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Effectiveness of vaccines produced by the Federal State-Financed Institution "ARRIAH" against topical genotype VII Newcastle disease viruses

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SUMMARY
In 2019, the situation regarding Newcastle disease in the Russian Federation worsened radically due to the spread of NDV subgenotype VII-L throughout the country from the Primorsky Krai to the Kursk Oblast. As a result, 17 infected settlements with backyard farms where unvaccinated poultry was kept were registered. In this study, immunogenicity of the vaccines produced by the FGBI "ARRIAH", as well as the effectiveness of various vaccination schedules to prevent genotype VII NDVs, relevant for the Russian Federation, was studied. It is known that the currently circulating ND agent is significantly more virulent compared to the viruses isolated in previous years, and it is able to bypass the immunity provided by live vaccines. Test results demonstrated that the vaccines against genotype VII NDVs produced by the FGBI "ARRIAH" are highly immunogenic, which allows to effectively prevent the disease when using them as part of a standard vaccination schedule. A 2-dose vaccination schedule using live vaccine from the La Sota strain as well as the "complete" vaccination schedule using inactivated vaccines provides immunity in 100% of chicks. The use of live vaccines in a single- and double-dose vaccination schedules prevents mortality and clinical disease in poultry, but does not prevent virus replication, while the addition of an inactivated vaccine to the immunization schedule does prevent the replication of the virulent virus. Thus, the use of domestically produced live and inactivated vaccines, primarily the ones containing the La Sota strain, with the following control of the immunity level and booster vaccination, if required, is the main tool for the disease control.

Keywords: Virulent genotype VII Newcastle disease virus, ND vaccines, effectiveness of ND vaccines.

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Эффективность вакцин против ньюкаслской болезни производства ФГБУ «ВНИИЗЖ» в отношении актуальных вирусов VII генотипа

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РЕЗЮМЕ

В Российской Федерации в 2019 году произошло резкое обострение ситуации по ньюкаслской болезни птиц с распространением вируса субгенотипа VII-L по всей территории страны – от Приморского края до Курской области. В итоге зарегистрировано 17 неблагополучных пунктов, где содержалось невакцинированное поголовье в личных подсобных хозяйствах граждан. В данной работе оценивали иммуногенность вакцин производства ФГБУ «ВНИИЗЖ», а также эффективность различных схем вакцинации для профилактики ньюкаслской болезни в отношении актуальных для Российской Федерации вирусов VII генотипа. Известно, что вирулентность циркулирующего в настоящее время возбудителя ньюкаслской болезни заметно возросла по сравнению с вирусами, выделенными в предыдущие годы, и он способен преодолевать поствакцинальный иммунитет, создаваемый живыми вакцинами. В результате исследований было установлено, что вакцины производства ФГБУ «ВНИИЗЖ» обладают высокой иммуногенной активностью в отношении вирусов VII генотипа, что позволяет эффективно профилактировать эту болезнь при их использовании в составе стандартных схем вакцинации. Схема вакцинации с двукратным применением живой вакцины из штамма «Ла-Сота» формирует иммунитет у 100% цыплят, так же как и «полная» схема вакцинации с использованием инактивированных вакцин. Применение живых вакцин в схеме вакцинации с однократным и двукратным введением предотвращает гибель птиц и клиническое проявление болезни, однако не препятствует репликации вируса, в то время как добавление в схему иммунизации инактивированной вакцины предотвращает, кроме того, и репликацию вирулентного вируса. Таким образом, использование живых и инактивированных вакцин отечественного производства, прежде всего на основе штамма «Ла-Сота», с последующим контролем напряженности иммунитета и проведением ревакцинаций по показаниям является главным инструментом в борьбе с заболеванием.

Ключевые слова: Вирулентный вирус ньюкаслской болезни VII генотипа, вакцины против ньюкаслской болезни, эффективность вакцин против ньюкаслской болезни.

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INTRODUCTION

Newcastle disease (ND) is a highly contagious viral disease that affects birds, including domestic poultry (mainly chickens). The virus affects the digestive, respiratory, and nervous systems. The disease is registered throughout the world, it is included in the OIE list of notifiable diseases, as it causes huge economic losses and hinders international trade [1–3].

To date, NDV strains have been classified into classes: Class 1 – avirulent strains (9 genotypes) and Class 2 – vaccine and virulent strains (at least 10 genotypes). This is the most diverse and constantly evolving group of viruses. Virulent viruses of the genus *Avian orthoavulavirus* 1 (AOAV1), formerly known as *Avian avulavirus* 1, *Avian paramyxovirus* 1, or Newcastle disease viruses, can infect and cause disease in a wide range of domestic and wild avian species worldwide. *Avian orthoavulavirus* 1 has high genetic variability. Currently, the AOAV-1 is divided into 2 classes containing more than 20 genotypes, some of which are further divided into about 30 subtypes. In recent decades, the most relevant for poultry farming have been genotype VII, widely distributed in the countries of the Old World, and genotype V (including the newly isolated genotype XIX), circulating in the Americas.

The emergence of new virulent class 2 genotype strains that cause epidemics can be explained by the fact that viruses of different genotypes develop simultaneously in different geographical areas around the world, which is facilitated by the large diversity of avian species susceptible to NDV [1, 4]. Over the past 20 years, NDV epidemics in many Asian and European countries have been caused by different subtypes of genotype VII viruses [1–3]. Two lineages of class 2 genotype VII (previously called subgenotypes VIIh and VIIi) were identified in Indonesia in 2010 [5]. Later, one of the lineages was introduced into Malaysia [6], China [7], a number of countries in South Africa [8] and Russia (NDV/chicken/Kaliningrad/184/2013). The other subgenotype was identified in Pakistan [9], India [10], Israel [11], Libya [12], Turkey, Georgia and Bulgaria [13].

In the Russian Federation, this genotype VII NDV caused an outbreak on a poultry farm in the Amur Oblast in 2006 for the first time. Currently it is used as a challenge strain [14]. In the following years, genotype VII NDV caused sporadic outbreaks in poultry kept on backyard farms in different regions of the country. ND outbreaks caused by subgenotype VIIi viruses were first reported in the Republic of Crimea at the end of 2015 and continued throughout 2016, which at that time was the largest and longest NDV epidemics in poultry in Russia over the past few decades (21 infected settlements). This suggests panzootic potential of both virus groups [15]. It is worth mentioning that viruses with genomes similar to those of the isolates belonging to these groups were detected later than in the mid-90s in the countries of the Far East and Southeast Asia, or sporadically on the islands of Indonesia. This suggests the existence of a permanent virus reservoir in the tropical area of Southeast Asia, in which new forms of virulent AOAV-1 develop. From time to time, they leave the reservoir.

In 2019, the situation regarding Newcastle disease in the Russian Federation worsened radically due to the spread of NDV subgenotype VII-L (VII 1.1 according to the

new classification [16]) throughout the country from the Primorsky Krai to the Kursk Oblast. As a result, 17 infected settlements with backyard farms where unvaccinated poultry was kept were registered.

NDV isolates of subgenotype VII-L are most closely related to some isolates from Iran, designated cluster VII-L [17]. Iranian scientists have shown high similarity between the isolates, the fact that they belong to genotype VII, their compliance with the criteria for new subgenotype identification, as well as close phylogenetic relationship with the already known and widespread subgenotype VIId NDVs. Later, the same authors [17] significantly increased the number of the studied isolates belonging to this group, showed their distribution in almost all the Iranian provinces and the phylogenetic analyses of partial F gene sequences revealed that the isolate recovered in the country back in 1999 was evolutionarily similar to the isolates belonging to this group. F. Sabouri et al. [18], as well as A. Molouki et al. [19], demonstrated that subtype VII-L viruses were common both on small-scale and commercial poultry farms. The emergence of the new genotype VII subline in this region speaks of the fact that similar processes may occur in other places, since subgenotype VIId viruses are endemic in many countries of Eurasia and Africa, and have been also found in South America [20].

There have been no registered cases of NDV of this subgenotype in industrial poultry farming in Russia so far.

In most countries, including the Russian Federation, vaccination of commercial poultry against NDV is mandatory [1, 4, 21]. The terms of the primary vaccination are determined based on the level of maternal antibodies. As a rule, blood sera are tested by the hemagglutination inhibition test (HI) 14–21 days after the primary vaccination. Immunization is considered successful if at least 80% of vaccinated poultry has an antibody titer of at least 3 $\log_2$ [22]. When using inactivated vaccines, the antibody titer should be at least 5 $\log_2$ [23].

Insufficient and heterogeneous specific antibody levels following routine vaccination may be due to the use of an inadequate vaccine strain in a specific epidemic situation, incomplete dose administration, technical failures, vaccination of poultry with high maternal antibody levels, and other reasons.

The aggravation of the epidemic situation in 2019 and the spread of genotype VII NDV throughout the Russian Federation served the basis for the experimental infection of poultry with actual viruses of the mentioned genotype to assess the protectivity of live and inactivated La Sota vaccines produced by the FGBI "ARRIAH" (Vladimir, Russia) following different vaccination schedules.

MATERIALS AND METHODS

Vaccines. The following ND vaccines (live and inactivated) produced by the FGBI "ARRIAH" were used in the study:

– live dry vaccine against Newcastle disease from La Sota strain, batch No. 140520 (release date 05.2020);

– combined inactivated emulsion vaccine against Newcastle disease, avian infectious bronchitis and egg drop syndrome-76, batch No. 010320 (release date 03.2020).

Viruses. Three genotype VII NDVs relevant to the Russian Federation were used in the challenge: NDV/chicken/Rus/Crimea/54/17, NDV/chicken/Rus/Krasnodar/9/19, NDV/chicken/Rus/Kaliningrad/184/13, which were further assigned the following names: "Crimea", "Krasnodar" and "Kaliningrad", respectively.

Experimental animals. Egg-producing chicks aged 14–21 days without antibodies to NDV, obtained from a poultry farm free from infectious avian diseases were used in the experiment.

All tests in animals were carried out in strict compliance with the interstate standard for keeping and care of laboratory animals GOST 33215-2014, adopted by the Interstate Council for Standardization, Metrology and Certification, as well as in accordance with the requirements of Directive 2010/63/EU of the European Parliament and of the Council of the European Union of 22.09.2010 on the protection of animals used for scientific purposes.

Experiment design. Four experimental groups of chicks were formed by random sampling. Group No. 1 (30 chicks) were vaccinated with a single dose of the La Sota vaccine. Group No. 2 (30 chicks) were vaccinated with two doses of the La Sota vaccine, booster immunization being carried out 28 days after the primary vaccination. Group No. 3 (30 chicks) were vaccinated with two doses of live vaccine against ND and then 21 days later – with a single dose of inactivated vaccine against ND. Group No. 4 (90 chicks) served as a negative control and consisted of unvaccinated chicks.

The following abbreviations were used to identify the vaccination schedules: 1 LV – single-dose immunization with live vaccine; 2 LV – 2-dose immunization with live vaccine; 2 LV+1 IV – 2-dose immunization with live vaccine and single-dose immunization with inactivated vaccine.

Live vaccines were administered intranasally at a dose of 6.7 lg EID_{50}, which corresponds to one immunizing dose of the La Sota vaccine produced by the FGBI "ARRIAH"; inactivated vaccine (single dose, 0.5 ml) was administered intramuscularly.

Control of the vaccine immunogenicity. The vaccine immunogenicity was assessed based on the challenge and serological test results.

The chicks were challenged in accordance with the OIE Manual for Diagnostic Tests and Vaccines for Terrestrial Animals [24]. Chicks from different experimental groups were challenged with virulent NDVs of genotype VII. The virulent strains were used at the following infective doses: NDV/chicken/Rus/Kaliningrad/184/13 – 5.9 lg EID_{50}; NDV/chicken/Rus/Crimea/54/17 – 6.6 lg EID_{50}; NDV/chicken/Rus/Krasnodar/9/19 – 6.9 lg EID_{50}. Chicks were inoculated intramuscularly with 0.5 ml of the inoculum and were monitored for 7–8 days. Each time, 60 chicks were randomly selected to make 6 experimental groups (10 chicks per group) subjected to the challenge:

group No. 1 – vaccinated chicks challenged with NDV/chicken/Rus/Crimea/54/17;

group No. 2 – vaccinated chicks challenged with NDV virus/chicken/Rus/Krasnodar/9/19;

group No. 3 – vaccinated chicks challenged with NDV virus/chicken/Rus/Kaliningrad/184/13;

group No. 4 – unvaccinated chicks challenged with NDV/chicken/Rus/Crimea/54/17 virus;

group No. 5 – unvaccinated chicks challenged with NDV virus/chicken/Rus/Krasnodar/9/19;

group No. 6 – unvaccinated chicks challenged with NDV/chicken/Rus/Kaliningrad/184/13.

Challenge was performed 21–28 days after each vaccination.

For serological studies, chick serum samples were collected from different experimental groups, tested by HI test using an HI kit for the detection of antibodies to Newcastle disease virus produced by the FGBI "ARRIAH".

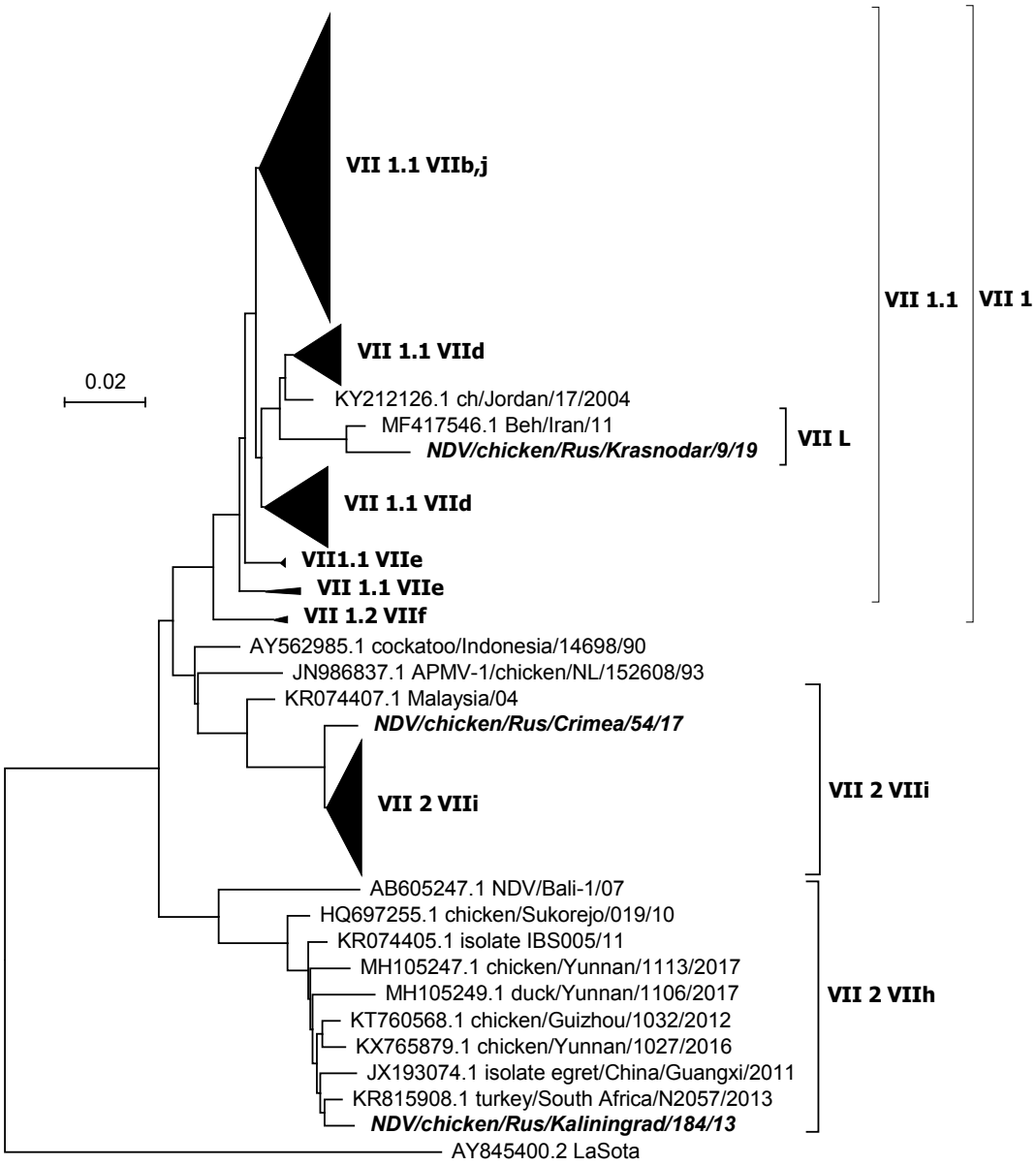

Fig. 1. Phylogenetic position of genotype VII isolates that have caused ND outbreaks in Russia in recent years. The dendrogram for complete F gene ORF sequences of 3 Russian and 304 previously published strains and isolates was obtained using the NJ program, MEGA 6.0 package. Russian isolates are shown in bold and italics. On the right are the names of phylogenetic groups according to D. G. Diel et al. [25] *(Roman numerals and Latin letters) and K. M. Dimitrov et al.* [16] *(Roman and Arabic numerals). Phylogenetic groups that do not contain the studied isolates are shown in a contracted form for convenience*

Рис. 1. Филогенетическое положение изолятов генотипа VII, вызвавших в России вспышки НБ в последние годы. Дендрограмма получена для полных последовательностей ОРС гена F 3 российских и 304 ранее опубликованных штаммов и изолятов с помощью программы NJ пакета MEGA 6.0. Российские изоляты выделены жирным шрифтом и курсивом. Справа приведены названия филогенетических групп по D. G. Diel et al. [25] *(римские цифры и латинские буквы) и по K. M. Dimitrov et al.* [16] *(римские и арабские цифры). Филогенетические группы, не содержащие изучаемых изолятов, для удобства показаны в свернутом виде*

Serum samples were collected before vaccination and before each challenge test, as well as 7–8 days after the challenge test from the survived chicks.

Nucleotide sequences of virulent NDV genes used for the challenge. Figure 1 shows the nucleotide sequences of NDV isolates and strains, characterized at the FGBI "ARRIAH" or published in the GenBank databases of the NCBI (www.ncbi.nlm.nih.gov/nucleotide/) and GISAID EpiFlu (https://www.gisaid.org/).

Nucleotide and their corresponding amino acid sequences were analyzed using BioEdit, version 7.0.5.3. Sequence alignment was performed using the ClustalW multiple alignment program. The phylogenetic tree was constructed using the NJ algorithm, MEGA package, version 6.0.

Analysis of test results. Immunogenicity of the vaccines and the effectiveness of the vaccination schedules used were assessed by measuring vaccination effectiveness, as well as based on the serological test results.

Table 1
Results of the challenge in chickens immunized following different vaccination schedules

Таблица 1
Результаты контрольного заражения цыплят, иммунизированных с применением различных схем вакцинации

Vaccination schedule	NDV virulent strain			Vaccination effectiveness, % $M \pm m$ ($n = 3$)
	"Crimea"	"Krasnodar"	"Kaliningrad"	
1 LV	2/10*	6/10	0/10	73 ± 18
2 LV	0/10	0/10	0/10	100
2 LV+1 IV	0/10	0/10	0/10	100
control	10/10 ($n = 3$)	10/10 ($n = 3$)	10/10 ($n = 3$)	0

* The ratio of the dead to the total number of infected chickens (Отношение павших к общему количеству зараженных цыплят).

Vaccination effectiveness (E) was calculated using the equation:

$$E = (n - n_i)/n \times 100\%,$$

where n_i is the number of dead chicks in the group, and n is the total number of chicks in the group.

To characterize the pathogenic effect of the virulent ND viruses, they used lethality rate calculated for a group of chicks vaccinated with a single dose of live vaccine. Lethality rate is the ratio between the number of dead animals and the number of susceptible animals, expressed as a percentage.

Lethality rate (L) was calculated using the equation:

$$L = n_i/n \times 100\%,$$

where n_i is the number of dead chicks in the group, and n is the total number of chicks in the group.

During statistical processing, the average vaccination effectiveness, lethality, antibody titers, and standard errors of the mean were calculated and analyzed using the Student's t-criterion to achieve 95% confidence level.

RESULTS

Immunogenicity of the vaccines and effectiveness of the vaccination schedules used in the experiment was assessed by the resistance to the challenge with virulent NDVs, as well as by serological test results.

Table 1 presents summarized results on the resistance of vaccinated chicks to the challenge with virulent NDVs. According to the table the effectiveness of single-dose vaccination in the groups varied from 40 to 100% and was 73% on average. The greatest effectiveness of single-dose vaccination was demonstrated for the Kaliningrad strain (10 out of 10 chicks survived), and the lowest – for the Krasnodar strain (4 out of 10 chicks survived).

Also, from the data shown in Table 1, it follows that vaccination effectiveness varied from 73 to 100%, depending on the schedule used. The lowest effectiveness was observed after a single dose of the live vaccine and the highest – after the administration of two doses of the live vaccine and an additional dose of the inactivated vaccine.

At the same time, in all the unvaccinated control groups, in three-stage testing, 100% lethality in chicks was observed on day 3–7 post-challenge.

Figure 2 presents lethality rate in chicks in group 1 LV after their challenge with genotype VII NDVs. According to the diagram, as well as based on the regression equation and the determination coefficient $R = 0.84$ or 84%, a high degree of correlation between lethality and the infective dose was established.

Figure 3 shows the correlation between the distribution of NDV antibody titers in experimental groups and the vaccination schedule used. The diagram demonstrates that the vaccination schedule 2 LV+1 IV resulted in high antibody titers, with the mean titer value of 11.9 $\log_2$. Following other schedules, when the chicks had received one or two live vaccine doses, the mean antibody titer values were 5.2 and 4.8 $\log_2$, respectively.

Table 2 presents results of serological tests to determine anti-NDV antibody titres in poultry sera by HI test after following different vaccination schedules, as well as after the challenge test.

The data in Table 2 demonstrates that the antibody titers after single (5.2 ± 0.3 $\log_2$) and double (4.8 ± 0.2 $\log_2$) vaccination were almost the same, since there was no statistical difference ($P > 0.05$). Vaccination of chicks with the inactivated vaccine resulted in a significant (statistically significant) increase in antibody titers ($P < 0.001$).

After the challenge, the antibody titers in group 1 LV and 2 LV increased significantly and exceeded the initial values by 48 and 119 times, respectively; as for the group 2 LV+1 IV the antibody titers were comparable to those before the challenge – 11.9 $\log_2$.

DISCUSSION OF THE RESULTS

Single-dose vaccination with the live vaccine produced by the FGBI "ARRIAH" resulted in high titers of humoral antibodies, which were comparable to those developed after two-dose vaccination. However, the effectiveness of single-dose vaccination was the lowest (73%), whereas after the administration of two doses of live vaccine and an additional dose of the inactivated vaccine, the effectiveness against virulent genotype VII NDVs was the greatest and amounted to 100%.

It should be noted that genotype VII NDVs' pathogenicity depended on the infective dose, and this could be observed in chicks vaccinated with a single dose of the

live vaccine. Further in the studies, when characterizing the effectiveness of the 2 LV and 2 LV+1 IV vaccination schedules, this correlation was mitigated. It should also be noted that it is almost impossible to find such virus concentration (about 5.9 lg EID_{50} or ~1,000,000 viral particles) in the wild, so it is most likely that single-dose vaccination with live La Sota vaccine will protect poultry from the infection with virulent genotype VII NDVs.

Apparently, two-dose immunization with live vaccine and the additional administration of the inactivated vaccine results in higher immunity levels and specific immunity, characterized mainly by "late" immunoglobulin G, which is more effective against virulent NDVs. However, immunization of poultry with live vaccines did not completely prevent the virulent virus replication, as evidenced by the 50–100 times increase in humoral antibody titers 7–8 days post-challenge.

The so-called "complete" vaccination schedule, using live and inactivated vaccines, resulted in high humoral antibody titers, prevented the virulent virus replication, and provided 100% protection against the infection.

CONCLUSION

It was found that vaccines are effective for the prevention of Newcastle disease, caused by virulent genotype VII viruses, when used following a specific vaccination schedule. Thus, a two-dose vaccination schedule using live vaccines, prevented poultry death and clinical manifestation of the disease, but did not prevent virus replication. While the vaccination schedule using live and inactivated vaccines prevented death, the development of clinical disease signs and replication of the virulent virus.

Therefore, vaccines against ND produced by the FGBI "ARRIAH" are highly immunogenic and effective in the prevention of disease caused by genotype VII NDVs.

The data obtained indicate that the currently circulating NDV is significantly more virulent than those isolated in previous years, and it is able to bypass the post-vaccination immunity induced by live vaccines. Therefore, the use of adequate domestically produced live and inactivated vaccines, primarily those containing the La Sota strain, with the following control of the immunity level and booster vaccination, if required, is the main tool for the disease control.

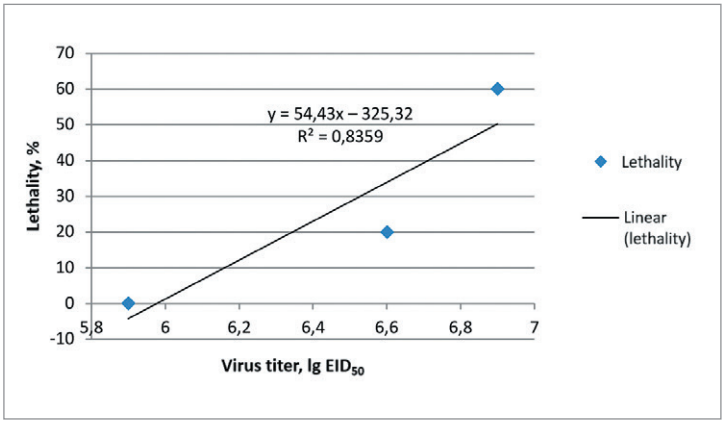

Fig. 2. Relationship between the infectious dose and the mortality rate in single-dose vaccinated chickens

Рис. 2. Влияние заражающей дозы на показатель летальности однократно вакцинированных цыплят

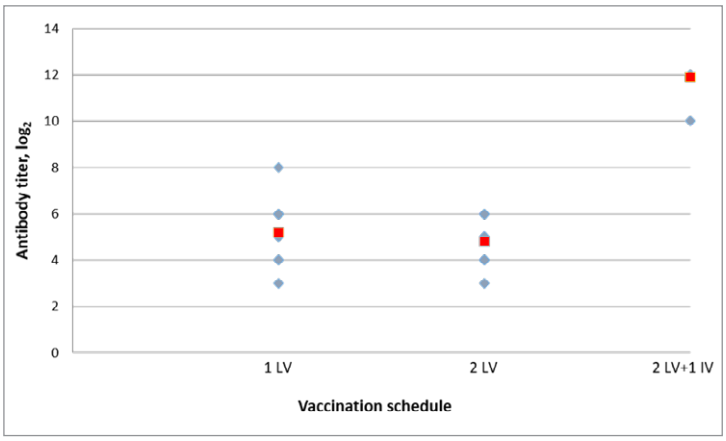

Fig. 3. Distribution of antibody titers by groups, according to the vaccination schedules used. The red markers indicate the average values of the corresponding set of variate values

Рис. 3. Распределение титров антител по группам, соответственно примененным схемам вакцинации. Красными маркерами выделены средние значения соответствующих вариационных рядов

Table 2
Serological response in chickens to vaccination following different ND vaccination schedules

Таблица 2
Серологический ответ цыплят на иммунизацию с использованием различных схем вакцинации против НБ

Vaccination schedule	Antibody titer (log_2) at different sample collection time points		
	0 b/v	21–28 p/v	7–8 p/ch
1 LV	3.2 ± 0.6	5.2 ± 0.3	10.8 ± 0.3
2 LV		4.8 ± 0.2	11.7 ± 0.1
2 LV+1 IV		11.9 ± 0.1	11.9 ± 0.1

b/v – days before vaccination (дней до вакцинации), p/v – days post-vaccination (дней после вакцинации), p/ch – days post-challenge (дней после контрольного заражения).

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