

The resolution of the meeting of the Public Coordination Council on pneumococcal disease and vaccination in Russia (board meeting)

On December 19, 2015, there was held a regular meeting of the Public Coordination Council on the research on pneumococcal disease and vaccination in Russia at the Scientific Center of Children's Health of the Ministry of Healthcare of the Russian Federation.

The meeting was attended by the senior specialists of the Ministry of Healthcare of Russian Federation: in Pediatrics (academician of the Russian Academy of Science (RAS) A.A. Baranov), in epidemiology (academician of the RAS N.I. Briko), in infectious diseases in children (academician of the RAS Y.V. Lobzin), in allergology and immunology (Corresponding member of the RAS L.S. Namazova-Baranova), in clinical microbiology and antimicrobial resistance (professor R.S. Kozlov), the representatives of the Union of Pediatricians of Russia, Federal State Budgetary Institution "Scientific Research Institute of Children's Infections" FMBA, Federal Budgetary "Central Scientific Research Institute of epidemiology" of Rospotrebnadzor (the Russian Agency for Health and Consumer Rights), Scientific Research Institute of antimicrobial chemotherapy SBEI HPE "Smolensk State Medical University" of the Russian Federation Ministry of Healthcare, FSBSU "Scientific Research Institute of vaccines and sera of I.I. Mechnikov."

The meeting was focused on a range of key issues:

- determination of recommendations on optimal schemes of vaccination against pneumococcal infection with the use of the polysaccharide and conjugate vaccines, concerning at risk of any age;
- continuation of epidemiological surveillance for pneumococcal infection in the Russian Federation;
- approaches to improve coverage and assessments of the results of immunization in the short and long term prospects.

In the course of the discussion of the issues mentioned above, the following was noted.

Federal Law № 157-FL of 17.09.1998 "On immunoprophylaxis of infectious diseases" (ed. Federal Law № 368-FL of 12.21.2013) approved the right for protection against pneumococcal infection and vaccination against it within the National calendar for preventive vaccinations for all children born since January 1, 2014. From the epidemiological point of view, the coverage and adherence to vaccination schedules are one of the key indicators of the efficiency of the whole immunization program. The vaccination coverage should be at least 85-95% of the target cohort for creating immune layer and achieving the effect of the antipneumococcal vaccination program (lower incidence of pneumonia, otitis, meningitis, creation of population protection). The vaccination, which is performed properly, effects the epidemic process, which, in turn, determines the effectiveness of preventive vaccination. Since pneumococcal disease is considered to be managed by vaccines at the present day, the quality of

the immunization performed (timeliness, completeness of coverage, compliance with the scheme) is the main factor, effecting the morbidity and mortality from this disease.

Pneumococcal conjugate vaccine came into the regions in late November 2014, which, combined with the season of acute respiratory infections and relatively loaded schedule of vaccination of children of the first year of life, due to the lack of combined vaccines, led to extender start of the program of the new vaccination. Thus, the analysis of the average condition of vaccination in the Russian Federation during 6 months of 2015 revealed the low coverage of primary vaccination of children born in 2014 (14.1% of the subject) and non-optimal immunization coverage of children born in 2015 (40.1% of the subject).

A variety of activities were held by the Ministry of Healthcare of the Russian Federation jointly with the expert community to improve the situation with the coverage and timely immunization against pneumococcal disease, including conference calls with the heads of regional healthcare regulatory bodies, distribution of informational and teaching materials for pediatricians and epidemiologists, promotional vaccination campaign for the population.

1. An information letter № 24-2-2031252 with explanations and recommendations on the vaccination schemes against pneumococcal infections in children born in 2014-2015 was sent to all regions in the Russian Federation. The letter emphasized that the immunization against pneumococcal infection is required for all children born in 2014, in addition, various schemes of catch-up vaccination depending on the age of children at the start of the immunization.
2. In August-September 2015 after the reanalysis of the course of the immunization campaign the heads of executive branches of the Russian federal subjects in healthcare were sent another letter (number 14-5/10/2-5995 of 09.10.2015), in which vaccination of all the categories included in the National calendar of preventive vaccinations categories of persons is recommended to be taken under special control.
3. From April to September 2015, a large-scale All-Russian promotional vaccination campaign "Vaccination - a healthy nation!" was held in all federal regions of Russia on the initiative of the Russian Ministry of Healthcare, with the involvement of federal experts, more than 100 representatives of local healthcare regulatory bodies and professional medical community and more than 230 journalists. The total coverage of the marathon, according to preliminary estimates, amounted to more than 60 million people.
4. The Union of Pediatricians of Russia and National Infection Control Association of Experts released Federal clinical guidelines "preventive vaccination against pneumococcal infection"¹, which present the basic principles concerning the treatment, surveillance and preventive vaccination against pneumococcal disease, including vaccination of patients of special risk groups and schemes for shifted vaccination schedule.
5. Over 20,000 pediatricians received a special package of informational and teaching materials on all the issues of preventive vaccination, composed by the Union of Pediatricians of Russia. The National Association of Experts in Control of Infections ("NAECI"), related to medical care, plans a similar campaign for epidemiologists.

¹ Available at: <https://www.rosminzdrav.ru/poleznye-resursy/klinicheskie-rekomendatsii-po-vaktsinoprofilaktike-pnevmokokkovoy-infektsii>

All these measures were effective, and, after the 10 months in 2015, the coverage of vaccination against pneumococcal disease in Russia, on average, amounted to 79% of children born in 2015.

Taking into account the experience gained, the basic aspects, which affect the quality and timeliness of immunization, were determined:

- determination of the cohort vaccinated (who is to be vaccinated: age groups, specific health conditions);
- compliance with immunization schedule considering Order 125-n by the Ministry of Healthcare of Russian Federation and the instructions for medical application of the vaccines;
- adequacy of the cohort planning with the creation of a 3-month rolling stock of vaccines.

Calculation of doses should be conducted according to the following formula:

$$(C \times 2 \times 95\%) + (CP \times 1 \times 95\%) + (C \times 25\%),$$

C — the size of the cohort of newborns in the territory according to the statistics for the year, CP — the size of the cohort of newborns in the territory according to the statistics for the previous year (dose for revaccination), 2 — the number of doses in the primary immunization scheme and in the catch-up immunization schedule for children of the second year of life, 1 — the number of doses for revaccination, 95% — the recommended vaccination coverage, 25% — carryover remainings for creating a supply of vaccine to maintain uninterrupted immunization program.

The calendar of preventive vaccinations on epidemic indications (Application № 2 to the Order of the Ministry of Healthcare of the Russian Federation of March 21, 2014 № 125-N) provides vaccination against pneumococcal infection for children aged from 2 to 5 years old, adults at risk, including those, who are to be called to military service². The funding of vaccination programs for children older than 2 years is entrusted to the regions, which need to make a choice in favour of the competent use of the budget with the maximum effect of vaccination.

For the prevention of pneumococcal infection are two qualitatively different types of non-interchangeable vaccines were reported in children 2-18 years: pneumococcal conjugate 13-valent (PCV13)³ and polysaccharide 23-valent (PPV23)⁴.

Pneumococcal conjugate 10-valent vaccine (PCV10)⁵ is applied in children up to 5 years.

Considering clinical trials, international recommendations and the accumulated regional experience, various immunization schemes against pneumococcal disease for patients at risk were observed. In order to achieve the maximum effect from vaccination, taking into account features of immunity developing in 2-18 years old children at high risk [patients with immunodeficiency, HIV infection, any oncological diseases; receiving immunosuppressive therapy, including corticosteroids; anatomic/functional asplenia; with established cochlear

² The Russia Federation Ministry of Healthcare Order of March 21, 2014 № 125n "About the National Calendar of preventive vaccinations and the Calendar of preventive vaccinations in case of epidemic indications".

³ Prevenar13 instruction (pneumococcal polysaccharide conjugated adsorbed 13-valent vaccine) LP 000798-140915.

⁴ Pneumo23 application instruction (pneumococcal polyvalent polysaccharide vaccine) of 18.02.2014 № 011092.

⁵ Instruction for the medical application of the drug Sinflorics LP 001412-110112.

implant or planning this operation; patients with cerebrospinal fluid leakage; with chronic lung diseases, including asthma and chronic obstructive pulmonary disease; chronic diseases of the cardiovascular system, liver (including chronic hepatitis B, chronic hepatitis C), kidney (including nephrotic syndrome, chronic renal failure, hemodialysis); diabetics; people, subjected to transplantation or people, who have received transplantation of organs, tissue and/or bone marrow], it is necessary to start vaccination against pneumococcal infections with PCV13, then, not earlier than in 8 weeks, it is recommended to administer a single dose of PPV23. In special cases (preparation for transplantation and/or immunosuppressive therapy, surgery interventions) the minimum allowable interval between PCI and PPV23 may not be less than 8 weeks. These recommendations are based on high strength evidence (1A-1B).

In addition, the Council of Experts highlights that there are other recommendations, with evidence of lower strength (2B, 2C) up to the present moment, according to which, there are two more risk groups for vaccination against pneumococcal disease:

- 2-18 year old children — after convalescence of acute otitis media, meningitis and/or pneumonia, who are recommended a single administration of PCV13 1 month after recovery (for 2-5 year old children a two-dose scheme PCV10 may be used, when the 2 doses are administered at interval of not less than 8 weeks);
- 2-18 year old children, often ill with respiratory infections, and infected with mycobacterium tuberculosis⁶, who are recommended a single administration or PPV23 PCV13 (for 2-5 year old children a two-dose scheme PCV10 may be used, when the 2 doses are administered at interval of not less than 8 weeks).

In the Russian Federation, according to the recommendations of the World Health Organization, the epidemiological data on the prevalence of circulating serotypes of *Streptococcus pneumoniae* have been received more than 2 years before the introduction of mass immunization program against pneumococcal disease. In 2010-2014, retrospective and prospective researches on seroepidemiology of pneumococcal infections in children and adults have been carried out in research centers in St. Petersburg, Moscow, Smolensk, Ekaterinburg, Murmansk and Barnaul, as well as in 14 other towns of Russia. According to the data of the Central Scientific Research Institute of Epidemiology of Rospotrebnadzor in 2014 (i.e. before the start of mass immunization in Russia PCV) 25% of purulent meningitis were caused by *S. pneumoniae*. Along with this, the identification results, demonstrated in 2015, showed that 76% of pneumococcal isolates were covered by serotypes, included in PCV13, and 46% — in PCV10.

It is also important to continue epidemiological monitoring after the implementation of vaccination for at least 5 years (WHO, 2012). The possibility of relative increasing of level of morbidity due to improved detection and reporting of cases of pneumococcal disease, as there are more improvements in diagnostic approaches, should also be considered; the similar situation has been observed in Germany.

To estimate the contribution of PCV13 vaccination to children's health and the dynamics of serotype landscape during 2015-2018, using the experience of Russian scientific research centers [SRIIC FMBA of Russia (St. Petersburg), Central Scientific Research Institute of Epidemiology (Moscow), SCCH (Moscow), CSRAC SBEI HPE "NSMU" of the Ministry of Healthcare of Russia (Smolensk)], with the expansion of a network of supporting centers in regions (Ekaterinburg, Chelyabinsk, Perm, Khanty-Mansiysk, Krasnoyarsk, Khabarovsk), with the support of the Charitable Foundation of Rostropovich-Vishnevskaya "In the Name of Health

There are only researches for PPV23 on the effectiveness in patients infected with mycobacterium tuberculosis. (Drozdenco T.S., Harith S.M., Dovgaluk I.F.) The tactics of vaccination of children with various manifestations of tuberculosis infection. Pediatric Pharmacology, 2011, volume 8, № 4, pp. 60-63)

and Future of Children", it was suggested to conduct an international, multicenter, prospective non-interventional observational epidemiological research of the pneumococcal infection features (SAPIENS). The development of a network of microbiological laboratories, operating on a single methodology for the identification, verification, typing and assessment of pneumococcal antibiotic resistance, will help to improve the quality of data received, increase their reliability and credibility for the results. The research objectives include:

- 1) identification of pneumococcal serotype landscape:
 - in healthy children aged ≤ 5 years;
 - in children with acute respiratory infections aged ≤ 5 years;
 - in healthy children aged 3-5 years in organized groups (kindergartens);
 - during otitis media in children aged 0-5 years;
 - community-acquired pneumonia in children and adults;
 - meningitis in children and adults;
- 2) identification of the profile of pneumococcal antibiotic resistance;
- 3) retrospective and prospective epidemiological analysis of the level of morbidity of community-acquired pneumonias, otitis media and meningitis;
- 4) serotype landscape in vaccinated and unvaccinated children (prospectively in similar age groups and comparing the historical data);
- 5) development of standard operating procedures for the etiological diagnosis of pneumococcal infection for microbiological and PCR laboratories.

Based on the data obtained at 2 and 3 years after the start of mass vaccination there will be carried out a comparative evaluation of the economic results of the vaccination and the results of the simulated effect with the subsequent analysis of influence factors and the forecast.

In continuation of the vigorous activity of the medical community to improve the population adherence to the vaccination All-Russian promotional vaccination campaign "Vaccination — a healthy nation", the experts have reviewed the scientific and practical project "HUMAN" of the Charitable Foundation of Rostropovich-Vishnevskaya "In the Name of Health and Future of Children", providing a survey by the healthcare professionals (pediatricians, paramedical personnel, healthcare administration) and parents with subsequent analysis of the results, setting up roundtables and focus groups for optimal communication for a campaign in the media aimed at both healthcare professionals and the population. Moreover, the Union of Pediatricians of Russia have prepared a book for doctors, "Vaccination: simple answers to difficult questions."

Thus, according to the results of the discussion, the Public Coordination Council considers the following recommendations necessary:

1. Conduct the catch-up immunization (in accordance with the schemes in Prevenar 13 instructions) covering all births in 2014 and 2015, for increasing the effectiveness of immunization and realization of children's right for protection against pneumococcal infection.

2. Carry out the vaccination of children born in 2016 routinely with the start of the vaccination at the age of 2 months. The calculation of the cohort, which is subjected to vaccination, should be carried out on the basis of the cohort of newborns with the need to reach a target of 100%.

3. The regulatory bodies of healthcare in federal subjects of Russia should monitor the orders for the supply of immunobiological drugs, as well as the report on the usage of immunobiological drugs, purchased within the National Calendar of preventive vaccinations.

4. Develop a strategic plan for the development of the National Calendar of preventive vaccinations, including the phased introduction of the vaccination against pneumococcal infection of people at risk.

5. Include the vaccination against pneumococcal infection in clinical guidelines and standards for the provision of high-tech medical care.

6. Improvement sanitary rules and norms of Rospotrebnadzor on vaccination against pneumococcal disease (indicating immunization schemes and the groups to be vaccinated).

7. Send proposals to the Ministry of Healthcare of the Russian Federation on the introduction of amendments to the order № 125-n "About the national calendar of preventive vaccinations and the calendar of preventive vaccinations in case of epidemic indications" of March 21, 2014 on intervals of vaccination in case of schedules nonfulfillment and risk groups.

8. Implement a commitment of preventional vaccination in programs of under- and postgraduate medical education. Supplement the Federal State Educational Standard (FSSES) of higher and secondary medical education by a unified working program on the issues of preventive vaccination with an end-to-end teaching on all faculties.

9. Include obligatory questions of preventive vaccination in the certification of the teaching staff of secondary and higher medical institutions and doctors in all specialties.

10. Inform the Rospotrebnadzor and the Ministry of Healthcare of the Russian Federation of the project on an international multicenter prospective non-interventional observational epidemiological research of the pneumococcal infection features (SAPIENS).

11. Introduce graphs for recording the incidence of vaccinated and unvaccinated children with pneumonia, meningitis, and otitis media (acute, recurrent and chronic) in the cities involved in the SAPIENS research, in the electronic system of immunization control.

12. Continue the education campaign on preventive vaccination for the population, with the content tracking in publications in the media and the provision of comments by medical experts in case of incorrect information delivery. Improve the legal framework in terms of the introduction of liability for false or defamatory information about vaccines.

13. Create an advisory authority on issues of preventive vaccination — the National Committee on Immunization — with the participation of the representatives of the medical expert community, the Ministry of Healthcare of the Russian Federation, Rospotrebnadzor, organizations and federal agencies responsible for the managing medicinal products (including vaccines), for optimization of the organizational and advisory activities on immunization issues and giving them a special significance in matters of public healthcare.