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СПОСОБЫ ПОВЫШЕНИЯ ИММУНОГЕННОСТИ ИНАКТИВИРОВАННЫХ ВАКЦИН ПРОТИВ МЫТА ЛОШАДЕЙ

[1]Неустроев М.П., [2]Донченко А.С.
[1]Якутский научно-исследовательский институт сельского хозяйства им. М.Г. Сафронова – обособленное подразделение Якутского научного центра Сибирского отделения Российской академии наук
Республика Саха (Якутия), Якутск, Россия
[2]Сибирский федеральный научный центр агробиотехнологий Российской академии наук
Новосибирская область, р.п. Краснообск, Россия

Представлены результаты исследований по специфической профилактике инфекционных болезней лошадей. Разработаны способы повышения иммуногенности экологически безопасных вакцин против мыта, который вызывается мытным стрептококком – *Sreptococcus equi*. Работа проведена в лабораторных условиях и коневодческих хозяйствах Республики Саха (Якутия). Токсичность и иммуногенность вакцины определяли общепринятыми методами на молодняке лошадей. На основании изучения иммунобиологической реактивности молодняка лошадей обосновано использование иммуномодуляторов при разработке инактивированных вакцинных препаратов. Вакцины с иммуномодуляторами испытывали и регистрировали согласно утвержденным методикам исследования лекарственных средств для ветеринарного применения. В качестве иммуномодулятора в составе вакцин использованы полирибонат (поливедрим) и культуральная жидкость (фугат) из штамма бактерий *Bacillus subtilis* ТНП-3. Для приготовления вакцины против мыта использовали штаммы бактерий *Streptococcus equi* Н-34 и *Streptococcus equi* «Н-5/1», которые депонированы во Всероссийской государственной коллекции штаммов микроорганизмов Всероссийского государственного Центра качества и стандартизации лекарственных средств для животных и кормов, используемых в ветеринарии и животноводстве. После иммунизации инактивированными вакцинами с иммуномодуляторами эффективность вакцин повышается на 20% и достигает 90%. Вакцины повышают иммунобиологическую реактивность организма. Наиболее эффективными отмечены вакцина «Табын» и вакцина из штамма *Streptococcus equi* «Н-5/1» с фугатом, штамма бактерий *Bacillus subtilis* ТНП-3. Вакцина с полирибонатом утверждена в России (2000 г.), вакцина «Табын» применяется в Казахстане (2018 г.). Данные вакцинные препараты, обеспечивающие высокую противоэпизоотическую эффективность, экологически безвредны, так как не содержат токсичные вещества и антибиотики.

Ключевые слова: штамм бактерий, вакцина, иммуномодулятор, иммунобиологическая реактивность, иммуногенность

WAYS TO INCREASE THE IMMUNOGENICITY OF INACTIVATED VACCINES AGAINST STRANGLES

[1]Neustroev M.P., [2]Donchenko A.S.
[1]M.G. Safronov Yakut Scientific Research Institute of Agriculture – a separate division of the Yakut Scientific Centre of the Siberian Branch of the Russian Academy of Sciences
Republic of Sakha (Yakutia), Yakutsk, Russia
[2]Siberian Federal Scientific Centre of Agro-BioTechnologies of Russian Academy of Sciences
Krasnoobsk, Novosibirsk region, Russia

The results of the study on the specific prevention of infectious diseases in horses are presented. Methods have been developed to increase the immunogenicity of environmentally friendly vaccines against strangles, caused by the beta-hemolytic streptococcus – *Sreptococcus equi*. The work was carried out in laboratory conditions and horse breeding farms of the Republic of Sakha (Yakutia). The toxicity and immunogenicity of the vaccine was determined by conventional methods on young horses. Based on the study of the immunobiological reactivity of young horses, the use of immunomodulators in the development of inactivated vaccine preparations has been substantiated. Vaccines with immunomodulators were tested and registered in accordance with approved research methods for medicinal products for veterinary use. Polyribonate (polyvedrim) and culture liquid (fugate) from the bacterial strain Bacillus subtilis TNP-3 were used in the composition of vaccines as an immunomodulator. To prepare a vaccine against strangles, strains of bacteria Streptococcus equi H-34 and Streptococcus equi "H-5/1" were used, which were deposited in the Russian State Collection of Microorganism Strains of the Russian State Center for Animal Feed and Drug Standardization and Quality. After immunization with inactivated vaccines containing immunomodulators, the effectiveness of vaccines increases by 20% and reaches 90%. Vaccines increase the body's immunobiological reactivity. The most effective were the “Tabyn” vaccine and the vaccine from the Streptococcus equi strain H-5/1 with fugate, the Bacillus subtilis strain TNP-3. The polyribonate vaccine was approved in Russia (2000), the “Tabyn” vaccine is used in Kazakhstan (2018). These vaccine preparations, which ensure high antiepizootic efficacy, are environmentally friendly, since they do not contain toxic substances and antibiotics.

Keywords: bacterial strain, vaccine, immunomodulator, immunobiological reactivity, immunogenicity

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The authors declare no conflict of interest.

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INTRODUCTION

The growth in the livestock and productivity of herd horse breeding is constrained by a number of factors, among which infectious diseases occupy a significant place. The most common, especially among young horses, is strangles which is caused by the mythosis streptococcus - Sreptococcus equi [1, 2]. It is believed that the pathogen of strangles has not changed for 700 years, although there are zonal features of its strains [3].

Horse strangles is most common in Novosibirsk, Irkutsk regions, Krasnoyarsk and Altai territories [4], the republics of Tyva[1], Khakassia and Sakha (Yakutia) [5] of the Russian Federation, as well as in Kazakhstan[2], Mongolia [6], Kyrgyzstan [7]. Cases of the disease were noted

[1]Chysyma R.B. Epizootic features and age-related immunoreactivity of foals with horse strangles: dis. abs. in Vet. sciences/ M., 1989. 15 p.

[2]Sansyzbaev A.R. Horse strangles in Kazakhstan (distribution, properties of the pathogen, development of specific prophylaxis and treatment means): dis. abs. Dr.habil. in Vet. sciences. M., 1993. 41 p.

[3]Khartford O.M., Foster T.D., Jakobs A.K. Strain and culture of strain Streptococcus equi TW 928 for horse vaccination. A.c. 2194752 (RU) IPC 7 A 61 K 39/09. Proprietor: Dze Provost FellousEhNDSkolars of DzeKolledzh of DzeKhOLIAndivajded TRINITI OF KvinEhLIZABET NEAR Dublin (IE). № 2194752 C2. Appl. 24.01.97. Published 30.12.02. https://findpatent.ru/patent/219/2194752.html.

in the Netherlands[3], the Arab Republic of Egypt [8], Korea [9], Brazil [10].

In the Republic of Sakha (Yakutia), the incidence of strangles in young horses is 57.8–62.7% of the total population; mortality, depending on the development of the epizootic process, is 4.0–22.0% [5]. In Mongolia and the Republic of Sakha (Yakutia), the spread of infection and an increase in the incidence of strangles are associated with a decrease in the immunobiological reactivity of animals in extreme climatic conditions, with the historically established features of the traditional industry and the lack of planned preventive measures [5, 6].

Strangles currently remains a serious problem due to the lack of specific means of preventing this disease. In the modern world, different types of vaccines are tested, manufactured and used: inactivated, attenuated, live. In the Netherlands, a live vaccine against horse strangles has been developed from the Streptococcus equi strain TW 928 (see footnote 3), but it is not registered in Russia. In the USA, a live vaccine from an attenuated strain, which induces the production of antibodies in blood serum after 7–10 days, and a modified intranasal vaccine Pinnacle IN, two-time use, have been developed and are being used. These vaccines are not used in Russia; they require two and three doses at intervals of several weeks, which is inconvenient for the use [11].

In Kazakhstan, an inactivated subunit vaccine from the Sreptococcus equi YUS-15 strain, the KazNIVI vaccine[4] and the Akyntai vaccine[5] have been developed. However, these vaccines contain antibiotics and cannot be used for organic production.

Currently, an effective method of fighting strangles is generally recognized - specific prophylaxis with vaccines, but in veterinary practice there are no ecologically harmless anti-epizootic vaccines. The problem of prevention of strangles acquires special significance in the period of market relations, when the value of breeding animals increases, sales of horse breeding products and the production of organic products are expanding.

The purpose of the study is to develop ways to increase the immunogenicity of ecologically safe vaccines against horse washing by using immunomodulators.

MATERIAL AND METHODS

The work was carried out in the laboratory of veterinary biotechnology of the Yakut Scientific Research Institute of Agriculture (YSRIA), SPC Khotu-Bakt LLC and in horse breeding farms in the Republic of Sakha (Yakutia).

To prepare a vaccine against strangles we used strains of bacteria Streptococcus equi H-34 and Streptococcus equi "H-5/1" which were deposited in the All-Russian State Collection of Microorganism Strains of the Russian State Center for Animal Feed and Drug Standardization and Quality (FSFI "VGNKI") used in veterinary and animal husbandry.

To accumulate the bacterial mass for the manufacture of the vaccine, we used meat-peptone broth (MPB) with 1% glucose and with the addition of horse blood serum. The prepared bacterial base was inactivated with 0.04% formalin solution. Aluminum hydroxide was used as an adjuvant.

The vaccine from the Streptococcus equi H-34 strain as an immunomodulator was supplemented with polyribonate (polyvedrim), developed by the Scientific Research, Design and Technology Institute of Biologically Active Substances SPA Vector and the Institute of Experimental Veterinary Medicine of Siberia and the Far East. Polyribonate was added to the vaccine at the rate of 0.5 mg / kg of live weight. An immunomodulator was added to the vaccine from the Streptococcus equi strain "H-5/1" - a culture liquid (fugate) from the bacterial strain Bacillus subtilis TNP-3 (registration number RCAM04759, certificate of deposit dated December 27, 2017). The strain was cultivated for 5 days in meat-peptone broth at 37 ° C. The

[4]Patent No. 36813 Republic of Kazakhstan. Vaccine against horse strangles/ A.B. Bizhanov, A.R. Sansyzbaev. 1999. Bul. No. 10.

[5]Patent No. 31032 Republic of Kazakhstan. Vaccine against horse strangles "Akyntai" / B.Sh. Karataev, N.A. Myrzakhmetuly, A.B. Bizhanov. 2016. Bul. No. 4.

bacterial mass containing 1 billion microbial cells was centrifuged at 7000 rpm for 15 min to separate the culture liquid (CL). It was filtered through membrane filters into sterile vials heated in a water bath at 95 ° C for 15 min. Fugate was added to the finished vaccine in a 2: 1 ratio.

The toxicity and immunogenicity of the vaccine were determined by conventional methods on young horses. The vaccine with the immunomodulator polyribonate was tested and recorded according to the approved rule[6]. The study of the vaccine with the fugate of the bacterial strain Bacillus subtilis TNP-3 was carried out according to the method[7].

The tests of the vaccine from the Streptococcus equi H-34 strain with the fugate of the Bacillus subtilis TNP-3 bacterial strain and the execution of scientific and technical documentation were carried out in accordance with the rules[8].

To assess the immunogenic properties of the horse strangles vaccine, the lethal dose of the industrial strains (LD_{50}) was preliminarily determined. The effectiveness of immunization was determined by the number of mice resistant in morbidity and mortality to infection in comparison with animals of the control group. Production trials of vaccines were carried out in the strangles dysfunctional farms of the Republic of Sakha (Yakutia).

RESULTS AND DISCUSSION

The immunobiological reactivity of the body of young horses has age and seasonal characteristics and is interrelated with the dynamics of the content of protein, mineral and vitamin components in the blood. The most critical periods in the development of foals in immunological and physiological terms, caused by the action of stress factors (weaning, abrupt type change and inadequate feeding, severe cold and infestation with helminths), are 2 months of age, as well as winter, especially the first two months after weaning. In this regard, the use of immunomodulators in the development of vaccine preparations is justified.

The inactivated vaccine made from the Sreptococcus equi H-34 strain with the immunomodulator polyribonate is harmless and nonreactive. When the drug is administered twice with an interval of 14 days, high-intensity immunity is induced in at least 90-100% of immunized laboratory mice and horses. Immunization causes an increase in the phagocytic ability of leukocytes, lysozyme and bactericidal activity of serum, induces the synthesis of precipitating antibodies and an increase in the concentration of immunoglobulins Ig G and Ig M. This indicates the stimulation of cellular and humoral factors of immunity providing its intensity.

In the study of target animals, it was proved that the addition of polyribonate to the vaccine against strangles increases its immunogenicity by 20%. Production tests for 1265 heads of young horses have shown that the vaccine with polyribonate protects up to 97.2% of immunized foals from strangles disease.

Based on the analysis of literature data and research results, polyribonate was chosen as an immunomodulator among possible immunostimulating agents. It has immunoregulatory, anti-stress properties that enhance the body's nonspecific resistance. The works of A.S. Donchenko et al. [12] established the ability of polyribonate to increase the immunogenic properties of the BCG[9] vaccine. The vaccine with polyribonate was approved in 2000 by the Veterinary Department of the Ministry of Agriculture of the Russian Federation and was widely used in the constituent entities of Russia. However, due to the high cost of polyribonate, the termination of its production and the expira-

[6]Regulation on the procedure for examination, testing and registration of veterinary drugs in the Russian Federation, approved on October 3, 1995 by the Veterinary Department of the Ministry of Agriculture and Food of the Russian Federation.

[7]The order of the Ministry of Agriculture of the Russian Federation No. 101 of March 6, 2018 "On Approval of the Rules for Conducting a Preclinical Study of a Medicinal Product for Veterinary Use, a Clinical Study of a Medicinal Product for Veterinary Use, and a Study of the Bioequivalence of a Medicinal Product for Veterinary Use."

[8]Rules for conducting state registration (re-registration) and maintaining the State register of veterinary drugs in the Republic of Kazakhstan, approved by the order of the Minister of Agriculture of the Republic of Kazakhstan dated October 31, 2002, No. 349.

tion of the registration period, this vaccine has been discontinued.

The new inactivated vaccine against horse strangles from the Streptococcus equi strain "H-5/1" contains a culture liquid (fugate) from the Bacillus subtilis TNP-3 bacterial strain as an immunomodulator.

The safety of the vaccine has been established in laboratory animals. The immunogenicity of the vaccine against strangles in laboratory white mice was 90%. Clinical trials carried out on 117 heads of young horses, showed a high efficiency of vaccine prevention (up to 100%). Currently, scientific and technical documentation has been prepared for approval by the Rosselkhoznadzor.

A vaccine "Tabyn" has been developed from the bacterial strain Sreptococcus equi H-34 with the culture liquid of the bacterial strain Bacillus subtilis TNP-3 for the use in the Republic of Kazakhstan. The immunizing ability of the Tabyn vaccine was compared with the previously developed vaccine against strangles with the polyribonate immunomodulator. 20 white mice were taken for each vaccine. Then the animals were inoculated with a daily culture of the pathogenic strain of strangles streptococcus at a dose of $5LD_{50}$. During 10 days of observation, animals from the first group of mice fell ill and 2 animals died, from the second group – 2 animals and in the control group - 17 animals. Immunization with the Tabyn vaccine protects up to 90% of white mice from experimental infection with a pathogenic strain of strangles streptococcus. The experience of challenging vaccinated foals with a pathogenic strain confirmed the high immunogenicity of the inactivated vaccine.

After immunization with the Tabyn vaccine on the 24th day, an increase in the parameters of the immunobiological reactivity of the organism (bactericidal and lysozyme activity of blood serum) was noted in the blood serum. By the end of the observation, an increase in the number of leukocytes with a noticeable increase in their phagocytic activity was recorded in foals immunized with the Tabyn vaccine.

On day 30, the blood of foals immunized with the Tabyn vaccine showed the highest titer of precipitating antibodies (1: 35), which is higher than that of young animals vaccinated with the polyribonate vaccine (1: 20).

The possibility of using the culture liquid of the bacterial strain Bacillus subtilis TNP-3 as a component of the inactivated vaccine against strangles was established. The antiepizootic efficacy of the Tabyn vaccine (vaccine from the Streptococcus equi H-34 strain + culture liquid of the Bacillus subtilis bacterial strain) is not inferior to the strangles vaccine inactivated with the immunomodulator polyribonate. The economic efficiency of the Tabyn vaccine is 2–3 times higher than its analogue.

This method of specific prophylaxis of strangles with the "Tabyn" vaccine of horses is ecologically, economically and epizootologically justified. Based on the research results, scientific and technical documentation was developed, which was approved by the Committee for Veterinary Control and Supervision of the Republic of Kazakhstan. The registration certificate was received (RK-VP-1-3750-18 dated November 27, 2018).

The high efficiency of inactivated vaccines with fugate of the Bacillus subtilis TNP-3 bacterial strain can be explained by the antigenic activity of the vaccine strains and the immunomodulatory component - the culture liquid (fugate) of the Bacillus subtilis TNP-3 bacterial strain. According to the research results, the bacterial strain Bacillus subtilis TNP-3 can induce the synthesis of interferon and stimulate the immunobiological reactivity of the organism, enhance the immunogenicity of inactivated bacterial and viral vaccines [13, 14]. The developed vaccine is not inferior in immunogenicity and even surpasses (up to 90%) the preparations developed in the Netherlands (see footnote 3), the USA [11], Kazakhstan (see footnotes 4, 5), and surpasses in terms of envi-

[9]Donchenko A.S., Alikin Yu.S., Donchenko V.N. Application of biologically active substances as immunomodulators in veterinary medicine and medicine. Literature review / AUAAS. Sib. Br. IEVMSiFE. Novosibirsk, 1989.

ronmental friendliness and harmlessness, since does not contain antibiotics.

The absence of toxicity of the vaccine with the culture liquid from the Bacillus subtilis TNP-3 bacterial strain is consistent with the previously obtained results, which showed the harmlessness of the Sakhabactisubtil preparation, consisting of the Bacillus subtilis TNP-3 and Bacillus subtilis TNP-5 bacterial strains in linear rats and mice in the development of a drug probiotic [15, 16].

CONCLUSION

Methods have been developed to increase the immunogenicity of ecologically safe vaccines against horse strangles. New inactivated vaccines with immunomodulators polyribonate and fugate of the bacterial strain Bacillus subtilis TNP-3 are presented. High immunogenicity of inactivated vaccines (up to 90%) has been established. The most effective are the vaccine "Tabyn" and the drug from the Streptococcus equi strain "H-5/1" with the fugate of the bacterial strain Bacillus subtilis TNP-3, which can be successfully used in Russia and in the countries of Eurasia.

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Информация об авторах

(✉) **Неустроев М.П.,** доктор ветеринарных наук, профессор, главный научный сотрудник; **адрес для переписки:** Россия, 677000, Республика Саха (Якутия), г. Якутск, ул. Бестужева-Марлинского; e-mail: mneyc@mail.ru

Донченко А.С., академик Российской академии наук, доктор ветеринарных наук, научный руководитель

Author information

(✉) **Mikhail P. Neustroev,** Doctor of Science in Veterinary Medicine, Professor, Head Researcher**; address:** 23/1, Bestuzhev-Marlinsky St., Republic of Sakha (Yakutia), Yakutsk, 677000, Russia; e-mail: mneyc@mail.ru

Alexander S. Donchenko, Academician of the Russian Academy of Sciences, Doctor of Science in Veterinary Medicine, Scientific Director

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