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Evaluation of the Effectiveness of Infectious Diseases Immunoprophylaxis: A Review of Our Own Research on the Model of Tick-borne Encephalitis

Galina N. Leonova*

Laboratory of Transmissible Infections, Somov Institute of Epidemiology and Microbiology, 690087, Vladivostok, Russia

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***Corresponding Author:**
Galina N. Leonova
Laboratory of Transmissible Infections
Somov Institute of Epidemiology and Microbiology
690087, Vladivostok, st. Sel´skay, 1
Email: galinaleon41@gmail.com
Tel/Fax: (423)244-14-38, (423)244-11-47

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ABSTRACT

Introduction: The tick-borne encephalitis (TBE) virus causes a dangerous neuroinfection in humans can serve as a model for studying the mechanisms of interaction of pathogens with specific antibodies during active and passive immunization. Several commercial vaccines are currently used against TBE. This review analyzes long-term studies aimed at explaining the active and passive efficacy of specific immunoprophylaxis against TBE. **Methods:** The effectiveness of "Encepur® adult" TBE vaccine has been studied in terms of seroconversion and strength of the immune response by serological reactions, namely IFA, ELISA and neutralizing were reviewed. **Results:** Rapid elimination of the virus (after 1-2 days) can occur in vaccinated individuals with antibodies in titers of more than 1: 400. Persons with antibodies in titers of 1: 100 and 1: 200, most likely, should be offered mandatory revaccination. It should also take into account the duration of the retention of post-vaccination antibodies. **Conclusion:** In the year of TBE vaccination, the immune response was at a high level and practically did not differ. A particularly high level of immune protection was observed in persons who were vaccinated by a combination of TBE vaccines of various producers.

Citation:

INTRODUCTION

Specific prophylaxis of infectious diseases provides for the prevention of the disease by creating artificial immunity to the pathogen through vaccination, which provide active immunization, or using drugs containing antibodies to the pathogen, which provide passive immunization. Immunoprophylaxis of infectious diseases is an important component of health protection and sanitary and epidemiological welfare of the population, and in some cases - the only effective measure for the prevention, reduction and elimination of infectious diseases [1].

The tick-borne encephalitis virus (TBEV), which causes a dangerous neuroinfection in humans, is a good model for studying the mechanisms of interaction of pathogens with specific antibodies during active and passive immunization. This virus, widespread in the temperate climatic zone of the Eurasian continent [2], is a member of the genus Flavivirus, the Flaviviridae family, which includes about 80 different types of viruses [3]. Many members of this family cause severe infectious diseases, such as yellow fever viruses, West Nile fever, Dengue fever, Japanese encephalitis, TBEV, and others. The TBEV consists of a spherical ribonucleocapsid surrounded by a lipoprotein membrane [4]. The genome TBEV, first deciphered by Russian researchers [5, 6], is represented by a single-stranded RNA of positive polarity, consisting of approximately 11,000 bases encoding one polyprotein, which has a size of 3414 amino acid residues (aa). The polyprotein, in turn, during maturation is cleaved by viral and cellular proteases to form 10 proteins, three of which are structural (M, C, E). The main structural membrane protein E mediates the binding of flaviviruses to cellular receptors, determining their tropism and virulence and providing the formation of neutralizing antibodies [7]. Based on its genetic structure and antigenic properties, TBEV was subdivided into three subtypes: Far Eastern, European and Siberian [8, 9].

Belikov S.I. *et al*. [10], analyzing the whole genome nucleotide sequences of TBEV strains of the Far Eastern subtype, concluded that there is a relationship between the TBEV genome regions and the virulence of the strains. Phylogenetic analysis of the complete genomes of 84 TBEV strains isolated in the Russian Far East showed significant variability of the Far Eastern virus population [11, 12, 13]. The 17 substitutions of amino acid residues identified by us significantly distinguished the strains that caused focal and subclinical forms of the disease. A detailed analysis of the location of key amino acid substitutions in the genomes of TBEV strains of the Far Eastern subtype showed that changes in the pathogenicity of strains causing diseases of various severities are most likely associated with amino acid

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substitutions in capsid protein C, PrM protein, and NS3 / NS2B protein complex. These proteins are involved in the formation of the nucleocapsid and its incorporation into the cell membrane for subsequent budding and exit from the cell. The efficiency and perfection of this process depends on the accuracy of the coordinated action of the above proteins, which contributes to the formation of TBEV strains with varying degrees of pathogenicity for humans. The study of the genetic variability and diversity of TBEV strains is the basis for the further development and improvement of methods for the prevention, treatment and diagnosis of TBE. The purpose of this review is to show the effectiveness of active and passive specific immunoprophylaxis of viral infectious diseases on the model of tick-borne encephalitis.

MATERIALS AND METHODS

Evaluation of "Encepur® adult"

The effectiveness of the vaccine "Encepur® adult" produced by GSK Vaktsins GmbH (Germany) has been studied in complex studies. The seroconversion and strength of the immune response were carried out by the following serological reactions. For experiments on the *in vitro* model, "Human immunoglobulin against tick-borne encephalitis" produced by NPO Microgen (series P609) has been used.

Indirect Fluorescent Antibody (IFA)

An IFA assay was used to detect antigens in a cell line kidney embryo pigs (PEK). Antigen of TBE virus inside the cells was detected by applying immune serum against TBEV and further against fluorescent immunoglobulin (FITS) with its operating dilution, as stipulated in the manufacturer's manual («MEDGAMAL» Branch, N.F. Gamaleya Research Institute of Epidemiology and Microbiology, Russian Academy of Medical Sciences).

ELISA

Antibodies of the IgG class were determined in ELISA, for which a "Vecto-TBE-IgG" kit (AO "Vector-Best", Novosibirsk) was used according to the manufacturer's instructions.

Determination of Neutralizing Antibodies

To determine neutralizing antibodies, a one-day monolayer of transplanted PEK cells, grown in 24-well plates, was used. The TBE virus, containing a standard dose of 2 log TCID/ml, was combined with 2-fold dilutions from 1:10 to 1: 3200 of the studied blood serum samples. The mixture was kept at a temperature of 37 ° C for 1 h, followed by application onto a monolayer of cells PEK. The results of the infectious activity of the non-neutralized virus were taken into account on the 5-6th day. A detailed presentation of the materials and research methods have been described in the specified publications by Leonova G.N. in the period from 2005 to 2020.

RESULTS

Vaccine prophylaxis against tick-borne encephalitis (active immunization)

To address the issues of specific prevention of TBE, several vaccines are currently used: "Tick-borne encephalitis vaccine cultural purified concentrated inactivated dry "(TBE-Moscow) and "Tick-E-Vak" produced by FGBNU "FNTSIRIP im. M. P. Chumakov RAS" (Russia), "EnceVir®" and "EnceVir® Neo for children" manufactured by FSUE NPO Microgen of the Ministry of Health of Russia (Russia), "FSME-Immun®"and "FSME-Immun® Junior" manufactured by Pfizer Inc. (Austria), Encepur® adult and Encepur® for children produced by GSK Vaktsins GmbH (Germany), SenTaiBao (Changchun, China). Modern high-tech inactivated purified concentrated whole-virion culture vaccines against TBE, with the general similarity of their production technologies by different manufacturers, have some differences that do not affect the final protective properties and safety of vaccine preparations, which can ensure their interchangeability [14].

We studied the features of the formation of the immune response during vaccination against TBE on the model of the vaccine preparation "Encepur® adult" (Germany) [15, 16]. According to experimental studies [17], the immunogenic (protective) activity of the Encepur® adult vaccine, which contains the lowest amount of TBEV protein - 1.5 μg, turned out to be significantly lower than the indicators established for domestic TBE vaccines and for the FSME-Immune vaccine. In persons vaccinated with the German vaccine, cases of TBE have not been described in the literature.

It is known that currently used vaccine preparations against various infections cause short-term, non-severe health disorders that do not leave persistent pathological changes, which are called post-vaccination reactions [18]. Despite the fact that the highly purified vaccine "Encepur® Adult" is practically devoid of protein impurities, some post-vaccination symptoms were registered in some of the vaccinated persons: soreness, hyperemia at the injection site, short-term low-grade fever, and general malaise. Moreover, in persons with a post-vaccination reaction, we revealed a general tendency for more active accumulation of IgG antibodies in ELISA, as well as neutralizing antibodies, which indicated the specific nature of this process. With the standard vaccination schedule, the most significant difference was demonstrated by immunological parameters in blood samples 1 month after the 3rd vaccination. In the group of vaccinated persons without post-vaccination complications, the indicator of the geometric mean antibody titer (GTA) in the virus neutralization test (NT) was significantly lower (1:97) than in the group of persons with a reaction (1: 194). It was also shown that young people with a high frequency of post-vaccination reactions had higher indicators of cellular and humoral immunity to TBEV than those vaccinated in the older age group [19]. Post-vaccination reactions in vaccinated individuals cannot be completely ruled out, since, as we have shown [15], they are also caused by a reaction to a foreign protein, the TBEV antigen, which is always present in any vaccines. An example of this is modern recombinant as well as inactivated new vaccines against the SARS-CoV-2 virus, the different degree of reactogenicity of which is also impossible to avoid [20].

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The differences in the strength of the immune response in men and women vaccinated against TBE are shown. In all age groups of women, a more pronounced immune response was found in comparison with men. This difference is especially pronounced after the 3rd vaccination: in women, the GTA indicator in the virus neutralizing test reached 1: 208, compared with this indicator in men - 1:91.

When studying the specific activity of the vaccine "Encepur® adult" in the reaction of inhibition of hemagglutination, IFA and the reaction of neutralization in relation to three regional strains of the TBE virus (Dal'negorsk, Primorye-202, Primorye - 69), the highest rates of the immune response were revealed to the highly virulent Dal'negorsk strain isolated from the brain of a deceased patient with focal TBE. The lowest rates of the immune response were determined to the Rrimorye-69 strain, which was isolated from the blood of a patient with an unapparent form of TBE [15]. At the same time, it was noted that over time, there is a gradual decrease in the indicators of the immune response in vaccinated individuals. It follows from this that for further revaccination; it is desirable to determine in the blood serum of these persons not only the presence (amount, %) of specific antibodies, but also the strength of the immune response (antibody titers).

The widespread use in practice of only ELISA indicators for the diagnosis of viral diseases, as well as for the study of the immunological effectiveness of vaccine prophylaxis, does not allow judging the functional activity of the detected antibodies [21]. In the acute period and during convalescence of patients with viral infections, a test for determining the avidity of specific IgG antibodies has begun to be widely used [22-25]. For example, in the study of rubella, it was shown how important it is to distinguish between immune antibodies after vaccination from antibodies that appear in the acute period of this infection [21].

Determination of the degree of avidity of antibodies in vaccinated against TBE was also informative. Using ELISA, we conducted a comparative analysis of the distribution of IgG avid antibodies depending on the duration of vaccination in vaccinated individuals [15]. It was shown that in the year of vaccination, highly avid antibodies prevailed. The proportion of persons with an avidity index of 80-89% was determined in 38% of cases, and with an avidity index of more than 90% - in 27.6%. Two years after vaccination, the proportion of people with high antibody activity in both groups dropped significantly to 17.6%.

Protective Titer of Specific Antibodies

The concept of protective antibody titer appeared in the study of the immunological activity of vaccines. In this case, the effectiveness of prophylactic vaccines against any infection is assessed by the level of immunological parameters that provide a protective effect [26]. In scientific literature, information on the protective titer of antibodies in persons vaccinated against TBE is rarely found [27], and until now the concept of protective antibody titer is a subject of discussion [28]. For the first time the titer of hemagglutinating antibodies to TBEV 1:10 was defined by Austrian researchers as protective in 1980 [29].

In recent years, more attention has been paid to this issue due to the fact that, according to the results of ELISA, low (1: 100) titers of IgG antibodies (up to 40-44%) are formed in persons vaccinated against TBE [30]. This is probably why vaccinated persons infected with TBEV can develop febrile forms of infection, and in rare cases even lethal outcomes have been described [31]. Although it is known that some people, even after a course of primary vaccination, can develop antibodies with high titers, which can persist for a long time [15, 27].

In previously published works [32, 33] (on an *in vitro* model), the level of immunological memory (1: 100) and the level of protective titer (1: 400) of specific antibodies were determined using ELISA. We decided that this level of specific antibodies could provide protection for patients in the early stages of infection immediately after a tick bite containing TBEV.

In addition, in experimental tests *in vitro* and *in vivo* 3, 24, 48, 72 h after infection with different strains of PEK culture cells and non-inbred mice, we showed different degrees of virus activity that was not neutralized by specific immunoglobulin [32]. It was found that specific immunoglobulin in a titer of 1: 100 did not have a protective effect; in a titer of 1: 400 it did not inhibit the highly virulent strain Dal'negorsk, but protected the weakly virulent strain Primorye-437, and only in a titer of 1: 3200 inhibited both strains completely. However, until now, in official practice, it is considered to be a protective titer of antibodies according to ELISA data 1: 100, and according to the neutralization reaction - 1:10 [29, 34].

In subsequent experiments, based on comparative experimental studies *in vitro*, ex vivo and *in vivo*, additional data were obtained to substantiate the antiviral activity of specific antibodies with different titers in relation to the highly virulent strain TBEV Dal'negorsk [33]. On an *in vitro* model, we used "Human immunoglobulin against tick-borne encephalitis" produced by NPO Microgen (series P609), its titer in ELISA was 1: 3200. Evidence was obtained for the direct neutralizing effect of specific class G antibodies with titer of 1: 100, 1: 400 and 1: 3200 on the TBE virus. At the same time, in the dynamics of observation up to 72 hours after infection, it was also shown that antibodies in a titer of 1: 400 are not able to completely eliminate TBEV in a titer of 3.0 log TCID / ml. Specific antibodies with only high titers (1: 3200) completely neutralized the virus and protected the PEK cell culture monolayer from the cytopathic effect of TBEV.

On another experimental model ex vivo (blood of vaccinated individuals with different titers of antibodies to TBEV: 1: 100; 1: 200; 1: 400; 1: 800; 1: 1600; 1: 3200), we obtained evidence of the effective action of specific antibodies in combination with other factors. Using this biological model - the closest to the natural model (a person vaccinated against TBE), we showed that in samples with specific antibodies in titers of more than 1: 400, the virus was neutralized quickly (after 24 hours). Under the action of antibodies in titers of 1:

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100 and 1: 200, the elimination of the virus also occurred, but at a later date - 3-4 days after infection of the blood samples. In addition, we also drew attention to the fact that the antibody titers according to ELISA and the neutralization reaction in the supernatant of the ex vivo experimental samples remained practically at the same level throughout the observation period. This allowed us to believe that the interaction of TBEV with specific antibodies does not reduce their titers if the amount is more than 1: 200. Delayed elimination of the virus occurred under the action of antibodies with titers of 1: 100-1: 200, reducing them to negative values, which indicated a rapid depletion of the antibody stock in these samples. Apparently, such circumstances (a low amount of antibodies in the presence of TBEV, more than 3.0 log TCID / ml) do not interfere with the reproduction of the virus. In vaccinated individuals with such titers of specific antibodies, cases of the disease may occur, which has been repeatedly described in the literature [31, 35]. The obtained ex vivo results required additional verification of the infectious activity of TBEV in experimental tests using a model of non-inbred white mice. The antiviral activity of antibodies with different titers was shown at different periods of observation (1 h, 24 h, 48 h, and 72 h). Experimental animals infected with a blood sample, 1 h after infection with TBEV, practically did not survive. In all experimental blood samples containing different titers of antibodies from 1: 100 to 1: 1600, 72 h after infection, TBEV was almost completely neutralized; therefore, animals infected with these samples survived 80–100% [33].

Therefore, what titer of specific antibodies is able to protect against the development of the infectious process of tick-borne encephalitis? Apparently, this indicator is individual with the inclusion of a complex of factors. It is believed that for each individual person, the risk of developing a manifest form of an infectious disease against the background of pre- or post-exposure prophylaxis depends on the combined influence of several factors: on the characteristics of the macroorganism, the properties of the pathogen and the conditions for using a specific immunoglobulin [36, 37]. The factors of the first group include age, gender, resistance of the organism, including acquired and genetically determined features of the immune system; the second - the molecular genetic properties of the virus and its infecting dose. The third group of factors, according to the authors, should include the amount (dose) of antibodies, the timing and frequency of their use relative to the moment of infection, the specificity of antibodies relative to structural and non-structural viral proteins.

The presented experimental data make it possible to understand the reasons for the development of the infectious process in vaccinated individuals after being bitten by a tick infected with a virus. To make the right decision on the timing of revaccination, we initially recommend testing the blood for the strength of immunity to TBEV. Based on the data obtained [32, 33, 38], we came to the conclusion that rapid elimination of the virus (after 1-2 days) can occur in vaccinated individuals with antibodies in titers of more than 1: 400. Persons with antibodies in titers of 1: 100 and 1: 200, most likely, should be offered mandatory revaccination. It should also take into account the duration of the retention of post-vaccination antibodies. In European countries revaccination is carried out 5 years after the full course of vaccination [39, 40], in Russia - after 3–6 years [41].

Our studies showed that in the year of vaccination, the immune response in the groups of people vaccinated with different vaccines against TBE was at a high level and practically did not differ [15]. A particularly high level of immune protection was observed in persons who were vaccinated with a combination of TBE vaccines of various producers. Indicators of seroconversion and strength of the immune response in different serological reactions (ELISA, IFA and NT) relative to the virulent and immunogenic strain TBEV Dal'negorsk in these individuals were high. Two years after the completion of the course of vaccination with mono-drugs of various manufacturers, as well as with combined vaccination, these indicators decreased. The gradual decline the level of immunological protection in these individuals indicated that this trend will continue in subsequent years. In this regard, during the period after the full course of vaccination and subsequent revaccination, we recommend periodically monitoring the intensity of humoral immunity, which will help protect persons affected by the bite of an infected tick with the TBE virus from disease.

Passive immunization, mechanisms of the protective action of specific antibodies against tick-borne encephalitis

In historical essays about the discovery of tick-borne encephalitis in the Far East in 1937 by the first expedition led by the virologist L.A. Zilber neurologist A.N.Shapoval [42] recalled that M.P. Chumakov suggested using serum from the blood of patients with TBE to treat severe forms of this neuroinfection. Already in those days, undeniable data on the therapeutic effect of serotherapy were obtained for the first time. However, over the entire historical period, serotherapy, and now immunoglobulin therapy, was assessed not only positively, but was also criticized by various authors (43, 44, 45).

Pinevskaya N.A. *et al*. [36, 37] analyzed the data accumulated in the literature and their own results on the study of the protective activity of antibodies to TBEV, optimal doses and timing of administration. In the course of the analysis, it was found that all works with a negative assessment of the effectiveness of anti-tick immunoglobulin (IG) drugs contain research results, the design of which from the standpoint of evidence-based medicine is unsuitable for solving this issue. For example, when using specific antibodies, the phenomenon of immune enhancement of the infectious process of TBE, which is widely discussed in the scientific community [46], has never been detected in medical practice [47-50]. At the same time, based on the analysis of numerous experimental and epidemiological observations, it was concluded that, along with the inconsistency of some of the results obtained, seroprophylaxis reduces the likelihood of TBE disease by 3-5 times [42]. According to Pen'evskaya N.A. [36, 37], despite the

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presence of gaps in modern knowledge about the mechanisms of antibody-mediated antiviral protection, the multi-vector action of specific antibodies differs in their pre-exposure and post-exposure use. First, specific antibodies suppress the entry of the virus into the eukaryotic cell and the exit from it of the replicated offspring. They can neutralize the virus on their own and with the participation of complement, inhibit the activation of the complement system and prevent complement-mediated tissue damage, and can also stimulate endogenous humoral and cellular immune responses, inducing long-term protective "vaccine-like effects". Specific antibodies promote the activation of T-cell mechanisms of antiviral defense, regulate the production and activity of cytokines; in cooperation with interferons, they can also suppress the reproduction of the virus within cells [47, 51-54].

This multi-vector judgment of different specialists about the effectiveness of specific immunoglobulin in emergency prevention and treatment of TBE has determined the need for experimental studies that clarify and complement the mechanisms of action and effectiveness of this drug [55]. Preclinical studies of the mechanisms of the protective action of specific antibodies against TBEV were carried out using an *in vitro* model. The effect of specific IgG on TBEV was assessed comprehensively in terms of virucidal, prophylactic, direct antiviral action and intracellular inhibition (therapeutic action). We used the results obtained in ELISA, on the titration of the virus and calculated by the coefficient of inhibition (IC). Using nonlinear regression analysis of the percentage of antigen-positive samples in ELISA, the values of half the maximum inhibitory concentration (IC50) of antibodies were obtained: at virucidal action - 3.8 ± 0.7 U / ml, prophylactic - 42.8 ± 9.9 U / ml, at direct antiviral - 7.2 ± 0.9 units / ml and therapeutic action - 1.7 ± 0.4 units / ml [55].

Considering the results of the virus-inhibiting properties of IG under different model research schemes, it is possible to explain the mechanisms of action of specific antibodies. Based on the data of the virucidal action of IG, quite expected results were obtained, indicating the neutralization of TBEV under the action of specific antibodies. The results of such experiments were described by us many times, in which in different variations of experiments *in vitro*, ex vivo, *in vivo*, a direct neutralizing effect of IG with respect to TBEV was established [27, 32, 33].

The scheme of a prophylactic model for the use of IG provided for the action of antibodies for 2 h directly on cells of a highly sensitive culture of PEK, followed by their infection with TBEV. At the same time, it is generally accepted in clinical practice that the prophylactic use of a particular IG consists in its application within 1-3 days after a tick bite, in which TBEV markers were identified. A.N. Shapoval [42] believed that specific antibodies can bind not only to TBEV, but also to cells of tissues sensitive to the virus, and thereby help to protect the body from the action of the virus. This means that in medical practice, it is more correct to consider specific immunoprophylaxis not as emergency prophylaxis, but as emergency treatment of a patient in the early period of TBEV infection. The effectiveness of such passive immunization, according to a number of authors, reaches more than 60% [56, 57]. The same effect of passive immunization can be observed in the experimental scheme of the direct antiviral action of IG on TBEV, including the simultaneous adsorbing effect of the virus and IG on PEK cells. Here, despite the short duration of the interaction of IG with the virus (1 h), the possibility of the transit of IG associated with the virus into sensitive cells was shown. Complete elimination of the virus occurred only at a drug concentration of 32 U / ml [55].

With prolonged action of IG (therapeutic scheme of the experiment), the highest efficiency of inhibition of the virus, which is not only outside the cells of PEK, but also penetrated into cells together with IG, was shown, which indicated the intracellular mechanism of the inhibitory action of IG on TBEV. Neutralization of the virus began to occur under the action of IG at a dose of 4 U/ml, and complete protection of the cells occurred at an IG concentration of 8 U/ml. This means that a virus directly associated with homologous antibodies penetrates into a sensitive cell and can provide a therapeutic effect of anti-tick-borne IG in various forms of the infectious process, as has been shown by many authors [43, 45].

DISCUSSION

This review analyzes long-term studies aimed at explaining the active and passive efficacy of specific immunoprophylaxis for tick-borne encephalitis. The knowledge gained can be used to address prevention issues for other viral diseases. Based on the experiments carried out, it was important to show that specific antibodies are capable of exerting a complex inhibitory effect on TBEV, having both a direct neutralizing activity directly on the virus and reducing its adsorption and intracellular replication [55]. This gives grounds to consider specific IG as a highly effective antiviral drug, reasonably used for the treatment and passive immunization of persons infected with TBEV [36, 37, 43, 44, 45]. The experience of the historically known serotherapy of TBE is being successfully introduced into the treatment of new previously unknown infections, such as, for example, COVID-19 [58]. At the same time, anti-TBE serum immunoglobulin preparations obtained from donor blood have disadvantages - an increased risk of infection with known and unknown pathogens, the indication of which is difficult or sometimes impossible [57]. Therefore, research on the development of new alternative drugs for the emergency prevention of TBE and other viral infections is currently relevant.

At the same time, the obtained data help to understand that it is unlikely that the antibodies contained in the IG preparation can actively affect directly the cells of the body, including the cells of the PEK culture sensitive to TBEV [55]. Complete protection of cells from TBEV in the prophylactic scheme of the experiment occurred only at a high concentration of antibodies (320 units / ml), which can be achieved in persons vaccinated against TBE. In this regard, in the period after the full course vaccination and booster, it is possible to recommend

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periodic monitoring of the intensity of humoral immunity, which will help to decide on the need for the next revaccination [32, 33]. In modern conditions, the risk group should include people working and living in endemic areas for tick-borne encephalitis [16, 34]. Due to the fact that this infection is an urgent problem for public health in Central, Northern and Eastern Europe, vaccination against tick-borne encephalitis is recommended at the national level in many countries (Czech Republic, Slovenia, Estonia and Latvia). In Russia, vaccinations against TBE are included in the National Calendar of Preventive Vaccinations [59].

The demonstrated effectiveness of complex vaccination against TBE with drugs from different manufacturers helps to understand the current challenges regarding vaccination for other viral infections, for example, against the newly emerging infection COVID-19, for the prevention of which various vaccine preparations are being developed [60]. This is due to the fact that at present, numerous vaccine preparations are constantly being created to prevent new infections, for example, COVID-19. In the future, it is necessary to study the effectiveness of their combined use in order to justify the widespread use of vaccines from different manufacturers.

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CONFLICT OF INTEREST

The author declares that she has no conflict of interest.

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