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ОРИГИНАЛЬНЫЕ ИССЛЕДОВАНИЯ

SCIENCE AND PRACTICE

Reactogenicity, safety and immunological efficacy of the live, pentavalent rotavirus vaccine in childhood immunization (results of the multicenter clinical trial)

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Introduction. Rotavirus infection (RVI) is the most common cause of severe gastroenteritis in infants and young children worldwide: 600,000 children die annually; it accounts for approximately 3 million hospitalizations and 25 million physician visits each year among children. Preventive vaccination is universally recognized as the most effective measure against this infection. **The purpose** of the study is assessment of reactogenicity, safety and immunogenicity of the pentavalent live vaccine for RVI prevention in childhood immunization.
Materials and methods. The first multicenter prospective, randomized, double-blind, placebo-controlled clinical trial of the pentavalent live vaccine for RVI prevention was conducted in Russia among healthy infants aged 2 months at the time of the first vaccination.
Results. The vaccine had a satisfactory safety profile and high immunologic activity when administered in a three-dose series for childhood immunization. No negative changes in the children's health condition were detected during the surveillance monitoring.
Discussion. The seroconversion rates, the seroconversion factor and the geometric mean antibody titer were consistent with the results obtained during trials of the above vaccine and its equivalents in other countries.

Keywords: *rotavirus infection; children; live, pentavalent vaccine; immunogenicity; safety; reactogenicity.*

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Реактогенность, безопасность и иммунологическая эффективность вакцины для профилактики ротавирусной инфекции пентавалентной живой при иммунизации детей (результаты многоцентрового клинического исследования)

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Введение. Ротавирусная инфекция (РВИ) является наиболее распространенной причиной тяжелого гастроэнтерита у детей раннего возраста во всем мире: ежегодно 600 тыс. детей в мире умирают, около 3 млн нуждаются в госпитализации, 25 млн требуется врачебная помощь. Основной мерой борьбы с данной инфекцией признана вакцинопрофилактика. **Цель** работы — оценка реактогенности, безопасности и иммуногенности вакцины для профилактики РВИ пентавалентной живой при иммунизации детей.
Материалы и методы. В России впервые проведено многоцентровое проспективное рандомизированное двойное слепое плацебо-контролируемое клиническое исследование вакцины для профилактики РВИ пентавалентной живой с участием здоровых детей в возрасте 2 мес на момент первой вакцинации.
Результаты. Вакцина характеризовалась удовлетворительным профилем безопасности и высокой иммунологической активностью при трехкратной иммунизации детей. Отрицательной динамики в состоянии здоровья детей в ходе наблюдения не выявлено.
Обсуждение. Показатели сероконверсии, фактора сероконверсии и средней геометрической титров антител были сопоставимы с результатами зарубежных исследований как данного препарата, так и его аналогов.

Ключевые слова: *ротавирусная инфекция; дети; вакцина пентавалентная живая; иммуногенность; безопасность; реактогенность.*

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Introduction

Rotavirus infection (RVI) is the most widespread enteric infection almost in all countries of the world. According to data from WHO experts, among 1.0–1.2 billion diarrheal disease cases reported annually, viral infections account for 49–67% [1, 2]. The factors contributing to the high prevalence of RVI are as follows: Impossibility to fight effectively the source of infection due to a large number of carriers and lack of etiotropic therapy, uncontrollable modes of transmission, high contagiousness of the virus and low efficiency of disinfectants [3–5]. Being highly contagious (children can excrete ≥10 billion viral particles per milliliter of feces, while the minimal infective dose is 10 plaque-forming units/ml), RVI is one of the most common causes of hospital-associated diarrhea cases, which during some seasons can reach 87% [6–9].

According to the data from WHO experts, the RVI incidence varied widely across countries: 250–3,000 cases per 100,000 children. Every year, the Unites States reports more than 1 million cases of severe rotavirus-related diarrhea among patients aged 1–4 years [10–13]. The US-based large-scale studies showed that before the RVI vaccination program was launched, 80% of children had been seropositive, i.e. had already experienced rotavirus infection. The similar studies conducted in Poland in 2008 confirmed RVI presence almost in every third child with acute enteric infection [14, 15].

According to WHO, RVI is the leading cause of gastroenteritis in children younger than 5 years of age both in high-income and low-income countries. A significant difference is observed only in mortality rates being much higher in developing countries, which account for 82% of all RVI deaths worldwide.

Yet, RVI remains to be a pressing problem in developed countries. European experts have estimated that there are 3.6 million episodes of rotavirus gastroenteritis annually among 23.6 million children under the age of 5, living in European Union countries; the estimated annual rate of clinical rotavirus gastroenteritis is 1 case in every 7 children [16]. The infection is responsible for 231 deaths, more than 87 thousand hospitalizations, and nearly 700 thousand outpatient visits annually. In EU countries, the rotavirus-associated mortality is low; however, it is RVI that

contributes to high incidence among pediatric population demonstrating a large number of clinical forms requiring hospitalization and emergency room visits. The average length of a hospital stay is 2–10 days; the cost of hospital stay is 1,500 euros [15]. In the total number of cases of acute gastroenteritis in children under 5 in European countries, the proportion of rotavirus gastroenteritis ranges from 25.3% (Greece) to 63.5% (Norway). In other countries, this proportion is 36–45% [16, 17].

According to the WHO data, RVI holds the second place after pneumococcal disease in the child mortality caused by vaccine-preventable diseases [18–21]. In 2011, diarrheal disease accounted for 9.9% of 6.9 million deaths in this age group, where more than 70% of the deceased were younger than 2 years [14, 18, 19]. Among the etiologically deciphered viral diarrheas, RVI is detected in 65% of cases, being responsible for 17.8% fatal diarrhea cases. Thus, 197 thousand deaths are annually attributable to rotavirus gastroenteritis, meaning that 23 children die of the infection every hour [14, 18, 20, 21].

In Russia, among acute enteric infections, the virus infections (rotavirus and norovirus infections) account for more than 50%. In Russia, RVI incidence has been demonstrating upward trend for the last 10 years, and in 2018 it was responsible for 81.3 cases per 100 thousand people. Apparently, this dynamics can be attributed to improved quality of laboratory diagnostics of acute enteric infections, thus giving a better picture of the main viruses causing acute gastroenteritis in Russian population [22]. The virus carriage rate among young children is 1.5–9.0% [23].

Preventive vaccination is the most effective measure against this infection. At present, vaccination against RVI is adopted in 69 countries and is included in immunization schedules in the United States, Belgium, Germany, Austria, some countries of Latin America, etc. [24–26]. The vaccination series consists of 2–3 doses administered orally at 4 to 8-week intervals during the first 6 months of life (concomitantly with diphtheria, tetanus, pertussis, polio and haemophilus influenza type B vaccines). The immunization effectiveness reaches 70–80% protection and shows 100% reduction in hospitalization or intravenous rehydration cases [27, 28]. In Mexico, RVI vaccination during the first 3 years resulted in 700 fewer deaths a year among children from the time of vaccination [25]. The Russian National Immunization Calendar (NIC) does not include immunization of children against RVI. Vaccination is performed only in some regions of Russia in accordance with regional immunization programs (schedules).

Two attenuated rotavirus vaccines are currently licensed and successfully used worldwide — pentavalent reassortant RotaTeq (Merck Sharp & Dohme B.V., The Netherlands) and monovalent Rotarix (GlaxoSmith-Kline Trading, Belgium). Only one vaccine, RotaTeq, has been registered in the Russian Federation. It contains 5 reassortant rotaviruses: 4 rotaviruses express VP7 outer capsid proteins of serotypes G1, G2, G3, G4 from the human rotavirus parent strain and the VP4 protein of serotype P7 from the bovine rotavirus parent strain. The fifth reassortant virus expresses the P1A protein from the human strain and the G6 protein from the bovine rotavirus parent strain [29, 30]. Russia has no home-produced vaccine against RVI.

In 2014, a new thermostable oral pentavalent vaccine based on bovine rotaviruses was created in India. Since 2018 it has been internationally available as a WHO-prequalified vaccine. This immunological formulation was tested in India where it demonstrated high efficacy (66.7%) [30, 31].

The clinical trials (phases I, II, and III) of the live, pentavalent RVI vaccine (BRV-PV) (Serum Institute of India Ltd., India) were conducted in India and Niger, with more than 15 thousand people scheduled for participation. The studied groups included adults, young children and infants. Safety and good tolerability of BRV-PV was demonstrated by all age groups during the clinical trials. No serious unsolicited events were reported. A few reported unsolicited events were mild to moderate and transient. No virus shedding was detected in stool samples.

The conducted clinical trials demonstrated the highest immunogenicity and protective efficacy of BRV-PV when administered to children aged 4–6 weeks as a 3-dose series. Three doses of the vaccine were administered concomitantly with diphtheria, tetanus, pertussis, haemophilus influenza type B, hepatitis B, and polio vaccines. This approach helped significantly expand the BRV-PV immunization coverage and cut expenses incurred by parents when visiting vaccination centers.

Considering the foregoing and to have the vaccine officially registered in Russia, healthy volunteers aged 18-45 years were invited to participate in a prospective, randomized, double-blind, placebo-controlled clinical trial of safety and efficacy of BRV-PV. The trial was conducted in compliance with the Clinical Trial Protocol No. PTB 001/18. The Ministry of Health of the Russian Federation issued the authorization for conducting clinical trials in children (No. 46, 29/1/2019).

The purpose of this study is to assess reactogenicity, safety and immunological efficacy of BRV-PV with participation of children. It is our first study of this vaccine during immunization of young children in Russia.

Materials and methods

Reactogenicity, safety and immunological efficacy of BRV-PV were studied during the multicenter prospective, randomized, double-blind, placebo-controlled clinical trial with participation of healthy children 2 months of age at the time of the first vaccination.

BRV-PV is sterile lyophilized powder of pink to yellow-white color, pH 6.8–8.8. The powder is diluted in citrate-bicarbonate buffer, which prevents inactivation of the formulation in a stomach acid medium. The citrate-bicarbonate buffer contains sodium bicarbonate and citric acid monohydrate. The diluent is a clear colorless liquid. The powder should be diluted immediately before use. One dose (2.5 ml) contains human and bovine live reassortant rotaviruses grown in Vero cells: Not less than $10^{5.6}$ FFU of each rotavirus type G1, G2, G3, G4 and G9. All strains contain the VP7 gene of the corresponding serotype from human rotavirus strains reassortant with the bovine rotavirus.

Bovine and human reassortant strains of serotype G1, G2, G3, G4 and G9 were received by the Serum Institute of India Ltd. (India) from Dr. Kapikian (The National Institutes of Health, USA). The Serum Institute of India Ltd. prepared the primary virus strain vaccine bank, the secondary virus strain vaccine bank and the working virus strain vaccine bank to be used in manufacturing of monovalent bulk vaccine. During manufacturing of future ready-to-use formulations, sucrose and glycine were used as stabilizers to provide stability of the vaccine at different temperatures.

The clinical trial with participation of children was conducted in compliance with the ethical rules and regulations specified in the Declaration of Helsinki (2013) and practice guidelines applicable to clinical trials conducted in Russia.

The trial was conducted in two clinical centers: Perm and Tyumen.

Inclusion criteria: healthy infant males or females aged 2 months at the time of the first vaccination, having no contraindications to immunization, whose gestational age is ≥37 weeks, birthweight is ≥2,500 g and who are vaccinated in accordance with their age-related immunization schedule. To have their child enrolled, the parents must sign their informed consent by their own hand and voluntarily as well as adhere to the requirements of the protocol.

Exclusion criteria:

- pre-existing diarrhea or blood in stool history or defecation disorder during the last 14 days;
- chronic diseases of the gastrointestinal tract, intussusception and congenital gastrointestinal tract defects;
- abdominal surgery;
- allergy to any components of the vaccine or to any previous vaccination;
- severe vaccine-induced reactions and complications associated with any previous vaccination;
- existence of any systemic disorder in lungs, the liver, kidneys, skin, the cardiovascular system, the gastrointestinal tract, the endocrine system, the immune system, the nervous system as well as oncology or autoimmune disease;
- congenital or genetic disorders;
- acute infectious or non-infectious diseases at the time of enrollment or less than 4 weeks after recovery;
- history of confirmed hepatitis B, diphtheria, tetanus, pertussis, polio, haemophilus influenza or pneumococcal disease;
- confirmed or suspected immunodeficiency condition (inherited or congenital immunodeficiency);
- continuous use of immunosupressors or immunomodulators, steroids, immunoglobulins or blood components.

The trial consisted of 3 phases. Phase I included a screening period for max 7 days and a 30-day follow-up period of primary monitoring of the child's development after the 1st dose of BRV-PV.

Phase II included the 2nd dose of BRV-PV and a 45-day follow-up period of secondary monitoring of the child's development.

Phase III included the 3rd dose of BRV-PV and a 30-day follow-up tertiary monitoring of the child's development in accordance with the universally accepted pediatric standards. Based on the data of clinical and laboratory studies a total of 100 children with the verified "good health" status were enrolled in the trial. All of them met the inclusion criteria and did not have any condition qualifying them for exclusion.

All the children were randomized to one of the two groups at a 1:1 ratio: The 1st group (n = 50) of children received three doses of BRV-PV orally at an interval of min 4 weeks, a 2.5 ml dose; the 2nd group (n = 50) of children received three placebo doses at an interval of min 4 weeks, a 2.5 ml dose.

All the children received other preventive vaccines in accordance with NIC: against pneumococcal disease (the first vaccination at the age of 2 months; the second vaccination at the age of 4.5 months), diphtheria, pertussis, tetanus, polio (the first vaccination at the age of 3 months; the second vaccination at the age of 4.5 months). The above vaccines could be received concomitantly with BRV-PV/placebo.

The reactogenicity and safety of BRV-PV were assessed by using physical examination, anthropometry, heart rate, respiratory rate, and body temperature measurements, frequency of occurrence of postvaccinal reactions, unsolicited events and laboratory tests during active (outpatient visits and phone calls) and passive (post-immunization diary cards filled out by the parents) monitoring of the trial participants.

After each dose of BRV-PV or placebo, all the participants were observed at the research center for 2 hours. Thirty and 60 minutes after the BRV-PV/placebo intake, the physician-researcher examined the children physically and measured the main vitals. Six hours after each vaccination, the physician-researcher made a phone call to the child's parents.

The postvaccinal reaction was assessed with a 4-point score and the following criteria:

- the reaction is not intense;
- mild reaction —slight symptoms, hyperthermia of 37.0–37.5°C;
- moderately intense reaction — symptoms noticeably interfering with the normal daily activities, hyperthermia of 37.6–38.5°C;
- severe reaction — symptoms impeding the normal daily activities, hyperthermia >38.6°C.

The laboratory tests included complete blood count (the hemoglobin level, erythrocyte sedimentation rate, formed elements, white blood cell count, relative platelet count, red blood cell count) and blood biochemistry (levels of alanine and aspartate aminotransferase, γ-glutamyl transferase, total bilirubin, total protein, blood urea nitrogen, creatinine, C-reactive protein, and glucose), a urinalysis (amounts of albumin, glucose, cell elements, salts, urine specific gravity, pH) and measurement of the total IgE level in blood sera of the participants.

The immunological efficacy of BRV-PV was assessed by rotavirus antibody (IgA) titer levels in the children's blood sera before and after three-dose BRV-PV vaccination. The anti-rotavirus IgA was examined at the Wellcome Trust Research Laboratory of the Christian Medical College (India) by using an enzyme-linked immunosorbent assay (ELISA) in accordance with the approved standard operating procedure, WTRL/ASA/035 "Detection of anti-rotavirus IgA with ELISA assay and 1% reagent for western blotting." The validated analytical procedure of the ELISA assay is designed for performing quantitative measurement of rotavirus IgA antibodies in human blood serum samples when analyzing results of clinical trials of rotavirus vaccines.

The assay was performed on purified rabbit anti-rotavirus IgG antibodies as immobilized antibodies for conjugation of rotavirus lysates. The conjugated rotavirus lysate immobilizes the anti-rotavirus antibody present in the test sample. The anti-rotavirus IgA antibody is detected by the biotinylated IgA secondary antibodies. The detection is amplified by using the prepared avidin–biotin horseradish peroxidase complex. The concentration of the rotavirus-specific IgA in the test sample was derived by extrapolation from the standard curve generated from several dilutions of the reference serum with the assigned quantity of anti-rotavirus IgA (in U/ml).

The laboratory tests were performed on 197 blood serum samples from young children who took part in the trial. The samples were stored at –20°C prior to the tests.

The immunogenicity of BRV-PV was assessed by the following parameters:

- geometric mean concentration (GMC) of IgA antibodies in children before the vaccination in min 4 weeks after the 3rd dose of the vaccine);
- seroconversion rate — the number and percentage of the children with a 2, 3, 4-fold and greater increase in IgA antibody titer in min 4 weeks after the 3rd dose of the vaccine as compared to the initial level;
- seroconversion factor — the ratio between GMC of IgA antibody titers in min 4 weeks after the 3rd dose of the vaccine and the initial titer level.

The statistical analysis was performed by using parametric and non-parametric statistical methods. The statistical significance was verified by using the Statistica 6.0 software, Student's *t*-distribution and a chi-square (χ^2) test. The level of statistical significance (the error probability) of 95% was estimated as statistical significance between two phenomena by using a one-way analysis of variance. The database was created with the help of MSExcel software. The analysis of the obtained results included calculation of mean values and standard deviation.

Results

During the trial, there were 55 postvaccinal reactions recorded in 25 participants.

No postvaccinal reactions were recorded 60 minutes after the 1st, 2nd and 3rd doses of the vaccine. Based on the phone calls made 6 hours after the 1st immunization, there were 7 postvaccinal reactions reported by the parents of 2 participants from the 1st group, namely irritability, restlessness, bloating, decreased appetite and elevated body temperature to 37.6°C. No postvaccinal reactions were reported in the 2nd group within 6 hours.

During 7 days after the 1st dose of the vaccine, a total of 11 postvaccinal reactions were recorded in 4 participants from the 1st group and 13 postvaccinal reactions were recorded in 5 participants from the 2nd group. Further on, during 7 days, 10 reactions were recorded in the vaccinated group after the 2nd dose of the vaccine, and 1 reaction was recorded after the 3rd dose. At the same time, 1 and 7 reactions were recorded, respectively, in the placebo-controlled group. Intensity-based characteristics of the postvaccinal reactions during all the trial phases are given in Table 1.

Thus, during the 7-day monitoring after the three-dose series vaccination, a total of 43 postvaccinal reactions were recorded. They were mild or moderate, except for one reaction accompanied by high fever in a child from the 2nd group. The corrective treatment aimed at removal of unsolicited symptoms was used only in 2 cases: To reverse the fever response after the 3rd dose in a child from the 2nd group and to reverse such symptoms as bloating and bellyaches after the 1st dose in a child from the 2nd group. All the reactions were short-term (lasting from several hours to 3 days) and were resolved in recovery without consequences.

No statistically significant differences in the frequency of the recorded postvaccinal reactions were detected between the groups.

Note that bellyaches, fatigue and crying were observed only in children from the 2nd group, thus exclud-

Table 1. Postvaccinal reactions recorded in the trial participants during the first 7 days after the vaccination

Clinical manifestations of reactions	Intensity	Phase I of the trial		Phase II of the trial		Phase III of the trial		Total		χ^{2*}
		1st group (*n* = 50)	2nd group (*n* = 50)	1st group (*n* = 49)	2nd group (*n* = 49)	1st group (*n* = 48)	2nd group (*n* = 49)	1st group (*n* = 50)	2nd group (*n* = 50)	
Bloating	Mild	1 (2%)	1 (2%)	1 (2,1%)	0	0	0	2 (4%)	1 (2%)	0,344
	Moderate	0	0	0	0	0	0			
	Severe	0	0	0	0	0	0			
Bellyaches	Mild	0	1 (2%)	0	0	0	0	0	2 (4%)	2,041
	Moderate	0	1 (2%)	0	0	0	0			
	Severe	0	0	0	0	0	0			
Diarrhea (loose stool)	Mild	1 (2%)	0	0	0	0	0	1 (2%)	0	1,010
	Moderate	0	0	0	0	0	0			
	Severe	0	0	0	0	0	0			
Elevated body temperature	Mild	1 (2%)	0	1 (2,1%)	0	0	0	5 (10%)	3 (6 %)	0,543
	Moderate	1 (2%)	1 (2%)	1 (2,1%)	0	1 (2,1%)	1 (2,1%)			
	Severe	0	0	0	0	0	1 (2,1%)			
Irritability	Mild	3 (6%)	1 (2%)	1 (2,1%)	0	0	1 (2,1%)	4 (8%)	3 (6%)	0,154
	Moderate	0	1 (2%)	0	0	0	0			
	Severe	0		0	0	0	0			
Restlessness	Mild	2 (4%)	1 (2%)	3 (6,2%)	0	0	1 (2,1%)	5 (10%)	3 (6%)	0,543
	Moderate	0	1 (2%)	0	0	0	0			
	Severe	0	0	0	0	0	0			
Decreased appetite	Mild	2 (4%)	3 (6%)	2 (4,1%)	0	0	1 (2,1%)	4 (8%)	4 (8%)	0,000
	Moderate	0	0	0	0	0	0			
	Severe	0	0	0	0	0	0			
Naughtiness	Mild	0	0	1 (2,1%)	0	0	0	1 (2%)	1 (2%)	0,000
	Moderate	0	0	0	0	0	1 (2,1%)			
	Severe	0	0	0	0	0	0			
Crying	Mild	0	2 (4%)	0	0	0	0	0	2 (4%)	2,041
	Moderate	0	0	0	0	0	0			
	Severe	0	0	0	0	0	0			
Decreased activity	Mild	0	0	0	1 (2,1%)	0	1 (2,1%)	0	2 (4%)	2,041
	Moderate	0	0	0	0	0	0			
	Severe	0	0	0	0	0	0			

Note. *The critical value of the Pearson chi-square (χ^2) is 3.841 at the significance level $p = 0.05$.

ing any connection with the BRV-PV administration. Furthermore, such reactions as elevated body temperature, irritability, crying, decreased appetite, and diarrhea are typical of Prevnar® 13 and Pentaxim® vaccines administered to the trial participants concomitantly with the studied vaccine in accordance with NIC. The postvaccinal reactions recorded during the 7-day monitoring period after the BRV-PV administration may have been caused by the concomitant vaccination.

During the entire monitoring period, along with the postvaccinal reactions, the children had 12 adverse events following the immunization and displayed as

Table 2. Immunological efficacy of BRV-PV

Group	GMC of antibodies, U/ml			Antibody titer ratio	Number of individuals with ≥2 seroconversions		Number of individuals with ≥3 seroconversions		Number of individuals with ≥4 seroconversions	
	before vaccination	after three-dose vaccination	*t* (*p*-value)							
	GMC [95% CI]				abs. (*n*)	% [95% CI]	abs. (*n*)	% [95% CI]	abs. (*n*)	% [95% CI]
1 (*n* = 48)	3,4 [1,64–6,87]	130,8 [79,3–215,6]	2,819 (0,007)*	39,05	40	83,3 [70,4–91,3]	39	81,3 [68,1–89,8]	38	79,2 [65,7–88,3]
2 (*n* = 49)	5,9 [2,7–11,2]	16,6 [8,2–32,0]	0,556 (0,581)	2,80	22	44,9 [31,9–58,7]	19	38,8 [26,4–52,8]	17	34,7 [22,9–48,7]
t (*p*-value)	0,385 (0,701)	3,499 (0,0007)*	–	2,493 (0,014)*	χ^2	15,531*		18,196*		19,534*

Note. *Statistically significant differences.

adverse symptoms, complaints or intercurrent diseases unrelated to the immunization, out of which 9 cases were recorded in children from the 1st group and 3 cases were observed in children from the 2nd group. All of them were characterized by mild to moderate severity, except for the elevated body temperature to 38.7°C in 1 child from the 2nd group, making it the case characterized as a severe condition. No statistically significant differences in the frequency of occurrence and severity level of adverse events were revealed between the groups after the immunization.

The obtained results for BRV-PV safety are compatible with the results obtained during the clinical trials of the RotaTeq vaccine, which is registered and successfully used in Russia. During the trials aimed to study the safety of the RotaTeq vaccine, unsolicited reactions were recorded during 42 days after the vaccination. The most frequently occurring unsolicited events were upper respiration tract infections, diarrhea, vomiting, acute otitis media, cough and irritability [29].

Based on the data from the foreign studies, the intake of the rotavirus vaccine was frequently associated with an increased incidence rate of intussusception, a rare form of bowel obstruction [32, 33]. During our clinical trial, no postvaccinal complications, including intussusception, as well as adverse unsolicited events were recorded.

The analysis of the impact of the vaccine on the complete blood count, blood chemistry and urinalysis results showed that all the laboratory test values recorded throughout the monitoring process were within the physiological range; no significant deviation from the baseline values was detected.

No allergenic characteristics were found in BRV-PV — the serum IgE levels did not demonstrate significant changes during the monitoring period.

No negative changes in the health condition of the children vaccinated both with BRV-PV and placebo were found. The children developed harmoniously, according to their age.

The results of the conducted laboratory tests confirmed that BRV-PV vaccination did not have any adverse impact on the main values of the complete blood count, blood biochemistry and urinalysis.

Thus, the obtained results were indicative of the satisfactory safety profile of BRV-PV when administered as a three-dose series childhood immunization. The obtained results were compatible with the data from foreign and Russian authors [30, 32].

The assessment of the immunological efficacy of BRV-PV showed that the children – participants of the clinical trial – who were seropositive and had rotavirus-specific IgA concentration ≥ 20 U/ml at the time of their enrollment in the trial, prior to the 1st dose accounted for 20.8% in the vaccinated group and 32.7% in the placebo-controlled group, thus confirming the previous data on infants' seropositivity that can be associated with high levels of the impact of natural rotavirus infection at a very young age (previously obtained results of the clinical trials of the studied vaccine in India and Niger), placental transmission of maternal antibodies to the child as well as the alimentary mode of transmission of maternal antibodies through breast milk [34].

The three-dose series vaccination of seropositive children made it possible to reach the 50% seroconversion rate. In the group of initially seronegative participants, 92.1% of the BRV-PV vaccinated had a fourfold and greater increase in the specific antibody titer. The increase in the level of specific IgA antibodies after the three-dose series vaccination of BRV-PV in the 1st group was significantly different from the increase in the IgA level in the placebo group ($t = 2.020$; $p = 0.047$).

The results of the assessment of the immunological efficacy of BRV-PV in the group of seronegative and seropositive children – participants of the trial – are given in Table 2.

Discussion

The obtained results demonstrate excellent immunogenic properties of BRV-PV and prove that with

three-dose immunization, seroconversion can be observed even in the individuals who were initially seropositive, thus confirming the previously obtained results of clinical trials. It can also imply high potential efficacy of the vaccine [35].

Thus, the conducted trials lead to the conclusion that BRV-PV is characterized by a satisfactory safety profile and high immunogenicity when administered as a three-dose series immunization to children. It can be recommended for registration as a vaccine for immunization of infants from 2 months of age. The solution on localization of RVI vaccine production at Russian factories, provided that the two registered vaccines are compatible in terms of their safety and immunogenicity, can be based on the results of a pharmacoeconomic analysis.

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