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Rabies: A Neglected Disease in Iran — A Mini-Review Based on World Rabies Day Activities

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ABSTRACT

Introduction: Rabies is a vaccine-preventable, nearly invariably fatal viral zoonosis caused by rabies virus, which belongs to the species *Lyssavirus rabies*. Transmission to humans usually follows exposure to infected saliva through animal bites or scratches, with dogs responsible for most human cases globally. Prompt post-exposure prophylaxis (PEP) prevents clinical disease. The objective of this study is to summarize selected evidence on rabies diagnosis, prevention, surveillance, and control relevant to Iran and World Rabies Day activities. **Methods:** This narrative mini-review draws on selected peer-reviewed studies, World Health Organization (WHO) guidance, and relevant published reports. It is not a systematic review and does not present newly collected surveillance data. **Results:** Antemortem diagnosis requires multiple specimen types and complementary assays; a single negative test cannot reliably exclude rabies. Postmortem testing of brain tissue remains central to laboratory confirmation. Molecular amplification methods and emerging Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-based assays warrant further evaluation for decentralized use. In Iran, integrated bite surveillance, timely PEP, mass dog vaccination, and collaboration across public-health and veterinary services are priority measures. **Conclusion:** Strengthening laboratory networks, access to PEP, population-level dog vaccination, and One Health coordination can support the global target of zero human deaths from dog-mediated rabies by 2030.

INTRODUCTION

Rabies is a vaccine-preventable zoonotic encephalitis caused by rabies virus (RABV), classified in the species *Lyssavirus rabies*, genus *Lyssavirus*, family *Rhabdoviridae*. Infection usually occurs when saliva from an infected mammal enters a wound or mucous membrane. Dogs account for most human rabies cases in endemic settings; once neurological symptoms develop, rabies is almost invariably fatal. Prompt exposure assessment, wound care, and post-exposure prophylaxis (PEP) are therefore essential. Rabies remains endemic in Iran, and its control requires sustained surveillance, timely access to human prophylaxis, and prevention of infection in animal reservoirs [1]. As a neglected tropical disease (NTD), rabies disproportionately affects underserved populations. The broader NTD group comprises diseases with varied infectious and noninfectious causes, often associated with poverty, limited access to care, and social and economic disadvantage [2]. The global Zero by 30 strategy aims to end human deaths from dog-mediated rabies by 2030 through coordinated human-health and animal-health interventions [3].

This narrative mini-review summarizes selected scientific publications, international guidance documents, and World Rabies Day-related material relevant to rabies in Iran. Rather than applying a formal systematic review protocol or analyzing primary surveillance datasets, the article offers a contextual synthesis of current literature and guidance.

Role of the WHO Collaborating Centre and national reference laboratories in rabies control in Iran

National reference laboratories and WHO collaborating centres contribute to rabies control through confirmation of suspected cases, quality-assured diagnostic testing, training, surveillance support, and

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technical advice. Linking laboratory findings with clinical and veterinary reporting systems is necessary to identify transmission risks and guide response activities. These functions support the One Health approach and the Zero by 30 objective; their effectiveness depends on timely specimen referral, consistent reporting, and coordination among participating institutions [3].

Antemortem and postmortem diagnosis of rabies

● Detection of viral RNA in antemortem saliva specimens by RT-qPCR

Viral RNA may be detected in saliva by real-time reverse transcription PCR (RT-qPCR) after onset of clinical disease. Because viral shedding in saliva is intermittent, a negative result from one sample does not exclude rabies; serial saliva specimens and complementary testing of other recommended specimens are important. Antemortem testing should be coordinated with a qualified reference laboratory and interpreted in the clinical and exposure context [4].

● Detection of rabies antigen in nuchal skin biopsy specimens

Nuchal skin biopsy is an important component of antemortem rabies testing. A specimen from the posterior neck at the hairline should include hair follicles and the cutaneous nerves at their bases. Detection can involve RT-qPCR and direct immunofluorescence on appropriately prepared sections. Unlike the direct fluorescent antibody test (FAT) of postmortem brain tissue, the performance of skin-biopsy antigen detection depends strongly on sampling, specimen handling, disease stage, and local laboratory procedures [5–7].

Recommended specimen-handling principles include the following:

a) Sampling: Obtain a skin biopsy approximately 5–6 mm in diameter from the posterior neck at the hairline, including at least 10 hair follicles and adequate depth to capture associated cutaneous nerves. Place the specimen in a sterile container without preservative and promptly consult the receiving reference laboratory for transport requirements [5–7].

b) Processing and antigen detection: Laboratory personnel should process tissue using a validated protocol; frozen-section immunofluorescence and RT-qPCR are established approaches. The choice of fixative, section preparation, staining procedure, and controls must follow the reference laboratory's standard operating procedure. Routine direct smears or touch impressions from skin are not interchangeable with validated frozen-section testing [5–7].

c) Interpretation: Specific fluorescence in nerves associated with hair follicles supports detection of rabies antigen. However, a negative result from an individual skin biopsy does not rule out infection. Results should be integrated with serial saliva testing, other appropriate specimens, and clinical assessment; repeat sampling may be required [5–7].

● Postmortem diagnosis using brain tissue

Postmortem confirmation relies on testing suitable brain tissue, particularly brainstem and cerebellum. The WHO-recommended FAT detects viral antigen in appropriately collected, fresh brain specimens and provides reliable results in experienced laboratories; RT-qPCR and other validated assays may supplement or corroborate the diagnosis. Formalin fixation can interfere with direct FAT procedures, so specimen choice and preservation must follow the receiving laboratory's instructions. Incomplete anatomical sampling can reduce confidence in a negative result [6, 8, 9].

Post-exposure prophylaxis

PEP is a medical emergency for persons with potentially infectious exposures. Immediate washing of the affected site with soap and running water for at least 15 minutes should be followed by risk assessment according to WHO exposure categories. Category II exposures generally require prompt vaccination, while Category III exposures require vaccination and, when indicated, rabies immunoglobulin (RIG) or an appropriate licensed monoclonal antibody product. Category I contact does not ordinarily require PEP. The regimen also depends on previous vaccination and immune status. PEP should not be postponed pending confirmation of rabies in the exposed person, and its administration should follow current national and WHO guidance [3, 6, 10, 11].

Developments in rabies research and diagnostics

Rabies virus genomic surveillance can distinguish circulating lineages, investigate probable transmission pathways, and identify sequence variation that may affect molecular assay design. Genomic differences should not be interpreted as evidence of increased virulence, immune escape, or vaccine failure without supporting functional or epidemiological evidence [12].

The rapid fluorescent focus inhibition test (RFFIT) and fluorescent antibody virus neutralization (FAVN) test measure virus-neutralizing antibody activity in serum. These tests are used in research, immunogenicity assessment, and defined regulatory or veterinary settings, but neither is a substitute for direct detection of infection in a clinically symptomatic patient. Interpretation of titers depends on test calibration, purpose, and relevant guidance [6, 13].

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Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated nucleic acid detection is an emerging research direction. A 2025 multiplex thermostatic-amplification/CRISPR-Cas12 platform included rabies virus targets, with analytical evaluation performed using cloned DNA targets. Such findings demonstrate proof of concept, not established clinical sensitivity in patients with rabies. Clinical validation across relevant viral lineages, specimen types, and field conditions is required before routine deployment [14].

Reverse transcription loop-mediated isothermal amplification (RT-LAMP) has been evaluated for rabies virus RNA detection. An Iranian study comparing RT-LAMP with RT-qPCR and FAT in brain samples reported promising diagnostic performance, while also illustrating that sensitivity and specificity depend on the evaluated specimen set and assay conditions. Standardized extraction, contamination controls, and independent validation remain necessary before wide field use [15].

Nucleic acid sequence-based amplification (NASBA) is another isothermal method used for RNA detection. A comparative study evaluated NASBA alongside real-time and conventional PCR for rabies viral RNA; the results support its role as a molecular research and diagnostic option but do not establish superiority over contemporary validated RT-qPCR protocols [16].

Epidemiological and economic evidence for policymaking

Rabies burden estimates are affected by underdiagnosis, limited surveillance, and differences among models. A widely cited 2015 analysis estimated approximately 59,000 annual human deaths from endemic canine rabies and global economic losses of US$8.6 billion, including approximately US$1.7 billion in direct PEP expenditures [17]. A WHO fact sheet updated in September 2026 reports an estimate of 44,203 annual rabies deaths based on its 2021 Global Health Estimates model; this is a different estimate rather than evidence of a directly comparable temporal reduction [18]. WHO estimates that approximately 40% of human rabies deaths occur in children younger than 15 years and that more than 29 million people receive rabies vaccine annually [18]. When interpreting these figures, differences in modeling periods, estimation uncertainties, and regional versus global PEP expenditures must be considered [17, 18].

Rabies control, elimination, and persisting challenges

Dog-mediated human rabies has been eliminated in several high-income countries and controlled in parts of Latin America, although rabies risk from wildlife or imported animals may remain. Effective programs combine sustained mass dog vaccination, timely PEP, community education, bite surveillance, laboratory confirmation, and cross-sector coordination. Vaccinating approximately 70% of dogs is a widely used planning target for interrupting transmission in endemic settings; actual program requirements vary with local conditions. Dog population management alone, including trap–neuter–return activities, is not a substitute for vaccination [3, 17–19].

In Iran, potential **program** challenges include heterogeneous animal-bite risk, geographic barriers to care, inconsistent public knowledge of exposure risks, and the need for integrated reporting across public-health, veterinary, and municipal systems. Evaluating potential nationwide vaccine or RIG shortages, changes in stray-dog populations, and the implementation of dog-control programs requires time-specific administrative data. Education, dog vaccination, prompt PEP, and quality-assured diagnostics remain important priorities [10, 17–19].

DISCUSSION

Rabies prevention requires immediate exposure management and sustained animal-health interventions. Molecular tests using serial saliva specimens and testing of nuchal skin can support antemortem diagnosis in suspected human cases, whereas appropriate brain-tissue testing remains central to postmortem confirmation. No single negative antemortem result is sufficient to exclude infection when suspicion is high, and testing must be interpreted in consultation with reference laboratories [4–7].

Iranian programs face logistical, behavioral, and surveillance challenges that differ among provinces. Recent national registry evidence documented prompt initiation of PEP for many reported exposures but also found exposure-category misclassification, gaps in records, and variation in recommended vaccine and RIG use [20]. A recent case series from northwestern Iran described fatal outcomes following delayed presentation despite availability of clinical services, emphasizing the importance of immediate risk assessment and public communication [21]. However, localized delays do not necessarily indicate a nationwide shortage of vaccines or RIG, as supply constraints must be assessed using dedicated procurement and facility-level data.

Experiences from countries that have controlled dog-mediated rabies emphasize repeated, high-coverage dog vaccination campaigns, dependable human prophylaxis, surveillance, and collaboration among veterinary, medical, and local-government services [17, 19]. Dog population management can contribute to animal welfare and community engagement but cannot replace vaccination. Development of field-adapted molecular diagnostics may improve reporting only if sensitivity,

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specimen handling, quality assurance, and implementation feasibility are demonstrated [14, 15].

Historical estimates of rabies mortality and economic impact show why prevention is an important public-health investment. However, estimates from different sources and modeling years should be compared cautiously, and total economic losses must be distinguished from the direct cost of PEP [17, 18].

Priority actions for Iran include better integration of human and animal surveillance data, strengthened specimen referral networks, consistent access to timely PEP, staff training in exposure classification, sustained dog vaccination, and public education regarding wound washing and immediate care. New assay platforms should complement rather than replace established validated diagnostic services until sufficient clinical evidence is available [3, 10, 14, 15, 19–21].

Progress toward the Zero by 30 target will require measurable indicators, transparent reporting, and sustained One Health coordination rather than reliance on World Rabies Day activities alone [3, 19].

This mini-review is limited by its selective, non-systematic source base, variation in reference years, and absence of newly collected national surveillance data. Furthermore, the overview of institutional activities presented here is descriptive rather than an independent program evaluation. Numerical estimates from different models are not directly comparable, and experimental molecular assays require additional clinical validation before routine field implementation.

CONCLUSION

The National Center and WHO Collaborating Centre for Reference and Research on Rabies at the Pasteur Institute of Iran can contribute to training, diagnostic quality assurance, surveillance, and public awareness. Key activity areas supporting national rabies-control programs include the following:

1. Specialized training of healthcare personnel: Training for clinicians, veterinarians, public-health personnel, and staff of exposure-management facilities should prioritize prompt wound care, risk classification, specimen referral, correct use of PEP, and reporting of suspected human or animal rabies cases [3, 10].

2. Public and professional education: World Rabies Day activities, targeted media messages, and educational materials can improve recognition of exposure risk and awareness of prevention. Their effect should be evaluated with predefined reach, knowledge, behavior, or health-service indicators rather than assumed from the number of activities conducted [10].

3. National and international collaboration: Coordination among human-health authorities, veterinary services, municipalities, and international rabies-control networks is necessary to link bite prevention, animal vaccination, reporting, and response systems [3, 10, 19].

4. Vaccine and diagnostic research: Relevant research priorities include assessment of vaccine-induced neutralizing antibodies, viral genomic surveillance, and independent evaluation of molecular diagnostic tools [6, 10, 12–15].

5. Diagnostic and advisory services: Referral laboratory services support suspected-case confirmation and consultation regarding human and animal specimens. Clinical PEP decisions should remain based on timely exposure assessment and the applicable guidance, rather than await testing of the exposed person [3, 6, 10].

In summary, the immediate priorities are equitable access to effective PEP, sustained vaccination of dogs, reliable surveillance, laboratory quality assurance, and consistent public communication. The institutional impact of these activities at the Pasteur Institute of Iran can be systematically monitored using measurable program indicators [3, 10, 19].

Future work should strengthen joint reporting by health and veterinary authorities; monitor vaccine and RIG availability with facility-level indicators; evaluate dog-vaccination coverage; expand laboratory proficiency and specimen referral systems; and assess rapid assays through independent, appropriately designed studies. These steps can improve prevention of avoidable human rabies deaths and support the Zero by 30 goal [3, 17–19].

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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AI DISCLOSURE

The authors report the use of ChatGPT for language and editorial assistance. The authors retain responsibility for checking all scientific statements, reference details, interpretations, and final published content.

DATA AVAILABILITY

No No new datasets were generated or analyzed for this narrative mini-review. The cited publications and guidance documents are available from their respective sources.

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AUTHORS' CONTRIBUTIONS

FS assembled and interpreted the literature and prepared the initial draft. MF contributed to the concept, supervised manuscript development, and critically revised the text.

ETHICS STATEMENT

Not applicable; this narrative mini-review involved no new human-participant or animal experiments.

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