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Optimization of rabies (*Rhabdoviridae: Lyssavirus*) dog vaccination schedule using a mathematical model

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Introduction. Most cases of human rabies are caused by dog (*Canis lupus familiaris*) bites. Therefore, the implementation of vaccination programs of these animals is one of the urgent tasks.
The work **aims** to identify the factors influencing the production of antirabies virus-neutralizing antibodies (VNAs) in vaccinated dogs, and to formulate recommendations for adjusting the vaccination schedule using mathematical modeling (MM).
Material and methods. We used a fixed-effects modeling procedure to estimate the two-compartment model parameters using log-transformed data (obtained by RFFIT, rapid fluorescent focus inhibition test; and FAVN, fluorescent antibody virus-neutralization test) on the VNAs levels in the serum of vaccinated dogs.
Results. More vigorous immune response after a two-dose primary vaccination is formed in juvenile dogs at the age of 3 months to 1 year compared to the adult dogs. Following the primary vaccination and revaccination 1 year after, VNAs were produced more intensively in adult stray dogs than in domestic dogs.
Discussion. The short-term immune response observed in dogs aged up to 3 months is due to the presence of colostral antibodies and the active growth of the organism at this age. The results of our study confirm that most of the dogs have a level of antirabies VNAs of ≥0.5 IU/ml up to two or more years following immunization. However, only regular annual revaccination ensures the protective VNAs level in animals that responded poorly to vaccination due to various factors.
Conclusion. The following antirabies vaccination schedule is recommended: primary vaccination of the dog at the age of 3 months up to 1 year with 1–2 month intervals, then revaccination annually. This work also demonstrates the possibility of a wider application of MM methods for solving problems of vaccine prevention.

Keywords: rabies, prevention and control, virus-neutralizing antibodies, vaccination, mathematical modeling, non-linear modeling

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Оптимизация схемы вакцинации собак против бешенства (*Rhabdoviridae: Lyssavirus*) при помощи математической модели

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Введение. Большинство случаев бешенства (*Rhabdoviridae: Lyssavirus*) у людей вызвано укусами домашних и диких собак (*Canis lupus familiaris*). В этой связи одной из актуальных задач является организация программ массовой вакцинации этих животных.
Цель работы – выявить факторы, влияющие на синтез вируснейтрализующих антител (ВНА) к вирусу бешенства у вакцинированных собак, сформировать рекомендации по корректировке схемы вакцинации с использованием методов математического моделирования (ММ).
Материал и методы. Разработана двухкомпартментная математическая модель, параметры которой откалиброваны на лог-трансформированных данных о содержании ВНА в сыворотке крови вакцинированных собак с использованием нелинейного моделирования с фиксированными эффектами. Результаты получены методами RFFIT (rapid fluorescent focus inhibition test, анализ быстрого ингибирования фокусов флюоресценции) и FAVN (fluorescent antibody virus-neutralization test, тест нейтрализации вируса флюоресцентными антителами).
Результаты. Установлено, что при двукратной первичной вакцинации у щенков в возрасте от 3 мес до 1 года формируется более напряжённый иммунный ответ по сравнению с таковым у взрослых особей. При первичной вакцинации и ревакцинации спустя 1 год и более ВНА у взрослых уличных собак синтезируются более интенсивно, чем у домашних.
Обсуждение. Менее длительный иммунный ответ у животных, вакцинированных в возрасте до 3 мес, объясняется как наличием колостральных антител, так и активным развитием организма в этот период. Результаты наших исследований и данные работ других авторов подтверждают наличие у большинства собак протективного уровня ВНА к вирусу бешенства ≥0,5 МЕ/мл на протяжении 2 и более лет после вакцинации. Однако лишь регулярная ежегодная ревакцинация способствует достижению и поддержанию этого показателя у особей, плохо отвечающих на вакцинацию в силу различных факторов.
Заключение. Рекомендована следующая схема вакцинации собак против бешенства: первичное введение вакцинного препарата в возрасте от 3 мес до 1 года с 1–2-месячным интервалом, в дальнейшем ежегодная ревакцинация. Настоящая работа демонстрирует возможность более широкого применения методов ММ для решения задач вакцинопрофилактики.

Ключевые слова: бешенство, профилактика, вируснейтрализующие антитела, вакцинация, математическое моделирование, нелинейное моделирование

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Introduction

Rabies is an acute, highly dangerous infection caused by a neurotropic virus in animals and humans; it kills an estimated 59,000 people every year worldwide. Half of the world's population lives in endemic zones, and more than 80% of rabies deaths occur in rural areas, where prevalence of rabies among domestic and wild carnivores (*Carnivora*) is high and the access to health services is limited or non-existent. In the vast majority of cases, rabies is transmitted to humans through bites of infected domestic and feral dogs (*Canis lupus familiaris*); therefore, in their attempts to prevent the infection, many countries have launched mass dog vaccination campaigns [1]. Monitoring the post-vaccination immune status is of high priority for further rabies vaccination programs. To measure levels of virus-neutralizing antibodies (VNAs) in blood sera from animals, the World Organization for Animal Health (formerly the Office International des Epizooties, OIE) recommended the rapid fluorescent focus inhibition test (RFFIT) and the fluorescent antibody virus neutralization test (FAVN) [2].

Application of mathematical modeling (MM) adds specification and quantitative description to theoretical and practical aspects of different biological processes [3]. MM plays an essential role in drug development [4, 5]; exploration of immunological processes [6], planning and assessment of effectiveness of mass vaccination programs for animals [7, 8].

The aim of our study was to identify the factors having an impact on the development of rabies virus-neutralizing in vaccinated dogs and to offer recommendations for animal vaccination schedule adjustments depending on the animals' physiological status and based on MM methods.

Materials and methods

Data on levels of rabies virus neutralizing antibodies in dog sera. The mathematical model was constructed using aggregate literature data on rabies VNA titers in sera of vaccinated dogs, which were obtained in three RFFIT- and FAVN-based studies focused on a three-year period after the primary vaccination (14 experimental groups, 180 measurements) (**Fig. 1**, **suppl. Table. 1***) [9–11].

The preliminary screening was aimed to find differences among identical groups from different studies, to identify reasons for these differences and to winnow out outliers (the details of the screening are omitted from the article). The data on annually revaccinated adult domestic dogs presented by Pimburage et al., 2017 [10] were excluded from the dataset, as they did not correlate significantly with other available data. The data on domestic puppies under 3 months of age, which were presented by Wallace et al., 2017 [11], were not included in the calibration dataset as being «noisy». Some values were also excluded from the groups of domestic puppies aged 3–4 months (3 measurements) and domestic juveniles aged 4 months to 1 year (1 measurement) from the study by Wallace et al., 2017 [11].

* supplementary appendix.

Construction and calibration of the model. We constructed, calibrated, and validated a two-compartment model incorporating various intensity of the antibody response after primary vaccination and revaccination of animals (**Fig. 2**) [12]. The results obtained by Cliquet et al. support the presence of a linear relationship between RFFIT and FAVN values, thus making it possible to correlate the data obtained by using different methods within the mathematical model [13]. In the offered model, the dynamics of VNA levels, regardless of measurement methods and vaccination time, is defined by the same fitting parameters: the absorption rate constant *ka* showing the changes in the development and accumulation of VNA in dogs' sera; the elimination rate constant k_{el} describing the changes in VNA degradation, and the VNA transfer rate constants for transfer from the central to the peripheral compartment (k_{12}) and back (k_{21}).

The rabies VNA levels measured using RFFIT and FAVN tests are presented as endpoint titers of VNA (**Formula 1**) resulting from the primary vaccination of animals and from the revaccination 1–2 months after and 1 year after the first administration of the vaccine:

$$VNA_{log} = \ln(Ac_1 + Ac_2 + Ac_3) \qquad (1),$$

where VNA_{log} (VNA_RFFIT_{log} and VNA_FAVN_{log}) are the VNA levels measured with RFFIT and FAVN, respectively;

Ac_1, Ac_2, and Ac_3 are the VNA titers induced by the primary vaccination, the revaccination 1–2 months and 1 year after the primary one, respectively.

The model was calibrated using log-transformed variables. Log transformation is important for reducing the variability of data, making them conform more closely to the normal distribution. In addition, it is very helpful when lower ranges of titers are involved, which is especially important as the protective VNA level is currently established at 0.5 IU/ml. The VNA titer values were incorporated into the model as absolute values (IU/ml). The additive residual error was selected for log-transformed variables of VNA titers in dog sera (obtained with RFFIT and FAVN) (**Formulas 2** and **3**, respectively):

$$y_1 = VNA\_RFFIT_{log} + a_1 \times e \qquad (2),$$
$$y_2 = VNA\_FAVN_{log} + a_2 \times e \qquad (3),$$

where y_1 and y_2 are the natural logarithms of the observed VNA titer values obtained with RFFIT and FAVN, respectively;

VNA_RFFIT_{log} and VNA_FAVN_{log} are the model-based predictable values;

a_1 and a_2 are the residual errors for each measurement method;

$e = 2.71828$ (the base of the natural logarithm).

The differences in RFFIT- and FAVN-measured VNA titers are described by the relative bioavailability parameter *F*, which is lognormally distributed. Thus, vaccination

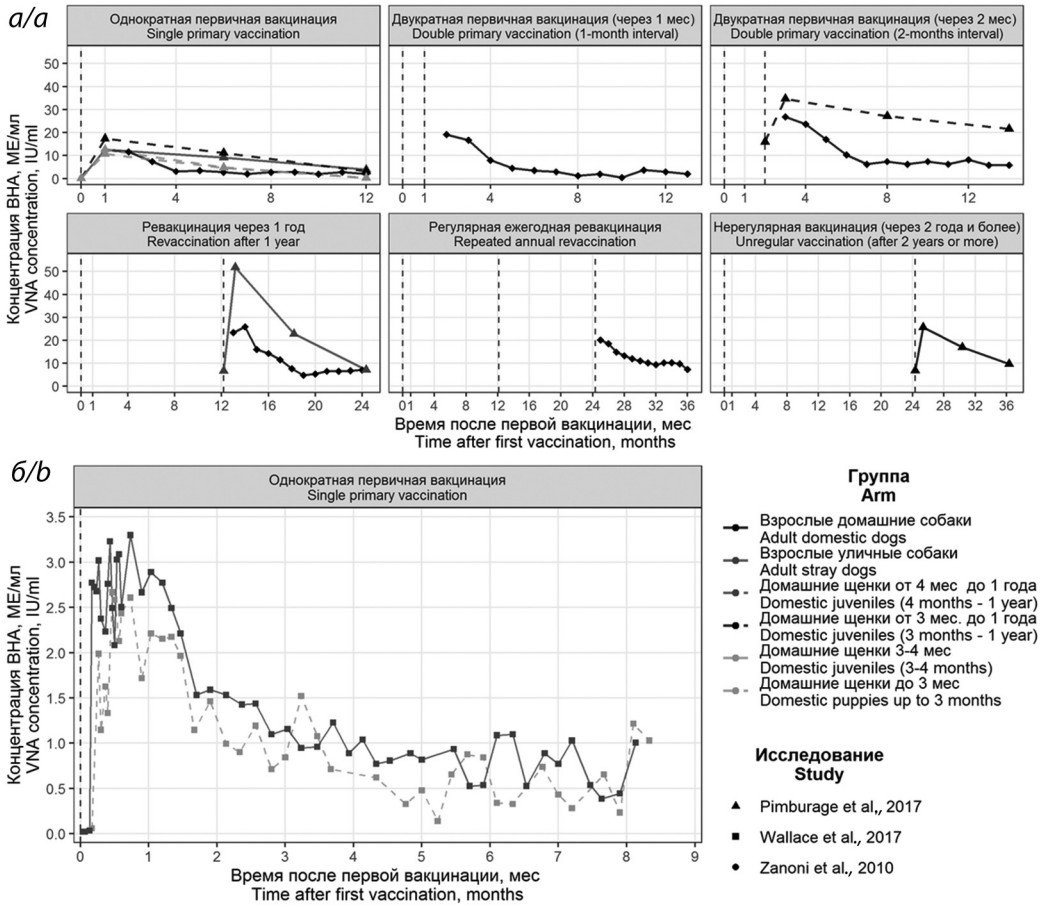

Fig. 1. Data on the antirabies virus-neutralizing antibodies (VNAs) levels in dogs' serum used for mathematical model calibration: *a),* obtained by the RFFIT method; *b),* obtained by the FAVN method.

Note. Vertical dashed lines represent vaccination times.

Рис. 1. Данные о содержании антирабических вируснейтрализующих антител (ВНА) в сыворотке крови собак, использованные для калибровки математической модели: *а* – полученные методом RFFIT, *б* – полученные методом FAVN.

Примечание. Вертикальные пунктирные линии обозначают время вакцинации.

can be represented by a relative dose of 1. The model provides individually fittable parameters *F1*, *F2*, and *F3* to address differences in the VNA synthesis dynamics after primary vaccination and revaccination. Their correlations for RFFIT and FAVN are defined by the fitting parameter *coef*: values $F1_{FAVN}$, $F2_{FAVN}$, and $F3_{FAVN}$ result from division of parameters $F1_{RFFIT}$, $F2_{RFFIT}$, and $F3_{RFFIT}$, respectively, by the value *coef*. The VNA synthesis start time after the initial contact with the antigen was shown by parameter t_{lag}, which, like parameter *ka*, was fitted solely by using the data obtained from the FAVN tests.

The initial VNA levels prior to the primary vaccination must be taken into consideration when modeling their changes. As no information about VNA levels in dogs' sera before the vaccination was available for any group, their values were fitted separately for RFFIT (parameter *BLr*) and FAVN (*BLf*) methods.

The fitting parameters for the system of ordinary differential equations were calibrated by using RFFIT and FAVN data on VNA levels in sera of vaccinated animals and the nonlinear fixed effects modeling method (**Table 1**). The quality of the model was assessed against the following criteria: the change in the value of the objective function (log likelihood function; Akaike's information criterion (AIC), diagnostic graph monitoring (**suppl. Fig. 1*, 2***), minimization of the relative standard error (RSE), consistency of parameters set when the model is based on different initial values.

The covariance analysis was used to measure the effect of different characteristics of the animal population on the dynamics of VNA production. For example, the rate constant of VNA transfer from the central to the peripheral compartment (k_{12}) depends on the living status of dogs (whether the dog is domestic or stray). For stray dogs, the parameter k_{12} is estimated through the parameter $\beta\_k_{12(stray\ dogs)}$ (**Formula 4**):

$$k_{12}\ (\text{for stray dogs}) = k_{12} \times e^{\beta\_k12\ (\text{stray dogs})} \qquad (4)$$

Additionally, it was found that the age affects the rate constant of VNA transfer from the peripheral to the cen-

* supplementary appendix.

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tral compartment. For domestic puppies under 3 months and juveniles aged 3 months to 1 year, the parameter k_{21} is estimated through parameters $\beta\_k_{21(puppies\ under\ 3\ months)}$ and $\beta\_k_{21(juveniles\ aged\ 3\ months\ to\ 1\ year)}$, respectively (**Formulas 5** and **6,** respectively):

$$k_{21}\ (\text{for puppies under 3 months}) = k_{21} \times e^{\beta\_k21\ (\text{puppies under 3 months})} \quad (5);$$

$$k_{21}\ (\text{for juveniles aged 3 months – 1 year}) = k_{21} \times e^{\beta\_k21\ (\text{juveniles aged 3 months – 1 year})} \quad (6).$$

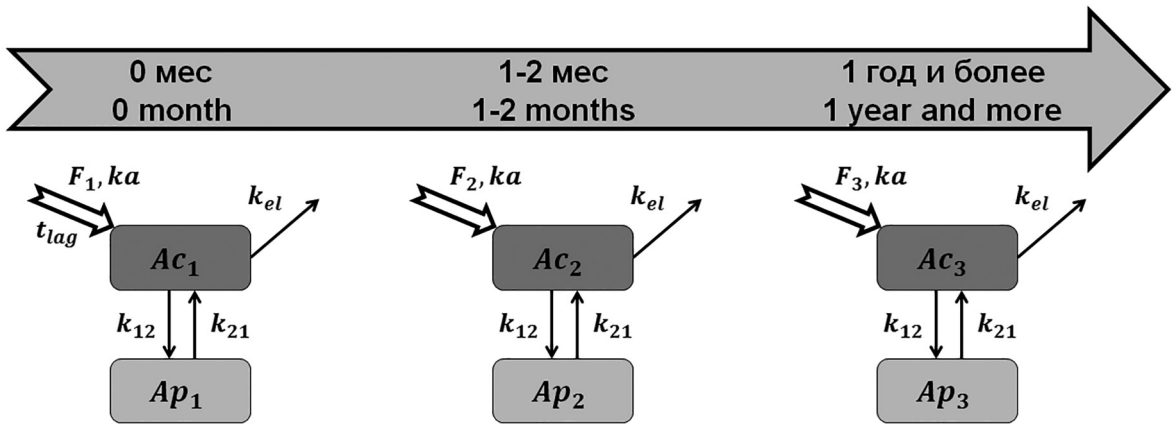

Fig. 2. Structural mathematical model of the synthesis of antirabies virus-neutralizing antibodies after vaccination of dogs.
Рис. 2. Структурная математическая модель синтеза вируснейтрализующих антител к вирусу бешенства после вакцинации собак.

Table 1. Parameters of the developed mathematical model
Таблица 1. Параметры разработанной математической модели

Parameter, units Параметр, единицы измерения	Mean value (*M*) Среднее значение (*M*)	RSE value (%) Величина RSE (%)	*p*-value *p*-критерий	Additional features and comments Дополнительные характеристики и комментарии
BLr, IU/ml *BLr*, МЕ/мл	0,1	27,9	–	–
BLf, IU/ml *BLf*, МЕ/мл	0,0227	30,8	–	–
$F1_{RFFIT}$	281	29,2	–	–
$F2_{RFFIT}$	229	36,6	–	–
$F3_{RFFIT}$	453	31,3	–	–
coef	9,82	17,4	–	–
ka, days^{-1} *ka*, сут$^{-1}$	0,0237	26,4	–	Fitted using FAVN data Откалиброваны на данных, полученных методом FAVN
t_{lag}, days t_{lag}, сут	3,98	0,69	–	
k_{el}, days^{-1} k_{el}, сут$^{-1}$	0,00095	–	–	Fixed Зафиксирован
k_{12}, days^{-1} k_{12}, сут$^{-1}$	0,203	24,9	–	–
$\beta\_k_{12(stray\ dogs)}$ $\beta\_k_{12(уличные\ собаки)}$	−0,605	39,2	0,011	See equation 4 См. формулу 4
k_{21}, days^{-1} k_{21}, дни$^{-1}$	0,00166	16,9	–	–
$\beta\_k_{21(juveniles\ aged\ 3\ months\ –\ 1\ year)}$ $\beta\_k_{21(щенки\ 3\ мес\ –\ 1\ год)}$	0,935	21,8	<0,001	See equation 5 См. формулу 5
$\beta\_k_{21(puppies\ up\ to\ 3\ months)}$ $\beta\_k_{21(щенки\ до\ 3\ мес)}$	−1,64	28,9	<0,001	See equation 6 См. формулу 6
a_1, IU/ml a_1, МЕ/мл	0,0559	7,54	–	See equation 2 См. формулу 2
a_2, IU/ml a_2, МЕ/мл	0,475	7,37	–	See equation 3 См. формулу 3

Note. RSE, relative standard error; «–» indicates the absence of data.

Примечание. RSE – относительная стандартная ошибка; «–» – отсутствие данных.

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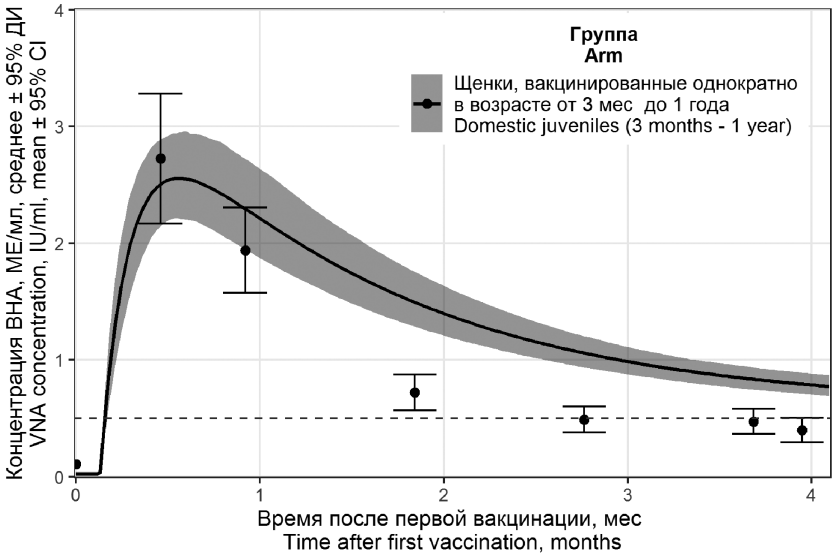

Fig. 3. Validation of the mathematical model using the data from J. Minke et al. [14] (FAVN as a method for virus-neutralizing antibodies (VNAs) detection).

Note. The dots represent the data from J. Minke et al. [14] (with the standard error of the mean, SEM), and the lines represent the model predictions (with 95% confidence interval, CI). The horizontal dashed line indicates a protective antibody level of 0.5 IU/ml.

Рис. 3. Валидация математической модели на данных J. Minke и соавт. [14] (метод определения вируснейтрализующих антител (ВНА) FAVN).

Примечание. Точками обозначены данные J. Minke и соавт. [14] (со стандартной ошибкой среднего – standard error of the mean, SEM), линиями – модельные предсказания (с 95% доверительным интервалом, ДИ). Горизонтальная пунктирная линия обозначает протективный уровень антител 0,5 МЕ/мл.

Software. The mathematical model was constructed and analyzed using the Monolix Suite 2019R2 software (Lixoft, France). The R v.3.5.1. software was used to prepare the dataset and to perform its exploratory analysis, to validate the model and to build model simulations. The simulation graphs and tables presenting pharmacokinetic parameters of VNAs show mean values (M) with 95% confidence intervals (CI), the number of simulated populations $n = 1000$. Any differences were seen as statistically significant at (p-value) $p \leq 0.05$.

Results

Validation of the model. The constructed mathematical model incorporates aggregate literature data on rabies VNAs levels in vaccinated dogs, which were obtained using RFFIT and FAVN methods (**suppl. Fig. 1* and 2***). The model tends to overpredict VNA titers for the data obtained with RFFIT and exceeding 20 IU/ml (**suppl. Fig. 1, a***and **1, b***).

The external validation of the model brought in the literature data that were not included in the calibration dataset [14]. The model provides an efficient tool for describing changes in the VNA titers during the first month following the vaccination, though it underpredicts a decrease in VNA levels 1 month after the vaccination (**Fig. 3**). The data offered by Minke et al. were obtained from a small number of 3–4-month-old beagle puppies, and differences in responses to the vaccination between beagles and other dog breeds had been described in earlier studies [15]. As no RFFIT data are available for dogs of this breed, the effect of the breed on dynamics of VNA levels remains unknown.

The model-calibrated initial values of rabies VNAs in dogs' sera prior to vaccination were 0.1 IU/ml in the RFFIT tests and 0.0227 IU/ml in the FAVN ones, demonstrating complete consistency with the data obtained by different researchers regarding pre-vaccination VNA levels lower than the protective titer threshold value of 0.5 IU/ml (**Table 1**) [10, 14].

Differences in levels of virus-neutralizing antibodies in domestic dogs of different age. The effect of such parameters as the age of animals and their living status (whether the dog is domestic or stray) on rabies VNA levels was evaluated. The constructed model also responds to different effect of the primary vaccination and subsequent revaccinations on the VNA synthesis.

In single vaccination, the areas under the pharmacokinetic concentration-time curve (the area under the curve, AUC) for VNAs detected during 1 year after the vaccination (AUC_{365}) in adult domestic dogs and domestic juveniles aged 3 months to 1 year are comparable (**Table 2**). No significant differences in maximum VNA concentrations (C_{max}) in sera of animals from these age groups were found (**Table 2**); however, the simulation of time profiles of VNA levels demonstrated higher values among puppies 2 and more months after the vaccine administration, thus suggesting better immunoprotection during the en-

* supplementary appendix.

tire year after the vaccination (**Fig. 4**). The comparative analysis of literature data on VNA titers in dogs of different age showed higher VNA levels in domestic juveniles aged 3 months to 1 year compared to the levels in adult domestic dogs after the double vaccination with 2-month spacing (**Fig. 1, *a***). Differences were found not only in the general profile of VNA concentration during the 1-year post-vaccination period (**Fig. 5**), but also in AUC_{365} (**Table 2**). They can be caused by the difference in animals' weight and, consequently, in the volume of distribution of the vaccine and vaccine-induced VNAs as well as by different intensity of immune response in dogs of different age. The unavailability of accurate information about the weight and breeds of the dogs does not make it possible to include the covariates addressing the above characteristics in the model.

No significant differences in VNA levels were found among puppies under 3 months, born from vaccinated and unvaccinated dogs (**Fig. 1, *a***); therefore, these 2 groups were combined into the category of domestic puppies under 3 months in the calibration dataset. The immature immune system in puppies of this age is associated with short-lived humoral immunity to the rabies pathogen both after single and double-dose primary vaccinations with 1- or 2-month spacing (**Fig. 4, 5**).

Differences in levels of virus-neutralizing antibodies in domestic and stray dogs. Another focus of our interest was to find out whether the living conditions of animals had any effect on the intensity of their immune response: domestic dogs live in more favorable conditions than stray dogs, who, on the other hand, are better adapted to different changes in the environment and are more frequently exposed to rabies virus antigens. It was found that after the primary vaccination (**Fig. 4; Table 2**) as well as after the revaccination 1 year or more years after the first vaccine administration, VNAs were developed more intensively in adult stray dogs than in domestic dogs (**Fig. 1, a; Fig. 6; Table 3**). It is demonstrated by different maximum VNA concentrations (C_{max}) and by different areas under the pharmacokinetic VNA curve during the second and the third years following the vaccination (**Table 3**). On the other hand, the time required to reach the maximum VNA concentrations (T_{max}) in sera of adult stray dogs is 5–6 days longer compared to domestic dogs (**Table 2**).

Optimization of the vaccination schedule for domestic dogs. Based on the model simulations of VNA levels in sera of domestic dogs vaccinated against rabies according to different schedules, it was found that the long-lived humoral immune response would develop after annual revaccination, whether or not the primary vaccination was single- or double-dose. Considering the immaturity of the immune system in puppies under 3 months as well as a high probability of colostrum-acquired antibodies present in them, we do not recommend administration of the first vaccination at this age. Although the protective VNA level during the first year after the vaccination is reached after the primary administration of the vaccine both to adult dogs and to juveniles aged 3 months to 1 year, a weak humoral response to the first vaccination may still develop in some animals. Therefore, the better option would be double vaccination of dogs aged 3 months and older, when the second dose is administered 1–2 months after the first one. The primary vaccination at the age

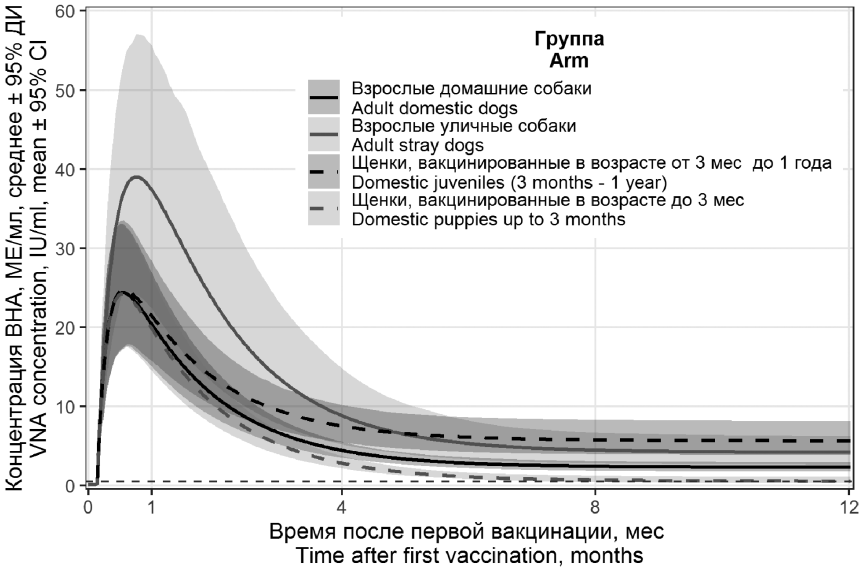

Fig. 4. Virus-neutralizing antibodies (VNAs) levels in dogs' serum after a single primary vaccination (RFFIT as a method for antibodies detection): the results of model simulations.

Note. The horizontal dashed line indicates a protective antibody level of 0.5 IU/ml; CI is the confidence interval.

Рис. 4. Содержание вируснейтрализующих антител (ВНА) в сыворотке крови собак после однократной первичной вакцинации (метод определения антител RFFIT), результаты модельных симуляций.

Примечание. Горизонтальная пунктирная линия обозначает протективный уровень антител 0,5 МЕ/мл; ДИ – доверительный интервал.

Table 2. Pharmacokinetic parameters of virus-neutralizing antibodies in the first year after dog vaccination: the results of model simulations (RFFIT as a method for antibodies detection)

Таблица 2. Фармакокинетические параметры вируснейтрализующих антител в первый год после вакцинации собак, результаты модельных симуляций (метод определения антител RFFIT)

Vaccination schedule Схема вакцинации	Arm Группа собак	Area under the curve AUC_{365}*, IU/ml Площадь под фармакокинетической кривой AUC_{365}*, МЕ/мл	Maximum concentration (C_{max})*, IU/ml Максимальная концентрация (C_{max})*, МЕ/мл	Time to reach maximum concentration (T_{max}), days Время достижения максимальной концентрации (T_{max}), сут
Single primary vaccination Однократная первичная вакцинация	Adult stray dogs Взрослые уличные	3819 (2356; 5749)	38,84 (25,32; 58,73)	23
	Adult domestic dogs Взрослые домашние	2119 (1678; 2691)	24,63 (18,21; 33,02)	17
	Domestic juveniles 3 months – 1 year Домашние щенки от 3 мес до 1 года	3154 (2313; 4224)	24,97 (18,52; 33,67)	18
	Domestic puppies up to 3 months Домашние щенки до 3 мес	1569 (1211; 2019)	24,46 (18,12; 32,82)	16
Двукратная первичная вакцинация (через 1 мес) Double primary vaccination (1-month interval between doses)	Adult stray dogs Взрослые уличные	6785 (4084; 10 221)	60,76 (36,92; 93,83)	44
	Adult domestic dogs Взрослые домашние	3729 (3033; 4609)	36,25 (27,36; 48,53)	40
	Domestic juveniles 3 months – 1 year Домашние щенки от 3 мес до 1 года	5520 (4200; 7207)	37,92 (28,60; 50,54)	40
	Domestic puppies up to 3 months Домашние щенки до 3 мес	2782 (2153; 3611)	35,39 (26,60; 47,80)	40
Double primary vaccination (2-months interval between doses) Двукратная первичная вакцинация (через 2 мес)	Adult stray dogs Взрослые уличные	6686 (4018; 10 085)	48,24 (28,20; 76,14)	76
	Adult domestic dogs Взрослые домашние	3675 (2989; 4527)	28,83 (21,09; 39,96)	71
	Domestic juveniles 3 months – 1 year Домашние щенки от 3 мес до 1 года	5386 (4105; 7019)	31,51 (23,16; 43,50)	72
	Domestic puppies up to 3 months Домашние щенки до 3 мес	2770 (2141; 3599)	27,43 (19,39; 38,78)	71

Note. *, data are presented as mean (*M*) with 95% confidence interval.

Примечание. * – данные представлены в виде среднего значения (*M*) с 95% доверительным интервалом.

of 3 months to 1 year results in higher VNA titers during the first year after the vaccination and, consequently, reduces the risk that an animal can be infected when exposed to the rabies pathogen during this period. Therefore, we recommend the following general vaccination schedule: The first and the second vaccination should be administered at the age of 3 months to 1 year, with 1–2-month spacing, to be further followed by annual revaccination (**Fig. 7**).

Discussion

To measure VNA levels in animal sera, the World Organization for Animal Health recommends two methods – RFFIT and FAVN [2]. The recent studies provide evidence attesting to the high correlation of the results obtained by using the above methods [13, 16]. For convenience of interpretation, the protective threshold VNA titer of 0.5 IU/ml, common for both methods, was adopted [2], thus permitting researchers to interpret RFFIT and FAVN results to be equivalent. However, the results of our exploratory analysis of the VNA titers in dogs' sera, which were measured using the above tests, show that the results cannot be seen as equivalent. The similar conclusion is implied by different peak VNA levels for animals of the same age (**suppl. Fig. 3***), time difference required by VNA titers to go below the protective threshold, and different values of the above parameter prior to vaccination. This leads to divergence of results obtained in studies of serum samples with VNA titers close to 0.5 IU/ml [16, 17].

Briggs et al. believe that the differences in the obtained results are not caused by using different methods; rather, they come from mutations in the control rabies virus, which is used in different laboratories for performing tests. They recommend that strains of the rabies virus from

* supplementary appendix.

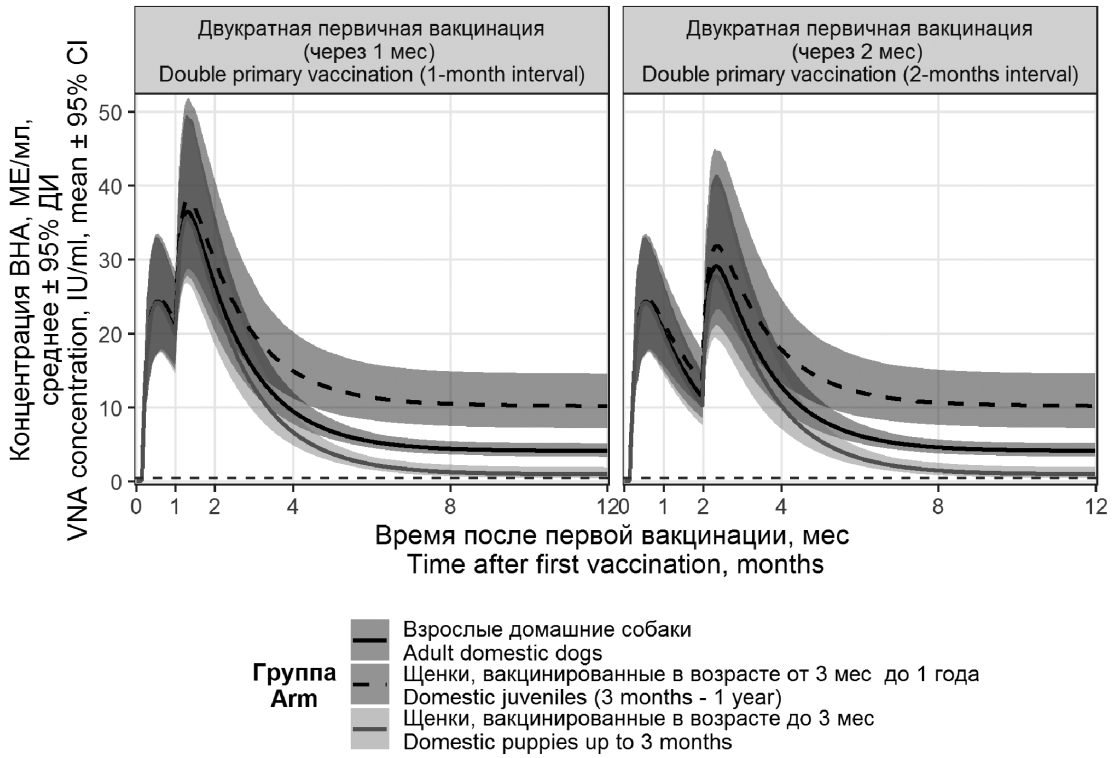

Fig. 5. Virus-neutralizing antibodies (VNAs) levels in dogs' serum after double primary vaccination with an interval of 1 and 2 months (RFFIT as a method for antibodies detection): the results of model simulations.

Note. The horizontal dashed line indicates a protective antibody level of 0.5 IU/ml.

Рис. 5. Содержание вируснейтрализующих антител (ВНА) в сыворотке крови собак после двукратной первичной вакцинации с интервалом 1 и 2 мес (метод определения антител RFFIT), результаты модельных симуляций.

Примечание. Горизонтальная пунктирная линия обозначает протективный уровень антител 0,5 МЕ/мл.

Table 3. Pharmacokinetic parameters of virus-neutralizing antibodies in domestic and stray dogs: the results of model simulations (RFFIT as a method for antibodies detection)

Таблица 3. Фармакокинетические параметры вируснейтрализующих антител у домашних и уличных собак, результаты модельных симуляций (метод определения антител RFFIT)

Arm Группа собак	Vaccination schedule Схема вакцинации	Area under the curve AUC*, IU/ml Площадь под фармакокинетической кривой AUC*, МЕ/мл			Maximum concentration (C_{max})*, IU/ml Максимальная концентрация (C_{max})*, МЕ/мл		
		1 год 1st year	2 год 2nd year	3 год 3rd year	1 год 1st year	2 год 2nd year	3 год 3rd year
Adult stray dogs Взрослые уличные	Revaccination after 1 year Ревакцинация через 1 год	3819 (2356; 5749)	7586 (4641; 11 297)	3875 (2466; 5707)	38,84 (25,32; 58,73)	66,02 (39,85; 99,92)	–
	Repeated annual revaccination Регулярная ежегодная ревакцинация			9941 (6032; 14 820)			72,49 (43,76; 109,24)
	Unregular vaccination (after 2 years or more) Нерегулярная вакцинация (через 2 года и более)		1520 (972; 2310)	7576 (4636; 11 281)		–	65,98 (39,83; 99,87)
Adult domestic dogs Взрослые домашние	Revaccination after 1 year Ревакцинация через 1 год	2119 (1678; 2691)	4182 (3347; 5242)	2153 (1754; 2623)	24,63 (18,21; 33,02)	41,39 (29,13; 55,81)	–
	Repeated annual revaccination Регулярная ежегодная ревакцинация			5480 (4343; 6845)			44,95 (31,97; 60,31)
	Unregular vaccination (after 2 years or more) Нерегулярная вакцинация (через 2 года и более)		855 (659; 1101)	4180 (3343; 5239)		–	41,38 (29,12; 55,80)

Note. *, data are presented as mean (M) with 95% confidence interval; «–» indicates the absence of data.

Примечание. * – данные представлены в виде среднего значения (*M*) с 95% доверительным интервалом; «–» – расчеты не проводились.

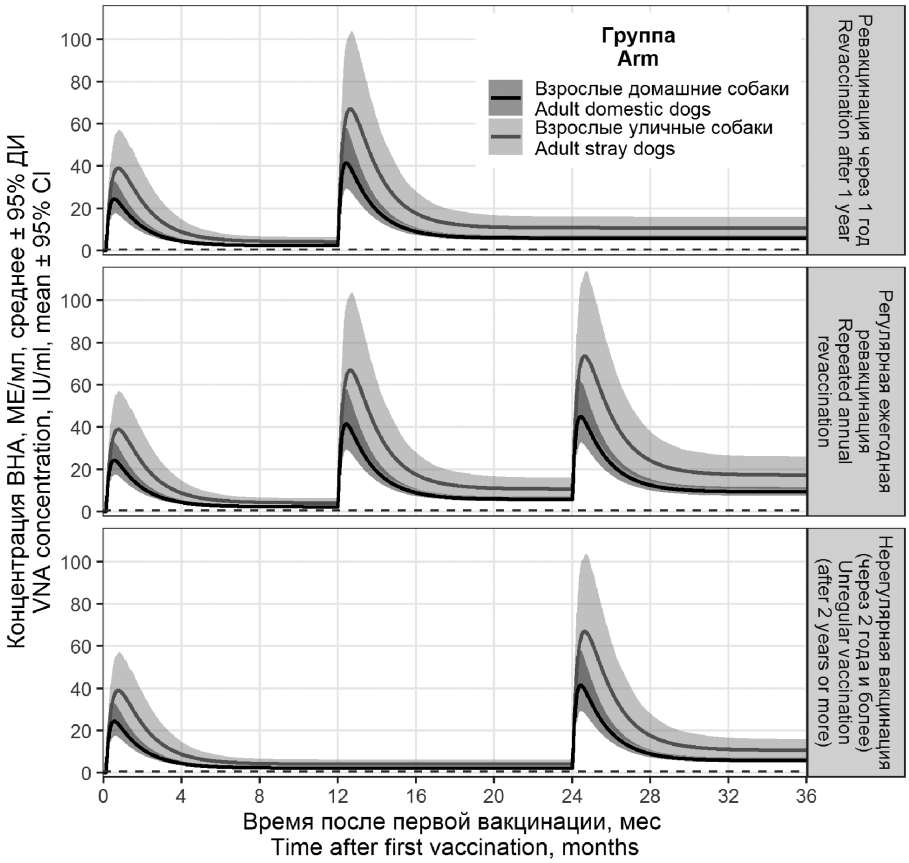

Fig. 6. Virus-neutralizing antibodies (VNAs) level in dogs' serum following the revaccination one year or more after the first vaccine administration (RFFIT as a method for antibodies detection): the results of model simulations.

Note. The horizontal dashed line indicates a protective antibody level of 0.5 IU/ml.

Рис. 6. Содержание вируснейтрализующих антител (ВНА) в сыворотке крови собак при ревакцинации через 1 год или позже от первого введения вакцины (метод определения антител RFFIT), результаты модельных симуляций.

Примечание. Горизонтальная пунктирная линия обозначает протективный уровень антител 0,5 МЕ/мл.

the same reference laboratory should be used to compare RFFIT and FAVN results [17]. We agree completely with our colleagues and see the correlation coefficient (*coef* = 9.82; RSE = 17.4%) obtained for RFFIT and FAVN results during the study as best-fit to our objective. We do not look at the above coefficient as the true correlation of RFFIT and FAVN results and do not recommend using this parameter in other studies and analyses. Note that model-calibrated initial values of rabies VNA titers in dog sera prior to the vaccination were 0.1 IU/ml in the RFFIT tests and 0.0227 IU/ml in the FAVN ones, demonstrating impeccable consistency with other researchers' data on pre-vaccination VNA levels lower than the threshold protective value of 0.5 IU/ml (**Table 1**) [2, 10, 14].

The humoral immune response of shorter duration found in the dogs vaccinated at the age under 3 months (**Fig. 4, 5**) also correlates with the data from other researchers [15, 18, 19]. The above phenomenon is explained by the presence of colostrum-acquired antibodies preventing robust humoral immune response to the vaccine and by the active development of the immune system and the entire body at this age [11, 20]. However, the results of our studies differ from the data presented by Nokireki et al., demonstrating that dogs under 1 year of age have a higher probability of VNA titers lower than 0.5 IU/ml [21]. One of the reasons can be that the dogs under study were not divided into age subgroups under 3 months and from 3 months to 1 year. Nokireki et al. pointed out that dogs under 1 year failed to reach the antibody titer of 0.5 IU/ml more often, if the time between the vaccination and the specimen collection was longer than 3 months. Shimazaki et al. also observed that dogs under 1 year had low VNA titers, which were insufficient for maintaining the protective level of antibodies for one year [22]. Such differences can be explained by the fact that the groups included a large number of animals vaccinated with a single dose before they reached the age of 3 months.

Unfortunately, the absence of individual data and detailed information about the breed, weight, and age of the animals as well as about the administered vaccines did not let us measure the effect of the above factors on the changes in rabies VNA levels in dogs' sera, as it had been done by other authors [15, 18, 21, 23]. Following Kennedy et al., we observed differences in the immune response to vaccination against rabies among beagle puppies [15]. Some researchers think that such differences can be asso-

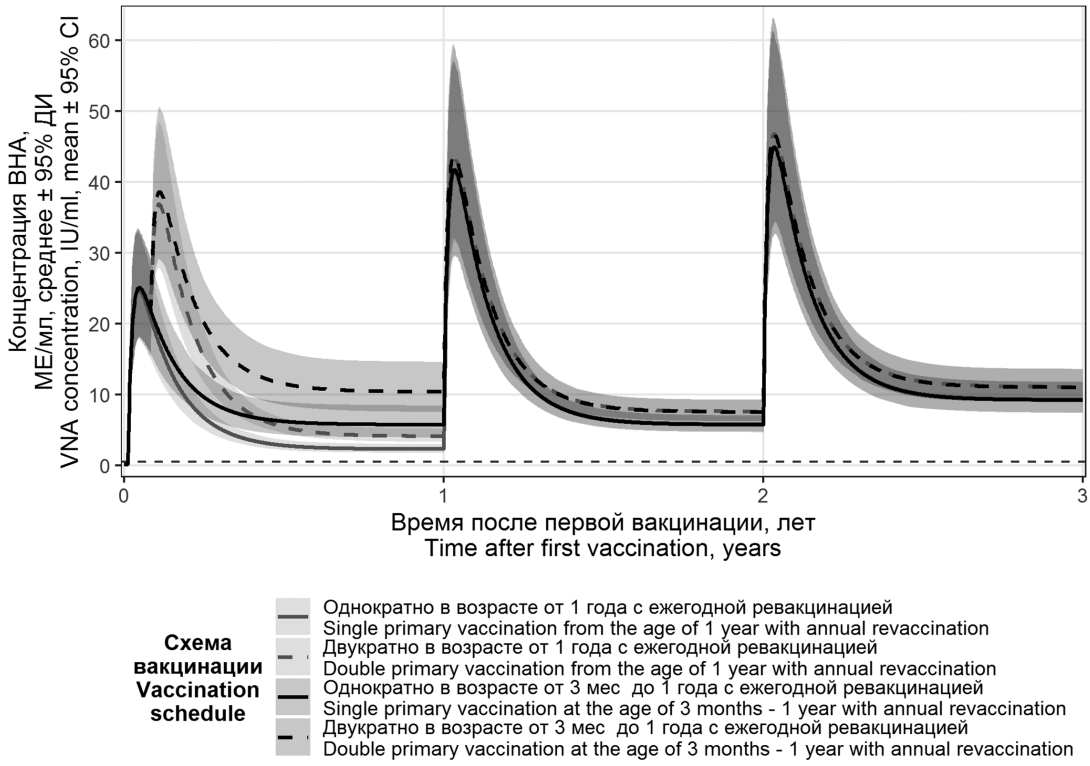

Fig. 7. Virus-neutralizing antibodies (VNAs) levels in dogs' serum following different vaccination schedules (RFFIT as a method for antibodies detection): the results of model simulations.

Note. The horizontal dashed line indicates a protective antibody level of 0.5 IU/ml.

Рис. 7. Содержание вируснейтрализующих антител (ВНА) в сыворотке крови собак при различных схемах вакцинации (метод определения антител RFFIT), результаты модельных симуляций.

Примечание. Горизонтальная пунктирная линия обозначает протективный уровень антител 0,5 МЕ/мл.

ciated with age-specific characteristics of animals rather than with their breed [18, 21].

Adherence to on-time revaccination of stray dogs can be highly challenging due to their free-roaming behavior and capturing costs. Our study shows that the revaccination of stray dogs with spacing of 1, 2, and even 3 years results in VNA titers reaching at least 0.5 IU/ml during the entire interim period (**Fig. 6**), demonstrating consistency with other authors' data. Following Moore et al. [24], we assume that the humoral immune response of longer duration will be induced in stray dogs after double-dose primary vaccination.

The detected differences in VNA levels in dogs' blood sera after single and double primary vaccination (**Fig. 7**) demonstrably support and provide the solid ground for MM-based assumptions incorporating the results of experimental studies. The importance of double-dose primary vaccination and ineffectiveness of single vaccination for dogs under 1 year were emphasized by many researchers [18, 23, 25–27]. However, quantitative measurement of the effect of the animals' age and vaccination schedule on changes in rabies VNA levels was frequently based on pair-wise comparison of groups by using different statistical criteria and a regression analysis [18, 27]. Only some authors used MM methods. For example, Suzuki et al. used a nonlinear mixed-effects model to assess humoral immune response after rabies vaccination of dogs in Bolivia [7].

The viability of annual revaccination of animals (including rabies revaccination) has been discussed for a long time [28, 29]. The results of our study (**Fig. 6**) and the data from other authors suggest that most of the dogs have rabies VNA titers not less than 0.5 IU/ml in their blood sera during 2 and more years after vaccination [30–32]. Refusal from annual revaccination is frequently equated with the concern about side effects associated with vaccines [33, 34]. Nevertheless, we recommend annual revaccination of dogs against rabies in compliance with the

[1]Order of Ministry of Agriculture of Russia dated November 25, 2020, No. 705 «On approval of the Veterinary rules for the implementation of preventive, diagnostic, restrictive and other measures, the establishment and cancellation of quarantine and other restrictions aimed at preventing the spread and elimination of rabies foci» (in Russian). Available at: https://rulaws.ru/acts/Prikaz-Minselhoza-Rossii-ot-25.11.2020-N-705/ (accessed 5 August, 2021).

[1]Приказ Минсельхоза России от 25.11.2020 N 705 «Об утверждении Ветеринарных правил осуществления профилактических, диагностических, ограничительных и иных мероприятий, установления и отмены карантина и иных ограничений, направленных на предотвращение распространения и ликвидацию очагов бешенства». Available at: https://rulaws.ru/acts/Prikaz-Minselhoza-Rossii-ot-25.11.2020-N-705/ (accessed 5 August, 2021).

Russian laws[1] and international recommendations [35], due to the adverse epizootic situation for this disease in the Russian Federation [36]. Annual revaccination is significant for generating and maintaining protective VNA levels in dogs having weak response to vaccination due to different factors (chronic diseases, age, breeds, etc.), thus protecting both the animal and its owner against rabies.

Conclusion

Based on the obtained results, we recommend the following rabies vaccination schedule for domestic dogs: the first and the second vaccination should be administered at the age of 3 months to 1 year, with 1–2-month spacing followed by annual revaccination. Further studies will provide an individual approach to vaccination with consideration for the breed, weight, age, previous vaccination schedule and general health of the animal to achieve higher effectiveness of vaccination and longer duration of immune protection against different infections. In addition, this work demonstrates the prospects for more extensive use of MM methods for preventive vaccination, including development and assessment of effectiveness of new vaccines, and, presumably, will give another impetus to development of this sector of research.

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