in neurons, leading to neuronal destruction, inflammation of the nervous tissue (formation of Negri bodies), and gliosis. Notably, the virus employs multiple mechanisms to evade the host immune system and prevent apoptosis of infected cells (Figure 2). The clinical pathology of the disease manifests in various forms, including the metallic form (mostly with symptoms of flaccid paralysis) and the furious form (with symptoms of hyperactivity, hallucinations, and fear of water), and ultimately leads to the death of the patient due to brainstem involvement and acute respiratory and cardiac failure.

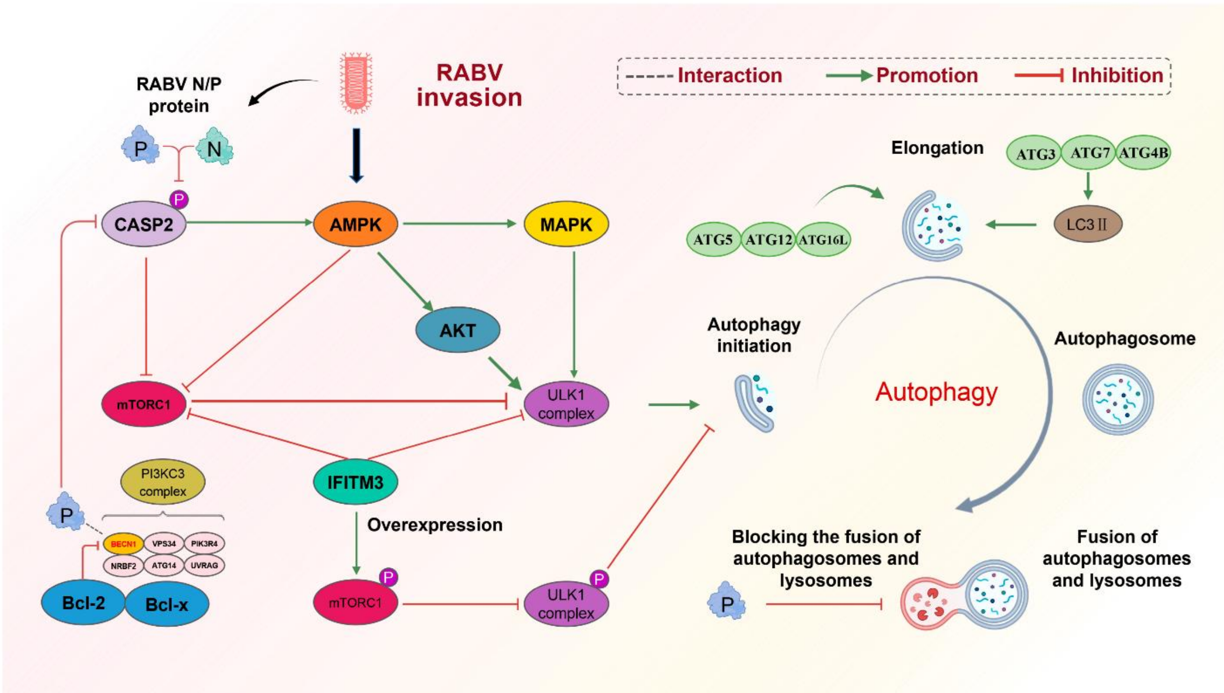


**Figure 2.** Mechanism of RABV-induced incomplete autophagy. (1) RABV activates the initiation of autophagy. RABV activates the AMPK signaling pathway upon invasion. On the one hand, activated AMPK inhibits mTORC1, thereby blocking mTORC1-mediated inhibition of the ULK1 complex. On the other hand, AMPK can positively regulate AKT and MAPK, thereby activating the ULK1 complex and initiating autophagy. In addition, the P protein of the rabies virus binds to Beclin1 in the PI3KC3 complex, reducing CASP2 phosphorylation and thereby positively regulating the AMPK signaling pathway and negatively regulating the mTORC1 signaling pathway, which initiates autophagy. (2) RABV prevents the fusion of autophagosome and lysosome: the P protein of RABV binds to Beclin1, wraps immature autophagosomes, inhibits the fusion of autophagosome and lysosome, and blocks the degradation of autophagosomes. (3) IFIM3 was able to directly inhibit the ULK1 complex and promote mTORC1 phosphorylation, indirectly inhibiting the ULK1 complex. Blocked the initiation of autophagy induced by RABV invasion (MDPI Copyright, 2024) [20].

### 3.2.Etiology

The etiology of rabies is clearly related to a virus of the genus Lyssavirus and the family Rhabdoviridae (Figure 3). This virus is a single-stranded, negative-sense RNA virus with a lipid envelope. Studies show that there are several genotypes of this virus, with genotype 1 (classical rabies virus) responsible for more than 99% of human and animal cases worldwide [21-23]. The main reservoir and host of the virus in nature are carnivorous and warm-blooded mammals, and dogs alone play a dominant role in the urban and human transmission cycle. Although in the wild, animals such as foxes, jackals, raccoons, and vampire bats also act as reservoirs and vectors. The definitive and main route of transmission is through the bite of a rabid animal and the transfer of infected saliva. However, contact of mucous membranes (e.g., eyes, nose, mouth) or open wounds with infected saliva can also lead to disease.

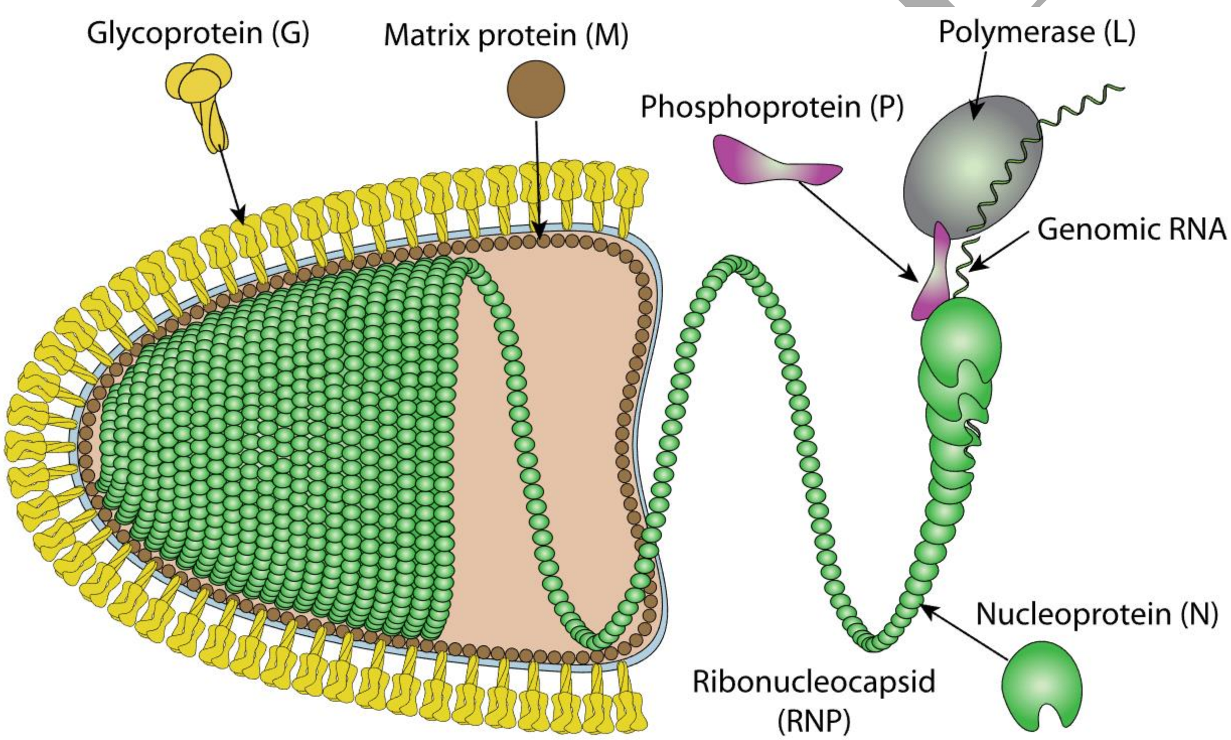


**Figure 3.** Lyssavirus is a genus of ssRNA viruses in the family Rhabdoviridae that infect neurons of mammals. Rabies virus (RabV) infections in humans are associated with fatal rabies encephalitis. Enveloped, bullet-shaped. 180 nm long and 75 nm wide. (Original source of the image: Philippe Le Mercier, SIB Swiss Institute of Bioinformatics) [24].

### 3.3.Epidemiological

Epidemiologically, rabies is a disease with a global distribution but with a disproportionate burden in developing countries, with more than 95% of human deaths from rabies reported in the continents of Asia and Africa [25-30]. Approximately 59,000 human deaths occur annually from this disease, with about 40% of victims being children under 15 years of age. In Iran, although the situation is more favorable than in many of its neighbors, the disease persists as endemic foci, especially in the northern, northwestern, and southeastern regions of the country, and stray and herding dogs play a significant role in transmitting the disease to humans and livestock (Figure 4). Lack of awareness, inadequate access to health services, and weakness in dog vaccination programs are the most important social determinants affecting the epidemiological pattern of the rabies.

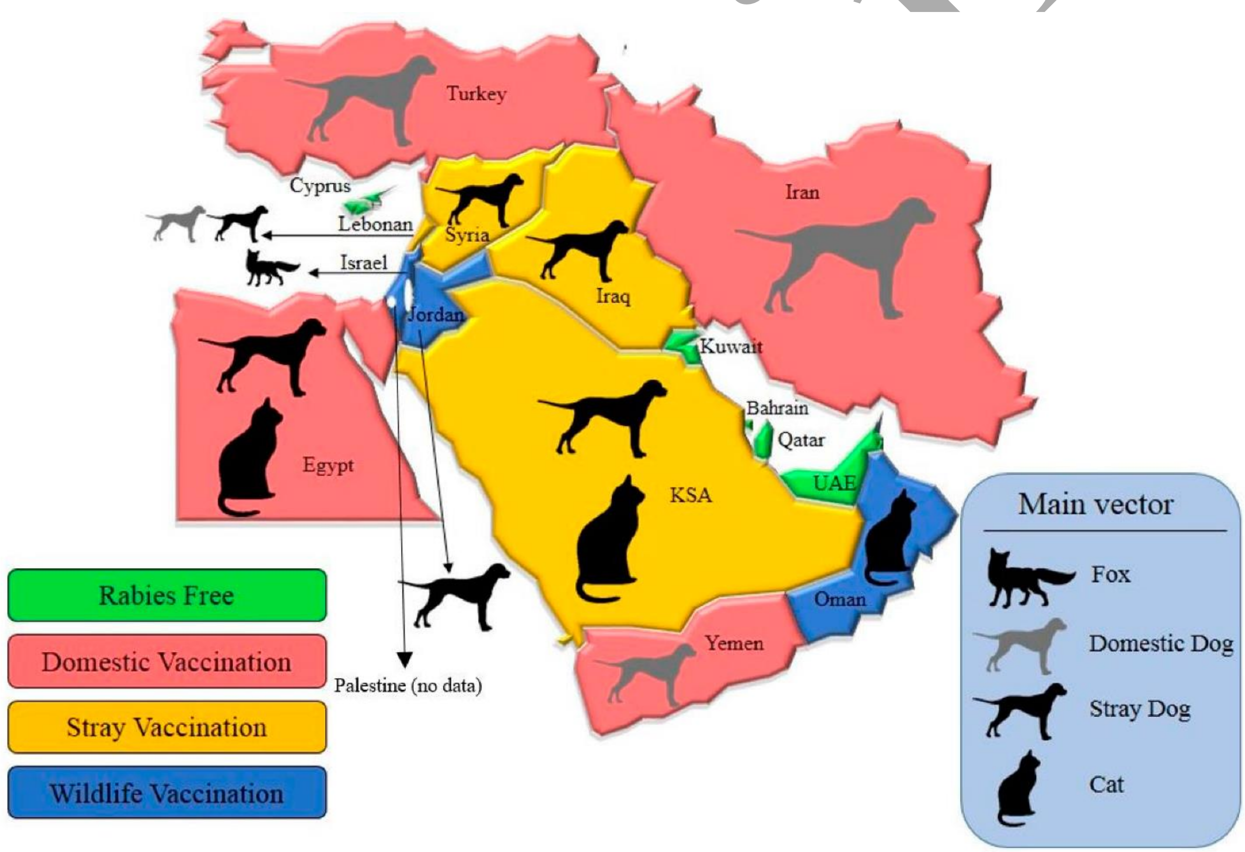


**Figure 4.** Countries are classified into four different rabies groups based on available data (MDPI Copyright, 2018) [31].

### 3.4.Diagnosis

The diagnosis of rabies at different stages requires different approaches and can generally be divided into two stages: diagnosis in the attacking animal and diagnosis in humans [32-34]. In cases of bites, examination of the attacking animal is of utmost importance, as the results will determine whether to initiate post-exposure prophylaxis (PEP) for the affected person. In live animals, saliva, cerebrospinal fluid, or a skin biopsy from the back of the neck (which contains nerve hair follicles) is collected for molecular testing, such as RT-PCR. However, the gold standard and definitive method for diagnosing rabies is the examination of the animal's brain tissue. In this method, the animal's brain is subjected to a direct immunofluorescence test (FAT) to detect Negri Bodies, specific inclusion bodies of rabies infection [35]. The FAT test, with its very high sensitivity and specificity, is considered the gold standard for diagnosis worldwide.

In humans, the definitive diagnosis of rabies is unfortunately often made after death by autopsy and examination of brain tissue by FAT or PCR [36]. However, during the course of the disease and before death, a set of highly suspicious clinical signs (such as hydrophobicity, altered consciousness, irritability, and autonomic signs) in conjunction with a history of exposure to an animal is the basis for the clinical diagnosis. To confirm the antemortem diagnosis, samples of saliva, cerebrospinal fluid (CSF), skin biopsy from the back of the neck, and serum are collected from the patient. In saliva and CSF, the viral genome can be detected by RT-PCR. In a skin biopsy, the viral antigen can be detected in the nerve endings around the hair follicles by immunofluorescence staining. Also, testing the patient's serum for neutralizing antibodies to the rabies virus in the CSF (rather than in the blood) can be diagnostic, as antibody production in the central nervous system is a definitive sign of infection. However, negativity in these tests does not rule out infection, and the final diagnosis is often based on a combination of epidemiological, clinical, and laboratory findings.

### 3.5.Control

In disease control, the most effective and cost-effective strategy is to interrupt the cycle of virus transmission from dogs to humans by mass vaccinating at least 70% of the dog population [14, 27, 37-39]. Numerous studies have confirmed the high effectiveness and high economic justification of this method in eliminating urban rabies. In addition, controlling the stray dog population through ethical and scientific methods, registering and certifying domestic dogs, and quarantining invasive animals are complementary elements of control programs. Establishing active, coherent surveillance and monitoring systems for rapid detection of animal and human cases, and performing accurate diagnostic tests (Figure 5) on suspect animals, is crucial for assessing the success of control programs and for timely identification of disease foci.

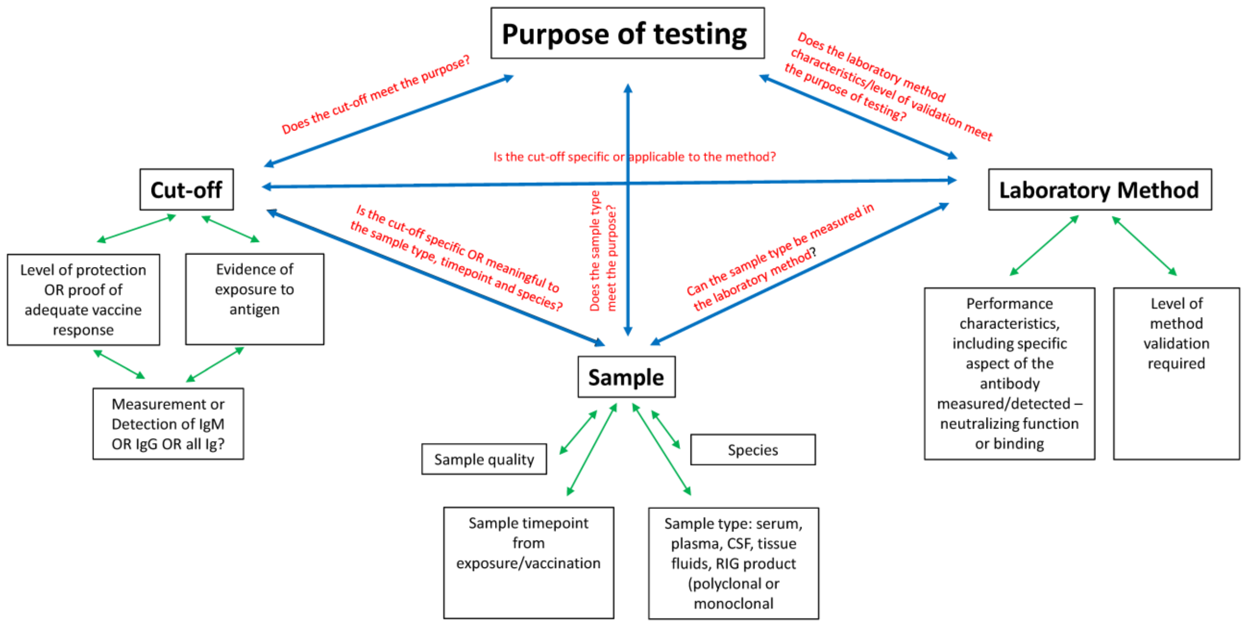


**Figure 5.** Factors affecting rabies serology interpretation and influences on the main issues of cut-off level, laboratory method, and sample (MDPI Copyright, 2021) [40].

### 3.6.Prevention

Rabies prevention has two main dimensions: pre-exposure prophylaxis for high-risk groups such as veterinarians, laboratory workers, and travelers to endemic areas, and PEP [41-44]. Immediate, thorough washing of the wound for at least 15 minutes with clean water and soap, or with a virucidal disinfectant, is the most important and effective step in reducing the risk of infection. According to WHO guidelines, the PEP regimen includes administering the vaccine on days 0, 3, 7, 14, and 28, and, in cases of third-degree exposure (bite, deep wounds, or contact with mucous membranes), simultaneous injection of rabies immunoglobulin (RIG) around the wound. Newer-generation vaccines based on cultured cells are highly immunogenic and have fewer side effects.

### 3.7.Treatment

Unfortunately, once clinical signs of rabies appear, there is no effective and definitive treatment, and the disease is almost always fatal [15]. All treatment measures at this stage are purely supportive and palliative, and include intensive care unit admission, induction of coma, use of anticonvulsant and antipsychotic drugs, and maintenance of vital body functions. The Milwaukee protocol, which combines induction of coma with ketamine and midazolam and the administration of antiviral drugs, is the only one to have led to survival in a few patients. However, its reproducibility has not been demonstrated in subsequent studies, and it has not been accepted as a standard treatment. Therefore, the focus of health systems should be on timely and effective prevention, primarily by ensuring strict adherence to the PEP regimen, since treatment initiated after symptom onset remains a significant challenge and is often unsuccessful [45-47].

## 4. Conclusion

The findings of this review clearly confirm that rabies remains a significant and unresolved public health challenge, especially in developing countries. Although the pathological and etiological mechanisms of the disease are well understood, there is a deep gap between scientific knowledge and the implementation of effective control strategies at the field level. The results of this review demonstrate that, despite its lethality, rabies is entirely preventable, underscoring the need to address implementation barriers.

From a pathological perspective, a detailed understanding of the virus's transmission routes in the nervous system and mechanisms of immune evasion could pave the way for the development of new therapeutic approaches. Although recent advances in laboratory therapies have been promising, there is still a long way to go before a definitive and reliable cure for symptomatic patients is achieved. The fact that the virus uses complex mechanisms to prevent apoptosis of infected cells explains how it can spread through the nervous system without provoking a strong immune response.

From an epidemiological perspective, the geographic concentration of more than 95% of deaths in Asian and African countries reflects profound inequalities in access to health services and prevention resources. This epidemiological pattern clearly demonstrates that rabies is a disease associated with poverty and that combating it requires a multidisciplinary approach and attention to the social determinants of health. The shocking number of deaths in children under 15 years of age also underscores the need for targeted educational programs in schools and local communities.

In the area of control, strong evidence suggests that mass vaccination of dogs is the most effective and cost-effective strategy. However, there are many practical challenges to implementing this strategy in disadvantaged areas, including limited financial resources, inadequate veterinary infrastructure, and insufficient political will. The successful experiences of some countries in eliminating rabies through widespread dog vaccination demonstrate that this goal is achievable, provided adequate resources are allocated, and long-term commitment is made.

In the field of prevention, the availability of safe and effective vaccines is a significant strength. However, several barriers, including the relatively high cost, the need for multiple injections, and the unavailability of immunoglobulin in many health facilities, prevent the proper completion of the PEP protocol. Immediate wound irrigation, as the simplest and most effective intervention, requires widespread public awareness, especially in high-risk communities.

In the field of treatment, the Milwaukee protocol's failure to reproducibly yield results has posed a serious challenge to researchers seeking to develop an effective treatment for symptomatic rabies. This failure highlights the importance of investing more in basic research into viral pathogenesis and of focusing on prevention. In the near future, new therapies based on novel technologies such as RNA interference or monoclonal antibodies will likely be investigated.

Ultimately, successful control and elimination of rabies require a “One Health” approach that coordinates the human, veterinary, and environmental health sectors. Establishing integrated surveillance systems, strengthening diagnostic laboratories, and developing international partnerships to provide resources and facilitate technology transfer are essential components of this approach. Only through cross-sectoral collaboration and sustained political commitment can the WHO goal of eliminating human rabies from dog bites by 2030 be achieved.

Although rabies is preventable, it still kills tens of thousands of people each year due to deep structural challenges in health systems in developing countries. The review found that successfully controlling this deadly disease requires a combination of three main strategies: first, widespread implementation of dog vaccination as the most effective strategy to break the chain of transmission; second, ensuring equitable and timely access to post-exposure prophylaxis services, including wound debridement, timely vaccination and immunoglobulin administration for those at risk; and third, strengthening surveillance and laboratory systems under a One Health approach. Investing in community education through awareness-raising campaigns and social media; regular and organized planning through partnerships and collaboration between the public and the government (municipalities, veterinary and quarantine departments, and health departments) to identify and vaccinate stray and herd dogs; and encouraging applied research into new diagnostic, preventive, and therapeutic approaches are other essential components of this effort. Eliminating rabies, while challenging, is entirely achievable with strong political will, adequate resource allocation, and intersectoral collaboration. Achieving this goal would be an important step towards health equity and improving global health.

**Declarations and statements**

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None

**Author contribution**

Conceptualization: [S.R.A.], …; Methodology: [All Authors], …; Formal analysis and investigation: [S.R.A.], …; Writing - original draft preparation: [All Authors]; Writing - review and editing: [M.Gh., S.R., M.S.], …; Funding acquisition: [Self-funding], …; Supervision: [S.R.A.]. All authors checked and approved the final version of the manuscript for publication in the present journal.

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The authors declare no conflict of interest.

**Ethical approval:**

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**Data availability:**

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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