

микробтардың деңгейін төмендетіп қана қоймайды, сонымен қатар жараларды тазартады, әсіресе иммундық жүйе мен дененің әртүрлі регенерациялық жүйелеріне инфекцияны тазартуға мүмкіндік береді.

Мақалада ветеринариялық қадағалау объектілерін дезинфекциялау үшін сутегі асқын тотығы негізінде жасалған жаңа дезинфекциялық заттың зертханалық зерттеулерінің нәтижелері берілген.

Препаратты сынау әртүрлі концентрацияларда 10, 15, 20 және 30 минут экспозициямен жүргізілді, ал препараттың шығынын зерттеу үшін зерттелетін объектілер 1 м<sup>2</sup> үшін 0,25 және 0,5 л есептеп қолданылды. Тест-беткейлерді дезинфекциялауда препараттың тиімділігінің критерийі микроорганизмдердің 100% жойылуы болып табылады.

Жүргізілген зертханалық зерттеулер сутегі асқын тотығы негізіндегі препарат тиімді дезинфекциялық құрал болып табылатынын және ветеринарлық қадағалау объектілерінде одан әрі өндірістік сынақтар үшін ұсынылуы мүмкін екенін анықтады.

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## **REACTIVITY, IMMUNOGENICITY AND ADJUVANT PROPERTIES OF AN ANTIPASTEURRELL VACCINE FROM STRAIN A 46 № 576**

### **ANNOTATION**

In our country, pasteurellosis of farm animals and birds is still widespread and causes significant damage to agriculture. An important place among the measures to combat pasteurellosis is occupied by vaccination. For the prevention of pasteurellosis, the use of inactivated sorbed and emulsified vaccines is known, which are not without drawbacks. The experience of industrial production of inactivated vaccines against pasteurellosis dates back several decades, however, until now, the problem of means for inactivating pasteurals and inactivation modes that allow the most complete preservation of the native structure of bacteria continues to be relevant.

The article presents the results of reactogenicity, immunogenicity and adjuvant properties of the anti-tuberculosis vaccine from strain A 46 No. 576.

As a result of the study of the vaccine prepared from pasteurall Chap-1, Kos-1 field isolates and deposited strain A 46 No. 576 after the addition of 6% aluminum oxide hydrate gel after 12 months of the study, the immunological efficacy coefficient was 58%, 69% and 99%, respectively.

As a result of using a 6% aluminum oxide hydrate gel, prolonged tense immunity was achieved. The protective properties of inactivated vaccines with an adjuvant also remained at the level

of 12 months (follow-up period). At the same time, the highest rates were noted in the vaccine from strain A 46 No. 576.

**Key words:** *immunogenicity, reactogenicity, adjuvant, efficacy, vaccine, pasteurella, strain, chickens, mice.*

**Introduction.** The intensification of poultry production and the difficulties of the transition to a market economy have created new problems in ensuring the epizootic well-being of poultry production. In recent years, there has been an increase in the departure of birds from colibacteriosis, salmonellosis, pasteurellosis, Newcastle disease, Marek, Gamboro and some invasive diseases such as ascaridosis and aemia. Immunoprophylaxis often does not have the desired effect due to the presence of mixed infections in bird populations and their hidden currents.

Birds are overwhelmed by field viruses, bacteria and invasive diseases, as well as by the use of a significant number of live vaccines during cultivation.

The viability of chickens and their resistance to diseases of different etiology depend on the state of general physiological reactivity, which is largely determined by maternal protective factors transmitted to chickens transovarially.

According to I.M.Karpun, M.P.Babina [1], initially the chickens are protected by maternal antibodies entering the egg 5-7 days before ovulation and high lysozyme content in egg protein. Furthermore, the egg yolk contains mainly immunoglobulin G (in the qualitative egg it is 36.13 1.598 g/l), in the protein it contains immunoglobulin A (20.43 1.760 g/l), immunoglobulin M (6.62 0.273 g/l) and lysozyme (8.9 10.7 mg/cm<sup>2</sup>). Therefore, the immune status of chickens depends on the quantity in the incubation egg of these non-specific protective factors.

According to B.M.Apatenko [2], it is necessary to use biostimulants in immunodeficiency in order to increase stability, productivity and survival of juveniles.

B.M.Mitushnikov [3] notes that unilateral breeding of birds with an emphasis on high productivity creates the risk of selecting individuals with low natural resistance and high sensitivity to adverse environmental factors, especially in industrial poultry breeding, when there are large numbers of people concentrated in a limited area. The author notes, however, that unlike specific immunity, natural resistance is hereditary and breedable, which helps breeders to create a highly productive and healthy bird. However, this does not mean that specific immunization can be neglected.

Currently, the common test for determining the level of natural resistance is the titration of lysozyme, and the stress of immunity on vaccination is the titer of antibodies in the serum of chickens or with the aid of a biological sample on birds and white mice.

In our country, pasteurellosis of farm animals and birds is still widespread and causes significant damage to agriculture. An important place among the measures to combat pasteurellosis is occupied by vaccination. For the prevention of pasteurellosis, the use of inactivated sorbed and emulsified vaccines is known, which are not without drawbacks. The experience of industrial production of inactivated vaccines against pasteurellosis dates back several decades, however, until now, the problem of means for inactivating pasteurals and inactivation modes that allow the most complete preservation of the native structure of bacteria continues to be relevant.

A method of manufacturing a sorbed anti-pasteurellosis vaccine is known, including suspension cultivation of industrial strains of pasteurella, precipitation of the resulting culture with a 10% solution of aluminum alum and inactivation with 0.16-0.18% formalin for 6 days (auth. svid. USSR No. 94044, 30 N 6, 17.02.1951 p.).

The disadvantage of the vaccine obtained by this method is the short duration of immunity in vaccinated farm animals, while vaccinations are carried out twice in relatively high doses, especially for calves: 50 cm<sup>3</sup> – the first, and the second - 10 cm<sup>3</sup>.

Various methods of inactivation of bacteria (viruses) are also known in the production of vaccines against bacterial (viral) diseases, including exposure to a living pathogen with ethylenimine or its derivatives (German patent No. 2309329, NCI 30 N 6, 29.08.1974.; US patent No. 3318775, NCI 424-89, 09.05.1967; German patent No. 1924303, NCI 30 N 6, 17.12.1970; USSR patent No. 594771, A 61 To 39/12, From 12 No. 7.04 To 07.07.1993). Here, the main disadvantage of using ethylenimine is its high toxicity, and working with it requires the strictest precautions. The disadvantage of production ethylenimine (acetyletthylenimine, ethylenimine, ethylenimine dimer) is

that their concentrations used for inactivation of bacteria (viruses) are not suitable for inactivation of pasteurilla.

The closest to the proposed method in terms of the totality of essential features is a method for manufacturing an emulsifying anti-masterellosis vaccine, including obtaining a suspension of the pathogen, its inactivation with 0.3-0.5% formalin solution and subsequent combination of the inactivated antigen with an oil adjuvant (auth. svid. USSR No. 1839092, A 61 To 39/102, 39/39, 30.12.1993).

Gusev A.A., Rusaleev V.S., Sosnitsky A.I. et al. summarizes the technical result of using the method in increasing the immunogenic activity and specific safety of the drug by preserving the initial properties of pasteurilla protein antigens during inactivation [4].

Common criteria for evaluating the reactogenicity of vaccine preparations are indicators such as the severity of general and local reactions. Preliminary evaluation of vaccine preparations is carried out on laboratory animals, in which, along with thermometry and weighing, a macroscopic examination of internal organs and histological studies of the immune, hematopoietic and nervous systems are carried out at autopsy.

However, these parameters, although necessary, do not give a complete picture of the degree of undesirable effects of vaccine preparations and, as a rule, do not allow predicting and preventing post-vaccination complications.

Methods for determining the immunological safety of vaccines are proposed. It is known that the function of the immune system is not only to ensure the immunity of the body to infection. The immune system ensures the maintenance of immunological homeostasis, carries out immunological supervision, creates tolerance to "its own", prevents the development of malignant neoplasms, reacts to all pathophysiological disorders of the internal environment of the body.

Various immunological reactions have been proposed to control the immunological safety of vaccines. There are two levels of studying the effect of vaccines on the immune system: laboratory-experimental (preclinical) and clinical trial.

A criterion is also proposed for assessing the damaging effect of vaccines on hematological parameters, in general, on hematopoietic stem cells in tests for determining endo- and exocolony formation in the spleen.

The reaction of inhibition of leukocyte migration (RTML), as indicated above, is proposed for the determination of HRT both during the trial of the vaccine at the preclinical stage and in clinical studies.

This method of determining the reactogenicity and immunological safety of vaccines was chosen by the authors as the closest analogue. However, the well-known "Procedure and methods for controlling the safety of vaccines." provides for the use of many well-known methods for analyzing cellular and humoral immunity, is laborious, requires complex special equipment and expensive reagents.

However, the method described by us is fundamentally different from the proposed method in that instead of many (about 20) immunological tests, one integrative test of cell migration of blood leukocytes for microcultures is used, in vitro and the reaction is performed in the presence of Shiga toxin in specially selected dilutions. Along with the inhibition of leukocyte migration, the alternative phenomenon of stimulation of leukocyte migration is taken into account, the detection and severity of which indicates the presence and severity of immunopathological disorders in the body as a result of immunization.

This is achieved by setting up a cell migration test, which allows taking into account not only the inhibition, but also, mainly, the acceleration of cell migration to microcultures, for example, STCM (cell migration screening test) and using a toxin as a resolving antigen Shiga, which detects antigen-specific hypersensitivity of blood leukocytes in pathological disorders in the body.

The method differs in that to determine the reactogenicity of vaccines, to assess the course of post-vaccination reactions and the vaccination process, a test is taken to determine the migration activity of peripheral blood leukocytes on microcultures in vitro, which reflects the complex relationship between T-, B-leukocytes and macrophages, lymphokines, including quantitative, qualitative and functional features of these reaction components at the time of the study. As a resolving antigen, a toxin widely distributed among Shiga bacteria is taken in specially selected

dilutions, revealing early antigen-specific hypersensitivity of blood leukocytes and manifested in the acceleration of their migration activity in immunopathological disorders in the body.

Thus, the determination of MAL (migration activity of leukocytes) to Shiga toxin is a highly sensitive antigen-specific indicator of leukocyte hypersensitivity in immunopathological disorders during vaccination. The enhancement of MAL to Shiga toxin is a test for determining the reactogenicity and immunological safety of vaccine preparations.

The main advantage of the method, especially when using Shiga toxin as a resolving antigen, is its high sensitivity and effectiveness in detecting pathological abnormalities of homeostasis, including immune, during the development and testing (preclinical and clinical) of vaccine preparations. The method differs from the well-known conventional methods for determining reactogenicity and immunological safety by its relative simplicity and accessibility, the possibility of using one indicator of the migration activity of blood leukocytes in an integrative test of the interaction of many immunocompetent cells and their mediators in a microculture in the natural quantitative ratio, the functional state in which they are in the body at the time of the study.

The invention has great economic efficiency, the value of which will depend on the breadth of its use in the above-mentioned areas of scientific, experimental and clinical research [5].

In the "Inactivated emulsified vaccine against avian pasteurellosis" developed by Boradina O.V., the drug aminoethylethylenimine at a concentration of 1% completely inactivates *Pasteurella multocida* bacteria, the oil adjuvant Montanide ISA-70 has moderate reactogenicity when used as part of a vaccine against avian pasteurellosis. The manufactured samples of the anti-tuberculosis vaccine are harmless, have moderate reactogenicity, and during storage at a temperature of 2-8 ° C retain their original immunogenic activity for a year [6].

Shubina E.A. when testing the toxicity, harmlessness and reactogenicity of a large number of adjuvants, it was found that the adjuvant, consisting of 92% of the mineral oil Marcol 52 and 8% of the emulsifier 139, is non-toxic and moderately reactogenic. The emulsion prepared on its basis is stable and has a low viscosity, which makes it easy to administer these drugs to animals.

Experimental series of anti-tuberculosis vaccine with a reduced number of cells were less toxic, weakly reactogenic. The immunogenicity of the experimental series was at the production level with respect to serological variants A and D and higher with respect to serological variants B due to the preservation of surface antigens [7-24].

**Materials and methods of research.** In the light of the above, our task was to study the reactivity and reactivity of the antipasteurellosis vaccine and its immunological and adjuvant properties.

In the process of perfecting the production of liquid inactivated bird pasteurellosis vaccine in 2002 we manufactured 50 liters of this bio preparation (Series 5). According to the developed normative and technical documentation, the stability, sterility, harmlessness, reactivity and immunogenic activity of the prepared vaccine is verified.

The immunological activity of a prepared inactivated bird pasteurellosis vaccine was tested with a biological sample on birds and white mice. In preliminary experiments, the incomplete Freund adjuvant was used to maintain the highly immunogenic properties of the inactive bird pasteurellosis vaccine. Various aluminum hydroxide solutions were used as a depositing agent. And we did that with a 6% aluminum oxide hydrate gel.

The effectiveness of a freshly prepared 12-month pasteurized vaccine with Freund's adjuvant has been studied in 125 chickens aged 5-6 months, vaccinated intramuscularly at a dose of 1.0 cm<sup>3</sup> in the femoral group and 25 chickens in the control group. In parallel, white mice were tested at the same rate as birds, with subcutaneous doses of 0.3 cm<sup>3</sup>. In these experiments the duration of the stress immunity under the action of the adjuvant (lengthener-deponton) after infection with the virulent epizootic culture of pasteurell was tested, as well as the reactivity of the said vaccine in vaccinated birds and white mice during the year (Table 1).

**Results and discussion of the studies.** Table 1 shows that once inoculated with an inactivated pasteurellosis vaccine protected birds from pasteurell infection for 12 months. The control chickens and white mice, after being infected with 18-day broth culture (4LD<sub>50</sub>), became acutely ill with acute pasteurellosis and fell for 24-48 hours. The blood of the heart revealed the original culture of the avian pasteurellosiscausative.

Table 1 – Immune stress in birds and white mice, Inoculated vaccine inactivated from *Pasteurella multocida* A №576 against bird pasteurella

| Deadli-<br>ne<br>hrane-<br>nia vac-<br>cine<br>(per<br>month) | Num-<br>ber<br>microb<br>ial<br>cells<br>in<br>1.0<br>cm <sup>3</sup><br>vac-<br>cines,<br>in<br>mlrd. | Quantity<br>immunized birds<br>and mice at<br>intramuscular<br>dose 1.0 cm <sup>3</sup><br>and 0.3 cm <sup>3</sup><br>subcutaneous.,<br>accordingly |           | Protective activity through:                                                                                                                        |           |               |           |               |           |                       |           |               |           |               |           |                       |           |               |           |               |           |                       |           |  |  |
|---------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------|-----------|---------------|-----------|---------------|-----------|-----------------------|-----------|---------------|-----------|---------------|-----------|-----------------------|-----------|---------------|-----------|---------------|-----------|-----------------------|-----------|--|--|
|                                                               |                                                                                                        |                                                                                                                                                     |           | Number of<br>infected birds<br>and mice at<br>dose<br>1.0 cm <sup>3</sup> in/m<br>and 0.3 cm <sup>3</sup><br>subcutaneous<br>(corresponding<br>to.) |           | 3 months      |           |               |           |                       |           | 6 months      |           |               |           |                       |           | 12 months     |           |               |           |                       |           |  |  |
|                                                               |                                                                                                        |                                                                                                                                                     |           |                                                                                                                                                     |           | Alive         |           | fell          |           | % -<br>of<br>survival |           | Alive         |           | fell          |           | % -<br>of<br>survival |           | Alive         |           | fell          |           | % -<br>of<br>survival |           |  |  |
|                                                               |                                                                                                        |                                                                                                                                                     |           |                                                                                                                                                     |           |               |           |               |           |                       |           |               |           |               |           |                       |           |               |           |               |           |                       |           |  |  |
| P o u l t r y                                                 | M o u s e                                                                                              | P o u l t r y                                                                                                                                       | M o u s e | P o u l t r y                                                                                                                                       | M o u s e | P o u l t r y | M o u s e | P o u l t r y | M o u s e | P o u l t r y         | M o u s e | P o u l t r y | M o u s e | P o u l t r y | M o u s e | P o u l t r y         | M o u s e | P o u l t r y | M o u s e | P o u l t r y | M o u s e | P o u l t r y         | M o u s e |  |  |
| Fresh<br>cooked<br>vaccine                                    | 9-10                                                                                                   | 25                                                                                                                                                  | 25        | 25                                                                                                                                                  | 25        | 5             | 5         | -             | -         | 100                   | 100       | 10            | 10        | -             | -         | 100                   | 100       | 10            | 10        | -             | -         | 100                   | 100       |  |  |
| 3                                                             | 9-10                                                                                                   | 25                                                                                                                                                  | 25        | 25                                                                                                                                                  | 25        | 5             | 5         | -             | -         | 100                   | 100       | 10            | 10        | -             | -         | 100                   | 100       | 10            | 10        | -             | -         | 100                   | 100       |  |  |
| 6                                                             | 9-10                                                                                                   | 25                                                                                                                                                  | 25        | 25                                                                                                                                                  | 25        | 5             | 5         | -             | -         | 100                   | 100       | 10            | 10        | -             | -         | 100                   | 100       | 10            | 10        | -             | -         | 100                   | 100       |  |  |
| 12                                                            | 9-10                                                                                                   | 25                                                                                                                                                  | 25        | 25                                                                                                                                                  | 25        | 5             | 5         | -             | -         | 100                   | 100       | 10            | 10        | -             | -         | 100                   | 100       | 10            | 10        | -             | -         | 100                   | 100       |  |  |
| Control                                                       |                                                                                                        | -                                                                                                                                                   | -         | 25                                                                                                                                                  | 25        | -             | -         | 5             | 5         | 0                     | 0         | -             | -         | 10            | 10        | 0                     | 0         | -             | -         | 10            | 10        | 0                     | 0         |  |  |

Of the 12 field isolates identified and mentioned above, only Chap-1, Cos-1 and the deposited strain A 46 №576 gave S-forms to the colonies. In their cultural, biological properties, they were close, but differed in their pathogenic and virulent properties. Therefore, our task was to check the immunological efficiency of the vaccine prepared from these bacteria after adding 6% aluminum oxide hydrate gel after 3, 6 and 12 months (Table 2).

Table 2 shows that the prepared vaccine from the Chap-1 field isolate containing 6% aluminum oxide hydrate gel had 66% KIE after 3 months, 62% after 6 months and 58% after 12 months. The vaccine from *Pasteurella multocida* A 46 №576 with 6% aluminum oxide hydrate gel was 100% KIE in 3 and 6 months and 99% in 12 months. Vaccination against the Kos-1 strain resulted in a lower percentage of KIE: 78 per cent, 74 per cent and 69 per cent after 12 months, respectively.

Thus, the highest immunological efficacy rate (KIE) of 99% with a prolongation of up to 12 months showed a vaccine from *Pasteurella multocida* A 46 №576, compared to bacteria prepared from Chap-1 and Cos-1. When 6% aluminum oxide hydrate gel was added to inactivated vaccines after 12 months, the CIE was 99%, 58% and 69% respectively.

Table 2 – Protective properties of inactivated vaccine from *Pasteurella multocida* A 46 №576, Chap-1 and Cos-1 strains containing 6%- aluminum oxide hydrate gel

| Strains for inactivated vaccines | Inactivated vaccine 10 ppm. and 6% aluminum oxide hydrate gel, KIE% |          |           | Estimation of the vaccine by the virulence of the original strain |                                        |                                          |                                                      |
|----------------------------------|---------------------------------------------------------------------|----------|-----------|-------------------------------------------------------------------|----------------------------------------|------------------------------------------|------------------------------------------------------|
|                                  |                                                                     |          |           | Quantity microbial cells (in LD <sub>50</sub> )                   | Infective dose                         |                                          |                                                      |
|                                  | 3 months                                                            | 6 months | 12 months |                                                                   | Quantity colonies at 1LD <sub>50</sub> | White mice fell at 1LD <sub>50</sub> (%) | Fell whites mice at the time of LD <sub>50</sub> (%) |
| A 46 № 576                       | 100± 0                                                              | 100± 0   | 99± 0,33  | 4,0                                                               | 9                                      | 50                                       | 100                                                  |
| Chap -1                          | 66±10,2                                                             | 62± 10,4 | 58± 8,2   | 220,0                                                             | 130                                    | 60                                       | 100                                                  |
| Cos -1                           | 78±11,4                                                             | 74± 10,6 | 69± 6,2   | 80,0                                                              | 37                                     | 50                                       | 100                                                  |

**Conclusion.** Prolonged stress immunity was thus achieved by using 6% aluminium oxide hydrate gel. The performance of inactivated adjuvant vaccines also remained at 12 months (observation period). The vaccine of strain A 46 №576 has the highest rates.

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## **ТҮЙІН**

Біздің елде ауылшаруашылық жануарлары мен құстардың пастереллезі әлі де кең таралған және ауыл шаруашылығына айтарлықтай зиян келтіреді. Пастереллезге қарсы шаралар арасында вакцинация маңызды орын алады. Пастереллездің алдын алу үшін белсенді емес сорбцияланған және эмульсияланған вакциналарды қолдану белгілі, олар кемшіліктерсіз емес. Пастереллезге қарсы инактивацияланған вакциналарды өнеркәсіптік өндіру тәжірибесі бірнеше ондаған жылдарға созылады, бірақ осы уақытқа дейін пастереллаларды инактивациялау құралдары мен бактериялардың табиғи құрылымын барынша толық сақтауға мүмкіндік беретін инактивация режимдері мәселесі өзекті болып қала береді.

Мақалада реактогенділік, иммуногенділік нәтижелері және А 46 № 576 штаммынан жасалған пастереллезге қарсы вакцинаның адьювантты қасиеттері келтірілген.

Пастерелл Чап-1, Кос-1 дала изоляттарынан дайындалған вакцинаны және А 46 №576 штаммын зерттеу нәтижесінде 12 айдан кейін 6% гелді алюминий оксиді гидратын қосқаннан кейін иммунологиялық тиімділік коэффициенті сәйкесінше 58%, 69% және 99% құрады.

Алюминий тотығы гидратының 6% гелін пайдалану нәтижесінде ұзаққа созылған қарқынды иммунитетке қол жеткізілді. Адьюванты бар белсенділігі жойылған вакциналардың

протективті қасиеттері де 12 ай деңгейінде қалды (бақылау мерзімі). Сонымен қатар, ең жоғары көрсеткіштер а 46 № 576 штаммынан алынған вакцинада байқалды.

### **РЕЗЮМЕ**

В нашей стране пастереллез сельскохозяйственных животных и птиц по-прежнему широко распространен и наносит значительный ущерб сельскому хозяйству. Важное место среди мер по борьбе с пастереллезом занимает вакцинация. Для профилактики пастереллеза известно применение инаktivированных сорбированных и эмульгированных вакцин, которые не лишены недостатков. Опыт промышленного производства инаktivированных вакцин против пастереллеза насчитывает несколько десятилетий, однако до настоящего времени проблема средств для инаktivации пастерелл и режимов инаktivации, позволяющих наиболее полно сохранить нативную структуру бактерий, продолжает оставаться актуальной.

В статье приведены результаты реактогенности, иммуногенности и адъювантные свойства противопастереллезной вакцины из штамма А 46 № 576.

В результате изучения вакцины, приготовленной из полевых изолятов пастерелл Чап-1, Кос-1 и депонированного штамма А 46 №576 после добавления 6%-ного геля гидрата окиси алюминия через 12 месяцев исследования коэффициент иммунологической эффективности соответственно составил: 58%, 69% и 99%.

В результате использования 6%-го геля гидрата окиси алюминия удалось достигнуть пролонгированный напряженный иммунитет. Протективные свойства инаktivированных вакцин с адъювантом также оставались на уровне 12 месяцев (срок наблюдения). При этом наиболее высокие показатели отмечены у вакцины из штамма А 46 № 576.

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