

REVIEW ARTICLE

FROM BITE TO BRAIN: A DEEP DIVE INTO THE RABIES VIRUS AND ITS IMPACTS**Babar Mumtaz Malik, Amnah Mutaq Al-Rasheedi, Areeba Asif*, Noman Aslam**, Maryam Hameed***, Muhammad Atif[†]**

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Rabies lyssavirus is an enveloped, neurotropic virus with a single-stranded, negative sense RNA genome of approximately 12 kilobases, and is responsible for rabies in animals and humans. Rabies virus (RABV) displays a bullet-shaped morphology and has a broad host range. Rabies is severe, often life-threatening disease, endemic in many regions of Africa and Asia, with cases frequently under reported due to limited laboratory diagnostics. Transmission primarily occurs via the infected animal's saliva, especially dogs, which account for over 99% of human rabies cases. Following exposure, the virus initially infects peripheral motor neurons and subsequently invades the central nervous system (CNS), leading to fatal outcomes once symptoms develop. Prevention relies on mass dog vaccination, prompt post-exposure prophylaxis, and thorough wound care. Administration of rabies vaccine and immunoglobulin is essential for effective prevention. Achieving the World Health Organization's (WHO) target of eliminating dog-mediated human rabies by 2030 depends on strong government support, targeted vaccination, and increased public awareness.

Keywords: Endemic, Infected animal, Neurotropic, Pathogenesis, Rabies virus

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INTRODUCTION

Rabies is an extremely fatal viral disease that evokes significant fear due to its severe neurological sign and symptoms and near-certain mortality once symptoms appear. Caused by a member of the lyssavirus genus, rabies primarily affects animals, with human cases being relatively rare.¹ Saliva of the infected animals is the main transmitter of rabies that typically occurs through bites or scratches. After entering the body, rabies virus spreads to peripheral nerves and then to the CNS, where it causes the inflammation of the brain and the spinal cord.² The incubation period typically ranges from several weeks to months, often delaying diagnosis, and initial symptoms resemble a flu-like condition before progressing to anxiety, hallucinations, hydrophobia, and ultimately coma, and death.³

Effective prevention remains the cornerstone of rabies control. Immunizing domestic animals such as cats and dogs, practicing good hygiene principles as pet owners is necessary to reducing transmission risk.⁴ For individuals exposed to rabid animals, prompt administration of post-exposure prophylaxis (PEP), including vaccination and immunoglobulin is vital.⁵ Despite advances in surveillance and prevention, rabies persists in areas with inadequate veterinary and healthcare infrastructure. This article will explore the symptoms, diagnosis, treatment, and prevention strategies for rabies.

HISTORY

Rabies, is one of the earliest known disease and the most

feared illness of humans and animals with records dating to ancient Egypt (2,300 BC), Greece (described by Aristotle), and zoroastrian Avesta in 6th century BCE Persia.⁶ Early Indian texts such as Susrutasamhita noted its transmission via rabid dog saliva, was later confirmed experimentally by Zinke in 1804.⁷ Louis Pasteur's development of the first rabies vaccine in 1885 was a major milestone and it successfully treated Joseph Meister, a boy severely attacked by an animal affected by rabies.⁸ The 20th century saw critical advancements: identification of RABV in 1903⁹, its spread among European foxes in 1940s¹⁰, and the launch of oral vaccination campaigns in 1978. By 1991, Finland was declared to be rabies free, highlighting the success of integrated control measures.¹¹

EPIDEMIOLOGY

In general, RABV occurs globally with an exception of some geographical regions such as islands. As for now, some countries including United Kingdom, Sweden, Ireland, Japan, Norway, Iceland, New Zealand, Australia, Singapore, majority of Malaysia, Papua New Guinea, most Pacific Island countries and some Indonesian islands had been free from rabies virus for many years.¹² Rabies poses a serious threat to birds, humans and their domestic animals and wildlife. Estimates of human rabies deaths globally are 30,000–50,000 causing loss of large number of domestic animals and wildlife annually.¹³

In Europe, the red fox is a vital reservoir of RABV and increased incidence of rabies in foxes is often followed by rising cases of rabies in domestic animal like

sheep, cattle, horses, dogs, and cats.¹⁴ The existence of the sylvatic (wildlife) and urban (dog-mediated) cycles substantially overlaps in some areas, while other regions have mainly the sylvatic cycles. For instance, in 2010, 90% of the animal rabies documented in the United States and Canada were because of wild animals. Rabies may cause serious conservation problems in certain species of animals that are either rare or endangered.¹⁵ In Africa, Ethiopian wolf (*Canis simensis*) and the African wild dog (*Lycaon pictus*) are endangered species that face significant threats from rabies virus.¹⁶

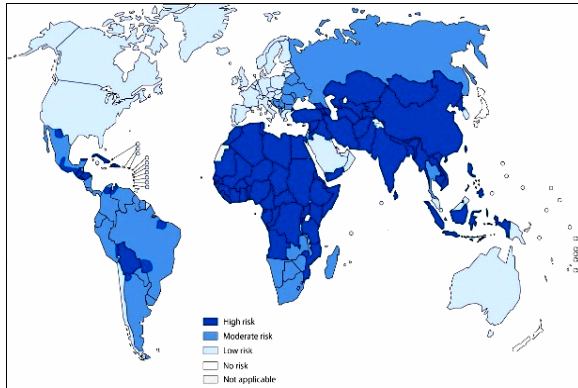


Figure-1: Geographical distribution of rabies virus¹⁷

HOST RANGE

Rabies can infect all mammals but transmission to humans and domestic animals is from certain species that serves as reservoir. These include species of the canid family (e.g., dogs, foxes, wolves, jackals, coyotes, and raccoon dogs), members of the mustelid family (e.g., skunks), members of the viverrid family (e.g., mongoose) members of the procyonid family (e.g., raccoons), and those forming the chiropteran order (bats). Rabies reservoirs are commonly divided into terrestrial species and bat species.¹⁸ Rabies is endemic in some populations and can be either accidental in man or a part of enzootic or epizootic cycles in animals. In the enzootic state, rabies persists as an endemic disease within a specific reservoir species in a particular area, maintaining a relatively stable incidence rate. An epizootic occurs when there is a sudden increase in rabies cases among the reservoir species. When rabies is inadvertently transmitted from a reservoir host species to a non-reservoir host species, the event is termed ‘spill over’. Common reservoir species include the raccoon (*Procyon lotor*), gray fox, striped skunk (*Mephitis*), red fox (*Vulpes vulpes*), coyote (infected with the dog variant), and Arctic fox (*Alopex lagopus*).¹⁹

TRANSMISSION

Rabies is transmitted from the bite, scratch, or by direct contact with saliva, tears, or neural tissue of a suspected or confirmed rabid animal with an open wound or mucous membrane. While the vast majority of human

rabies cases result from the bite of a rabid animal or contact of infected saliva with broken skin, rare cases have been linked to inhalation of airborne virus in laboratory settings or in bat caves densely crowded by the infected bats.²⁰

REPLICATION

The life cycle of the RABV involves a viral infection of the CNS, consists of a highly coordinated sequence of events within the host (Figure-2). It affects the host when an infected animal bites or scratches, introducing the virus through saliva into the wound. The virus initially replicates in local muscle tissues before spreading into peripheral nerve tissue and subsequently the CNS.²¹ After the virus enters the host cell it attaches itself to nicotinic acetylcholine receptors and gains entry through endocytosis.²² It releases its RNA to enter the cytoplasm where the viral RNA dependent RNA polymerase copies the genome into a *mRNA*. This *mRNA* is translated into nucleoprotein, glycoprotein, phosphoprotein, matrix protein, and RNA polymerase which are important viral structural and replicative proteins.²³

Synthesizing new viral genomes takes place along with the production of negative sense RNA strand from which positive sense RNA genomes are synthesized. These new viral RNA and proteins go to the cytoplasm of the infected host cell, and form ribonucleoprotein complexes.²⁴ The new virions bud off from the host cell by acquiring new envelop from the host cell membrane that consists of viral glycoproteins and in the process, the host cell is often killed. Such highly ordered replication ensures the production of a large number of virions that are capable of further infecting new cells and ultimately to new hosts.¹⁷

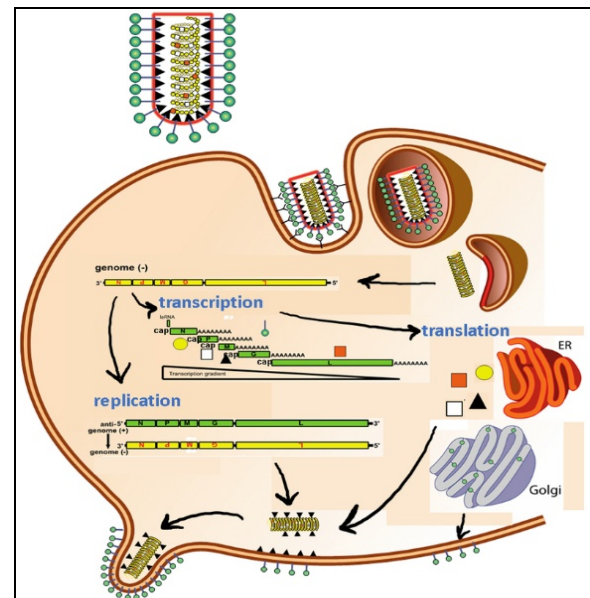


Figure-2: Replication Cycle of Rabies Virus¹⁹

PATHOGENESIS

Rabies lyssavirus typically enters the body through breaks in the skin or mucous membranes, as intact skin acts as a barrier to infection. After initial infection in muscle tissue near the entry site, the virus targets the motor neurons at neuromuscular junctions for entry into nervous system.²⁵ The virion undergo rapid retrograde axonal transport via dynein-mediated movement along microtubules. Upon reaching the CNS, the virus spreads trans-synaptically, leading to encephalitis characterized by neuronal dysfunction and apoptosis.²⁶ Fatal outcomes primarily result from brainstem involvement causing respiratory failure, often accompanied by metabolic disturbances like keto-alkalosis due to hyperventilation and neuromuscular hyperactivity.¹⁵

CLINICAL SIGNS AND SYMPTOMS

The clinical presentation of rabies in animals varies by species, individuals, and disease stage, but generally progresses through three phases.²⁷ After some time, there are clinical manifestations of the disease. The first stage commonly lasts about 1–3 days and may include minimal changes in behaviour such as aggression in normally calm animals, day time activity in animals that are active at night, the lack of fear of humans in wild animals, or abnormal eating and vocalization.²⁸ This is followed by the excitement or furious phase, characterized by increased aggression, irritability, and a tendency to bite objects, animals, or people. Affected animals may display excessive vocalization and abnormal behaviour. In some cases, seizures and hyperactivity occur, and wild animals may lose their fear of humans.²⁹ The final paralytic or ‘dumb’ phase involves progressive paralysis, starting with the hind limbs and facial muscles, leading to difficulty in swallowing, excessive drooling, and ultimately complete paralysis and death due to respiratory failure.³⁰

DIAGNOSIS

Diagnosing rabies involves a combination of clinical assessment, laboratory testing, and careful review of the patient’s exposure history. This can be challenging because early signs and non-specific and early markers are limited. Clinician assess the patient’s symptoms and medical history, with close attention to any recent animal exposure, especially bites or scratches from potentially infected animals. Early signs can include fever, headache, and discomfort or pain at site of bite. As the disease progress, more characteristic features may appear such as hydrophobia, hypersalivation, hallucinations, paralysis and seizures.³¹ The detection of rabies virus antigen or nucleic acid is both rapid and sensitive method of diagnosing rabies virus infection. Various immunoassay techniques can be used for the detection of rabies antigen which include direct fluorescent antibody (DFA), enzyme-linked

immunosorbent assay (ELISA), immunochemistry (e.g., direct rapid immunochemical test or dRIT, indirect rapid immunochemistry test or IRIT), or immunoblot (immunochromatography, dot-blot). Among them, DFA test is considered the gold standard test, which detects the presence of rabies virus antigen in infected tissues, especially in the brain.³²

PCR tests can detect rabies virus RNA in saliva, cerebrospinal liquid, or tissue specimens and is especially valuable for diagnosing rabies in living animals or humans before the appearance of clinical signs. PCR assays have high sensitivity and specificity, allowing early detection and timely intervention.³³ Serological tests, such as enzyme-linked immunosorbent test (ELISA) or rapid immuno-chromatographic tests, detect antibodies produced by the immune system in response to rabies virus exposure. These tests are valuable for screening people who are at high occupational risk of rabies, such as veterinarians, animal handlers, and laboratory personnel, and for determining whether they require a booster vaccination.³⁴ Magnetic resonance imaging (MRI) or computed tomography (CT), may be performed to evaluate neurological anomalies related with rabies diseases. These imaging procedures offer assistance visualize structural changes in the brain and spinal cord, helping in diagnosis and monitoring the disease progression.³⁵

TREATMENT

Once clinical symptoms of rabies develop, treatment is generally limited to supportive care, as there is no effective cure available at this stage. Care is focused on alleviating distress and addressing complications. Patients are often sedated to reduce pain, agitation, fever, suffering, and may require intensive supportive measures like management of paralysis, and mechanical ventilation. Ketamine, a dissociative anaesthetic, has been investigated for its potential to inhibit RABV replication in neuronal tissues and is considered a suitable agent for sedation in these cases.³⁶

Lyssaviruses are easily inactivated by exposure to sunlight, thorough washing, and aeration. Immediate and meticulous wound care is critical in rabies prevention. Studies in animal models suggest that prompt wound cleansing within the first three hours after exposure can nearly eliminate the risk of infection. The recommended procedure is to clean the affected area thoroughly for at least 15 minutes with water and antiseptic soap, followed by use of a virucidal agent such as povidone-iodine or alcohol to further reduce viral presence.³⁷ For post-exposure prophylaxis (PEP), the CDC advises administering human rabies immunoglobulin (HRIG) directly into and around the wound, using as much of the calculated dose as anatomically feasible, with any remaining volume given intramuscularly at a site distant from vaccination spot.³⁰

Table-1: Documented cases of human recovery from RABV infection

Transmission	Incubation period	Complications	Treatment	Outcome	Reference No.
Bite from a clinically rabid dog (dog died 4 days later)	21 days	Quadriparesis, cerebellum dysfunction, cardiac arrhythmia, altered consciousness	Suckling-mouse brain rabies vaccine should be administered 10 days after exposure	Recovery with two relapses following booster doses; gradual resolution over 1 year	38
Head bite by rabid dog	19 days	Encephalitis, convulsions, deep coma, quadriplegia	Vero cell-derived vaccine without rabies immunoglobulin, given the next day	Minor improvement; response to pain, persistent blindness and deafness; death after 34 months	39
Thumb bite by rabid brown bat	20 days	cardiac arrhythmia, encephalitis, coma, paralysis	Duck-embryo vaccine without rabies immunoglobulin, given the next day	Intensive care provided; complete recovery achieved in six months	40
Bites to face and hand by stray dog (dog died after 4 days)	16 days	Hallucinations, focal seizures, coma, hydrophobia	No wound cleaning and chick embryo rabies vaccine without immunoglobulin, same day	Three months in coma; slow improvement with spasticity, tremors, and involuntary movements at 18 months	41
Inhalation of aerosols containing fixed RABV in laboratory	21 days	Encephalitis, impaired consciousness, spastic hemiparesis	Pre-exposure duck-embryo cell vaccine only	Gradual improvement; long-term sequelae including personality disorder and dementia	42

PREVENTION

Rabies prevention centres on a combination of public education, animal vaccination, and prompt medical intervention following exposure. The most effective therapy is mass vaccination of dogs, as they are the main source of infection. Responsible pet ownership-including keeping pets' rabies vaccinations up to date and preventing their contact with wild or stray animals-significantly reduces risk.⁴³ Avoiding contact with unknown, sick, or wild animals, and teaching children to report animal bites, are also crucial preventive measures. If exposure occurs, immediate and thorough wound cleansing with water and soap should be done and then rabies vaccine should be

administered and, when indicated, rabies immunoglobulin is nearly 100% effective at preventing disease onset.⁵ Community awareness campaigns and coordinated efforts between veterinary and public health authorities further strengthen rabies control and prevention.⁴⁴ Rabies is always fatal in unvaccinated humans due to neurological symptoms that appear. PEP immunization is particularly effective for disease prevention when administered promptly, ideally before the onset of symptoms. Even when there are delays or barriers to accessing PEP, initiating the treatment as soon as possible still offers a chance of preventing the development of rabies.³⁰

Table-2: Vaccine and therapeutic agents for prevention of RABV infection

Drug	Type of vaccine	Purpose	Mechanism of action	Comments	Reference No.
Inactivated rabies vaccine	Inactivated vaccine	Pre- and PEP	Induces virus-neutralizing antibodies (VNA) via B cells	Licensed in the United States; not effective as treatment after symptom onset	45
Live rabies vaccine	Live- attenuated vaccine	Oral vaccination of wildlife	Stimulate CD4, CD8 cells, innate immunity, and VNA (B cells)	Administered orally to wildlife; not approved for human rabies treatment	46
IFN-alpha	Immunoregulatory protein	Experimental treatment	Inhibits viral replication	Associated with CNS toxicity, spastic diplegia, and psychosis	47
Rabies immunoglobulin	Polyclonal VNA or monoclonal antibody cocktail	PEP	Neutralizes virus at the site of exposure	Used only for PEP; not effective as treatment for established rabies	48
Ketamine	Dissociative anaesthetic, NMDA receptor antagonist	Experimental therapy	Inhibits RABV transcription in vitro; provides neuroprotection	In vivo antiviral efficacy is inconsistent; primarily used for sedation	49

CONCLUSION AND FUTURE PERSPECTIVES

Eradication of rabies is achieved through implementation of robust diagnostic tests and early detection of disease progression. Enhanced surveillance is necessary to monitor circulating RABV variants, especially those prevalent among wildlife, as the true frequency in these populations remain unclear. Comprehensive studies are needed to elucidate the role of wild animals in transmission of rabies, along with to identify emerging or

atypical RABV variants in non-reservoir species. Given that RABV is transmissible through contact of saliva infected with rabies with broken skin or mucous membrane, strict precautionary measure are essential. It is imperative for veterinary and medical professionals to be well-informed about rabies transmission routes to effectively educate the public, particularly individuals living in endemic regions and those working in abattoirs, hence decreasing the risk of disease spread. Prompt reporting to healthcare professionals and prioritization of PEP are critical components of rabies control.

Advancements in molecular diagnostics, such as RT-PCR, have significantly improved the specificity and sensitivity of rabies detection. Early diagnostic strategies using biotechnology tools should be developed to confirm infection and differentiate between RABV genotypes. Researchers should pay attention to evolving pathology of RABV and to facilitate the development of effective antiviral therapies. Molecular biology has played a pivotal role in the production of new-generation rabies vaccines, which are crucial for controlling both human and animal cases of rabies. Children in developing countries are more vulnerable to RABV, often due to the bite of rabid dog, which contribute to endemic outbreaks. Therefore, travellers to risk areas should ensure they receive pre-exposure rabies vaccination. While oral vaccines are available, their effectiveness varies among different wildlife species, highlighting the need to assess post vaccination immune responses and vaccine stability. The development of edible vaccines for wild and domestic ruminants may further aid in rabies control. Many countries have successfully achieved rabies-free status, demonstrating that elimination is possible in high-risk areas through comprehensive preventive measures. The use of scientifically validated medicines and vaccines, combined with widespread public awareness and strong political commitment, remains essential for the global eradication of rabies.

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