



Brief Overview on Rabies: A Fatal and Preventable Virus

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ABSTRACT

Rabies is a fatal and acute infection of the brain. The virulence factor of this infection is the Rabies virus, which belongs to the Rhabdoviridae family. It is a zoonotic disease that can be transmitted from animals to humans. The common ways of transferral of Rabies in humans are the transmission of rabies by the bite of a rabid animal and transmission due to saliva and consumption of meat and milk of rabid animals. Some wild animals, e.g., skunks, dogs, raccoons, foxes, and bats, can also transfer rabies in humans, mammals, and other animals. The incubation period of Rabies is at least 2 weeks to a maximum of 6 years, with an average duration of 2 to 3 months. Given its status as a significant zoonotic disease, it is crucial to have an accurate and prompt diagnosis to facilitate early treatment and implement effective measures for prevention and control. This study comprehensively analyzes epidemiology, transmission, etiology, advancements in diagnostics, immunization, therapy methods, and effective prevention and control techniques. The main objective of this study is to brief the threat of rabies and its management along with providing some brief knowledge related to rabies. The web sources (e.g., Google Scholar, Pubmed) were used to collect data regarding Rabies and briefly explained. As a result, it is clear that rabies is a big threat to the whole world so management strategies are required to target and overcome this threat. This study concludes that the Rabies virus can be managed by following the preventive and managerial strategies.

Keywords: Rabies, Zoonotic Disease, Wildlife, Diagnosis, Prevention, Control.

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INTRODUCTION

"Rabies" came from the Latin word 'rabere', which implies "mad". The sickness has been recognized from the beginning of human civilization. The initial authoritative record of rabies was reported in the pre-composite Eshmun ordinance of Babylon in the twenty-third century before Christ (Tarantola, 2017). In the 1880s, Louis Pasteur said the Rabies virus was the etiological agent of the disease (Tarantola, 2017). Despite the availability of vaccines, rabies remains a significant problem for people in developing countries. This is evident in global statistics. More than 60,000 humans die due to this contagious disease each year. Approximately 15 million people are getting treatment after being affected by Rabies.

Rabies is globally prevalent and affects all species with warm-blooded physiology. Despite widespread global efforts, the deployment of comprehensive control measures, and public health awareness agendas, there are more than 95% of deaths occur in several countries in Asia and Africa (Singh et al., 2017). Approximately 20,000 fatalities are due to Rabies yearly in India because of the

bite of a rabid dog. Rabies in humans is invariably a fatal disease, even with the implementation of modern therapeutic interventions. Rabies ranks sixth in terms of the severity of fatality among infectious diseases worldwide.

Rabies affects the nervous system of mammals. Rabies Virus is a neurotropic, negative sense, unsegmented, single-stranded RNA virus. The virus primarily causes acute encephalomyelitis in carnivores and bats. Rabies is significantly affecting population dynamics. The significance of rabies stems from its high mortality rate, lack of specialized antiviral treatment, and global distribution. The disease is dispersed over all continents except some areas of Antarctica and Australia. The disease poses significant public health concerns in Asia and Africa. The occurrence of this condition has been recorded to range between 20% to 50% among several kinds of household animals. Animals show different levels of susceptibility towards rabies, which are affected by factors like species, genetic make-over, age, variant, biotype, virus amount, and exposure method. However, control programs have effectively contributed to reducing cases in nations such as the USA. The mortality rate from infectious rabies disease is often low in underdeveloped countries due to factors such as under-reporting, cultural beliefs, insufficient rabies diagnostic facilities, and limited understanding of the disease's transmission and prevention methods. This endemic in developing countries has failed to accurately register the number of rabies cases, leading to the disease being overlooked by medical professionals. As a result, there has been limited support from the international community and donor organizations. An alarming issue regarding lyssavirus is the presence of many genotypes in various regions worldwide, with the majority of these genotypes leading to illness in humans. Diagnosing the disease in humans is challenging due to the low quantities of virus in easily accessible samples such as saliva and cerebrospinal fluid (CSF) (Otolorin et al., 2015). In this review, we will provide a brief overview of rabies, epidemiology, history, and its management, which will be helpful for readers in managing rabies or preventing themselves from getting rabies.

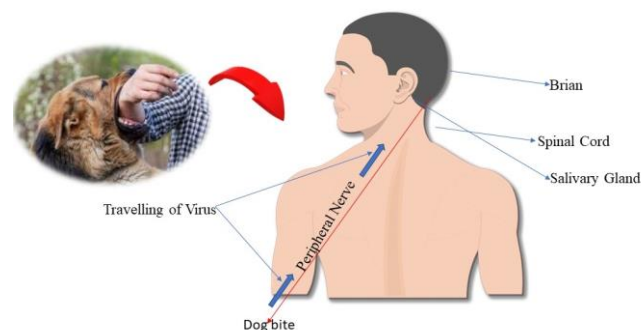


Figure 1 illustrates the sequential process following an animal bite or peripheral inoculation of the rabies virus (RABV).

The process of virus reproduction in muscle tissue and the movement of the virus through nerve fibres in the peripheral nervous system (PNS) by retrograde axonal transport. After that, the virus replicates in the motor neurons of the spinal cord and quickly spreads to the brain (Katz et al., 2017).

History of Rabies

Rabies is an outdated and highly feared transferable disease affecting humans and animals (Table 1). The identification of rabies dates back to approximately 2300 BC in Egypt and was extensively documented by Aristotle in ancient Greece (Jones, 2021). Dog rabies was written in Persia before the sixth century (BC) and during India's first centennial (BC). Zinke recognized the contagiousness of drool from infected puppies in 1804. Before Pasteur's breakthrough in 1885, there were no viable methods for preventing or curing animal diseases. In 1881, Pasteur provided evidence of neurotropism of the pathogenic virus. In 1885, Pasteur identified and obtained a booster for rabies, even before

comprehending the configuration and characteristics of the rabies virus. In that year, he provided the vaccination of infection for the first time to Joseph Meister, whom a rabies-infected animal had severely bitten. That day was a significant turning point in infectious illnesses, specifically disease control and prevention, and paved the way for modern scientific advancements. Two scientists "Remlinger" and "Riffat-Bay" discovered the rabies virus in 1903 (Robardet et al., 2016). In the 1940s, RABV originated in the genus of red foxes (*Vulpes vulpes*) in the surroundings of Kaliningrad and expanded to Central America and Western Europe in a relatively short period. The inaugural wildlife rabies oral vaccination campaign occurred in Switzerland in 1978, followed by similar initiatives in other European nations. In 1988, a field trial was conducted to test the effectiveness of oral immunization movements and obligatory vaccination of rabid animals near the outbreak. The SAD B19 bait was used for this purpose. As a result of these efforts, in 1991, Finland was endorsed to be a rabies-free state (AHAW, 2015).

Epidemiology

Rabies is an exceptional viral illness that may infect various hosts, including animals with warm blood. Rabies is widespread worldwide, except in islands. All countries, except Australia and Antarctica, have endemic cases of rabies. The Asian subcontinent is comprised of several countries that are free from rabies, including Andaman, Bahrain, Cyprus, Hong Kong, Japan, Maldives, Malaysia, Qatar, Singapore, Lakshadweep, and Nicobar Islands of India, and Timor-Leste. Territories such as Antigua and Barbuda, Bahamas, Barbados, Belize, Falkland Islands, Jamaica, Saint Kitts and Nevis, Trinidad and Tobago, Uruguay in the American subcontinent, and Albania, E.Y.R. of Macedonia, Finland, Gibraltar, Greece, Iceland, Isle of Man, Malta, Portugal, Norway, the United Kingdom, and Spain have also achieved the status of being free from rabies. Three African countries are Cape Verde, Congo, and Libya. Mauritius, Reunion, and Seychelles are devoid of rabies. The group of Islands, including Fiji, Cook Islands, Vanuatu, Guam, French Polynesia, New Zealand, New Caledonia, Solomon Islands, and Papua New Guinea, have been designated rabies-free (Singh et al., 2017). According to the World Health Organization (WHO) studies, a state can be regarded as rabies-free if it has not had any patients of rabies in humans or animals acquired within its borders for two years. This is determined through surveillance and import regulations. Travellers with compassion for domesticated animals may encounter challenges in avoiding stray dogs and cats while visiting impoverished countries, disregarding the recommended safety precautions. To preserve a rabies-free status, the government must implement rigorous and ongoing monitoring, enforce quarantine measures for imported animals, and specify rules to restrict the entry of the virus, primarily through the importation or introduction of diseased animals.

While analyzing the prevalence of rabies in Asia, it becomes evident that most developing nations in this subcontinent are severely affected by rabies infection (Hampson et al., 2015). According to the World Health Organization Global Vaccines Research Forum, dog(canine) rabies affects more than 3 billion people in the whole world, with over 30,000 casualties occurring yearly in Asia. This implies that every 15 minutes, one person in Asia dies from rabies. However, it is a distressing reality that 15% of deaths caused by rabies occur in youngsters below the age of 15. The officially documented human rabies cases often do not accurately reflect the number of rabies cases in many situations. This phenomenon is common in evolving countries, particularly in areas of Africa. The prevalence of the infection is highest in the south Asia. Nepal has the highest number of human rabies deaths among all nations in the globe. Pakistan ranks among the top five countries globally in terms of having a high preponderance of human rabies. Being a South Asian nation, the prevalence of human rabies is significant, resulting in an approximated perennial mortality rate of 2,000 to 5,000 individuals. In Pakistan, the initial documented instance of human rabies was a work-related incident in which a butcher unintentionally contracted the RABV virus while removing the skin from a rabid calf that had been slaughtered. Pakistan had a high occurrence of human rabies cases, comparable to India and

Bangladesh, making it one of the highest in the subcontinent. The global illness burden study done in 2016 indicated a significant decrease in human rabies cases (n=928) in Pakistan. This fall can be attributed to the absence of confirmed and estimated rabies cases (Blum et al., 2018). According to the World Health Organization report on rabies control efforts in Pakistan, almost 97,000 incidents of dog bites were documented in public sector hospitals in 2010. Pakistan did not submit any cases of rabies in dogs, cats, or other domestic animals to the OIE from 2011 to 2013 due to the absence of surveillance mechanisms. The number of dogs that received standard vaccinations was 8,751 in 2011, 10,419 in 2012, and 5,032 in the first half of 2013 (Organization, 2014). However, Pakistan experiences an annual report of over 100,000 incidents of dog bites. Dog bites' incidence and spatial pattern exhibit variability in response to annual weather and climate fluctuations. Male teenagers experienced the highest number of dog bites during the warmer months of June, July, and August, as observed in other studies (Ahmed et al., 2019).

Mode of transmission

RABV, originating from the Central Nervous System (CNS), travels to the salivary glands in the mouth by cephalic nerves such as the trigeminal and ninth cranial nerve. It is subsequently expelled in saliva, aiding the pathogen transfer to the next individual. The primary mode of transfer for infection, which accounts for 90% of cases, is the bite of infected critters such as dogs and cats. This is due to their proximity and human interaction (Acharya et al., 2020). The majority of countries worldwide, especially in Asia and Africa, account for 85%–95% of human rabies cases caused by dog bites (Shite et al., 2015). These instances typically result in both physical and emotional damage for the victims (Balcha & Abdela, 2017). RABVs usually make their way to the body through wounds or cuts, preferably through unbroken skin. The transmission of RABV occurs through the movement of the virus from salivary glands or damaged brain tissue into bite wounds, open wounds on the exterior surface, and mucosa. The likelihood of contracting rabies from a bite of rabid dogs is between 5 and 80%, which is around 50 times higher than the risk posed by scratches or abrasions, which occur at a rate of 0.1% to 1%. The fatality rate of RABV virus infection is contingent upon the intensity of infection, the bite wound's site, and the existence of enough virus in the saliva.

Non-bite transmission

Over the past five decades, minimal instances of non-bite exposure have been recorded in humans. However, the incidence of non-bite-transmitted rabies cases is lower. Non-bite exposure refers to instances where the body is exposed to a higher concentration of aerosolized rabies virus (RABV) through inhalation. This can occur through various means, such as receiving organ or corneal transplants or fouling injuries, bruises, or mucous lining with saliva-containing rabies virus antigens or contagious material like neural matter from an infected animal. In the early 2000s, it was reported that disease can be transmitted by tissue grafting, namely keratoplasty, in European patients. Unprotected interaction with diseased individuals and direct connection with secretions carrying a high virus engagement can pose a possible risk to relatives and health workers (Ma et al., 2020). It is important to follow standard barrier precautions when providing care to an ill person to decrease the potential for spreading disease.

Exposure to vaccinations containing live attenuated virus during animal immunization may cause Rabies. Both conditions of pre- and post-disclosure prevention are necessary to address the disease. Slaughterhouses and abattoirs holding animal doctors are exposed to danger while dealing with the skinning and handling of rabies-infected carcasses. Thus far, there has been no news of rabies being conveyed through blood transfusion or the presence of the virus in the bloodstream during RABV infection in animals and people. Dog slaughtering is the major cause of transmission in several governments where dog meat is considered an delicacy. These countries include China, South Korea, Vietnam, Thailand, and various African nations (Vu et al., 2021).

Critical factors in the spreading of rabies in dog butchery encompass rabid animal marketing, annihilation procedures, and the utilization of meat. Dogs with no medical records are confined in a cramped enclosure, heightening rabies transmission within the dog population. The intermediaries involved in detaining the dogs are at significant risk since they frequently face the danger of being scratched or bitten, exposing themselves to the possibility of contracting rabies while consuming dog meat alone does not presently lead to the transmission of the rabies disease (Nayak et al., 2022). However, the risk of transmission is heightened during activities such as capturing, handling, loading, confinement, transportation, and slaughtering of dogs. In addition, most butchers employed in butcher houses have either no or minimal education about the spread of the virus and lack fundamental attention to the zoonotic significance of rabies (Voigt et al., 2018).

Transmission of Rabies Virus (RABV) can occur through non-bite techniques such as sniffing in RABV particles, receiving organs and cornea transplants, and coming into contact with saliva and cranial tissue from an infected rabid animal through open injuries, abrasions, and mucous layers. Bats are legally kept safe in most European countries through several international treaties and National laws focused on environmental protection. Research on bat rabies is crucial for understanding whether rabies in bats poses a genuine threat to public health. Comprehending the bulk of rabies in different bat families is equally vital. Nonresistant management of rabies infection in bat species is an adequate method for gathering information regarding the presence of rabies in bats without conflicting with bat conservation efforts. Understanding the presence of infectious bats, the plurality of rabies in certain classifications of bats, and the potential risks to both public and animal health are essential for raising public awareness and promoting the conservation of bats. Therefore, it is imperative to establish a strong collaboration between bat conservationists and organizations engaged in bat research.

Pathology of rabies

Despite its deadly prognosis and severe neurologic symptoms, rabies typically shows few or no noticeable pathological changes in the central nervous system (CNS) due to a subtle inflammatory response. Following RABV infection, ganglion cells are degenerated in the peripheral nerves, spinal cord, and brain. Additionally, mononuclear cells infiltrate the nerves and blood vessels, and the destruction of neurons; in Rabies, neuronal degeneration results in the malfunctioning of neurons rather than their death. Gangliocyte infection leads to an initial 'axotomy reaction' followed by the formation of several autophagic compartments. In severe stages of degeneration, gangliocytes have partly membrane-bound empty vacuoles.

Rabies vaccination

The widely used intradermal (ID) injection strategy was first developed and implemented at the Queen Saovabha Memorial Institute of Bangkok in 1986. As a result, it is commonly referred to as the Thai Red Cross (TRC) regimen (Arslan & Vahaboglu, 2022). In 1991, the World Health Organizational Expert Committee suggested using contemporary rabies vaccines through intradermal administration for post-exposure prophylaxis, as stated in the WHO Report 1996.

Management of Rabies

Palliative treatment is when the virus reaches neurons and damages them. The virus would not go through neurons in most cases if vaccines are taken right after getting bitten by a rabid animal. Now, all forms of rabies treatment are soothing due to the lack of established treatments. The objective is to reduce agitation and alleviate suffering through the use of sedatives, analgesics, and antipsychotics. The coma induction therapy, termed the Milwaukee protocol, involving elevated doses of anaesthetic medications such as barbiturate, midazolam, and ketamine, is used widely to deal with the infection. Along with the use of therapy, the administration of ribavirin and amantadine is ineffective and is not recommended by the World Health Organization.

The development of rabies involves a complex process that includes both imperfect autophagy and the inability of the host's defence system to eliminate the virus. It is justifiable to administer the rabies vaccine to patients showing symptoms if they have not formerly encountered any post-exposure prophylaxis. Nevertheless, it is not recommended to provide intravenous or intrathecal human RIG to individuals with symptomatic rabies since it may exacerbate paralysis in patients with furious rabies (Du Pont et al., 2019). Avoid using corticosteroids and other immunosuppressive medications since they can worsen the ability to eliminate the virus, reduce the time it takes for symptoms to appear, and accelerate mortality.

Two drugs, amantadine and ribavirin, have demonstrated *in vitro* efficacy against viral rabies infection, but their effectiveness *in vivo* has not been established. Previous attempts to utilize these drugs in conjunction with the Milwaukee regimen have yielded no positive outcomes (Yamada et al., 2019). Interferon-alpha has been administered in patients with human rabies. However, studies have demonstrated no positive effects. Favipiravir, a more recent antiviral with a wide range of effectiveness, explicitly targets viral RNA polymerase and diminishes the reproduction of rabies in neural cells. Favipiravir has demonstrated antiviral efficacy in a mouse model infected with RABV, suggesting its potential as a therapeutic agent for treating rabies.

Rabies is highly dependent on immunological modulation to invade the body successfully. Relying just on vaccines and antiviral treatments would eventually fail. Existing neuroprotective therapies, such as therapeutic hypothermia, may have the potential to be employed as an additional therapy to slow down the spread of the virus. The increasing fascination with medical cannabis has prompted further investigation into the human endocannabinoid system, precisely its neuroprotective capabilities.

Cannabis can potentially manage the disrupted balance in the body caused by the rabies virus. It can help the survival of specific infected cells and stimulate complete autophagy and viral dismissal in another group of cells (Yamada et al., 2019). The utilization of medicinal cannabis as an adjunctive treatment for rabies, in conjunction with other therapeutic modalities, is desirable. Additionally, it can offer relief in cases of indicative rabies illness thanks to its anaesthetic, soothing, anti-convulsive, and anti-epileptic characteristics.

METHOD

In this review, data regarding Rabies was systematically collected from reputable online sources, primarily utilizing Google Scholar and PubMed. These platforms were selected due to their extensive coverage of scholarly literature in the fields of medicine, virology, epidemiology, and public health.

Google Scholar

Google Scholar served as a comprehensive search engine for academic papers, theses, books, and conference proceedings across diverse disciplines. Specific keywords related to Rabies including "Rabies virus," "Rabies transmission," and "Rabies epidemiology" were employed to retrieve relevant literature.

Search Strategy

We conducted systematic searches using appropriate search strings, ensuring the inclusion of recent and pertinent studies related to Rabies.

Filtering and Sorting

Search results were filtered based on relevance and publication date to prioritize recent research findings and scholarly contributions.

PubMed

PubMed, a specialized search engine for biomedical literature, provided access to a vast repository of articles and abstracts from biomedical journals and life science publications.

Medical Subject Headings (MeSH) Terms

Utilizing MeSH terms related to Rabies, we refined our searches to access articles indexed with specific biomedical concepts, enhancing the relevance of retrieved literature.

Advanced Search Functionality

PubMed's advanced search features enabled us to customize search parameters, including publication types, study designs, and date ranges, facilitating the identification of relevant studies and reviews.

Data Collection and Evaluation

Extraction of Key Data Points

Relevant data on Rabies epidemiology, pathophysiology, clinical manifestations, prevention, and treatment strategies were extracted from identified articles and studies.

Critical Appraisal

Each retrieved source was critically evaluated for its methodological rigor, relevance to the research questions, and credibility of the authors. By employing systematic search strategies and leveraging the robust databases of Google Scholar and PubMed, we ensured the comprehensive and reliable collection of data about Rabies for this review paper.

RESULTS AND DISCUSSION

Epidemiological

The analysis of the research gathered yielded extensive information about the worldwide impact of Rabies, including the rates at which it occurs, the patterns of its geographic distribution, and the people that are impacted. Table 1 contains some epidemiological data and history of rabies

Table 1. History of Rabies Virus

Year		Scientist	Discovery
Before 2300 (Before Christ)	(Shabansalmani et al., 2022)	Aristotle	Infection of rabies was initially reported in Egypt and Greek
1804	(Алиев et al., 2020)	Zinke	Recognition of the infectious nature of infected dog saliva
1881	(Monteil, 2022)	Louis Pasteur	Elaborated on the neurotropic rabies virus/toxin
1885	(Pasteur, 1885)	Louis Pasteur	We have formulated a new vaccine by getting cells from the spinal cord of an infected rabbit.
1885	(Pasteur, 1885)	Louis Pasteur	Did first trial on a young kid, Joseph Meister,
1903	(Fooks & Jackson, 2020)	C. Hanlon and J. Childs 2013	Described the structure of the rabies virus (Remlinger and Riffat-Bay)
1940s	(Robardet et al., 2016)	Robardet et al., 2019	RABV popped up in a genus of foxes (<i>Vulpes vulpes</i>) in the region of Kaliningrad and then circulated to Median and Western Europe
1978	(Maki et al., 2017)	Wandeler et al., 1988	The primary oral immunization movement for fauna was organized in Switzerland and later in other European nations.
1988	(Mähl et al., 2014)	Niin et al., 2008	First trail of oral vaccination .
1991	(DJ, 2003)	Sihvonen, 2001	Finland was announced as free from rabies.
2002	(Jackson, 2016)	Pounder, D., 2003	One causality ensued in an exposed bat environmentalist in Dundee who squeezed a rabies virus infection and did not receive susceptibility prevention. It comes out to be the first statement after the UK declared safe from rabies in 1920

Pathophysiological Understanding

Significant discoveries have revealed the precise molecular processes involved in the transmission of the Rabies virus, its ability to target the nervous system, and the immune responses of the host. These results have provided valuable insights into the intricate interactions between the virus and its host. The literature study provided a comprehensive account of the clinical signs of Rabies at all phases of the disease, as well as the diagnostic criteria and methodologies used for precise diagnosis.

Preventive Measures and Treatment Strategies

The studies found that vaccination is crucial in preventing Rabies. They also looked into post-exposure prophylaxis and therapeutic interventions to slow down the disease and improve patient outcomes.

CONCLUSION

Rabies is passed along mainly by dog saliva, which enters the body through open wounds or torn skin. Timely vaccines can prevent mortality from this neglected disease. Most first cases of rabies can be ruled out by diagnostic testing or illness progression. Rabies prevention and consideration must be prioritized early on. Improved monitoring of RABV variants in rabid animals, especially wildlife, is needed. The lack of reliable data on rabies frequency in wild animals requires more research to evaluate their disease transmission contribution. Monitoring less familiar non-reservoir species is important for determining new rabies virus variants. Highly uncompromising precautions are needed because saliva can spread RABV through torn skin or mucous membranes.

Rabies-prone people must be immunized and have their antibody levels checked every two years. This is essential for illness prevention. Unfortunately, dog bites are the most likely way for children to get rabies, especially in developing countries with endemic rabies. Travelers, especially those moving to remote areas, may benefit from pre-exposure rabies vaccination. In endemic regions, assessing the presence and risk of rabid dog acerbity and ensuring local availability of rabies immunoglobulins and immunizations are urgent. Although oral/bait vaccinations are available, they do not work for all wild animal species. Real-world testing of vaccine durability and immune response is essential. This study concludes that the Rabies virus can be managed by following the preventive and managerial strategies.

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