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A Decade of Experience in the use of 13-Valent Conjugated Polysaccharide Pneumococcal Vaccine in Russian Federation

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Резюме

Pneumococcal infection remains a significant global health problem, and vaccination is the main measure for its prevention. To date, the period of use of pneumococcal conjugated polysaccharide vaccines in Russia exceeds 14 years, and 13-valent conjugated polysaccharide pneumococcal vaccine (PCV13) - more than 10 years. During this time, extensive experience has been accumulated in the use of this type of vaccines, and many studies have been carried out to evaluate their effectiveness and safety. The purpose of this review is to summarize the experience of using PCV13 in Russian Federation with an assessment of its epidemiological and clinical effectiveness. A search was made for scientific publications devoted to the study of the epidemiological efficacy, the safety as well as cost-effectiveness of PCV13 use in Russian Federation. The review included original studies published in Russian journals. The results of the studies carried out indicate the efficacy and safety of PCV13 for both adults and children. The effectiveness of immunization of children at risk (premature, suffering from congenital pathology, having chronic diseases and often ill) was demonstrated, the need and safety of the timely start of vaccination (from 2 months of age) of newborns was shown, the possibility of its combination with immunization against other infections within the framework of the national vaccination schedule, the importance of following the recommended vaccination schedule in accordance with the age of the child. The effectiveness of vaccination of adults suffering from chronic diseases has been shown both in terms of preventing the aggravation of the course of the underlying pathology and reducing the risk of pneumonia. Positive experience has been gained in immunizing adults from occupational risk groups - medical workers, conscripts and persons exposed to a harmful production factor and having occupational lung diseases. The conducted studies have shown a high cost-effectiveness of PCV13 vaccination, however, with any changes in price and epidemiological parameters, it is necessary to clarify the economic feasibility of vaccination under the changed conditions. Taking into account the positive experience gained in immunization, it seems appropriate to further maintain a high level of vaccination coverage of the child population, expanding risk groups among the adult population subject to vaccination against pneumococcal infection within the framework of the National Immunization Schedule, taking into account its epidemiological, clinical and economic efficiency.

Keywords. Vaccine prevention, pneumococcal infection, vaccines, risk groups, epidemiological efficiency, cost-effectiveness. No conflict of interest to declare.

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Introduction

Pneumococcal infections (PIs) are a significant global health problem [1]. The socioeconomic and epidemiological burden of PI-associated diseases in Russia is high as well [2]. *Pneumococcus* is the cause of extremely common forms of the upper respiratory tract diseases in children (including acute otitis media (AOM), one of the key causative agents of community-acquired pneumonia (CAP) in adults and children. It is also associated with the development of relatively rare but threatening diseases such as bacteremia, including pneumonia, and pneumococcal meningitis [3].

The risk groups for the disease and severe course of pneumococcal infection include both children and several groups of the adult population. Risk groups include, first of all, young children (especially under 2 years of age), premature infants, children with developmental disorders, children with chronic pathology (especially immunodeficiency disorders), frequently ill children, and children living in permanent-stay institutions (orphanages, boarding schools, etc.) [4].

Among adults, pneumococcal infection is especially dangerous for people with immunocompromising diseases and conditions (HIV-infected, receiving immunosuppressive therapy, etc.), chronic diseases (respiratory diseases, cardiovascular diseases, diabetes mellitus, etc.), and people over 65 years of age. There are also a number of risk groups associated with social and occupational risk factors: people from organized groups and those in permanent-stay places (military personnel and conscripts in army, persons working on a rotational basis, those living in social institutions — homes for the disabled, residential care facilities, etc.), persons working in production harmful to the respiratory system (coal, oil and gas, chemical industry, etc.), medical and social workers, persons in disaster areas (floods, earthquakes, etc.) [4].

Vaccination is the basis for pneumococcal infection prevention. Two types of pneumococcal vaccines are currently available and actively used — polysaccharide pneumococcal vaccines (PPCV) and polysaccharide conjugate vaccines (PCV). They are used both individually and in combined vaccine regimen [5]. The advantage of pneumococcal conjugate vaccines is that they can be administered to children including infants (above 2 months) and can stimulate the development of immune memory cells, providing a long-lasting effect and herd effect [6].

In this regard, PCVs are used for routine vaccination in children. A 13-valent pneumococcal conjugate vaccine (PCV13) is currently used for vaccination of children in National Immunization Programs (NIPs) in 127 countries worldwide (data available in October 2022) and is also recommended for use in adults in certain risk groups and age categories in 50 countries worldwide [7].

As of 2022, it is estimated that the introduction of PCV13 into childhood immunization programs has prevented 175.2 million cases of infection and 625

thousand deaths worldwide [8]. The effectiveness of PCV is proved in the world clinical practice: immunization programs have shown a decrease in the incidence of invasive forms of pneumococcal infection caused by vaccine-specific serotypes by 84%, bacteremic pneumonia by 74–91%, a decrease to 77.4% in the incidence of complicated AOM, and have reduced the prevalence of antimicrobial resistance [9, 10].

In the Russian Federation, pneumococcal vaccination was included in the NIP in 2014 [11]. Prior to inclusion in the calendar, experience with conjugate vaccines (first 7-valent (PCV7) and then 13-valent (PCV13) was gained in children and adults at risk. Thus, the current experience of using conjugate vaccines in Russia exceeds 14 years (PCV7 was registered in 2009) and PCV13 — 10 years (Prevenar 13 vaccine was authorized in Russia in 2011). Extensive experience in using this type of vaccine has been accumulated for this period, and many studies have been conducted to assess its effectiveness and safety.

Purpose – to summarize the experience of using the 13-valent pneumococcal polysaccharide conjugate vaccine in the Russian Federation with assessment of its epidemiological and clinical efficacy.

Materials and methods

A search for scientific publications was conducted to study the epidemiological, clinical and economic effectiveness and safety of the 13-valent pneumococcal polysaccharide conjugate vaccine in the Russian Federation. Original studies published in Russian language journals were included in the review.

Results

Efficacy/effectiveness and safety of PCV in children

Before including the pneumococcal vaccination into the NIP Russia had extensive experience with both PCV7 and PCV13. Thus, about 50,000 children had been vaccinated by PCV7/PCV13, and more than 90,000 doses had been administered in 49 regions of the Russian Federation by 2013 [12].

In 2013, a team of authors (Ilyina S. V. et al., 2013) published a review article on the assessment of effectiveness and safety of pneumococcal conjugate vaccines in the Russian Federation. It presented the experience of using primarily the 7-valent conjugate vaccine. The review includes studies conducted in different regions of the country (Moscow, Astrakhan Region, Yaroslavl Region, Krasnoyarsk Region, Republic of Sakha (Yakutia), and others). These studies demonstrated the high epidemiological efficacy of vaccination, which was demonstrated by a reduction in the number of pneumococcal diseases (CAP, AOM, acute respiratory infections) and related hospitalizations. In all the studies conducted, special attention was paid to assessing the safety of immunization. More specifically, the review presents the results of one of the first studies on the use of PCV7 in children under 5 years of age with various

health conditions and risk factors for the development of invasive pneumococcal diseases (IPI), which revealed high clinical and immunological efficacy and safety of immunization regimens using the pneumococcal conjugate vaccine in children at risk [13].

Based on these data, the authors of the review concluded that PCV is effective and well tolerated (including among premature infants) when started at 2 months of age and administered simultaneously with other vaccines in the Russian NIP [12].

The accumulated experience served as a basis for introducing vaccination against pneumococcal infection into the National Immunization Program.

A program of mass immunization with pneumococcal conjugate vaccine (PCV) of children of the first and second year of life, including premature infants, in St. Petersburg was as a pilot project before including the vaccine in the NIP. This program started in June 2013. It used PCV13 vaccine, which was chosen basing on the results of monitoring the pneumococci serotypes circulating in St. Petersburg. Based on the use of more than 38,000 doses of the vaccine, its high safety was confirmed both when administered separately and in combination with other vaccines of the National Calendar [14].

Thus, the data were obtained proving the epidemiological, clinical, and economic feasibility of including the pneumococcal vaccination in the National Immunization Calendar. As a result of efforts of the Ministry of Health of Russia, Chief Freelance Specialists, the Union of Pediatricians of Russia, and the Russian Society for Pediatric Infectious Diseases, pneumococcal vaccination has been included in the National Immunization Program since 2014 (the schedule 2+1) [15].

Experience of immunization of children with PCV13 after introducing vaccination against pneumococcal infection into the NIP

Shortly after the PI vaccination was introduced into the National Calendar, a number of papers were published to evaluate its efficacy at the regional level.

Thus, a team of authors (Semerikov V. V., et al., 2019) analyzed the impact of immunization of children against pneumococcal infection on the morbidity and mortality of community-acquired pneumonia among children under 5 years of age in Perm. The analysis was performed considering selective (vaccination of children at risk in 2011–2014) and mass (vaccination of children under 1 year of age in 2015–2018) immunization strategies. The material was based on state federal statistical observation forms (period of mass immunization) and sampling data (period of selective immunization).

The authors noted that under selective vaccination conditions (2011–2014) among vaccinated people of the risk group — frequently ill children — after immunization, the incidence rate of community-acquired pneumonia decreased 4.0-fold, and the mortality rate among children under one year of age decreased

2-fold. The introduction of mass vaccination against pneumococcal infection in children of the first year of life in Perm led to a decrease in the incidence of community-acquired pneumonia among children under 2 years of age, absence of multiple foci of pneumococcal infection in children's organized groups, a decrease in the number of hospitalizations and ensured the absence of pneumonia mortality among children in the first year of life by the third year of implementation of this immunization strategy [16].

Another large-scale experience with PCV13 was the immunization program in a region (Amur Region) affected by a natural disaster (floods in 2013) [17].

The study group included 5000 children aged 2 to 5 years who were immunized against pneumococcal infection. The main factor determining the selection of patients for vaccination was the negative health impact of the flood and the consequent decline in social and environmental conditions. The monitoring program included five visits over a period of three years for follow-up.

According to the study [17], the incidence of acute respiratory diseases and pneumonia in the vaccinated population decreased 2.5-fold compared to the pre-vaccine period.

Somova A. V. et al. evaluated the epidemiological efficacy of PCV13 vaccine in the city of K. — a large industrial center in the Sverdlovsk Region. The authors conducted a retrospective observational epidemiological study ($n=192$) to evaluate the effect of PCV13 vaccination on the incidence of unspecified CAP in children aged under 6 years. According to the findings, the incidence of CAP among vaccinated children was 3.2 per 1000 in children under 1 year of age, 6.1 per 1000 in children aged 1–2 years, and 7.8 per 1000 in children over 2 years of age. In contrast, the incidence of community-acquired pneumonia among unvaccinated children was 7.1 per 1000 in children under 1 year of age, 9.2% in children aged 1–2 years, and 17.2% in children over 2 years of age. The incidence of pneumococcal infection was higher in individuals who were not immunized ($t > 2$; $p < 0.05$) across all age groups compared to those who were immunized. As noted by the authors, the epidemiological efficacy of the PCV13 vaccine against unspecified pneumonias is high. Individuals who did not receive the vaccine had a pneumococcal disease incidence 1.9 times higher than those who were immunized; the epidemiological efficacy factor was 48.65% [18].

However, the vaccination campaign faced a number of challenges. Thus, when discussing the interim results of implementation of universal vaccination against pneumococcal infection in infants of the first year of life under the NIP in Russia, the expert council of pneumococcal infection specialists pointed out that only a small proportion of infants (approximately 30% on average in the country) receive the first pneumococcal vaccine dose at the recommended age of 2 months to start immunization [19].

A team of authors analyzed the results of the first three years of routine vaccination of children against PI at the national level [20]. The authors performed a retrospective comparative evaluation of the morbidity and mortality of pneumonia in the pediatric population, and the incidence of acute otitis media in children under the age of 14 in the pre-vaccination period and within three years after the start of routine vaccination with PCV13. Federal statistical observation forms were used for the study. The study found that routine PCV vaccination under the NIP of the Russian Federation led to a 35% reduction in mortality rate among children under 1 year of age from CAP and also reduced the incidence of AOM. However, the low proportion of community-acquired pneumonias with specified etiology (29%) made it difficult to assess the effect of pneumococcal pneumonia vaccination [20].

Moreover, the study found that although the pneumococcal vaccination coverage rate among children in the first two years of life was high (87%), a large proportion of children (73%) were not vaccinated on time in most of the RF subjects, i.e., only 27% of children were vaccinated before the age of 6 months and within the allowed timeframe. In 2016, 3.4% and 9.3%, similarly in 2017, 3.4% and 8% of infants under one year of age remained unvaccinated due to medical exemptions and refusals, respectively [21].

Other authors also raised concerns regarding the adherence and timeliness of vaccination. The study previously mentioned, performed in the large industrial center of the Sverdlovsk Region (Somova A. V., et al, 2018), demonstrated that the highest epidemiological efficacy of PCV13 (54.8%) was achieved through timely and regulated immunization [18].

The need for timely initiation of vaccination is also emphasized in the paper by Kharit S. M. et al. (2016). The authors conducted a retrospective comparative study to investigate the clinical efficacy of vaccinating children under three years of age with PCV13. The incidence of acute respiratory infections (ARIs), AOM and pneumonia during the first three years of life was assessed ($n=370$, $n=184$ PCV13 vaccinated, $n=186$ unvaccinated children of equal age). It was shown that those vaccinated in the first year of life, compared with those not vaccinated, had 5.5 times fewer ARIs per child in the third year of life (0.42 and 2.31 cases), 6.8 times fewer otitis media cases in the second year of life (7.6% and 52.1%; $p < 0.01$), and 34.7 times fewer cases in the third year of life (1.1% and 38.2%; $p < 0.01$). CAP was 6.3 times less frequent (1.1% and 6.9%) in all three years for those vaccinated before one year of age. Moreover, children who were vaccinated during their first year of life experienced fewer ARIs per child in the third year compared to those vaccinated later (0.42, 1.02, 2.03 in the first, second, and third years of follow-up, respectively). There was a significant difference in the incidence of otitis media between children vaccinated in the first and third

years of life (1.1% and 15.6%, respectively; $p < 0.01$).

The authors conclude that vaccinating children under the age of one is necessary to decrease the incidence of ARIs, otitis media, and pneumonia. Immunization in the second and third years of life, "catch-up" immunization is effective, although to a lesser extent [22].

Efficacy/effectiveness and safety of PCV13 in children at risk group

Studies assessing the effectiveness and safety of PCV vaccination in children at risk, primarily premature and with congenital disorders, deserve special attention.

In the study (S. V. Ilyina, Yu. I. Lysanov, 2013), conducted even before the mass vaccination campaign, the national experience of vaccination of such patients was obtained. Over 700 children at risk, including premature infants, children with congenital heart defects, and broncho-pulmonary dysplasia aged between 2 months to 2 years, received the PCV7 and PCV13. 193 immunized children were monitored for a period of 1.5 years. The results showed that the frequency of general disorders (increase in body temperature from 37.6 to 38.0 °C) was 4%, local reactions and other adverse reactions were not registered in the post-vaccination period. It should be noted that in 59.1% of cases pneumococcal vaccine was administered in combination with other calendar vaccines.

No cases of pneumococcal disease (pneumonia, meningitis, acute otitis media, or broncho-obstructive syndrome) were registered in the vaccinated children during the 18-month follow-up period after vaccination. The study authors demonstrated the appropriateness, safety and effectiveness of vaccinating premature infants having congenital heart defects and broncho-pulmonary dysplasia with PCV13 starting from as young as 2 months, if necessary, simultaneous vaccination with other vaccines from the Vaccination Calendar [23].

The appropriateness and safety of vaccination of premature infants with broncho-pulmonary dysplasia were also demonstrated in the study of V. V. Semerikov et al. conducted in the Perm Region. The study group included vaccinated preterm infants with broncho-pulmonary dysplasia ($n = 29$), the comparison group included unvaccinated preterm infants with broncho-pulmonary dysplasia ($n = 29$) and 30 vaccinated full-term children. PCV13 vaccine was used. Vaccination of premature children having broncho-pulmonary dysplasia with the 13-valent pneumococcal conjugate vaccine has been shown to have high prophylactic effect (absence of cases of CAP among the vaccinated children under prospective observation for 3 years), good tolerability (absence of clinical manifestations of broncho-obstructive syndrome and negative effects on the respiratory system in the form of apnea and desaturation among the vaccinated children), weak reactogenicity ($17.2 \pm 0.57\%$), and similar

tolerability of the vaccine in preterm infants ($16.5 \pm 0.55\%$) [24].

The authors' findings are crucial for achieving maximum epidemiological and social efficacy of vaccination since infants under the age of one, especially premature children and children with health problems, are at a very high risk of invasive pneumococcal infections that can lead to severe consequences. The timely vaccination, which has been shown to be appropriate, safe and effective in these studies, is a critical factor in reducing the burden of pneumococcal disease in children of this risk group.

A number of studies examined the efficacy and safety of immunization in children with chronic diseases and those who are frequently ill. Thus, a group of authors (V. P. Vavilova, 2015) conducted a prospective comparative study to evaluate the efficacy of PI prevention in children with chronic nasopharyngeal diseases (adenoiditis, pharyngitis, tonsillitis, recurrent otitis media), as well as in children with recurrent acute respiratory infections (more than 5 times per year) using PCV13 vaccination. The study included 876 children aged 2–5 years, of whom 448 were in the PCV13 group and 428 were in the control group (unvaccinated). The results showed that the PCV13 group had 2 times ($p < 0.001$) fewer cases of acute respiratory infections, 2.4 times fewer cases of pneumonia ($p = 0.042$), 2.5 times fewer cases of acute bronchitis ($p = 0.008$), and 2.2 ($p = 0.001$) and 2.3 times ($p = 0.004$) fewer cases of acute otitis media and exacerbations of chronic maxillary sinusitis than the control group during the year. Thus, PCV13 vaccination was shown to reduce the risk of acute respiratory and ART- infections in children with chronic nasopharyngeal disease [25].

Another study (Fedoseenko M. V. et al.) presented the experience of PCV13 vaccination of children with health conditions of the Vaccine Prophylaxis Department of the Research Institute of Preventive Pediatrics and Restorative Treatment of the National Medical Center for Children's Health. The study involved 110 children aged 2 months to 5 years, healthy and with different types of health problems (with allergic forms of diseases; cardiovascular system (congenital heart defect), broncho-pulmonary system (bronchial asthma, broncho-pulmonary dysplasia) diseases). Children were vaccinated with PCV13 according to age-appropriate schedules. In most cases, PCV immunization was combined with the other vaccines of the NIP. The safety and tolerability of the vaccination was evaluated. The study showed that the incidence of local reactions in vaccinated children did not exceed 33%, while the incidence of general reactions was 11%. A similar frequency of negative reactions occurred in both relatively healthy children and those with different health conditions. PCV13 vaccination was concluded to be well-tolerated by both healthy children and patients with various pathological conditions [26].

These findings are supported by the results presented in the paper authored by Kurdup M. K. et al.

This study evaluated the safety and epidemiological efficacy of pneumococcal vaccination in children with chronic cardiovascular conditions. The study involved 82 children aged 1 month to 7 years with chronic cardiac conditions who were examined and/or treated at the cardiology and cardiac surgery departments. The 13-valent pneumococcal conjugate vaccine was used.

No complications during the postvaccination follow-up period were recorded in the vaccinated children. Twelve children experienced a subfebrile temperature rise lasting from several hours to two days, while 13 children had mild to moderate local reactions. The standardized follow-up examination after vaccination revealed no increase in the degree or functional class of congestive heart failure (CHF). During the 1st year after vaccination, no child was diagnosed with acute otitis media, meningitis and no exacerbation or aggravation of the course of the underlying disease was observed [27]

Cost-effectiveness of PCV13 vaccination in children

Several pharmacoeconomic studies on childhood vaccination against pneumococcal infection have been conducted in the Russian Federation [16,28–30]. Modeling was conducted in 2014 with a ten-year study horizon using data from clinical trials, global PCV13 vaccination experience, and Russian epidemiological data. According to the analysis, the cost for an additional life year and quality-adjusted life year (QALY) was calculated to be 32,400 rubles, and preventing one death would cost 140,100 rubles. Additionally, vaccination costs for ten years would be only 111.5 rubles per child. Thus, mass vaccination of children under 1 year of age with PCV13 was shown to be highly cost-effective and allowing significant reduction of costs of therapy of pneumococcal infections in the Russian Federation [30].

Vaccination against pneumococcal infection was demonstrated to be more cost-effective than selective vaccination of children from risk groups based on the results obtained from vaccinating children in Perm in 2019 [16].

Thus, the national experience of using the 13-valent pneumococcal conjugate vaccine in children has shown its safety, epidemiological, social, and economic efficacy.

Epidemiological and clinical efficacy of PCV13 in adults at risk

There is extensive experience worldwide with the use of PCV13 in adults at risk and a large number of studies have been conducted on the efficacy and safety of the vaccine. The largest foreign trial evaluating the efficacy of the 13-valent pneumococcal conjugate vaccine in the adult population is the double-blind, randomized, placebo-controlled CAPITA trial, which enrolled 84,496 patients over the age of 65. The mean follow-up period was 3.97 years [31].

The results of the study showed that the efficacy of PCV13 in reducing the risk of community-acquired pneumococcal pneumonia caused by vaccine-specific serotype was 45.6% (95% CI 21.8-62.5%) and in reducing the risk of IPI was 75.0% (95% CI 41.4-90.8%). Subsequent analysis showed an even greater efficacy among patients with diabetes mellitus — 89.5% (95% CI 65.5–96.8%) in reducing the risk of pneumococcal pneumonia caused by vaccine-specific serotype. It should be noted that according to the results of various epidemiological studies, the risk of developing community-acquired pneumonia in patients with DM increases 1.3-1.5-fold and the risk of hospitalization — 1.3-1.8-fold [32].

In the Russian Federation, adult vaccination against pneumococcal infection is included in the preventive vaccination calendar for epidemic indications. Thus, according to it, adults of the following risk groups are subject to vaccination: persons subject to military service, persons over 60 years of age with chronic lung diseases, elderly persons living in nursing homes [11]. Each year, an increasing number of adults are vaccinated against pneumococcal infection (2018—more than 640 thousand, 2022 — more than 1 million 450 thousand). At the same time, the coverage of the adult population is also increasing. Thus, while in 2018, 1.6% of persons aged 18 to 36 years and 2.3% of persons older than 60 years were vaccinated against PI, this number increased to 5.3% and 11.2%, respectively, by 2022 [33].

However, the coverage rate in specific risk groups remains unknown. In 2018, a team of authors conducted a study to analyze pneumococcal vaccination coverage rates in risk groups of adult population. The source of information on the size and composition of the adult population vaccinated against pneumococcal infection was the healthcare authorities in the constituent entities of the Russian Federation. It was shown that the main adult groups vaccinated between 2015 and 2018 against pneumococcal infection were: patients with chronic diseases (55%, including 27.5% of patients with chronic lung diseases) persons subject to military conscription (30%) and various occupational risk groups (11%). Less than 5% vaccinations were received by other risk groups. Maximum coverage was achieved among adults with chronic lung disease (15.1%). Among patients with chronic non-pulmonary diseases, the coverage was as follows: 4% for liver diseases, 3.8% for cardiovascular system diseases, 2.8% for endocrine system diseases, and 1% for immunocompromising conditions and diseases. In other chronic patient groups, the coverage was even lower. Among adults with occupational risk factors and in special stay conditions, the maximum vaccination coverage was achieved among conscripts (67.4%). Vaccination was administered in negligible amounts to other categories of occupational risk: 4.9% among healthcare professionals, 3.1% among employees of open-type educational organizations (schools, kindergartens, etc.) [34].

The low vaccination coverage is unlikely to have had a significant impact on the incidence of pneumococcal infections among the adult population in the Russian Federation. Nevertheless, the available experience of regional programs and data from sample studies allow assessing the efficacy of pneumococcal vaccination among adults of different risk categories.

For example, in 2015, the Krasnoyarsk region developed and implemented a comprehensive action plan to reduce mortality from respiratory diseases, which included, among other things, vaccination of adults and children at risk against influenza and pneumococcal infection. A total of 1700 children aged 2 to 5 years in orphanages, as well as frequently and long-term ill children and 14,863 adults with chronic respiratory and cardiovascular system diseases and diabetes mellitus were vaccinated. The majority (82.7%) received the PCV13 vaccine, of whom 42% were vaccinated along with the influenza vaccine. 12,080 adults at risk were examined within 1 year of vaccination and included in the analysis [35].

Within a year after vaccination, the number of exacerbations or decompensations of the underlying diseases among vaccinated individuals was shown to decrease 3-fold, the number of hospitalizations for exacerbation and decompensation of the underlying disease — 11.5-fold, the incidence of pneumonia — 4.8-fold, and the incidence of acute respiratory diseases or influenza — 6.6-fold. According to the authors, the results obtained indicate the high efficacy of vaccination against pneumococcal infection in preventing pneumonia, reducing the incidence of respiratory infections, reducing the number of hospitalizations for exacerbations or decompensations as a result of the stabilized course of the underlying disease [35].

One of the largest risk groups are patients with chronic lung disease (CLD), particularly chronic obstructive pulmonary disease (COPD). Currently available data suggest that COPD affects approximately 1% of the general population, and the prevalence increases with age, reaching 10% among individuals aged 40 years and older [24]. Comorbidity is a frequent phenomenon in COPD. Thus, according to various authors, the combination of COPD and diabetes mellitus occurs in 2 to 35.8% of patients. [36,37]

A number of studies have been conducted in Russia to comprehensively evaluate the efficacy of PCV13 vaccination of patients with COPD, including those with comorbidity (diabetes mellitus (DM), coronary heart disease (CHD), chronic heart failure (CHF)) in terms of various outcomes. Vaccination efficacy was assessed by parameters describing the course of the underlying disease (number of exacerbations, need for hospitalization, change in functional tests) and the risk of pneumonia.

The studies explored a number of important clinical issues in vaccinating patients with chronic diseases against pneumococcal infection. First of all, these

are papers aimed at determining the optimal vaccination regimen. Thus, in the study (Protasov A. D. et al, 2017) 112 patients with mild, moderate, severe, and extremely severe COPD were divided into 4 groups with a different vaccination scheme applied: 1). PCV13 mono-vaccination (n=32); 2). PPCV23 mono-vaccination (n=23); 3). sequential vaccination: PPCV23 (n=32) after 12 months - PCV13; 4). PCV13, then (after 2 months) with PPCV23 (n=25). All patients received baseline therapy according to the severity of the disease. Comparable in comorbidities and age, the groups received a comparable amount of baseline COPD therapy, which remained the same throughout the study.

It was shown that the best result was achieved in the group of sequential administration of PCV13 followed by PPCV23. Thus, 4 years after vaccination in this group, the number of patients with COPD exacerbations decreased by 50% ($p<0.001$), the number of courses of antimicrobial chemotherapy — by 47.8% ($p<0.001$), the number of hospitalizations — by 87.5% ($p<0.001$) compared to the pre-vaccination period. It should be emphasized that long-term efficacy (4 years after immunization) in terms of preventing exacerbations of the underlying disease was noted only in this group of patients [38].

Similar results were obtained in bronchial asthma: the best long-term efficacy (4 years after vaccination) was achieved with the combined PCV13+PPCV23 vaccination regimen. The authors noted that starting the sequential regimen with a conjugate vaccine was more effective than starting with a polysaccharide vaccine [39].

This confirmed that the combined use of two types of vaccines is the most optimal immunization regimen for patients with chronic diseases. The PCV13 vaccine first generates immune memory, while the use of PPCV23 expands the number of serotypes against which the patient is protected. It should also be noted that this is the approach recommended by national guidelines for adult vaccination against pneumococcal infection [5].

Clinically important parameters such as the effect of vaccination on the quality of life of COPD patients and their compliance (adherence) to therapy of the underlying disease were also studied. For example, the study by Kostinov M.P. et al, 2015, using a sample of 58 people with COPD, showed that vaccination against pneumococcal infection contributes to a significant improvement in quality of life parameters. Changes in quality of life over time were assessed using the COPD Assessment Test (CAT) questionnaire, comparing mean scores 1 year before and 1 year after vaccination. Patients were immunized with either PCV13 (n = 33) or PPCV23 (n = 25). A decrease in the CAT (quality of life improvement) score of 10.3 points was observed in the PCV13 group and 8.8 points in the PPCV23 group ($p < 0.05$) [40].

And the paper by G.L. Ignatova and V. N. Antonov showed that including PCV13 vaccine prophylaxis

in the treatment plan of patients with COPD (n=394) not only allows to reduce the degree of dyspnea and stabilize the main functional parameters of the respiratory system during at least 4 years of follow-up, but also significantly increases patient compliance and adherence to therapy. The authors explain this effect by a significant improvement in the patient's general condition and a reduction in dyspnea [41].

A number of studies examined the efficacy of vaccination in the highest risk group of adults — patients with comorbidity and those with a history of pneumonia. G. L. Ignatova in her papers analyzed the results of vaccination of COPD patients in combination with type 2 diabetes mellitus, adults with COPD and heart conditions — CHD, including in combination with CHF [42,43].

All of these studies produced results that supported the efficacy of PCV13. Including preventive vaccination in the treatment plan of patients with COPD combined with DM (n=309) was found to reduce the severity of dyspnea, stabilize the main functional parameters of the respiratory system not only in the short-term period, but also during at least 5 years of follow-up. PCV13 vaccination can improve quality of life and prognosis in patients with COPD combined with DM 2 [43].

Using PCV13 in patients with combined cardiopulmonary disease (COPD+CHD, COPD+CHF, COPD+CHD+CHF) allows reducing the degree of dyspnea and stabilizing the main functional parameters of the respiratory and cardiovascular systems not only in the short-term, but also during at least 5 years of follow-up, provides a significant 8-fold decrease in the level of COPD exacerbations and consequently — a 4-fold reduction in the number of hospitalizations [42].

A retrospective analysis of the effect of preventive vaccination with PCV13 and PPCV23 on the risk of recurrent pneumonia in COPD patients (n=302, all patients had an episode of pneumonia of any etiology during a 5-year follow-up period) showed that a significant reduction in the number of recurrent pneumonias was observed only when the conjugate vaccine was used [44].

PCV-13 and influenza co-vaccination was another issue.

It is well known that increases in the incidence of pneumonia often follow those of influenza. In this case, pneumococcus is the main pathogen causing secondary bacterial pneumonia after influenza [45]. In this regard, it is recommended to combine influenza vaccination with immunization against pneumococcal infection [5]. Ignatova G. L. et al. conducted a study to analyze the clinical and economic efficacy of preventive vaccination with PCV13 and influenza vaccination in patients with COPD (n=153). Combined preventive vaccination with pneumococcal conjugated and influenza vaccines allows reducing the degree of clinical disorders and stabilizing the main functional parameters of the respiratory system at a significantly

lower level compared to monovaccination with pneumococcal vaccine alone. Simultaneous PCV13 and influenza preventive vaccination can reduce the risk of adverse events in COPD and decrease the number of exacerbations, associated hospitalizations, and cases of pneumonia [46].

Thus, the studies demonstrated high epidemiological and clinical efficacy of PCV13 vaccination in immune-competent adults with a chronic condition, including patients with comorbidities, preserving quality of life and improving patient compliance to therapy. Long-term efficacy in reducing the risk of exacerbations of the underlying disease and associated hospitalizations particularly with a combined regimen of PCV13 followed by PPCV23 vaccination and appropriateness of PCV13 vaccination in combination with influenza immunization were shown.

The most vulnerable category of adults are those with immunocompromising diseases and conditions. Zhestkov A. V. et al. conducted a study to assess changes in the composition of the upper respiratory tract microflora and cellular immunity parameters 1 year after administration of the 13-valent pneumococcal conjugate vaccine in adult HIV-infected patients. The study enrolled 100 individuals of both genders (50% males and 50% females) aged 18 to 71 years with different stages of HIV infection. Four of them had stage III disease, 80 had IVA, 15 had IVB, and 1 patient had IVB. All patients had received antiretroviral therapy for at least 6 months prior to study entry. PCV13 vaccination was shown to result in a statistically significant reduction in *Streptococcus pneumoniae* carriage 1 year after vaccination ($p=0.012$). One year after PCV13 vaccination, patients had a statistically significant increase in total T cells, T helper cells, and cytotoxic T cells compared to prevaccination levels [47].

An important issue is the protection against pneumococcal infection of persons of occupational and social risk groups. The experience of PCV13 vaccination among conscripts, healthcare professionals, persons exposed to harmful production factors and having occupational lung diseases was obtained and described in our country.

Thus, the epidemiological efficacy of PCV13 for the prevention of CAP in military conscripts was evaluated. The total size of the observation group was 1727. PCV13 and PPCV23 vaccines were used. The incidence of CAP among those vaccinated with PCV13 during the 5-month follow-up period was shown to be 4.5 times lower than in the comparison group ($p < 0.001$), the efficacy rate was 77.7%, and the incidence of community-acquired pneumonia among those vaccinated with non-conjugated polysaccharide vaccines was demonstrated to be 2.8 times lower ($p < 0.001$), the efficacy rate was 64.3%. The authors concluded that PCV13 is not inferior in efficacy to the 23-valent pneumococcal polysaccharide vaccine in preventing community-acquired pneumonia in military personnel and, in its

absence, can be used for vaccination of conscripts one month before conscription and recruits not covered by vaccination against pneumococcal infection before conscription [48].

Analysis of PCV13 efficacy in preventing occupational pneumococcal infection among healthcare professionals ($n=157$) showed that vaccination resulted in a 2.1-fold reduction in the incidence of all pneumococcal infections, 2.2-fold reduction in bacteremia, 2.1-fold reduction in pneumococcal respiratory infections, a 33% reduction in respiratory infections of any cause, $p<0.05$ during a 12-month follow-up compared to the same period before vaccination. The number of days of disability due to respiratory infections decreased among vaccinated healthcare professionals. Thus, the authors found that vaccination of healthcare professionals with PCV13 effectively reduced the incidence of occupational respiratory infections and *St. pneumoniae* carriage [49].

The study of the effect of pneumococcal vaccines on exacerbations in persons with occupational lung diseases (pneumoconiosis, including anthracosilicosis, occupational bronchitis) showed that after vaccination with 2 vaccines (PPCV23 and PCV13 one year later) there was a decrease in the number of exacerbations by the end of the 1st year after PCV13; the obtained result was maintained during the next 3 years and the number of exacerbations decreased statistically significantly by the end of the 4th year. Retrospectively analyzed data of patients with pneumoconiosis who were first vaccinated with PCV13 alone show that the number of exacerbations significantly decreases by the end of the 1st year after vaccination, the decrease continued in subsequent years, by the end of the 5th year after vaccination reaching a similar result obtained in the group of persons vaccinated with PCV13 and PPCV23. The authors of the study developed the following recommendations for vaccination of patients in this group: PCV13 vaccination is indicated once for all patients with occupational lung diseases; when preventive vaccination is included in the treatment plan of patients with pulmonary dust disease, the number of exacerbations is significantly reduced [50].

Cost-effectiveness of PCV13 vaccination in adults

The cost-effectiveness of adult vaccination against pneumococcal infection was evaluated in different patient groups [51–65]. Thus, based on the data of an observational study conducted in the Chelyabinsk Region and including patients with COPD, the cost-effectiveness of PCV13 vaccination was evaluated. It was found that budget cost savings with vaccination could be as high as 89% in 3 years and 79% in year 4 of the estimated costs for these patients [52,53]. The identified savings are mainly due to a reduced incidence of COPD exacerbations after vaccination.

A modeling pharmacoeconomic cost-effectiveness study of PCV13 vaccination in men of the working age

with chronic diseases was also conducted. The analysis was based on extrapolation of data from national and foreign studies for patients with chronic respiratory diseases, circulatory diseases, or diabetes mellitus and allowed predicting a significant reduction in the risk of complications of the underlying disease ($HR=0.58$, $p<0.05$), the number of hospitalizations ($HR=0.02$, $p<0.05$), and expected mortality after vaccination. The model analysis shows that budget savings are achieved from the second year after vaccination and increase in subsequent years [55,56].

Another modeling study was conducted on 20-, 40-, and 60-year-old patients with risk factors 1, 2, and 3. The study horizon was 15 years. The number of deaths averted when 100,000 patients with risk factors 1, 2, and 3 were vaccinated at age of 20 were 32, 64, and 132, respectively; at the age of 40—88, and 207, respectively; and at the age of 60—95, 238, and 687, respectively. When analyzed from a healthcare system perspective, vaccination against pneumococcal infection with PCV13 followed one year later by PPCV23 in 60-year-old patients with at least 1 risk factor and in patients of any age with at least 2 risk factors can be considered cost-effective. Vaccination with 1 dose of PCV13 in patients of any age with at least 1 risk factor when analyzed from a healthcare system perspective can be considered a cost-effective intervention [59].

In 2021, the results of a cost-effectiveness evaluation of vaccination of the elderly were published. It demonstrated that PCV13 vaccination of 100,000 Russian citizens aged 65 years would prevent 547 cases of community-acquired pneumonia (CAP), 93 cases of invasive pneumococcal infection (IPI), and 72 deaths from pneumococcal infection over 5 years. PCV13 + PPCV23 vaccination of 100,000 individuals aged 65 years would prevent 611 cases of CAP, 161 cases of IPI, and 97 deaths from pneumococcal infection. The costs per one additional year of life with PCV13 vaccination amounted to 630.21 thousand rubles, and with PCV13+PPCV23 vaccination — 1050.90 thousand rubles. The costs per prevented lethal outcome of pneumococcal infection with PCV13 vaccination amounted to 1498.97 thousand rubles, and with PCV13+PPCV23 vaccination — 2488.59 thousand rubles. An additional quality-adjusted life year (QALY) with PCV13 vaccination costs 785.27 thousand rubles, and with PCV13+PPCV23 vaccination — 1303.06 thousand rubles. The calculation per 1 QALY is a universal measure; it is appropriate for any medical intervention because each intervention affects either life expectancy, quality of life, or both. When interpreting the results, it should be taken into account that, although the threshold of willingness to pay for 1 QALY has not been officially approved in the Russian Federation, in accordance with WHO recommendations, an intervention can be considered cost-effective if the cost of 1 QALY does not exceed GDP per capita, and economically

acceptable if it does not exceed triple GDP per capita [66]. At the time of the study [61] the value of GDP per capita in the Russian Federation amounted to about 731.8 thousand rubles (at the end of 2022 — 1047.9 thousand rubles). An assessment of the effect on the healthcare system budget showed that over 5 years, 24% of funds would be returned to the budget with PCV13+PPCV23 vaccination and 33% of funds with PCV13 vaccination [61].

Since individual risk factors differ somewhat in their impact on patient morbidity and prognosis, a detailed cost-effectiveness analysis of vaccination of 40- and 65-year-old patients with type 2 diabetes mellitus was performed, taking into account current Russian epidemiologic data. The evaluation was conducted from the perspective of the healthcare system. Vaccination regimens of 1 dose of PCV13 with 1 dose of pneumococcal PPCV23 administered 1 year later and vaccination with only 1 dose of PCV13 were evaluated. The study time horizon was 5 years. The study found that vaccinating 100,000 65-year-old patients with PCV13 + PPCV23 would prevent 3,454 cases of community-acquired pneumonia and 273 deaths of CAP over 5 years. PCV13 + PPCV23 vaccination of 100,000 individuals aged 40 years would prevent 2509 cases of CAP and 165 cases of CAP-related deaths. PCV13 vaccination of 100,000 individuals aged 65 years would prevent 3244 cases of CAP and 256 deaths from pneumococcal infection. PCV13 vaccination of individuals aged 40 years would prevent 2335 cases of CAP and 154 cases of CAP-related deaths per 100,000 vaccinated individuals.

Vaccination of 65-year-old patients with DM2 is extremely cost-effective: incremental costs per 1 additional QALY with PCV13 + PPCV23 vaccination are 189.27 thousand rubles, while PCV13 vaccination results in a cost reduction of 371.92 rubles per 1 vaccinated person. When vaccinating 40-year-old patients, the incremental cost per 1 additional QALY would be 491.31 thousand rubles for PCV13 + PPCV23 vaccination and 55.31 thousand rubles for PCV13. [62].

A cost-effectiveness evaluation of pneumococcal vaccination in patients with chronic heart failure was published in 2023. A vaccination regimen of 1 dose of PCV13 with 1 dose of PPCV23 administered 1 year later and vaccination with only 1 dose of PCV13 was evaluated. The study horizon was 5 years. The analysis showed that PCV13 + PPCV23 vaccination of 100,000 individuals aged 65 years would prevent 3986 cases of CAP and 315 lethal outcomes of CAP over 5 years. PCV13 + PPCV23 vaccination of 100,000 individuals aged 40 years would prevent 2461 cases of CAP and 162 cases of CAP-related deaths over 5 years.

PCV13 vaccination of 100,000 individuals aged 65 years would prevent 3559 cases of CAP and 281 lethal cases. PCV13 vaccination of patients aged 40 years would prevent 2163 cases of CAP and 142 cases of lethal outcomes per 100,000 vaccinated individuals.

The cost-effectiveness of vaccination of both 65-year-old and 40-year-old patients with CHF was found to be very high: incremental costs per 1 additional QALY with PCV13 + PPCV23 vaccination are 113.24 thousand rubles, while PCV13 vaccination results in a cost reduction of 556.50 rubles per one vaccinated person. In vaccination of 40-year-old CHF patients with PCV13 + PPCV23, the incremental costs per 1 QALY would be 519.72 thousand rubles, while with PCV13 — 99.33 thousand rubles. Thus, pneumococcal vaccination of patients with CHF is highly cost-effective [65].

Conclusion

The 10-year experience of using the 13-valent pneumococcal polysaccharide conjugate vaccine has shown its efficacy and safety for both adults and children.

It has been demonstrated to be effective both when used in the format of selective immunization of children at risk (premature, with congenital disorders, and frequently ill) and within routine vaccination under the National Immunization Calendar. The necessity and safety of a timely start of vaccination (from 2 months of age) of newborns, including premature infants, the possibility of combining it with immunization against other infections according to the NIP, the importance of compliance with the recommended vaccination regimen in accordance with the age of the child are shown.

Regarding pharmacoeconomic efficacy, although all studies conducted have shown high cost-effectiveness of vaccination, in case of any changes in price and epidemiologic parameters (vaccine price, cost of pneumococcal infection therapy, morbidity, coverage of pneumococcal serotypes PCV13 and PCV23), new data on vaccine efficacy against infection caused by vaccine-specific pneumococcal serotypes and duration of effect, it is necessary to clarify the economic feasibility of vaccination under changed conditions. The reliability of the results obtained from modeling studies should be verified by analyzing their sensitivity to changes in model parameters within realistic limits.

When deciding whether to include certain populations in vaccination programs, it is important to consider that the cost-effectiveness of vaccination depends on the risk of pneumococcal infection in certain patient populations, the length of time that healthcare providers are willing to wait for a return on the funds invested in the vaccination program, the types of costs included in the analysis, the efficacy of the vaccine in certain patient subpopulations, and a number of other parameters.

Currently, the adult population at risk for pneumococcal infection is under-vaccinated, especially those with occupational risk factors (including healthcare professionals). At the same time, the effectiveness of this measure has been demonstrated both in terms of preventing aggravation of the underlying disease (exacerbations and associated need for hospitalization) in people with chronic conditions (bronchial asthma, COPD, including in combination with CHD, CHF, DM) and in reducing pneumonia morbidity in this population. It has been shown that maximum efficacy, including long-term results (4 years and more after vaccination), is achieved by using a combined regimen: first immunization with PCV13 followed by revaccination with PPCV23, as well as simultaneous vaccination against influenza and pneumococcal infection. However, it should be noted that revaccination with PPCV23 after PCV13 vaccination significantly increases the burden on the healthcare budget with a relatively small increase in the number of pneumococcal infections prevented.

Russian researchers have gained positive experience of immunization of adults from professional risk groups — healthcare professionals, military conscripts, and persons exposed to harmful production factors and having occupational lung diseases.

It seems advisable to further expand risk groups among adults who should be vaccinated against pneumococcal infections according to the National Immunization Calendar (vaccination for epidemic indications), to monitor the epidemiological and social effectiveness of routine immunization of the child population at the national level, and to monitor changes in the serological structure of circulating pneumococci under the influence of preventive vaccination.

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