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Routes of Human Rabies Infection and Prophylaxis as Methods of Prevention

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ABSTRACT

The rabies virus is responsible for one of the most severe diseases transmitted from animals to humans. Rabies is associated with an almost 100% case-fatality rate once clinical symptoms develop. The aim of this study is to present the principal routes of rabies virus transmission to humans and to discuss strategies for limiting viral spread through preventive measures, based on the available literature concerning the pathogenesis, epidemiology, and prophylactic methods applied in both animals and humans.

The primary route of transmission to humans is a bite from an infected animal. However, other, less common routes of infection are also possible, including contact of secretions from an infected animal with mucous membranes or damaged skin. Extremely rare cases of transmission

have also been reported through aerosol exposure or through organ transplantation from an infected donor.

In Europe, wild animals constitute the main reservoir of the rabies virus, with particular emphasis on foxes, highlighting the critical role of oral vaccination programs targeting these species. Vaccination of domestic animals, as well as pre-exposure and post-exposure prophylaxis in humans, also remain essential components of rabies prevention. A multidisciplinary approach to rabies control, integrating the efforts of veterinary and medical services through infection control in animal populations, improved access to vaccines and rabies immunoglobulin, and increased public awareness regarding the disease, its transmission routes, and preventive measures, may ultimately contribute to the complete elimination of human rabies in the future.

Keywords: Rabies, Human Rabies, Rabies Prophylaxis, Rabies Transmission, Rabies in Fox, Rabies in Dogs

Introduction

Among infectious diseases affecting humans, as many as 62% are zoonoses. Wild animals play a significant role in their transmission, acting both as reservoirs and sources of infection [1].

Rabies is a zoonotic disease caused by the rabies virus (RABV), a member of the *Rhabdoviridae* family. Although rabies in humans is relatively rare, once clinical symptoms develop the disease becomes invariably fatal. According to the World Health Organization (WHO) and the World Organisation for Animal Health (OIE; currently WOA – World Organisation for Animal Health), nearly 59,000 people die from rabies each year [2].

Given the considerable number of deaths caused by the rabies virus and the nearly 100% fatality rate once clinical symptoms occur, the prevention of rabies infection remains a crucial public health issue.

According to the World Health Organization, the primary route of rabies virus transmission to humans is through bites from infected dogs. This highlights the important role of vaccination among domestic animals in reducing the risk of human infection. In Europe, the principal natural reservoir of the rabies virus is the red fox (*Vulpes vulpes*), while wolves and bats also

contribute to virus maintenance to a lesser, yet still significant, extent [3, 4, 5]. It should also be noted that numerous species of wild animals in Europe are susceptible to rabies, including wild boars, deer, roe deer, moose, European bison, fallow deer, and hares [1].

Pathogenesis

The incubation period of rabies varies depending on the virulence of the virus and the location of the wound. In animals, it typically ranges from 21 to 80 days, although it may be significantly shorter or longer. In foxes, the incubation period ranges from 11 days to as long as 11 months, although it usually does not exceed 30 days. The more densely innervated the site of infection and the closer it is to the brain and spinal cord, the shorter the incubation period tends to be. The virus is generally present in saliva for 3–10 days prior to the onset of the first clinical symptoms [6].

In addition to the nervous system, the virus may be detected in small quantities in blood, urine, faeces, milk, and in striated muscles near the site of infection. Following entry into the body, the virus initially replicates at the site of inoculation and subsequently spreads via peripheral nerves to the spinal cord and brain, where intensive replication occurs. It then migrates through neural pathways to the salivary glands, where it replicates and is secreted in saliva. The virus may also be released from sensory nerve endings within the mucosa of the oral cavity and nasopharynx. In rare cases, systemic dissemination of the virus may occur through the bloodstream.

As a consequence of infection, non-suppurative inflammation of the brain and spinal cord develops, accompanied by inflammation of nerve ganglia and salivary glands. Characteristic eosinophilic intracytoplasmic inclusion bodies, known as Negri bodies, are observed in infected neurons, particularly in pyramidal cells of the hippocampus and Purkinje cells. These inclusions represent sites of active viral replication.

The primary clinical manifestation of rabies in animals is a change in behaviour. Two main forms of the disease are recognized: the furious form, characterized by varying degrees of aggression, and the paralytic (or “dumb”) form [7].

Humans most commonly become infected through bites from rabid animals; however, other portals of entry may include abrasions and scratches of the skin, open wounds, the nasal mucosa, or conjunctiva contaminated with saliva or brain tissue from infected animals [7].

Animal bites are not a rare occurrence. The incidence of dog bites in humans has been estimated in studies conducted in various countries at approximately 9–18 cases per 1,000 inhabitants annually. Medical attention due to dog bites is required in approximately 3 cases per 1,000

inhabitants per year, with the number of cases among children being 3 to 5 times higher than among adults [8]. In Poland, there is no unified national system for recording dog bite incidents. Based on data from District Veterinary Inspectorates and District Sanitary-Epidemiological Stations, it is therefore not possible to determine what proportion of dog bites result in severe or even fatal outcomes [8].

Other Routes of Infection

There are no documented cases of infection with rabies virus (RABV) through the consumption of meat from infected animals or through the consumption of milk from infected cattle; however, such practices are strongly discouraged. An unusual and extremely rare route of viral transmission is via the aerosol route following exposure to a high concentration of viral particles suspended in the air, for example in caves inhabited by large colonies of bats with a high prevalence of infection [9, 10, 11].

Due to the specific microclimatic conditions present in caves – such as relatively constant, usually low temperatures, high humidity, limited air circulation, and the absence of ultraviolet radiation from sunlight – favourable conditions exist for the survival and potential airborne transmission of the rabies virus. Consequently, although rare, this atypical route of infection is considered possible and potentially dangerous.

Attempts to capture bats may also result in breaches of skin integrity through scratches or bites, which can serve as portals of entry for the virus in humans. Aerosol transmission through bat saliva and dust contaminated with dried bat faeces containing the rabies virus has been reported, as well as infections resulting from wounds inflicted by infected vampire bats (subfamily *Desmodontinae*, genera *Desmodus*, *Diphylla*, and *Diaemus*). Among these species, the common vampire bat (*Desmodus rotundus*) is regarded as the most important vector and reservoir of the rabies virus, as a proportion of infected individuals are capable of surviving infection [12].

Human-to-Human Transmission

The only documented cases of human-to-human transmission of RABV involve the transfer of the virus through organ or tissue transplantation from infected donors, as well as isolated cases of perinatal transmission. Nevertheless, because RABV has been detected in human nervous tissue and in bodily secretions such as saliva, tears, and urine, the risk of infection through contact with biological material from infected individuals should not be disregarded.

Transmission through breastfeeding by an infected mother is considered unlikely; however, available data on this route of transmission remain limited [13, 14, 15].

Oral Vaccination of Foxes as a Preventive Measure for Human Rabies

Foxes play a major role in maintaining the circulation of the rabies virus within wildlife populations and may transmit the infection to other species through bites. Based on epidemiological data collected in Poland between 1999 and 2007, analysis of 8,335 confirmed rabies cases indicated that 70.7% occurred in red foxes, 9% in raccoon dogs, 6.7% in cattle and other livestock, 5.6% in cats, 4.3% in other wild animals (excluding bats), 3% in dogs, and 0.7% in bats [16].

The epidemiological situation in Poland began to improve significantly after the introduction of a nationwide rabies control program involving mass vaccination of foxes in 1993. Initially implemented in six provinces, the program was expanded in 2002 to cover the entire country and has been conducted annually since then. Immunization is carried out using an oral vaccine containing a live attenuated virus, distributed in bait either by aerial dropping from aircraft or by manual placement.

Following the implementation of this program, the number of rabies cases in foxes decreased steadily each year, raising the possibility of the complete elimination of the disease in non-flying mammals. Consequently, since 2015 the distribution of vaccine baits has been limited to eastern and southeastern regions of the country. However, in 2021, 29 cases of rabies in wild animals were detected in provinces not covered by the vaccination program. Consequently, necessary measures were undertaken to prevent further spread of the disease, including the reintroduction of fox vaccination campaigns in the provinces where cases had been identified and where regular vaccination had not previously been implemented [17].

Similar control measures have led to the near elimination of rabies in terrestrial mammals across Western Europe. In recent years, the few reported cases in this region have occurred almost exclusively in bats and, occasionally, in dogs or cats illegally imported from outside the European Union [17].

Dog Vaccination and Human Bite Incidents – Legal Regulations

Although foxes constitute the principal reservoir of the rabies virus in Europe, as mentioned previously, the greatest risk of transmission to humans results from bites by companion animals, as these are the species with which humans have the most frequent contact. Unvaccinated dogs and free-roaming cats in areas adjacent to forests pose a particularly significant risk. It is

noteworthy that cats may represent an even greater risk than dogs for transmitting rabies from foxes.

Analysis of the previously mentioned cases recorded in Poland between 1999 and 2007 confirmed that cats were diagnosed with rabies almost twice as often as dogs, accounting for 5.6% and 3% of cases, respectively. This observation is not surprising, as dogs are generally vaccinated against rabies on a regular basis and, during outdoor activities such as walks, they typically remain under at least partial control of their owners. In contrast, owners usually have little or no control over cats that roam freely outdoors [17]. An additional contributing factor is the considerably stronger hunting instinct observed in cats compared with dogs.

To reduce the risk of infection, a number of preventive measures have been implemented aimed at eliminating rabies among both companion animals and wildlife. Under the provisions of the Polish Act on the Prevention and Control of Infections and Infectious Diseases in Humans [18], every case of a dog bite involving a human must be reported as a potential rabies exposure. Despite this requirement, an analysis conducted by Fiszdon and Boruta indicated that up to half of dog owners fail to vaccinate their animals, even though annual rabies vaccination is mandatory [19] and subject to legal penalties for noncompliance. Furthermore, existing regulations do not adequately address cases of cat bites, which – according to the aforementioned data – may pose an even greater risk than dog bites.

Pre-Exposure Prophylaxis in Humans (PrEP)

According to recommendations issued by the World Health Organization (WHO), individuals at high risk of rabies virus exposure should consider pre-exposure prophylaxis (PrEP). High-risk groups include individuals with occupational exposure, such as veterinarians, forestry workers, and laboratory personnel conducting research involving the rabies virus.

The vaccination schedule recommended by WHO involves the intradermal administration of two doses of vaccine at two separate anatomical sites seven days apart (two doses on day 0 and two doses on day 7), or alternatively, a single intramuscular dose on day 0 followed by one intramuscular dose on day 7. According to WHO guidelines, the second administration of vaccination should not be delayed by more than one year after the initial dose; otherwise, the entire vaccination series should be repeated.

For individuals at the highest risk of exposure due to constant or particularly frequent occupational contact with potentially infected animals or materials, regular monitoring of rabies virus – neutralizing antibodies (VNA) is recommended. If the VNA level falls below 0.5 IU/ml, a single booster dose of vaccine administered either intradermally or intramuscularly is

recommended. If regular serological monitoring is not feasible, periodic booster vaccination may be considered following an assessment of the relative risk of exposure.

For travellers, an individual assessment of the risk of exposure to the rabies virus is recommended by WHO. Pre-exposure prophylaxis should be considered for individuals traveling to regions where rabies is endemic and where access to post-exposure prophylaxis may be limited. It should also be considered for travellers planning activities associated with an increased risk of exposure, such as visiting caves inhabited by bat populations.

Pre-exposure prophylaxis should likewise be considered for residents of regions where rabies is endemic. In areas where hematophagous (blood-feeding) bats are present, or where the annual incidence of dog bites exceeds 5%, vaccination of local populations may also be advisable. Decisions regarding the implementation of population-level prophylaxis programs in a given region should be preceded by an assessment of the feasibility of controlling transmission routes, including efforts to reduce the occurrence of rabies virus infections in animal populations [20, 21, 22, 23].

Post-Exposure Prophylaxis for Rabies in Humans (PEP) – The Role of Rabies Immunoglobulin

The most critical component of post-exposure prophylaxis in humans is the completion of the full vaccination series. An additional element of prophylaxis is the administration of rabies immunoglobulin (RIG). The administration of RIG at the site of the bite allows for the neutralization of rabies virus (RABV) before the host immune system produces virus-specific antibodies in response to post-exposure vaccination.

According to guidelines issued by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), the largest possible proportion of the RIG dose should be infiltrated directly into and around the wound. If any portion of the dose remains after local infiltration, it may be administered intramuscularly at a site distant from the vaccination site. RIG should not be administered in the same anatomical location as the vaccine, as this may reduce the effectiveness of both preparations. As indicated in *Rabies vaccines: WHO position paper – April 2018*, local administration of RIG directly into and around the bite wound is effective, whereas the benefits of intramuscular administration at a distant site are likely limited [23].

However, data from regions where rabies is endemic indicate that even in the absence of RIG administration, patient survival remains approximately 99% provided that the wound is

thoroughly cleansed, vaccination is initiated immediately, and the complete PEP vaccination schedule is completed [24].

Rabies immunoglobulin preparations are derived either from human blood (human rabies immunoglobulin, hRIG) or from equine serum (equine rabies immunoglobulin, eRIG). These preparations are generally considered to have comparable efficacy [25]. Due to the limited availability of RIG in many rabies-endemic countries, it is estimated that globally fewer than 2% of patients with category III exposures receive RIG as part of post-exposure prophylaxis [23].

Dosage of Rabies Immunoglobulin

The dosage of rabies immunoglobulin varies depending on the type of preparation used. The recommended dose for human rabies immunoglobulin is 20 IU/kg of body weight, whereas the dose for equine rabies immunoglobulin is 40 IU/kg of body weight. The dose is calculated based on the patient's body weight and does not depend on the size or number of wounds.

The calculated dose should not be exceeded, as excessive administration may weaken the immune response to the vaccine. RIG may be administered up to seven days after the first dose of vaccine, although it is ideally given on day 0 [26, 27, 28].

In 2017, a monoclonal antibody preparation against rabies was registered in India. Its advantages include standardized quality, the possibility of large-scale production, greater effectiveness compared with traditional RIG preparations, a lower risk of adverse effects, and the absence of a need to use animals in the production process [23].

Post-Exposure Management

Post-exposure management depends on the type of exposure and the patient's immunization status. The World Health Organization (WHO) classifies exposure to the rabies virus into three categories [23]:

- **Category I** – touching or feeding animals, or licks on intact skin; no exposure.
- **Category II** – nibbling of uncovered skin, minor scratches or abrasions without bleeding; exposure.

In the case of contact with bats, such exposure should be treated as **Category III**.

- **Category III** – single or multiple bites or scratches resulting in a breach of the skin, contamination of mucous membranes with saliva, licking of damaged skin, or direct contact with bats; severe exposure.

Although the risk of developing rabies more than one year after a Category III exposure is very low, every patient with such exposure should receive vaccination, even if months or years have passed since the incident.

The post-exposure prophylaxis regimen should be selected based on the availability of vaccines and immunoglobulin. The first vaccine dose should be administered as soon as possible and should not be delayed due to the lack of rabies immunoglobulin. Depending on the type of injury, additional management may include analgesics, tetanus vaccination, and antibiotic therapy [23].

Management of Previously Unvaccinated Individuals

According to guidelines issued by the WHO, for Category I exposure, management consists of washing the exposed skin surface. Administration of vaccine or immunoglobulin is not required. For Category II exposure, in addition to washing and thorough wound cleansing, immediate vaccination is required. Recommended vaccination schedules include:

- Intradermal administration at two sites (arms or thighs) on days 0, 3, and 7
 - Intramuscular administration at one site (arm or thigh) on days 0, 3, 7, and between days 14 and 28
 - Intramuscular administration at two sites on day 0, followed by one site on days 7 and 21
- Administration of rabies immunoglobulin is not indicated for Category II exposure.

For Category III exposure, the recommended management is the same as for Category II exposure, with the additional administration of rabies immunoglobulin [23].

Management of Previously Vaccinated Individuals

For Category I exposure management consists solely of washing the exposed skin surface; administration of vaccine or immunoglobulin is not recommended.

For Category II and III exposures, management is the same and includes thorough wound cleansing and immediate vaccination. Possible vaccination regimens include:

- Intradermal administration at one site (arm or thigh) on days 0 and 3
- Intradermal administration at four different sites on day 0
- Intramuscular administration at one site on days 0 and 3

Administration of rabies immunoglobulin in previously vaccinated individuals after Category II or III exposure is not recommended [23].

Re-Exposure After Previous Post-Exposure Prophylaxis

In individuals who experience re-exposure within three months after completing a full post-exposure prophylaxis (PEP) vaccination course, only wound management is required. Regardless of the exposure category, administration of vaccine or immunoglobulin is not necessary.

In patients who experience re-exposure more than three months after completing a full PEP course, the vaccination schedule recommended for previously immunized individuals should be followed [23].

Management of the Suspected Animal

If the animal responsible for the injury is known and is a domestic dog, cat, or ferret, it should be subjected to 15-day observation. This period may be extended with the consent of the district veterinary officer. The veterinary authority may also authorize euthanasia of the animal if necessary.

If the suspected animal does not belong to these species, it should be humanely euthanized and examined to rule out rabies. If rabies is excluded either by laboratory examination of the euthanized animal or through observation of a domestic animal, post-exposure prophylaxis may be discontinued.

Post-exposure prophylaxis is not recommended in cases of exposure through consumption of meat or milk from infected animals [23].

Prophylaxis in Pregnant and Breastfeeding Women

Both rabies vaccines and rabies immunoglobulin are considered safe and effective in pregnant and breastfeeding women. Neither pregnancy nor breastfeeding should delay or prevent the administration of post-exposure prophylaxis. Any of the vaccination regimens recommended by the World Health Organization (WHO) may be used in these populations [29, 30, 31, 23].

Prophylaxis in Individuals Infected with HIV and in Patients with Other Immunodeficiencies

Patients infected with HIV who are receiving antiretroviral therapy, remain in good clinical condition, and are considered immunocompetent (in children under 5 years of age: CD4 >25%; in children older than 5 years and in adults: CD4 count ≥ 200 cells/mm³) may receive rabies vaccination as part of both pre-exposure and post-exposure prophylaxis.

In patients with impaired immunity (including HIV-infected individuals who do not meet the above criteria for immunocompetence), particularly after Category II and III exposures, thorough wound cleansing is strongly recommended, along with the administration of a full course of rabies vaccination, even if the patient has previously received pre-exposure prophylaxis. Consultation with a specialist in infectious diseases or an immunologist is also recommended.

Vaccination regimens recommended by WHO for immunocompromised patients include:

- Three-visit regimen – administration of the vaccine intradermally or intramuscularly on days 0, 7, and between days 21 and 28.
- Two-visit regimen – administration of the vaccine intradermally or intramuscularly on days 0 and 7, followed by serological testing 2 – 4 weeks after the first dose in order to determine whether an additional booster dose is required [23].

Conclusion

Although rabies has been known to humanity for nearly 4,000 years, it remains one of the most dangerous zoonotic diseases. The disease is characterized by an almost 100% fatality rate once clinical symptoms appear. Despite the availability of effective preventive measures, rabies continues to represent a significant public health problem in many regions of the world.

A key role in rabies prevention is played by measures aimed at reducing the incidence of the disease among animals, particularly through vaccination of domestic animals and foxes, which reduces the risk of virus transmission to humans. Equally important are pre-exposure and post-exposure prophylactic measures in humans. The implementation of these strategies significantly reduces the risk of rabies development following exposure.

In summary, effective rabies prevention requires close cooperation between veterinary and medical services in controlling the disease within animal populations, improving access to both pre-exposure and post-exposure prophylaxis in the form of vaccination and rabies immunoglobulin, and increasing public awareness through education. Such integrated efforts offer hope for the eventual eradication of human rabies in the future.

Supplementary Materials

Not applicable.

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Declaration of the use of generative AI and AI-assisted technologies in the writing process

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