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Comparative effectiveness of liquid and freeze-dried vaccines for oral vaccination of dogs against rabies

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SUMMARY

Currently, vaccination is the main measure to combat rabies in domestic and wild animals. Inactivated and live vaccines are used for this purpose. Oral vaccines for wild carnivores contain live attenuated rabies viruses in liquid or freeze-dried form, which are packaged inside edible baits. Since there are no consistent data showing advantages of liquid and freeze-dried oral products for vaccine-induced immunity against rabies in animals, we compared effectiveness of these rabies vaccines produced from rabies virus strain VRC-RZ2. Immunogenicity was tested in mongrel dogs aged 3 months and older that are seronegative for rabies virus antigens. The animals were randomly divided into three groups: two experimental and one control group. Group One was fed a block-type bait containing a blister with liquid virus-containing suspension, Group Two was given a block-type bait containing a gelatin capsule with freeze-dried virus suspension. On Day 21 post vaccination, blood samples were taken from all the animals and the obtained sera were examined in virus neutralization test to measure virus neutralizing antibodies titers. The level of the immune response against rabies in the vaccinated dogs was assessed by intracerebral infection of animals with virulent rabies virus strain CVS. The carried out research demonstrated that both groups of the vaccinated dogs had approximately the same titers of virus neutralizing antibodies that ranged from 3.25 to 4.33 $\log_2$. The virus neutralizing antibodies observed in the immunized dogs ensured good protection from virulent CVS strain. All animals of the control group died after infection demonstrating clinical signs of paralytic rabies. The results obtained show that both forms of the oral rabies vaccines are effective.

Keywords: rabies virus, oral vaccine, liquid vaccine, freeze-dried vaccine, antibodies, immunity

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Сравнительная эффективность вакцин в жидкой и лиофилизированной формах при оральной вакцинации собак против бешенства

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РЕЗЮМЕ

В настоящее время основной мерой борьбы с бешенством является вакцинопрофилактика домашних и диких животных, для этого используют инактивированные и живые препараты. Вакцины для оральной иммунизации диких плотоядных животных содержат живые аттенуированные вирусы бешенства, которые в жидком или лиофилизированном виде помещают внутрь съедобной приманки. В связи с отсутствием однозначных данных о преимуществах жидкого и лиофилизированного перорального препарата при формировании у животных поствакцинального иммунитета против бешенства было проведено сравнительное изучение эффективности данных антирабических вакцин, изготовленных из штамма VRC-RZ2 вируса бешенства. Иммуногенную эффективность изучали на беспородных, серонегативных к антигенам вируса бешенства собаках в возрасте от 3 мес. и старше. Животных случайным образом разделили на три группы: две опытные и контрольную. В первой группе собакам скармливали брикет-приманку, содержащую блистер с жидкой вируссодержащей суспензией, во второй группе – брикет-приманку, внутрь которой помещена желатиновая капсула с лиофилизированной суспензией вируса. Через 21 сут после иммунизации у всех животных отбирали пробы крови, полученные из них сыворотки исследовали в реакции нейтрализации для определения титров вируснейтрализующих антител. Напряженность антирабического иммунитета у вакцинированных собак оценивали путем интрацеребрального заражения животных вирулентным вирусом бешенства штамма CVS. В результате проведенного исследования установлено, что в обеих группах иммунизированных собак титры вируснейтрализующих антител были примерно одинаковыми и находились в диапазоне от 3,25 до 4,33 $\log_2$. Выработанные у иммунизированных собак вируснейтрализующие антитела обеспечивали надежную защиту от вирулентного вируса штамма CVS. Все животные контрольной группы после заражения погибли с клиническими признаками паралитической формы бешенства. Полученные результаты свидетельствуют об эффективности обеих форм оральных вакцин против бешенства.

Ключевые слова: вирус бешенства, пероральная вакцина, жидкая вакцина, лиофилизированная вакцина, антитела, иммунитет

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INTRODUCTION

Rabies is a viral disease affecting central nervous system of mammals, including humans [1]. Currently, this disease is endemic in more than 150 countries around the world. Despite the fact that rabies is preventable, according to the World Health Organization (WHO), 59 thousand people die from it every year in the world, mainly in the poorest and most vulnerable communities. About 40% of the victims are children under the age of 15 living in Asia and Africa [2].

The global response to rabies has been fragmented and poorly coordinated so far. Currently, a collective initiative "Unite Against Rabies" is being implemented under the WHO, the goal of the initiative is to achieve zero human deaths from rabies transmitted by dogs by 2030 [3]. A set of joint actions of the the CIS Member States was adopted at the meeting of the CIS Council of Heads of State in 2018 to prevent and control rabies for the period up to 2025 [4].

Wildlife rabies control tactics have changed critically over the past few decades, partially due to the latest scientific discoveries. Historically, rabies control measures mainly consisted in destruction of target animal species [5]. However, scientific breakthroughs have made it possible to develop a method of oral immunization of wild animals by packaging rabies vaccine inside edible baits for carnivores.

There are now various types and forms of baits. Most of them have approximately the same structure and consist of a blister with a vaccine packaged inside a tasty bait, with slight variations in size, bait compositions and types of blisters [6, 7].

Most viruses used in production of live oral rabies vaccines originate from the attenuated Evelyn-Rokitnicki-

Abelseth (ERA) strain, which was derived from the original Street-Alabama-Dufferin (SAD) strain. The parental SAD strain was isolated from the salivary glands of a rabies-infected dog in the USA, in 1935, and then attenuated by serial passages in mice, chicken embryos and various cell lines and was renamed as ERA [8]. The modified SAD Bern vaccine strain was obtained as a result of serial passages of the ERA strain in cell cultures, it was used in the first trials of an oral rabies vaccine in Switzerland [9].

The success of wildlife rabies control by oral immunization has been demonstrated in a number of European countries, such as Estonia, France, Italy and Switzerland. It should be noted that these countries were declared rabies-free only after several years of oral vaccination campaigns using baits containing SAG2 vaccine strain (France also used the recombinant V-RG vaccine) [10–12].

SAG2 (SAD Avirulent Gif) rabies virus strain is a modified live virus selected from SAD Bern in 1990 as a result of two successive mutations [13].

Canada and the USA demonstrated successful use of recombinant vaccines based on vaccinia virus and human adenovirus serotype 5: RABORAL V-RG® (Boehringer Ingelheim Animal Health Inc., USA) and ONRAB® (Artemis Technologies Inc., Canada) for immunization of wild animals [14–17]. These vaccines were produced on the basis of a viral vector, which was created in 1984 as a recombinant vaccinia virus V-RG expressing G-protein gene of ERA rabies virus strain [11, 12, 18].

There are also freeze-dried oral rabies vaccines. One of them was developed by scientists from VNIIVVIM (Russia)[1], the product contains a fixed rabies virus strain TS-80, obtained in 1980 by G. A. Safonov et al. and deposited in the VGNKI on February 17, 1988 [19]. RABIGEN® SAG2 vaccine, developed by Virbac laboratory scientists (France), is another means of specific prevention that has been used in practice. This product is a live modified attenuated rabies vaccine based on recombinant SAG2 rabies virus strain selected from SAD Bern strain during a two-stage amino acid mutation using neutralizing monoclonal antibodies. The effectiveness of RABIGEN® SAG2 has been demonstrated in accordance with the EU requirements for red fox and raccoon dog in Estonia, France, Italy and Switzerland [10].

Despite the fact that the effectiveness of oral immunization of wild carnivores was experimentally confirmed, in order to develop and improve vaccines it is critically important to understand how vaccine viruses penetrate into the host cell and replicate there.

In order to prevent rabies in the field, many countries use blisters with a vaccine (filled with virus-containing suspension prepared from different virus strains). However, some researchers have noted that the distribution of block-type baits in cold weather can make the main immunogenic component freeze, therefore, when the bait is eaten by animals, the vaccine does not have contact with mucous membrane of the oral cavity, but gets into the stomach, thus reducing effectiveness of vaccination [20]. A possible solution to this problem is to use the vaccine with an acid-protective coating that protects the virus from the inactivating effects of gastric juice, or to use freeze-dried oral vaccine that is stable at low temperatures and does not require chewing for the vaccine virus to have contact with the oropharyngeal mucosa [21, 22].

The aim of the study is to compare immunogenic effectiveness of liquid and freeze-dried rabies vaccine produced from rabies virus strain VRC-RZ2.

MATERIALS AND METHODS

The vaccine strain of the virus. Fixed rabies virus strain VRC-RZ2 was obtained from an organ/tissue rabic isolate (puppy brain) and deposited in the collection of microorganisms of the RSE "Research Institute for Biological Safety Problems" (RSE "RIBSP", Kazakhstan) with the registration number P-7-04/D. This strain is recommended for production of rabies vaccine used for oral immunization of animals (Patent RK No. 17453[2]). The titer of the vaccine strain is 6.0–6.5 lg MLD_{50}/0.03 cm^3.

Vaccine. Oral vaccines from VRC-RZ2 strain were used for the research. The vaccines were used in two forms:

– liquid – the product weighing – 25–30 g contains 10 cm^3 of rabies virus suspension in a blister packaged in a block-type bait. The virus titer in one vaccine dose is $10^{6.75}$ $TCID_{50}$/cm^3.

– freeze-dried – the product weighing – 25–30 g contains 10 cm^3 of freeze-dried suspension of rabies virus with a stabilizing and acid-resistant polymer in a gelatin capsule packaged in a block-type bait. The virus titer in one vaccine dose is 10^7 $TCID_{50}$/cm^3.

Challenge virus. Reference rabies virus strain CVS was used in the experiment. It is maintained and stored in the collection of microorganisms of the RSE "RIBSP" (Kazakhstan). The infectious activity of the virus is 4.5–5.0 MLD_{50}.

Animals and preparing them for the experiment. 15 mongrel dogs aged 3 months and older were used in the research.

Before the experiment started, the animals were identified and quarantined for 14 days. During the quarantine they were dewormed, subjected to clinical examination and their sera were tested for specific antibodies to rabies virus in virus neutralization test (VNT) [23]. For the purposes of the experiment, we used those dogs who had no specific antibodies to rabies virus and had not been previously vaccinated against this disease.

Experiments on animals were carried out in accordance with national and international laws and regulations on protection and welfare of animals. The protocol was approved by the Ethical Committee on Animal Experimentation of RSE "RIBSP" of the Committee of Science of the Ministry of Education and Science of the Republic of Kazakhstan (Authorization Number: 0701/20).

Experiments on animals. At the end of the quarantine, the dogs were kept without food for one day, then they were randomly divided into three groups (5 dogs in each). Animals of Group One were fed a block-type bait with liquid vaccine in a blister, dogs of Group Two were fed a block-type bait with freeze-dried vaccine in a gelatin capsule. Group Three was used as a control. On Day 21 post

[1] Khripunov E. M., Isakova N. B., Evseeva S. D., Vishnyakov I. F., Nedosekov V. V., Zhesterev V. I., et al. Virus vaccine against rabies for oral immunization of carnivores. Patent No. 2157700 Russian Federation, MPK A61K 39/205(2006.01), C12N 7/00(2006.01). VNIIVViM. Application 25.01.1999. Publ. 20.10.2000.

[2] Rusanova A. M., Zhilin Ye. S., Troitsky Ye. N., Mamadaliev S. M., Barakbayev K. B., Demchenko A. G. Fixed rabies virus strain VRC-RZ2 for preparation of preventive and diagnostic products. Patent No. 17453 Republic of Kazakhstan, MPK C12N 7/00, C12R 1/93, A61K 39/205. Application 10.12.2004. Publ. 15.12.2009. Bulletin No. 12.

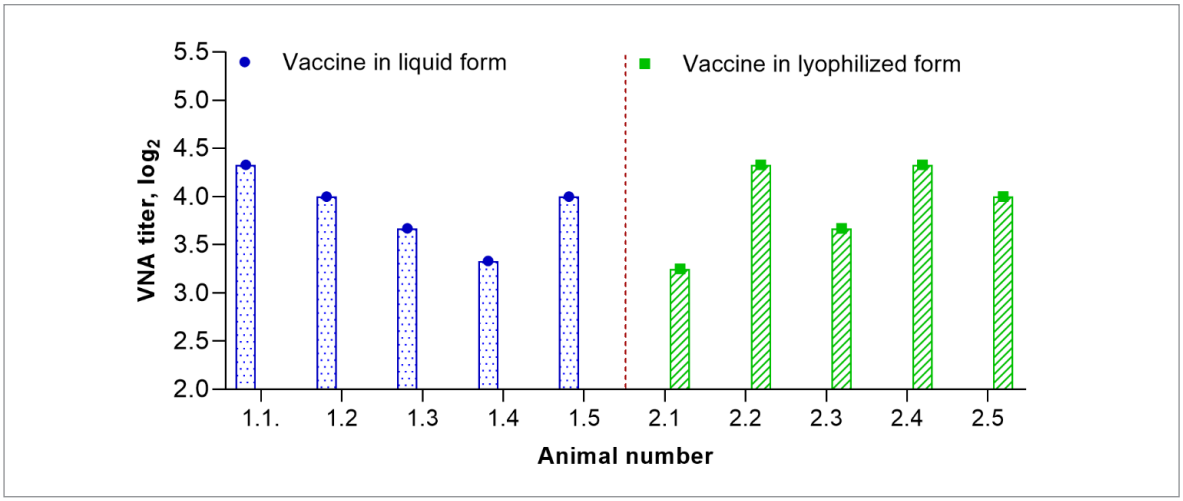

Fig. Effectiveness of oral vaccination of dogs with liquid and freeze-dried vaccines

Table
Challenge of vaccinated dogs with virulent CVS strain of rabies virus

Animal Group	Animal Number	Infection dose, MLD_{50}	Result
Group One (experimental)	1.1	100	–
	1.2	100	–
	1.3	100	–
	1.4	1,000	–
	1.5	1,000	–
Group Two (experimental)	2.1	100	–
	2.2	100	–
	2.3	100	+
	2.4	1,000	–
	2.5	1,000	–

"+" – the animal is affected;
"–" – the animal is not affected.

vaccination, blood samples were taken from all the dogs, the obtained sera were tested in VNT [23] to determine the titers of virus neutralizing antibodies (VNA).

Challenge. In order to assess anti-rabies immunity, on Day 21 post vaccination all the animals were intracerebrally infected with virulent rabies virus strain CVS at a dose of 100 and 1,000 MLD_{50} and clinically observed for 21 days.

Diffusion precipitation reaction (DPR). DPR was carried out according to GOST 26075-2013[3].

Statistical data processing. Statistical analysis was performed using GraphPad Prism Version 8.0.1. Two-way ANOVAs test was used to analyse serological test results after vaccination with both vaccines, as well as the difference between the groups after the challenge. The value of $P \leq 0.05$ was considered statistically significant. The difference in the vaccination effectiveness between the groups was assessed by One-Sided Fisher's Exact Test for two proportions at the Alpha significance level < 0.05.

RESULTS AND DISCUSSION

Observation of the vaccinated animals revealed that dogs remained healthy for 21 days after immunization, no changes in behavior or rabies clinical symptoms were recorded, thus, suggesting that the oral vaccines used in the experiment were safe.

Postvaccinal immunity was assessed by the level of rabies VNA in the vaccinated animals. The experiment results are shown in the figure.

It was found that dogs from Group One vaccinated with the liquid vaccine had VNA titers ranging from 3.33 to 4.33 log_2. VNA titre in Group Two immunized with freeze-dried virus-containing suspension was in the range from 3.25 to 4.33 log_2. Despite different forms of the oral

[3] GOST 26075-2013. Animals. Methods of Laboratory Diagnostic of Rabies. Moscow: Standartinform; 2014. 10 p. Available at: https://base.garant.ru/70995746.

vaccine used in the experiment, the maximum level of VNA in both groups of the vaccinated animals was 4.33 $\log_2$, while there was no significant difference between VNA titers in Group One and Group Two ($P > 0.05$).

It was demonstrated that the VNA developed in dogs of both groups immunized with different forms of the oral vaccine protected against infection with virulent rabies virus strain CVS. The experiment results are given in the table.

After intracerebral infection, all animals of Group One remained clinically healthy for 21 days, regardless of the infection dose. In Group Two, one dog (No. 2.3) died on Day 3 after infection, the rest of the animals were clinically healthy throughout the whole observation period, regardless of the dose of infection. As DPR showed no specific rabies virus antigen was detected in the brain samples taken from the dead dog. All animals of the control group died within 5–8 days demonstrating clinical signs of paralytic form of rabies. Specificity of the disease and the death of dogs were confirmed in the DPR.

The results obtained show that both forms of the oral rabies vaccines are effective.

CONCLUSION

Analyzing the data obtained, it can be concluded that both tested rabies vaccines, produced on the basis of rabies virus strain VRC-RZ2 and used orally for dog vaccination, induce virus neutralizing antibody response resulting in 100% protection against intracerebral infection with virulent rabies virus strain CVS. Taking into account that the freeze-dried oral vaccine is more stable at low temperatures, it can be used in various geographical zones of Kazakhstan.

REFERENCES

1. OIE Rabies. Available at: https://www.oie.int/en/disease/rabies.

2. WHO. Rabies. Available at: https://www.who.int/news-room/fact-sheets/detail/rabies (date of access: 10.06.2021).

3. WHO Expert Consultation on Rabies: Third Report. *WHO Technical Report Series, No. 1012*. Geneva; 2018. 183 p. Available at: https://apps.who.int/iris/handle/10665/272364.

4. Ispolnitel'nyi komitet Sodruzhestva Nezavisimykh Gosudarstv. Itogi 86-go zasedaniya Ekonomicheskogo soveta SNG (30 iyunya 2020 g.) = Executive Committee of the Commonwealth of Independent States. Results of the 86th Meeting of the CIS Economic Council (June 30, 2020). Available at: https://cis.minsk.by/news/15259/itogi_86-go_zasedanija_ekonomicheskogo_soveta_sng_ %2830_ijunja_2020_goda%29 (date of access: 10.06.2021). (in Russ.)

5. Rosatte R. Evolution of wildlife rabies control tactics. *Adv. Virus. Res*. 2011; 79: 397–419. DOI: 10.1016/B978-0-12-387040-7.00019-6.

6. Gruzdev K. N., Metlin A. E. Animal Rabies. Vladimir: FGBI "ARRIAH". 2019. 394 p. eLIBRARY ID: 41355659. (in Russ.)

7. Linhart S. B., Wlodkowski J. C., Kavanaugh D. M., Motes-Kreimeyer L., Montoney A. J., Chipman R. B., et al. A new flavor-coated sachet bait for delivering oral rabies vaccine to raccoons and coyotes. *J. Wildl. Dis.* 2002; 38 (2): 363–377. DOI: 10.7589/0090-3558-38.2.363.

8. Abelseth M. K. An attenuated rabies vaccine for domestic animals produced in tissue culture. *Can. Vet. J.* 1964; 5 (11): 279–286. PMID: 17421745.

9. Steck F., Wandeler A., Bichsel P., Capt S., Häfliger U., Schneider L. Oral immunization of foxes against rabies. Laboratory and field studies. *Comp. Immunol. Microbiol. Infect. Dis*. 1982; 5 (1–3): 165–171. DOI: 10.1016/0147-9571(82)90031-5.

10. Mähl P., Cliquet F., Guiot A. L., Niin E., Fournials E., Saint-Jean N. Twenty year experience of the oral rabies vaccine SAG2 in wildlife: a global review. *Vet. Res*. 2014; 45 (1):77. DOI: 10.1186/s13567-014-0077-8.

11. Kieny M. P., Lathe R., Drillien R., Spehner D., Skory S., Schmitt D., et al. Expression of rabies virus glycoprotein from a recombinant vaccinia virus. *Nature.* 1984; 312 (5990): 163–166. DOI: 10.1038/312163a0. PMID: 6548799.

12. Wiktor T. J., Macfarlan R. I., Reagan K. J., Dietzschold B., Curtis P. J., Wunner W. H., et al. Protection from rabies by a vaccinia virus recombinant containing the rabies virus glycoprotein gene. *Proc. Natl. Acad. Sci. USA*. 1984; 81 (22): 7194–7198. DOI: 10.1073/pnas.81.22.7194.

13. Lafay F., Bénéjean J., Tuffereau C., Flamand A., Coulon P. Vaccination against rabies: construction and characterization of SAG2, a double avirulent derivative of SAD Bern. *Vaccine*. 1994; 12 (4): 317–320. DOI: 10.1016/0264-410x(94)90095-7.

14. Amann R., Rohde J., Wulle U., Conlee D., Raue R., Martinon O., Rziha H. J. A new rabies vaccine based on a recombinant ORF virus (parapoxvirus) expressing the rabies virus glycoprotein. *J. Virol*. 2013; 87 (3): 1618–1630. DOI: 10.1128/JVI.02470-12.

15. Mainguy J., Rees E. E., Canac-Marquis P., Bélanger D., Fehlner-Gardiner C., Séguin G., et al. Oral rabies vaccination of raccoons and striped skunks with ONRAB® baits: multiple factors influence field immunogenicity. *J. Wildl. Dis.* 2012; 48 (4): 979–990. DOI: 10.7589/2011-12-316.

16. Maki J., Guiot A. L., Aubert M., Brochier B., Cliquet F., Hanlon C. A., et al. Oral vaccination of wildlife using a vaccinia-rabies-glycoprotein recombinant virus vaccine (RABORAL V-RG®): A global review. *Vet. Res.* 2017; 48 (1):57. DOI: 10.1186/s13567-017-0459-9.

17. Fehlner-Gardiner C., Rudd R., Donovan D., Slate D., Kempf L., Badcock J. Comparing ONRAB® and RABORAL V-RG® oral rabies vaccine field performance in raccoons and striped skunks, New Brunswick, Canada, and Maine, USA. *J. Wildl. Dis*. 2012; 48 (1): 157–167. DOI: 10.7589/0090-3558-48.1.157.

18. Follmann E., Ritter D., Swor R., Dunbar M., Hueffer K. Preliminary evaluation of Raboral V-RG® oral rabies vaccine in Arctic foxes (*Vulpes lagopus*). *J. Wildl. Dis*. 2011; 47 (4): 1032–1035. DOI: 10.7589/0090-3558-47.4.1032.

19. Elakov A. L. Measures of fight against rabies of neglected and wild animals. *VetPharma*. 2013; 5 (6): 24–27. Available at: https://www.elibrary.ru/download/elibrary_21020254_52439858.pdf. (in Russ.)

20. Follmann E. H., Ritter D. G., Donald W. H. Oral vaccination of captive arctic foxes with lyophilized SAG2 rabies vaccine. *J. Wildl. Dis*. 2004; 40 (2): 328–334. DOI: 10.7589/0090-3558-40.2.328.

21. Follmann E. H., Ritter D. G., Hartbauer D. W. Safety of lyophilized SAG2 oral rabies vaccine in collared lemmings. *J. Wildl. Dis*. 2002; 38 (1): 216–218. DOI: 10.7589/0090-3558-38.1.216.

22. Hermann J. R., Fry A. M., Siev D., Slate D., Lewis C., Gatewood D. M. Stability of vaccinia-vectored recombinant oral rabies vaccine under field conditions: A 3-year study. *Can. J. Vet. Res*. 2011; 75 (4): 278–284. PMID: 22468025.

23. Rabies (infection with rabies virus and other lyssaviruses). *In: OIE. Manual of Diagnostic Tests and Vaccines for Terrestrial Animals*. Chapter 3.1.17. Available at: https://www.oie.int/fileadmin/Home/eng/Health_standards/tahm/3.01.17_RABIES.pdf.

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