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**Analyzing the Efficacy and Safety of Pneumococcal Vaccination in Children with  
Various Health Deviations**

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*This article provides the results of the assessment of tolerability of vaccination against pneumococcal infection in children with various health disabilities as well as the results of a follow-up observation of vaccinated children. This survey was conducted at the Department of immunization of CHSC, RAMS. It is shown that vaccination against pneumococcal infection is safe to perform in both healthy children and in children having various health disabilities. In the post-immunization period no serious negative events were observed (frequency of general and local post-immunization reactions did not exceed 3%). The health status of children one year after vaccination remained stable concerning the treated disease (if any). It was proved that there was a significant reduction in acute respiratory infections in the group of sickly children, compared with the previous year.*

**Keywords:** *pneumococcal disease, prevention, vaccination, children having health deviations, efficiency, safety.*

**Characteristics of the pathogen.** The causative agent of pneumococcal infection is *Streptococcus pneumoniae*, which is a gram-positive diplococcus, protected by a thick polysaccharide capsule. Pneumococcal serotypes contained in the capsule is determined by the polysaccharides, which are the main virulence factor [1]. Currently, there are identified about 90 serotypes of pneumococcus. Each serotype has an individual structure and stimulates the production of antibodies, opsonizing and anticapsule ones.

The high invasiveness of the pneumococcus is caused by the capsule, which can withstand the phagocytes and the complement until the owner receives reinforcement in

the form of specific antibodies [2]. *S. pneumoniae* is considered to be opportunistic inhabitant of the mucous membrane of the upper respiratory tract, and its colonization is constrained by local immune defense mechanisms. It is pneumococcus carriers who are a reservoir of infection and contribute to the spread of pneumococcal disease in the community and society as a whole. The frequency of pneumococcal carriage increases during the first year of life, reaching 15% and above. Particularly high frequency of carriers was observed in pre-school units. The carrying of one type of pneumococcus can last from one to several months, then microorganism eliminates, which, however, does not prevent the colonization of another type of pneumococcus. If a new strain of *S. pneumoniae* colonize the nasopharynx, there may develop the disease [3]. Children of all ages, especially children younger than five years, are exposed to diseases associated with pneumococcus.

**Clinical evidence.** *S. pneumoniae* is the most common pathogen of bacterial respiratory infections, and also a significant etiological agent for bacteremia, meningitis and peritonitis [4]. All these states are regarded as serious, often life-threatening, and requiring intensive and expensive treatment. Being the causative agent of pneumonia, *S. pneumoniae* is more often fatal than other agents of pneumonia. Pneumococcal pneumonia may be complicated by pleural empyema, which complicates the treatment and sometimes may require surgical intervention. Children with pneumococcal pneumonia are exposed to the very high risk of bacteremia [5].

Pneumococcal bacteremia is a life-threatening form of pneumococcal infection, so when bacteria get into the bloodstream and begins to multiply rapidly, it may lead to septicemia with further development of severe shock organ damage. The mortality rate for this form of the disease makes up to 20% [3]. According to published data, *Streptococcus pneumoniae* is the third in frequency after the meningococcus and Hib-infection among the causative agents of meningitis in Russia.

Proportion of pneumococcal meningitis in different cities of Russia varies from 5 to 20%, but the incidence of pneumococcal meningitis deaths and complications of the disease leading to disability, is significantly higher than in other causes of meningitis [6]. Pneumococcal disease is one of the most common causes of otitis media in young children. In studies performed with the use of crop contents, that was obtained by puncture of the eardrum, pneumococcus was found in 27-52% of cases, and Hib-infection - at 16-52% [7, 8]. Pneumococcal disease is one of the most common causes of sinusitis. In acute sinusitis pneumococcus is found in 31-60% of cases [1]. Acute purulent sinusitis, flowing from the tissue edema of the orbit, is most often caused by pneumococcus. So,

diseases associated with the pneumococcus, possess a serious health problem that deserves special attention.

The frequency of invasive pneumococcal infections in children under 2 years is 10 times higher than that in adults, due to the anatomical features (eg, structure of the Eustachian tube, causing the rapid development of acute otitis media), the imperfection of humoral immunity and frequent viral and allergic diseases. After disease there is created immunity, built of anticapsule antibodies. Immunity is shaky, and after pneumonia, it remains only for 6-12 months [9].

There is a group of serotypes of pneumococcus, that most frequently colonizes the nasopharynx of young children and causes complications such as pneumonia, otitis, sinusitis, frontal sinusitis. It includes serotypes 6A, 6B, 9V, 14, 19F, 23F, 3, 9A [10]. Another group of serotypes consists of "infectious outbreaks" serotypes, which are seldom sown from nasopharynx of young children, but are characterized by the ability to cause severe invasive infections (meningitis, pneumonia, bacteremia, peritonitis). Such type of serotypes include 1, 4, 5, 7F, 18C ones [1]. Participation of individual serotypes in the development of pneumonia and otitis media is also different. Most types of pneumonia are associated with types 1-4, 6-8, 14, 18 and 19.

In 2009-2010 in CHSC, RAMS, there was carried out a survey on serotyping pneumococcal strains taken from children with chronic bronchopulmonary diseases, acute and chronic pathology of upper respiratory tract, and also from healthy carriers, which was conducted by the method of multiplex polymerase chain reaction (PCR). There were typed 68 strains of *S. pneumoniae*, and 16 serotypes were identified. In terms of frequency three dominant serotypes (6A / B, 19F, 23F) accounted for about 60% of all typed strains. Serotypes 15B / C and 9V had smaller proportion (5-6% each). The remaining 11 serotypes occurred with a frequency of 1.5-4%, and collectively they accounted for less than 30% of strains typed: 10A, 11A, 14, 18, 33F, 34, 3, 35B, 19A, 22F, 38. Further analysis of the distribution of serotypes showed that it had its own characteristics depending on the surveyed patients and the type of material where the pneumococcus was taken from. In patients having chronic bronchopulmonary diseases, the material of *S. pneumoniae* was taken from laryngotracheal aspirate.

Another group of surveyed patients comprised of children from whom *Streptococcus pneumoniae* was taken isolated from nasopharyngeal swabs (a group of carriers). In patients having chronic bronchopulmonary diseases there were found 13 serotypes of pneumococcus, which were usually common serotypes 6A / B, 19F, 23F, 9V; their share in aggregate was 56%. In the group of carriers serotype spectrum was represented by 11

serotypes of *S. pneumoniae*, and there could be clearly distinguished two leaders - serotypes 6A / B, and 19F (total share - 58%) [11].

The existing pneumococcal vaccine does not cover the entire spectrum of pneumococcal polysaccharides. They include polysaccharides of only those serotypes that are based on the results of epidemiological studies and are among the pathogens of most *S. pneumoniae*-associated diseases. Since the spectrum of serotypes may differ in different areas, information about the actual distribution of serotype pneumococcus is one of the main factors for the successful introduction of pneumococcal vaccine in any country. The vaccine 'Prevenar', which is registered in this country, consists of seven serotypes of pneumococcal polysaccharides 4, 6B, 9V, 14, 18C, 19F, 23F, most of which (according to N.A. Mayansky) circulate in the Russian population.

**Diagnosis.** The serological diagnostic method allows to divide pneumococci into more than 90 different capsular types, which became known as "serotypes". Serological typing is considered to be the "gold standard" differentiation of pneumococci, although has some drawbacks (complexity, high cost of serum, the subjectivity in interpreting the results, high demands on staff, etc.). In addition, most pneumococcal serotypes rarely cause severe illness, narrowing the list of clinically relevant serotypes up to 15 species [11]. The rapid development of molecular-biological methods of research in recent years made PCR available in many laboratories. In this regard, molecular serotyping of pneumococcus, which is based on some simple manipulations and objective evaluation of results, became quite widespread [12].

**High-risk groups.** There are 4 groups exposed to risk of pneumococcal infection. First one is babies. Although they receive their mother's antibodies to many types of pneumococcus, after the loss of maternal antibodies (ages 5-6 months) they produced their own antibodies to pneumococcus only after acute respiratory infections. In the future, until these children reach the age of 3, the level of antibodies to *S. pneumoniae* remains low, reaching the adult level only at school age. Therefore, young children are particularly susceptible to pneumococcal infection. The second group of risk is the elderly, whose antipneumococcal immunity gradually fades; as well as patients having chronic diseases. The third group includes the risk of new recruits in the army, in which the incidence of pneumococcal pneumonia (in 41.1% of pneumococcal pneumonia) is also high. The fourth risk group includes those in need of organ transplants; patients receiving immunosuppressive therapy; patients having severe kidney problems (nephrotic syndrome), heart and lung problems [13].

**Prevention.** Given the need for prevention of pneumococcal disease in Russia, since 2000

there is actively used the vaccine "Pneumo 23» (Sanofi Pasteur, France). It is a polyvalent vaccine containing polysaccharides of 23 pneumococcal serotypes, which includes 85% of the serotypes circulating in Europe. This polyvalent polysaccharide vaccine (PPV) is used on children aged two years and adults at risk. The mechanism of action of vaccine is that the pneumococcal capsular polysaccharide antigens stimulate production of antibodies of specific serotype that enhance opsonization, complement-dependent phagocytosis and destruction of pneumococci by leukocytes and other phagocytic cells [14].

The concentrations of these antibodies begin to increase during the first week after vaccination, and for most vaccine antigen titers they exceed pre-vaccine titers in healthy adults during 5 years. Immunization safety of children having severe disease by pneumococcal vaccine was confirmed by Russian and foreign scientists [15, 16]. Unfortunately, the pneumococcal polysaccharides are T-independent antigens, so their immunogenicity and immunologic memory is not a long-lasting one, especially in young children [17].

At present, there have been developed vaccines in which the capsular polysaccharides are conjugated to protein carriers, in particular with diphtheria toxoid. These vaccines induce a full immune response and are effective for the prevention of pneumococcal infections [18]. When there were introduced conjugated vaccines, there has also been developed a 7-valent pneumococcal conjugated vaccine (PCV) - "Prevenar» (Pfizer, USA), which includes seven serotypes of pneumococcal polysaccharides (4, 6B, 9V, 14, 18C, 19F, 23F), that cause up to 80% of invasive pneumococcal infections. In the PCV polysaccharides are individually conjugated to diphtheria protein and are adsorbed on aluminum phosphate. It is prescribed for all children from 2 months to 5 years for the prevention of diseases such as meningitis, pneumonia, bacteremia, sepsis, and acute otitis media. PCV belongs to the T-dependent vaccines and is highly immunogenic; it induces the development of immunological memory, and also promotes the formation of an indirect (population) immunity. The effectiveness of PCV has been proven by large-scale clinical studies conducted in different countries [3, 19].

A study, conducted at the Department of vaccination of children having disabilities in health of CHSC RAMS, was designed to assess tolerability of vaccination against pneumococcal disease, as well as to analyze the incidence of acute respiratory infections (ARI) in children 1 year after immunization. In the period of 2010-2011 there were vaccinated 275 children aged 3 months to 12 years. There were used two vaccines against pneumococcal infection. 185 children under 5 years of age received conjugated vaccine (PCV).

Depending on the age, each child received one, two or three doses (according to the instructions on the use of the vaccine). 90 children older than 2 years of age received a single dose of polysaccharide vaccine (PV). There were performed both concomitant (the child received the vaccine simultaneously with the vaccine against pneumococcal infection) and mono- vaccination (there was used only vaccine against pneumococcal infection). In 85% of children PCV was administered along with other vaccines (AaKDS, vaccines against hepatitis B, polio, measles, mumps and rubella). PPV was introduced in combination with vaccines against *Haemophilus influenzae* and meningococcal disease only in 50% of the cases. The children were divided into health groups. PCV was introduced into 149 (81%) healthy children, and 36 patients (19%) having different types of pathologies (allergies, kidney, lungs, nervous system, etc.). PPV was introduced into 55 healthy children (61%) and 35 patients (39%) having various disabilities of health. Both vaccines were administered at a dose of 0.5 ml intramuscularly in the anterolateral surface of the femur (upper third) in children aged 3-4 years, or in the deltoid muscle in children older than 3-4 years. Depending on the initial health status medication preparation prior to vaccination was assigned when necessary.

Tolerability of vaccination (frequency and severity of general and local post-vaccination reactions) against pneumococcal disease was evaluated separately in healthy children and in those having different pathologies. Analysis revealed no significant differences in frequency and severity of general and local post-vaccination reactions to the introduction of two vaccines between the two groups of healthy and children having various health deviations ( $p > 0.05$ ).

After CPR introduction, increased temperature and general malaise were observed in 26 children (14%), of which 20 were healthy and 6 were having various health deviations (Table 1). Strong reactions (rise in temperature above 38,5 ° C) were observed in only 3 children (2%) - 2 healthy and 1 with allergies who received CPR in conjunction with acellular vaccine against pertussis, diphtheria and tetanus. These reactions were stopped in all cases by a single dose antipyretic drug intake.

Common reactions to immunization of PPV were observed in 11 children (12%) - 5 and 6 healthy patients having various pathologies (see Table. 1). Most complaints were on slight indisposition, naughty behavior on the day of vaccination. Low-grade fever was observed in 7% of cases (in three healthy and three children with disabilities in the state of health).

Only in 2 children (2%) post-vaccination reaction was regarded as severe (temperature rise above 38,5 ° C). The high temperature was treated by intake of antipyretics during 1-2 days.

Local reactions (pain and redness at the injection site) when using PCV were found in 17 children (8.5%) - in 14 healthy and 3, with variations in health status (Table 2). Severe local reactions (redness and pimple of more than 5-6 cm in diameter) were observed only in 3 children (2%) - 2 healthy and in 1 child having allergy. All strong reactions were treated within 2-4 days by intake of local antihistamine (dimetinden). Local reactions on use of OPV in the form of redness, soreness at the injection site were recorded in 11 children (12%) – that is in six healthy ones and five having impaired health status; and only 2 patients (2%) – that is one healthy and one child having ENT disorder - had strong reactions (redness and swelling of more than 8 cm in diameter; see Table 2).

A separate goal of this survey was a long observation of the vaccinated children, which was conducted during 1 year after immunization. There was analyzed health state of patients, and primary and comorbid conditions of their diseases. There were identified no significant changes in health status of children (both healthy and those having various health deviations), who were vaccinated against pneumococcal infection, within 1 year after the complete course of immunization.

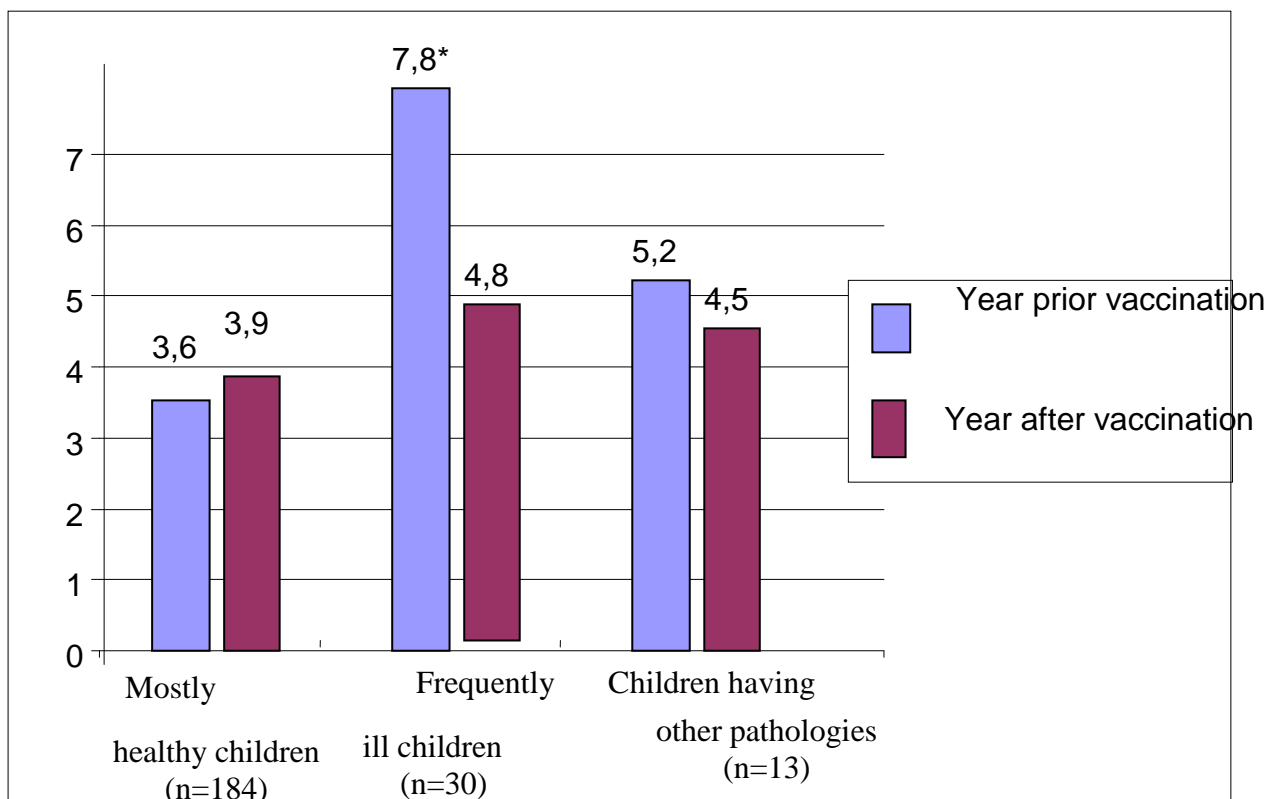
To evaluate the effect of pneumococcal vaccination on the health of our children, a comparative analysis of the incidence of ARI in children was carried out before and after vaccination, which was assessed by the frequency of episodes within 1 year after vaccination in comparison with the year prior to vaccination. A comparison was conducted separately for healthy children and children having health deviations. Given these recent studies on the impact of vaccination on the incidence of sickly children [20, 21], we decided to evaluate the incidence of these children (sickly) separately. It is important to note that the frequency of ARI before and after pneumococcal vaccination was analyzed only for those children who did not receive any additional vaccines that could influence the incidence of respiratory infection (*Haemophilus influenzae*, and influenza) during this period. We obtained the following data.

The difference in the incidence of ARI before and after vaccination was 7.5% in the group of healthy children and is considered unreliable. In the group of sickly children the incidence of ARI after vaccination reduced significantly ( $p < 0.005$ ). In children having other types of pathology, difference in the number of ARI before and after vaccination is negligible and not statistically significant (Fig. 1).

According to data from our observations, both vaccines against pneumococcal infection are well tolerated. No substantial variations in health status of vaccinated

children have been identified during a long-term observation. The frequency of ARI in the group of children having diseases decreases within 1 year after immunization.

**Fig. 1.** The number of ARI within 1 year prior to the vaccination in comparison with 1 year after the vaccination



Note. \* —  $p < 0,005$ .

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**Table 1.** Common reactions to vaccination with pneumococcal conjugate vaccine (PCV) and the polyvalent polysaccharide vaccine (PPV)

Children	Vaccine	Common reaction			
		No reaction	Weak reaction (t<37,5°C)	Moderate reaction (t 37,6 - 38,4°C)	Sufficient (t>38,5°C)
Healthy n= 149 (81%)	PCV	129 (86,5)	13 (8,5)	5 (3,5)	2 (1,5)
Having pathology n= 36 (19%)		30 (83,5)	3 (8)	2 (5,5)	1 (3)
Healthy n= 55 (61%)	PPV	50 (90,5)	3 (5,5)	1 (2)	1 (2)
Having pathology n=35 (39% )		29 (83)	3 (8,5)	2 (5,5)	1 (3)

**Table 2.** Local reactions to PCV and PPV vaccination

Children	Vaccine	Common reaction			
		No reaction	Weak reaction (less than 2,5 cm)	Moderate (2,5–5 cm)	Sufficient (more than 5 cm)
Healthy n= 149 (81%)	PCV	135 (90,5)	7 (4,5)	5 (3,5)	2 (1,5)
Having pathology n= 36 (19%)		33 (91)	1 (3)	1 (3)	1 (3)
Healthy n= 55 (61%)	PPV	49 (89)	3 (5,5)	2 (3,5)	1 (2)
Having pathology n=35 (39% )		30 (86)	2 (5,5)	2 (5,5)	1 (3)