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Rabies Virus: A Review of Pathogenesis, Diagnosis, and Prevention

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Abstract

Rabies virus is considered as one of the deadliest known infectious agents in medical science with a case-fatality rate of nearly 100% once clinical symptoms take place. Although there are good vaccines and post-exposure prophylaxis, the disease claims between 59,000 human lives each year and the majority of these are in low- and middle-income countries in Africa and Asia. Recent developments in molecular virology have clarified the key factors of viral neuroinvasion, immune evasion, as well as host-pathogen interaction. At the same time, there have been new technologies in diagnostic technologies such as point-of-care molecular assays and rapid field-deployable systems that have increased surveillance in resource-constrained environments. Global prevention efforts have developed by incorporating One-Health approaches which focus on cross-sectoral integration between human health, veterinary services and the environmental sector. This overall discussion summarizes the existing knowledge of the pathogenesis of rabies virus, with a particular focus on molecular pathways of neurotropism and immune subversion, current diagnostic methods with respect to sensitivity and field use, and prevention and control measures such as mass immunization of dogs, simplified pre-exposure and post-exposure prophylaxis, and new vaccine systems. The continuous obstacles to international extermination are addressed, such as infrastructural obstacles, economic limitations, sluggish care-seeking habits, and surveillance systems deficits. To realize the goal of the World Health Organization to reduce death by 2030 due to dogs as the primary causative agent of human rabies, continued investment on animal vaccination, increased access to biologics, the implementation of rapid diagnostics, and the enhancement of intersectoral coordination in One-Health models is mandatory.

Keywords

Rabies virus, Neurotropism, Immune evasion, Rabies diagnosis, Dog-mediated rabies

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1. Introduction

The prototype strain of the Lyssavirus genus of the rhabdoviridae family, rabies virus (RABV), has been known to cause substantial public health and economic challenges in the 21st century, despite being identified as a major zoonotic pathogen millennia ago [1]. It has an estimated 59,000 human fatalities each year with 95 percent of the cases being reported within Africa and Asia where domestic dogs are the main reservoir and vectors of the virus [2]. It is the disease with the acute and progressive encephalomyelitis, the development of which invariably leads to the death of the patient in several days to weeks [3].

Rabies virus is transmitted mostly when an infected mammalian host bites a person whereby the saliva contains viruses and inoculates the wounds. Other, but not the most prevalent modes of transmission are via the mucous membrane, inhalation through aerosol in a laboratory or one of the bat-infested caves, and organ transplantation with an unknown donor [4]. The incubation period has shown quite a lot of variability that ranges between days and a number of years, but usually between a month and three months based on different factors like the viral load, the location of the bite in regard to the central nervous system as well as host immune responses [5].

Although rabies is completely avoidable when the method of post-exposure prophylaxis (PEP) is provided promptly and avoidable when dogs are vaccinated in bulk, there have been considerable differences in access to such life-saving measures [6]. Developed countries have been able to eradicate canine rabies using extensive vaccination and surveillance measures but most of the endemic countries are still grappling with poor resources, lack of sufficient health care facilities and political will [7].

Recent scientific progress has greatly contributed to the knowledge of rabies pathogenesis on molecular and cellular levels, the revelation of complex viral immune evasion mechanisms, and the evolution and creation of better diagnostic platforms and novel vaccine candidates [8]. More so, the One-Health approaches that acknowledge the interdependence of human, animal, and environmental health have been effective in enhancing the efforts of rabies control within various nations [9]. This review offers an extensive literature review on the existing literature on the pathogenesis of the rabies virus, diagnostic tools, and preventive interventions, especially focusing on studies that have been conducted since 2010 and their implications on the elimination of this virus globally.

2. Viral Structure and Molecular Biology.

Rabies virus has a unique bullet-shaped morphological appearance of rhabdoviruses with a length of about 180 nm and a diameter of about 75 nm [10]. The viral genome is comprised of a single-strand, negative-sense RNA molecule with a length of about 12 kilobases that encode five structural protein which are order 3'-N-P-M-G-L-5'. All of the proteins play essential parts in viral replication, assembly and pathogenesis.

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The genomic RNA is encapsidated by the nucleoprotein (N), which results in the formation of a ribonucleoprotein complex that is the template of transcription and replication and protects the viral genome against the cellular innate immune sensitizers [12]. The phosphoprotein (P) acts as a key cofactor to the viral RNA-dependent RNA polymerase (L protein) and is the central immunologically related minimization by countering host interferon reactions [13]. The matrix protein (M) coordinates viral assembly, the condensation of ribonucleoprotein complexes and leads to the budding of progeny virions off of infected cells [14].

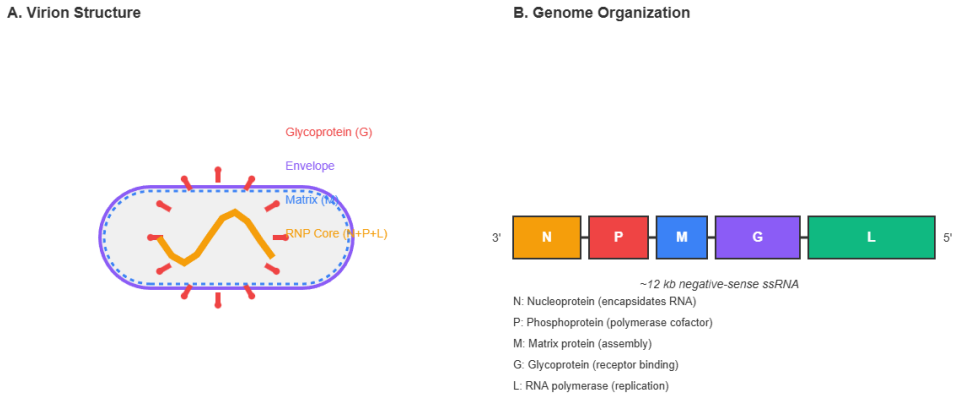

Figure 1. Schematic representation of rabies virus structure showing the bullet-shaped morphology (A) and genomic organization (B). The viral envelope contains glycoprotein (G) trimers responsible for receptor binding. The internal ribonucleoprotein core consists of negative-sense RNA genome (12 kb) encapsidated by nucleoprotein (N), associated with phosphoprotein (P) and RNA polymerase (L). Matrix protein (M) underlies the envelope. The genome encodes five structural proteins in the order 3'-N-P-M-G-L-5'.

The glycoprotein (G) is the only protein that is surface-exposed and it is involved in important processes of viral entry, tissue tropism, and immunogenicity [15]. The G protein trimeric spikes the viral envelope and binds with various host cell receptors, such as nicotinic acetylcholine receptors at neuromuscular junctions, neural cell adhesion molecule (NCAM) and the low affinity neurotrophin receptor p75NTR [16]. These interactions allow the viral attachment to neurons and internalization by use of receptor-mediated endocytosis. Neutralizing antibodies are also most likely to attack the G protein hence it is the most important immunogenic constituent of rabies vaccines [17].

RNA-dependent RNA polymerase (L protein) is used in all the enzymatic activities needed to support the activities of the viral genome transcription and replication, such as polymerase, methyl-transferase, and polyadenylation [18]. The L protein is a large multi-domain enzyme and together with the phosphoprotein cofactor, ensures efficient viral RNA production and has fidelity that is high enough to maintain genome integrity through transmission cycles [19].

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3. Pathogenesis and Neuroinvasion.

3.1 Initial Infection and Peripheral Replication

Age-associated alterations in the immune system influence the infection and natural infection process by modifying the susceptibility, course, and progression of the infections further.

After inoculation using a bite wound, rabies virus is first replicated in muscle cells around the point of entry [20]. It is a localized amplification step that is made possible by viral glycoprotein attaching to neuromuscular junction nicotinic acetylcholine receptor clusters. The period of peripheral replication may range between days and weeks and is a time-sensitive period during which post-exposure prophylaxis is very effective [21].

Viral particles then have access to peripheral motor and sensory nerve endings of neuromuscular junction and cutaneous receptors. Invasion into the nervous system is one of the most important stages in pathogenesis, because neurons offer the secluded habitat and new equipment to enable viral propagation to the central nervous system [22].

Axonal retrograde transport is best described as the reversal of direction in transport of goods and services.

3.2 Retrograde Axonal Transport

At best, axonal retrograde transport can be defined as the reversal of the movement of goods and services.

When the rabies virus enters into the peripheral neurons, it takes advantage of the retrograde axonal transport system of the host cell to travel between the nerve endings to the neuronal cells assemblies in the spinal cord and the brain [23]. Viral ribonucleoprotein complexes are carried away in endosomes along microtubules supported by a dynein motor protein at 50-100 mm/day rates [24]. This is a retrograde movement mechanism through which the virus is able to circumvent the circulation of immune responses and enter the immunologically privileged sites in the central nervous system.

The phosphoprotein has also been found to engage directly with components of the dynein complex of motors indicating that viral proteins play an active rather than passive role in facilitating movement of cells [25]. Moreover, neural dissemination pathway defines the cascade of brain areas that are impacted and, thereby, affects disease clinical manifestations [26].

3.3 Infection of the Central Nervous System.

When the rabies virus reaches the central nervous system, it replicates in large quantities in the neurons of the spinal cord, the brainstem, the limbic system, and the cortex [27]. It is important to note that viral infection is mostly replicated in a non-cytotoxic fashion, and infected neurons develop impaired functionality in place of apoptotic demise on a mass scale [28]. This maintenance of neuronal structure

is what makes rabies encephalitis differ from a lot of other viral central nervous system infections, and is another reason why the disease is so lethal with comparatively small histopathological lesions.

Several different mechanisms mediate the neuronal dysfunction in rabies; these include the interference of the neurotransmitter systems, especially the gamma-aminobutyric acid (GABA), serotonin, and acetylcholine pathways [29,31]. Disturbed neurotransmission is an element of such typical clinical signs as hydrophobia, aerophobia, hyperactivity and autonomic instability in furious rabies. Moreover, viral proteins disrupt the axonal transport, the work of the synapses, and the work of the ion channels, which leads to further progressive neuronal impairment [30].

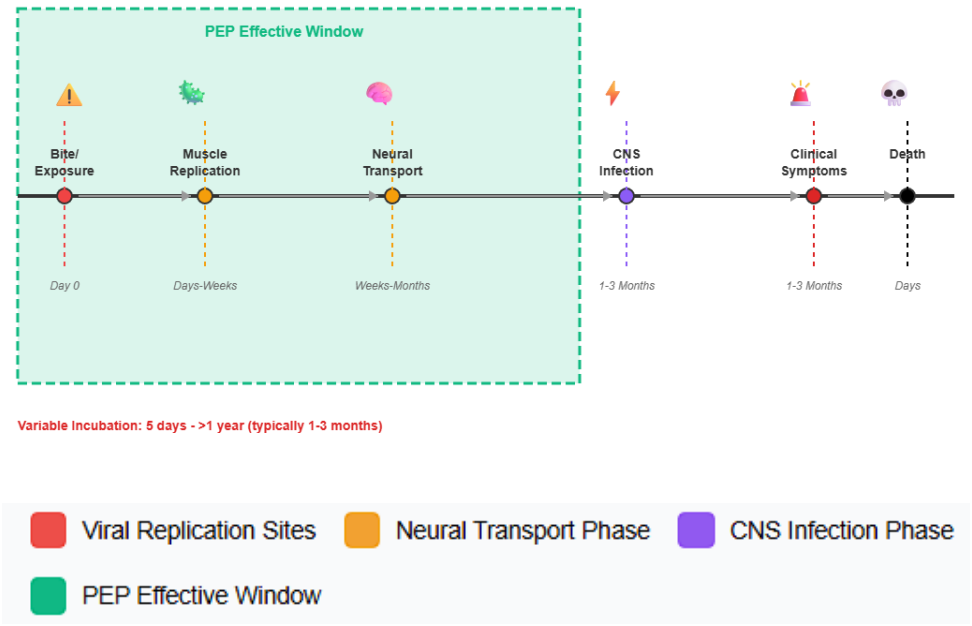

Figure 2. Temporal sequence of rabies pathogenesis from initial exposure to clinical manifestation.

Following bite inoculation (Day 0), the virus undergoes limited replication in muscle tissue at the wound site (days-weeks). Viral particles then enter peripheral nerves via neuromuscular junctions and undergo retrograde axonal transport to the CNS (weeks-months). Upon reaching the brain, rapid viral amplification occurs throughout neural tissues, followed by centrifugal spread to peripheral organs including salivary glands. The green shaded area indicates the period during which post-exposure prophylaxis (PEP) remains highly effective. Clinical symptoms typically appear 1-3 months post-exposure, after which the disease is almost invariably fatal.

3.4 Immune Evasion Mechanisms

Rabies virus has developed advanced mechanisms of avoiding host immune systems that allow a long-term stay in the neural tissue, to be subsequently spread [31]. It is a strong antagonist of type I interferon responses through the phosphoprotein that inhibits interferon regulatory factor 3 (IRF3) and the signaling pathways of STAT1 [32]. This interference eliminates the induction of interferon-stimulated genes which would otherwise induce a state of antiviral in infected and nearby cells.

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The matrix protein has also been found to prevent nuclear translocation of host transcription factors which also represses the expression of innate immune genes [33]. Viral genomic RNA has an effect of protecting the genome because it is sequestered owing to the formation of nucleoprotein complexes, which would otherwise stimulate strong interferon generation via pattern recognition receptors like RIG-I and MDA5 [34].

The blood-brain barrier offers further resistance against adaptive immune response, restricting the entry of the antibodies and immune cells into the central nervous system [35]. Rabies-specific antibodies are not produced in time and the virus with the help of which the widespread infection of the central nervous system takes place is commonly already beyond the limits of humoral immunity.

3.5 Centrifugal Spread

Rabies virus is centrifugally distributed to peripheral tissues after being repeated extensively in the central nervous system to the nerves whose terminal end consists of salivary glands [36]. This centrifugal distribution is the one that is essential to the transmission since the shedding of the virus in saliva allows other hosts to infect by bites. Other organs such as heart, lungs, kidneys, and skin have also been found to have the virus, but they do not seem to be the best places where the virus can be transmitted naturally [37].

4. Clinical Manifestations

Rabies has two major clinical manifestations: encephalitic (furious) and paralytic (dumb) rabies with the former manifesting about 80% prevalence [38]. The disease has specific stages of progression, i.e. incubation, prodrome, acute neurological phase, and coma to death.

Prodromal stage is 2-10 days and is not specific with symptoms such as fever, headache, malaise, and frequent paresthesia or pain at the bite location [39]. These early presentations have not much diagnostic specificity but could trigger the consideration of those who have a known history of exposure.

Renal rabies is characterized by hyperactivity, agitation, hydrophobia, aerophobia, hypersalive, and autonomic dysfunction alternating with the period of lucidity [40]. Hydrophobia, which is induced by drinking or even the perception of water, is a painful spasm of the pharynx and larynx and is one of the pathogenic characteristics of its presence. Aerophobia, which is also triggered by air currents on the face, is also a result of the increased brainstem reflexes. A cardiorespiratory arrest usually results in the death of a patient in a few days.

Paralytic rabies has a progressive flaccid paralysis that mimics Guillain-Barré syndrome, which is usually difficult to diagnose and diagnosed late [41]. The sensory symptoms are few and mental status change takes place later during the disease progression than furious rabies. The duration of survival is, on average, more than in furious rabies, up to in excess of two weeks.

Rabies is practically always fatal once clinical manifestations have appeared, and fewer than 20 cases of survivors have been documented worldwide, the majority of whom had experienced severe

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neurological sequelae [42]. The apparent homogeneity of fatal outcome makes the prevention of fatalities with immunization and prompt prophylaxis after exposure highly essential.

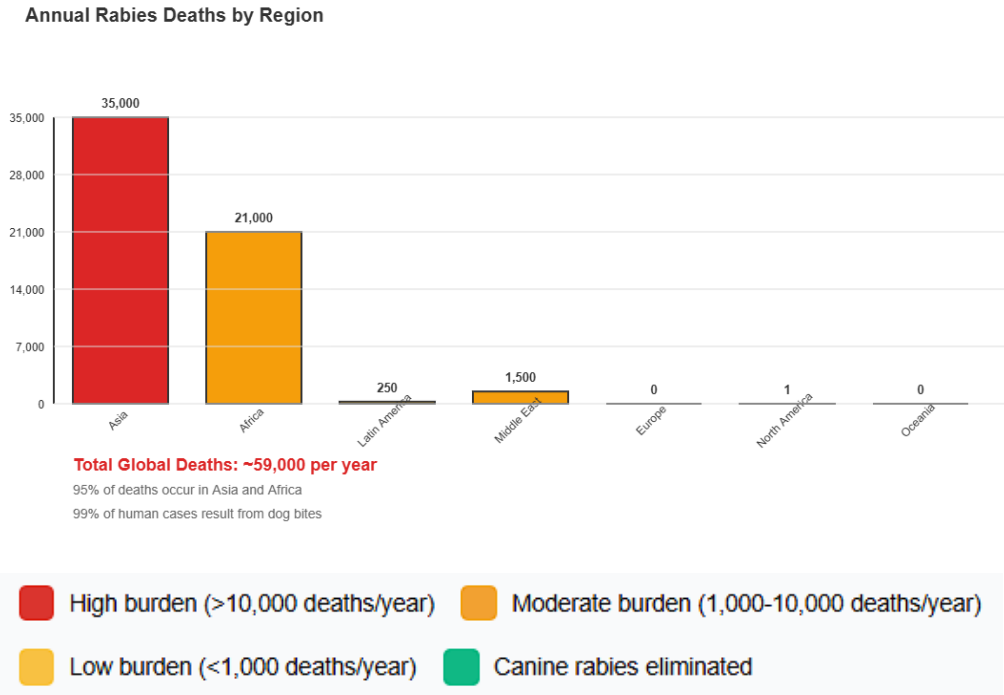

Figure 3. Geographic distribution and estimated annual mortality from dog-mediated rabies by region. Asia accounts for approximately 35,000 deaths annually (59% of global burden), with India alone contributing nearly 20,000 deaths. Africa accounts for approximately 21,000 deaths annually (36% of global burden). Latin America has achieved substantial reductions through mass dog vaccination, with fewer than 20 human deaths per year. High-income nations in North America, Western Europe, and Australia have eliminated canine rabies through comprehensive vaccination and control programs. Total global mortality is estimated at 59,000 deaths per year, with 95% occurring in rural areas where access to post-exposure prophylaxis is limited.

5. Diagnosis

Rabies should be diagnosed correctly and promptly to enable proper clinical management, epidemiological surveillance and response by the public health sector. The diagnostic methods applied depend on the ante-mortem or post-mortem nature of the patient and the level of laboratory facilities.

5.1 Post-Mortem Diagnosis

The gold standard of post-mortem diagnosis of rabies is the direct fluorescent antibody (dFA) test done on a brain tissue, which is recommended by the World Health Organization and World Organization to Animal Health [1,13]. The test identifies viral antigens in brain impressions with fluorescein-labeled anti-rabies antibodies with the results being obtained in less than several hours and the sensitivity and specificity of the test are above 95% in cases when the test is applied by skilled workers to the right specimen [13].

Aca. Intl. J. Vet. Med. 2025;3(2)28-42. DOI: https://doi.org/10.59675/V324

The sampling sites that are recommended are the brainstem, cerebellum, and the hippocampus since these areas normally contain the largest quanta of viruses [43]. It is very important to collect and handle the specimen properly, because autolysis may result in poor performance of the test. dFA test involves fluorescence microscopy apparatus and professional technicians, which restrict its use in certain resource-restricted environments.

5.2 Ante-Mortem Diagnosis

The ante-mortem diagnosis is more difficult because of less and more fluctuating viral loads in the available tissues at an early clinical stage. Several samples and retests can be required to obtain sufficient sensitivity.

Reverse transcription polymerase chain reaction (RT-PCR) has been used as a key tool of ante-mortem diagnosis that is capable of identifying the presence of viral RNA in saliva, cerebral spinal fluid, skin biopsies at the base of the neck and corneal impressions [14]. RT-PCR is sensitive and specific when the shedding of the virus is underway, but a negative outcome does not rule out rabies because the shedding is intermittent. There have been real-time RT-PCR protocols which can be used to give an assessment of the viral load quantitatively and distinguish the rabies virus and other lyssaviruses [44].

Immunofluorescence or immunohistochemistry of skin biopsies especially hair follicle at the nape of neck is another ante-mortem method of diagnosis [45]. Although not as invasive as a brain biopsy, it has a sensitivity of between 50-80% at various stages of disease and quality of the specimen.

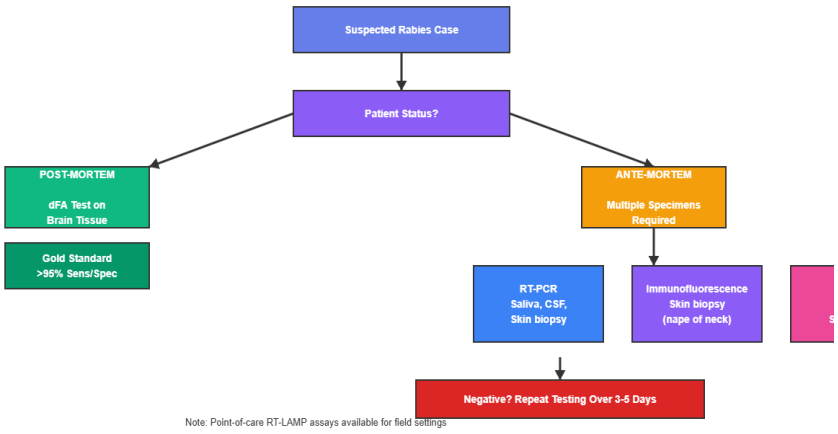

Figure 4. Clinical decision pathway for rabies diagnosis in suspected cases. Post-mortem diagnosis utilizes direct fluorescent antibody (dFA) testing on brain tissue specimens (gold standard, >95% sensitivity/specificity). Ante-mortem diagnosis requires multiple specimen types due to intermittent viral shedding: (1) RT-PCR on saliva, CSF, and skin biopsies from nape of neck; (2) immunofluorescence on skin biopsies; (3) serology for virus-specific antibodies in serum/CSF. Negative results do not exclude rabies; repeated testing over consecutive days increases diagnostic sensitivity. Point-of-care molecular assays (RT-LAMP) enable field diagnosis in resource-limited settings.

Aca. Intl. J. Vet. Med. 2025;3(2)28-42. DOI: https://doi.org/10.59675/V324

5.3 Serological Testing

Serological tests are used to identify antibodies of rabies virus in blood or cerebral fluid. The neutralizing antibodies are measured by the rapid fluorescent focus inhibition test (RFFIT), and it is commonly employed to measure the immune responses after vaccination or to confirm the diagnosis in unvaccinated patients that have developed antibodies which are usually produced later during the disease [16]. The presence of antibodies in the cerebral fluid and lack of a vaccine history are strong evidence of the diagnosis of rabies.

5.4 Point of Care and Field Diagnostics.

The latest innovations in technology have produced portable molecular diagnostic platforms that can be deployed in resources constrained environments [15]. The RT-LAMP assays are rapid methods to detect rabies virus RNA and do not need advanced thermal cycling systems, and the results can be obtained within 30-60 minutes [46]. Multiple RT-LAMP protocols have been demonstrated to run in the field and have potential in the decentralization of rabies diagnostics.

Immunoassays on a lateral flow and rapid immune-chromatography are being developed; however, the current versions do not have the sensitivity needed to be used in routine clinical applications [47]. Further development of point-of-care diagnostics is also a priority area toward improving rabies surveillance in endemic areas.

6. Prevention and Control

6.1 Post-Exposure Prophylaxis

The pillar of prevention of rabies after possible exposure is still the use of post-exposure prophylaxis, which has shown significant effectiveness in the prevention of the disease when taken promptly and as recommended by WHO [18]. PEP regimen is a combination of three important elements which include: Immediate comprehensive wound cleansing with soap and water, Infiltration of rabies immunoglobulin at the wound site and in surrounding regions as well as a course of doses of rabies vaccine.

The initial and the most vital one is wound cleansing, which can minimize the viral load with the help of mechanical elimination and the inactivation of viruses using the detergents of soap [48]. Sufficient irrigation of at least 15 minutes should be done and wounds should not be suture unless necessary so that viral retention is minimal.

Rabies immunoglobulin (RIG) is a passive immunization that neutralizes the immunization with immediate antibodies and the active immunization is formed under the influence of vaccination [49]. Human rabies immunoglobulin (HRIG) or equine rabies immunoglobulin (ERIG) are to be instilled at the site of exposure within the anatomy before virus is neuroinvasive. HRIG is recommended to take 20 IU/kg body weight and ERIG, 40 IU/kg. These shortages and high prices of rabies immunoglobulin have prompted the advancement of monoclonal antibody cocktails with the same effectiveness and better safety profiles and scale of production [19].

Aca. Intl. J. Vet. Med. 2025;3(2)28-42. DOI: https://doi.org/10.59675/V324

Active immunization against modern cell-culture vaccines is done with intramuscular or intradermal administration [50]. According to the WHO, there is a variety of vaccination regimes, which include the simplified version of Thai Red Cross (2-site intradermal on day 0, 3, 7, and 28), which requires less vaccine volume and is cheaper than others but still immunogenic [51]. Immediately after exposure, vaccination must be started but PEP is recommended even months after exposure because of the elastic incubation period.

6.2 Pre-Exposure Prophylaxis

Pre-exposure prophylaxis is prescribed to people who are at high risk of rabies exposure, such as veterinarians, animal handlers, laboratory workers, wildlife biologists, and travelers to the endemic areas with limited access to the post-exposure prophylaxis [20]. The WHO now suggests a simplified two-dose intramuscular program on day 0 and 7 or two-site intradermal program on day 0 and 7 both of which have shown to be non-inferior to the established three-dose programs in immunogenicity and better compliance and cost [52].

Pre-exposure vaccination, instead of eradicating the post-exposure prophylaxis, makes it easier by eliminating the necessity of rabies immunoglobulin and also by lowering the amount of vaccine that must be inoculated [53]. It may be reasonable to periodically monitor serology in people who are at risk and maintain the level of protective antibodies.

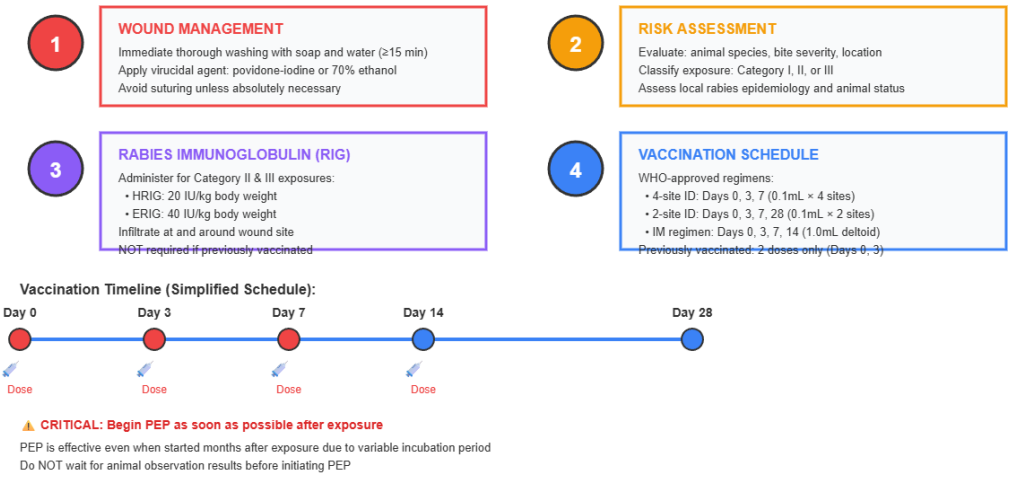

Figure 5. Comprehensive post-exposure prophylaxis protocol following WHO guidelines (2018).

Step 1: Immediate wound management with thorough cleansing using soap and water for ≥15 minutes, followed by application of virucidal agent (povidone-iodine or 70% ethanol).

Step 2: Risk assessment considering animal species, bite circumstances, vaccination status of animal, and local rabies epidemiology.

Step 3: For Category II (nibbling, minor scratches/abrasions without bleeding) and Category III (single/multiple transdermal bites, contamination of mucous membranes with saliva, bat exposures) exposures: administer rabies immunoglobulin (RIG) 20 IU/kg for HRIG or 40 IU/kg for ERIG, infiltrated at/around wound site.

Step 4: Initiate vaccination using cell-culture vaccine via intramuscular (deltoid) or intradermal routes. WHO-approved schedules include: (a) 1-week 4-site ID regimen (0.1 mL at 4 sites on days 0, 3, 7); (b) Thai Red Cross 2-site ID regimen

Aca. Intl. J. Vet. Med. 2025;3(2)28-42. DOI: https://doi.org/10.59675/V324

(0.1 mL at 2 sites on days 0, 3, 7, 28); (c) IM regimen (1.0 mL on days 0, 3, 7, 14). Previously vaccinated individuals required only 2 doses without RIG.

6.3 Vaccines

Modern rabies vaccines are generated with cell culture or embryonated egg substrate and include purified chick embryo cell vaccine (PCECV), purified Vero cell rabies vaccine (PVRV) and human diploid cell vaccine (HDCV) [54]. These novel vaccines have shown high immunogenicity and safety profiles and have substituted older nerve tissue vaccines, which have high risks of adverse events.

The next-generation vaccine platforms are being researched, and recombinant vaccines, viral vector-based vaccines, and mRNA vaccines are promising in preclinical research [21]. Oral recombinant vaccines made using vaccinia virus or adenovirus vectors by introducing rabies glycoprotein gene have also been effective in conducting vaccination campaigns on wild animals [55]. The application of these technologies to human use may be translated into even easier vaccination approaches and increase access to vaccination worldwide.

6.4 Mass Dog Vaccination

Dog vaccination is a long-term measure that is the most cost-effective means of elimination of human rabies because in case of the stop of transmission in dog populations, the main source of human infection is eliminated [22]. It is demonstrated through mathematical modeling and field experience that continuous vaccination of 70% or more in dog populations can be used effectively to interrupt transmission [56].

The issues associated with implementation are obtaining sufficient coverage of free-roaming dogs' population, sustaining coverage by conducting annual campaigns, having integrity of cold chain of vaccines and getting long-term funding [57]. Engagement of the community, integration with the available veterinary services, and the use of oral bait vaccines among inaccessible dogs has increased the effectiveness of the program in a number of countries [58].

6.5 One-Health Approaches

The elimination of rabies is only possible through a concerted effort in the human health, veterinary and environmental sectors under One-Health frameworks [23]. Combined bite case management systems, which link human bite patients and the animal surveillance and vaccination schemes have been effective in those countries that are on the way to elimination [59].

Whole-genome sequencing as a Genomic epidemiology has advanced the knowledge of transmission patterns, cross-species spillover, and importation of variants of the virus, providing information on control intervention decisions [24]. Improved monitoring involving animal rabies, human exposures, and laboratory diagnostics offer the information that is required to make evidence-based decisions and allocate resources [69].

7. Arguments against Global Elimination.

In spite of the fact that there are effective prevention tools available, there are several obstacles hindering the achievement of rabies eradication in the world. Inaccessibility to post-exposure prophylaxis through

lack of stock to the vaccine, prohibitive affordability, and distance to medical centers leads to preventable fatalities, especially rural ones [28]. It is estimated that post exposure prophylaxis is given to between 25 million people annually and millions of people do not get the treatment because of accessibility barriers [41].

Poor surveillance mechanisms in most of the endemic countries cloud the real disease burden and block the assessment of the impact of control programs [38]. The underreporting is significant with the real cases being estimated to be 10-100 times greater than the initial numbers that are officially reported in certain areas [51].

Mortality is preventable due to delayed care-seeking behavior that is associated with lack of awareness about rabies, cultural beliefs, economic problems, and preference to traditional healers [50]. Interventions focused on community-based education have shown the potential to enhance the behavior of care-seeking [58].

Mass dog vaccination campaigns have logistical problems such as the ability to reach free-roaming dogs, cold chains and yearly continuity of the campaigns which have limited coverage in most of the endemic zones [57]. Political good will and financial sustainability are not stable across endemic nations and rabies priorities tend to be undermined as compared to other health issues [29].

8. Conclusion

Rabies virus is still a major issue to the general population even though it is totally preventable by vaccination and post exposure prophylaxis. The recent achievements in viral pathogenesis knowledge encompass the well-developed neurotropism and immune-evasion mechanisms, and the introduction of molecular diagnostic methods has improved the surveillance opportunities even within the resource-constrained environment. The development of preventive measures, including simplified vaccination regimes, monoclonal antibodies-immunoglobulins, and One-Health models, has enhanced the prevention activities across the world.

It is possible, yet multi-sectoral coordination, commitment to dog vaccination campaigns, increased access to biologics, the application of rapid field diagnostics, and expanded access to biologics will be required to achieve the goals of the World Health Organization of eradicating dog-mediated human rabies deaths by 2030. Experience in countries that have successfully eliminated canine rabies indicates that long term, integrated interventions provide actual outcomes. As the political will is intensified, more investment will be made and the scientific innovation will remain, this will push the world to the eradication of this ancient scourge.

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