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Immune status improvement in piglets through the use of interferon-containing products during specific prevention of porcine pleuropneumonia

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SUMMARY

Specific prevention is one of the most effective methods for the control of infectious diseases causing considerable economic damage to commercial pig farms, among which is porcine pleuropneumonia. In order to improve the effectiveness of preventive vaccination, various immunomodulators that differ in their origin and mechanism of action are used. The paper presents the results of the study of the effect of such products as biferon-S and prostimul containing species-specific recombinant interferons on the immune status of piglets during specific prevention of porcine pleuropneumonia. Tests were carried out in clinically healthy 30–35-day-old piglets immunized with Ingelvac® APPX vaccine (Boehringer Ingelheim Vetmedica GmbH, Germany). It was found that the use of biferon-S and prostimul together with the vaccine administration is accompanied by immune status improvement in the animals, which is manifested as an increase, in comparison with vaccinated animals that received no interferon-containing products (base case), in serum levels of γ-globulins – by 34.6 and 53.7% (in case of prostimul and β-globulins – by 10.1%), total immunoglobulins – by 32.8 and 37.8%, large circulating immune complexes – by 37.5 and 52.6%, a less significant increase in the levels of small complexes and, as a result, pathogenicity coefficient reduction by 5.4 and 12.4%, respectively. Tests for post-vaccination immunity levels in piglets showed a 3.8-fold increase in the levels of specific antibodies against the antigen of porcine pleuropneumonia agent, and in case of the vaccine administration in combination with biferon-S and prostimul – a 4.0-fold and 4.9-fold increase, respectively. The use of prostimul was accompanied by a more considerable improvement of immune status in the piglets, and this is attributable to the fact that vitamins A, E and C, which have antioxidant properties and improve the effectiveness of interferons, natural resistance and specific immunity, are included in its composition in addition to recombinant type 1 cytokine.

Keywords: porcine pleuropneumonia, piglets, specific prevention, vaccine, immune status, biferon-S, prostimul, vitamins A, E and C

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Повышение иммунного статуса у поросят интерферонсодержащими препаратами при специфической профилактике актинобациллезной плевропневмонии

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РЕЗЮМЕ

Специфическая профилактика является одним из наиболее эффективных методов борьбы с инфекционными заболеваниями, наносящими значительный экономический ущерб промышленным свиноводческим хозяйствам, к числу которых относится актинобациллезная плевропневмония свиней. Для повышения эффективности вакцинопрофилактики применяются различные иммуномодулирующие средства, отличающиеся по происхождению и механизму действия. В статье представлены результаты изучения влияния препаратов биферона-С и простимула, содержащих видоспецифичные рекомбинантные интерфероны, на иммунный статус поросят при специфической профилактике актинобациллезной плевропневмонии. Исследования проведены на клинически здоровых поросятах 30–35-суточного возраста, иммунизированных вакциной Ingelvac® APPX (Boehringer Ingelheim Vetmedica GmbH, Германия). Установлено, что применение биферона-С и простимула одновременно с введением вакцины сопровождается повышением иммунного статуса животных, проявляющимся увеличением по сравнению с базовым вариантом содержания в сыворотке крови γ-глобулинов на 34,6 и 53,7% (при назначении простимула и β-глобулинов – на 10,1%), общих иммуноглобулинов – на 32,8 и 37,8%, крупных циркулирующих иммунных комплексов – на 37,5 и 52,6%, менее значимым увеличением комплексов мелких размеров и снижением в результате этого коэффициента патогенности на 5,4 и 12,4% соответственно. Исследование напряженности поствакцинального иммунитета у поросят показало, что уровень специфических антител к антигену возбудителя актинобациллезной плевропневмонии повысился в 3,8 раза, а при введении вакцины в сочетании с бифероном-С и простимулом – в 4,0 и 4,9 раза соответственно. Применение простимула сопровождалось более существенным повышением иммунного статуса у поросят, обусловленным наличием в его составе кроме рекомбинантного цитокина первого типа витаминов А, Е и С, обладающих антиоксидантными свойствами, повышающих эффективность интерферонов, естественную резистентность и специфический иммунитет.

Ключевые слова: актинобациллезная плевропневмония, поросята, специфическая профилактика, вакцина, иммунный статус, биферон-С, простимул, витамины А, Е и С

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INTRODUCTION

Porcine pleuropneumonia caused by *Actinobacillus pleuropneumoniae* has high economic and epidemiological significance for commercial pig farms [1–4]. *A. pleuropneumoniae,* one of the most important respiratory bacterial pathogens of pigs, can cause monoinfection and, in association with influenza, porcine reproductive and respiratory syndrome viruses and mycoplasmas, plays the leading role in the development of the complex of porcine respiratory diseases [4, 5]. Specific prevention of porcine pleuropneumonia is the main method for the infection control [4].

Routine vaccination against porcine pleuropneumonia carried out in piglets aged 3 to 4 weeks coincides with the late suckling period when, against the background of physiological immunodeficiency or stress response to weaning, lipid peroxidation activation and a decline in antioxidant defence and the levels of humoral and cellular factors of non-specific resistance occur [6, 7].

Immunodeficiency recorded before vaccination negatively affects the development of specific immunity; ligfol, ligaverin, selekor having adaptogenic and immunomodulatory properties were tested and found to contribute to specific immunity improvement in sows and piglets immunized against escherichiosis and salmonellosis [8, 9].

The following immunomodulators used during vaccination are effective for increasing antibody levels and antibody persistence: salmozan, glicopin, immunofan, roncoleukin, polyribotan, etc. [10].

When studying the possibility of using recombinant cytokines as adjuvants during vaccination, A. S. Simbirtsev et al. found that interleukin-1 used during immunization against viral hepatitis B has the highest adjuvant activity: it neutralizes the negative effect of a biological on the functional activity of neutrophils and contributes to the increase in specific antibody titers [11].

Biferon-S containing recombinant porcine *α*- and *γ*-interferons was found to have a positive impact on specific immunity development when used during vaccination against porcine circovirus disease [12], colibacteriosis [13], circovirus infection and mycoplasmosis [14].

The study is aimed at investigating the effect of biferon-S and prostimul on the immune status of piglets during specific prevention of porcine pleuropneumonia.

MATERIALS AND METHODS

The tests were carried out in 2020 in an industrial pig production complex in the Tambov Oblast that had been porcine pleuropneumonia infected since 2016 due to the introduction of replacement gilts being *A. pleuropneumoniae* serotype 2 carriers. The animals for the tests were selected from the production group of piglets ($n = 1300$) moved to the nursery at the same time. Each animal's body weight was 9.0 ± 0.94 kg. The tests were carried out in 150 clinically healthy 30–35-day old piglets without distinction as to their sex; 3 groups, each comprising 50 animals, were formed. Control group animals (base case) were immunized with Ingelvac® APPX vaccine (Boehringer Ingelheim Vetmedica GmbH, Germany) administered twice at a 14-day interval at a dose of 2 ml; test group 1 piglets received biferon-S at a dose of 0.1 ml/kg as an adjuvant simultaneously with the vaccine administration, test group 2 piglets received the same dose of prostimul according to the similar scheme.

Ingelvac® APPX vaccine is manufactured using *A. pleuropneumoniae* serotype 1, 2, 3, 4, 5, 7 cultures, ApxI, ApxII, ApxIII toxoids inactivated with formalin (0.2% by volume) with addition of aluminum hydroxide (0.5% by volume) and isotonic sodium chloride solution.

Biferon-S contains porcine recombinant *α*- and *γ*-interferons with total antiviral activity of at least 1.0×10^4 $TCID_{50}/cm^3$ in the solvent supplemented with stabilizing agents.

Prostimul contains a recombinant cytokine as an active ingredient, ascorbic acid, vitamins A, E and C, sodium benzoate, sodium sulfite, ethylenediaminetetraacetic acid, non-ionogenic solvent, glycerin and water.

Biferon-S and prostimul are manufactured by OOO "Scientific and Production Centre "ProBioTekh" (the Republic of Belarus).

The animals were clinically observed for 2 months.

Blood samples were collected from piglets ($n = 6$) of each group before the administration of the vaccine and the above-mentioned products (baseline), as well as 14 days after their second administration and tested at the Research Centre of the FSBSI "ARVRIPP&T".

Sera from the piglets were tested for total protein, protein fractions, circulating immune complexes (CICs): large (3%), medium (3.5%) and small (4%) according to the Methodical recommendations for immune status evaluation and improvement in animals [15], total immunoglobulins (Ig) [16], CIC pathogenicity coefficient (C4/C3 ratio) [17]. Titers of antibodies against *A. pleuropneumoniae* were determined with enzyme-linked immunosorbent assay (ELISA) with subsequent reading of results with a Uniplan-TM spectrophotometer according to the instruction for ID Screen® APP Screening Indirect test kit (France).

The statistical analysis of the findings was performed using Statistica v 6.1 software; the significance of differences was estimated using Student's *t*-criterion.

RESULTS AND DISCUSSION

The piglets' clinical status during the experiment was within the norm.

Baseline biochemical tests showed no significant differences in the levels of total protein, *β*-globulin, *γ*-globulin and total immunoglobulins in the piglets of both test groups (Table 1).

Control group piglets demonstrated lower albumin levels than test group piglets, the lowest CIC pathogenicity coefficient and higher *α*-globulin and large CIC levels.

Test group 1 piglets demonstrated lower levels of large and medium CICs than test group 2 and control group animals and, consequently, the highest pathogenicity coefficient.

With advancing age, the biochemical status of the animals underwent changes influenced by vaccination and interferon-containing products (Table 1).

Total protein content increased by 16.2% in control group piglets, by 12.7% – in test group 1 piglets,

Table 1
Biochemical blood parameters in piglets

Parameters	Groups		
	Control group	Test group 1	Test group 2
Before vaccination			
Protein, g/l	49.50 ± 1.49	51.10 ± 1.45	49.90 ± 0.65
Albumins, %	47.90 ± 1.34	52.00 ± 2.93	54.40 ± 0.79
Globulins: %			
α	16.90 ± 0.94	13.10 ± 1.26	13.30 ± 0.45
β	21.90 ± 0.67	21.30 ± 0.95	19.90 ± 0.99
γ	13.30 ± 0.86	13.60 ± 1.09	12.30 ± 0.45
Total immunoglobulins, mg/ml	25.60 ± 1.23	23.80 ± 1.41	22.50 ± 0.68
CICs, 3.5% mg/ml	0.370 ± 0.029	0.26 ± 0.04	0.430 ± 0.037
CICs, 3.0% mg/ml	0.280 ± 0.001	0.16 ± 0.01	0.19 ± 0.02
CICs, 4.0% mg/ml	0.37 ± 0.03	0.37 ± 0.02	0.43 ± 0.06
C4/C3	1.32 ± 0.14	2.210 ± 0.009	2.09 ± 0.18
After vaccination			
Protein, g/l	57.50 ± 0.81**	57.60 ± 1.23**	59.10 ± 1.43***
Albumins, %	46.10 ± 0.88	48.80 ± 1.37	47.60 ± 0.97***
Globulins: %			
α	15.20 ± 0.53	11.50 ± 0.45	11.80 ± 0.73
β	21.90 ± 0.46	21.40 ± 0.57	21.90 ± 0.62
γ	16.90 ± 0.84*	18.30 ± 0.83**	18.90 ± 0.52***
Total immunoglobulins, mg/ml	30.90 ± 0.78**	31.60 ± 0.70***	31.00 ± 0.69***
CICs, 3.5% mg/ml	0.290 ± 0.023*	0.230 ± 0.027	0.240 ± 0.036**
CICs, 3.0% mg/ml	0.36 ± 0.02*	0.22 ± 0.02*	0.29 ± 0.01**
CICs, 4.0% mg/ml	0.59 ± 0.03***	0.50 ± 0.02**	0.53 ± 0.02
C4/C3	1.76 ± 0.11*	2.09 ± 0.15	1.83 ± 0.09

* $p < 0.05$, ** $p < 0.005$, *** $p < 0.0005$ – against baseline values.

by 18.4% – test group 2 piglets; this is indicative of hepatic protein synthesis activation, especially in the animals that received the vaccine in combination with prostimul containing vitamins A, E and C that have antioxidant properties.

Significant changes were observed in the proteinogram in the vaccinated animals, especially in those that had received the vaccine in combination with biferon-S and prostimul. Control group animals demonstrated a decrease in the levels of albumins by 3.8% and *α*-globulins – by 10.1%, and an increase in the levels of *γ*-globulins, which contain predominantly antibodies, by 27.1%. Test group 1 and 2 piglets demonstrated a decrease in the levels of albumins by 6.2 and 12.5%, of *α*-globulins – by 12.2 and 11.3%, and an increase in the levels of *γ*-globulins by 34.6 and 53.7%, respectively. The levels of *β*-globulins containing complement components and a part of immunoglobulins in control group and test group 1 animals practically did not differ from baseline values; the levels of *β*-globulins in piglets immunized in combination with prostimul administration increased by 10.1%.

The changes observed in the proteinogram in the vaccinated animals and in the animals immunized with simultaneous administration of interferon-based products are indicative of immune system transformation which is the most pronounced in case of the vaccine administration in combination with prostimul and manifested as a significant increase in the levels of *γ*-globulins and an increase in the level of *β*-globulins responsible for humoral protection.

The vaccinated animals of the control group demonstrated an increase in total immunoglobulin levels by 20.7%, in case of vaccine administration in combination with biferon-S and prostimul – by 32.8 and 37.8%, respectively, and this is indicative of a significant enhancement of humoral protection in the piglets, especially when specific prevention is carried out in combination with the use of interferon-containing products, mainly prostimul.

The positive effect of immunomodulators on the immune status of animals vaccinated against porcine pleuropneumonia is demonstrated by the results of tests of circulating immune complexes that are the product of antigen, antibody and complement reactions and play an important role in the maintenance of homeostasis in the body.

In particular, control group piglets demonstrated a significant increase in the levels of small CICs – by 59.5%, of large CICs – by 28.6% and a decrease in the levels of medium CICs by 21.6% in comparison with baseline values. At the same time, CIC pathogenicity coefficient (C4/C3 ratio) increased by 33.3%, and this is probably due to a high antigen load in piglets.

Table 2
Specific immunity parameters in piglets

Parameters	Titres of antibodies against *A. pleuropneumoniae*		
	control group	test group 1	test group 2
Before vaccination	11.90 ± 2.10	12.11 ± 2.96	9.40 ± 2.23
After vaccination	45.10 ± 3.82*	48.90 ± 2.49*	46.10 ± 2.21*

* $p < 0.0001$ – against baseline values.

The animals immunized in combination with the use of biferon-S demonstrated a more significant, as compared with control group animals, increase in the levels of large CICs (by 37.5%), a less pronounced increase in the levels of small CICs (by 35.1%) and a decrease in the levels of medium CICs – by 11.5%; at the same time, their pathogenicity coefficient decreased by 5.4% in comparison with baseline values.

In test group 2 piglets subjected to vaccination with simultaneous administration of prostimul, large CIC levels increased by 52.6% and were significantly higher than those in test group 1 and control group animals, their medium CIC levels decreased by 44.2%, an increase in small CIC levels (by 23.3%) was less significant, and that resulted in pathogenicity coefficient reduction by 12.4%.

Serological test results presented in Table 2 are indicative of humoral protection improvement in the piglets after vaccination, especially in combination with administration of interferon-based products.

It was found that titers of specific antibodies against *A. pleuropneumoniae* antigen in control group piglets increased by a factor of 3.8 in comparison with baseline values, and when the vaccine was administered in combination with biferon-S and prostimul – by a factor of 4.0 and 4.9, respectively.

Thus, the use of interferon-containing products during specific prevention of porcine pleuroneumonia is accompanied by immune status improvement in piglets due to recombinant porcine interferons and a number of excipients included in their composition.

Alpha interferon contained in biferon-S has immunomodulatory properties: it increases the activity of natural killer cells, T helpers, phagocytes, the intensity of B lymphocyte differentiation [18, 19]. Gamma interferon has a pronounced immunomodulatory effect, activating macrophages, cytotoxic T lymphocytes, natural killer cells [18, 20, 21].

Alpha and beta interferons contained in prostimul have immunoregulatory effect: they modulate antibody production, enhance cellular cytotoxity of T lymphocytes and natural killer cells, inhibit the proliferation of lymphocytes, T-cell suppression and facilitate preferential differentiation of T helpers into Th1 lymphocytes [22].

Vitamins A, E and C contained in prostimul improve the antioxidant status of the body by restraining accumulation of lipid peroxidation products [23, 24], have antioxydant effect on immune system cells by protecting them from oxygen-dependent types of apoptosis [25, 26], as well as potentiate the effectiveness of inteferons [23]; as a result, prostimul can do more, than biferon-S, to improve the immune status of piglets during specific prevention of porcine pleuropneumonia.

CONCLUSION

The study showed that the use of biferon-S and prostimul together with administration of the vaccine against porcine pleuropneumonia is accompanied by immune status improvement in piglets, which is manifested as an increase, in comparison with vaccinated animals that received no interferon-containing products (base case), in serum levels of *γ*-globulins, and when prostimul and *β*-globulins were used – of total immunoglobulins, specific antibodies against *A. pleuropneumoniae* antigen,

CIC pathogenicity reduction. The use of prostimul that contains vitamins A, E and C having antioxidant properties potentiates the effectiveness of interferons, improves natural resistance and specific immunity.

REFERENCES

1. Sidorov M. A., Skorodumov D. I. Haemophilus infections in animals [Gemofilezy zhivotnyh]. M.: Agropromizdat; 1986. 174 p. (in Russian)

2. Lebedev N. V., Potekhin A. V, Frolovtseva A. A. Porcine *Actinobacillus pleuropneumnia*: diagnosis prophylaxis and control measures. *Veterinary Science Today*. 2012; 3 (3): 24–30. eLIBRARY ID: 22480810. (in Russian)

3. Potekhin A. V., Kovalishin V. F. *Actinobacilosis pleuropneumonia* (APP): diagnosis, prevention and control measures. *Veterinary Science Today*. 2014; 3 (10): 18–29. eLIBRARY ID: 22445539.

4. Gottschalk M., Broes A. Actinobacillosis. *In: Diseases of Swine*. Eds. J. J. Zimmerman, L. A. Karriker, A. Ramirez, K. J. Schwartz, G. W. Stevenson, J. Zhang. 11th ed. New York: John Wiley&Sons; 2019; Chapter 48: 749–766. DOI: 10.1002/9781119350927.ch48.

5. Orlyankin B. G., Aliper T. I., Mishin A. M. Porcine infectious respiratory diseases: etiology, diagnosis and prevention [Infekcionnye respiratornye bolezni svinej: etiologiya, diagnostika i profilaktika]. *Pig-Breeding*. 2010; 3: 67–69. eLIBRARY ID: 17711236. (in Russian)

6. Retsky M. I., Buzlama V. S., Shakhov A. G. The role of antioxidant status in adaptive heterogenicity and immune resistance in animals [Znachenie antioksidantnogo statusa v adaptivnoj geterogennosti i immunologicheskoj rezistentnosti zhivotnyh]. *Veterinarnaya patologiya*. 2003; 2 (6): 63–65. eLIBRARY ID: 9164252. (in Russian)

7. Shakhov A. G., Sashnina L. Yu., Vladimirova Yu. Yu., Tarakanova K. V. Haemomorphological, biochemical and immune status in piglets under stress, caused by weaning from sows and crossover to nursery. *Issues of Legal Regulation in Veterinary Medicine*. 2019; 3: 182–186. DOI: 10.17238/issn2072-6023.2019.3.182. (in Russian)

8. Nikolaeva O. N., Andreeva A. V. The dynamics of indicators of humoral immunity at prevention of associative infections of young growth of farm animals. *Russian Electronic Scientific Journal*. 2014; 8 (14): 186–193. eLIBRARY ID: 26494610. (in Russian)

9. Shakhov A. G., Retsky M. I., Masyanov Yu. N., Brigadirov Yu. N., Zaiko A. M. The use of immunomodulators and antioxidants to improve the effectiveness of immunization in pigs [Ispol'zovanie immunomodulyatorov i antioksidantov dlya povysheniya effektivnosti immunizacii svinej]. *Topical Issues of Animal Infectious Pathology and Immunology*: *Proceedings of the International Research-to-Practice Conference (May 16–17, 2006)*. M.: Izograf; 2006; 522–525. eLIBRARY ID: 41447034. (in Russian)

10. Deyeva A. V., Mekhdikhanov G. G., Sokolov V. D., Belousova R. V. The use of immunomodulators in production animals [Primenenie immunomodulyatorov produktivnym zhivotnym]. *Veterinariya*. 2008; 6: 8–12. eLIBRARY ID: 11149494. (in Russian)

11. Simbirtsev A. S., Petrov A. V., Pigareva N. V., Nikolaev A. T. New opportunities for using recombinant cytokines as adjuvants for vaccination. *Biopreparats (Biopharmaceuticals)*. 2011; 1 (41): 16–20. eLIBRARY ID: 20369106. (in Russian)

12. Kudin K. V., Kudina I. V., Prokulevich V. A. The effect of recombinant cytokine-based product Biferon-S on the growth, development and immunization of piglets against PCV-2 [Vliyanie preparata «Biferon-S» na osnove rekombinantnyh citokinov na rost, razvitie i immunizaciyu porosyat k CVS-2]. *Biotechnology: Advances and Development Prospects: Proceedings of the III International Research-to-Practice Conference* (*November 22–23, 2018*). Pinsk: Polessky State University; 2018; 78–81. eLIBRARY ID: 36624367. (in Russian)

13. Zaitsev V. V., Biletsky M. O., Biletsky O. R., Zaitseva A. V. The effect of procine recombinant alfa- and gamma-interferons on the immunogenicity of *Escherichia coli* antigens. *Uchenye zapiski Educational Establishment "Vitebsk State Academy of Veterinary Medicine"*. 2018; 54 (1): 9–13. eLIBRARY ID: 34999020. (in Russian)

14. Shakhov A., Shabunin S., Zheynes M. Correction of cellular immunity with biferon-C in piglets in case of specific prevention of circovirosis and mycoplasmosis. *E3S Web of Conferences DAIC-2020.* 2020; 222:02056. DOI: 10.1051/e3sconf/202022202056.

15. Shakhov A. G., Masyanov Yu. N., Retsky M. I., Brigadirov Yu. N., Anufriyev A. I., Belyayev V. I., et al. Methodical recommendations for immune status evaluation and improvement in animals [Metodicheskie rekomendacii po ocenke i korrekcii immunnogo statusa zhivotnyh]. *In: New Methods of Research on Veterinary Medicine Issues. P. III. Methods of Research on the Issues of Non-Contagious Pathology in Production Animals*. M.: RAAS; 2007; 216–292. (in Russian)

16. Kondrakhin I. P., Arkhipov A. V., Levchenko V. I., Talanov G. A., Frolova L. A., Novikov V. E. Veterinary clinical laboratory diagnostic methods [Metody veterinarnoj klinicheskoj laboratornoj diagnostiki]: Reference book. Under general editorship of. I. P. Kondrakhin. M.: KolosS; 2004. 520 p. (in Russian)

17. Skibo Y. V., Kurmaeva N. S., Tsibulkina V. N., Mustafin I. G., Abramova Z. I. The characteristics of serum circulating immune complexes of patients with atopic asthma with different severity degree. *Kazan Medical Journal*. 2013; 94 (5): 744–748. DOI: 10.17816/KMJ1934. (in Russian)

18. Sologub T. V., Tsvetkov V. V., Deeva E. G. Interferon gamma-cytokine with antiviral, immunomodulatory and antitumor action. *I. P. Pavlov Russian Medical Biological Herald*. 2014; 22 (3): 56–60. DOI: 10.17816/PAVLOVJ2014356-60. (in Russian)

19. Harrison G. A., McNicol K. A., Deane E. M. Type I interferon genes from the egg-laying mammal, *Tachyglossus aculeatus* (short-beaked echidna). *Immunol. Cell Biol*. 2004; 82 (2): 112–118. DOI: 10.1046/j.0818-9641.2004.01230.x.

20. Ike K., Uchida Y., Nakamura T., Imai S. Induction of interferon-gamma (IFN-gamma) and T helper 1 (Th1) immune response by bitter gourd extract. *J. Vet. Med. Sci*. 2005; 67 (5): 521–524. DOI: 10.1292/jvms.67.521.

21. Laouar Y., Sutterwala F. S., Gorelik L., Flavell R. A. Transforming growth factor-beta controls T helper type 1 cell development through regulation of natural killer cell interferon-gamma. *Nat. Immunol*. 2005; 6 (6): 600–607. DOI: 10.1038/ni1197.

22. Ketlinsky S. A., Simbirtsev A. S. Cytokines [Citokiny]. St. Petersburg: Foliant; 2008. 552 p. (in Russian)

23. Malinovskaya V. V. Ontogeny of interferon system and issues of therapy in neonatal period [Ontogenez

sistemy interferona i problemy terapii v neonatal'nom periode]. *In: Interferon-2011*. Ed. by RAMS Member, prof. F. I. Yershov and prof. A. N. Narovlyansky. M.; 2012; 35–51. Available at: http://interferons.ru/downloads/glava1.pdf. (in Russian)

24. Gavrilova O. A. Features of lipid peroxidation process in normal conditions and in various pathological conditions in children (review of literature). *Acta Biomedica Scientifica*. 2017; 2 (4): 15–22. DOI: 10.12737/article_59fad50f919f18.64819381. (in Russian)

25. Martynova Ye. A., Morozov I. A. The role of nutrition in the maintenance of the functional activity of immune system and development of adequate immune response [Rol' pitaniya v podderzhanii funkcional'noj aktivnosti immunnoj sistemy i razvitii polnocennogo immunnogo otveta]. *Russian Journal of Gastroenterology, Hepatology, Coloproctology. Annex No. 14. Current Issues of Digestive Physiology and Pathology: Proceedings of the XVI Session of the Academic School-Workshop named after A. M. Ugolev (Puschino-on-Oka, May 14–17, 2001)*. 2001; 11 (4): 28–38. Available at: https://gastroportal.ru/nauchnye-uchrezhdeniya-shkoly/akademicheskaya-shkola-seminar-im-a-m-ugoleva/pitanie-i-immunitet-rol-pitaniya-v-podderzhanii-funktsionalnoy-aktivnosti-immunnoy-sistemy-i-razvitii-polnotsennogo-immunnogo-otveta.html. (in Russian)

26. Strelchenko E. A. Study of the effect of vitamin C on human physiological systems. *Scientific works of KubSTU*. 2019; 1: 319–330. eLIBRARY ID: 36944395. (in Russian)

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