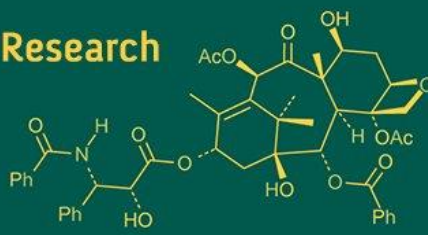


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Rabies dynamics: Exploring epidemiology, pathogenesis, and immune evasion mechanisms

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Abstract

Rabies is a severe and often fatal zoonotic viral disease caused by Lyssavirus species within the Rhabdoviridae family, leading to acute encephalomyelitis in both humans and other mammals. The virus has a bullet-shaped, enveloped structure with a negative-sense RNA genome. Transmission most commonly occurs through the bite of an infected animal. Viral entry into neurons is facilitated primarily by nicotinic acetylcholine receptors (nAChR), neuronal cell adhesion molecules (NCAM), and tumour necrosis factor receptor superfamily member 16. After initially infecting peripheral motor neurons, the virus travels to the central nervous system, where it replicates and induces neurological dysfunction. The incubation period ranges from 2 weeks to 6 years, depending on factors such as bite location and viral dose. Diagnosis relies on the direct fluorescent antibody test, regarded as the gold standard. Once clinical symptoms appear, rabies is invariably fatal and incurable. The proximity of the bite to the brain accelerates the onset of disease. Despite this, vaccines for both humans and dogs are available, and immediate post-exposure prophylaxis can prevent disease if administered promptly. Pre-exposure vaccination schedules are at days 0, 7, and 28, while post-exposure regimens are at days 0, 3, 7, 14, and 28. The WHO recommends a vaccine potency of 2.5 IU per human dose and 1 IU per animal dose. This mini-review summarizes key aspects of rabies epidemiology, modes of transmission, pathogenesis, immune evasion strategies, receptors, immunisation responses, diagnostic approaches, and strategies for prevention and control.

Keywords: Rabies, encephalomyelitis, nervous system, Negri bodies, nucleoprotein, glycoprotein, acetylcholine receptors, pre-and post-exposure

Introduction

Rabies is a zoonotic disease that affects the brain and causes acute encephalomyelitis in animals and humans. It results in tens of thousands of deaths annually, with the highest impact in Asia and Africa [1]. The global economic burden is estimated at \$8.6 billion per year. Children under 15 represent 40% of those bitten by suspected rabid animals. Approximately 5,000 animal rabies cases are reported to the CDC each year, with over 90% occurring in wildlife. The eclipse phase ranges from 2 weeks to 6 years, depending on viral load, inoculation site, and innervation density [2]. Rabies is transmitted by RNA viruses in the Lyssavirus genus.

The rabies virus is a neurotropic, bullet-shaped, single-stranded, negative-sense RNA virus. Lyssaviruses encode five highly conserved viral proteins. The genomic RNA is encapsulated with nucleoprotein and phosphoprotein, forming a ribonucleoprotein (RNP) complex that supports viral replication in the host cell cytoplasm. The nucleocapsid protein is a key diagnostic target due to its conserved gene, while the glycoprotein determines pathogenicity and induces protective immunity [3]. At the bite site, the virus enters peripheral nerves via synapses, then migrates to central nervous system neurons, where it replicates and causes cerebral damage. Rabies presents as either furious or paralytic forms, both leading to coma and death. Diagnosis is based on the development of severe neurological symptoms and subsequent paralysis.

Once clinical symptoms appear, rabies is universally fatal and cannot be cured or prevented at this stage. In developing regions, dogs are the primary reservoir, while wildlife serves as the main host in developed countries [4].

This mini-review provides an overview of rabies virus epidemiology, transmission, pathogenesis, immune evasion mechanisms, receptors, immunization response, diagnostics, prevention, and control.

Etiology

Rabies is considered one of the world's oldest infectious illnesses, caused by RNA viruses from the family Rhabdoviridae and the genus *Lyssavirus* [5]. "Rabies" is derived from the Sanskrit word "rabhas," meaning "harm" (India). The term "Lyssavirus" is derived from "Lyssa," the Greek goddess of rage. It is a zoonotic illness that affects both animals' and humans' central nervous systems and is one of the seventh most common infectious illnesses in the world. It is transmitted by bites, licks, and scratches from infected animals [6]. *Lyssavirus* is one of seven genera that comprise the Rhabdoviridae family, a part of the Monogegavirales order. It consists of the classical rabies virus (RABV; genotype 1), the Lagos bat virus (LBV; genotype 2), the Mokola virus (MKV; genotype 3), the Duvenhage virus (DV; genotype 4), the European bat lyssavirus 1 (EBLV-1; genotype 5), the European bat lyssavirus 2 (EBLV-2; genotype 6) and the Australian bat lyssavirus (ABLV; genotype 7) [7]. In addition, four novel viruses identified from insectivorous bats have recently been proposed as members of the *Lyssavirus* genus: Irkut virus (IV), Khujand virus (KV), Aravan virus (AV), and West Caucasian bat virus. Although lyssaviruses differ antigenically, they are morphologically and neurotropically identical [8].

Genome organisation

Rabies virus is neurotropic, bullet-shaped (180nm x 75nm), Single-stranded, negative-sense, non-segmented, enveloped, linear RNA virus with a ~12 kb genome [9]. There are seven genotypes of the rabies virus, and over 16 different

lyssaviruses have been identified. Among these, genotype 1 of the rabies virus is the primary cause of the disease in mammals. Lyssaviruses encode five highly conserved monocistronic viral proteins, arranged in the following sequence from 3' to 5': the nucleoprotein (N) with a length of 1334 base pairs and a molecular weight of 57 kDa, the phosphoprotein (P) measuring 978 base pairs and 38.5 kDa, the matrix protein (M) at 840 base pairs and 25 kDa, the glycoprotein (G) comprising 1647 base pairs and 67 kDa, and the large RNA-dependent RNA polymerase protein (L) with a length of 6381 base pairs and a molecular weight of 200 kDa [10]. The RNP forms a helix that M encapsulates, connecting the RNP to the lipid bilayer membrane envelope—the RNP complex aids viral growth in the cytoplasm of host cells. The exterior of the virion is enclosed with projecting spikes made up of viral G protein trimers (10nm long). The glycoprotein is the only viral surface protein responsible for viral pathogenicity and promotes protective immunity against rabies. The functions of rabies proteins are described in Table 1, and the Rabies viral proteins (A) and the domain structure of Rabies glycoprotein (B) are shown in Figure 1. Besides that, there are intergenic elements between the coding regions of the genome: N-NS, NS-M, M-G, and G-L, where the lengthy intergenic element between G and L is known as the pseudogene. It has been used as a reference for distinguishing different rabies genotypes [11]. Sodium hypochlorite, 45-75 percent ethanol, phenol, quaternary ammonium compounds, iodine preparations, ether, formaldehyde, trypsin, propiolactone, and several other detergents can all inactivate the rabies virus. It is also inactivated by extremely low pH (below 3) or extremely high pH (greater than 11). This virus is susceptible to UV light. It is quickly inactivated by sunlight and drying, and it does not persist in the environment for extended periods when found in dried blood and secretions [12].

Table 1: Rabies proteins and their functions

Protein	Function
N	- Protein exhibits precipitating, complement fixing, immunofluorescent & ELISA activity - Major role in diagnosis & virus identification - Amount of N protein-determines the transition between transcription & replication activities of genomic RNAs
P	- Rabies virus-survival & replication in muscle cells - The P protein forms NC - That encloses the viral RNA along with the N and L proteins and is involved in transcription & replication along with the L protein. - The P protein also functions as a chaperone of soluble nascent N protein - Act as an important determinant in retrograde transport of the virus within axons after binding with dynein light chain LC8.
M	Responsible for the assembly & budding of the virus by regulating transcription and replication
G	- Acts as protective and neutralizing antigen - Responsible for binding with the target cell receptors (pH-dependent)
L	Vital for pathogenesis along with G protein, survival & replication of rabies virus

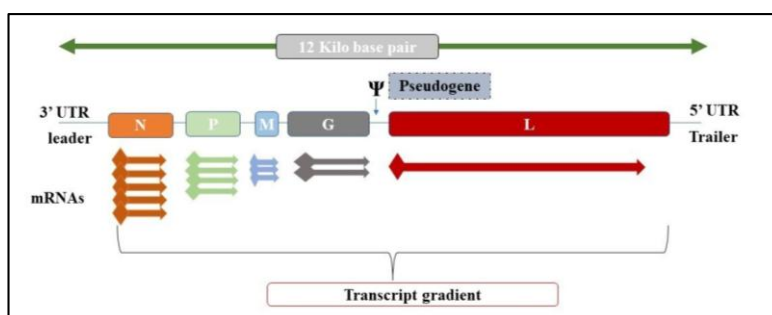


Fig 1: Genome structure of rabies virus. Five structural proteins of the Rabies virus: N, P, M, G, and L and its transcription gradient.

Replication and transcription

The infection spreads through the bite of an infected rabid animal. Substantially greater interaction between G protein and acetylcholine receptors in the peripheral nervous system indicates viral attachment ^[13]. The virus subsequently enters the CNS via endocytosis. The pH decreases within the endosome, triggering conformational changes in the G protein that promote fusion of the viral membrane with the endosomal membrane, culminating in the discharge of the viral nucleocapsid ^[14]. Because mammalian cells cannot transcribe negative-stranded RNA, the Rabies virus encodes its RNA-dependent RNA polymerase. The virion-associated RNA polymerase transcribes the single-stranded RNA genome into positive-sense mRNA, and it encodes the proteins. Although G protein production initiates on free ribosomes, it is completed and glycosylated in the Endoplasmic Reticulum and Golgi apparatus. The genome RNP serves as a blueprint for complementary positive-sense RNA, which generates negative-sense progeny RNA ^[15]. The L-P polymerase complex penetrates neither nucleocapsid at the 3' end, known as the leader RNA, which is neither capped nor polyadenylated. Following transcription termination, the polymerase resumes transcription of the nucleoprotein mRNA, which has been capped and polyadenylated by the viral polymerase complex.

Later in the infection, L activity shifts toward replication, generating full-length positive-strand RNA copies lacking caps or poly (A) tails. These complementary RNAs, or cRNAs, are likewise encapsidated by nucleoprotein and attached to the L-P complex. They provide templates for forming new negative-strand RNA genomes, enclosed by N, to generate new nucleocapsids. During the assembly phase, the N-P-L complex wraps negative-stranded genomic RNA to form the RNP core, and the M protein manufactures a capsule around the RNP. The RNP-M complex relocates to a plasma membrane region containing glycoprotein inserts, and the M-protein begins to coil. The M-RNP complex attaches to the glycoprotein, and the virus emerges from the plasma membrane. The viral matrix protein creates a layer inside the envelope, while the viral glycoprotein produces the spikes on the outside ^[16].

Epidemiology

Chronicle of rabies

For thousands of years, civilisations have been scared of rabies. The first mention of rabies is said to have appeared in the Laws of Eshunna (Iraq) in the 23rd century BC ^[14]. Rabies is an old illness and a highly feared infection in humans and animals. Rabies in Canine species were also mentioned in the Avesta (Persia) in the sixth century BC and the Susrutasmhita in the first century (India) ^[17]. Celsus, a Roman scholar, accurately proposed in the first century A.D. that the saliva of the infected animal spread rabies. In the 1880s, the first effective treatment for rabies was developed ^[18]. Louis Pasteur, a French chemist, was experimenting with fowl cholera when he realised that virulent colonies no longer produced the disease. He also discovered that chickens inoculated with this weaker, or "attenuated strain", were resistant to new, virulent strains. Pasteur then tested an attenuated anthrax vaccine on cattle. It was successful. He next turned his attention to rabies, the world's scourge. His preliminary animal trials were

encouraging, but Pasteur desired more time to refine his attenuated vaccine before testing it on humans. In 1881, he also showed the neurotropism of the rabies virus. On July 6, 1885, a rabid dog attacked a 9-year-old boy called Joseph Meister. A neighbourhood physician treated the wounds and informed the family that Louis Pasteur was the only person who could rescue Joseph. Pasteur consented only after speaking with a few genuine physicians who declared that Joseph was a "dead kid walking," despite considerable convincing ^[19]. Joseph recovered completely after receiving 13 injections in 11 days. The news spread, and patients began to pour in from around the world. Over 20,000 patients had received Pasteur's post-exposure prophylactic vaccination by the time he died nine years later.

Territorial distribution

Every year, rabies claims the lives of tens of thousands of individuals. Apart from Antarctica, many nations are rabies-endemic. Because rabies is avoidable worldwide, several countries have achieved rabies-free status through stringent quarantine and geographic isolation ^[20]. According to the WHO, a nation can claim rabies-free status if it has no evidence of indigenously acquired animal or human rabies cases over the past 2 years, owing to surveillance and import controls. Despite wildlife immunisation initiatives, there remains a risk of reintroduction from neighbouring nations. Some countries such as Bahrain, Cyprus, Hong Kong, Maldives, Qatar, Singapore, Timor-Leste, Antigua, Belize, Falkland, Jamaica, Trinidad, Tobago, Albania, Finland, Gibraltar, Greece, Isle of Man, Portugal, Norway (except Svalbard), Congo, Libya Mauritius, Guam, Vanuatu, Cook Islands, New Caledonia, Solomon Islands, Papua New Guinea, New Zealand, Malaysia, Andaman & Nicobar Islands of India, Lakshadweep, Japan, Bahamas, Saint Kitts, Iceland, United Kingdom, Sweden, Australia, and Singapore have been free of this virus for many years ^[21]. According to the WHO worldwide vaccines research forum, rabies kills over 30,000 people in Asia each year, killing at least 24,000 people in Africa. The high death rates are in rural areas and among children below age 15 (approximately 40 percent). The main reason for the spread of rabies in this region is urbanisation. Bangladesh and India are the most affected, followed by Nepal, Myanmar, Bhutan, Thailand, and Indonesia ^[22].

Species affected and reservoirs

All mammals, including wild animals, are vulnerable to the rabies virus and can spread it. Carnivorous animals are the principal reservoir. Humans become infected by coming into contact with diseased animals. Although all animals are vulnerable to rabies, merely a small number of species act as reservoir hosts ^[23]. They include Canidae, Procyonidae, Viverridae, Mustelidae, and Chiroptera (bats). The virus spreads in two interconnected epidemiological cycles. Stray and neighbourhood dogs mostly keep the urban cycle going. Pet dogs, cats, and wild animals serve as reservoirs for the sylvatic cycle ^[21]. The term "spillover" refers to the intermittent spread of rabies from the reservoir to non-reservoir species. Raccoon (*Procyon lotor*), striped skunk (*Mephitis mephitis*), coyote (*Canis latrans*, infected with the dog variant), grey fox (*Urocyon cinereoargenteus*), Arctic fox (*Alopex lagopus*), and red fox (*Vulpes vulpes*) are the reservoir species ^[24].

Rabies transmission

The most common route of entry for the rabies virus is through saliva or contaminated tissue, via infected open-bite wounds or incisions in mucous membranes, rather than through unbroken skin. Following local muscle infection and viral absorption into peripheral neurons, the virus is transmitted to the central nervous system (through rapid retrograde transport) and replicated in the brain. During the slaughtering process, handling, catching, holding, and keeping canines in cages increases the risk of spreading to the butchers [25]. Non-bite exposure methods include inhaling aerosolized rabies virus, organ/cornea transplants, mucous membranes, open wounds, contamination of abrasions, and abrasions with rabies-infected saliva or infected brain samples from rabid animals. The risk of rabies infection from a bite (5-80%) is at least 50 times higher than the risk from a scratch [26]. The mortality rate from untreated bites by rabid dogs varies between 38% and 57%, influenced by factors such as the severity and location of the wound, as well as the assumed viral concentration in the saliva. However, because bat viruses multiply more quickly in muscle cells and at lower temperatures than dog rabies viruses, they may be more infectious when implanted superficially into the epidermis. Contact with animal vaccines may be significant when an attenuated vaccination is employed. Rabies prophylaxis is required in these cases [27].

Rabies pathogenesis

The rabies eclipse phase varies considerably, from 2 weeks to 6 years (average: 2 to 3 months), depending on viral concentration, inoculation site, and innervation density. Bites to the head, face, neck, and hands that bleed pose the most danger (generally related to a shorter incubation period due to decreased length and the greater number of neurons) [28]. Infected animals (domestic dogs, cats, and ferrets) may shed for up to 10 days before clinical indications appear. Virus shedding has been seen in wild animals for several weeks before symptoms start. The human incubation period is 1 to 3 months. Dogs infected with rabies typically show symptoms between 21 and 80 days after exposure [23], though the incubation period can vary significantly, being either shorter or longer. One known case of rabies in a person in the United States had an incubation time confidently calculated to be more than eight years [29]. The virus replicates at the inoculation site and then enters the peripheral nerve cells through nicotinic acetylcholine receptors. After reaching the CNS, the virus infects and damages many nerve cells. This damage to nerve cells is responsible for exhibiting rabies-specific symptoms. As a result, the virus begins to spread away from the central nervous system (centrifugal spread) along neuronal pathways, primarily through the parasympathetic nervous system, which then infects the skin, heart, and other organs. The axonal retrograde transport mechanism in neurons moves at rates of 12-100 mm/day [25].

Host infection

Virus entrance points are peripheral nerves, neuromuscular junction motor endplates, and other innervated tissues [30]. The virus is retained in endosomal transport vesicles after receptor-mediated entry and is retrogradely transported through axons via microtubules [31]. RNP complexes are produced and released from vesicles in the neuronal soma,

and primary transcription begins, leading to the synthesis of viral proteins [32]. The accumulation of viral proteins leads to the formation of cytoplasmic inclusion bodies, which serve as sites of viral RNA production (secondary transcription). Newly created RNPs are transported from replication sites, within inclusion bodies, to postsynaptic membranes [33]. The new Virions are formed and trans-synaptically transferred to next-order neurons via a viral glycoprotein mechanism. Budding in the synaptic cleft is followed by the receptor-mediated entrance at presynaptic membranes [34]. The virus eventually infects the brain; which areas are affected depends on which motor neurons innervate the site of entry. The virus moves from the brain to the salivary glands and is sporadically expelled in the saliva, ready to be transferred to another host [35]. Local symptoms begin when the virus spreads to the CNS, travels centrifugally, and reaches the dorsal root ganglia, which correspond to the nerves at the entrance site [36]. Viral replication in the dorsal root ganglia triggers inflammation, leading to pain, paraesthesia, and itching. The virus may also infiltrate peripheral nerves, causing inflammation and weakening in paralytic rabies patients [37].

Receptors

The key receptors involved in rabies virus-cell entry include the Nicotinic acetylcholine receptor (nAChR), the Neuronal cell adhesion molecule (NCAM), and the Tumour necrosis factor receptor superfamily member 16 (TNFRSF16; also known as p75NTR). Virus proliferation in muscle cells, followed by progeny virion budding in the synaptic cleft [29], may enhance neuroinvasion via receptors on presynaptic axonal membranes. The nAChR functions as an attachment receptor, concentrating exogenous virus in the synaptic cleft for delivery to receptors such as NCAM and p75NTR on the presynaptic membranes of motor neurons [38]. The location of nAChR proximal to the post-synaptic membranes of muscle cells within neuromuscular junctions may facilitate the infection of muscle cells before neuronal infection. RABV can sometimes attach directly to neural receptors and infect neurons without requiring nAChR binding or muscle cell infection [39].

Advancement of rabies in the nervous system

The rabies virus enters the motor endplate and, after receptor-mediated endocytosis just at the presynaptic membrane, travels to the neuron soma via retrograde axonal transport in a dynein-dependent manner, with transport directionality, measured transport velocities, and cotransport with the dynein-motor transported tumour necrosis factor receptor superfamily member 16 (p75NTR) [40]. The RNP is free from the endocytic vesicle in the soma, and initial transcription generates a 5' cap in addition to polyadenylated (AAA) viral mRNAs, a procedure mediated by the virion-associated large RNA polymerase protein (L) and the phosphoprotein (P) [41]. Except for the glycoprotein, which is translated through the ER and Golgi networks [42], viral proteins are translated on free ribosomes in the cytoplasm. Later in the process, the matrix protein (M) alters the activity of the RNA polymerase complex (enzymatic component L and cofactor P) from transcriptase to replicase, enabling the replication of the full-length RNA genome [43]. The negative-sense RNA genome is first transcribed into full-length positive-sense RNA strands, which are then transcribed into full-length negative-sense

RNA strands ^[44]. While the replication process is ongoing, both replication products, full-length positive-sense and negative-sense RNA genomes, begin to be assembled with the nucleoprotein (N) to form new RNPs, which can then be utilised as templates for additional RNA synthesis, where full-length genome replication and mRNA transcription occur or encapsidated into progeny virions ^[45]. M177 primarily participates in virion assembly and budding. M accumulates at cellular membranes and is found in the cytoplasm, inclusion bodies, and the nucleus ^[46]. M Oligomerisation at membranes might boost M's affinity for lipid bilayer and play a role in membrane curvature, RNP envelopment, and viral aggregation. A late domain (a protein interaction motif that plays a role in the budding process) in M improves viral aggregation efficiency ^[47]. The glycoprotein (G) on the membrane of virions is necessary for receptor binding and subsequent endocytic vesicle membrane fusion. The secretory route transports the G protein to budding sites. G is glycosylated during surface transport and generates homotrimers that are integrated into budding virions ^[48].

Neuronal endurance

RABV, a PDZ-binding motif in the cytoplasmic tail of a glycoprotein engaged in the organised events of neuronal survival through binding to microtubule-associated serine/threonine-protein kinase 2, might also directly influence neuronal cell death (MAST2) ^[26]. The attachment of glycoprotein to MAST2 may affect the pro-apoptotic activity of the MAST2-PTEN complex ^[49]. Furthermore, increased glycoprotein affinity for the PDZ-binding domain of Tyrosine-protein Phosphatase non-receptor type 4 (PTPN4) is linked with virulence attenuation. The significant attachment of glycoprotein to the PDZ-binding region of PTPN4, as an attenuated RABV, promoted cell death; RABV promoted pathogenicity and apoptosis ^[50]. Apoptosis appears to be more common in infections caused by attenuated or fixed viruses ^[51]. RABV multiplication in the CNS appears to be characterised by poor pathogen detection and immune responses ^[52]. Although type I interferon is the primary mediator of antiviral innate immune responses, RABVs are poor inducers of type I interferon, and such dampened type I interferon responses at peripheral virus entry sites may only partially abolish replication ^[53]. RABV-induced upregulation of FASLG73 and Fas ligand might cause the death of antigen-activated T cells and contribute to the termination of the immune response ^[54]. HLA class I histocompatibility antigen, chain G (HLA G), a nonclassical, immunosuppressive HLA74, an increase in the expression of programmed cell death ligand 1 (PDL1-also known as B7H1) might limit T cell proliferation and apoptosis ^[55].

Mechanisms of rabies viral proteins in immune evasion

To oppose these inherent signalling cascades, the rabies virus (RABV) has evolved in several ways. Viral infection initiates many signalling cascades, including the activation of genes encoding type I interferons ^[56] and the induction of chemoattractive and inflammatory responses, resulting in an antiviral environment and effective innate immune responses. The transcription factor nuclear factor- κ B (NF- κ B) regulates the expression of antiviral cytokines ^[57]. NF-B is a homodimeric or heterodimeric complex of several proteins, the most prevalent of which appears to be the

heterodimeric complex formed of transcription factor p65 (p65) and NF-B p50 subunit (p50). RABV matrix protein inhibits p43 ^[58], a p65 variation that stabilises and promotes the activation of p50-containing dimers (M). The innate immune system recognises intracellular RABV replication via intracellular receptors, such as the probable ATP-dependent RNA helicase DDX58 (also known as retinoic acid-inducible gene 1 protein [RIG-1]), which promotes phosphorylation of type I interferon regulatory factor 3 (IRF3) and IFN transcription ^[59]. The nucleoprotein (N) of RABV reduces RIG 1 activation, whereas the phosphoprotein (P) of RABV decreases IFN induction via inhibiting IRF3 phosphorylation ^[60]. Interferon binding to its receptors causes phosphorylation, dimerisation, association with interferon regulatory factor 9 (IRF9), and nuclear import of signal transducer and activator of transcription 1 (STAT1) and STAT2 heterodimers, which promote transcription of interferon-stimulated genes (ISGs) ^[61]. P193 prevents STAT1 and STAT2 nuclear import, and an N-terminal truncated phosphoprotein version of P (P3) interferes with STAT1-STAT2-dependent transcription within the nucleus. P also blocks type II IFN-dependent signalling via STAT1 homodimers ^[56].

Response to immunisation

The strain, dosage, and injection method all significantly affect the immune response and may contribute to immune suppression. Immune systems that guard against rabies virus infection have demonstrated that inactivated rabies vaccines can stimulate the generation of cytotoxic T cells ^[62]. Additional research in mice on the role of cell-mediated immunity demonstrated that cytotoxic T cells ^[63], alone do not protect against rabies, as reducing CD8 + T cells did not affect disease resistance or survival rate in vaccinated animals ^[64]. According to research, inactivated rabies vaccines activate B cells and CD4 + cells via MHC-II mechanisms and protect by inducing an immune response that includes the activation of lymphocytes, CD4 + antibody-secreting plasma cells, and neutralising antibodies that migrate into the nervous system parenchyma ^[10]. The activation of CD4 + T-lymphocytes leads to the production of RVNAs that target and kill the rabies virus, thereby helping prevent rabies patients from developing the illness. Plant-derived antigens elicited robust mucosal and humoral immune responses in mice, whether administered orally or intramuscularly ^[65]. A DNA-based vaccination should be capable of inducing a cell-mediated cytolytic CD8 + T cell response, CD4 + T cells and VNA ^[66].

The spectrum of clinical rabies

The clinical manifestations of rabies can vary significantly between patients, making a diagnosis based on observable symptoms critical ^[67]. Individuals with furious rabies exhibit altered behaviour, hallucinations, aerophobia, hydrophobia, increased salivation, and hostility, whereas these symptoms are absent in dog rabies except for aerophobia and hydrophobia ^[68]. Throughout the prodromal phase of paralytic rabies, the patient is aware. However, disorientation or sleepiness might occur sporadically during the acute neurological phase, though not to the same extent as in the furious form of the illness. Common symptoms include fever, malaise, lethargy, headache, loss of appetite, and tingling at the incision site ^[9]. Humans usually have an incubation period of 4 to 12 weeks, whereas animals

typically have 3 to 11 weeks, with some cases lasting up to 6 months. In furious rabies, the average period from the commencement of appearance of illness to death is 7.8 days, whereas paralytic rabies takes 11 days ^[69].

Diagnosis of rabies

Clinical indications such as itching, discomfort at the location of the bite wound and gastrointestinal disturbance are used to make a first-round diagnosis ^[70]. Diagnosis in the past was mainly based on histopathological methods, such

as various staining techniques for detecting cytoplasmic viral inclusions and Negri bodies. Now techniques like Nucleic acid amplification, reverse transcriptase-polymerase chain reaction, rapid fluorescent focus inhibition test, fluorescent antibody virus neutralization test, enzyme-linked immunosorbent assay, and direct rabid immunohistochemistry test, histological identification of Negri bodies, mouse inoculation test, direct fluorescent antibody test (gold stranded test), as well as Rabies tissue culture infection test as described in Figure 2 ^[71].

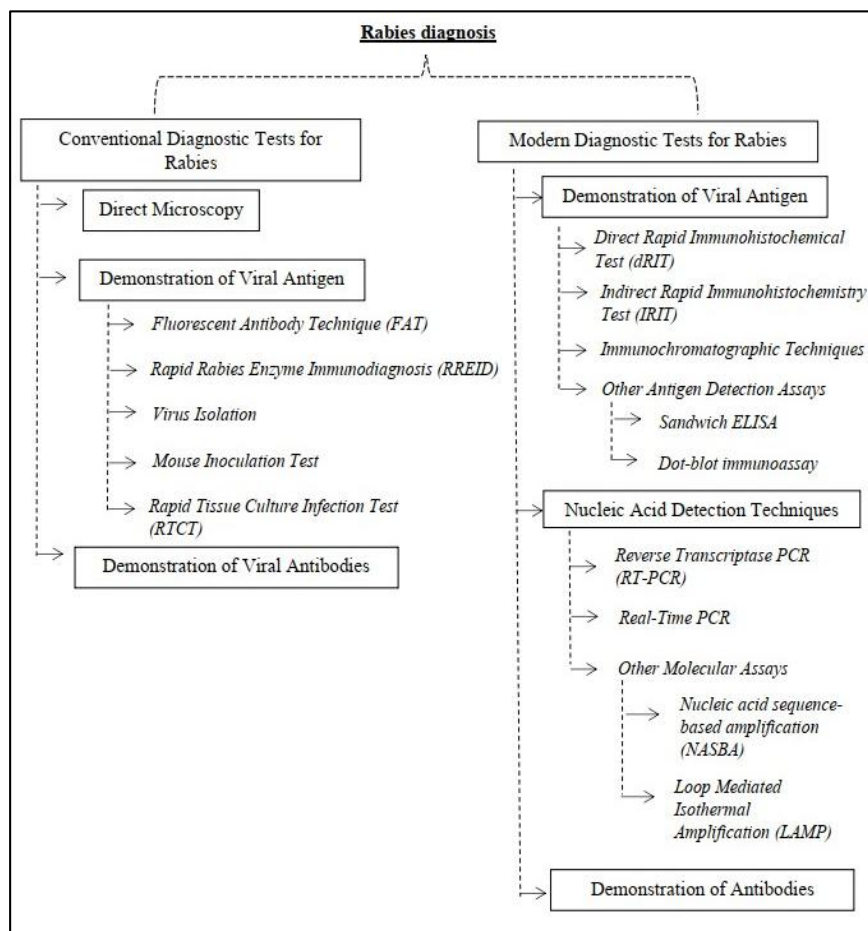


Fig 2: Rabies diagnostic methods: conventional and modern method of rabies diagnosis.

Therapeutic approach

Because dog bites cause nearly all human rabies deaths globally, mass vaccination of dogs remains the primary technique for eliminating urban rabies in endemic regions. However, in most countries, the main preventive approaches for limiting rabies transmission in reservoirs include various methods of culling free-roaming dogs ^[72]. Because the reduction in the vector population was minimal, it didn't stop the spread of rabies. Furthermore, mass vaccination of dogs must be supplemented with bait immunisation of wild animals to prevent disease spread from them ^[4]. Distributing bait rabies vaccines in high-risk areas is an effective way to reduce wildlife rabies. In general, vaccination coverage of around 70% of the vector population is adequate to prevent rabies transmission. However, current rabies vaccines for humans and animals have inherent limitations. Thus, efforts have been made to improve traditional rabies vaccines through technological innovation. Passive immunisation with human and horse rabies immunoglobulins is presently accessible. However, cleaning the bite or scratch site with large amounts of water or detergent within 15 minutes of

exposure will lower the virus load. Apply a topical iodine-containing or similarly viricidal treatment ^[73]. Never use ingredients such as Chile, salt, lemon, herbs, etc. After categorising the bite or scratch location, treatment was carried out. An animal-like on the intact skin, touching and feeding animals are deemed categories I (No exposure), minor scratches lacking bleeding and nibbling of uncovered skin are regarded as categories II (Exposure), single or numerous transdermal bites or scratches, saliva infectivity of mucous membranes or broken skin, and contact with infected wild mammals are considered categories III (Exposure) (Severe exposure) ^[74]. The closer the virus is to the brain, the faster it infects it.

Pre-and post-exposure prophylactic measures are used in rabies vaccination strategies. Pre-exposure prophylaxis is suggested for those at high risk, such as isolated populations, travellers, and individuals at occupational risk in highly endemic environments with inadequate access to effective post-exposure prophylaxis ^[72]. The pre-exposure immunisation strategy includes vaccinations at 0, 7, and 28 days, and after the last vaccination, a serological antibody

test should be performed within 1 to 3 weeks. Laboratory professionals should be re-examined every six months, and other diagnosticians should be re-examined every two years. Booster immunisation is strongly advised even if the titer falls below 0.5 International Units (IU) per ml. When serological surveillance is not available, a one-year booster immunisation is advised, followed by vaccinations every one to three years [75]. The regimen for post-exposure immunisation includes vaccinations at 0, 3, 7, 14, and 28 days. Vaccines and rabies immunoglobulins are required for post-exposure prophylaxis. In category I, wound cleaning is sufficient; in category II, wound washing with vaccinations is necessary; and in category III, rabies immunoglobulins are administered in addition to vaccines and wound treatment. VaxiRab-N, Verorab, Rabivax-S, and Rabipur are rabies vaccinations that the WHO has prequalified. Intradermal and intramuscular routes are used for immunisation; the injection sites for both routes are the same [6]. WHO recommends a vaccination efficacy of 2.5 IU per single intramuscular injection; a minimum serum titer of 0.5 IU/mL is considered protective. For veterinary vaccines, the potency must be 1 IU per dose [76]. Rabies immunoglobulins are indicated for category III exposure and are not advised if you have had rabies vaccination as pre-exposure prophylaxis and your first post-exposure prophylaxis dosage was more than seven days ago. Rabies immunoglobulins must be injected deep into and around all wounds; they can be diluted for multiple wounds if the need exceeds the maximum dose [21]. It comprises either human (HRIG) or equine (ERIG) rabies antibodies. Because immunoglobulins cannot cross intact blood-brain barriers, they are rendered ineffective once the virus has reached the brain and clinical signs have begun. The immunoglobulin, HRIG dosage 20 IU/kg body weight; ERIG dosage 40 IU/kg body weight, is injected locally around the bite location. The remainder is administered intramuscularly, far from the vaccination site [72].

Prophylaxis and control

There is no particular therapy for rabies, which is a lethal illness that is preventable but incurable. There is a shortage of knowledge about rabies treatment and prevention in both people and animals. People are aware of the disease's dangers but prefer to treat it with various traditional and religious treatments rather than seeking appropriate post-exposure prophylaxis [23]. Most people employ a wide range of traditional treatments in situations of rabid animal bites (mainly dogs). The persistent presence of conventional rabies treatment professionals in the community demonstrates the disease's importance. Rabies control in impoverished nations may be highly successful if proper planning, health education, 70 percent vaccination coverage for dog populations, and epidemiological surveillance are implemented [72]. Mass dog vaccination is the most realistic and cost-effective strategy to eliminate Canine Rabies, saving the lives of both canines and people [30]. All canines, regardless of age, weight, or health, should be vaccinated during mass vaccination efforts. A single or two inoculations one month apart can be used for primary immunisation. Vaccines are then administered yearly, biannually, or triannually to strengthen their immunity, depending on their effectiveness [15]. In the United States, the first successful example of a massive immunisation in a canine population happened in 1948 in Memphis and Shelby

County, Tennessee, which reduced both animal and human illnesses to zero [32]. Dogs, cats, and ferrets that have never been inoculated and subjected to a rabid animal must be put down immediately. If the owner refuses, the animals should be placed in strict isolation for 6 months. To meet pre-exposure vaccination guidelines, the rabies vaccine should be administered either upon entry into isolation or within 28 days prior to release. Human rabies can be avoided by a) avoiding rabies virus exposure, b) giving suitable rabies pre-exposure prophylaxis, and c) providing immediate local treatment of bite wounds in conjunction with proper rabies post-exposure prophylaxis. In addition, inactivated human vaccines are available for at-risk veterinary employees, other animal caretakers, wildlife officers, laboratory workers, and others [21].

Conclusion

Rabies is a fatal viral disease in both humans and animals that have not been vaccinated. Dog-borne rabies is expected to be eradicated worldwide in all endemic areas by 2030. Rabies in animals would also need to be controlled to prevent the virus from regularly switching hosts from wildlife reservoirs to domestic canines. Control measures include increasing public awareness and vaccinating both wild and domestic animals against lyssavirus. Human exposure to rabies is significantly reduced when rabies is eradicated from dog populations. The most excellent cost-effective technique for controlling and eliminating canine rabies is the mass immunisation of dogs. To prevent rabies, it's crucial to avoid direct contact with rabid animals and ensure that wildlife personnel, veterinarians, animal caretakers, and lab employees receive proper training and guidance.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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