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SAFETY ASSESSMENT OF AN ORAL RABIES VACCINE BAIT FOR WILD CARNIVORES IN A SERONEGATIVE DOG MODEL

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ABSTRACT

Rabies remains one of the most dangerous zoonotic diseases, causing tens of thousands of deaths annually. One of the key challenges in combating rabies is the vaccination of wild carnivores, domestic, and farm animals, which play a crucial role in the circulation of the virus in nature. The aim of the present study was to evaluate the safety and immunogenicity of an oral rabies vaccine in the form of a baited briquette using seronegative dogs as a model. During the experiment, clinical parameters, serological markers, and the behavior of animals following immunization and controlled infection were assessed. The obtained data indicate good vaccine tolerance, high bait acceptance, and the formation of a strong immune response in the vaccinated animals. The oral vaccine did not cause any adverse effects and provided protection against infection in the majority of vaccinated dogs. The results of the study confirm the potential for using this vaccine form in field conditions, both for target and non-target animals.

Keywords: Rabies virus, Lyssavirus, immunization, oral bait vaccine, virus-neutralizing antibodies

INTRODUCTION

Rabies virus, belonging to the genus *Lyssavirus* of the *Rhabdoviridae* family, is a neurotropic pathogen that causes one of the most dangerous zoonotic diseases affecting all warm-blooded animals and humans. Unlike most viruses, it spreads in the body not through the bloodstream but primarily via neurons. Infection typically occurs through bites, scratches, or contact with damaged skin and mucous membranes of infected animals. The pathogen enters the central nervous system (CNS), causing progressive damage accompanied by paralysis, loss of consciousness, respiratory failure, and ultimately death. Once the virus reaches the brain or spinal cord, the mortality rate from rabies reaches 100% [1].

The virus genome consists of a single-stranded RNA with a negative sense, containing between 11,615 and 11,966 nucleotides [2]. The genetic information is packaged in the form of a ribonucleoprotein complex, in which ssRNA is bound to the nucleoprotein (N). The viral RNA genome includes five highly conserved genes that encode the nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G), and large structural protein (RNA polymerase) (L) [3]. Rabies virus enters host cells through various receptors, such as nAChR and NCAM, using the G protein, which initiates its transport into the CNS [4] via the axonal retrograde pathway [5]. However, the specific mechanism of retrograde axonal transport remains poorly understood.

Initially, the virus replicates in the muscle tissue near the site of entry, but gradually is released and enters the axons through motor end plates at the neuromuscular junction. An important role in suppressing the innate immune response is played by the P protein, which can inhibit interferon production throughout the viral replication period [6, 7]. The immune system is activated only after the virus enters the CNS, but by this point, the process becomes irreversible. The virus spreads through neurons, causing irreversible destructive changes in brain tissue and glial structures, and also enters peripheral organs, including the salivary glands, which further facilitates viral transmission [8, 9].

According to data from the World Health Organization (WHO), approximately 59,000 people die from rabies worldwide each year, with the mortality rate for infected individuals and animals reaching nearly 100% [10].

Analyzing the literature on the epizootiological situation of rabies in the Republic of Kazakhstan, it can be concluded that in recent years, the threat of rabies transmission among animals and the occurrence of human cases has not decreased. Below is an overview of the rabies situation in the Republic of Kazakhstan for the period 2012–2023, according to the Ministry of Agriculture of the Republic of Kazakhstan (Figure 1).

The most active natural foci are registered in almost all regions of the country. The primary reservoirs of the virus are wild carnivores, particularly foxes, which are capable of transmitting the virus to domestic and livestock animals, as well as to humans [11]. As a result, a key preventive measure is the elimination of infection foci among wild animals.

One effective prevention method is oral vaccination of wild carnivores using baited vaccines [12, 13]. Traditional immunization methods (intramuscular, subcutaneous, or aerosol vaccination) are practically unfeasible in field conditions. Oral administration of the vaccine via ingestion of baits appears to be the most realistic and effective approach.

The aim of this study is to evaluate the safety of an oral rabies baits-based vaccine designed for wild carnivores using a seronegative dog model. The use of seronegative dogs as a model [14] allows for an accurate assessment of the immune response to the vaccine and identification of potential side effects, which is an important step towards the future application of the vaccine in target animal species and in field conditions. It is expected that the results of this study will form the basis for the development of effective methods for rabies prevention among wild carnivores.

In addition to safety studies on target and non-target species, it is essential that the vaccine is also highly effective,

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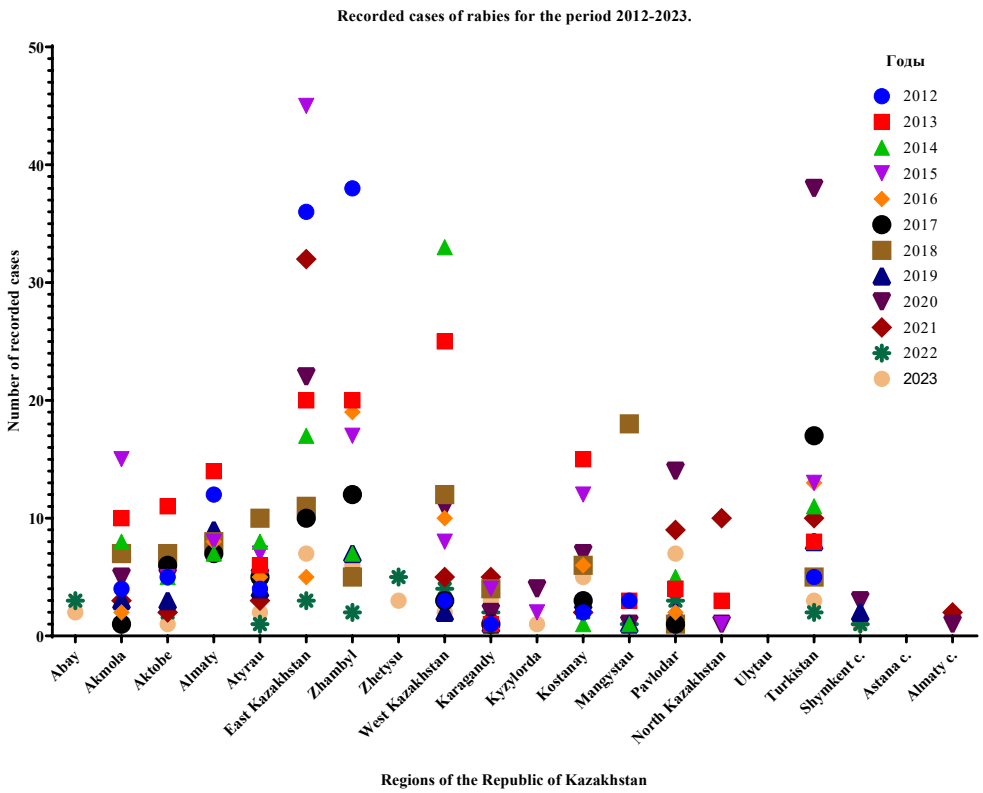

Figure 1. Epizootic situation of rabies in the Republic of Kazakhstan (2012–2023).

meaning it should induce a protective immune response after the consumption of a single dose of the bait. A key part of mandatory testing is research demonstrating protection of vaccinated animals from infection after a specified period. Based on the successful completion of the study presented here, it can be concluded that this vaccine virus meets all necessary safety and efficacy standards. This will help overcome existing barriers to the vaccination of wild carnivores, particularly in areas where parenteral vaccination is impractical or inaccessible, providing broader protection against rabies and contributing to the eventual eradication of the infection in the country.

MATERIALS AND METHODS

Vaccine bait

The bait vaccine was developed at the Research Institute of Biological Safety Problems (RIBSP) and is not currently commercialized. The oral bait vaccine consisted of a vaccine suspension containing the fixed rabies virus strain, Rabies virus fix/NIIPBB/2024 (NIIPBB stands for RIBSP), with a biological activity of 6.00 MLD_{50}/cm^3 (volume – 3.0 mL). This suspension was dispensed into flexible pouches («soft blisters») and then placed into edible baits made from fishmeal, ensuring the bait's attractiveness to wild animals.

Animals

A total of 17 mongrel dogs from a kennel were used in the study. Upon arrival, the dogs were at least 3-4 months old. All dogs were clinically healthy, and each animal was individually marked with a collar bearing a four-digit identification number. Upon arrival, all dogs underwent deworming with albendazole ("Alben" preparation) and were kept in quarantine for 14 days. Prior to infection, all animals were housed in an outdoor laboratory facility with free-range access.

After vaccination, the dogs were divided into groups and housed in individual cages. The animals were fed twice daily with special dog food (Chappi, Russia). Water was provided in unlimited quantities. All dogs were under daily observation, at least once a day, to monitor their general health, food intake, and defecation. After immunization, if any abnormal clinical signs were observed during examination, it was assessed whether the condition was related to rabies infection. In cases of severe clinical signs, the dogs were humanely euthanized.

Treatment and sample collection were generally carried out without anesthesia. However, during the control infection and in certain cases for blood collection, animals were euthanized using Xyla (Interchemie, Holland) intramuscularly at a dose of 0.15 mL/kg body weight, and ketamine (0.1 mL/kg or 6/10 mg/kg). For euthanasia induction, deep general anesthesia was applied at a dose of 0.3 mL/kg body weight.

At the end of the experiment, all dogs that successfully underwent the trials were humanely euthanized as described above. The disposal of biological waste was conducted in accordance with the waste disposal regulations approved by the Minister of Agriculture of the Republic of Kazakhstan on April 6, 2015, Order № 16-07/307.

Vaccination protocol

The dogs were divided into four groups:

Group 1 (n = 4) received 10 vaccine baits to assess the safety and harmlessness of the vaccine baits.

Group 2 and *Group 3* (n = 5 and n = 5) received one vaccine bait per dog and an oral vaccine liquid of 3 ml.

Group 4 served as the control group and received a placebo (a packet filled with water).

The study was conducted in a blinded manner, with only

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the vaccinator knowing which animals were vaccinated and which were not. All other participants in the study, including observers and animal caretakers, were unaware of which group was the control or experimental group.

After the formation of rabies virus-neutralizing antibodies (VNAs), the dogs were infected intracerebrally with the reference control CVS virus at a titer of 10^4 MLD, with 0.5 ml administered per dog.

Sample collection protocol

Blood samples were taken the day before vaccination, as well as on the 7th, 14th, and 21st days after vaccination. Blood samples (approximately 6-8 ml per sample) were collected from large superficial veins in the hind limbs (legs) using 10 ml medical syringes (Bioject 10 ml, Jiangsu Kanghua Medical Equipment Co., Ltd.) with 23G*1 needles. The collected blood was divided into two tubes: special tubes with K3 EDTA from Avatube (Ecopharm) were used for the general blood analysis, and tubes with a clotting activator and gel from Avatube (Ecopharm) were used for serum collection.

All blood samples were centrifuged at 3000g for 15 minutes, after which the sera were stored at −20 °C until laboratory analysis for the presence of rabies virus-neutralizing antibodies (VNA).

The general blood analysis was performed immediately after the blood samples were collected. To ensure the reliability of the results, the VNA reaction test was performed in triplicate.

Additionally, saliva swabs were collected on the 1st, 5th, 7th, 10th, and 14th days after vaccination. After infection, the dogs' condition was monitored and recorded at least twice a day for clinical signs of rabies. Animals that showed clinical signs of rabies were euthanized, and brain samples were examined for the presence of the virus.

Rapid Fluorescent Focus Inhibition Test (RFFIT)

Serum samples were tested for the presence of virus-neutralizing antibodies (VNA) using a modified rapid fluorescent focus inhibition test (RFFIT), with the reference CVS strain as the test virus and BSR cell culture in triplicate. The serum samples were diluted from 1:2 to 1:256. The presence of fluorescence in the samples was considered positive for rabies virus, while the absence of fluorescence was considered negative. VNA titers were determined using the method based on calculating the 50% end-point titers of antibodies that neutralize the rabies virus, according to Reed and Muench's method.

Laboratory diagnosis of Rabies

The presence of rabies virus antigen in brain samples was confirmed using the fluorescent antibody test (FAT) [15]. The procedure involved making smears from a piece of brain tissue on a microscope slide, air-drying, and fixing with acetone. The slides were then stained with commercially available anti-rabies hyperimmune serum FITC (Anti-Rabies Monoclonal Globulin, FITC, Fujirebio Diagnostics Inc, Seguin, USA) and examined under fluorescent lighting using the EVOS M7000 imaging system.

Compliance with Ethical Standards

All applicable international, national, and/or institutional guidelines for animal care and use were followed. The animals were housed in accordance with the current directives.

All procedures involving animals were conducted in compliance with the Animal Welfare Act of the Republic of Kazakhstan (Law №97-VII RK, Republic of Kazakhstan, December 30, 2021) and other applicable guidelines. The research protocols were approved by the Bioethics Committee of the Research Institute of Biological Safety Issues (Protocol № 3-03-10-2023) before the commencement of the studies. Throughout the experiment, institutional codes, operational procedures, and animal handling guidelines were strictly adhered to.

Statistical Analysis

The calculation and construction of graphs (geometric) of mean titers and 95% confidence intervals were performed using GraphPad Prism 8.0 (GraphPad Software Inc., San Diego, California, USA).

RESULTS

Composition of the vaccine briquette and palatability of the vaccine bait

Before the arrival of the animals, two types of placebo baits were prepared: a gelatinous bait and a briquetted bait. Both baits were immediately consumed by the dogs; however, the animals in Group 1 took a longer time to consume the bait, with the eating period lasting 2–4 hours. This may have been related to the amount of vaccine provided (Figure 2).

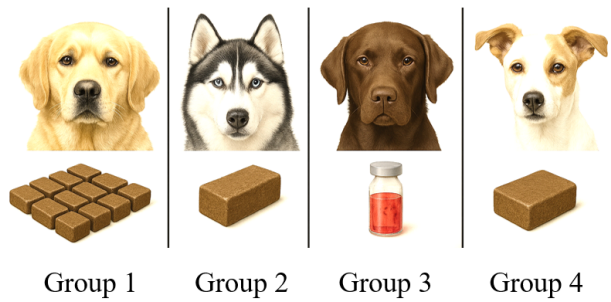

Figure 2. Safety and Immunogenicity Assessment of Vaccine Baits in Dogs: Experimental Design
Group 1 – 10 baits with the vaccine to determine vaccine safety; Group 2 – 1 bait with 3 ml of vaccine; Group 3 – 3 ml of vaccine suspension; Group 4 – control group, received placebo baits (water).

Based on the analysis (Figure 3), the optimal choice for vaccination was the briquetted bait, which was convenient to use and contained microcrystalline cellulose (MCC) with fishmeal in its composition. On the day of immunization, all dogs offered the vaccine bait consumed it completely.

Temperature changes after vaccination

The results of the experiment showed that the body temperature of vaccinated dogs remained within normal limits for 14 days (Figure 4). However, occasional slight fluctuations in temperature were observed, which may be a typical immune system response to the vaccine administration. It is important to note that these temperature fluctuations did not reach extreme levels and were not accompanied by severe symptoms or systemic complications. This is a good indication that the vaccine induces a moderate, but controlled immune response, without causing significant stress or overload on the animals' bodies.

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Figure 3. Process of immunizing seronegative dogs with the oral briquette vaccine and vaccine solution against rabies virus (2, 3 and 4 groups).

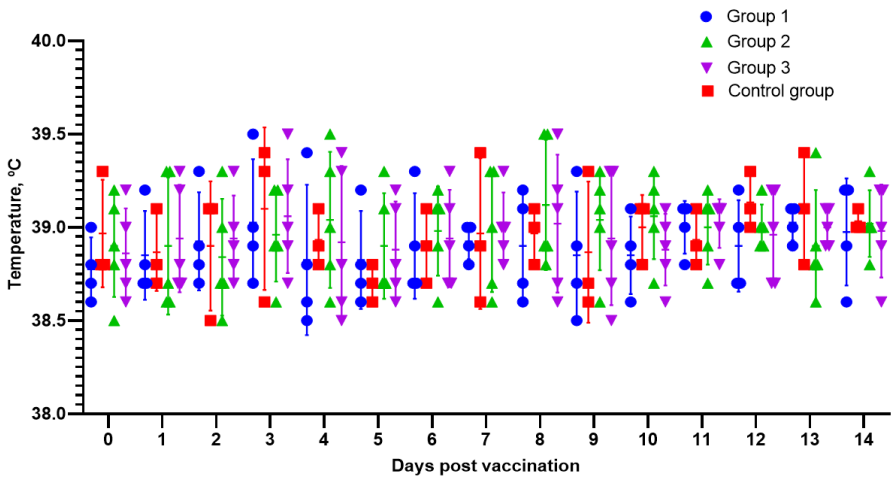

Figure 4. Changes body temperature of dogs in different groups

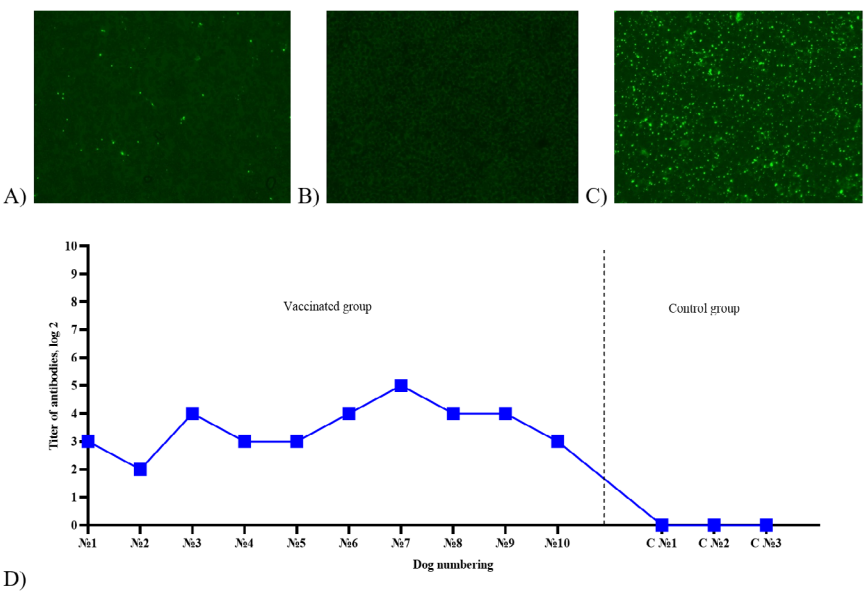

Figure 5. Dynamics of antibody titers
A) Negative RFFIT result (1/128); B) Positive RFFIT result (presence of antibodies, titer 1/8); C) FAT of the fixed vaccine strain *Rabies virus fix/NIIPBB/2024*; D) Dynamics of antibody titers in vaccinated and control groups of animals. (Figures A, B, and C were obtained using the EVOS M7000 imaging system at 10x magnification)

Such clinical reactions are typical for most vaccines and indicate that the animal's body is responding appropriately to the invasive effect of the virus through vaccination. The absence of extreme increases in overall temperature also confirms that the vaccine carries a low risk of severe side effects, which is an important aspect when considering its use in veterinary practice.

After the control infection, body temperatures of the animals were not measured for safety reasons, to avoid possible contact with infected animals and reduce the risk of transmission.

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Results of serological tests

As a result of serological tests, it was found that all dogs were seronegative to the rabies virus before the start of the experiment. On the 14th day after vaccination, antibodies to the studied virus were detected in the vaccinated groups using the RFFIT method (Figure5). In turn, animals in the control group, which received the placebo, remained seronegative throughout the observation period.

As shown in Figure 4, the vaccinated dogs did not have antibodies against the rabies virus prior to the manipulation. On the 7th day after immunization, antibodies were not detected, but seroconversion was observed in two dogs. On the 14th day, active seroconversion was observed in all vaccinated dogs, and on the 21st day after vaccination, all animals had antibody titers above 1:8, except for one dog, in which the RFFIT test showed a titer of 1:4.

Vaccine Safety

In addition to efficacy and immunogenicity, another important parameter for oral vaccines is their safety. Studies on the effects of vaccine overdose provided evidence of the safety of the immunopreparation used for dogs, even at high doses. The vaccine virus did not replicate in the body, and as a result, it was not actively excreted through saliva.

Animal clinical observations

During the research involving the infection of dogs with a control virus, the following results were obtained. By the end of the observation period (14 days), all animals in the control group (100%) showed signs of rabies and were euthanized. In contrast, 2 out of 10 immunized dogs (20%), which received the vaccine dose along with the bait or vaccine liquid, died without any signs of infection. A possible cause of death in these dogs could be brain damage from the intracerebral virus injection during the control infection. This could be explained by the fact that the infection might have caused an additional source of shock and stress for the animals, which affected their survival. The remaining 8 vaccinated dogs (80%) remained clinically healthy without signs of rabies after the control infection. Their behavior and clinical condition were satisfactory, they were healthy, alert, had a good appetite, and their body temperature remained within the normal range. This suggests a high effectiveness of the immune response triggered by the oral brick vaccine against rabies.

DISCUSSION

Rabies in dogs is the leading cause of death among humans from any zoonotic disease worldwide [16]. Currently, the infection is reported in 122 countries, primarily in low-income nations [17]. To prevent rabies, vaccination of reservoir species (usually dogs and foxes) is considered the most cost-effective and consistent solution to combat the infection [18, 19, 20]. Conducting effective parenteral vaccination in low-income countries faces significant challenges, such as lack of funding, inadequate infrastructure, low political support, weak procedural organization, the inability of owners to control their dogs, difficulties in reaching free-roaming animals without extraordinary effort, and a significant proportion of dogs that are not under constant human supervision [18, 21–24]. Oral rabies vaccine (ORV) for free-roaming dogs has been proposed to cover populations of dogs that are inaccessible through parenteral vaccination routes [25]. This idea was subsequently adapted for wild carnivores, which are often found in remote or hard-to-reach areas. This approach significantly simplifies the process of mass vaccination without the need for direct contact with each animal.

Studies assessing the effectiveness and safety of oral rabies vaccines have been conducted by various researchers in other countries for many years. For example, Aboulfidaa N. and colleagues in Morocco used different types of baits—fish, eggs, and local boiled bull intestines—to evaluate their palatability in local dogs. In the experiment, sachets containing 3.0 ml of the SPBN GASGAS vaccine (107.5 FFU/ml) were used, and serological tests were conducted to assess the immune response [26]. Similarly, research by Yale G. and other co-authors confirms the successful use of oral rabies vaccines in dogs in India, demonstrating the high effectiveness of this approach in controlling the spread of the disease, especially in areas with limited access to traditional vaccination methods [27].

One of the key aspects of our study was also the comparison of the compositions of the vaccine baits. Since we used a line for pelletizing, difficulties arose in determining the composition of the baits. Initially, jelly-like baits were prepared in laboratory conditions, but the results of the experiments showed that the pelletized bait, containing microcrystalline cellulose with fishmeal, demonstrated greater stability compared to the jelly-like form. All animals that received both forms of bait consumed them entirely, which confirms the high palatability of these baits.

Special attention was also given to evaluating the vaccine's safety in the event of a potential overdose. The results confirmed the absence of vaccine virus replication and its excretion through saliva or feces, which significantly reduces the risk of secondary transmission of the vaccine virus and confirms its epizootiological safety.

Rabies vaccination remains one of the most effective methods for preventing this deadly disease, and serum antibody titers against the rabies virus (RABV) are traditionally considered an important indicator of protective immunity following vaccination. However, despite the widely accepted use of these titers as surrogate markers of protection, more comprehensive studies on vaccine efficacy are required to meet regulatory standards. Specifically, such studies must include provocation infections in both vaccinated animals and control groups to confirm real protection against the disease. This approach is essential to ensure the accuracy and reliability of the results, as only clinically proven vaccine efficacy can guarantee that it is truly capable of preventing infection under real-world conditions.

Our efficacy study using the *Rabies virus fix/NIIPBB/2024* strain of the rabies virus met the Pharm EU and WOAH requirements [28, 29], as 80% (8/10) of the vaccinated dogs survived, while 100% (3/3) of the control animals died from the infection. In other words, vaccinated dogs remained clinically healthy and showed no signs of rabies following the challenge infection, while the control group of animals did not survive the test. This confirms the vaccine's ability to provide protection against the deadly disease and the fundamental usefulness of the immunological product.

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In the context of animal clinical care, the absence of fever in vaccinated dogs may indicate a robust adaptive immune response to the vaccine without signs of overwhelming the animal's system. This is also valuable for assessing vaccine side effects, as an elevated body temperature is one of the most common symptoms following vaccination. The mild clinical reaction to the vaccine suggests its high safety profile and a low likelihood of adverse effects.

CONCLUSION

The results of the conducted study demonstrate the high efficacy, safety, and practical applicability of the oral rabies vaccine in the form of an edible bait. The bait was eagerly consumed by all the dogs, emphasizing its attractiveness and ease of use in field conditions. The vaccine induced a specific immune response in the majority of animals, confirming its immunogenicity, and also displayed protective properties during the controlled challenge.

The absence of severe clinical reactions and side effects in vaccinated animals indicates the favorable safety profile of the vaccine. Moreover, the efficacy of the oral form of the vaccine opens new opportunities for rabies control among wild carnivores, especially in regions with limited access to veterinary services and high epizootiological risks.

Thus, the use of the oral bait vaccine for rabies can be regarded as an effective and practical measure for expanding vaccination coverage, particularly among wild and hard-to-reach animals. This approach should be considered when developing and implementing national strategies for the control and elimination of rabies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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LITERATURE

1. Chen S.J., Rai C.I., Wang S.C., Chen Y.C. Infection and Prevention of Rabies Viruses // *Microorganisms. – 2025. – Vol. 13. – No.* 2. – *P.* 380. https://doi.org/10.3390/microorganisms13020380

2. Lafon M. Evasive strategies in rabies virus infection // Adv Virus Res. – 2011. – Vol. 79. – P. 33-53. https://doi.org/10.1016/b978-0-12-387040-7.00003-2

3. Finke S., Conzelmann K.K. Replication strategies of rabies virus // Virus Res. – 2005. – Vol. 111(2). – P. 120-31. https://doi.org/10.1016/j.virusres.2005.04.004

4. Yidi G., Ming D., Xinping W., Jie G., Zhenhong G., Maolin Z. Early events in rabies virus infection – Attachment, entry, and intracellular trafficking // Virus Research. – 2019. – Vol. 263. – P 217-225. ISSN 0168-1702. https://doi.org/10.1016/j.virusres.2019.02.006

5. Aurélie A.V. Albertini, Rob W.H. Ruigrok, Daniell B. Chapter 1 - Rabies Virus Transcription and Replication, Editor(s): Alan C. Jackson, Advances in Virus Research, Academic Press. – 2011. – Vol. 79. – P. 1-22.

6. Zhang H., Huang J., Song Y., Liu X., Qian M., Huang P., Li Y., Zhao L., Wang H. Regulation of innate immune responses by rabies virus // Animal Model. Exp. Med. – 2022. – Vol. *5*. – *P* 418–429. https://doi.org/10.1002/ame2.12273

7. Rieder M., Conzelmann K.K. Interferon in rabies virus infection // *Adv. Virus Res.* – 2011**.** – Vol. *79.* – P. 91–114. https://doi.org/10.1016/B978-0-12-387040-7.00006-8

8. Fooks A.R., Cliquet F., Finke S., Freuling C., Hemachudha T., Mani R.S., Müller T., Nadin-Davis S., Picard-Meyer E., Wilde H. Rabies // Nat. Rev. Dis. Primers 3. – 2017. ISSN 2056-676X. https://doi.org/10.1038/nrdp.2017.91

9. Jackson A.C. Rabies // Can J Neurol Sci. – 2000. – Vol. 27. – No 4. – P. 278-82. https:// doi.org/10.1017/s0317167100000998

10. World Health Organization. Brief review // https://www.who.int/ru/news-room/fact-sheets/detail/rabies

11. Mazbayeva D., Bulatov Y., Abitaev R., Sametova Z., Toktyrova D. Oral vaccine: as a means of preventing rabies in wildlife // Eurasian Journal of Applied Biotechnology. – 2024. – Vol. 4. – *P.* 60–72. https://doi.org/10.11134/btp.4.2024.6

12. MacInnes C.D., Smith S.M., Tinline R.R., Ayers N.R., Bachmann P., et al. Elimination of rabies from red foxes in eastern Ontario // J Wildlife Dis. – 2001. – Vol. 37. – P 119–132 https:// doi.org/10.7589/0090-3558-37.1.119

13. Rosatte R.C., Power M.J., Donovan D., Davies J.C., Allan M., Bachmann P., Stevenson B., Wandeler A., Muldoon F. Elimination of arctic variant rabies in red foxes, metropolitan Toronto // Emerg Infect Dis. – 2007. – Vol. 13(1) – P. 25-27. https://doi: 10.3201/eid1301.060622.

14. Bobe K., Ortmann S., Kaiser C., Perez-Bravo D., Gethmann J., Kliemt J., Körner S., Theuß T., Lindner T., Freuling C., Efficacy of Oral Rabies Vaccine Baits Containing SPBN GASGAS in Domestic Dogs According to International Standards // *Vaccines.* – 2023. – *Vol 11.* 307. https:// doi.org/10.3390/vaccines11020307

15. OIE Terrestrial Manual, Chapter 3.1.17 Rabies (Infection with rabies virus and other lyssaviruses). – 2018 // P. 578-612.

16. Fooks A.R., Banyard A.C., Horton D.L., Johnson N., McElhinney L.M., Jackson A.C. Current status of rabies and prospects for elimination // Lancet. – 2014. 384: 1389–99. // doi.org/10.1016/S0140-6736(13)62707-5

17. Hampson K., Coudeville L., Lembo T., Sambo M., Kieffer A., Attlan M., Estimating the global burden of endemic canine rabies // PLoS Negl Trop Dis. – 2015. – Vol. 9. – e0003709 // doi.org/10.1371/journal.pntd.0003786

DOI: 10.11134/btp.3.2025.10

18. Wallace R.M., Undurraga E.A., Blanton J.D., Cleaton J., Franka R., Elimination of dogmediated human rabies deaths by 2030: needs assessment and alternatives for progress based on dog vaccination // Front Vet Sci. – 2017. – Vol 4. – No. 9 https://doi: 10.3389/fvets.2017.00009

19. Elser J.L., Hatch B.G., Taylor L.H., Nel L.H., Shwiff S.A. Towards canine rabies elimination: Economic comparisons of three project sites // Transbound Emerg Dis. – 2018. – Vol. 65(1). – P. 135-145. https://doi: 10.1111/tbed.12637

20. Anderson A., Shwiff S.A., The cost of canine rabies on four continents // Transbound Emerg Dis. – 2015. – Vol. 62. – *P.* 446–52. https://doi.org/10.1111/tbed.12168

21. Castillo-Neyra R., Brown J., Borrini K., Arevalo C., Levy M.Z., Buttenheim A., Barriers to dog rabies vaccination during an urban rabies outbreak: qualitative findings from Arequipa, Peru // PLoS Negl Trop Dis. – 2017. – Vol. 11. – e0005460 https://doi.org/10.1371/journal.pntd.0005460

22. Muthiani Y., Traore A., Mauti S., Zinsstag J., Hattendorf J., Low coverage of central point vaccination against dog rabies in Bamako, Mali // Prev Vet Med. – 2015. Vol. 120:203–9 // doi.org/10.1016/j.prevetmed.2015.04.007

23. Jackman J., Rowan A.N., In: Salem D, Rowan AN, editors. Free-roaming dogs in developing countries: The benefits of capture, neuter, and return programs. The state of animals IV // Washington, DC: Humane Society Press. – 2007. – P. 55–78.

24. World Health Organization. Report of WHO consultation on dog ecology studies related to rabies control // Geneva: World Health Organization. – 1988 // Available online: https://pesquisa.bvsalud.org/portal/resource/pt/who-58695

25. World Health Organization. Oral vaccination of dogs against rabies. Geneva: World Health Organization. – 2007 // Available online: https://pesquisa.bvsalud.org/portal/resource/pt/who-331036

26. Aboulfidaa N., Cliquet F., Robardet E., Darkaoui S., Wasniewski M., Kaiser C., Bobe K., Vos A., Fihri O.F., Evaluation of Bait Acceptance and Immune Response in Local Dogs during an Oral Rabies Vaccination Field Study in Morocco // *Trop. Med. Infect. Dis.* – 2024. – Vol. *9.* – 142. https://doi.org/10.3390/tropicalmed9070142

27. Yale G., Lopes M., Isloor S., Head J.R., Mazeri S., Gamble L., Dukpa K., Gongal G., Gibson A.D. Review of Oral Rabies Vaccination of Dogs and Its Application in India // *Viruses.* – 2022. – *Vol. 14.* – 155. https://doi.org/10.3390/v14010155

28. Council of Europe. Rabies vaccine (live, oral) for foxes and raccoon dogs 01/2014-0746. // In European Pharmacopoeia 10.0; EDQM: Strasbourg, France. – 2019. – P. 1050–1051.

29. OIE. Terrestrial Manual Chapter 3.1.18 Rabies (Infection with Rabies Virus and Other Lyssaviruses) // OIE, Paris, France. – 2018 // Available online: https://www.woah.org/Health_standards/tahm/3.01.18_RABIES

REFERENCES

1. Chen S.J., Rai C.I., Wang S.C., Chen Y.C. Infection and Prevention of Rabies Viruses // *Microorganisms. – 2025. – Vol. 13. – No.* 2. – *P.* 380. https://doi.org/10.3390/microorganisms13020380

2. Lafon M. Evasive strategies in rabies virus infection // Adv Virus Res. – 2011. – Vol. 79. – P. 33-53. https://doi.org/10.1016/b978-0-12-387040-7.00003-2

3. Finke S., Conzelmann K.K. Replication strategies of rabies virus // Virus Res. – 2005. – Vol. 111(2). – P. 120-31. https://doi.org/10.1016/j.virusres.2005.04.004

4. Yidi G., Ming D., Xinping W., Jie G., Zhenhong G., Maolin Z. Early events in rabies virus infection – Attachment, entry, and intracellular trafficking // Virus Research. – 2019. – Vol. 263. – P 217-225. ISSN 0168-1702. https://doi.org/10.1016/j.virusres.2019.02.006

5. Aurélie A.V. Albertini, Rob W.H. Ruigrok, Daniell B. Chapter 1 - Rabies Virus Transcription and Replication, Editor(s): Alan C. Jackson, Advances in Virus Research, Academic Press. – 2011. – Vol. 79. – P. 1-22.

6. Zhang H., Huang J., Song Y., Liu X., Qian M., Huang P., Li Y., Zhao L., Wang H. Regulation of innate immune responses by rabies virus // Animal Model. Exp. Med. – 2022. – Vol. *5.* – *P* 418–429. https://doi.org/10.1002/ame2.12273

7. Rieder M., Conzelmann K.K. Interferon in rabies virus infection // *Adv. Virus Res.* – 2011**.** – Vol. *79.* – P. 91–114. https://doi.org/10.1016/B978-0-12-387040-7.00006-8

8. Fooks A.R., Cliquet F., Finke S., Freuling C., Hemachudha T., Mani R.S., Müller T., Nadin-Davis S., Picard-Meyer E., Wilde H. Rabies // Nat. Rev. Dis. Primers 3. – 2017. ISSN 2056-676X. https://doi.org/10.1038/nrdp.2017.91

9. Jackson A.C. Rabies // Can J Neurol Sci. – 2000. – Vol. 27. – No 4. – P. 278-82. https:// doi.org/10.1017/s0317167100000998

10. World Health Organization. Brief review // https://www.who.int/ru/news-room/fact-sheets/detail/rabies

11. Mazbayeva D., Bulatov Y., Abitaev R., Sametova Z., Toktyrova D. Oral vaccine: as a means of preventing rabies in wildlife // Eurasian Journal of Applied Biotechnology. – 2024. – Vol. 4. – *P.* 60–72. https://doi.org/10.11134/btp.4.2024.6

12. MacInnes C.D., Smith S.M., Tinline R.R., Ayers N.R., Bachmann P., et al. Elimination of rabies from red foxes in eastern Ontario // J Wildlife Dis. – 2001. – Vol. 37. – P 119–132 https:// doi.org/10.7589/0090-3558-37.1.119

13. Rosatte R.C., Power M.J., Donovan D., Davies J.C., Allan M., Bachmann P., Stevenson B., Wandeler A., Muldoon F. Elimination of arctic variant rabies in red foxes, metropolitan Toronto // Emerg Infect Dis. – 2007. – Vol. 13(1) – P. 25-27. https://doi: 10.3201/eid1301.060622.

14. Bobe K., Ortmann S., Kaiser C., Perez-Bravo D., Gethmann J., Kliemt J., Körner S., Theuß T., Lindner T., Freuling C., Efficacy of Oral Rabies Vaccine Baits Containing SPBN GASGAS in Domestic Dogs According to International Standards // *Vaccines.* – 2023. – *Vol 11.* 307. https://doi.org/10.3390/vaccines11020307

15. OIE Terrestrial Manual, Chapter 3.1.17 Rabies (Infection with rabies virus and other lyssaviruses). – 2018. - P. 578-612.

16. Fooks A.R., Banyard A.C., Horton D.L., Johnson N., McElhinney L.M., Jackson A.C. Current status of rabies and

DOI: 10.11134/btp.3.2025.10

prospects for elimination // Lancet. – 2014. 384: 1389–99. // doi.org/10.1016/S0140-6736(13)62707-5

17. Hampson K., Coudeville L., Lembo T., Sambo M., Kieffer A., Attlan M., Estimating the global burden of endemic canine rabies // PLoS Negl Trop Dis. – 2015. – Vol. 9. – e0003709 // doi.org/10.1371/journal.pntd.0003786

18. Wallace R.M., Undurraga E.A., Blanton J.D., Cleaton J., Franka R., Elimination of dogmediated human rabies deaths by 2030: needs assessment and alternatives for progress based on dog vaccination // Front Vet Sci. – 2017. – Vol 4. – No. 9. https://doi: 10.3389/fvets.2017.00009

19. Elser J.L., Hatch B.G., Taylor L.H., Nel L.H., Shwiff S.A. Towards canine rabies elimination: Economic comparisons of three project sites // Transbound Emerg Dis. – 2018. – Vol. 65(1). – P. 135-145. https://doi: 10.1111/tbed.12637

20. Anderson A., Shwiff S.A., The cost of canine rabies on four continents // Transbound Emerg Dis. – 2015. – Vol. 62. – *P.* 446–52. https://doi.org/10.1111/tbed.12168

21. Castillo-Neyra R., Brown J., Borrini K., Arevalo C., Levy M.Z., Buttenheim A., Barriers to dog rabies vaccination during an urban rabies outbreak: qualitative findings from Arequipa, Peru // PLoS Negl Trop Dis. – 2017. – Vol. 11. – e0005460 https://doi.org/10.1371/journal.pntd.0005460

22. Muthiani Y., Traore A., Mauti S., Zinsstag J., Hattendorf J., Low coverage of central point vaccination against dog rabies in Bamako, Mali // Prev Vet Med. – 2015. Vol. 120:203–9 // doi.org/10.1016/j.prevetmed.2015.04.007

23. Jackman J., Rowan A.N., In: Salem D, Rowan AN, editors. Free-roaming dogs in developing countries: The benefits of capture, neuter, and return programs. The state of animals IV // Washington, DC: Humane Society Press. – 2007. – P. 55–78.

24. World Health Organization. Report of WHO consultation on dog ecology studies related to rabies control // Geneva: World Health Organization. – 1988 // Available online: https://pesquisa.bvsalud.org/portal/resource/pt/who-58695

25. World Health Organization. Oral vaccination of dogs against rabies. Geneva: World Health Organization. – 2007 // Available online: https://pesquisa.bvsalud.org/portal/resource/pt/who-331036

26. Aboulfidaa N., Cliquet F., Robardet E., Darkaoui S., Wasniewski M., Kaiser C., Bobe K., Vos A., Fihri O.F., Evaluation of Bait Acceptance and Immune Response in Local Dogs during an Oral Rabies Vaccination Field Study in Morocco // *Trop. Med. Infect. Dis.* – 2024. – Vol. *9.* – 142. https://doi.org/10.3390/tropicalmed9070142

27. Yale G., Lopes M., Isloor S., Head J.R., Mazeri S., Gamble L., Dukpa K., Gongal G., Gibson A.D. Review of Oral Rabies Vaccination of Dogs and Its Application in India // *Viruses.* – 2022. – *Vol. 14.* – 155. https://doi.org/10.3390/v14010155

28. Council of Europe. Rabies vaccine (live, oral) for foxes and raccoon dogs 01/2014-0746. // In European Pharmacopoeia 10.0; EDQM: Strasbourg, France. – 2019. – P. 1050–1051.

29. OIE. Terrestrial Manual Chapter 3.1.18 Rabies (Infection with Rabies Virus and Other Lyssaviruses) // OIE, Paris, France. – 2018 // Available online: https://www.woah.org/Health_standards/tahm/3.01.18_RABIES

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ОЦЕНКА БЕЗОПАСНАСТИ ПЕРОРАЛЬНЫЙ ВАКЦИНЫ ПРОТИВ БЕШЕНСТВА В ВИДЕ ПРИМАНКИ ДЛЯ ДИКИХ ПЛОТОЯДНЫХ ЖИВОТНЫХ НА СЕРОНЕГАТИВНОЙ МОДЕЛИ СОБАК

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АННОТАЦИЯ

Бешенство остается одним из самых опасных зоонозных заболеваний, ежегодно вызывая десятки тысяч летальных исходов. Одной из ключевых задач в борьбе с бешенством является вакцинация диких плотоядных, домашних и сельскохозяйственных животных, которые играют важнейшую роль в циркуляции вируса в природе. Целью настоящего исследования была оценка безопасности и иммуногенности пероральной вакцины против бешенства в форме брикета-приманки на серонегативных собаках в качестве модельных животных. В ходе эксперимента оценивались клинические параметры, серологические маркеры, поведение животных после иммунизации и контрольной заражении. Полученные данные свидетельствуют о хорошей переносимости вакцины, высокой восприимчивости к приманке и формировании стойкого иммунного ответа у вакцинированных животных. Оральная вакцина не вызывала побочных эффектов и обеспечивала защиту от заражения большинства вакцинированных собак. Результаты исследования подтверждают перспективность применения данной формы вакцины в полевых условиях как для целевых, так и для нецелевых видов животных.

Ключевые слова: Вирус бешенства, Lyssavirus, иммунизация, пероральная брикет вакцина, вируснейтрализирующие антитела

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СЕРОНЕГАТИВТІ ИТ ҮЛГІСІНДЕ ЖАБАЙЫ ЖЫРТҚЫШТАРҒА АРНАЛҒАН АУЫЗ ҚУЫСЫ АРҚЫЛЫ ТҰТЫНЫЛАТЫН ҚҰТЫРУҒА ҚАРСЫ ВАКЦИНАНЫҢ ҚАУІПСІЗДІГІН БАҒАЛАУ

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ТҮЙІН

Құтыру жыл сайын ондаған мың адамның өліміне себеп болатын ең қауіпті зооноздық аурулардың бірі болып саналады. Құтыру ауруымен күресудегі басты міндеттердің бірі вирустың табиғат айналымында маңызды рөл атқаратын жабайы жыртқыштарды, үй және ауыл шаруашылығы жануарларын вакцинациялау болып табылады. Бұл зерттеудің мақсаты үлгі жануарлар ретінде серонегативті иттерге ауыз қуысы арқылы тұтынылатын құтыруға қарсы брикет вакцинаның қауіпсіздігі мен иммуногенділігін бағалау болып табылады. Тәжірибе барысында клиникалық көрсеткіштер, серологиялық маркерлер, иммунизациялаудан және бақылаулық жұқтырудан кейінгі жануарлардың мінез-құлқы бағаланды. Алынған мәліметтер вакцинаның жақсы төзімділігін, брикет вакцинаның жоғары тұтынылуын және вакцинацияланған жануарларда тұрақты иммундық жауаптың қалыптасуын көрсетті. Ауыз қуысы арқылы тұтынылған вакцина жанама әсерлер тудырмады және вакцинацияланған иттерде инфекцияға қарсы қорғауды қамтамасыз етті. Зерттеу нәтижелері осы вакциналық форманы дала жағдайында мақсатты және мақсатты емес жануарлар түрлері үшін де қолдануға болатынын растайды.

Кілт сөздер: Құтырық вирусы, Lyssavirus, иммундау, пероральді брикет вакцина, вирусты бейтараптандыратын антиденелер