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ASSESSMENT OF THE IMMUNE RESPONSE IN BULL CALVES TO THE ADMINISTRATION OF POLYANTIGENS AT DIFFERENT DOSES

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Annotation. Immunization of animals is a critical aspect of veterinary practice aimed at enhancing their resistance to infectious diseases. One effective immunization strategy involves the use of polyantigens, which enable the development of immunity against multiple pathogens simultaneously. This study investigates the effect of administered polyantigen doses on antibody levels in young bulls. Understanding the dose-dependent response to antigens can significantly improve vaccine development and the prevention of infectious diseases in livestock. For the experiment, bulls aged 2–3 years were selected and divided into three groups. Each group received different doses of antigens at 7-day intervals over 56 days. The immune response was assessed using an enzyme-linked immunosorbent assay for viral infections and an agglutination reaction for bacterial infections. The results showed that increasing antigen doses led to a rise in antibody titers in the animals' blood, indicating a dose-dependent immune response The highest antibody titers were observed in bulls that received the maximum antigen doses. However, excessively high doses resulted in signs of immune system overload, leading to a decline in antibody activity. This highlights the need to optimize antigen dosage to achieve the most effective immune response. The study demonstrated that administering increasing doses of polyantigens significantly influences antibody levels in the blood of bulls, with an optimal dosage existing for eliciting the most pronounced immune response. It is essential to note that excessively high doses may lead to immune overload, thereby reducing the effectiveness of the immune response. The findings of this study may be helpful in the development of vaccines for livestock and in practical immunization strategies to enhance resistance to infectious diseases.

Keywords: polyantigen, immunization, antibodies, agglutination reaction, antibody titer, vaccination, infectious diseases.

Introduction. Immunoprophylaxis remains one of the most important strategies in the control of infectious diseases in farm animals, particularly under conditions of intensified animal husbandry and increasing epizootic risks [1-3]. At present, particular importance is attached to the development of various probiotic [4-6] and polyvalent immunobiological preparations capable of inducing a stable and targeted immune response against a broad spectrum of pathogens that most commonly cause diseases in calves [7-9]. Polyvalent vaccines and sera enable the immune system to simultaneously recognize and neutralize multiple infectious agents, which is particularly important in the case of polyetiological diseases such as viral-bacterial diarrhea in calves. However, to achieve optimal results, it is essential to refine the parameters for antigen and serum production, as well as to carefully select the composition and dosage of antigens. Both insufficient and excessive antigenic load may reduce the effectiveness of the immune response or lead to undesirable side effects [10].

The present study aims to investigate the dose-dependent development of humoral immunity in bull calves following administration of polyantigenic compositions, with the goal of identifying optimal parameters for the production of highly effective hyperimmune sera intended for the prevention and treatment of infectious diseases. The research utilizes epizootically significant strains of viruses and bacteria, thereby enhancing its practical relevance for veterinary immunology and biotechnology. Furthermore, this work contributes to a deeper understanding of the mechanisms underlying the interaction of multiple antigens within the animal organism when administered concurrently. This has both theoretical and applied significance, as the findings may be used to improve immunization protocols, including hyperimmunization regimens for donor bulls involved in the production of therapeutic sera. The study will also examine the influence of various factors—such as antigen dosage, timing of administration, and individual animal characteristics—on antibody production and the overall immune response. The results of this research may facilitate the development of novel approaches to improving treatment strategies for infectious diseases in cattle. Immunization of animals, particularly livestock, remains a critical component of infectious disease prevention, as such diseases can significantly reduce productivity and may lead to widespread outbreaks within herds. In recent years, increasing attention has been given to the use of polyantigenic formulations, which enable the development of an immune response against multiple infectious agents simultaneously. This is especially relevant for livestock such as cattle, which are at constant risk of infection by a wide range of viral and bacterial pathogens [3, 11, 12].

Polyantigenic vaccines represent an effective means of providing simultaneous protection of animals against multiple diseases, thereby reducing the number of required vaccinations and, consequently, the overall cost of immunization. However, the issue of optimizing antigen dosages in the application of such vaccines remains insufficiently studied. The main challenges lie in the fact that excessively high antigen doses may trigger undesirable reactions, such as immune system overload or the development of autoimmune disorders [13–15]. On the other hand, insufficient antigen doses may fail to elicit an adequate immune response, leaving the animal vulnerable to infections. The effect of antigen dosage on the immune response in animals has been the subject of numerous studies. Some investigations have demonstrated that increasing the antigen dose up to a certain threshold enhances the concentration of antibodies in the bloodstream. However, exceeding this threshold does not necessarily lead to a stronger immune response and may, in some cases, result in adverse side effects. Various studies have indicated that excessively high doses of polyantigens can lead to immune hyperreactivity in animals, which in turn reduces the overall efficacy of the vaccine [14–18].

Despite the considerable number of studies on the dose-dependent immune response to antigen administration, the issues of dose optimization and the evaluation of their impact on the efficacy of immunization in cattle remain incompletely resolved. An important aspect is that modern vaccines often contain multiple antigens, which significantly complicates the study of dose dependence. Precise determination of the optimal dose for each type of antigen within a polyantigenic vaccine can help prevent both excessive immune reactions and insufficient immune activation. Moreover, the immune response is commonly assessed using techniques such as enzyme-linked immunosorbent assay (ELISA) and agglutination reaction, which allow for accurate measurement of antibody titers produced in response to antigen exposure. These methods have gained widespread use due to their high sensitivity and specificity, making them ideal tools for such investigations [19–21].

This study is highly relevant in the context of enhancing the biological safety of livestock production, developing new generations of immunobiological preparations, and implementing scientifically grounded approaches to the immunization of farm animals. Its findings can be applied in the production of polyvalent prophylactic agents against infectious diarrhea in calves and other mixed infections, which is particularly important for regions with high livestock density and unfavorable epizootic conditions. The investigation of the dose-dependent immune response to polyantigen administration in animals represents a significant scientific challenge. The results

obtained may contribute to the development of more effective and safer vaccines for agricultural animals, ultimately leading to improved animal protection and increased productivity in the agro-industrial sector.

Materials and Methods. During the experiment, epizootic isolates of viral and bacterial pathogens obtained from calves suffering from infections of various etiologies were used. The following viral isolates served as antigenic material: infectious bovine rhinotracheitis virus (IBR) – isolate "IBR-1"; bovine viral diarrhea virus (BVDV) – isolate "BVD-2"; parainfluenza-3 virus (PI-3) – isolate "PI-3-1"; rotavirus (RV) – isolate "RV-7"; and coronavirus (CoV) – isolate "CoV-2". Bacterial antigens included the following: the causative agent of colibacillosis – E. coli isolate "Coli-1"; and the causative agent of salmonellosis – *Salmonella dublin* isolate "Dublin-1".

To cultivate the viruses, continuous cell lines were used: BHK-21 (baby hamster kidney cells) and VERO (African green monkey kidney cells). Standard nutrient media and solutions were employed: 0.5% lactalbumin hydrolysate (LAH) in Hank's solution; Eagle's minimum essential medium (MEM) with glutamine (pH 7.5–7.6); synthetic medium 199; microbiological media (MPA, MPB, MPPB, Sabouraud, Kitt-Tarozzi); 0.9% sodium chloride solution (pH 7.2–7.4); 0.1 M phosphate-buffered saline (PBS) and PBS with Tween (PBST), pH 7.2–7.4; and 0.01 M carbonate-bicarbonate buffer (CBB), pH 9.6. Experimental studies were conducted on nine bull calves aged 2–3 years, divided into three groups of three animals each. The animals received polyantigenic preparations in increasing doses. The immunization schedule included seven subcutaneous injections administered in the middle third of the neck on the following days of the experiment: days 1, 21, 28, 35, 42, 49, and 56. The dosage distribution by group was as follows: group 1: 5, 5, 10, 20, 40, 60, 80 ml; group 2: 10, 10, 20, 40, 80, 120, 160 ml; group 3: 20, 20, 40, 80, 160, 240, 320 ml

Antigens were mixed in equal proportions. The protein concentration in each dose ranged from 1.0 to 1.8 mg/cm³. Prior to the first injection, blood samples were collected from all animals to determine baseline antibody levels and to rule out the influence of pre-existing background immunity. The specific immune response was evaluated based on antibody titers using enzyme-linked immunosorbent assay (ELISA) for viral antigens and agglutination reaction (AR) for bacterial antigens. Serum samples were collected on days 55, 63, 70, and 73 of the study.

Results. Analysis of the results revealed a pronounced dose-dependent response of the animals' immune system to the administration of polyantigens. The dynamics of antibody titers in relation to antigen dose are presented in Table 1.

Table 1 – Dynamics of antibody levels in young bulls following administration of different doses of polyantigen antigens

№	Antigen doses, mL	Reciprocal values of the mean antibody titer to the antigen in ELISA and agglutination reaction (M±SE)			
		55 days	63 days	70 days	73 days
1	**2**	**3**	**4**	**5**	**6**
	Bovine Viral Diarrhea Virus (BVDV)				
1	5-80	553±2,45	760±1,45	1048±2,93	935± 4,92
2	10-160	567±3,18	885± 2,18	1121±3,51	922 ±4,83
3	20-320	502±2,87	873±3,95	1095±1,73	921±4,91
4	Control	0	0	0	0
Bovine Parainfluenza-3 Virus (PI-3V or BPI3V)					
1	5-80	528± 3,67	605±3,53	1108±4,21	959± 5,72
2	10-160	615 ±3,94	832± 3,65	1202±4,87	968 ±3,86
3	20-320	635±4,16	797±4,37	1063±3,63	908±5,23
4	Control	0	0	0	0

1	2	3	4	5	6
	Bovine Coronavirus (BCoV)				
1	5-80	564± 3,51	724±2,51	1047±3,74	927± 5,45
2	10-160	625 ±3,67	826±4,74	1174±5,35	1095 ±6,28
3	20-320	678±3,72	865±5,29	1089±4,37	926±5,79
4	Control	0	0	0	0
	Escherichia coli pathogen in calves				
1	5-80	114± 3,61	385±1,83	452±2,46	410± 5,34
2	10-160	268 ±3,82	453±2,36	516±3,57	468 ±3,74
3	20-320	252±3,15	324±2,84	502±3,98	450±4,62
4	Control	0	0	0	0
	Causative agent of salmonellosis in calves (*Salmonella* spp.)				
1	5-80	221± 2,31	296±1,73	426±2,43	320± 5,34
2	10-160	262 ±1,84	326±2,27	558±3,47	423 ±3,83
3	20-320	305±2,45	361±2,76	501±3,94	405±4,83
4	Control	0	0	0	0

The highest levels of specific antibodies were observed in the group of animals that received antigen doses ranging from 10 to 160 ml (Group 2). The peak antibody titers reached the following values: against bovine viral diarrhea virus – 1:1121 ± 3.51; against parainfluenza-3 virus – 1:1202 ± 4.87; against bovine coronavirus – 1:1174 ± 5.35; against *Escherichia coli* – 1:516 ± 3.57; and against *Salmonella dublin* – 1:558 ± 3.47. In the group receiving the highest doses (20–320 ml), antibody titers were lower compared to Group 2, despite an intensified local inflammatory reaction at the injection site. This suggests the presence of an immune stimulation threshold, beyond which an excessive antigen load leads not to enhancement but to suppression of the immune response. In the group with the lowest doses (5–80 ml), antibody levels were significantly lower, indicating insufficient immunogenic stimulation. A clear correlation was established between the volume of administered antigen and the level of specific antibody production, identifying the optimal dosage range (10–160 ml) for future application in hyperimmunization programs for donor bulls and in the development of hyperimmune sera.

Figure 1 illustrates the dynamics of antibody production against each pathogen over the course of the experiment for different antigen doses.

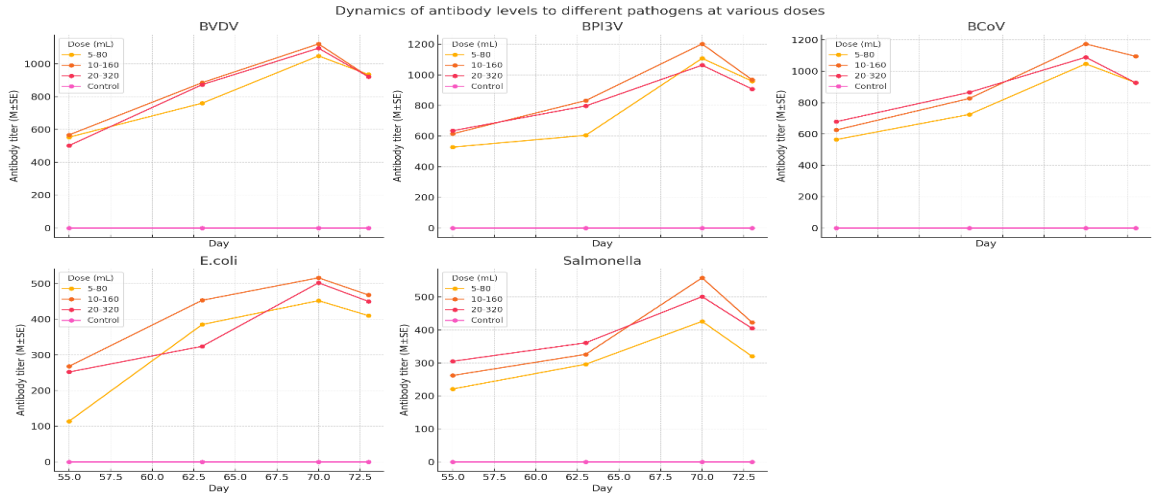

Figure 1 – Dynamics of specific antibody titers in bull calves after administration of different polyantigen doses

A steady increase in antibody titers was observed up to day 70, followed by a slight decline in most groups by day 73. The 10–160 mL dose consistently elicited the highest antibody levels across all antigens, while both lower (5–80 mL) and higher (20–320 mL) doses resulted in reduced humoral responses. The control group maintained baseline values throughout the study.

Figure 2 presents the peak antibody titers recorded for each antigen at different doses. The data clearly show that the optimal immune response was achieved with the 10–160 mL dose, which outperformed both lower and higher doses in most cases. This visual representation supports the conclusion that there is an immune stimulation threshold, beyond which excessive antigen load may suppress antibody production rather than enhance it.

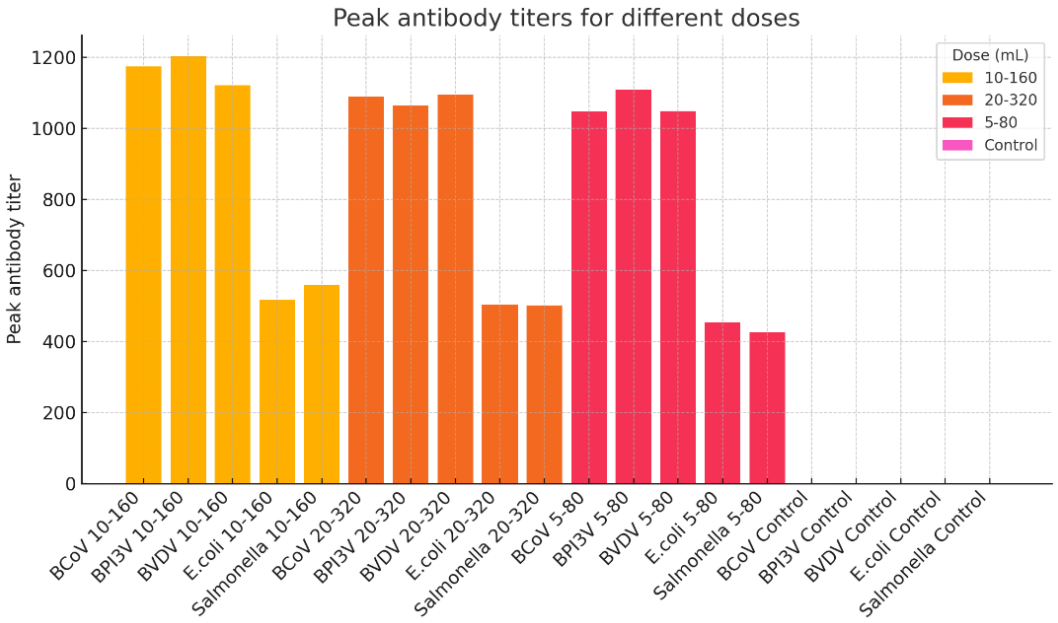

Figure 2 – Peak antibody titers against viral and bacterial pathogens at different antigen doses

The conducted study demonstrated that immunization of bull calves with polyantigens induced a pronounced accumulation of specific antibodies against a range of viral and bacterial pathogens, with peak titers recorded on day 70 of the experiment. The most effective antigen dose was within the range of 10–160 ml, which elicited the most robust humoral response: antibody titers reached 1:1121 ± 3.51 for bovine viral diarrhea virus, 1:1202 ± 4.87 for parainfluenza-3 virus, 1:1174 ± 5.35 for bovine coronavirus, 1:516 ± 3.57 for *E. coli*, and 1:558 ± 3.47 for *Salmonella dublin*. With increased doses of 20–320 ml, antibody levels were lower despite a stronger local inflammatory reaction, indicating antigen excess and its potential reactogenicity. In the group receiving 5–80 ml, antibody production was less pronounced, pointing to insufficient immune stimulation. These findings highlight the critical importance of antigen dosage when using polyantigenic formulations. The in vivo experiment results have high practical significance for veterinary immunology, as they provide deeper insight into the mechanisms of immune response to multicomponent antigenic preparations. Studying antigen interactions within polyantigenic compositions opens new prospects for the development of hyperimmune sera, particularly for the prevention and treatment of infectious diarrhea in calves. The research established that a carefully selected dosing scheme and immunization intervals contribute to the formation of a stable and specific immune response—an essential requirement in the production of hyperimmune sera from donor bulls. Furthermore, the study showed that both underdosing and overdosing of antigens may reduce the efficiency of the humoral response, emphasizing the necessity for individualized dosage selection and immunization protocols. These results can be applied in the development of more effective prophylactic and therapeutic agents for animals, as well as in the improvement of current

vaccination methods in agriculture.

In recent decades, there has been growing interest in the development and application of polyantigenic vaccines for the immunization of farm animals. Polyantigens are combinations of antigens targeting multiple disease-causing agents. This vaccination strategy improves preventive efficacy and reduces the number of required immunizations. However, despite the clear advantages of polyantigenic vaccines, the issue of optimal antigen dosing remains unresolved. The dose-dependent immune response—i.e., the variation in immune system activity depending on the administered antigen dose—is a key factor in vaccine development. It is essential to consider that both insufficient and excessive antigen doses may reduce the effectiveness of vaccination. High doses can overload the immune system and lead to side effects such as inflammatory reactions and autoimmune disorders. On the other hand, inadequate antigen dosing may fail to provide sufficient protection against infection. Therefore, accurately determining the optimal antigen dose that promotes the most effective immune response is critical.

In this study, using 2- to 3-year-old bull calves as a model, the effect of various polyantigen doses on antibody levels will be analyzed to establish a dose-dependent relationship of the immune response. The findings of this research are of great importance to veterinary practice, as they will help determine the optimal polyantigen dose for immunizing farm animals. A well-selected antigen dosage ensures maximum vaccine efficacy while minimizing the risk of side effects, such as immune system overload. These results may contribute to the development of more effective vaccines and the optimization of immunization programs, ultimately improving animal protection against infectious diseases and reducing economic losses in agriculture.

In future research, it will be important to further clarify dose dependence for other types of antigens, as well as for different age and breed groups of animals. This will enable the creation of individualized vaccination strategies, contributing to improved herd health and productivity. The data obtained may be applied in the development and implementation of effective cattle vaccination protocols aimed at reducing morbidity and increasing overall biosecurity in livestock production. These results are particularly relevant under conditions of elevated epizootic risk and the need for comprehensive protection against a wide range of pathogens.

Further studies are required to determine the optimal polyantigen doses considering the animal's age, breed, and physiological status. It is also important to explore the potential inclusion of additional immunomodulators or adjuvants to enhance the specific immune response without risking immune system overload. Consequently, immunization of bull calves with polyantigens in increasing doses represents an effective method for stimulating a specific immune response. However, achieving the best results requires selecting a dosage that provides maximum immune protection without adverse effects on the animals' health.

Conclusion It has been demonstrated that the conducted study confirmed a direct relationship between the level of specific immune response in 2–3-year-old bull calves and the dose of administered polyantigen. An increase in dosage was accompanied by a rise in antibody titers, indicating dose-dependent activation of the immune system. It was established that the most pronounced and stable immune response was observed with the administration of medium to high antigen doses in the second group. At the same time, animals in the third group, which received the highest doses, showed signs of potential immune system overload, highlighting the need for careful dose optimization. The use of enzyme-linked immunosorbent assay (ELISA) and the agglutination reaction (AR) enabled the acquisition of objective and reproducible data on the state of humoral immunity. These methods proved effective for monitoring antibody production over time. The study revealed the promising potential of polyantigen use, as the results confirmed the high efficacy of polyantigens in eliciting a robust immune response, provided that the dosage is properly selected. This makes polyantigenic preparations a promising tool for the mass immunization of farm animals.

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БҰҚАЛАРҒА ӘРТҮРЛІ ДОЗАДА ПОЛИАНТИГЕНДЕР ЕНГІЗУ КЕЗІНДЕГІ ИММУНДЫҚ ЖАУАПТЫ БАҒАЛАУ

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Аңдатпа. Жануарларды иммундандыру – олардың жұқпалы ауруларға төзімділігін арттыруға бағытталған ветеринариялық практиканың маңызды аспектісі болып табылады. Иммундандырудың тиімді әдістерінің бірі – полиантигендерді қолдану, бұл бір мезгілде бірнеше қоздырғышқа қарсы иммунитет қалыптастыруға мүмкіндік береді. Осы зерттеуде бұқаларға енгізілген полиантигендердің әртүрлі дозаларының антидене деңгейіне әсері талданды. Антигенге дозалық тәуелді жауапты түсіну ауыл шаруашылығы жануарларына арналған вакциналар мен жұқпалы аурулардың алдын алу әдістерін әзірлеуді едәуір жақсартуға мүмкіндік береді. Эксперимент үшін жасы 2–3 жастағы бұқалар таңдалып, олар үш топқа бөлінді. Әр топқа антигендер 7 күндік интервалмен, 56 күн бойы әртүрлі дозаларда енгізілді. Иммундық жауапты бағалау үшін вирус инфекцияларына қатысты – иммунферменттік талдау, ал бактериялық инфекцияларға қатысты – агглютинация реакциясы қолданылды. Зерттеу нәтижелері көрсеткендей, антиген дозасы артқан сайын жануарлардың қанындағы антидене титрі де жоғарылады, бұл иммундық жауаптың дозалық тәуелділігін дәлелдейді. Ең жоғарғы антидене титрі максималды дозада антиген енгізілген бұқаларда байқалды. Алайда тым жоғары дозалар қолданылған жағдайларда иммундық жүйенің шамадан тыс жүктелуі белгілері тіркеліп, нәтижесінде антиденелердің белсенділігі төмендеген. Бұл жағдай антиген дозасын оңтайландыру қажеттілігін растайды, себебі бұл ең тиімді иммундық жауапқа қол жеткізудің маңызды шарты болып табылады. Зерттеу барысында полиантигендерді біртіндеп жоғарылатылған дозаларда енгізу бұқалардың қанындағы антидене деңгейіне елеулі әсер ететіні анықталды, әрі тиімді иммундық жауап алу үшін белгілі бір оңтайлы дозаның болуы қажет екендігі көрсетілді. Айта кету керек, тым жоғары дозалар иммундық жүйенің шамадан тыс жүктелуіне алып келіп, иммундық жауаптың тиімділігін төмендетуі мүмкін. Зерттеу нәтижелері ауыл шаруашылығы жануарларына арналған вакциналарды әзірлеу және оларды жұқпалы ауруларға қарсы иммундандыру тәжірибесінде пайдалы болуы мүмкін.

Тірек сөздер: полиантиген, иммунизация, бұқалар, антиденелер, агглютинация реакциясы, антидене титрі, вакцинация, жұқпалы аурулар.

ОЦЕНКА ИММУННОГО ОТВЕТА БЫЧКОВ НА ВВЕДЕНИЕ ПОЛИАНТИГЕНОВ В РАЗЛИЧНЫХ ДОЗАХ

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Аннотация. Иммунизация животных является важным аспектом ветеринарной практики, направленным на повышение их устойчивости к инфекционным заболеваниям. Одним из эффективных методов иммунизации является использование полиантигенов, которые позволяют развить иммунитет против нескольких возбудителей одновременно. В данном исследовании проводится анализ влияния различных доз вводимых полиантигенов на уровень антител у бычков. Понимание дозозависимого ответа на антиген может существенно улучшить разработку вакцин и методов профилактики инфекционных заболеваний у сельскохозяйственных животных. Для эксперимента были отобраны бычки возрастом 2-3 года, которые были разделены на три группы. Каждой группе вводили антиген в разных дозах с интервалом в 7 дней в течение 56 дней. Изучение иммунного ответа проводилось с помощью иммуноферментного анализа для вирусных инфекций и реакции агглютинации для бактериальных инфекций. Результаты показали, что с увеличением дозы антигенов наблюдается рост титра антител в крови животных, что свидетельствует о дозозависимом иммунном ответе. Наибольший прирост титра антител был зафиксирован у бычков, которым вводились антиген в максимальных дозах. Однако при слишком высоких дозах наблюдались признаки перегрузки иммунной системы, что привело к снижению активности антител. Это подтверждает необходимость оптимизации дозы антигена для достижения наиболее эффективного иммунного ответа. Исследование продемонстрировало, что введение полиантигенов в повышающих дозах оказывает значительное влияние на уровень антител в крови бычков, при этом существует оптимальная дозировка для достижения наиболее выраженного иммунного ответа. Важно учитывать, что слишком большие дозы могут привести к иммунной перегрузке и снижению эффективности иммунного ответа. Результаты исследования могут быть полезными при разработке вакцин для сельскохозяйственных животных и в практике их иммунизации для повышения устойчивости к инфекционным заболеваниям.

Ключевые слова: полиантиген, иммунизация, бычки, антитела, реакция агглютинации, титр антител, вакцинация, инфекционные заболевания.