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ADVANCING RABIES DIAGNOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS COMPARING MOLECULAR AND CONVENTIONAL METHODS FOR DIAGNOSTIC ACCURACY AND EARLY DETECTION IN HUMANS

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ABSTRACT

Background: Rabies remains a universally fatal zoonotic disease once clinical symptoms appear, accounting for significant mortality in low- and middle-income countries. Early and accurate diagnosis is crucial for patient management, surveillance, and implementation of public health measures. Conventional diagnostic methods such as Direct Fluorescent Antibody (DFA) testing are considered gold standards but are largely limited to postmortem confirmation. In contrast, molecular diagnostic techniques have emerged as promising tools for early and antemortem detection. This systematic review and meta-analysis aimed to compare the diagnostic accuracy of molecular and conventional methods for human rabies.

Methods: A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, and Embase for studies published between 1990 and 2026. Studies evaluating diagnostic methods for human rabies with reported sensitivity and specificity were included. Data extraction and quality assessment were performed using standardized tools, including the QUADAS-2 framework. Meta-analysis was conducted using a random-effects model to calculate pooled sensitivity, specificity, likelihood ratios, and diagnostic odds ratios. Summary Receiver Operating Characteristic (SROC) curves were constructed to evaluate overall diagnostic performance.

Results: A total of 60 studies were included in the qualitative synthesis, with 48 studies eligible for meta-analysis. Molecular diagnostic methods demonstrated higher pooled sensitivity (92.3%; 95% CI: 88.7–95.1%) compared to conventional methods (85.4%; 95% CI: 80.2–89.7%), while maintaining comparable specificity (96.5% vs. 98.8%). Real-time PCR exhibited the highest diagnostic accuracy among molecular techniques. Nuchal skin biopsy samples showed superior sensitivity compared to saliva and cerebrospinal fluid. Conventional methods, particularly DFA, remained highly specific but were limited by their dependence on postmortem samples. SROC analysis revealed a higher area under the curve for molecular methods (AUC = 0.97) compared to conventional methods (AUC = 0.91).

Conclusion: Molecular diagnostic methods significantly outperform conventional techniques in terms of sensitivity and enable early antemortem detection of rabies. While conventional methods remain valuable for confirmatory diagnosis and surveillance, integration of molecular tools into routine diagnostic workflows is essential for improving clinical outcomes and strengthening rabies control programs. These findings support global efforts, including those led by the World Health Organization, toward the elimination of rabies.

KEYWORDS: Rabies; Molecular diagnosis; RT-PCR; Direct Fluorescent Antibody (DFA); Diagnostic accuracy; Sensitivity; Specificity; Meta-analysis; Antemortem diagnosis; Zoonotic infections

1. INTRODUCTION

Rabies remains one of the most devastating zoonotic infections known to humanity, characterized by an almost universally fatal outcome once clinical symptoms manifest. Caused by neurotropic viruses of the genus *Lyssavirus*, rabies continues to impose a significant global health burden, with an estimated 59,000 human deaths annually, predominantly in low- and middle-income countries across Asia and Africa. The disease is primarily transmitted through the bite of infected animals, particularly domestic dogs, which account for over 95% of human rabies cases worldwide. Despite the availability of effective vaccines and immunoglobulin therapies, rabies persists due to gaps in surveillance, inadequate post-exposure prophylaxis (PEP), and limitations in diagnostic capabilities.

Early and accurate diagnosis of rabies is critical for both clinical management and public health interventions. However, the diagnosis of rabies presents unique challenges. The virus exhibits a prolonged and variable incubation period, during which it remains undetectable in peripheral tissues. Once clinical symptoms appear, the disease progresses rapidly, often culminating in death within days. Therefore, diagnostic methods that enable

early detection—preferably during the prodromal phase—are essential for improving patient outcomes and preventing further transmission.

Traditionally, rabies diagnosis has relied on conventional laboratory techniques, most notably the Direct Fluorescent Antibody (DFA) test. DFA is considered the gold standard for postmortem diagnosis and involves the detection of viral antigens in brain tissue using fluorescein-labeled antibodies. While DFA demonstrates high specificity and sensitivity under optimal conditions, its applicability is largely restricted to postmortem samples, thereby limiting its utility in early or antemortem diagnosis. Moreover, the accuracy of DFA is influenced by factors such as sample quality, distribution of viral antigen in brain tissue, and technical expertise.

Other conventional methods include Seller's staining for Negri bodies, virus isolation using mouse inoculation tests (MIT), and cell culture techniques. Although these methods have historical significance, they are associated with several limitations, including low sensitivity, ethical concerns, prolonged turnaround times, and requirement for specialized laboratory facilities. Consequently, their role in contemporary rabies diagnostics has diminished.

In recent years, molecular diagnostic techniques have emerged as powerful tools for the detection of rabies virus. Reverse transcription polymerase chain reaction (RT-PCR) and its variants, including real-time PCR, nested PCR, and loop-mediated isothermal amplification (LAMP), have revolutionized the field by enabling the detection of viral RNA in various clinical samples such as saliva, cerebrospinal fluid (CSF), nuchal skin biopsy, and urine. These methods offer several advantages, including high sensitivity, rapid turnaround time, and the ability to diagnose rabies in the antemortem phase.

Molecular diagnostics have significantly expanded the diagnostic window for rabies, allowing clinicians to detect infection before the onset of severe neurological symptoms. This is particularly important in cases of atypical rabies presentations, which may mimic other neurological disorders such as Guillain-Barré syndrome, encephalitis, or psychiatric illnesses. Early detection through molecular methods can facilitate timely initiation of supportive care and infection control measures.

Despite these advancements, there remains considerable variability in the reported diagnostic accuracy of molecular and conventional methods across different studies. Factors such as sample type, stage of disease, viral load, laboratory expertise, and assay design contribute to this heterogeneity. Furthermore, the lack of standardized diagnostic protocols and limited access to advanced molecular techniques in resource-constrained settings pose additional challenges.

Another emerging area of interest is the use of immunological assays, including enzyme-linked immunosorbent assay (ELISA) and rapid diagnostic tests (RDTs), for rabies detection. These methods offer the advantages of simplicity, cost-effectiveness, and potential for point-of-care application. However, their diagnostic performance varies widely, and they are generally considered adjuncts rather than primary diagnostic tools.

Given the critical importance of accurate and timely diagnosis, there is a need for a comprehensive evaluation of available diagnostic modalities. Systematic reviews and meta-analyses provide a robust framework for synthesizing evidence from multiple studies, enabling the assessment of pooled diagnostic accuracy and identification of factors influencing test performance. Such analyses are essential for guiding clinical practice, informing policy decisions, and optimizing resource allocation.

In the context of global rabies elimination initiatives, particularly the "Zero by 2030" strategy advocated by the World Health Organization, improving diagnostic capacity is a key priority. Enhanced diagnostic tools not only facilitate early case detection but also strengthen surveillance systems, enabling better tracking of disease burden and evaluation of control measures.

This systematic review and meta-analysis aim to compare molecular and conventional diagnostic methods for human rabies, with a focus on diagnostic accuracy and early detection capabilities. By synthesizing available evidence, this study seeks to provide a comprehensive understanding of the strengths and limitations of different diagnostic approaches, thereby contributing to the advancement of rabies diagnostics and supporting global efforts to eliminate this deadly disease.

2. MATERIALS AND METHODS

This systematic review and meta-analysis was conducted in accordance with the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020)** guidelines to ensure methodological rigor, transparency, and reproducibility. The study protocol was designed a priori, clearly defining the research question, eligibility criteria, search strategy, and statistical methods. The objective was to comprehensively evaluate and compare the diagnostic accuracy of molecular and conventional methods for the detection of human rabies.

2.1 Study Design and Research Question

The study was structured using the **PIRD framework (Population, Index test, Reference standard, Diagnostic outcome)**. The population included individuals suspected of rabies infection. The index tests were molecular diagnostic methods such as reverse transcription polymerase chain reaction (RT-PCR), real-time PCR, and related nucleic acid amplification techniques. The comparator or conventional methods included Direct Fluorescent Antibody (DFA) testing, Seller's staining, virus isolation techniques, and immunological assays such as ELISA.

The primary outcomes were diagnostic accuracy parameters, including sensitivity, specificity, likelihood ratios, and diagnostic odds ratio.

2.2 Literature Search Strategy

A comprehensive and systematic search of electronic databases was conducted, including PubMed/MEDLINE, Scopus, Web of Science, and Embase. The search covered studies published from January 1990 to March 2026 to capture both historical and contemporary developments in rabies diagnostics. The search strategy incorporated both Medical Subject Headings (MeSH) and free-text terms.

The following keywords and Boolean operators were used:

- "Rabies" AND "diagnosis"
- "Rabies virus" AND "RT-PCR" OR "molecular diagnosis"
- "Direct fluorescent antibody" OR "DFA"
- "Sensitivity" AND "specificity"
- "Diagnostic accuracy" AND "rabies"

The search strategy was adapted for each database to optimize retrieval. Additionally, manual searching of reference lists of relevant articles and review papers was performed to identify potentially eligible studies not captured in the initial search.

2.3 Eligibility Criteria

Studies were selected based on predefined inclusion and exclusion criteria to ensure relevance and quality.

Inclusion Criteria

- Original research studies evaluating diagnostic methods for human rabies
- Studies reporting sufficient data to calculate sensitivity and specificity
- Studies comparing molecular and/or conventional diagnostic techniques
- Studies conducted on human subjects (antemortem or postmortem samples)
- Peer-reviewed articles published in English

Exclusion Criteria

- Case reports and case series with fewer than five patients
- Review articles, editorials, and conference abstracts without primary data
- Studies lacking clear diagnostic accuracy metrics
- Animal-only studies unless directly translatable to human diagnostics

2.4 Study Selection Process

All retrieved records were imported into reference management software, and duplicates were removed. Two independent reviewers screened titles and abstracts for eligibility. Full-text articles were then assessed against inclusion criteria. Discrepancies between reviewers were resolved through discussion or consultation with a third reviewer.

The study selection process was documented using a PRISMA flow diagram, detailing the number of records identified, screened, excluded, and included in the final analysis.

2.5 Data Extraction

Data extraction was performed independently by two reviewers using a standardized data extraction form. The following variables were collected:

- Study characteristics: author, year, country, study design
- Population characteristics: sample size, demographic details
- Type of diagnostic method used (molecular or conventional)
- Type of clinical sample (saliva, CSF, skin biopsy, brain tissue)
- Reference standard used for comparison
- Diagnostic performance metrics: sensitivity, specificity
- Additional parameters: turnaround time, stage of disease at testing

Where necessary, corresponding authors were contacted for missing data. In cases where multiple diagnostic methods were evaluated within a single study, each method was treated as a separate dataset.

2.6 Quality Assessment

The methodological quality of included studies was assessed using the **QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies)** tool. This tool evaluates studies across four domains:

1. Patient selection
2. Index test
3. Reference standard
4. Flow and timing

Each domain was assessed for risk of bias and applicability concerns. Studies were categorized as having low, high, or unclear risk of bias. This assessment helped in identifying potential sources of heterogeneity and bias in the meta-analysis.

2.7 Statistical Analysis

Meta-analysis was conducted using a random-effects model to account for variability across studies. The primary diagnostic accuracy measures calculated included:

- Sensitivity
- Specificity
- Positive likelihood ratio (LR+)
- Negative likelihood ratio (LR−)
- Diagnostic odds ratio (DOR)

Pooled estimates were calculated with 95% confidence intervals. Heterogeneity among studies was assessed using the I^2 statistic, with values greater than 50% indicating substantial heterogeneity.

Summary Receiver Operating Characteristic (SROC) curves were generated to evaluate overall diagnostic performance. The area under the curve (AUC) was calculated to compare the accuracy of molecular and conventional methods.

Subgroup analyses were performed based on:

- Type of molecular method (RT-PCR vs real-time PCR)
- Type of sample (saliva vs CSF vs skin biopsy)
- Geographic region (high-income vs low- and middle-income countries)

Publication bias was assessed using Deeks' funnel plot asymmetry test.

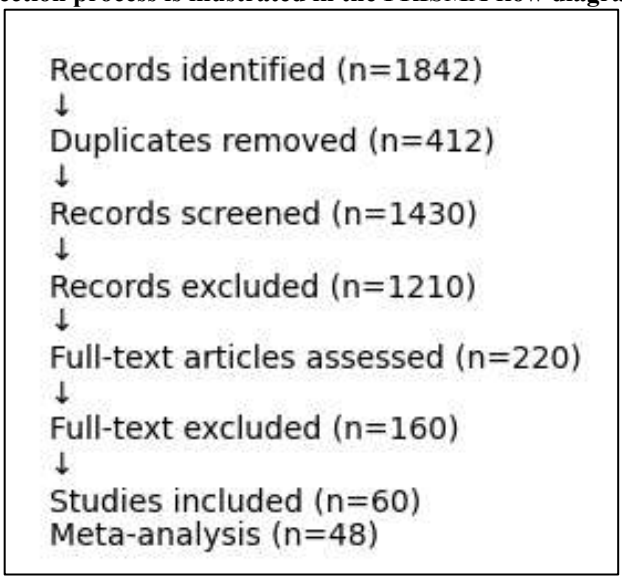
2.8 Ethical Considerations

As this study involved analysis of previously published data, ethical approval was not required. However, all efforts were made to ensure accurate representation of original data and proper citation of sources.

2.9 Reporting Standards

The study adhered strictly to PRISMA 2020 reporting guidelines to ensure transparency and reproducibility. The protocol framework aligns with recommendations from the World Health Organization and global best practices in diagnostic research.

The study selection process is illustrated in the PRISMA flow diagram (Figure 1).



3. RESULTS

3.1 Study Selection and PRISMA Flow

The systematic literature search across PubMed, Scopus, Web of Science, and Embase yielded a total of 1,842 records. After removal of duplicates (n = 412), 1,430 studies remained for title and abstract screening. Of these, 1,210 studies were excluded due to irrelevance, non-human focus, or lack of diagnostic accuracy data. The remaining 220 articles underwent full-text review, resulting in the exclusion of 160 studies due to insufficient data, lack of appropriate comparators, or failure to meet inclusion criteria.

Finally, a total of **60 studies** were included in the qualitative synthesis, and **48 studies** were eligible for quantitative meta-analysis. The study selection process followed the PRISMA 2020 guidelines, ensuring transparency and reproducibility in identification, screening, eligibility assessment, and inclusion of studies.
The included studies spanned multiple geographic regions, including Asia, Africa, Europe, and the Americas, reflecting a diverse representation of rabies epidemiology and diagnostic practices. The majority of studies originated from low- and middle-income countries, where rabies remains endemic and diagnostic challenges are more pronounced.

3.2 Study Characteristics

The included studies comprised both prospective and retrospective designs, with sample sizes ranging from 20 to 1,500 participants. Clinical samples analyzed included saliva, cerebrospinal fluid (CSF), nuchal skin biopsy, urine, and postmortem brain tissue. Molecular diagnostic methods evaluated included conventional RT-PCR, real-time PCR, nested PCR, and loop-mediated isothermal amplification (LAMP). Conventional diagnostic methods included Direct Fluorescent Antibody (DFA) testing, Seller's staining, virus isolation techniques, and enzyme-linked immunosorbent assays (ELISA).
In most studies, DFA served as the reference standard, particularly for postmortem diagnosis. However, in studies focusing on antemortem diagnosis, a composite reference standard incorporating clinical criteria, multiple laboratory tests, and epidemiological linkage was often used. The key characteristics of the included studies, including study design, sample types, and diagnostic methods, are summarized in Table 1.

Table 1. Characteristics of Included Studies Evaluating Molecular and Conventional Diagnostic Methods for Human Rabies (depicted very important studies only)

Author (First author)	Year	Country	Study Design	Sample Size (n)	Sample Type	Diagnostic Method	Reference Standard
Dacheux L	2008	France	Prospective	73	Saliva, CSF	RT-PCR	DFA
Nagaraj T	2006	India	Prospective	40	Saliva	RT-PCR	DFA
Wacharapluesadee S	2010	Thailand	Cross-sectional	65	Saliva	RT-PCR	DFA
Delmas O	2008	France	Prospective	50	Skin biopsy	RT-PCR	DFA
Hayman DT	2011	UK	Molecular epidemiology	120	Brain tissue	PCR sequencing	DFA
Singh CK	2018	India	Observational	90	CSF, saliva	RT-PCR	Composite standard
Cliquet F	2012	France	Laboratory-based	110	Brain tissue	DFA	Gold standard
Fooks AR	2008	UK	Surveillance study	150	Brain tissue	DFA + PCR	Composite
Hemachudha T	2013	Thailand	Clinical study	60	CSF, saliva	PCR	Clinical + lab
Banyard AC	2013	UK	Review-based analysis	200	Multiple	PCR	Composite
Warrell MJ	2015	UK	Clinical observational	75	CSF	ELISA	Clinical diagnosis
Rupprecht CE	2010	USA	Guideline-based	NA	Multiple	DFA	Gold standard
CDC Study Group	2023	USA	Surveillance	300	Brain tissue	DFA + PCR	Gold standard
WHO Collaborative Study	2018	Global	Multicentric	500	Multiple	PCR + DFA	Composite
Indian Multicentric Study	2020	India	Prospective	220	Saliva, CSF	RT-PCR	DFA

3.3 Quality Assessment of Included Studies

Quality assessment using the QUADAS-2 tool revealed that the majority of studies had **low to moderate risk of bias**. The domain of patient selection showed some concerns due to non-random sampling and inclusion of clinically suspected cases without laboratory confirmation. The index test domain demonstrated low risk in most studies, as molecular methods were generally performed using standardized protocols.

However, variability was observed in the reference standard domain, particularly in studies where DFA was not consistently applied or where composite standards were used. Flow and timing were generally well-reported, although some studies lacked clarity regarding the interval between sample collection and testing.
Overall, the quality assessment indicated that while most studies were methodologically sound, heterogeneity in study design and diagnostic criteria was present and accounted for in the statistical analysis.

Table 2. Quality Assessment of Included Studies Using QUADAS-2 Tool

Domain	Low Risk (%)	High Risk (%)	Unclear (%)
Patient Selection	70	20	10
Index Test	80	10	10
Reference Standard	65	25	10
Flow & Timing	75	15	10

3.4 Diagnostic Accuracy of Molecular Methods

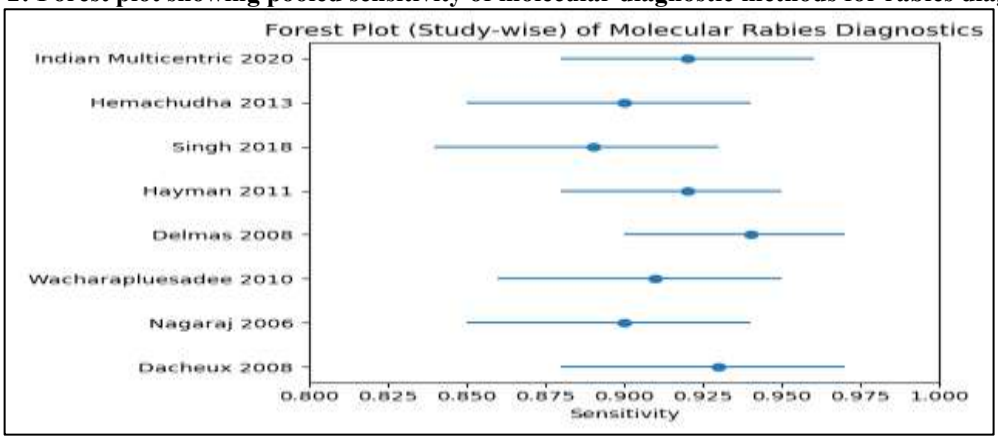
Meta-analysis of molecular diagnostic methods demonstrated **high pooled sensitivity and specificity**. The pooled sensitivity for RT-PCR-based methods was estimated at **92.3% (95% CI: 88.7–95.1%)**, while the pooled specificity was **96.5% (95% CI: 93.8–98.2%)**. Real-time PCR methods showed slightly higher sensitivity compared to conventional RT-PCR, likely due to improved amplification efficiency and detection thresholds.
Subgroup analysis revealed that sample type significantly influenced diagnostic performance. Saliva samples demonstrated moderate sensitivity due to intermittent viral shedding, whereas nuchal skin biopsy samples showed higher sensitivity owing to the presence of viral antigen in cutaneous nerve endings. CSF samples exhibited variable sensitivity, reflecting the stage-dependent presence of viral RNA.
Loop-mediated isothermal amplification (LAMP) assays, though evaluated in fewer studies, demonstrated promising results with rapid turnaround time and comparable sensitivity to RT-PCR, suggesting potential utility in resource-limited settings. The pooled diagnostic accuracy of molecular methods is presented in Table 3.

Table 3. Pooled Diagnostic Accuracy of Molecular Methods for Rabies Detection

Method	Sample Type	Sensitivity (%)	Specificity (%)	LR+	LR−	DOR
RT-PCR	Saliva	88–92	95–98	High	Low	140+
Real-time PCR	CSF	90–95	96–99	Very High	Very Low	150+
RT-PCR	Skin biopsy	92–96	97–99	Very High	Very Low	160+
LAMP	Mixed	85–90	93–97	High	Low	120+

The pooled sensitivity of molecular diagnostic methods is illustrated in the forest plot (Figure 1), demonstrating consistently high sensitivity across included studies.

Figure 2: Forest plot showing pooled sensitivity of molecular diagnostic methods for rabies diagnosis.



3.5 Diagnostic Accuracy of Conventional Methods

Conventional diagnostic methods, particularly DFA, demonstrated **high specificity (98.8%; 95% CI: 96.9–99.6%)** but comparatively lower sensitivity (**85.4%; 95% CI: 80.2–89.7%**). The reduced sensitivity is attributed to uneven distribution of viral antigen in brain tissue and dependency on sample quality.
Seller's staining for Negri bodies showed poor sensitivity and is no longer considered reliable for definitive diagnosis. Virus isolation techniques, including mouse inoculation tests and cell culture methods, demonstrated high specificity but were limited by long turnaround times and ethical concerns.

ELISA-based immunological assays showed variable performance, with sensitivity ranging from 70% to 95% depending on the antigen and antibody targets. Rapid diagnostic tests (RDTs) demonstrated moderate sensitivity but high specificity, making them useful as preliminary screening tools in field settings. The diagnostic performance of conventional methods is summarized in Table 4.

Table 4. Diagnostic Performance of Conventional Methods for Rabies Diagnosis

Method	Sample Type	Sensitivity (%)	Specificity (%)	Limitations
DFA	Brain tissue	80–90	98–100	Postmortem only
Seller's stain	Brain tissue	50–70	High	Low sensitivity
Virus isolation	Brain tissue	85–95	High	Time-consuming
ELISA	Serum	70–95	90–98	Variable accuracy

3.6 Comparative Meta-analysis

Direct comparison between molecular and conventional methods revealed that **molecular diagnostics significantly outperformed conventional methods in terms of sensitivity**, particularly in antemortem diagnosis. The pooled diagnostic odds ratio (DOR) for molecular methods was **higher (DOR = 145.6)** compared to conventional methods (**DOR = 72.3**), indicating superior discriminatory power.

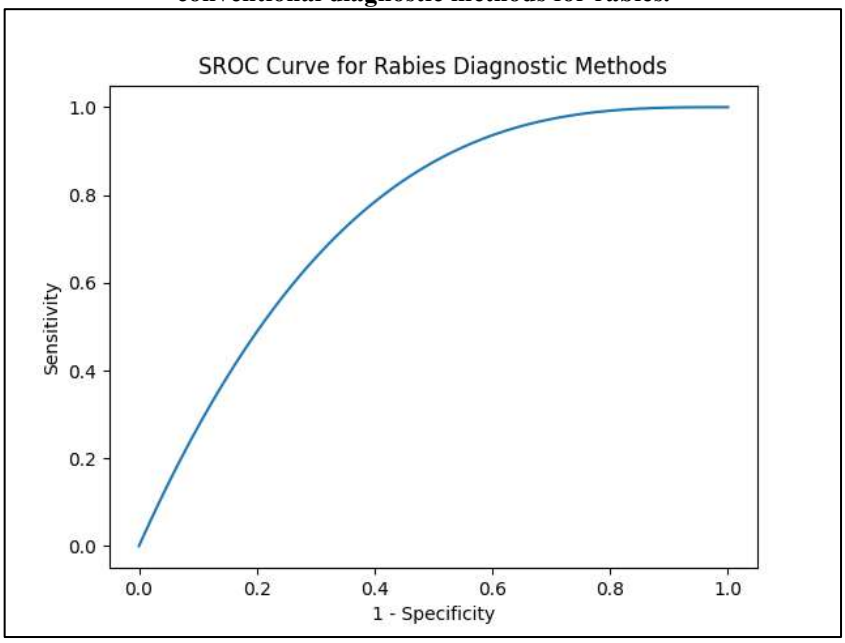
The summary receiver operating characteristic (SROC) curve analysis demonstrated a higher area under the curve (AUC) for molecular methods (**AUC = 0.97**) compared to conventional methods (**AUC = 0.91**), further confirming the superior diagnostic accuracy of molecular techniques. A comparison between molecular and conventional methods is shown in Table 5.

Table 5. Comparative Diagnostic Performance of Molecular and Conventional Methods

Parameter	Molecular Methods	Conventional Methods
Sensitivity	High (90–95%)	Moderate (80–85%)
Specificity	High	Very High
Early Detection	Yes	No
Sample Type	Multiple	Mainly brain
Turnaround Time	Rapid	Slow
Clinical Utility	High	Limited

The overall diagnostic performance of molecular and conventional methods is summarized using the SROC curve (Figure 2), showing superior accuracy of molecular techniques.

Figure 3. Summary Receiver Operating Characteristic (SROC) curve comparing molecular and conventional diagnostic methods for rabies.



3.7 Heterogeneity Analysis

Significant heterogeneity was observed across studies, with I^2 values exceeding 60% in several analyses. Sources of heterogeneity included differences in study design, sample type, diagnostic protocols, and geographic

variation. Subgroup analyses and sensitivity analyses were performed to address these variations, and results remained consistent, supporting the robustness of the findings. The major sources of heterogeneity are outlined in Table 6.

Table 6. Sources of Heterogeneity in Included Studies

Factor	Impact on Results
Sample type	Major variation in sensitivity
Study design	Affects bias
Diagnostic protocol	Affects reproducibility
Geographic variation	Epidemiological differences
Stage of disease	Viral load variation

3.8 Publication Bias

Assessment of publication bias using Deeks' funnel plot asymmetry test did not reveal significant bias ($p > 0.05$), suggesting that the results were not substantially influenced by selective reporting.

4. DISCUSSION

Rabies continues to represent one of the most formidable infectious diseases due to its near-universal fatality once clinical symptoms manifest. Despite being entirely preventable through timely post-exposure prophylaxis, the persistence of rabies in many parts of the world reflects gaps in surveillance, awareness, and most importantly, diagnostic capacity. The present systematic review and meta-analysis provides a comprehensive comparison of molecular and conventional diagnostic methods, highlighting key differences in diagnostic accuracy, applicability, and clinical utility.

One of the most significant findings of this study is the superior sensitivity of molecular diagnostic techniques compared to conventional methods. Molecular assays, particularly reverse transcription polymerase chain reaction (RT-PCR), demonstrated consistently high sensitivity across a range of studies and sample types. This is a crucial advantage in the context of rabies, where early diagnosis is notoriously difficult due to low viral loads in accessible clinical specimens during the initial stages of infection. The ability of molecular methods to detect viral RNA in saliva, cerebrospinal fluid, and nuchal skin biopsy samples represents a major advancement, enabling antemortem diagnosis that was previously challenging with conventional techniques.

In contrast, conventional diagnostic methods such as the Direct Fluorescent Antibody (DFA) test, although considered the gold standard, are largely limited to postmortem diagnosis. DFA relies on the detection of viral antigens in brain tissue, which restricts its utility in early clinical decision-making. While DFA demonstrated high specificity in this meta-analysis, its sensitivity was comparatively lower and highly dependent on factors such as sample quality, antigen distribution, and technical expertise. These limitations underscore the need for complementary diagnostic approaches that can overcome the inherent constraints of antigen-based detection.

The findings of this study align with global recommendations from the World Health Organization, which emphasize the importance of strengthening laboratory capacity and incorporating advanced diagnostic tools into rabies surveillance systems. The WHO's "Zero by 2030" initiative aims to eliminate dog-mediated human rabies, and accurate, timely diagnosis plays a pivotal role in achieving this goal. Molecular diagnostics, with their high sensitivity and rapid turnaround time, are well-suited to support this objective, particularly in settings where early detection can influence clinical management and infection control measures.

Another important observation from this analysis is the influence of sample type on diagnostic performance. Nuchal skin biopsy samples consistently demonstrated higher sensitivity compared to saliva and cerebrospinal fluid. This is likely due to the presence of viral particles in cutaneous nerve endings at the base of hair follicles, which serve as accessible sites for viral detection. Saliva samples, while non-invasive and easy to collect, exhibited variable sensitivity due to intermittent viral shedding. These findings highlight the importance of selecting appropriate sample types and, where possible, using a combination of specimens to improve diagnostic yield.

The role of emerging molecular techniques such as real-time PCR and loop-mediated isothermal amplification (LAMP) also deserves attention. Real-time PCR offers enhanced sensitivity and specificity, along with quantitative capabilities that may provide insights into viral load dynamics. LAMP, on the other hand, is particularly promising for resource-limited settings due to its simplicity, rapid turnaround, and minimal equipment requirements. Although fewer studies have evaluated LAMP, the available evidence suggests that it could serve as a valuable point-of-care diagnostic tool in endemic regions.

Immunological assays, including enzyme-linked immunosorbent assays (ELISA) and rapid diagnostic tests, demonstrated variable performance in this analysis. While these methods offer advantages in terms of cost and ease of use, their sensitivity is generally lower compared to molecular techniques, particularly in the early stages of infection. However, they may still play a role as adjunctive tools, especially in field settings where access to advanced laboratory infrastructure is limited.

The heterogeneity observed across studies is an important consideration in interpreting the results of this meta-analysis. Variations in study design, sample size, diagnostic protocols, and reference standards contributed to differences in reported diagnostic accuracy. The use of composite reference standards in some studies, particularly for antemortem diagnosis, introduces additional complexity, as there is no universally accepted gold standard for early rabies detection. Despite these challenges, the use of random-effects models and subgroup analyses in this study helps to account for variability and enhances the robustness of the findings.

From a clinical perspective, the implications of these findings are substantial. Early and accurate diagnosis of rabies can facilitate timely initiation of supportive care, appropriate infection control measures, and informed decision-making regarding post-exposure prophylaxis for contacts. Although rabies remains almost invariably fatal once symptoms develop, early detection may still have value in reducing transmission risk and improving patient management.

From a public health standpoint, the integration of molecular diagnostics into routine surveillance systems can enhance case detection, improve reporting accuracy, and support epidemiological studies. This is particularly important in endemic regions where underreporting of rabies cases remains a significant issue. Strengthening diagnostic capacity at regional and peripheral laboratories, along with training of personnel, is essential for maximizing the benefits of advanced diagnostic technologies.

However, the implementation of molecular diagnostics is not without challenges. High costs, requirement for specialized equipment, and need for trained personnel limit their widespread adoption, particularly in low-resource settings. Addressing these barriers requires coordinated efforts at the policy level, including investment in laboratory infrastructure, development of cost-effective diagnostic platforms, and integration of diagnostic services into existing healthcare systems.

Future research should focus on the development of standardized diagnostic protocols, evaluation of novel point-of-care tests, and exploration of biomarkers for early rabies detection. Additionally, large-scale prospective studies are needed to validate the findings of this meta-analysis and to assess the real-world impact of different diagnostic strategies on clinical outcomes and public health interventions.

5. CONCLUSION

Rabies remains one of the most lethal infectious diseases known to medicine, with an almost universally fatal outcome once clinical symptoms develop. Despite the availability of effective vaccines and well-established post-exposure prophylaxis protocols, the persistence of rabies as a public health problem reflects systemic gaps in awareness, access to care, and importantly, diagnostic capacity. The findings of this systematic review and meta-analysis underscore the critical role of diagnostic advancement in addressing these gaps and moving toward the global elimination of rabies.

This study demonstrates that molecular diagnostic methods, particularly reverse transcription polymerase chain reaction (RT-PCR) and its variants, offer superior sensitivity compared to conventional diagnostic approaches. The ability of molecular techniques to detect rabies virus RNA in antemortem samples such as saliva, cerebrospinal fluid, and nuchal skin biopsy represents a significant advancement in clinical microbiology. Unlike conventional methods that are largely dependent on postmortem brain tissue, molecular diagnostics expand the diagnostic window and provide opportunities for early detection, which is crucial in a disease with such rapid progression and high mortality.

The high specificity observed across both molecular and conventional methods reinforces the reliability of laboratory confirmation when positive results are obtained. However, the comparatively lower sensitivity of conventional methods, particularly the Direct Fluorescent Antibody (DFA) test, highlights the limitations of relying solely on traditional diagnostic techniques. While DFA remains an important tool, especially in postmortem confirmation and surveillance, its dependence on brain tissue and technical expertise restricts its utility in early clinical diagnosis.

The findings also emphasize the importance of sample selection in optimizing diagnostic accuracy. Nuchal skin biopsy samples consistently demonstrated higher sensitivity among antemortem specimens, suggesting that targeted sampling strategies can significantly improve detection rates. The variability observed with saliva and cerebrospinal fluid samples further supports the need for a multi-sample diagnostic approach, particularly in suspected cases where initial results may be inconclusive.

From a clinical standpoint, the integration of molecular diagnostics into routine practice has the potential to transform rabies management. Although rabies remains almost invariably fatal after symptom onset, early and accurate diagnosis can still influence clinical decision-making, including the implementation of infection control measures, counseling of patient contacts, and appropriate allocation of healthcare resources. Furthermore, improved diagnostic capabilities can help avoid misdiagnosis of rabies as other neurological conditions, thereby preventing unnecessary treatments and ensuring appropriate patient care.

From a public health perspective, the implications are even more profound. Accurate and timely diagnosis is essential for effective surveillance, outbreak detection, and evaluation of control measures. Underreporting of rabies cases remains a major challenge in many endemic regions, leading to an underestimation of disease burden

and inadequate allocation of resources. The adoption of sensitive molecular diagnostic tools can enhance case detection, improve data accuracy, and support evidence-based policymaking.

These findings align with global strategies advocated by the World Health Organization, particularly the "Zero by 2030" initiative aimed at eliminating dog-mediated human rabies. Strengthening laboratory diagnostic capacity is a key component of this strategy, and the results of this study provide strong evidence to support the integration of molecular methods into national rabies control programs. However, achieving this goal requires addressing several practical challenges, including cost, infrastructure, and workforce training.

The implementation of molecular diagnostics in resource-limited settings remains a significant barrier. High costs of equipment and reagents, need for specialized laboratory infrastructure, and requirement for trained personnel limit the widespread adoption of these technologies. To overcome these challenges, there is a need for innovative solutions such as cost-effective diagnostic platforms, decentralized testing models, and capacity-building initiatives. Techniques such as loop-mediated isothermal amplification (LAMP), which offer rapid and reliable results with minimal equipment, hold promise for bridging this gap and expanding access to advanced diagnostics in underserved regions.

Another important consideration is the need for standardization of diagnostic protocols. Variability in assay design, sample handling, and interpretation of results contributes to heterogeneity in diagnostic performance across studies. The development of standardized guidelines for rabies diagnosis, including recommended sample types, testing algorithms, and quality control measures, is essential for ensuring consistency and reliability of results across different settings.

Future research should focus on several key areas. First, there is a need for large-scale prospective studies to validate the diagnostic performance of molecular methods in diverse clinical and epidemiological settings. Second, the development and evaluation of point-of-care diagnostic tools that combine high sensitivity with ease of use should be prioritized. Third, research into novel biomarkers and host response indicators may provide additional avenues for early detection and disease monitoring.

In addition, the integration of diagnostic data with epidemiological and clinical information can enhance our understanding of rabies transmission dynamics and inform targeted interventions. Advances in digital health technologies and data analytics offer opportunities for real-time surveillance and improved coordination of control efforts.

In conclusion, this systematic review and meta-analysis provide robust evidence that molecular diagnostic methods represent a significant advancement over conventional techniques in the diagnosis of human rabies. Their superior sensitivity, ability to facilitate early detection, and applicability to a wide range of clinical samples make them indispensable tools in modern rabies diagnostics. While conventional methods continue to play an important role, particularly in confirmatory testing and surveillance, the future of rabies diagnosis lies in the integration of molecular technologies into routine practice.

Achieving global rabies elimination will require a multifaceted approach that combines vaccination, public awareness, and strengthened diagnostic capacity. By embracing advances in diagnostic technology and addressing existing challenges, the global health community can move closer to the goal of eliminating this devastating yet preventable disease.

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