according to the protocol decision of the NITAG
dated 15.06.2020 No. 2

National Immunization Technical Advisory Group (NITAG)

POSITION PAPER No.15-06/2020-2
(official statement)
that presents recommendations to the Ministry of Health of Ukraine on the introduction of pneumococcal vaccine into the National Immunization Programme of Ukraine

General information[1]

Pneumococcal infections can lead to serious invasive diseases such as meningitis, septicaemia and pneumonia, as well as milder but more common illnesses such as sinusitis and otitis media. The causative agent, Streptococcus pneumoniae, that frequently colonizes the human nasopharynx, is transmitted from person to person mainly through respiratory droplets. Infants and children under 5 years are the main pathogen reservoir. The prevalence of individuals carrying the pathogen among the population of low- and middle-income countries can reach up to 85%.

As of today, more than 90 pneumococcal serotypes of *S.pneumoniae* are known. Before the introduction of pneumococcal vaccines (PCV), 6-11 serotypes of the pathogen have been responsible for 70% of invasive pneumococcal diseases.

Pneumococcal infection can affect different body systems. Penetration of *S. pneumoniae* into the bloodstream causes bacteremia, a precondition for causing infection of other organs and systems, such as nervous system (meninges), joints and peritoneum. In other cases, the immediate penetration of a pathogen from the nasopharynx can cause such diseases as otitis media and sinusitis. Pneumonia often occurs as a result of pneumococcus aspiration from the nasopharynx, but can also be caused by the spread of pathogen through the bloodstream. In case of association with pneumococcal bacteremia, pneumonia is classified as an invasive pneumococcal disease.

The risk of pneumococcal infection is the highest during the first years of child's life. Subsequently, the risk declines due to the acquisition of natural immunity and rises again in late adulthood due to "immunologic aging" and increased sensitivity to pneumococci because of the concomitant pathological conditions.

People with HIV infection or sickle cell disease are at high risk of developing pneumococcal infection, that is why the timely vaccination of such people is especially important.

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[1] Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. Weekly epidemiological record 2019;8(94):85-104

Disease burden

Morbidity and mortality

According to WHO estimated data[1] of 2015, the number of deaths among children under 5 years of age due to pneumococcal infection around the world accounted for 294,000 persons. Before the introduction of PCV, the incidence rate (per 100,000 of population) of pneumococcal infection in children under 5 years of age totaled to 44.4 cases per year in Europe and 167 cases per 100,000 children under 5 years in the United States of America. The accurate data on the prevalence of this disease in middle- and low-income countries are not available due to the lack of capacity to conduct laboratory diagnostics.

Cochrane systematic reviews on PCV efficacy in children under 2 years of age have shown that at least 27% of radiologically confirmed pneumonia cases could be caused by *S. pneumoniae*.[2]

Analysis of the PCV efficacy against radiologically confirmed pneumonia in children under 5 years of age demonstrated that the fraction of pneumonia caused by *S. pneumoniae* accounted for 34%.

WHO estimated data for Ukraine[3]

The World Health Organization, in collaboration with the partners, had conducted the estimation of disease burden of Hib and pneumococcal infection-related diseases, which was completed in 2009. In 2020, according to the estimated data, 55 925 children under 5 years of age developed pneumococcal pneumonia, meningitis and sepsis, and 39 children died from these diseases in Ukraine.

According to the data[4] of the reporting form No.2, approved by the Order of the Ministry of Health of Ukraine No.378 dated 02.06.2009, the incidence rate of pneumococcal meningitis among children in Ukraine in 2015, 2017, 2018, 2019 stood at 0.1, comparing to 0.2 per 100 000 population in 2016. The most vulnerable to pneumococcal meningitis were children (0-17 years) in comparison to the adult population – the incidence rate in this age group ranged from 0.4 in 2016 and 0.1 in 2018. However, it should be noted that the existing incidence rate is not correct and reflects the minimum morbidity rate of pneumococcal meningitis. This assumption can be made when looking at significant differences in the number of confirmed cases of pneumococcal meningitis among children in different regions of Ukraine: the

[2] Pneumococcal conjugate vaccine review of impact evidence (PRIME): summary of findings from systematic review, October 2017. Geneva: World Health Organization; 2017 (http://www.who.int/immunization/sage/meetings/2017/october/3_FULL_PRIME_REPORT_2017Sep26.pf?ua=1, accessed March 2020).

[3] Estimated Hib and pneumococcal deaths for children under 5 years of age, 2008. Geneva, WHO, 2009 (https://www.who.int/immunization/monitoring_surveillance/burden/estimates/Pneumo_hib/en/) (accesses March 2020)

[4] Reporting Form No. 2 "Report on particular infections and parasitic diseases per year" approved by order No. 378 of the Ministry of Health of Ukraine dated 02.06.2009 "On approval of reporting forms for infectious and parasitic diseases, vaccinations against certain communicable diseases and their completion guidelines"

quantitative indicator ranged from 9 cases in Zakarpatska oblast to the absence of confirmed cases in Volynska, Kyivska, Poltavska, Ternopilska, Chernivetska oblasts during the 5-year period (2015- 2019).

According to the meta-analysis of studies conducted in other countries[5], the long-term neurological consequences, such as hearing loss, mental disorders, motor impairment and seizures are observed in 24.7% of people who suffered from pneumococcal meningitis in childhood.

Pneumococcal vaccines data[6]

Vaccines

As of 01.06.2020, three conjugate polysaccharide pneumococcal vaccines have been prequalified by WHO[7]: two 10-valent (PCV10) vaccines and one 13-valent (PCV13) vaccine:

1. PCV10 – Synflorix®, GlaxoSmithKline Biologicals S.A. production.

2. PCV-10 – Pneumosil®, Serum Institute of India Pvt.Ltd. production.

3. PCV-13 – Prevenar®13, Pfizer production.

Comparison of *Streptococcus pneumoniae* serotypes contained in PCV vaccines[7]

Serotypes	**1**	**3**	**4**	**5**	**6A**	**6B**	**7F**	**9V**	**14**	**18C**	**19A**	**19F**	**23F**
Pneumosil (PCV10)	x			x	x	x	x	x	x		x	x	x
Prevenar 13 (PCV13)	x	x	x	x	x	x	x	x	x	x	x	x	x
Synflorix (PCV10)	x		x	x		x	x	x	x	x		x	x

As of 01.06.2020, Ukraine have registered the conjugate polysaccharide vaccines PCV10 and PCV13 of the mentioned below manufacturers and in such presentation:

PCV10[8] – *SYNFLORIX*™ (UA/15363/01/01; PBX J07AL52), manufactured by

[5] Edmond K, et al. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. Lancet Infect Dis. 2010;10(5):317–28.

[6] Pneumococcal conjugate vaccine review of impact evidence (PRIME): summary of findings from systematic review, October 2017. Geneva: World Health Organization; 2017 (http://www.who.int/immunization/sage/meetings/2017/october/3_FULL_PRIME_REPORT_2017Sep26.pdf?ua=1,accessed March 2020).

[7] WHO Prequalified Vaccines (https://extranet.who.int/gavi/PQ_Web/)

[8] State Register of Medicines of Ukraine (http://www.drlz.com.ua/)

GlaxoSmithKline Biologicals SA (Belgium); injectable suspension, 1 dose (0.5 ml) in a prefilled glass syringe or 1 dose (0.5 ml) in a monodose glass vial and/or 2 doses (1 ml) in a multidose vial. One dose (0.5 ml) contains: 1 μg of pneumococcal polysaccharide of serotypes $1^{1,2}$, $5^{1,2}$, $6B^{1,2}$, $7F^{1,2}$, $9V^{1,2}$, $14^{1,2}$, $23F^{1,2}$ and 3 μg of pneumococcal polysaccharide of serotypes $4^{1,2}$, $18C^{1,3}$ and $19F^{1,4}$ (^{1} – adsorbed on aluminum phosphate – 0.5 mg of Al3+; ^{2} – conjugated to protein D (derived from non-typed strain *Haemophilus influenzae*) ~ 13 μg; ^{3} – conjugated to tetanus toxoid protein ~ 8 μg; ^{4} – conjugated to diphtheria toxoid protein ~ 5 μg).

PCV13[6] – *PREVENAR® 13* (UA/15864/01/01; PBX J07AL02), manufactured by Wyatt Pharmaceuticals (Great Britain)/Pfizer Ireland Pharmaceuticals (Ireland)/Baxter Pharmaceutical Solutions LLC (USA)/Pfizer Manufacturing Belgium NV (Belgium); injectable suspension, 1 dose (0.5 ml) in a prefilled syringe. One dose (0.5 ml) contains: 2.2 μg of pneumococcal polysaccharide of serotypes 1*, 3*, 4*, 5*, 6A*, 7F*, 9V*, 14*, 18C*, 19A*,19F*, 23F* and 4.4 μg – of serotype 6B*; CRM_{197} carrier protein ~ 32 μg (*conjugated to CRM197 carrier protein and adsorbed on aluminum phosphate (0.125 mg of aluminum)).

Immunization schedule

WHO recommends a three-dose vaccination schedule for children under 1 year of age. As part of a routine infant immunization programme, two vaccination schemes can be applied. The first scheme: 2+1, the minimum interval between the first and the second doses is 8 weeks, and between the second and third doses – from 9 to 28 months. The second scheme: 3+0, the minimum intervals between the first and the second doses and between the second and the third doses are 4 weeks. For both schemes, the minimum vaccination age is 6 weeks. 2+1 vaccination scheme is more preferable as higher levels of antibodies are produced when a single dose is administered during the second year of a child's life, which may be important in terms of herd immunity. The 3+0 scheme is more preferable for the countries that face difficulties in providing high immunization coverage among children over 1 year of age.

Previously unvaccinated or not fully vaccinated children who have had an invasive pneumococcal infection should be immunized according to the immunization schedule. An interrupted immunization schedule should be resumed without re-administration of previously received doses.

Efficiency in post-licensing period

By 2020, 195 countries worldwide have included pneumococcal vaccines into their national routine immunization schedules.[9] The results of a systematic literature review

[9] https://www.who.int/immunization/monitoring_surveillance/data/en/

indicate a significant (about 90-100%) reduction in the incidence of invasive pneumococcal diseases in young children.[10]

Replacement of pneumococcal serotypes after vaccine introduction[1]

Since the introduction of the 7-valent pneumococcal vaccine in some countries, they started registering the increase of incidence of pneumococcal disease caused by the serotypes that were not the part of the used vaccine – the phenomenon called "serotype substitution". The surveillance data from 21 countries have shown that one year after the vaccine introduction, the risk of invasive pneumococcal infections caused by any *S. pneumoniae* serotypes in children decreased by 55% compared to the pre-vaccination period and have remained at this level for 7 years. The risk of pneumococcal infection caused by *S.pneumoniae* serotypes, that were contained in the vaccine, had been gradually decreasing annually during 7 years and ultimately dropped by 99%. However, the risk of pneumococcal infection caused by serotypes, that were not contained in the vaccine, had increased in 2.8 times within 7 years. The higher risk was mainly associated with the 19A *S. pneumoniae* serotype. A systematic data review on the PCV10 and PCV13 serotypes replacements is currently underway. Factors other than vaccination, that could lead to serotype replacements in these countries, should be considered. These include: natural changes in circulation of various *S. pneumoniae* serotypes that had occured before the vaccine introduction; changes in surveillance conditions before and after the vaccination as well as outbreaks of these infections caused by a particular *S. pneumoniae* serotype.

Duration of protective effect[1]

Duration of protective effect is at least 2-3 years after complete immunization of children under 1 year of age. However, vaccine immunogenicity data suggest that vaccination provides protection for a much longer period.

Herd immunity

Data of systematic literature review and meta-analysis[11] have shown that children vaccination has a significant indirect effect on the morbidity of pneumococcal infection caused by pneumococcal serotypes contained in a vaccine. Herd immunity leads to a significant (90%) reduction in morbidity not only in children but also in older aged groups who have not been immunized against pneumococcal infection. In countries that achieved high levels of pneumococcal vaccination coverage in children (Canada, the Netherlands, the United Kingdom, the United States), serotype-related

[10] Strategic Advisory Group of Experts on Immunization. Pneumococcal Conjugate Vaccine (PCV) Review of Impact Evidence (PRIME) Summary of Findings from Systematic Review. WHO, 2017. https://www.who.int/immunization/sage/meetings/2017/october/3_FULL_PRIME_REPORT_2017Sep26.pdf?ua=1 (accessed 20 March 2020)

[11] Shiri T., Indirect effects of childhood pneumococcal conjugate vaccination on invasive pneumococcal disease: a systematic review and meta-analysis. The Lancet Global Health 2017; 5(1):e51-e59

pneumococcal infection has been virtually eliminated in general population, including the elderly.

Vaccine safety[1]

Vaccines registered in Ukraine have shown a high degree of safety according to the results of clinical trials and studies were conducted after the widespread use of pneumococcal vaccines. The most common adverse events that followed the administration of PCV10 in children under 1 year of age have been redness and irritability at the injection site which occurred in approximately 41% and 55% of vaccine receivers respectively. These adverse events were more common after the third vaccine dose. An increase in body temperature was reported in 30- 40% of vaccinated infants, however, high temperature (> 40°C) was observed only in 3.9% of cases after the first and the second doses of the vaccine and in 2.9% after the third dose. Similarly, redness (24-42%) and swelling (20-32%) were also the most common local adverse events observed after the administration of PCV13, with higher rates of AEFI after the third dose. The most common systematic AEFI was hyperexcitability observed in 85.6% of vaccinated children. Fever was reported in 24-36% of infants vaccinated with PCV13, although severe fever was registered only in 0.1-0.3% of vaccine receivers.

Concurrent administration of PCV13 and the DTaP (diphtheria, tetanus and pertussis) vaccine resulted in the increase in body temperature among 15-34% of vaccinated children with even higher rates of AEFI after the second dose. Simultaneous administration of a trivalent inactivated influenza vaccine and PCV13 was associated with a higher risk of febrile seizures comparing to when they were given on a separate day (incidence rate ratio is 3.5% at 95% CI, 1.13-10.85). However, the absolute risk of post-vaccination febrile seizures remains low.

Available evidence suggests that both vaccines are safe for immunocompromised children.

Contraindications [1]

PCV is contraindicated for persons with a history of anaphylactic reactions or severe allergic reactions when receiving previous doses of vaccine or any vaccine components.

PCV's immunogenicity and reactogenicity do not change significantly when co-administered with monovalent or combined vaccines against pertussis (with whole-cell and acellular pertussis component), diphtheria and tetanus, hepatitis B, poliomyelitis (inactivated and live oral vaccines), hemophilia type B infection, measles, mumps, rubella, chickenpox, meningitis C (conjugate vaccines) or rotavirus.

Choice of vaccine[1]

Both PCV10 and PCV13 vaccines that are registered in Ukraine, have shown a significant effect on the reduction of the incidence of pneumonia, otitis, invasive pneumococcal diseases (invasive pneumonia, meningitis, sepsis) caused by *S.*

pneumoniae contained in the vaccines, as well as the rate of nasal carriage of theses serotypes. Currently, there is no sufficient evidence to confirm that PCV10 and PCV13 are somewhat different in terms of their effect on the overall decrease of disease burden (morbidity and mortality from pneumococcal infection). PCV13 may provide an additional positive effect in the territories where significant disease burden exists due to pneumococci of serotypes 19A or 6C. Moreover, PCV10 registered in Ukraine may have an additional effect because of its efficacy in preventing acute otitis media related to atypical haemophilus influenzae due to its use as protein D conjugate (derived from an atypical strain of *Haemophilus influenzae*).[12]

Vaccine characteristics summary

According to the data of clinical trials and studies conducted during post-licensing period, both pneumococcal vaccines (PCV10 and PCV13) are highly effective and safe. The use of these vaccines led to a significant (90-100%) reduction in the risk of pneumococcal infection in children under 5 years of age. Children vaccination leads to a significant reduction in the incidence of pneumococcal infection in older age groups due to the herd immunity. In many countries, children vaccination against pneumococcus has led to near elimination of pneumococcal disease caused by the serotypes contained in the vaccines among general population. The positive vaccination effect on overall morbidity and mortality due to pneumococcal infection significantly exceeds the potential risk of the growth in the number of pneumococcal diseases caused by serotypes that are not contained in the vaccines.

Both PCV10 and PCV13 have received WHO prequalification, which confirms their effectiveness and safety.

According to the position paper of WHO Global Advisory Committee on Vaccine Safety (GACVS), PCV10 and PCV13 have demonstrated a high safety profile based on the outcomes of post-licensing pharmacovigilance on AEFI and during conducted clinical trials.

The studies data confirm that PCV does not cause serious AEFI. The expected adverse events are not serious and do not require the provision of any treatment. Contraindications for pneumococcal vaccines administration would the occurrence of the anaphylaxis or severe allergic reactions to the administration of previous vaccine doses or its components.

In Ukraine, the most preferable vaccination scheme within the framework of the standard neonatal immunization programme would be the 2+1 scheme (two doses of vaccine in the first year of life and one dose in the second year of life). This scheme is the most beneficial in terms of cost-effectiveness ratio and the vaccine load that children receive within the first year of their life in comparison with the 3+1 scheme.

[12] Prymula R, Peeters P, Chrobok V, et al. Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both *Streptococcus pneumoniae* and non-typable *Haemophilus influenzae*: a randomised double-blind efficacy study. *Lancet*. 2006;367(9512):740–748

The administration of the third dose in the second year of life ensures a higher level of antibodies for a longer term compared to the 3+0 scheme.

Vaccination schedule by age: 2 months (1st dose), 4 months (2nd dose), 18 months (3rd dose), combined with the administration of vaccines in accordance with the immunization schedule.

Previously unimmunized or not fully immunized children who have had invasive pneumococcal disease should be vaccinated according to the schedule.

Children born after vaccine introduction

Children under 1 year of age that have not been vaccinated with PCV in compliance with the schedule, should be vaccinated according to the 2+1 schemes at their first visit to a healthcare facility: administrate 2 doses of 0.5 ml with an interval of at least 1 month between doses; the third dose is recommended in the second year of life with an interval of at least 9 months between the doses.

Children aged 1-2 years should receive 2 doses of PCV with an interval of at least 2 months between the doses.

Children under 2 years of age who have not been vaccinated with PCV according to the immunization schedule should be vaccinated during their first visit to a health carefacility in compliance with the recommended schedule. Children aged from 2 to 5 years should receive 1 dose of PCV.

Vaccination of children over 5 years of age is not recommended.

In case of violation or interruption of immunization schedule in children under 2 years of age, the vaccination should be continued without re-administration of the previously received doses.

Economic efficiency[13]

A systematic literature review on cost-effectiveness of pneumococcal vaccination in low- and middle-income countries have shown that the introduction of PCV into a routine national immunization programme schedule is cost-effective (in 20 of the 22 studies included in the review). The sensitivity testing identified that the following factors demonstrated the greatest influence on the cost-effectiveness indicator: clinical efficacy of vaccines, vaccines price, the disease burden, donor support.

[13] Saokaew S, Cost Effectiveness of Pneumococcal Vaccination in Children in Low- and Middle-Income Countries: A Systematic Review. PharmacoEconomics 2016;34:1211–1225

Conclusions

Taking into account such factors as:

- significant burden of pneumococcal diseases among children of early age in Ukraine;
- high level of workload on the health system due to a severity of invasive diseases caused by pneumococcus that require inpatient care, including intensive therapy;
- high financial burden on the health system due to long hospitalization period, expensive treatment, as well as the high risk of serious complications that can lead to disability;
- availability of effective and safe vaccines prequalified by WHO that led to near elimination of pneumococcal diseases caused by the serotypes, contained in vaccines, in the countries which introduced the pneumococcal vaccines into their national routine immunization schedule;
- high cost-effectiveness of the introduction of pneumococcal vaccines in the countries supported by GAVI;
- upward trend in the level of vaccination coverage within the current immunization schedule in recent years;
- willingness of medical community to successfully introduce a vaccine to prevent pneumococcal infection and achieve high coverage rates;
- predominantly positive attitude of parents toward the introduction of pneumococcal vaccine into the immunization schedule;
- WHO recommendations for all countries on the necessity to introduce the pneumococcal vaccine into their routine national immunization schedule for children.

The NITAG suggests the following recommendations for the introduction of pneumococcal vaccine into the National Immunization Programme Schedule:

1. Recommend to the Ministry of Health to introduce the conjugate pneumococcal vaccine into the National Routine Immunization Schedule of Ukraine until 2022 for children under 1 year of age.
2. Recommend pneumococcal conjugate vaccine to children who need to be vaccinated by their age, as well as to children born before the vaccination inclusion into the immunization program, but who were less 5 years of age at the time of vaccination introduction according to the schedule.
3. Further recommendations, including the schemes of PCV administration and the number of doses, will be reviewed by the NITAG Working Group and submitted to the Ministry of Health of Ukraine after their approval at the NITAG meeting.