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Comprehensive Update on Rabies: A Neglected Zoonotic Disease of Public Health Concern

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Abstract: Rabies, a deadly viral zoonosis, that has driven mankind for centuries continues to be a major global public health threat, primarily affecting under developed areas. The virus targets the central nervous system of warm-blooded animals and claims the lives of over 60,000 individuals annually. Often categorized as a "neglected" disease, zoonoses constitute the majority of emerging infectious ailments. India carries the greatest share of worldwide mortalities resulting from rabies transmitted by dogs to humans. Despite this, rabies is not definable in India, and it continues to be denied adequate consideration when it comes to public health issues. Dogs serve as the primary reservoirs for the rabies virus, transmitting it through direct contact with their saliva including bites, scratches, and exposure to broken

skin and mucous membranes. Despite, the fact that the cure for rabies remains elusive, it is possible to prevent this fatal disease through proper pre- and post-exposure prophylaxis and early laboratory diagnosis. Diagnostic technologies like RT PCR, qPCR, dRIT, dFAT, and LFA are highly sensitive and specific in the rapid detection of rabies virus and play a crucial role in preventing the disease. Furthermore, vaccination both, pre- and post-exposure prophylaxis, coupled with increased public awareness, can significantly mitigate the impact of health concerns at the community level. Hence this comprehensive review emphasizes its transmission dynamics, diagnostic techniques, and preventive strategies aiming to raise awareness and enhance efforts to combat this neglected zoonotic disease.

Keywords: Rabies virus; prophylaxis; rabies immunoglobulins; vaccination; viral replication

1. Introduction

Rabies, often referred to as a "neglected zoonotic disease," has remained a pressing concern for public health worldwide, posing an invisible but pervasive threat. The virus was first recognized in the 4th century B.C. as pertaining to the genus *Lyssavirus*, order Mononegavirales, and family *Rhabdoviridae* [1]. The disease was identified with vigorous nervous symptoms resulting in paralysis followed by death [2]. It enters the central nervous system via the neuronal junction in the bite site, travels to the peripheral nerves, and multiplies and ravages the brain. Rabies poses a substantial health concern in the majority of Southern and Eastern Mediterranean and Middle Eastern countries [3]. The viral disease, which seems to go back a long way in human history, persists in having a negative impact on animal and human populations. Around 3000 BC, the term rabies emerged from the ancient word ‘rabha’ meaning violence. With a history spanning over 4300 years, rabies stands as one of the most persistent and widespread infectious diseases known to mankind [4]. This ancient ailment often referred to as “rabere” in Latin continues to causes deadly encephalitis in all warm-blooded animals, including humans [5,6]. Louis Pasteur and Emile Roux identified the virus as the root cause of the disease and discovered the first-ever human immunization [7].

Approximately 20,000 individuals in India lose their lives each year due to rabies contracted from dog bites [8]. Globally, this virus is responsible for an annual death of 59,000 people annually, although the reported cases vary significantly, ranging from 25,000 to 1,59,000. In addition to its devastating effects on people's lives, rabies has a significant economic burden, with estimated cost ranging from 2.9 to 21.5 billion USD [9]. This

multifaceted challenge warrants a closer examination due to its profound impact on both public health and the economy. Furthermore, it exacts a substantial tax on human well-being, resulting in a global total of 3.7 million disability-adjusted living years (DALYs), with estimates ranging from 1.6 to 10.4 million [10]. In developing nations, dogs are the primary carriers of the rabies virus, and they are responsible for more than 99% of all recorded instances of the disease in humans [11,12].

The COVID-19 pandemic has confronted healthcare systems, especially in low- and middle-income countries, with an unprecedented challenge. These systems formerly struggled with a lack of resources and dealt with an even deeper load that is made worse by the ongoing risk of human rabies. To date, there have been more than 237 million COVID-19 cases, with many people have succumbed to the virus infection [13]. The significant transmissibility of SARS-CoV-2 stimulated the World Health Organization (WHO) to declare the COVID-19 pandemic in March 2020, as the virus rapidly disseminated worldwide [14-23]. The occurrence of new variants prompted researchers to investigate the evolutionary linkages and molecular variations among different coronavirus strains [24-25]. The Omicron variant exhibited a higher transmission rate than other variants of concern (VOC) and, thus, was a threat in many countries, including Malaysia [26-28]. Besides the signs and symptoms of typical COVID-19 infection, many individuals also presented with respiratory issues, gastrointestinal complications, and psychological symptoms [29-32]. Vaccination and secondary measures (practicing social distancing, wearing face masks, and maintaining proper hygiene) was the most effective approach in mitigating the pandemic effectively [33-37]. Unfortunately, animal disease monitoring and infectious disease control were neglected during crises like the COVID-19 outbreak [38]. Neglecting prevention activities in the wake of the COVID-19 pandemic has had significant effects on the prevalence of rabies among humans [13]. The reduction in vaccination coverage of dogs, as well as reduced monitoring, contributed to a prolonged lifespan of infected dogs, therefore uplifting the risk of a significant proliferation in rabies cases among dogs and, in turn, posing an increased threat of rabies transmission to humans [38].

To achieve the best possible health outcomes by 2030, WHO, the World Organization for Animal Health (OIE), and the Food and Agriculture Organization of the United Nations (FAO) are primarily focusing on eliminating human rabies deaths caused by canine transmission in countries where rabies is prevalent [39]. Canine rabies is enzootic in India, with between 30% and 60% of cases involving children with the majority occurring in rural regions. It is estimated that 36% of rabies deaths worldwide (roughly 20,000 or more) occur in India [40] and the majority of cases are in rural areas of Africa and Asia. Due to a lack of

rabies awareness, substantial expenses, and the distance from remote locales to health clinics in these areas, patients rarely seek post-exposure prophylaxis (PEP) after a bite or scratch [41]. As a result of increased travel to distant regions throughout the globe, the possibility of a newly developing virus being imported into the UK is rising. In 2001, the UK received two confirmed instances of human rabies, one each from the Philippines and Nigeria [42]. The high prevalence of unvaccinated stray and pet dogs, occupational risks (such as dog butchers in Vietnam), the lack of the rabies vaccine in rural areas, and false information about the importance of seeking medical attention after dog bites are all contributing factors to the spread of rabies in Southeast Asia [43]. It is a preventable disease through timely post-exposure prophylaxis and vaccination. Avoiding contact with rabid animals and ensuring pets regularly receive rabies vaccinations is the best way to prevent rabies infection [11,12]. This review provides an essential framework for the forthcoming exploration of this critical issue. We have highlighted the predominant importance of rabies as a neglected zoonotic disease, emphasizing its significant impact on etiology, pathophysiology, diagnostics, and preventive strategies. By introducing the significant subjects and topics that will be discussed in the review, we aim to provide readers with an unambiguous guide for comprehending the broad nature of rabies and its implications for both human and animal populations.

2. Rabies and its genotypes

The word "rhabdovirus" (Greek) means rod, and refers to the shape of the virions which is believed to be peculiar. Animal rhabdoviruses were characterized as being shaped like a bullet or a cone, while plant rhabdoviruses were described as being shaped like a rod with two rounded ends.

Rhabdoviridae comprises two officially recognized genera, *Vesiculovirus* and *Lyssavirus,* by ICTV (International Committee on Taxonomy of Viruses) [36]. The family *Rhabdoviridae* comprises 265 species that have been recognized among the plants, invertebrates such as arthropods, nematodes, and vertebrates such as mammals, amphibians, reptiles, birds, and fish after being approved by the ICTV in 2022 [44]. Currently, *Rhabdoviridae* consists of three subfamilies *Alpharhabdovirinae, Betarhabdovirinae*, and *Gammarhabdovirinae*, of which two are known to infect fish and marine animals.

Currently, there are 7 different genotypes of Rabies virus (RABV) identified in nature. The genotype 1 strains of rabies virus, found in the streets and laboratory settings, are the predominant variants responsible for over 99% of rabies cases in humans and animals worldwide. The remaining six genotypes are generally known as rabies-related viruses

(RRVs), and include the Mokola bat virus (genotype 3), the Lagos bat virus (genotype 2), the Duvenhage virus (genotype 4), the European bat lyssaviruses (genotypes 5 and 6), and the Australian bat lyssavirus (genotype 7). According to Knobel [45], these viruses are common in several regions of Australia, Western and Eastern Europe, and Africa. Four unique genotypes were also found in bats in Eurasia, including Aravan, Irkut, Khujand, and West Caucasian [46-47]. The Lyssavirus genus contains seventeen different viral species, including the Aravan virus (*Lyssavirus aravan*), Australian bat lyssavirus (*Lyssavirus australis*), Bokeloh bat lyssavirus (*Lyssavirus bokeloh*), West Caucasian bat virus (*Lyssavirus caucasicus*), and Duvenhage virus (*Lyssavirus duvenhage*), Ikoma lyssavirus, Lleida bat lyssavirus, Irkut virus, Khujand virus, Mokola virus, Lleida bat lyssavirus, Taiwan bat (*lyssavirus*), Gannoruwa bat lyssavirus, European bat lyssavirus 1 and 2, European bat lyssavirus 2 and Helsinki virus. Based on nucleic acid relatedness, rabies and its related virus were grouped under various phylogroups. Phylogroup 1 refers to rabies viruses found in humans, domestic animals, and bats. These viruses include the Bokeloh bat lyssavirus, Aravan virus, Gannoruwa bat lyssavirus, Khujand virus, and Kotalahti bat lyssavirus. Phylogroup 2 contains the Shimoni bat virus, Lagos bat virus and Mokola virus. On the other hand, phylogroup 3 was used to group the West Caucasian bat lyssavirus (WCBV), Lleida bat lyssavirus (LLEBV), and Ikoma lyssavirus (IKOV). Viruses like Kotalahti bat lyssavirus (KBLV) and Taiwanese Bat Lyssavirus (TBLV) are still considered speculative species within the Lyssavirus genus until they have undergone thorough characterization [48].

The single-stranded RNA genome of the rabies virus has a negative sense and is shaped like a bullet. It contains five structural proteins: nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G), and big RNA polymerase protein. The genomic size of these viruses is roughly 12 kb. The nucleocapsid (NC) is made up of the proteins N, P, and L. The viral genome and the NC join forces to produce a ribonucleoprotein (RNP) complex.

The RNP serves as crucial for viral transcription and replication. In order to create the virus's envelope, the G and M proteins collaborate [49]. In particular, the G protein stimulates the production of virus-neutralizing antibodies (VNA) and controls cellular tropism and absorption by brain cells [50-51]. Together, these five structural proteins support viral transcription, replication, and immune evasion. Figure 1 shows the rabies virus's physical makeup.

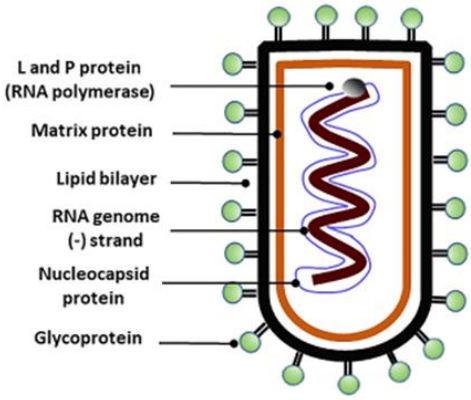

Figure 1. Structure of rabies virus.

3. Replication of rabies virus

Replication of rabies in the host will occur in 9 phases: -

Step A- Viral attachment: The surface protein known as glycoprotein helps viruses adhere to host cells.

Step B - Endocytosis and endosomal fusion: The attachment of viral surface protein (glycoprotein) initiates the host cell's endocytosis process, in which the host cell's plasma membrane folds inward and creates a membrane-bound vesicle known as an endosome around the virus. It causes the virion to become trapped in the host cell's endosome.

Step C- Uncoating: The virion is constructed throughout two phases. After the first nucleocapsid forms in the cytoplasm, the virion is pushed through the cell membranes during the budding process.

Step D & E- Genome replication and Transcription: The virus uses the host cell machinery to transcribe the viral RNA within the cytoplasm. Each encoded protein results in the production of one of the five mRNAs.

Step F & G- Assembly: The virion is assembled in two phases – During the process of budding, the virion is forced through the cell plasma membranes after the creation of the first nucleocapsid in the cytoplasm.

Step H- Budding: The membrane that maintains the virion in its envelope is partially removed during budding and the new virion is now prepared to infect various host cells. The replication of the rabies virus inside the host cell is depicted in Figure 2.

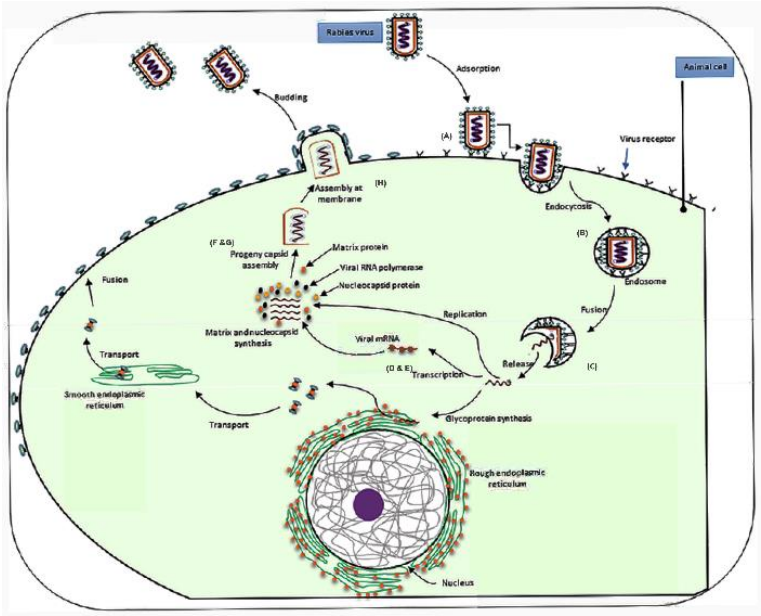

Figure 2. Replication of rabies virus inside the host cell. A: attachment, B: endocytosis, C: uncoating, D& E: Replication and Transcription, F-H: Assembly and Budding.

4. Mode of transmission

All warm-blooded species are susceptible to lyssavirus infection; however, cold-blooded animals can also develop lyssavirus infection [52]. The transmission of rabies virus occurs when it comes in contact with bite wounds, open skin wounds, or mucous membranes through exposure to infected saliva, nerve tissue, inhalation of aerosolized virus, or organ transplantation with contaminated tissues [53-54]. Due to their close interaction with humans, dogs are approximately 50 times more likely to bite someone than lick or scratch them, which only happens between 0.1% and 1% of the time [55-57]. This is because 85%-95% of rabies cases are transmitted by dog bites. The acerbity of the disease, site of the bite wound, and virus concentration in the saliva will influence the fatality of the illness. The incubation period for rabies is usually 2–3 months but may differ from one week to a year. In general, 54% of cases may last 1 to 3 months, 30% could last 30 days, and 15% for about three months. The incubation period for the remaining 1% of the infections may last longer than a year. In extremely rare cases, it may even stretch up to 25 years depending on the viral load, the virulence of the strain, the severity, and the area of the bite [58-63]

In rare instances, viruses can enter the body through non-bite exposures such as aerosols, organ and cornea transplantation, infection of open wounds with saliva, mucosal membranes, or contaminated substances [64-68]. Although it is theoretically conceivable, it is not a practical option for the virus to propagate through infected human bites [69-71]. There was only one recorded instance of a narcolepsy person biting another person [72]. The unsafe contact with the diseased people and connections to discharges with higher virus concentrations can cause a severe hazard to health workers [56,60]. Transmission of rabies virus among the community is depicted in Figure 3.

Proper management should be taken for pre- and post-exposure prophylaxis. Rabies virus precisely resides in the intra-neuronal state during the incubation stage. However, it is unknown if healthy blood donors might transfer the disease to the recipient during the incubation period. Hence, it is forbidden to donate organs and blood for a year after post-exposure prophylaxis against the rabies virus.

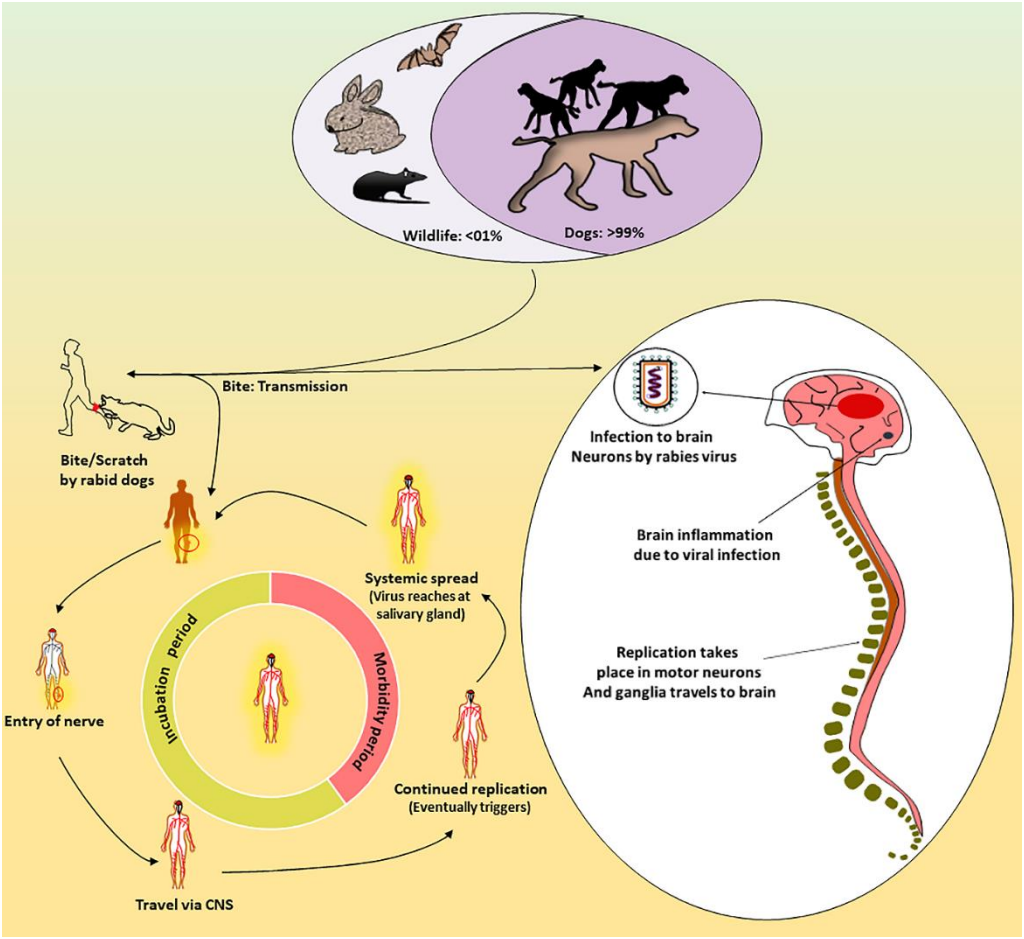

Figure 3. Transmission of rabies virus.

5. Diagnosis

The wide availability of specific laboratory tests, along with a consistent history and symptoms, make it easier for the astute physician to make the diagnosis of rabies. There should be at least one national reference center in each country where the disease is endemic to facilitate diagnosis and analysis both before and after death. When an encephalopathy presents with a rapid downward trajectory and other more prevalent viral and non-infectious illnesses have been ruled out, suspicion should be raised [72-76]. The rabies infection can only be identified, once the symptoms start to appear [12]. The diagnosis of rabies is made either using in-vivo techniques or autopsy [77]. Lyssavirus infections are difficult to detect via ante-mortem studies. Even though hydrophobia is very suggestive, there are no pathognomonic medical symptoms of infection with this disease. The historical dependence on the identification of accumulating Negri-bodies is no longer adequate in support of the diagnostic evaluation as a few other lab-based diagnostics for infection confirmation have been established [2]. Evidence suggests that symptoms are unrelated to the location of viral replication in the brain [78-79].

There are two well-known types of rabies: paralytic and furious (also known as encephalitic). They can be recognized by specific symptoms even though the origins of development of each kind are still not fully known [78,80]. A case definition, however, is frequently not verified until the disease has progressed to the acute neurological phase. The majority of patients experience symptoms 20 to 90 days after exposure, although incubation durations may vary substantially [81]. This variance is presumably influenced by the site of virus entry, viral load, species, and strain of the infecting virus, as well as the host's immunological capabilities. Viral replication during the incubation period in the nervous system and induced pain numbness will generate the initial symptoms after exposure [58]. During the prodromal phase, the virus reaches the brain and infects the brainstem and hippocampus, which causes the acute neurological phase with typical symptoms. The symptoms are typically neurological, like irregular anxiety, hydrophobia, seizures, disorientation, and hypersalivation. In comparison to furious rabies, infected patients with paralytic rabies experience muscle weakness and paralysis, as well as a longer acute neurological phase [79]. Both the rabies types cause coma and death. The rabies virus infection can be strongly detected with classic symptoms like aerophobia or hydrophobia. However, the confirmation of rabies infection results from diagnostic laboratory tests as other possible differential diagnoses [12]. The non-appearance of specific characteristic symptoms like inconstant consciousness, respiratory failure, and autonomic stimulation can show a rabies infection. However, early diagnosis of rabies is essential; since if the patient starts to exhibit

clinical symptoms owing to a lack of diagnosis tool, a poor late diagnosis will result in the death of the infected person [81].

The rabies virus can be detected by removing any brain tissue from the afflicted animal, preferably from the brainstem and cerebellum [82]. There are many ways to detect rabies in animals, including the direct fluorescent antibody test, fluorescent antibody virus neutralization, rapid fluorescent focus inhibition test, mouse inoculation technique, rabies tissue culture isolation test, direct immunohistochemical test, lateral flow assay, reverse transcriptase-polymerase chain reaction, loop-mediated isothermal amplification assay, and recombinase polymerase amplification assay [83]. Only laboratory tests, preferably using post-mortem tissue taken from the skull, can confirm the presence of rabies [84]. Additionally, detection is carried out on skin biopsies, serum, and saliva samples taken from hair follicles at the back of the neck [82]. It is advised to confirm a clinical case of rabies using laboratory-based procedures because clinical diagnosis alone is challenging and frequently inaccurate. The RABV antigen is directly detected by immunofluorescence, immunoperoxidase technique (IPT), and enzyme immunoassays [85-86]. A diagnostic tool for RABV and other lyssavirus nucleic acid segment identification is the DNA microarray [87]. The most effective method of post-mortem diagnosis is to use a fluorescent antibody test (FAT) to identify the rabies virus antigen in infected tissues, ideally brain smears or touch imprints obtained from a biopsy. The WHO recommends FAT because it provides accurate results on fresh specimens in 95–99% of instances within a few hours. It has been demonstrated that other lyssavirus antigen detection techniques, such as direct fast immunohistochemistry testing, have sensitivity and specificity that are comparable to the FAT. WHO suggests that direct fast immunohistochemistry assays be developed further as an alternative to the FAT to enhance decentralized laboratory-based surveillance in endemic areas. The ability to diagnose rabies before death or during life using intra-vitam methods depends on the virus's ability to propagate widely throughout the nervous system. Since the sensitivity varies widely depending on the stage of the illness, immunological status, intermittent viral excretion, and technical personnel training, it is strongly discouraged for the diagnosis of rabies in animals.

For comprehensive antemortem diagnosis, Faye et al. [88] created reverse transcription recombinase polymerase amplification (RT-RPA). According to McElhinney et al. [89], the monoclonal antibody-based rapid diagnostic test (RDT)-immunochromatography or LFA was regarded as a quick and user-friendly rabies diagnosis test that confirms rabies in both lab and field settings. The direct rapid immuno-histochemical test (DRIT) is considered a better substitute for DFAT in remote areas [90]. The ingenious biosensing technologies such as optical, piezoelectric, thermal, and electrochemical biosensors could be a better alternative

to rabies detection as it is an empathetic, fast and effective method [91]. Chip-based RT PCR tests, Lateral flow device base RT-LAMP assay is advanced technology in rabies diagnosis and can adapt to the clinical laboratories that lack resources [92-93]. Meishen Ren et al. [94] developed a nucleic-acid-based RPA-CRISPR method to diagnose rabies virus in mammals, specifically animals with high capability in early detection. There is currently no method that has been authorized for the early diagnosis of the rabies virus. For low positive instances, Lisa Dettinger et al. [95] describe improved sensitivity and simplicity of LN34 RT-qPCR interpretation. The LN34 RT-qPCR has the potential to supplement or replace the DFA as a test for animal rabies diagnosis because of its improved sensitivity, objectivity, and technological convenience. Several researchers have emphasized the effectiveness of mass spectrometry in detecting rabies, which does not employ microscopy or antibodies and offers a next-generation technology platform for detection [96-97]. Lodha et al. [98] evaluated the effectiveness of the Truenat rabies assay, a quick, semiautomated, portable, and closed PCR-based system, in the detection of rabies in both humans and animals.

6. Prevention and control

Human post-exposure prophylaxis (PEP) and dog rabies management, which can only be achieved through widespread dog vaccination, are the two main elements of human rabies prevention. These are widely implemented immunization initiatives sought to be under scientific surveillance. The following methods can be used to lower human mortality caused by dog-associated rabies: giving post-exposure prophylaxis to those who have been exposed; vaccinating enough dogs to break the transmission cycle; or combining both methods simultaneously [99]. To protect humans from rabies, pre- and post-exposure vaccination regimes are utilized. Pre-exposure immunizations are indicated for persons who are at a higher risk of infection, such as wildlife professionals, veterinarians, and dog catchers, even though post-exposure vaccine is still required following a likely encounter with the virus. Everybody who might have encountered a rabid animal is given post-exposure immunization [100].

Washing and sufficient flushing of the bite area are the essential steps in the post-exposure therapy of bite wounds. As soon as is feasible after exposure a series of post-bite immunizations must be administered and Rabies Immunoglobulins (RIG) must be injected into/around the bite site [12]. Using Cell Culture Vaccines (CCV), Purified Chicken Embryo Cell Vaccines (PCECV), and Purified Duck Embryo Vaccines (PDEV), the creation of the rabies vaccine from "Pasteur-treatment" has significantly improved.

The first widespread dog vaccination program is thought to have taken place in Japan in 1920 for rabies, one of the first diseases for which a canine vaccine was developed [101].As dogs are the main reservoir for RABV, many experts believe that to entirely eradicate canine rabies, at least 70% of dogs must be immunized [102-103]. Contrarily, it has been asserted that vaccination of even 35% of the dog population may be sufficient to eradicate the illness from this population due to the lower basic reproduction number (R0) for rabies[104] .In order to rule out vaccine failures brought on by insufficient injection or a break in the cold chain procedure, parenteral vaccination of dogs that are allowed to roam freely produces a significant immunological response and is the preferred way of immunization when done properly [12]. Free-ranging dogs are difficult to reach for vaccinations due to the difficulties in locating, catching, and restraint, which can pose a risk of a dog biting or injuring the handlers as well as the dogs themselves [105]. Therefore, in many areas with a large population of free-ranging dogs, the target of achieving 70% "herd immunity" is still challenging to achieve. The most current report from the WHO conference on rabies suggests utilizing the oral rabies vaccine (ORV) in addition to parenteral coverage [12]. Although the oral rabies vaccine has successfully eradicated fox rabies from Europe [106], it is unknown whether it will be able to induce a strong enough immune response in stray dogs due to immunological and delivery concerns.

Since its initial deployment in Switzerland in 1978, the history of effective ORV in wildlife in Europe spans four decades of incremental development of various vaccine types and intervention tactics. The most widely used substitutes for attenuated rabies virus vaccinations (SAD Bern, RV-97) (ERA 333) are recombinant vaccinia viruses that express the glycoprotein from ERA strains (V-RG) and selected monoclonal antibody escape mutant vaccines (SAD VA1, SAG1, and SAD2) that were created through reverse genetics [107].

The effectiveness of the ORV is affected by the timing, regularity, and type of baits used in interventions. Dogs must thoroughly chew the sachet or blister containing the immunization for it to be efficiently deposited into the oral mucosa, in addition to choosing the necessary baiting requirements like embedding the vaccinations in meat- or egg-based decoys. The modified live or recombinant construct vaccine also needs to be replicated in order to elicit an immune response in the host. Despite these challenges, it is nevertheless recommended to use ORV to immunize dogs that are free to roam but cannot get parenteral vaccination [108]. Prevention of rabies virus in the community is depicted in Figure 4.

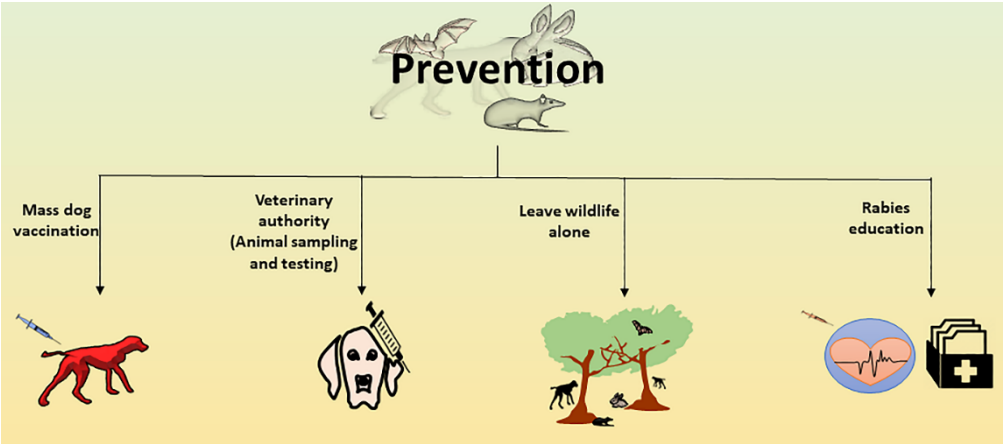

Figure 4. Prevention of rabies virus among the community.

7. Rabies immunoglobulin and vaccination

Rabies immunoglobulin (RIG) induction and vaccination are both part of post-exposure prophylaxis (PEP), although those who have appropriate pre-exposure prophylaxis should not receive RIG instead of a booster shot. The main goal of giving rabies immunoglobulin is to neutralize the virus at the bite region and block the spread of infection to produce an adequate immune response to vaccination. If it is not accessible, human rabies immunoglobulin can be replaced by equine rabies immunoglobulin (chromatography-purified, pepsin-digested immunoglobulin). For human rabies immunoglobulin (20 I.U./kg) and equine rabies immunoglobulin (40 I.U./kg), the WHO has approved weight-based dose estimation. Rabies immunoglobulin insufficiency is found in rabies-prone areas because of high manufacturing costs and limitations in large-scale production [109]. Production of equine rabies immunoglobulin is easier and more effective than human rabies immunoglobulin and is highly accessible in endemic countries [110].

Studies have examined the application of rabies immunoglobulin to wounds only, avoiding the injection of the frequently sizable remaining volume of rabies immunoglobulin to distant places to conserve rabies immunoglobulin supplies for upcoming patients. With this strategy, all patients with category III exposure might receive post-exposure prophylaxis, even in countries with inadequate resources and an active rabies epidemic [111]. Even when rabies immunoglobulin is accessible, it might not be used due to a lack of information about the potential post-exposure prophylaxis tools. Bai et al. [112] evaluated the effectiveness of photodynamic and immunotherapy to inactivate the rabies virus in an in-vivo model. They used photosensitizer (TPA-Py-PhMe) to generate Reactive Oxygen Species (Type I & II) and pro-inflammatory factors which were able to reduce viral load in infected mice.

A remote vaccine is suggested in addition to the injection of rabies immunoglobulins. An intradermal or intramuscular booster regimen has been recommended by the WHO for those who have already had a vaccination [12,2]. Since all vaccines are believed to be equally effective, the regimen chosen depends on the readily available vaccine and the knowledge of the neighborhood medical center. For unvaccinated people, several vaccine regimens are approved for post-exposure prophylaxis [12]. According to Wilde et al. [113], patients with compromised immune systems and those with low CD4+ T cell counts may not respond to immunizations at all or just ineffectively. Such patients demand rigorous PEP, which involves vaccination and wound care with RIG infiltration to elicit a strong immune response. Patients on hemodialysis may potentially have lower immunological responsiveness to vaccinations, even if the rabies vaccination is safe and effective if administered before the onset of symptoms [114]. However, it will take more than ten years before any of the numerous other promising immunobiological that are currently under development have any direct applications to people.

Even though DNA-based vaccines have shown promise in animal models, such as nonhuman primates, they frequently require at least a primary inoculation before being given a booster dose to be effective, and they might not have the quick kinetics needed for postexposure application [115-116]. In the event that diminished, modified live vaccinations are ever demonstrated to be safe and effective, recombinant rabies vaccines have been suggested as a method of producing exogenous antibodies and as a means of delivering foreign substances to the central nervous system. They allow the integration of new genes into untranslated regions of the viral genome [117-118]. If neutralizing monoclonal antibodies can be generated affordably, they may offer an alternative to rabies immunoglobulin [119]. Rabies prevention must continue to be firmly concentrated on disease control in the animal reservoir because there are pure, potent, secure, and effective veterinary immunizations available for a small percentage of the cost of human vaccines [120-121].

Implementing mass vaccination and contraception programs for stray dogs represents a cost-effective approach to long-term human rabies prevention [122]. Public health authorities, animal welfare organizations, and local communities need to work together to implement and sustain such programs effectively.

8. Conclusion

Rabies has been a zoonotic, dreadful, and highly neglected disease over the past many years. The disease can be eradicated with early detection and careful management of the virus. Many countries are still considered high-risk rabies-prone areas, and just a few have

achieved rabies-free status. Creating awareness among the public about advances in medicines can also play a significant role in controlling rabies. On the part of veterinarians, suitable authorities are to follow proper diagnosis and reporting of the disease, which can reduce the mortality rate of the victims. A collaborative effort from all parties will be required to develop and implement a comprehensive intervention strategy (mass free-roaming dog (FRD) vaccination, management of the FRD population, garbage management, sustained educational outreach to children, increased scope and frequency of awareness campaigns, incentives to persuade people to adopt FRD and develop responsible ownership behaviors, and expanding the availability of PEP to all community members). An intervention program also needs a strong monitoring system that enables the reporting and testing of deceased FRD using inexpensive diagnostic kits. Despite all of the challenges, the eradication goal ought to encourage worldwide efforts that empower the pharmaceutical industry, global organizations, governments, philanthropies, and non-governmental organizations to work together in the quest to eradicate human rabies globally.

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