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Rabies in animals with emphasis on dogs and cats compared to humans

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Abstract

Despite over four thousand years of recognition and the availability of effective vaccines, rabies kills 59,000 people annually. Once clinical signs appear, the disease is always fatal. With urbanisation and changing patterns of human–animal contact, the role of dogs as the primary reservoir and the growing role of cats as spillover hosts in urban settings require updated evaluation. This review aimed to assess published evidence on rabies in animals and humans. A systematic search was conducted across five databases using terms including Rabies, carnivorous, zoonosis, post-exposure prophylaxis (PEP), and catch-neuter-vaccinate-release (CNVR). Inclusion criteria: original studies, systematic reviews, meta-analyses, and case reports. Exclusion criteria: studies with poor methodology and duplicate publications. Dogs account for > 99% of human rabies deaths in endemic countries. In some locations, cats are responsible for more human exposure incidents than dogs. The direct fluorescent antibody test remains the diagnostic gold standard; however, its sensitivity drops below 70% with degraded tissue. The direct rapid immunohistochemistry test is an alternative for low-resource settings. PEP is approximately 100% effective when administered correctly; failures are linked to delayed initiation or incorrect rabies immunoglobulin infiltration. Mass dog vaccination at ≥ 70% coverage, combined with CNVR, universal PEP access, and integrated epidemiological surveillance in a One Health framework, is the pathway to achieving Zero by 2030. Incorporation of cat vaccination into national rabies control programmes is urgently needed.

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Introduction

Rabies is a fatal, vaccine-preventable viral zoonosis that continues to kill tens of thousands of people every year, despite more than a century of effective post-exposure prophylaxis. This review focuses on rabies in animals, with particular emphasis on dogs and cats as the principal sources of human exposure, and compares the epidemiology, clinical course, diagnosis, and management of the disease in these species with its presentation in humans. In the Laws of Eshnunna, a Mesopotamian legal code predating Hammurabi, there is a provision holding the owner of a rabid dog liable if the animal bites someone and the victim dies. This is the oldest known written record of rabies, dating to approximately 2300 BCE, more than four thousand years ago. Over the millennia that followed, the disease itself did not change. What changed was our understanding of it, yet not sufficiently to prevent 59,000 deaths each year (Taghbakhsh *et al.,* 2023; WHO, 2023).

Louis Pasteur took the first decisive step in 1885, rescuing a nine-year-old boy who had sustained fourteen bites and introducing the concept of post-exposure prevention to medicine. Since then, improved vaccines, immunoglobulins, refined protocols, and a deeper understanding of pathogenesis have all been developed. And yet the majority of rabies deaths still occur in Asia and Africa, where access to these tools remains limited (WHO, 2023). Translating available knowledge into effective implementation remains the central challenge of rabies control in this century.

Two recent epidemiological developments are particularly relevant to this update. First, Fehlner-Gardiner *et al*. (2024) demonstrated that cats, traditionally regarded as incidental hosts, have become the principal source of human exposure in certain urban areas. Second, Lodha *et al*. (2025) argued that the dFAT diagnostic standard, unchallenged for decades, must be supplemented by multi-method approaches. These developments illustrate why an updated epidemiological and clinical picture of rabies in animals, particularly dogs and cats, compared to the disease in humans, is timely.

This article is written for veterinarians, physicians, and public-health policymakers. The central questions addressed are: How do the clinical manifestations of rabies differ among dogs, cats, and humans? Where do current diagnostic methods perform well and where do they fall short? Under what circumstances does PEP fail, and why? And is Iran on the correct trajectory towards the elimination of human rabies? Rabies is caused by neurotropic RNA viruses of the genus *Lyssavirus*, transmitted primarily through the bite of an infected animal. The disease affects virtually all warm-blooded mammals, though bats and terrestrial carnivores serve as the principal reservoirs. The domestic dog remains the dominant source of human infection worldwide, responsible for more than 99% of human rabies deaths in endemic regions. However, epidemiological surveillance data from multiple countries now suggest that cats are assuming an increasingly significant role as a source of human exposure, particularly in urban environments where stray cat populations are large and vaccination rates are low (Fehlner-Gardiner *et al.,* 2024). The global burden of rabies is unevenly distributed. Despite the existence of safe and effective vaccines for both animals and humans, the disease continues to claim tens of thousands of lives annually, with the vast majority of deaths occurring in low- and middle-income countries in Asia and Africa, where access to post-exposure prophylaxis (PEP) remains inadequate. Children under 15 years of age bear a disproportionate share of this burden, largely because they are more likely to be bitten on the face and neck and less likely to report bites to caregivers (Jane Ling *et al.,* 2023; WHO, 2023). From a One Health perspective, rabies exemplifies the inextricable link between animal health, human health, and the environment. Control of the disease in the animal reservoir, particularly through mass dog vaccination, is both the most cost-effective and the most ethically defensible approach to eliminating human deaths. The international community has set an ambitious target: zero human deaths from dog-mediated rabies by 2030. Achieving this goal requires not only technical interventions but also political will, sustained funding, and genuine cross-sectoral coordination between veterinary and public health authorities (WHO/FAO/OIE/GARC, 2023). In Iran, rabies remains a public health concern, particularly in border provinces and areas with high stray dog and jackal populations. National data indicate that dogs account for the majority of recorded bite incidents, with cats representing a growing proportion. The overlap of wildlife reservoirs with livestock and human settlements in several

provinces creates conditions for continued transmission. This review was undertaken to consolidate and critically evaluate the most recent evidence on the epidemiology, pathogenesis, diagnosis, and control of rabies in animals, with particular emphasis on dogs and cats, and to compare these findings with the clinical picture in humans, with specific relevance to the Iranian context.

Methodology

Study design and search strategy

This study was a systematic review designed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Searches were conducted across five databases, PubMed/MEDLINE, Scopus, Web of Science, Embase, and SID (Scientific Information Database of Iran), covering literature published from January 2023 to June 2026. Boolean combinations of key terms were employed: (Rabies or *Lyssavirus*) and (dog or canine or cat or feline or human or zoonosis); as well as PEP or CNVR or vaccination or diagnosis or epidemiology.

In addition to electronic searches, reference lists of retrieved articles were manually screened to identify studies potentially missed in the primary search. Guidelines from international organisations, including WHO, OIE/WOAH, FAO and GARC, were included in the search. The Merck Veterinary Manual (2024 edition) was used as the standard clinical reference. Quality assessment of original studies was performed using the Newcastle–Ottawa Scale for observational studies and the Cochrane Risk of Bias tool for interventional studies. Systematic reviews were evaluated using AMSTAR-2. In total, 17 original articles, together with four guideline and reference documents, were included.

Inclusion and exclusion criteria

Inclusion criteria: (1) original studies with clearly described study design and adequate methodology; (2) systematic reviews with documented search strategies; (3) studies covering at least one of the following topics: epidemiology, pathogenesis, diagnosis, treatment or control of rabies in animals or humans; (4) case reports of exceptional clinical significance.

Exclusion criteria: (1) studies with poor methodology or substantial bias; (2) duplicate studies whose results were fully incorporated into subsequent publications by the same research group; (3) studies for which full text was unavailable.

Data extraction and analysis

Data extraction was carried out independently by two authors using a structured Microsoft Excel spreadsheet; disagreements were resolved through consultation with a third author. The extraction sheet captured the following variables for each included study: authors, year of publication, country of study, study design, study population and species, sample size, exposure route, epidemiological parameters (incidence, prevalence, reservoir species, geographic distribution), clinical and pathological findings, diagnostic methods and their performance characteristics, PEP protocols and outcomes, vaccination coverage data, and methodological quality score. Owing to high heterogeneity across studies, differences in design, population and outcomes, quantitative pooling (meta-analysis) was not feasible; a narrative qualitative synthesis was therefore employed. Results were presented in comparative structured tables.

Aetiological agent

Structure and classification

Rabies virus belongs to the family Rhabdoviridae, subfamily Lyssavirinae, genus *Lyssavirus*. Under electron microscopy, it has a bullet-like appearance, 75 nm wide and 180 nm long, enclosed by a lipid bilayer envelope. Its single-stranded, negative-sense RNA genome encodes five proteins in the order N, P, M, G, and L (Taghbakhsh *et al.,* 2023).

Glycoprotein “G” (Gp-G) is the sole protein projecting from the viral surface and fulfils two pivotal roles: it is the key mediating viral cell entry through binding to nicotinic acetylcholine receptors (nAChR), neural cell adhesion molecule (NCAM), and the low-affinity nerve growth factor receptor (p75NTR); and it is the only protein capable of inducing true virus-neutralising antibodies (VNA). All currently available commercial vaccines are designed to elicit a response against Gp-G (Taghbakhsh *et al.,* 2023;

Kaye *et al.,* 2024).

Phosphoprotein "P" has a dual function described in detail by Taghbakhsh *et al*. (2023): it is a component of the RNA-dependent RNA polymerase (RdRp) and simultaneously blocks JAK–STAT interferon signalling by interfering with the phosphorylation of STAT1 and STAT2. This duality explains the remarkable efficiency with which rabies virus suppresses the innate host response. Nucleoprotein "N" forms the protective capsid around the genomic RNA and is, for this reason, the primary target of the dFAT assay, it is the most stable and abundant antigen detectable in infected tissue.

Genetic diversity

Of the 17 recognised species within the genus *Lyssavirus*, classical RABV is responsible for more than 99% of human rabies worldwide. The division of this genus into two phylogenetic groups carries direct clinical importance. Group I includes RABV, EBLV-1, EBLV-2, ABLV, DUVV, and KHUV, all of which show adequate cross-neutralisation with RABV vaccines. Group II includes MOKV, LBV, IKOV, and SHIBV, which exhibit weak or insufficient cross-neutralisation, meaning that current vaccines do not provide full protection against them (Taghbakhsh *et al.,* 2023; Reinhardt *et al.,* 2026). A summary of these species and their key epidemiological characteristics was provided in Table 1.

Reinhardt *et al*. (2026) reviewed the situation in Europe in Deutsches Ärzteblatt International. Their key finding was that EBLV-1, which principally infects European serotine bats, and EBLV-2, prevalent in Daubenton's bats, are each capable of infecting humans, though rarely, with fewer than 10 confirmed human cases in recorded history. The practical implication: any contact with a bat in Europe, even in countries where canine rabies has been eliminated, must be evaluated for PEP with the same seriousness as a dog bite.

Table 1. Key *Lyssavirus* species and epidemiological characteristics.

Species	Region	Primary reservoir	Human cases	Response to RABV vaccine
RABV	Global	Dog, jackal, wolf, bat	> 99% of all human rabies	Complete (Group I)
EBLV-1/2	Europe	Serotine / Daubenton's bat	<10 confirmed cases	Partial (Group I)
ABLV	Australia	Fruit bat	3 confirmed cases	Partial (Group I)
DUVV	Southern Africa	Woermann's bat	Several cases	Likely insufficient (Group I)
MOKV / LBV	Africa	Rodent, cat, bat	Rare cases	Insufficient (Group II)

Source: Taghbakhsh *et al.,* 2023; Reinhardt *et al.,* 2026

Epidemiology

Two transmission cycles

Rabies in nature follows two distinct pathways, each with its own control requirements. The urban cycle (dog-mediated) predominates in endemic countries: domestic and stray dogs maintain the virus within their population and transmit it to humans, cats and livestock through bites. This cycle accounts for more than 99% of human rabies deaths (WHO, 2023). The sylvatic cycle (wildlife-mediated) circulates in bats, foxes, raccoons, skunks, and jackals, reaching dogs, cats, and livestock, and subsequently humans, through spillover events (Taghbakhsh *et al.,* 2023; WHO/FAO/OIE/GARC, 2023).

The difference between these two cycles has direct practical consequences for control strategy. Where the urban cycle predominates, mass dog vaccination is the primary intervention. Experience in North America and Western Europe shows that successful elimination of the urban cycle makes the sylvatic cycle more prominent. Aluska *et al*. (2026), in a historical and contemporary review of Alabama, showed that following the elimination of canine-mediated rabies, raccoons and bats became the primary sources of transmission. Countries approaching the transition towards control would do well to keep this in mind.

From an international perspective, Jane Ling *et al*. (2023) estimated the annual rabies burden in South-East Asia alone at approximately 10,000 deaths, while acknowledging that substantial underreporting means actual figures are likely higher. These data highlight the true burden of the disease and suggest that surveillance systems substantially undercount the number of cases.

Animal reservoirs

The domestic dog is the principal protagonist of the global rabies narrative. In many large cities of endemic countries, the stray dog population numbers in the hundreds of thousands. The virus is shed in saliva 3–7 days before clinical signs appear, the biological basis for the 10-day quarantine rule: if the dog remains healthy for 10 days after the bite, it had no virus in its saliva at the time of the incident (Amani *et al.,* 2023; Merck Veterinary Manual, 2024).

The golden jackal serves as a bridge between the wildlife cycle and rural dogs across the Middle East, Iran, Central Asia and the Balkans. The red fox was the primary reservoir of the wildlife cycle in Europe and Northern Asia until oral vaccination programmes brought it under control in Western Europe (WHO/FAO/OIE/GARC, 2023; Reinhardt *et al.,* 2026). Bats are the most complex of all reservoirs. Whitehouse *et al*. (2023), in their analysis of fatal PEP failures published in The Lancet Infectious Diseases, found that several of these failures involved bat contact, minor scratches that had been overlooked or not taken seriously. The threshold for recognising bat exposure, then, has to be set far lower than for dog exposure; even waking in a room where a bat has been present should be treated as a potential exposure.

Cats occupy a particular position. Fehlner-Gardiner *et al*. (2024), in Viruses, published the first comprehensive review dedicated to rabies in cats. They demonstrated that in certain urban areas of the United States, cats are responsible for more human exposure incidents than dogs, not because they are more efficient transmitters, but because they are less commonly vaccinated, have greater contact with wildlife (bats, rodents), and when they become infected they attack family members without warning. A 2025 CDC report (Ludmer *et al.,* 2025) documenting a rabies outbreak in an urban feral cat colony showed that free-roaming cats can serve as a local amplifier linking the wildlife cycle to residential neighbourhoods.

Global distribution

Jane Ling *et al*. (2023), in a systematic review of 38 studies from South-East Asia published in BMJ Open, identified three principal determinants of death following exposure: limited access to PEP, delayed presentation, and poverty. A notable finding was that even in countries where PEP was available, completion of the full vaccination series, essential for complete protection, remained incomplete in many patients. Active patient follow-up after exposure is clearly needed, not just availability of the vaccine itself.

Al-Zahrani *et al*. (2025), applying a One Health approach to the Arabian Peninsula in the European Journal of Public Health, found that migrant workers and livestock handlers constituted the highest-risk groups. They also highlighted the weakness of reporting systems, estimating that actual deaths in the region may be five to ten times higher than official figures. This underreporting is not merely a statistical problem; it constitutes a genuine barrier to resource allocation.

In Iran, a retrospective study by Amani *et al*. (2023) in Mazandaran Province and the national surveillance of laboratory-confirmed animal rabies cases (National Surveillance, 2024) indicate that the geographical pattern of rabies overlaps with border provinces and areas of high livestock density. In Mazandaran, dogs account for more than 65% of recorded bite incidents, followed by cats. This pattern matches regional findings elsewhere and points to the need for continuous surveillance of stray dog populations in high-risk provinces. Table 2 summarised and compared these regional epidemiological patterns.

Table 2. Comparative epidemiology of rabies in different global regions.

Region	Annual deaths	Dominant reservoir	High-risk groups	PEP and vaccination status
South Asia	~ 28,000	Dog (> 95%)	Children < 15 y, farmers	Limited access; RIG often unavailable
South-East Asia	~ 10,000	Dog, mongoose	Rural children	Variable; series completion often incomplete (Jane Ling *et al.,* 2023)
Sub-Saharan Africa	~ 21,000	Dog, jackal	Livestock workers, children	Inadequate; high underreporting (Al-Zahrani *et al.,* 2025)
North America	1–5	Bat, raccoon	All groups	Fully accessible; bat is primary risk (Aluska *et al.,* 2026)
Western Europe	< 5	EBLV in bats; imported	Travellers, veterinarians	Fully accessible (Reinhardt *et al.,* 2026)
Iran	1–10 human	Dog, cat, jackal, fox	Border areas, farmers	Free state provision; dog vaccination coverage variable (Amani *et al.,* 2023; Jackson, 2023)

Source: WHO, 2023; Jane Ling *et al.,* 2023; Reinhardt *et al.,* 2026; Aluska *et al.,* 2026; Amani *et al.,* 2023.

Pathogenesis and neuroimmunology

The virus's journey from wound to brain

When the virus enters tissue through a bite wound, it binds to nAChR receptors at the neuromuscular junction. This receptor represents an evolutionarily optimal target: abundant, accessible and a direct gateway into the nervous system. Through endocytosis, the virus enters the axon of motor neurons and retrograde axonal transport begins, driven by dynein molecular motors along microtubule tracks. The speed of this movement, 12 to 100 mm per day, explains the variability in incubation period: a bite on the forehead may reach the brain within two weeks, while a bite on a toe can take months (Taghbakhsh *et al.,* 2023; Reddy *et al.,* 2025).

Taghbakhsh *et al*. (2023) examined this transport mechanism in molecular detail. They emphasised that throughout this entire journey, from the wound to the spinal cord, no clinical signs are present. The animal or person appears entirely healthy. This asymptomatic window is precisely the period during which PEP must be deployed. Once the virus reaches the CNS, Whitehouse *et al*. (2023) found, intervention is largely futile.

Following arrival at the spinal cord and brain, extensive replication occurs in the hippocampus, amygdala, hypothalamus, thalamus, brainstem and cerebellum. In histological sections, Negri bodies, eosinophilic cytoplasmic inclusions containing viral nucleoprotein "N", are detectable. Jackson (2023) noted that the trigeminal ganglion is substantially involved, with ganglionic inflammation and neuronophagia clearly evident. This finding indicates that rabies is a neuroanatomically diffuse disease rather than simply an encephalitis.

Why is the disease untreatable after the onset of signs?

Jackson (2023), writing in the Journal of Medical Virology, examined this question with molecular precision. Rabies virus has, through evolution, developed such effective mechanisms of immune evasion that by the time it reaches the brain it is virtually invulnerable. Protein "P" blocks STAT1 and STAT2 phosphorylation, severing interferon signalling. Infected neurons downregulate MHC class I expression, preventing cytotoxic T cells from recognising them. The blood–brain barrier excludes the vaccine-induced antibodies circulating in the periphery. PD-L1 expression on infected neurons is upregulated, silencing T cells.

Jackson (2023) observed that neuronal injury in rabies is caused primarily by the host's own ineffective inflammatory response rather than by direct viral cytopathic effect. The virus does not kill the neuron; it replicates within it. The host attempts to destroy infected neurons, but this response causes further damage to the brain. This

mechanism explains why the Milwaukee Protocol, which attempted to buy time by inducing pharmacological coma, failed in most cases. The only exceptions were individuals who had received partial vaccination prior to the onset of signs.

Another aspect receiving increasing attention in the recent literature is the role of the PD-1/PD-L1 axis in immune evasion, the same pathway implicated in cancer. Jackson (2023) noted that PD-1 inhibitors have shown early promising results in animal models, but no definitive clinical evidence exists in humans. This represents a field in which future research may prove highly impactful.

Clinical manifestations

Rabies in dogs

Rabies in dogs proceeds through three stages that must be viewed together to appreciate the full picture. The prodromal stage lasts 1–3 days and is frequently overlooked. Behavioural changes are subtle: a calm dog becomes restless, a sociable dog withdraws. The animal may scratch or lick the site of an old wound, a manifestation of local paraesthesia reflecting viral activity in the sensory ganglia. Mild fever (39–40°C) and a change in bark quality have also been recorded during this stage (Taghbakhsh *et al.,* 2023; Merck Veterinary Manual, 2024). Table 3 provided a detailed side-by-side comparison of clinical manifestations across dogs, cats, and humans.

In the encephalitic stage (1–7 days), the furious form is better known: unprovoked aggression, snapping at objects and at the air, purposeless movement, pica (ingestion of foreign objects), pronounced hypersalivation secondary to dysphagia, mydriasis and hypersensitivity to light and sound. The paralytic (dumb) form must not be overlooked: some dogs never become aggressive. Dropping of the lower jaw, causing the tongue to protrude, is the most characteristic finding; the owner may assume something is lodged in the animal's throat. Taghbakhsh *et al*. (2023) emphasised that this form is readily missed without a careful history of potential exposure.

The final stage comprises progressive paralysis, coma, and death within 2–4 days. The case fatality rate in dogs after the onset of signs is 100%. The most important epidemiological point is that virus is shed in saliva 3–7 days before signs appear, the biological principle underpinning the 10-day quarantine: if the dog remains healthy for 10 days, it had no virus in its saliva at the time of the bite (Amani *et al.,* 2023; Merck Veterinary Manual, 2024).

Rabies in cats

Fehlner-Gardiner *et al*. (2024) published the first comprehensive review specifically addressing rabies in cats. They demonstrated that the furious form is not only more prevalent in cats than in dogs but is also more sudden, with unprovoked attacks occurring without warning. A cat that had been sitting on its owner's lap in the morning may attack the owner's face without any provocation in the afternoon. From a public health standpoint, that is precisely what makes cats more hazardous than dogs, the owner of a rabid dog usually has time to withdraw.

Characteristic signs in a rabid cat include: sudden behavioural change, hypersalivation, neglect of grooming (an unkempt appearance highly unusual in a healthy cat), a harsh and abnormal vocalisation, severe photophobia, and in rare cases self-mutilation at the wound site. The 2025 CDC report (Ludmer *et al.,* 2025) on a rabies outbreak in an urban feral cat colony showed that free-roaming cats can act as a local link, transmitting virus from the wildlife cycle into residential neighbourhoods.

From an exposure management perspective, an important point is that cat scratches, far more common than cat bites, can transmit virus if the claw has been contaminated with saliva. Fehlner-Gardiner *et al*. (2024) noted that cat vaccination is optional or entirely absent from national programmes in many countries. In countries that already carry a rabies burden, this gap needs to be closed.

Table 3. Detailed comparison of clinical manifestations of rabies in dogs, cats, and humans.

Feature	Dog	Cat	Human
Incubation period	10–60 days (up to 6 months)	2–6 weeks	1–3 months (7 days–10 years)
Predominant form	Furious more common	Furious; unprovoked attack	Furious 80–85%
Dropped jaw	+++ key finding	+/−	Absent
Hydrophobia / aerophobia	Absent	Absent	+++ pathognomonic in humans
Hypersalivation	+++ prominent	++	+++
Paraesthesia at bite site	Possible	Reported	50–80% of cases (important sign)
Unprovoked attack	+	+++ primary hazard	Intermittent agitation
Virus shedding in saliva before signs	3–7 days (documented)	Less well documented	Rare
Duration of acute phase	3–10 days	3–7 days	7–14 days
Case fatality rate after signs	~ 100%	~ 100%	> 99%; < 15 known survivors worldwide

Source: Taghbakhsh *et al.,* 2023; Fehlner-Gardiner *et al.,* 2024; Reddy *et al.,* 2025.

Rabies in humans

The incubation period in humans averages 1–3 months but ranges from 7 to 10 years. Determining factors include: site of bite (face/neck → shorter), wound depth, viral titre in saliva, age and immune status (Whitehouse *et al.,* 2023; Reddy *et al.,* 2025). The prodromal stage lasts 2–10 days and is easily confused with influenza: fever, headache, malaise, nausea. The almost-specific sign to seek is paraesthesia or pain at the old wound site, present in 50–80% of patients (WHO, 2023; Reddy *et al.,* 2025).

Hydrophobia, painful spasm of the pharyngeal and laryngeal muscles triggered by the sight of water, its sound or even the thought of drinking, is pathognomonic of human rabies and is not seen to this degree in any other species. Aerophobia, in which an air current triggers the same spasm, is even more specific. These signs are present in 80–85% of patients (furious form). In the remaining 15–20% (paralytic form), hydrophobia is absent and the disease progresses as an ascending paralysis from the bitten limb, resembling Guillain–Barré syndrome (WHO, 2023; Reddy *et al.,* 2025).

Whitehouse *et al*. (2023), in their analysis of fatal cases despite PEP in The Lancet Infectious Diseases, found that delayed diagnosis, particularly in the paralytic form, was a contributing factor to failure. Patients with ascending paralysis were initially managed under a diagnosis of GBS, and PEP was delayed. In practice, this means asking about animal contact in the preceding months for any patient with ascending paralysis, even if the patient regards it as trivial.

Differential diagnosis

In the early stages of rabies, signs are so non-specific that even experienced clinicians and veterinarians may miss the diagnosis. The most important diagnostic tool is not a laboratory test but the clinical history: a bite, scratch or mucosal contact with a suspect animal in the preceding weeks or months. Without this history, even the most skilled clinician may miss the diagnosis. Table 4 listed the principal differential diagnoses to be considered in dogs, cats, and humans.

Table 4. Differential diagnosis of rabies by species.

Species	Competing diagnoses	Distinguishing feature from rabies
Dog	Distemper, tetanus, lead or organophosphate poisoning, foreign body obstruction, bacterial encephalitis	Rabies: exposure history + progressive paralysis without high fever + dropped jaw; tetanus: muscle spasms with preserved consciousness; distemper: ocular/nasal discharge, skin lesions
Cat	CNS trauma, neurological FIP, toxoplasmosis, poisoning, pharyngeal foreign body	Rabies: sudden behavioural change + history of wildlife contact; FIP: inflammatory CSF; toxoplasmosis: positive serology
Human	Guillain–Barré syndrome, herpes encephalitis (HSV), methanol poisoning, tetanus, conversion disorder	Rabies: bite history + hydrophobia + paraesthesia at bite site; GBS: albuminocytological dissociation in CSF; HSV encephalitis: temporal abnormalities on MRI

Source: Taghbakhsh *et al.,* 2023; Merck Veterinary Manual, 2024; Reddy *et al.,* 2025.

Laboratory diagnosis

Principles of sample collection

In animals, definitive diagnosis is usually performed post-mortem or following euthanasia. Brain tissue, brainstem, cerebellum, and hippocampus, is the standard sample. Storage at +4°C and dispatch within 24–48 hours is essential; if delay is unavoidable, storage in 50% glycerol or freezing is recommended. Microbial contamination or tissue decomposition can produce false-negative dFAT results, a common pitfall with samples that arrive late at the laboratory (Taghbakhsh *et al.,* 2023; Merck Veterinary Manual, 2024).

Lodha *et al*. (2025) in Molecular Diagnosis & Therapy presented a well-reasoned argument that the era of relying on a single test must end (Lodha *et al.,* 2025). Their systematic review of the literature showed that while dFAT on fresh tissue achieves sensitivity exceeding 98%, this figure falls below 70% with degraded, contaminated or late specimens. Their recommendation: any reference laboratory should employ at least two parallel methods.

For diagnosis in a living human patient, the principal challenge is access to brain tissue. Multiplex RT-PCR on multiple sample types, saliva, CSF, and skin biopsy from the nape of the neck (which contains viral antigen in the perifollicular pilosebaceous units), represents the best available diagnostic approach. The highest sensitivity is achieved by performing RT-PCR concurrently on all three sample types (Taghbakhsh *et al.,* 2023; Reddy *et al.,* 2025).

Comparison of diagnostic methods

The dFAT, with sensitivity exceeding 98% and specificity of approximately 99% on fresh tissue, remains the global gold standard. The DRIT, which works with conventional light microscopy, is a valuable option for laboratories lacking fluorescence microscopy. WHO has endorsed it for low-resource settings (Merck Veterinary Manual, 2024), a point of practical relevance for many veterinary diagnostic laboratories in Iran that may not be equipped with fluorescence microscopes. Table 5 compared the sensitivity, specificity and resource requirements of the principal diagnostic methods discussed in this section.

The Rapid Fluorescent Focus Inhibition Test (RFFIT) is the gold standard for measuring virus-neutralising antibody titres. A titre of ≥ 0.5 IU/ml is considered protective. Fishbein *et al*. (1988) showed decades ago that injection site affects the final antibody titre: deltoid injection produces substantially higher responses than gluteal injection, where fat tissue slows absorption. This older but still relevant finding deserves repeating in healthcare worker training.

Table 5. Comparison of diagnostic methods for rabies.

Method	Sensitivity	Specificity	Sample	Turn around	Notes
dFAT	> 98%	~ 99%	Fresh brain	2–4 hours	Gold standard; requires fluorescence microscope
DRIT	95–98%	> 98%	Fresh brain	4–6 hours	Light microscopy; low-resource alternative to dFAT (Lodha *et al.,* 2025)
RT-PCR (saliva)	60–95%	> 95%	Saliva (living patient)	4–8 hours	Best option for living patient
RT-PCR (nape skin)	60–90%	> 90%	Skin biopsy	8–12 hours	Combined with saliva + CSF raises sensitivity
RFFIT	Variable	> 95%	Serum / CSF	1–2 days	Vaccine response assessment; deltoid > gluteal (Fishbein *et al.,* 1988)
IHC / Negri bodies	50–80%	~ 100%	Formalin-fixed brain	24–48 hours	Pathognomonic if positive; absence does not exclude diagnosis

Source: Fishbein *et al*., 1988; Taghbakhsh *et al.,* 2023; Merck Veterinary Manual, 2024; Lodha *et al.,* 2025.

Control, prevention and exposure management

Vaccines

Kaye *et al*. (2024) published a comprehensive review of rabies vaccines for prophylaxis and treatment in Cureus. Human cell-culture vaccines, purified chick embryo cell vaccine (PCEC), human diploid cell vaccine (HDCV), and purified Vero cell rabies vaccine (PVRV), are all inactivated preparations that act by stimulating a response against glycoprotein "G". Their principal differences lie in the cell substrate used for culture, price and accessibility. Kaye *et al*. (2024) drew attention to the progress of mRNA platforms at the animal study stage, which may generate more rapid responses, although sufficient clinical data in humans remain unavailable.

For animals, killed adjuvanted vaccines are the standard. The standard protocol for dogs and cats is: primary vaccination at three months of age, booster one year later, then every 1–3 years. In humans, beyond injection site, vaccine brand, patient age and immune status all influence the serological response after PEP. The most important practical message: gluteal injection, still practised in some centres, should be abandoned (Fishbein *et al.,* 1988).

The oral vaccine V-RG (vaccinia-vectored, expressing Gp-G) has been successful for wildlife in Europe and North America, where vaccine-laden baits are distributed by aircraft. This strategy effectively eliminated fox-mediated rabies in Western Europe, a successful example demonstrating that control is achievable even in the sylvatic cycle (WHO/FAO/OIE/GARC, 2023; Reinhardt *et al.,* 2026).

Post-exposure prophylaxis: details

Whitehouse *et al*. (2023), reviewing 15 fatal cases despite PEP in The Lancet Infectious Diseases, identified the causes of failure. Five categories were identified: (1) delay exceeding 14 days in initiating PEP, the most common cause; (2) use of substandard vaccine or incorrect storage; (3) failure to use RIG or administration at the wrong site; (4) incomplete dosing schedule; (5) exposure to non-RABV lyssaviruses in countries such as Australia where ABLV is present. In other words, correctly administered PEP really is close to 100% effective, failures are almost entirely attributable to human error.

Step 1: Wound washing (immediately): Soap and water for 15 minutes. This mechanical action is more important than simple disinfection, it removes a substantial proportion of virus before it can bind to neural receptors. Apply 10% povidone-iodine or 70% ethanol thereafter. The wound should not be sutured immediately (WHO, 2023).

Step 2: RIG (rabies immunoglobulin): Dose of 20 IU/kg for unvaccinated individuals. Whitehouse *et al*. (2023) made an important point worth repeating: as much of the full RIG dose as anatomically feasible should be infiltrated into and around the wound, rather than administered exclusively as a distant intramuscular injection. When RIG is injected intramuscularly far from the wound, it does not reach the site where the virus is located. This error is common in practice.

Step 3: Vaccine series: The Essen 4-dose protocol (days 0, 3, 7, 14) or Zagreb (2+1+1). Warrell (2023) evaluated single-visit PrEP protocols that can provide adequate protection for travellers using two intradermal doses on a single day, an important simplification that increases uptake.

CNVR and stray dog population management

Tidman *et al*. (2025) in Frontiers in Microbiology, in a scoping review of 42 studies, demonstrated that CNVR combined with vaccination achieves the greatest impact. The essential prerequisite for success is simultaneous vaccination coverage of at least 70%. They also emphasised underutilised synergies: in many endemic countries, CNVR and vaccination programmes are implemented separately and without coordination, substantially reducing their effectiveness.

Asres *et al*. (2025) in PLoS Neglected Tropical Diseases, in a meta-analysis from Ethiopia, found that traditional medicine use after exposure was independently associated with death. The median delay in PEP for those who initially consulted a traditional healer was 10 days greater than in controls. Education on this point needs to be culturally sensitive, not simply a matter of medical training.

Discussion

Direct comparison of the 2023–2026 epidemiological studies presents a heterogeneous picture from which important lessons emerge.

In contrast, Al-Zahrani *et al*. (2025) in the Arabian Peninsula identified a different pattern: the primary risk group was not rural children but adult migrant workers, a population less visible in the Jane Ling *et al*. (2023) findings. Prevention and education programmes, in other words, need to define their target groups according to local reality rather than global patterns. In Iran, seasonal livestock migration across borders with neighbouring countries creates a specific high-risk group that deserves dedicated attention in national surveillance systems.

Aluska *et al*. (2026) in Alabama and Reinhardt *et al*. (2026) in Europe reported from two regions that have successfully controlled canine-mediated rabies. Their comparison is instructive: both note the increased prominence of bats following canine rabies elimination. However, in North America raccoons also play a significant role, whereas in Europe EBLV-1 and EBLV-2 remain the principal residual reservoirs. Even within a single category of developed-country settings, then, control strategies have to be tailored to local reservoir species.

The most significant diagnostic debate of this period was ignited by Lodha *et al*. (2025), who argued that dFAT should be reclassified from ‘gold standard’ to ‘conditional gold standard’, a standard valid only with fresh tissue and a well-equipped laboratory. This position has met with resistance: reference organisations such as CDC and OIE continue to recommend dFAT as first choice. Nevertheless, the Lodha *et al*. (2025) argument regarding its practical limitations under non-ideal conditions is persuasive.

The deltoid-versus-gluteal injection finding may sound like a minor technical detail, but it carries real clinical weight. Deltoid injection produces significantly higher antibody titres than gluteal injection, a difference long recognised since Fishbein *et al*. (1988) first documented it. Whitehouse *et al*. (2023) further showed that the site of RIG injection (into the wound versus distant intramuscular) may be even more important than the vaccine injection site. The two findings, taken together, point to the same conclusion: the details of PEP administration, not merely its prescription, determine whether it succeeds.

In the domain of animal diagnosis, Jackson (2023) documented trigeminal ganglion involvement in rabid dogs, consistent with his broader neuroimmunological findings in the same publication. Both observations indicate that rabies involves more systemic neurological involvement than previously appreciated, a picture that may

eventually point towards new diagnostic targets, such as CSF biomarkers detectable before the onset of clinical signs.

The finding by Fehlner-Gardiner *et al*. (2024) regarding the role of cats is arguably the most policy-relevant finding of this period.

The 2025 CDC report (Ludmer *et al.,* 2025) on a rabies outbreak in an urban cat colony confirmed this with field data. A feral cat colony can function as a local amplifier, not because the virus is maintained within the cat population (cats are spillover hosts, not true reservoirs) but because they generate frequent contact with wildlife sources and transmission to family members. This subtle but important distinction means that the control programme for a reservoir and a spillover host must differ.

Jane Ling *et al*. (2023), in their South-East Asia review, mentioned cats as a source of exposure but lacked sufficient data for independent analysis. That gap is telling in itself: cats are frequently not recorded separately from dogs in epidemiological surveillance systems. In Iran's surveillance systems, cat-bite incidents should be recorded separately from dog bites so that locally analysable data are available in the future.

Taken as a whole, the studies reviewed here converge on a consistent narrative even though they were conducted in very different settings. Wherever dog vaccination coverage has been pushed past the 70% threshold, human and canine rabies incidence has fallen accordingly; wherever it has not, dogs remain the dominant source of exposure. The recurring theme across the South-East Asian, Middle Eastern, African, European and North American literature surveyed in this review is not a disagreement about what works, but a persistent gap between the interventions known to be effective and their actual implementation on the ground. This review's contribution is to bring the cat-related evidence, the diagnostic debate, and the PEP failure literature together into a single synthesis, which to our knowledge has not previously been attempted for the 2023–2026 period.

Zero by 2030 and the way forward

In 2018, WHO, FAO, OIE, and GARC announced an ambitious target: zero human deaths from dog-mediated rabies by 2030. This goal is technically achievable, the tools exist. However, evidence from 2023 to 2026 indicates that progress is not occurring rapidly enough. The greatest barrier is sustained political will and genuine inter-sectoral coordination, not a lack of technology (WHO/FAO/OIE/GARC, 2023; Tidman *et al.,* 2025).

Tidman *et al*. (2025) highlighted opportunities for integrating rabies programmes with other livestock health initiatives. Where brucellosis or foot-and-mouth disease registration and vaccination programmes are already operating, dog rabies vaccination can be appended at marginal additional cost. These integration opportunities can dramatically reduce per-capita costs.

Asres *et al*. (2025) from Ethiopia provide a lesson applicable across Africa and Asia: until cultural and educational barriers are removed, even the availability of PEP is insufficient. The 10-day median delay attributable to initial consultation with traditional healers eliminates many treatment windows. In Iran, delay may stem from different causes, distance from healthcare facilities, cost concerns, or the belief that a bite is a trivial injury. Understanding local barriers is the first step to addressing them.

Suggestions

A prospective cohort study to determine the true burden of rabies in Iran, with separate recording of bites by dogs, cats, wildlife, and bats, is the foremost research priority. Molecular phylogenetics of circulating RABV strains and their relationship to strains from neighbouring countries can identify viral entry routes and inform border health measures. Evaluation of the direct rapid immunohistochemistry test (DRIT) as a practical alternative to dFAT in veterinary diagnostic laboratories in Iran's border provinces represents work of high immediate value. Investigation of cultural and behavioural barriers to PEP-seeking in high-risk rural areas is equally important for translating policy into practice. It must be acknowledged as a limitation of this review that the published literature does not currently provide reliable province-level estimates of dog vaccination coverage in Iran's high-risk provinces, the proportion of bite-exposed individuals in border areas who complete the full PEP series rather than merely initiating it, or data on whether DRIT is currently operational at any

Iranian veterinary diagnostic laboratory. These three gaps are themselves a finding: they represent the most critical priorities for Iran's national rabies surveillance system. Without this baseline data, the policy recommendations in this section, while scientifically grounded in the international literature, cannot be calibrated against Iran's actual starting point.

From a public health and policy perspective, achieving vaccination coverage of at least 70% among dogs in all provinces, not only major cities, is the primary operational objective. Ensuring a sustainable and geographically equitable supply of rabies immunoglobulin at border and rural hospitals, which serve as the nearest access points after bite incidents, is a critical measure that must be addressed through procurement planning. Mandatory training of veterinarians and physicians in the correct technique for infiltrating RIG into and around the wound, with emphasis on the findings of Whitehouse *et al*. (2023), should be incorporated into continuing professional education programmes. Inclusion of domestic cat vaccination in the national rabies control programme, in light of the evidence from Fehlner-Gardiner *et al*. (2024), is the logical next step; and separate recording of cat bites in national surveillance systems will generate the locally analysable data required for evidence-based decision-making.

Rabies in the twenty-first century is a preventable disease for which all necessary tools have been available for decades. Vaccines, immunoglobulin, and documented post-exposure protocols exist and are effective. And yet 59,000 people still die each year. The gap between existing knowledge and its application in practice was the central theme of this review.

The evidence reviewed here yields several clear lessons. First: dogs remain the central driver of the disease in endemic countries, and no strategy can succeed without mass dog vaccination. Second: cats are the missing link in urban rabies control and must be formally incorporated into national programmes. Third: PEP failures are almost entirely attributable to human error, delay or incorrect RIG injection, not to vaccine failure. Fourth: diagnostic standards must be adapted to field realities, including degraded tissue and low-resource laboratories.

The zero by 2030 target is realistic for Iran, but requires several concrete changes: raising dog vaccination coverage above 70% in all provinces; ensuring a sustainable RIG supply in underserved areas; training healthcare personnel in correct PEP technique; and incorporating cats into the national control programme. When these steps are accompanied by sustained political will and genuine coordination between the Veterinary Organisation and the Ministry of Health, Iran can relegate human rabies to history.

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Conflict of Interest

The authors declare that they have no financial or personal relationships with other people or organisations that might inappropriately influence or bias the work reported in this manuscript.

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