YEVROSIYO PEDIATRIYA AXBOROTNOMASI
ЕВРАЗИЙСКИЙ ВЕСТНИК ПЕДИАТРИИ

TIBBIY ILMIY-INNOVATSION JURNAL

МЕДИЦИНСКИЙ НАУЧНО-ИННОВАЦИОННЫЙ ЖУРНАЛ

2 (17)
2023

ISSN 2181-1954
ESSN 2181-1962

YEVROSIYO PEDIATRIYA AXBOROTNOMASI/ЕВРАЗИЙСКИЙ ВЕСТНИК ПЕДИАТРИИ

ЕВРОСИЁ ПЕДИАТРИЯ АХБОРОТНОМАСИ
ЕВРАЗИЙСКИЙ ВЕСТНИК ПЕДИАТРИИ

Тиббий илмий-инновацион журнал
Медицинский научно-инновационный журнал

Учредители:
Ташкентский педиатрический медицинский институт
Санкт-Петербургский государственный
педиатрический медицинский университет

Зарегистрирован агентством информации и массовых коммуникаце при Администрации Президента Республики Узбекистан 08.05. 2019 г.
Свидетельство №1023

Журнал с 01.09. 2019 года включень в список иностранных журналов ВАК Республики Узбекистан. Протокол № 268/7 от 30.08. 2019 года.

Адрес редакции:
100140 Республика Узбекистан
г. Ташкент ул Богишамол , 223
тел: +99871 - 260-28-57;
факс: +998971 - 262 - 33-14;
www: tashpmi.uz/ru/science/journal pediatry

2(17) 2023
Март-апрель

Received: 20.05.2023, Accepted: 30.05.2023, Published: 15.06.2023.

UDC 615.3.71

SPECIFIC IMMUNE RESPONSE TO VACCINATION WITH DIFFERENT TYPES OF PNEUMOCOCCAL VACCINES IN CHILDREN

I.A.Karimdzhanov[1] https://orcid.org/0000-0002-9356-4780
E.A.Shamansurova[2] https://orcid.org/0000-0003-1670-2675
M.P.Kostinov[3] https://orcid.org/0000-0002-1382-9403
P.M.Madrakhimov[4] https://orcid.org/0009-0004-5338-9045

[1]Tashkent Medical Academy 100109, Tashkent, Uzbekistan Farabi Street 2. Tel: +99878 1507825; E-mail: info@tma.uz
Tashkent Pediatric Medical Institute, Uzbekistan 100140, Tashkent, 223 Bogishamol St, tel: 8 71 260 36 58 E.mail: interdep@tashpmi.uz
[3]Research Institute of Vaccines and Serums. I.I. Mechnikova, Moscow, Russia 105064, Moscow Maly Kazenny pereulok, 5a Tel: +7 (495) 917-49-00 e-mail: mech.inst@mail.ru
[4]Urgench branch of the Tashkent Medical Academy Uzbekistan, Khorezm region, Urgench city, Al-Khorezmi street No. 28 Tel: +998 (62) 224-84-84 E-mail: info@urgfiltma.uz

Resume

Two types of pneumococcal vaccines for children are registered in Uzbekistan: Prevenar-13 (Pfizer, USA) contains capsular polysaccharides of thirteen pneumococcal serotypes conjugated with genetically engineered diphtheria toxoid and 10-valent conjugate vaccine Pnevmosil (India). Until 2020, children were vaccinated with the 13-valent vaccine Prevenar-13, after 2020 - Pnevmosil-10. We conducted a study to assess the humoral immune response (IgG) to 15 pneumococcal CPS in ELISA in children with pneumonia, as well as in relatively healthy children. Analysis of the same sera showed a higher level of IgG in the post-vaccination period to the Prevenar-13 vaccine to a greater extent than to the 10-valent vaccine (1.3-2 times).

Key words: pneumococcus, capsule polysaccharides, children, specific antibodies against capsule polysaccharides, vaccines

СПЕЦИФИЧЕСКИЙ ИММУННЫЙ ОТВЕТ НА ВАКЦИНАЦИЮ РАЗЛИЧНЫМИ ВИДАМИ ПНЕВМОКОККОВЫХ ВАКЦИН У ДЕТЕЙ

И.А.Каримджанов[1] https://orcid.org/0000-0002-9356-4780
Е.А.Шамансурова[2] https://orcid.org/0000-0003-1670-2675
М.П.Костинов[3] https://orcid.org/0000-0002-1382-9403
П.М.Мадрахимов[4] https://orcid.org/0009-0004-5338-9045

[1]Ташкентская Медицинская Академия (TMA) Узбекистан, 100109, Ташкент, Алмазарский район, ул. Фароби 2, тел: +99878 1507825, E-mail: info@tma.uz
[2]Ташкентский педиатрический медицинский институт, 100140, Узбекистан Ташкент, ул. Богишамол, 223, тел: 8 71 260 36 58 E.mail: interdep@tashpmi.uz
[3]Научно-исследовательский институт вакцин и сывороток. И.И. Мечникова, Москва, Россия 105064, Москва Малый Казенный переулок, д.5а Тел: +7 (495) 917-49-00 эл.почта: mech.inst@mail.ru
[4]Ургенчский филиал Ташкентской медицинской академии Узбекистан, Хорезмская область, город Ургенч, улица Ал-Хорезми №28 Тел: +998 (62) 224-84-84
E-mail:info@urgfiltma.uz

ISSN 2181-1954. EISSN 2181-1962

Резюме

В Узбекистане зарегистрированы два вида пневмококковых вакцин для детей: Prevenar-13 («Пфайзер», США) и Пневмосил-10 (Индия). Prevenar-13 содержит полисахариды тринадцати серотипов пневмококка, конъюгированных с генно-инженерным дифтерийным анатоксином, в то время как Пневмосил-10 содержит полисахариды десяти серотипов пневмококка. До 2020 года детей прививали вакциной Превенар-13, а после 2020 года - вакциной Пневмосил-10. Наше исследование оценивало уровень иммунного ответа (IgG) к 15 серотипам пневмококка у детей с пневмонией и у здоровых детей. Анализ сывороток показал, что после прививки уровень IgG был выше в случае вакцины Prevenar-13 в большей степени, чем при использовании 10-валентной вакцины (в 1, 3-2 раза).

Ключевые слова: пневмококк, капсульный полисахарид, вакцинация, дети, антитела против пневмококка

BOLALARNI TURLI XIL PNEVMOKOKK VAKTSINALARI BILAN EMLASHDAN KEYIN IMMUN-REAKTSIYANING O'ZIGA XOSLIGI

I.A.Karimdzhanov[1] https://orcid.org/0000-0002-9356-4780
E.A.Shamansurova[2] https://orcid.org/0000-0003-1670-2675
M.P.Kostinov[3] https://orcid.org/0000-0002-1382-9403
P.M.Madrakhimov[4] https://orcid.org/0009-0004-5338-9045

[1]Toshkent tibbiyot akademiyasi, 100109 Toshkent, O‘zbekiston Farobiy ko’chasi 2, Tel: +998781507825 E-mail: info@tma.uz
[2]Toshkent pediatriya tibbiyot instituti, O‘zbekiston 100140, Toshkent, ko‘chasi. Bog‘ishamol, 223, tel: 8 71 260 36 58 E.mail: interdep@tashpmi.uz
[3]Vaktsinalar va sarumlar ilmiy-tadqiqot instituti. I.I. Mechnikova, Moskva, Rossiya 105064, Moskva Maly Kazenny pereulok, 5a Tel: +7 (495) 917-49-00 e-mail: mech.inst@mail.ru
[4]Toshkent tibbiyot akademiyasi Urganch filiali O‘zbekiston, Xorazm viloyati, Urganch shahri, Al-Xorazmiy ko‘chasi 28-uy Tel: +998 (62) 224-84-84 E-mail: info@urgfiltma.uz

Rezyume

O'zbekistonda bolalar uchun pnevmokokka qarshi vaktsinalarning ikki turi ro'yxatga olingan bo`lib : Prevenar-13 (“Pfizer”, AQSH) difteriya anatoksini yordamida gen- injenerlik usulida konyugatsiyalangan, tarkibida o'n uchta pnevmokokk serotyping capsulali polisaxaridlari bo`lgan vaksina va 10 valentli Pneumosil (Hindiston) 10 ta pnevmokokk serotiplarining (1, 4, 5, 6B, 718, 719F, 719F, 718F) 10 ta capsulyar polisaxaridlarini o'z ichiga Olga konjugatsiyalangan vaktsinasidir. 2020 yilgacha bolalar 13 valentli Prevenar-13 vaksinasi bilan, 2020 yildan keyin esa Pnevmosil-10 vaktsinasi bilan emlangan. Biz pneumonia bilan og'rigan bolalarda, shuningdek, nisbatan sog'lom bolalarda 15 capsules polisaxaridli pnevmokokka nisbatan humoral immune javobini (IgG) baholash uchun tadqiqot o'tkazdik. Har ikkala vaksina bilan emlangandan keyin olingan tahlillar natijalari shuni ko`rsatdiki, IgG miqdori 10 valentli konyugatsiyalangan Vaksinaga Nisbatan Prevenar-13 Vaksinasidan keyin ko'proq hosil bo'lgan (1.2-2marta)

Kalit so'zlar: pnevmokokk, kapsulyar polisaxarid, emlash, bolalar, pnevmokokkga qarshi antitanachalar.

Relevance

One of the leading causes of morbidity and mortality among children under the age of 3 years is pneumococcus [1, 10, 13, 14].

In conclusion, the introduction of planned vaccination against pneumococcal infection in Russia has led to a 35% reduction in mortality from community-acquired pneumonia in children and a decrease in the incidence of acute otitis media. However, children with altered immune status or frequent bronchopulmonary diseases may experience a decrease in specific antibodies to many CPS included in the vaccines in the case of invasive disease [3, 5, 6, 9, 15, 16, 17, 18].

Polysaccharides cause an immune response by a T-independent mechanism, therefore, they stimulate the formation of antibodies in children older than a year, and for serotypes 6A, 14, 19F and 23A, a high titer is not formed until the age of

ISSN 2181-1954. EISSN 2181-1962

5 years. After vaccination, specific IgM and IgG antibodies are formed. The peak of IgG is reached only by 70-100 days after vaccination and persists for about five years, slowly decreasing and returning to the level before immunization.
Various studies have determined protective titers of 0.05 to 0.4 μg/mL 6-8 weeks' post-vaccination, this may need to be done later [2, 11, 12].

Some individuals may have a reduced immune response to certain serotypes of pneumococcus included in the vaccine, which could be related to genetic factors and the HLA system. Maternal antibodies provide a certain level of antibodies to pneumococcal polysaccharides at birth, but this decreases after 2 months. When the first dose of vaccine is administered at around 1 year of age, a high immune response is observed against certain strains, while others elicit a moderate or low titer of antibodies. When the first dose of vaccine is administered at around 1 year of age, a high immune response is observed against strains 3, 4, 8, 9N, a moderate level of antibodies against 1, 2, 7F, 18C, 19F, 25, and a low titer against 12, 14, 23, 6A, 6B.

The vaccination schedule in Uzbekistan follows a planned approach, with vaccinations given at 2 and 3 months of age with a minimum interval of 4 weeks, and a booster dose at 12 months.

This suggests that a significant proportion of the serotypes causing pneumonia in Uzbekistan are covered by both the PCV-13 and PCV-10 vaccines. However, the PCV-13 vaccine provides coverage for a greater number of serotypes compared to the PCV-10 vaccine. In the pre-vaccination era, serotypes 1, 3, 5, 6A, 14, and 19 were commonly identified in patients with pneumonia in Uzbekistan, with the 6A/B serogroup being the most frequently identified. When comparing the serotypes included in the PCV-13 vaccine with those isolated from patients, there was overlap in 78.3% of cases. Similarly, there was overlap with serotypes included in the PCV-10 vaccine in 62.7% of cases. This suggests that vaccination has the potential to reduce pneumonia-related morbidity and mortality in children in Uzbekistan. [4].

When studying the serotype landscape of pneumococcus 2-3 years after the introduction of the Prevenar-13 vaccination, we identified only the group serotype 6A/B/C/ D, the remaining serotypes were not detected [8]. Identification of serogroup 6A/B/C/D can be attributed to the features of the pneumococcal landscape in our country. The disappearance of the most common pneumococcal serotypes after vaccination indicated the effectiveness of vaccination.

Another measure of the immune response is the seroconversion rate. The WHO Expert Working Group defined the seroconversion rate as an immunological correlate of efficacy, i.e. the proportion of individuals with the level of type-specific antibodies of the IgG class at a concentration above 0.35 μg/ml of vaccination [11, 12].

This statement suggests that the effectiveness of the PCV vaccine can be influenced by various factors, including the number and timing of vaccine doses, the interval between doses, the region where the individual lives, and whether they receive simultaneous DTP immunization. The duration of mass vaccination campaigns can also impact the level of immunity provided by the vaccine.

Purpose of the study: to assess the humoral immune response (IgG) to 15 pneumococcal capsular polysaccharides.

Materials and methods

To evaluate the immune response to pneumococcus, researchers examined the blood of children who had received either Prevenar-13 or a 10-valent vaccine. The study focused on children hospitalized with community-acquired pneumonia, with 11 having received Prevenar-13 before 2020 and 15 having received the 10-valent vaccine Pneumosil from India. As a control group, blood sera of 12 children without pneumonia (children who were in the hospital for various surgical conditions (dislocation of the forearm, nasal trauma, calculous cholecystitis, etc.) were studied.

For the analysis of sera, the method of solid-phase ELISA was used. Collapsible plates for ELISA, produced by " Greiner " (Germany). For sorption of plates, a portion of each of the CPS preparations (1, 3, 4, 5, 6 B, 7 F, 9 N, 9 V, 14, 15 B, 18 C, 19 A, 19 F and 23 F) was dissolved in phosphate- saline buffer solution (PBS) with pH = 7.2-7.4 to a concentration of 5 μg / ml. The volume of CPS solution introduced into the well is 100 μl. Duration of sorption was 2 hours at 37 °C and 16-18 hours at 8-10°C. 30 minutes at a temperature of 18-20 ° C. After being freed from the solution, working solutions of the analyzed sera were added to the wells in duplicate. The working dilution of sera was 1:200. A pool of sera from 100 clinically healthy people in the same dilution was used as a negative control. The reaction of sera with immunosorbent (antigen on polystyrene) lasted 1 hour at 18-20° C. Then the contents of the wells

ISSN 2181-1954. EISSN 2181-1962

were shaken out, the wells were washed with saline containing 4% tween-20. 100 µl of working dilution of CG (peroxidase - labeled monoclonal antibodies diagnostic against human IgG, produced by POLYGNOST LLC, St. Petersburg), diluted in PBS with BSA to a ratio of 1:4000, was added to each well and incubated for 30 minutes at 18-20 ° C After washing the wells of the plates from unbound CG, 100 µl of a substrate mixture containing TMB was added and after 10 minutes the reaction was stopped by adding 50 µl of 2M HCL. Optical density was determined at 450 nm. The results are presented in terms of OD, ΔOP and c.u., which are calculated by the formula: $\frac{ОП_{ан}}{ОП_{К-}+0,25}$x100. N for adult clinically healthy people - (OP $_{K-}$ +0.25) or up to 100 c.u.

Results and discussion

We have analyzed the immunological efficacy of immunization after routine vaccination with the pneumococcal vaccine Prevenar-13 (Pfizer, USA) and the 10-valent pneumococcal conjugate vaccine Pnevmosil. To assess the immunological efficacy, we determined specific anti- SPP IgG antibodies to Streptococcus capsular polysaccharides pneumoniae by ELISA in immunized children no earlier than 2 months after the last vaccine administration. There were 11 children who received Prevenar - 13, and 15 children who received the 10-valent vaccine. As a control group, sera of children who did not receive vaccination against pneumococcus (12 children) were studied.

When analyzing the sera of children with CAP (n=11) vaccinated with a 13-valent vaccine (Table 1), it was found that the level of specific antibodies to individual CPS in them is in a wide range of values - from 35 c.u. e. to CPS Pn-9 N up to 101 cu e. to KPS Pn- 23 F.

The researchers found that the average lower limit for most CPS (capsular polysaccharides) was between 30 and 40 cu. units, while the upper limit was around 60-100 cu. units. When calculating the average level of antibodies, they discovered that for the majority of CPS, it was around 40-50 cu. units. This difference was statistically significant ($p < 0.05$).

Table - 1.

Immunological efficacy of vaccination against pneumococcal infection in children

	The level of specific antibodies in children with CAP (c.u.)	
	Prevenar-13	Pneumosil
Pn1	67.4±22.6	40.6±8.3^
PN 3	41.3±6.4	33.2±3.8*^
PN 4	44.2±6.4	42.2±4.2
Pn 5	53.9±10.9	46.7±5.3*
Pn 6A	41.4±7.9	33.2±3.0^
Pn 6B	41.7±5.8	40.2±4.1
Pn 7F	38.8±6.7*	42.4±7.2
Pn 9N	35.1±4.5	37.1±5.6
Pn 9V	47.0±6.9	49.9±7.9
Pn 14	53.4±9.4	49.4±6.9*^
Pn 15B	44.8±6.9*	36.3±4.3*^
Pn 18C	63.0±26.3*	30.5±2.6*^
Pn 19A	50.1±6.6	62.7±17.8*
Pn 19F	59.1±14.8	42.1±3.9*^
Pn 23F	101.0±29.3*	54.1±11.9^

Note: (- P <0.05); ^ - reliability of data in relation to the group of vaccinated children until 2020 (^- P<0.05).*

ISSN 2181-1954. EISSN 2181-1962

At the same time, for the KPS Pn-23 F was more than 100 cu. units, which is associated with the presence of individuals with a high level of antibodies (AT) to it. The conducted studies showed that in all children of the control group (11 children) a diagnostically significant level of IgG to one or several CPS was determined. When analyzing the sera of children vaccinated with a 10-valent vaccine, it was found that the level of specific antibodies to individual CPS was in a lower range of values (30-40 units) than that of vaccinated Prevenar-13.

It was found that after vaccination with Prevenar -13, the level of IgG to CPS Pn-1, Pn-18C most often increased and the level of antibodies to Pn-23 (2 times) increased significantly, which probably indicates a higher immunogenicity of these CPS in Prevenar -13. The weakest was the increase in the level of antibodies to CPS PN-3, 4, 6A, 6B, 7 F, 9 N, 9 V, 14, 15 B. Children vaccinated with 10 - valent vaccine had levels of antibodies to 70% CPS (Pn 1, 3, 4, 6 A, 6B, 7 F, 9 N, 9 V, 14, 15 B) significantly lower than those vaccinated with Prevenar-13. It should be noted that in those vaccinated with the 10-valent vaccine, the levels of antibodies to only two CPS (Pn 19 A and 7 F) significantly increased.

When analyzing sera (n=12) of the control group of children without pneumonia, the following results were obtained (Table 2).

Table - 2.

Level of IgG to individual S.pneumoniae capsular polysaccharides and vaccines Prevenar-13 and Pnevmosil in vaccinated and unvaccinated children (c.u.)

	Control group	Main group	
		Prevenar 13	Pneumosil
Pn1	53.2±9.7	67.4±22.6	40.6±8.3^
PN 3	54.9±13.9	41.3±6.4	33.2±3.8*^
PN 4	56.4±16.5	44.2±6.4	42.2±4.2
Pn 5	60.5±16.3	53.9±10.9	46.7±5.3*
Pn 6A	41.8±8.6	41.4±7.9	33.2±3.0^
Pn 6B	46.9±11.4	41.7±5.8	40.2±4.1
Pn 7F	41.7±10.1	38.8±6.7*	42.4±7.2
Pn 9N	43.7±10.1	35.1±4.5	37.1±5.6
Pn 9V	49.8±12.6	47.0±6.9	49.9±7.9
Pn 14	58.5±10.4	53.4±9.4	49.4±6.9*^
Pn 15B	63.1±8.4	44.8±6.9*	36.3±4.3*^
Pn 18C	45.8±10.9	63.0±26.3*	30.5±2.6*^
Pn 19A	55.6±14.7	50.1±6.6	62.7±17.8*
Pn 19F	61.9±18.7	59.1±14.8	42.1±3.9*^
Pn 23F	55.9±11.8	101.0±29.3*	54.1±11.9^

*Note: * - reliability of data in relation to the control group (* - P <0.05); ^ - reliability of data in relation to the group of vaccinated children until 2020 (^- P<0.05).*

In the control group of children (who did not receive vaccination) for Pn 1, the average level of AT was 53.2 c.u. ($p < 0.05$) (Table 2). However, the average values for CPS Pn-3, Pn-14, Pn-7 F, Pn-5, Pn-15B and Pn-19F in unvaccinated children were 1.3-1.5 times higher. For other CPS (Pn-6A, Pn-6 B, Pn-9 N, Pn-4, Pn-9 V) the difference was not significant. In addition to those described, an analysis was made of the frequency of increasing the level of antibodies to each CPS in the post-vaccination period.

Researchers conducted a study on children who were hospitalized with community-acquired pneumonia and had received either Prevenar-13 or

ISSN 2181-1954. EISSN 2181-1962

the 10-valent vaccine. They analyzed the immune response by examining the blood samples of these children. The study found that the average lower limit for most capsular polysaccharides (CPS) was between 30 and 40 cu. units, while the upper limit was around 60-100 cu. units. The average level of antibodies for most CPS was around 40-50 cu. units, which was statistically significant compared to other groups. The study also observed that unvaccinated children in this group had higher lower limits of antibody levels for most CPS, indicating repeated exposure to pneumococcal infection. The Prevenar-13 vaccine did not show an increase in antibodies to CPS Pn-9N, which could be due to the absence of this polysaccharide in the vaccine.

Thus, the analysis of the same sera showed a higher level of IgG in the post-vaccination period to the Prevenar-13 vaccine to a greater extent than to the 10-valent vaccine (1.3-2 times).

Conclusion

In the study of blood sera using enzyme immunoassay, which is based on 15 immunosorbents containing CPS of serogroups / serotypes of pneumococcus (1, 3, 4, 5, 6 B, 7 F, 9 N, 9 V, 14, 15 B, 18 C, 19 A, 19 F and 23 F) showed that the highest level of IgG to 15 CPS pneumococcus in the pre-vaccination period was demonstrated by the sera of children in the control group. The second place in terms of the level of antibodies to CPS pneumococcus was occupied by the sera of children who received Prevenar -13, and the third place was taken by the blood sera of children vaccinated with the 10-valent vaccine (Table). In vaccinated Prevenar -13, the highest level of antibodies was observed to CPS 23 F (more than 100 c.u.), the lowest to CPS serotypes absent in the 13-valent vaccine (9 N, 15B). As noted above, children who received the 10-valent vaccine had significantly lower levels of antibodies than in the previous group. This can be explained by the greater effectiveness of the 13-valent vaccine.

However, high levels of antibodies were found for some serotypes (19A, 23F). Children in the control group showed a high level of specific antibodies, this fact can be explained by the absence of diseases in them that lead to an immunodeficiency state and, as a result, a good immune response. The study concludes that some individuals may have had previous pneumococcal infections or their immune response may have been activated by another agent. The low level of antibodies to some of the vaccines used suggests that a certain portion of individuals may not be fully protected from pneumococcal infection in an unfavorable epidemic situation.

In conclusion, while vaccination with commercial pneumococcal vaccines generally protects most vaccinated children, those with altered immune status or frequent bronchopulmonary diseases may experience a decrease in specific antibodies to many CPS included in the vaccines in the case of invasive disease.

LIST OF REFERENCES:

1. Baranov A.A. The role of S.pneumoniae in the structure of bacterial infections in children hospitalized in hospitals in Moscow in 2011-2012 / Baranov A.A.. Namazova-Baranova L.S., Mayansky N.A. et al. // Pediatric pharmacology. 2013;10(5):6-12.
2. Bayazitova L.T. Community-acquired pneumonia of pneumococcal etiology and microbiological aspects of nasopharyngeal carriers - Streptococcus pneumoniae in children in the Republic of Tatarstan, Tyupkina O.F., Chazova T.A. et al. // Infection and immunity. 2017;7(3):271-278.
3. Briko N.I., Korshunov V.A., Namazova-Baranova L.S. The results of a three-year vaccination of children against pneumococcal infections in Russia // Ped. Pharmacology. 2018;15(4):23-26.
4. Daminov T.A., Tadzhieva N.U., Tuychiev L.N. The results of the study of S. Pneumoniae serotypes isolated from sick children with pneumococcal infection // Infection, immunity and pharmacology. - Tashkent, 2017;2:50-55.
5. Instructions for use of the vaccine Prevenar 13 – instruction. - LP-000798-041016.
6. Immunization vaccines and biologicals. Pneumococcal infection. Available from: http://www.who.int/immu-nization/diseases/pneumococcal/ru/ (accessed: 07.14.2020).
7. Lazareva M.A. Nasopharyngeal carriage of Streptococcus pneumoniae in pupils of orphanages, preschool institutions and unorganized children under 5 years old /Lazareva M.A., Kulichenko T.V. et al. // Questions of modern pediatrics. 2015;14(2):246-255.
8. Makhkamova G.T. The role of Streptococcus Pneumoniae in the etiology of respiratory diseases in children, effectiveness: autoref. diss.... PhD. - Tashkent, 2020;51.

ISSN 2181-1954. EISSN 2181-1962

9. Somova A.V., Romanenko V.V., Golubkova A.A. Epidemiology of S. pneumoniae - associated pneumonia and analysis of the effectiveness of vaccination against pneumococcal infection in children under 6 years of age //Epidemiology and Vaccinal Prevention. 2018;17(1):25-32.
10. Tatochenko V.K. Pneumococcal infection: modern a look at the problem and prevention // Issues of modern pediatrics. 2007;6(1):85-90.
11. Kholodok G.N. Frequency of detection and characterization of Streptococcus strains pneumoniae isolated from carriers and sick children in the Khabarovsk Territory/ Kholodok G.N., Morozova M.V., Alekseeva I.N. et al.// Journal. microbiol. 2010;4:92-96.
12. Yastrebova N.E., Grishchenko N.V., Kostinov M.P. Experience in the use of pneumococcal vaccines for the study of humoral immunity // Journal. microbiol. 2012;2:12-17.
13. Troeger C. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 19902016: a systematic analysis for the Global Burden of Disease Study 2016/ Troeger C., Blacker B., Khalil I A. et al.// Lancet Infect Dis. – 2018;18(11):1191-1210. doi: https://doi.org/10.1016/S1473-3099(18)30310-4
14. Wahl B. Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15/ Wahl B., O'Brien K.L., Greenbaum A. et al. //Lancet Glob Health. 2018;6(7):744-757. doi.: https://doi.org/10.1016/S2214-109X (18)30247-X
15. Pneumococcal disease. Surveillance and Reporting. Available from: https://www.cdc.gov/pneumococcal/surveillance.html (accessed: 07.14.2020).
16. European Center for Disease Prevention and Control. Invasive pneumococcal disease. In: ECDC. Annual epidemiological report for 2017. Stockholm: ECDC; 2019 Available from: https://www.ecdc.europa.eu/en/publications-data/invasive-pneumococcal-disease-annual-epide-miological-report-2017.
17. Ouldali N. Invasive pneumococcal disease incidence in children and adults in France during the pneumococcal conjugate vaccine era: an interrupted time-series analysis of data from a 17-year national prospective surveillance study/ Ouldali N., Varon E., Levy C. et al. //Lancet Infect Dis. 2020;21(1):137-147. doi: https://doi.org/10.1016/S1473-3099 (20)30165-1
18. Desmet S. Dynamic changes in pediatric invasive pneumococcal disease after sequential switches of conjugate vaccine in Belgium: a national retrospective observational study / Desmet S., Lagrou K., Wyndham-Thomas C. et al. //Lancet Infect Dis. 2021;21(1):127-136. doi: https://doi.org/10.1016/S1473-3099 (20)30173-0

Entered 20.06.2023

ISSN 2181-1954. EISSN 2181-1962

МУНДАРИЖА * CONTENTS * СОДЕРЖАНИЕ

Редакторы : Дизайн и верстка: А. Асраров
Узбекский текест: Л.М.Шагиязова Формат 60x84 1/8, усл.печ.л.
16. Заказ No 0196/2
Русский текст: Н. Мехмонова Подписано в печать 20. 03. 2022 Английский текст: Д.Д. Буранова Отпечатано в ООО “Gredo Print” г. Ташкент, ул Богишамол 160.