Review Article

Review on Vaccination and Control Options of Rabies Virus

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Abstract

Warm-blooded animals, such as humans, are susceptible to the fatal viral infection rabies. The WHO states that once clinical signs start to show, rabies is almost usually fatal. Vaccination was shown to be a viable method of preventing rabies, especially in reservoir hosts. Considerable attempts were made over the last 50 years to create and enhance vaccinations that will help control and prevent the disease in both humans and animals. Several laboratory and animal experiments have evaluated early rabies vaccines, including live-attenuated and inactivated vaccines. However, modern advancements have led to the development of innovative options to enhance the immunogenicity and clinical effectiveness of vaccines. These include recombinant vaccines, vaccines utilizing viral vectors, cell culture-based formulations, and adjuvant-enhanced vaccines, genetic approaches like DNA and RNA-based platforms, and chimeric vaccine models. Notwithstanding such developments, nothing is known about the immunogenic potential, safety, and effectiveness of these vaccinations. This review seeks to compile findings from in vitro and in vivo research, offering a comprehensive analysis of rabies vaccines across diverse categories. Furthermore, it evaluates their immune response capabilities, effectiveness, and safety while addressing their clinical trial performance.

Keyword: Rabies, immunoglobulin, Rabies vaccine, post-exposure vaccination

Introduction

Since the fourth century BC, rabies had been recognized as one of the zoonotic diseases that is brought on through viruses belonging to Lyssavirus genus (family Rhabdoviridae, order Mononegavirales). Majorly transmitted by the biting of infected mammals, rabies virus is the most prevalent cause of the disease and its prototype. [1,2] Dog bites are responsible for over 99 percent of human rabies incidents worldwide. Rabies is still enzootic in some areas despite though it is completely avoidable with vaccination, making it a recurring public health concern in the twenty-first century [3]. According to epidemiology, rabies is common in more than 150 nations, with Africa and Asia bearing the burden of the disease, which claims over 59,000 lives each year. Under-privileged groups are disproportionately affected by the disease, frequently in rural areas with inadequate access to vaccinations and knowledge. In addition to being a biological issue, rabies is also a societal one, closely associated with poverty, ignorance, and disinformation [4]. The virus begins its pathogenesis at the bite site, replicating and invading peripheral nerves. It subsequently travels to the central nervous system, causing extensive neural damage. Clinical manifestations are divided into two categories: paralytic rabies, which is defined by coma and muscle weakness, and furious rabies, which is characterized by hallucinations and hyperactivity. Once symptoms start to show up, both types of rabies always result in death [5]. Rabies rates have been considerably reduced in North America, Europe,

and several regions of Latin America as a result of the management of both domestic and wild reservoirs. Emphasizing integrated attempts between the sectors of animal, human, and environmental health to fight zoonotic diseases, such achievements confirm the "One Health" method [6]. By the year 2050, global agencies like the Food and Agriculture Organization and WHO hope to have eradicated dog-mediated human rabies in endemic nations.

Rabies Virus and Its Genome Structure

Rabies virus is one of the members of the Mononegavirales order whose nature is defined by their negatively stranded, non-segmented RNA genomeIt belongs to the Lyssavirus genus in Rhabdoviridae family and typiclly affects the CNS. The rabies virus is bullet shaped and is 180nm long and roughly 75 nm wide[7]. Five separate proteins vital for its function and structure are encoded by the viral genome.

- Among the transmembrane proteins necessary for viral entrance and pathogenesis is **glycoprotein (G)**.
- Non-enzymatic polymerase cofactor **phosphoprotein (P)**, which helps to synthesize RNA[8].
- The RNA genome is formed from **nucleoprotein (N)**, which also forms the nucleocapsid.
- **Large protein (L)**, a 2130 amino acid RNA-dependent polymerase involved in transcription and replication.
- A structural protein linked to the viral membrane, **matrix protein (M)**.

As seen in Fig. 1 (A, B, C), the arrangement and placement regarding the genes encoding such proteins in the rabies virus genome greatly affect its structure [9]. The interaction regarding the proteins of the rabies virus determines its development; the complex of nucleoprotein-phosphoprotein interacts with neighboring nucleoproteins in the nucleocapsid. Throughout RNA synthesis, phosphoprotein binds to the large protein (L) therefore enabling its attachment to the nucleoprotein-RNA template [10]. This binding induces conformational changes opening the RNA for transcription and replication. Important for such activities is the resultant ribonucleoprotein complex made of RNA, phosphoprotein, nucleoprotein, and large protein. Furthermore membrane-associated are the glycoprotein (G) and matrix protein (M). Essential for viral access into host cells, the glycoprotein also significantly influences the pathogenesis regarding the rabies virus.

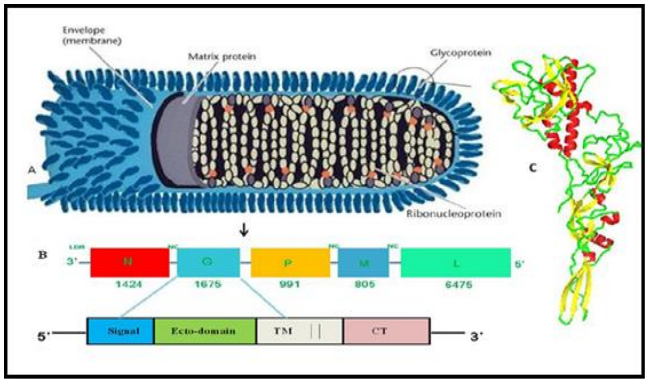

Figure 1: Structural and Genomic Representation of Rabies Virus. **A)** A diagrammatic depiction of the bullet-shaped morphology (~75 nm x 180 nm) of the rabies virus. **B)** The encoding of several proteins within the rabies virus genome, highlighting their lengths and roles. Glycoprotein (G) has distinct domains: ectodomain, signal, transmembrane, C-terminal (CT) regions. **C)** A 3-D structure regarding the Rabies Virus Glycoprotein (RVG), demonstrating its critical role in viral pathogenesis [9].

Immune Evasion by the Rabies Virus

The rabies virus employs sophisticated strategies for evading the host's immune system, enabling its proliferation and survival. The virus minimizes local immune activation at the site of infection by reducing the release of pro-

inflammatory cytokines. This lets it establish a foothold without starting an immediate immune response. Moreover, the virus hides by means of mechanisms to prevent antigen presentation, therefore impairing the capacity of the immune cells of the host to identify and respond to the infection [10]. Using the immune-privileged status of neural tissues, the virus travels across the peripheral nervous system (PNS) to CNS. The virus essentially hides from circulating antibodies and immune cells—which have restricted access to these sites by propagating within neurons. The virus also interferes with interferon signaling pathways, a vital part of the host's antiviral defense, therefore reducing the innate immune response. These immune evasion techniques not just help the virus to spread, yet support the great mortality rate of rabies. Once the virus gets to the CNS, immune responses are mostly useless, which causes great neurological damage and finally death. Knowing such systems emphasizes the clinical difficulties in treating rabies and the need of early immunization as preventive measure [11].

Pathogenesis

All mammals are susceptible to the viral disease rabies, which is mainly spread via an infected animal's bite. The most frequent way for the virus to transmit is still through bites, although it could spread through mucosal membranes like the mouth, eyes, or nose [12]. The virus enters the body through a bite, replicates locally in the skin or muscle, and then spreads to the peripheral nerves. Since nerve tissues are stationary, it moves slowly from one nerve cell to the next in the direction of the brain. Since the virus hardly ever enters the bloodstream and cannot multiply there when it does, blood from a rabid animal is not regarded as infectious (Fig 2). The virus might take anywhere from two weeks to several months to incubate, or move from the site of the bite to the brain [13]. Depending on how close the bite incision is to the brain, the incubation time for cats and dogs is usually two months. A bite to the neck, for instance, reduces the travel distance and may result in a reduced incubation period [14]. The virus travels to the salivary glands after entering the brain, where it grows and is expelled into the saliva. At this stage, the infected animal begins shedding the virus and can transmit it through a bite. Interestingly, the animal may not exhibit any symptoms during the first three days of viral shedding. Over time, the virus disrupts brain function, leading to changes in behavior such as unexplained aggression, varying degrees of paralysis, or severe depression. Symptoms can vary significantly among animals, with some displaying the well-known "furious" form, characterized by aggression, while others exhibit the "dumb" form, appearing lethargic and dazed [15]. Animals typically succumb to the disease within five days of symptom onset [16].

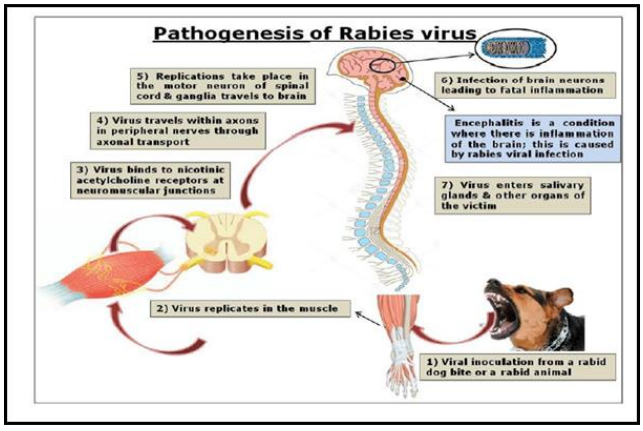

Figure 2: Pathogenesis of rabies virus. After producing encephalitis in the brain, the virus travels to salivary glands, skin, mucosal surfaces, and gastrointestinal tract, among other organs [9].

Immune responses and host manipulations

Rabies needs to be able to evade the host's immune system in order to keep infected neurons

viable. The notion that the CNS is an immune-privileged cellular environment was called into question when it was shown that peripheral immune cells can penetrate an intact blood-brain barrier and that CNS neurons and glia might regulate macrophage as well as lymphocyte responses. It is thus reasonable to assume that the cellular environment in which RABV replication takes place in the CNS is completely immune-competent [17]. However, in experimental studies, pathogenic and attenuated strains of RABV induce different host characteristics as well as inflammatory markers. In mice infected with pathogenic strains of RABV, the amount of virus cleared from the brain, which correlates with levels of B cell infiltrations and anti-body secretions in CNS, is reduced. Those results support the idea that RABV infections naturally impair adaptive immune responses [18]. Adequate virus clearance requires improving the blood-brain barrier's permeability to immune cell infiltrations. In experimental models, more excellent permeability led to increased clearance regarding attenuated RABV from CNS. Permeability related to the blood-brain barrier is not increased by wild-type RABV infection, which is consistent with results obtained from the canine model in which the infected animals only experience modest immune responses [19]. In dogs and humans, diffusion tensor imaging (in dogs) has shown that blood-brain barrier's permeability is unaffected throughout the early stages of clinical disease in furious and paralytic rabies patients [20]. The blood-brain barrier's permeability is one of the primary causes of the uncommon survival of patients with clinical rabies, and it may one day serve as a viable target for therapeutic interventions. However, more research is needed to determine whether the decreased immune response seen in patients with wild-type lyssavirus infections is due to decreased blood-brain barrier permeability or virus-dependent suppression regarding the infiltration of the immune cells to the CNS. In any case, it is thought that virus-neutralizing antibodies that may be seen in humans' acute neurological phase of naturally occurring RABV infection cannot stop the infection from having a fatal consequence [21].

Clinical diagnosis in humans

The clinical diagnosis of rabies is made in three stages: prodromal, paralytic, and excitation. Nevertheless, the individual did not exhibit any of these stages [22]. The initial clinical indication is neuropathic pain caused by viral replication at the site of the infection or wound. The particular species may display one or both of the paralytic or excitation forms of the disease following the prodromal phase. Additionally, cats are considered to be at a higher risk of developing severe rabies compared to dogs [23]. In certain cases, there are no symptoms, and the rabies virus has been linked to sudden deaths. The diagnosis can just be made by laboratory testing on CNS tissue taken from the cranium, preferably post-mortem. Furthermore, skin biopsies taken from hair follicles at the nape of the neck, saliva, and serum are tested [24].

Prevention

Primary prevention is the optimal method of preventing rabies. It involves eliminating canine rabies through vaccination campaigns, educating people about the disease and its preventative options, and promoting responsible dog ownership and vaccinations—particularly in endemic areas where it might be necessary to alter long-standing cultural norms in order to carry out such interventions. Immunization against rabies is recommended whenever possible for visitors to regions where the

disease is endemic [25]. This advice might not be heeded very often, though. However, without a system in place to support such efforts, secondary prevention uses post-exposure prophylaxis to try to avoid the formation of clinical disease [26]. The necessary course of action is determined by evaluating the exposure category as stated by WHO. Whether or not it was administered, careful wound care and applications are nearly always effective in preventing death cases. The combination could efficiently prevent infection in almost 100% of instances [27].

Rabies vaccines

Rabies vaccines are critical in protecting domestic animals and humans from the disease. There are several kinds of vaccines available, such as live-attenuated and subunit vaccines made specifically for vaccinating wildlife as well as inactivated Rabies Virus vaccinations for humans and domestic animals. Vaccines against human rabies could be given intramuscularly or intradermal [28]. For preventing infections, the primary objective of vaccination is to produce virus-neutralizing antibodies (VNAs) against the rabies virus's glycoprotein. The efficiency regarding contemporary vaccines has greatly increased, despite the fact that the mechanism and precise site by which VNAs prevent viral replication are still unknown. Lyophilized, inactivated, cell-culture-based vaccines have shown enhanced antigenicity, reduced the required doses and clinic visits, and increased patient compliance [29]. Figure 3 illustrates the various types of rabies vaccines and their specific applications**.** The WHO has prequalified three inactivated rabies vaccines for human use, emphasizing their safety and efficacy. Serious adverse events following vaccination are infrequent. However, mild reactions, such as localized swelling or moderate fever, are more common and should not cause alarm [30]. These vaccines are suitable for pre-exposure prophylaxis (PrEP) as well as post-exposure prophylaxis (PEP)**.**

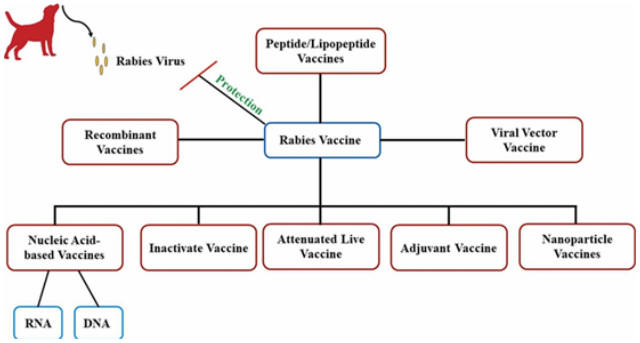

Figure 3: Overview of Rabies Vaccine Types The image demonstrates the available rabies vaccines, categorized by their use for PrEP and PEP. It highlights the dosage, administration routes (intramuscular and intradermal), and their intended targets (domestic animals, humans, or wildlife). The importance of timely vaccination to prevent rabies infection is also emphasized [31].

Primary prevention: pre-exposure immunization.

As a result of the nearly 100% rate of fatality cases as well as high case incidence regarding RABV infections in children who are less than 15 years old, it has been suggested that this must be taken into account as part of the recommended pediatric vaccination approach in the areas of high risk. Regimens are presently made up of the administration of 4 vaccination dosages on days [32]. For optimal protection and the durability of antibody response, it is crucial to evaluate serological positivity everywhere it is used. Furthermore, even in the absence of rabies immunoglobulin treatment, rabies vaccine administrations as part of a pediatric Expanded Immunization program may result in increasing the probability that exposed individuals would not develop a clinical disease [33]. PEP is the main barrier to reducing

mortality, though, because the availability of vaccines is constrained in endemic areas due to economic issues, making widespread coverage impossible. Additionally, those who work with bats, scientists, and other professionals with a higher risk of exposure to lyssaviruses must get one. Travelers to endemic regions may not be aware of the requirement for vaccination, and even if they are, a false notion of the risks connected with vaccinations may discourage them from seeking it out [34].

Rabies immunoglobulin and vaccination.

Even though those who had an appropriate vaccination must only receive a booster shot rather than RIG, PEP could also include the administration of RIG. The direct administration regarding the RIG to the wound aims to eliminate any live viruses near the site and prevent the spread of the virus for as long as it takes for a person to develop adequate immunity in response to vaccinations [35]. It is possible to employ humans or, if neither is available, pepsin-digested, chromatography-purified equine. WHO advises using weight-based total dosage calculations: If possible, the residual estimated dosage of the RIG must be injected in the wounds; any residual RIG must be given intra-muscularly at different locations [36]. Yet, RIG is frequently hard to come by in endemic countries due to high manufacturing costs and challenges with large-scale productions. The creation of novel alternatives is necessary even though it is secure, more straightforward to produce than adequate, and becoming more prevalent in nations where rabies is endemic [37]. Researchers evaluated the RIG applied solely to the wound, avoiding injections of RIG's often significant residual volume to distant areas to conserve resources for upcoming patients. With this strategy, all patients can receive the appropriate care, even in low-resource rabies-endemic countries. Even if a tool may be available, it could not be utilized due to a lack of awareness about the available options [38]. Besides administering RIG, vaccination is advised at another site. For individuals who have already had a vaccine, WHO recommended an intramuscular or intradermal booster regiment. Various vaccination regimens are advised for PEP for unvaccinated individuals since all vaccinations are thought to be equally efficacious; the regimen used depends on the vaccine's availability and the local medical center's level of knowledge. Individuals with low cell counts and weakened immune system might respond badly or not at all after vaccine-ation [39].

Management

There aren't many differences in the treatment for paralytic and furious rabies. Due to the wide range of rabies presentations, treatment methods are primarily symptomatic and may vary from case to case. Additionally, the accessibility of therapies differs substantially between nations [40]. Although a few patients might have a 1- to 3-month survival extension after receiving critical care, the prognosis is generally poor once clinical symptoms and signs of rabies appear, with death occurring within 5 to 11 days [41].

Assessment of Exposure

The initial assessment of patients presenting with encephalitis of undefined origin must include a comprehensive examination that focuses on searching for the small bites that could’ve been missed and inspection of any open wounds. Any aggravating variables, like underlying illnesses or (allergic) reactions to prior vaccines or medications, must be mentioned in the anamnesis (patient’s medical history).

When domestic animals are involved, and exposure to RABV is suspected, PEP must be started after 10 days of clinical sign observation on the animal. If the suspect animal is still healthy after being quarantined, treatment could be terminated [42]. The negative FAT result, which has been confirmed by a different reference test, as advised by OIE, is the only way to rule out rabies in an animal that exhibits clinical disease, and it is available for testing. In the areas in which terrestrial rabies was eliminated, bat rabies makes up a small yet insignificant threat to human health, which is why [43].

Conclusions

This review emphasizes the significant advancements in rabies vaccine development, focusing on their application in controlling the disease in reservoir animals, protecting livestock, and safeguarding individuals exposed to rabid bites. Despite these advancements, pursuing a universally effective vaccine remains a challenge. Current efforts have also extended to designing vaccines specifically targeted at wildlife populations, such as vampire bats, addressing gaps in the efficacy of traditional vaccines for use in these environments. The development regarding novel vaccination platforms that are affordable, widely available, and able to handle a variety of epidemiological situations must be the top priority of future research. Furthermore, implementing successful eradication efforts that integrate cutting-edge immunization programs and public health measures requires global coordination. The long-term objective of eradicating rabies as a danger to global public health depends on such initiatives.

Conflict of interest

None

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