VACCINE PREVENTION OF PNEUMOCOCCAL RESPIRATORY DISEASES OF CHILDREN

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Abstract*. In this article, the author presents the results of studies assessing the effect of vaccination against Streptococcus pneumoniae on the incidence of respiratory diseases in children, in addition, data from the author's own studies of pneumococcus in young children. 495 sick children of early and older age with acute respiratory infections who were under observation at the TashPMI clinic and the city children were examined in hospital number 1 of Tashkent.*

Keywords*: streptococcus pneumoniae, nosology, nasopharyngitis, S.aureus, S.viridans, H influenzae, M catarrhalis*

Actuality the theme. The problem of diagnosis and treatment of pneumococcal diseases continues to be one of the most pressing in modern healthcare. The most effective and cost-effective method of preventing pneumococcal infection is vaccination. According to WHO, "...vaccination is the only way to significantly influence the incidence of pneumococcal infection" (*WHO recommendations for routine immunization, 2019).* Therefore, it is necessary to develop and implement measures to prevent these diseases in children. According to the WHO, "...in many countries, routine use of pneumococcal conjugate vaccines has sharply reduced the number of cases of serious illness caused by this microorganism," including pneumonia." *(Pneumococcal conjugate vaccines for infants and children under 5 years of age: WHO position paper, February 2019 //https://www.who.int/immunizationPP_pneumococcal_2019_RU).*

Considering the serotype diversity of pneumococcus, it is especially important to study circulating pathogenic strains of Streptococcus pneumoniae. To assess the effectiveness of vaccination, the study of the effect of vaccination against Streptococcus pneumoniae on the incidence of respiratory diseases in children, as well as the serotype spectrum of pneumococcus in young children deserves the most attention [5,7,8,11,12].

In world practice, special attention is paid to research into the modern serotype landscape of pneumococci. Mass vaccination with pneumococcal vaccines over several years has sharply reduced the incidence of invasive pneumococcal infections associated with vaccine strains of pneumococcus [1,2,3,4,6]. However, the spectrum of circulating serotypes *Streptococcus pneumoniae* may vary between countries, so regional data on the most relevant pneumococcal serotypes are required to develop new vaccines and study their epidemiological effectiveness. In this regard, studying the serotype landscape after the introduction of the vaccine, as well as assessing the impact of vaccination on morbidity, is extremely relevant. In Uzbekistan, isolated work has been carried out on the diagnosis and treatment of pneumococcal infections in children (Daminov T.A., Tuychiev L.N., Tadjieva N.U., 2015). The authors determined the spectrum of circulating pneumococcal serotypes before the introduction of the vaccine against Streptococcus *pneumoniae.* However, to assess the effectiveness of vaccination, data on the incidence, as well as on the serotype spectrum of pneumococcus after inclusion of vaccination in the CPT, is needed. Data on the incidence and serotype landscape of pneumococcal infections can be considered as a criterion for predicting the effectiveness of national vaccination programs (Azimova G.A., 2014;

Daminov T.A., Tadjieva N.U., Tuychiev L.N., 2017). The analysis of literature data shows that currently studying the effectiveness of vaccine prevention against pneumococcal infection is extremely relevant. In this regard, it is especially relevant to study the carriage *Streptococcus pneumoniae,* carriage of pneumococcus leads to the spread of pneumococcal diseases in contact children. The study of the serotype spectrum remains unexplored *Streptococcus pneumoniae* after the introduction of vaccination. All of the above confirms that pneumococcal infection is an important and dangerous pathology that requires vaccine prevention. In purpose to assess the effect of vaccination against Streptococcus pneumoniae on the incidence of respiratory diseases in children, as well as the serotype spectrum of pneumococcus in young children, 495 sick children of early and older age with acute respiratory infections who were under observation at the TashPMI clinic and city children's hospital No. 1 were examined; as well as 153 organized and unorganized healthy children from 1.5 to 6 years old. A prospective study was conducted using general clinical, bacteriological, serological, molecular genetic and statistical research methods.

To determine nasopharyngeal carriage of *S.pneumoniae* in healthy children before the introduction of vaccination we conducted a survey of 76 healthy children attending and not attending kindergartens aged from 1.5 to 6 years. To confirm the etiological role of S. Pneumonia, we used a bacteriological method, which is recognized as the “gold standard” for diagnosis. We used a nasopharyngeal swab as a biomaterial. The bacteriological method and Gram staining were used, and then sensitivity to antibiotics was determined. Sensitivity was determined to amoxicillin, amoxicillin/clavulanate, cefazolin, azithromycin, cefepime, ceftriaxone, cefuroxime, metronidazole.

In addition, a clinical and laboratory examination was carried out on 96 children with diseases of the lower respiratory tract aged from 2 months to 9 years, who were undergoing inpatient treatment at the clinic of the Tashkent Pediatric Medical Institute and the City Children's Clinical Hospital No. 1 of Tashkent. The number of girls, there were 51 (53.1%), exceeded the number of boys - there were 45 (46.9%). In order to determine the etiological spectrum of pathogens of acute otitis media (AOM) in children, 91 children were examined, among them 48 (52.7%) boys and 43 (47.3%) girls, 30 (33.0%) children with bilateral process and 61 (67.0%) - with unilateral. The age gradation of children ranged from 1 year to 15 years (6.9±0.3 years). They had bacteriological studies of nasopharyngeal mucus and ear discharge according to standard methods, and sensitivity to antibiotics was determined.

Determination of pneumococcal antigen in urine using an immunochromatographic test (“BinaxNOW Streptococcus pneumonia Test”, USA) was carried out in 52 children from 1 to 5 years old hospitalized for pneumonia, of which 66.7% were boys. The average age was 2.6 years. The test was performed to confirm pneumococcal etiology in combination with culture and other methods. On average, the detection of Streptococcus pneumonia antigen in urine required 1 day, while cultural methods for isolating Streptococcus pneumonia required 3-4 days.

To identify nasopharyngeal carriage of *S.pneumoniae* after the introduction of vaccination, a bacteriological study of nasopharyngeal mucus for the presence of *S.pneumoniae* was carried out in 77 healthy children vaccinated with the PCV-13 vaccine, which contains polysaccharide capsular antigens of pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, conjugated to non-toxic diphtheria carrier protein CRM 197 (CRM cross-reactive material). PCV dose – 13 - 0.5 ml. The vaccine contains aluminum phosphate as an adjuvant. The PCV 13 vaccine is presented in the form of single-dose vials and a single-dose syringe tube, which does not contain

latex. All children were vaccinated three times with PCV 13 Prevenar vaccines according to the schedule. The study was conducted 2 years after the child received the 3rd dose of pneumococcal vaccine (Table 1).

Table № 1

Vaccination schedule for children with Prevenar vaccine

Age of start of vaccination	Dosa	Number of doses	Schema
From 2 to 6 months.	0,5 ml	2+1 revaccination	2 + 1: two doses with an interval of at least 4 weeks between administrations. The first dose was administered at 2 months of life, the second - from 3 months of life. Revaccination was carried out once every 12 months.

In order to identify S.pneumoniae serotypes, a PCR study of materials was carried out in the laboratory of the Research Institute of Virology of the Ministry of Health of the Republic of Uzbekistan.

"Assessment of the rationality of the use of antibacterial drugs and the frequency of nasopharyngeal carriage of S.pneumoniae among healthy children and children with respiratory infections before vaccination". The results of a study on the rationality of the use of antibacterial drugs for acute respiratory infections in children in outpatient settings showed that of the observed 308 children in the structure of ARI, the first place was occupied by acute respiratory infections of the upper respiratory tract of unspecified localization (75 cases; 24.4%), the second - acute bronchitis (60 children; 19.5%); third - acute tonsillitis (52 children; 16.9%), fourth - acute pharyngitis, nasopharyngitis (47 children; 15.3%); fifth - acute tracheitis (24 children; 7.8%), in the process of decreasing, acute rhinosinusitis and laryngitis were later encountered (20 children, 6.5%; 10 children, 3.2%). As can be seen from Diagram 1, uncomplicated forms predominated in the structure of ARI (74.0%; 228 children out of 308). Uncomplicated ARIs included respiratory episodes, which were designated in outpatient records as acute respiratory viral infection, pharyngitis, laryngitis, tracheitis (Fig. 1).

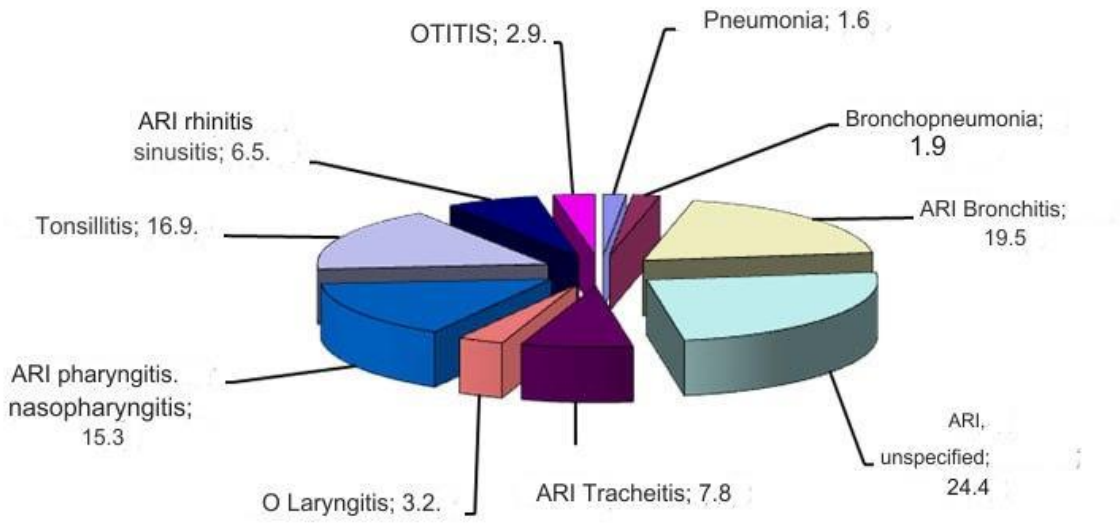

Fig. 1. Structure of ARI in children by nosology

Among 26.0% of complicated forms, 60 children were diagnosed with acute bronchitis (simple or obstructive) and 11 patients were diagnosed with acute pneumonia and bronchopneumonia. In 9 children, ARI was accompanied by the development of acute otitis media. Among uncomplicated forms of ARI, antibiotic therapy was prescribed in 78.5% (179 children out of 228). For complicated forms, antibiotic therapy was prescribed in 75% of cases of the total number of complicated ARIs. When choosing an antibiotic for the treatment of ARI, general practitioners preferred cephalosparin drugs (95.1%). The frequency of prescription of macrolides, which are an alternative to penicillins in the outpatient treatment of upper respiratory tract infections, was 80.2%.

A study of the tactics of using drugs for bronchitis and pneumonia on an outpatient basis showed a high frequency of their use, which amounted to 75%. The range of antibacterial drugs used was different. What they had in common was their unreasonable prescription for uncomplicated forms of ARI and acute bronchitis. Primary care doctors, out of habit, use antibacterial therapy for mild hyperthermia, rhinitis, and minor redness of the pharyngeal mucosa. This obviously increases the number and distribution of antibiotic-resistant strains of bacteria, since the ineffectiveness of antibacterial drugs for viral ARI is well known, since it does not prevent bacterial complications and does not have any effect on an uncomplicated acute respiratory process, however, it is widely used in practice. Our data indicate that doctors need to adhere to a wait-and-see approach and mandatory dynamic observation in case of ARI without complications. To validate antibacterial treatment for ARI in outpatient settings, strict accounting of the antibacterial drugs used in each child is necessary, especially in groups of frequently ill patients and young children. Prescribing antibacterial treatment without the necessary reasons increases the risk of side effects and disruption of the child's microbiotic flora, leading to antibiotic resistance.

The next stage was to study the microbial landscape in practically healthy, unvaccinated, unorganized children aged 1.5-3 years, and also kindergarten students aged 3-6 years. When examining the nasopharynx, growth of normal microflora was noted in 23.6% (18/76) of cases (Table 2).

Table № 2

Microbial spectrum during nasopharyngeal carriage in organized and unorganized children before vaccination

	Microflora	Disorganized children (n-34)		Children attending kindergarten (n-42)		Total	
		abs	%	abs	%	abs	%
1	*S.pneumoniae*	6	17,6	13	31*	19	25
2	*H influenzae*	3	8,8	9	21,4*	12	16
3	*M catarrhalis*	6	17,6	8	19,0	14	18,4
4	*S.aureus*	6	17,6	4	9,5*	10	13,1
5	*S.viridans*	1	2,9	7	16,7*	8	10,5
6	*Прочая*	12	35,3	1	2,4*	13	17,1
7	Всего	34	100	42	100	76	100

Note: * - reliability of data between organized and disorganized children (P<0,05)

Those. the growth of potentially non-pathogenic flora (we designated it as normal flora) was noted in a quarter of children from kindergartens (23.6%. Normal flora was represented mainly by staphylococci, viridans streptococci, etc. There were no significant differences in the frequency of occurrence of these microorganisms among unorganized children (7/34) - 20.5% and as organized (11/42) - 23.6% of children were not, at the same time S.aureus was more often found in unorganized compared to organized (17.6 and 9.5%), and S .viridans, on the contrary (2.9% and 16.7%), conditionally pathogenic flora was more common in organized children - 71% (30/42) compared to unorganized ones - 44% (15/34). Pneumoniae was 25%, while carriage of N. influenzae was noted in 16%, and M. cataralis in 18.4% of children.

The study of the antibiotic sensitivity profile of isolates to antimicrobial drugs was studied using the disk diffusion method in 76 healthy children who were not vaccinated. When interpreting, the definitions resistant, insensitive, sensitive, and highly sensitive were used. Antibiotic susceptibility data showed decreased sensitivity to amoxicillin/clavulanate and resistance to metronidozole (Table 3).

Table № 3

Antibiotic sensitivity of isolated S. pneumoniae strains in healthy unvaccinated children

Antibacterial drugs	Highly sensitive	Sensitive	Insensitive/resistant
Azithromycin	100		
Amoxicillin	100		
Cefazolin	100		
Cefepime	100		
Cefuroxime	100		
Ceftriaxone	100		
Metronidazole		10	90

In order to identify the pathogen, a clinical and laboratory examination was carried out on 96 children from 2 months to 9 years with acute diseases of the lower respiratory tract, in which the S. Pneumoniae strain was isolated in 32.2% of cases.

Based on the results of the study, it can be said that pneumococcus is the predominant pathogen in respiratory diseases of the lower respiratory tract in children (Fig. 2).

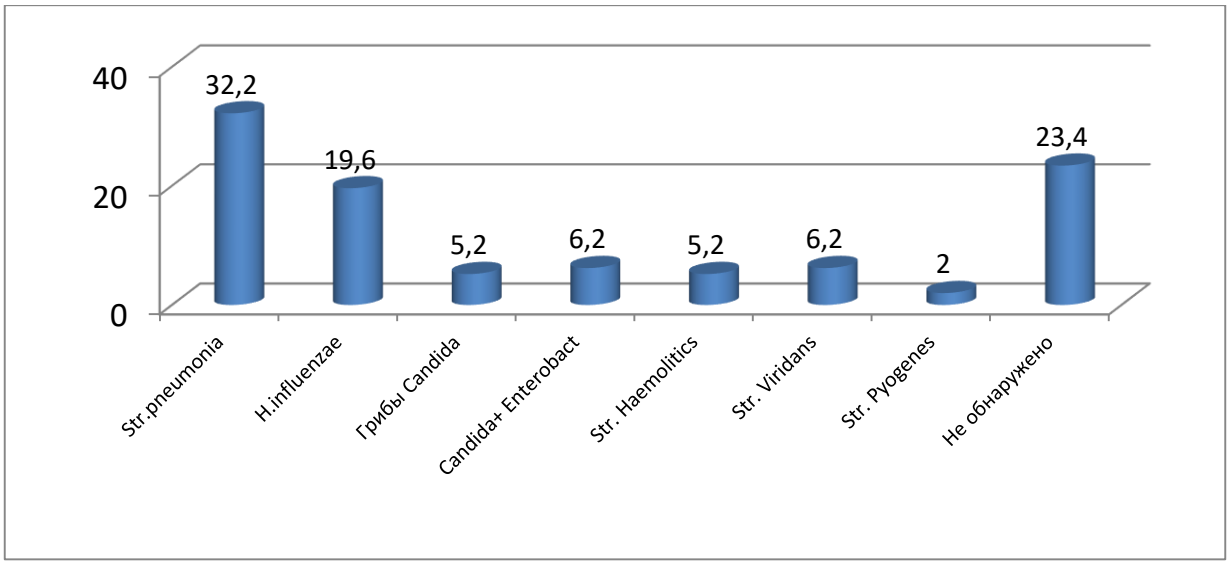

Fig. -2. Microbial spectrum in respiratory diseases of the lower respiratory tract in children.

When considering the frequency of detection of S.pneumoniae in 96 patients with lesions of the lower respiratory tract in terms of age, we found that out of 31 positive cases, *S.pneumoniae* was more often detected in the age group of 4-10 years and 1-3 years. Those *S.pneumoniae* is the predominant causative agent of respiratory diseases in both young and older children (Table 4).

Table № 4

Frequency of isolation of *S.pneumoniae* in children with lower respiratory tract lesions depending on age

Age	Number of children	Number of positive cases (abs.)	Positive Case Rate (%)
Up to 1 year	44	6	13,6
from 1 to 3 years	42	17	40,4%
from 4 to 10 years	10	8	80%
Total	96	31	32,2%

Next, the sensitivity of the isolated pneumococcal strains to antibiotics used in hospitals in Tashkent was determined. The research results showed that out of 31 samples obtained, 12.9% (4) of patients had weak sensitivity to azithromycin, and in 100% of cases there was no sensitivity to metronidazole.

It should be noted that the high sensitivity of pneumococcus to injectable cephalosporins remains, however, cephalosporins are not recommended for widespread use in community-acquired pneumonia in children. To preserve the antibiotic sensitivity of pathogens, it is advisable to limit their use in community-acquired pneumonia. Our study revealed a trend of increasing antibiotic resistance of pneumococcus to macrolides and metronidazole (Table 5).

Table № 5.

Results of determining the sensitivity of S. pneumoniae strains to antibiotics (%)

Antibiotics	Highly sensitive	Sensitive	Low sensitive/Resistant
Azithromycin	87,1	-	12,9
Amoxicillin	100	-	-
Cefazolin	100	-	-
Cefepime	100	-	-
Cefuroxime	100	-	-
Metronidazole	-	-	100

When determining pneumococcal antigen in the urine of 52 children with pneumonia, S. pneumoniae was identified in 35 cases (67.5%). Naturally, we cannot say that Streptococcus pneumoniae in these cases was the etiological factor in the development of pneumonia, however, this test can be used in combination with microbiological, immunogenetic and serological tests. Thus, detection of pneumococcal antigen in urine is an additional test for diagnosing the etiology of pneumococcal pneumonia. If a positive result is obtained, it becomes possible to optimize antimicrobial therapy, which leads to improved clinical outcomes of the disease. This test effectively complements traditional microbiological studies.

Determining the role of Streptococcus pneumoniae in the development of acute suppurative otitis media in 91 children also showed that the most common bacterial pathogen was Streptococcus pneumoniae (31.9%) (Fig. 3).

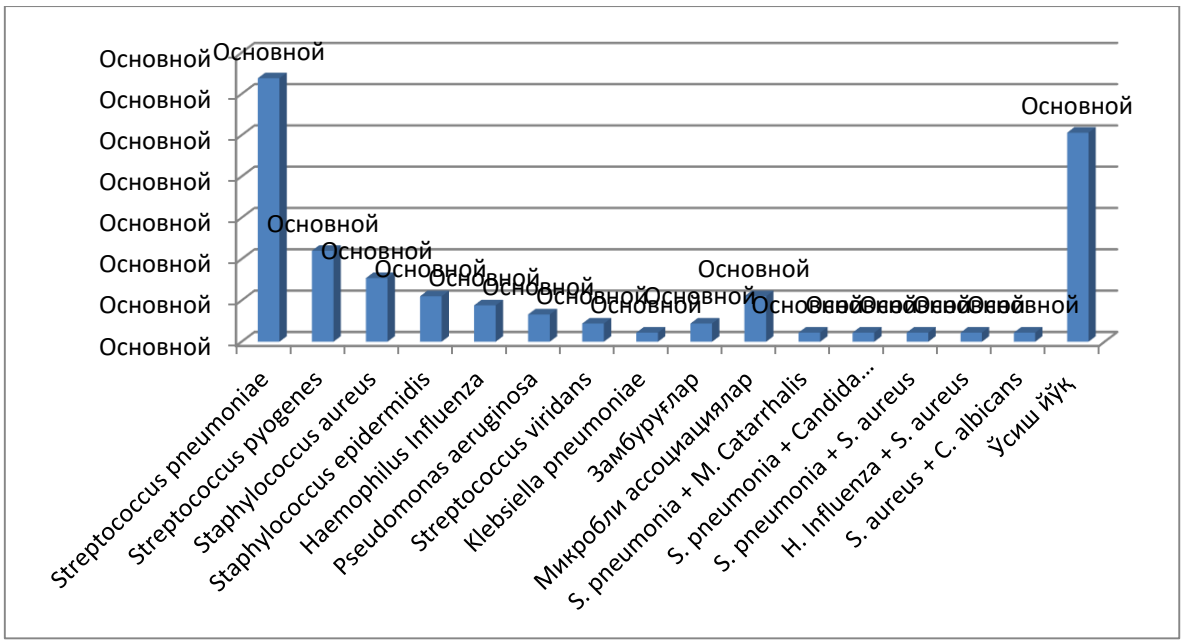

Fig.3. Frequency and spectrum of bacterial pathogens of acute purulent otitis media in children

Antibacterial therapy (amoxicillin, amoxicillin/clavulanate, cefuroxime, cefixime, cefazolin, cefotaxime, ceftriaxone, azithromycin, clarithromycin) was administered to 28 patients with otitis media (30.8%) within 30 days before illness. A complicated course of otitis was found in 2 children (2.2%). According to our data, when determining the sensitivity of AOM pathogens to antibiotics, it was revealed that S. pneumonia remains highly sensitive to pefloxacin, cefazolin, and cefuroxime. Insensitive and resistant strains have been identified to macrolides (azithromycin) "Frequency of nasopharyngeal carriage of S.pneumonia among examined children after vaccination". The results of examination of healthy children for nasopharyngeal carriage of *S.pneumonia* after the introduction of vaccination were studied. As is known, the pneumococcal vaccine was included in the preventive vaccination calendar in November 2015.

A study of the microbial spectrum in healthy children was carried out 2 years after vaccination. The results of the study showed that out of 77 children, S. Pneumoniae was isolated from 12 children, which amounted to 15.6% (Fig. 4).

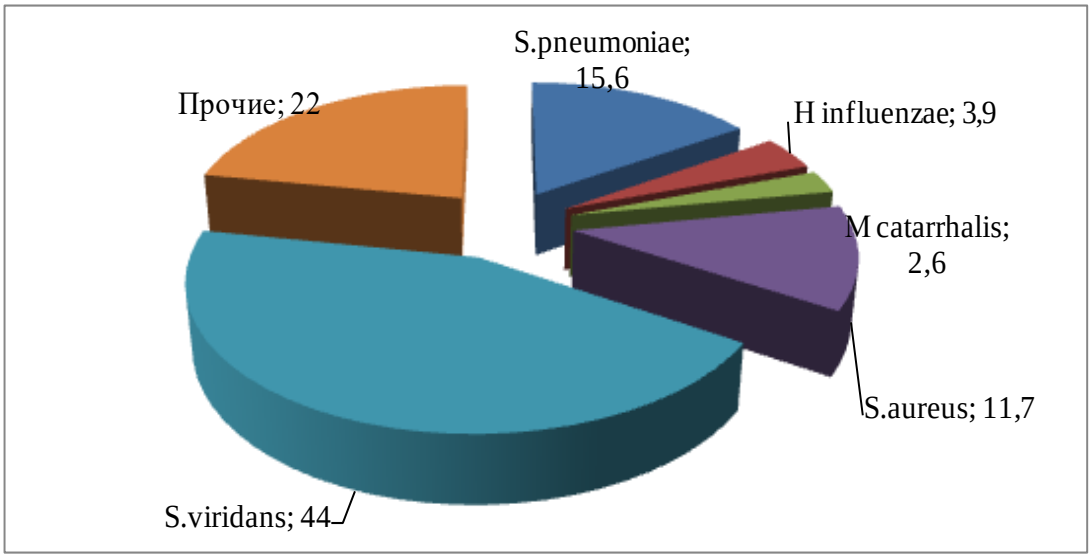

Fig. 4. Structure of isolated strains in nasopharyngeal swabs from healthy vaccinated children

We isolated only the most significant respiratory pathogens. This group of children who received vaccination against pneumococcus was unorganized, i.e. the children did not attend kindergarten.

A comparison of the microbial spectrum in nasopharyngeal carriage in children before and after vaccination showed that the frequency of detection of respiratory pathogens *H influenzae S. pneumoniae and M. catarrhalis* was significantly lower in the group of children who did not attend kindergarten compared to the group of organized children. Also, conditionally pathogenic microorganisms were sown 2 times more often in children who did not receive vaccination against pneumococcus and amounted to 42% (15/34) compared to 22% (17/77).

If we compare the microbial spectrum in general in children who did not receive vaccination with the spectrum of microorganisms in children who received vaccination, we can state that vaccination against pneumococcal infection leads not only to a decrease in the carriage of S. pneumoniae, but also other opportunistic pathogens (Table 7).

Table № 7

Microbial spectrum in nasopharyngeal carriage in children before and after vaccination

№	Microflora	Frequency of detected microorganisms before vaccination		Frequency of detected microorganisms after vaccination		P
		Абс.	%	Абс.	%	
1	*S.pneumoniae*	19	25	12	15,6	>0,05
2	*H influenzae*	12	16	3	3,9	<0,05
3	*M catarrhalis*	14	18,4	2	2,6	<0,05
4	*S.aureus*	10	13,1	9	11,7	>0,05
5	*S.viridans*	8	10,5	34	44	>0,05
6	*Others*	13	17,1	17	22	>0,05
7	*Overall*	76	100	77	100	

In order to study the serotype spectrum of S. Pneumoniae after the introduction of vaccination, nasopharyngeal swabs were taken from 77 healthy children under 5 years of age (Fig. 5).

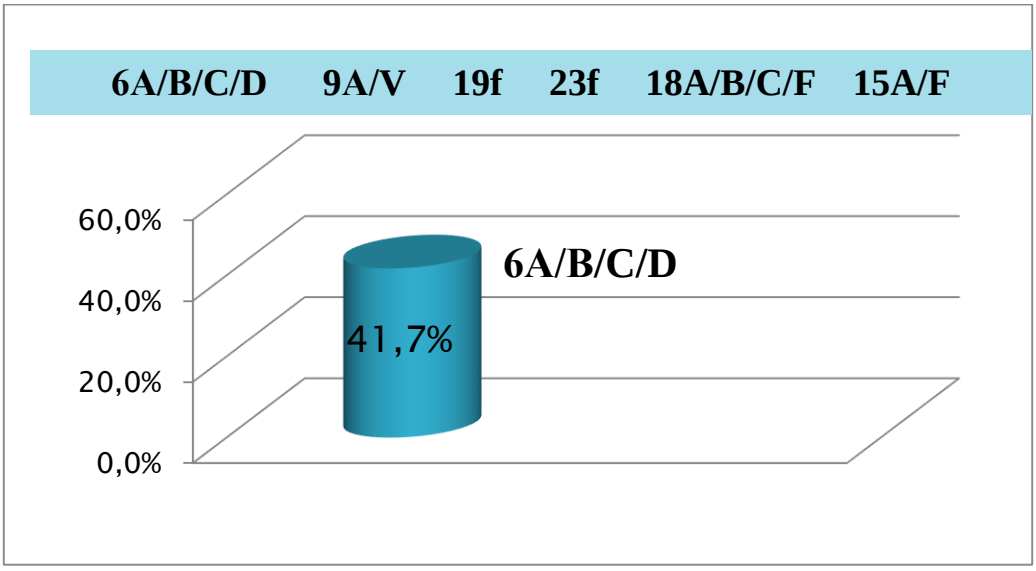

Fig. 5. Serotypes of pneumococci in healthy vaccinated children

Of these, 12 strains of S. Pneumoniae were identified. For serotyping, primers 6A/B/C/D, 9A/V, 23F, 19F, 18A/B/C/F, 15A/F serotypes were used (manufactured at the Research Institute of Children's Infections, St. Petersburg, Russian Federation). In 5 out of 12 isolated samples, only serotype 6A/B/C/D was detected; the remaining serotypes were not detected. The isolated 6A/B/C/D serotype of pneumococcus in the examined children is part of PCV -13.

Pneumococcal serotypes isolated from the respiratory tract of patients with acute community-acquired pneumonia before the introduction of vaccination in the republic (T.A. Daminov, L.N. Tuychiev, N.U. Tadjieva, 2015) were represented by serotypes 1, 3, 5, 6A/B /C/D, 14, 19, and according to foreign studies, the most common serotypes isolated from patients with pneumonia were serotypes 19, 23, 1, 5, 6B and 3. The disappearance of the most common pneumococcal serotypes after vaccination indicates the effectiveness of vaccination.

Along with this, the sensitivity to antibiotics of 77 strains of *S. pneumoniae* was studied. The panel of antibiotics studied included aminopenicillins (ampicillin, penicillin), amoxicillin, azithromycin, rifampicin, fluoroquinolones (ciprofloxacin), third generation cephalosporin antibiotic (cefatoxime), chloramphenicol

The results showed that *S. pneumoniae* remains susceptible to rifampicin, ciprofloxacin, cefatoxime and chloramphenicol. It was noted that a decrease in sensitivity to penicillin and ampicillin was detected, as well as a sharp decrease in sensitivity to azithromycin (70%). The data we obtained on the resistance of strains to ampicillin and azithromycin are apparently associated with the common practice in previous years of frequent use of these antibacterial agents for acute respiratory infections.

Thus, our data once again demonstrate the need for continuous monitoring of the prevalence of antibiotic-resistant pneumococcal strains and studying their sensitivity in order to improve empirical antibacterial therapy.

To assess the effectiveness of vaccination against pneumococcal infection and to study the relationship between vaccination of children and the incidence of invasive and non-invasive forms of pneumococcal infection, we used data from statistical reports on SP No. 7 in Tashkent, Tashkent PMI clinics, outpatient cards of children (form 112, child development history) and medical records for 2017 - 2019. The results of three-year observations in SP No. 7 of the Ulugbek district of Tashkent for 2016-2019 on the incidence of respiratory diseases in children under 5 years of age show: if in general in SP No. 7 of the Ulugbek district of Tashkent in 2017 the absolute number children under 5 years of age with respiratory infections amounted to 4097 cases, then 2 years after the introduction of abs. the number of children under 5 years old with respiratory infection decreased to 2711 cases. That is, thanks to vaccination, there was a decrease in the incidence of respiratory diseases among the served population (Table 9).

Table № 9

Incidence of respiratory infections in children under 5 years of age according to Stationary Policlinics No. 7 in Tashkent

Year	Number of children with respiratory infections	% lowing
2016	4189	
2017	4097	15-20
2018	3391	25-30
2019	2711	40-45

A study of vaccination coverage showed that in 2016 the coverage was 96-97%, in 2017-2019 this figure increased and amounted to 98-100%, i.e. Vaccination coverage was good. This was facilitated by minimal side reactions in the form of a slight rise in temperature and no pronounced local reactions. Over the 4 years of observation from 2016 to 2019, there were no cases of post-vaccination complications. There were isolated adverse reactions at the injection site (hyperemia, pain, slight thickening of the tissue).

Vaccination against pneumococcal infection also influenced the frequency of hospitalizations of children with respiratory diseases. Data on hospitalization at the TashPMI clinic for 2017-2019. indicate a decrease in the number of patients with respiratory diseases

If the total number of children under 5 years old admitted to the TashPMI clinic in 2015 was 2068, then in 2016 - 2013, 2017 - 1815, 2018 - 1682, 2019 - 1538.

Thus, over the period that has passed since the introduction of routine vaccine prevention of pneumococcal infection, a high level of vaccination coverage has been achieved (98%). Although most children received vaccinations late, 98-100% of children were vaccinated before 16-18 months of age. The introduction of routine vaccination against infection has reduced the number of hospitalizations by 25%, as well as reduced the incidence of acute respiratory diseases.

Conclusion.

1. The frequency of nasopharyngeal carriage of *S.pneumoniae* in unorganized healthy children under 6 years of age before vaccination was 17.6%, and in those attending kindergarten 31%.

2. Vaccination against pneumococcal infection led to a decrease in pneumococcal carriage to 15.6%, as well as a decrease in the overall incidence of respiratory infections in children by 40-45%.

3. Vaccination against pneumococcal infection led to the disappearance of serotypes that were present before the introduction of vaccination, which indicates the effectiveness of vaccination for the 13-valence vaccine Prevenar.

4. In the etiological structure of acute otitis in young children, according to microbiological analysis of middle ear fluid, the leader is S. pneumoniae (31.9%), the second most common is *S. Pyogenes* (11%), H. influensae is less common (4.4 %) and *M.catarralis* (1.1%).

5. In children with acute respiratory diseases, both in inpatient and outpatient settings, irrational prescription of antibacterial agents was revealed with a preference for cephalosporin antibiotics.

6. During the period 2015-2019. a decrease in the sensitivity of circulating S.pneumoniae strains to macrolide antibiotics (azithromycin) was recorded by up to 30%.

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