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Pneumococcal Infections in Adults: Issues of Vaccine Prevention

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ABSTRACT

The authors highlighted the issues of prevention of pneumococcal infections in adults. It was noted that the approach to vaccination of the adult population should be different and it depends from the presence of chronic somatic diseases in the patient and the of immunocompromising conditions. In addition, according to studies, the introduction of vaccination in risk groups, there are certain prospects for the simultaneous use of pneumococcal and influenza vaccines, such a vaccination strategy, is accompanied by a decrease in the risk of death from pneumonia in adults with chronic obstructive pulmonary diseases.

Despite the fact that the causative agent of pneumococcal infections - *Streptococcus pneumoniae* was discovered more than 100 years ago, this day this pathogen is a significant cause of morbidity and mortality worldwide. *S. pneumoniae* is the most common cause of a number of non-invasive diseases (bacterial sinusitis, otitis media, community-acquired pneumonia (non-severe forms) and invasive diseases (bacteremia, meningitis, severe community-acquired pneumonia). According to the some authors date, *S. pneumoniae* cause annually 500,000 cases of pneumonia, 50,000 cases of bacteremia (60-87% of which are associated with pneumonia), 3,000 cases of meningitis, and 40,000 cases of deaths in the USA [1, 6, 21].

Provided researches on the role of *S. pneumoniae* in purulent meningitis, community-acquired pneumonia, and acute otitis media in children in various clinics of Tashkent city have shown that pneumococcus plays a significant etiological role in the development of these diseases, being an etiological agent of 51,4% purulent meningitis, 55,5% community-acquired pneumonia and 25,3% acute otitis media cases in children [7].

S. pneumoniae is often isolated in patients with chronic respiratory diseases [10]. *S. pneumoniae* is also the cause of 50% of hospitalizations of community-acquired and nosocomial pneumonia [15], 20% of all cases of pneumococcal pneumonia are bacterial with a mortality rate of up to 50% in the elderly and inpatient medical care costs of approximately \$ 2 billion annually. Community-acquired pneumonia is one of the 6 leading causes of death and the most common cause of death from infectious diseases in the United States [17, 22].

An assessment of the long-term dynamics of the morbidity of invasive forms of pneumococcal diseases showed that since 1990 the number of invasive pneumococcal diseases (IPD), such as bacteremia and meningitis, complicated pneumonia (pleurisy, empyema and necrosis) has steadily increased [2, 9, 16]. This trend lengthens the duration of the disease, increases the need for additional medical procedures, an increase in the number of days of taking antibiotics and an increase in bed days. The main reason for this is the genetic heterogeneity and genomic plasticity of *S. pneumoniae*, which can develop antibiotic resistance [2, 9], as well as the increasing number of immunocompromised elderly patients and patients with premorbid background. At risk groups for pneumococcal diseases are elderly people, patients with transplantation of solid organs, recipients of hematopoietic stem cells, HIV-infected people, patients with hyposplenism and chronic lung diseases [4, 13].

Adverse factors that disturbing the stability of the organism (acute respiratory infections, influenza, hypothermia, stress, impaired protective drainage mechanisms - cough push, mucociliary clearance, etc.) contribute to the penetration of pneumococcus into the distal respiratory tract, paranasal sinuses, middle ear, causing local (non-invasive) forms of pneumococcal infection (sinusitis, conjunctivitis, otitis media, bronchitis, community-acquired pneumonia (CAP)). Invasive pneumococcal infection (IPI) includes bacteremia, meningitis, pneumonia and other pathological conditions when a causative agent is extracted from organs and tissues which are normally sterile (blood, cerebrospinal fluid, less common synovial, pleural or pericardial fluid). IPI is characterized by severe course and potentially high mortality [16].

Epidemiology of pneumococcal infection. Pneumococci spread from one individual to another by droplet transmission. Children and adults, being healthy nasopharyngeal carriers, are considered the main epidemiological reservoir of the pathogen and the main condition for the spread of antibiotic-resistant strains. In England, according to study of 2012-2013 years, the prevalence of carriers of pneumococcal infection (PI) among various age groups was established 6 years after vaccination of infants with conjugated pneumococcal vaccine (PCV). It was found to be maximal in children under the age of 5 years - 48%, in the group from 5 to 20 years - 22% and in people over 20 years of age - 3%. At the same time, the total prevalence of pneumococcal carriers was consistent with indicator of 2001-2002 years (before global vaccination of infants). However, during this period the percentage of carriers of serotypes contained in used PCV-13 vaccine decreased from 75 to 5% [19].

According to data in 2016, the level of nasopharyngeal carriage of *S. pneumoniae* in the group of examined healthy children amounted to 73,6%, indicating a high level of carriage of *S. pneumoniae*. The results of the study showed that the most significant factors in maintaining *S. pneumoniae* carriage among healthy children were factors such as the presence of chronic ENT diseases, a burdened allergic history, visiting an organized group, and smoking parents [8].

During periods of seasonal increase in the incidence of influenza, *Streptococcus pneumoniae* takes the leading position, ahead of *Staphylococcus aureus* and *Haemophilus*

influenzae [2, 5]. According to the literature data, in 2013 in Russia the incidence of adult pneumonia was 382,5 cases per 100 thousand people, and mortality from pneumonia exceeded half of all cases of deaths from respiratory diseases (51,7%) – 26,7 cases per 100 thousand population [2]. Increasing the incidence of community-acquired pneumonia (CAP) annually, amid rising the level of influenza incidence in the cold season, which emphasizes the relevance of the prevention of pneumococcal infection [5].

More than 90 serotypes of *S. pneumoniae* are distinguished depending on the chemical structure and antigenic properties of the polysaccharide capsule. The serotype of pneumococcus has an individual structure, determines the form and severity of pneumococcal infection, the level of resistance to antibiotics and the degree of virulence of the pathogen. Certainly, the big problem in the fighting against pneumococcal infection is the antibiotic resistance of the pathogen, complicating the treatment of patients with PI, compelling the use of reserve antibacterial drugs. This increases the cost of treatment and the inpatient duration. According to foreign literature data, the level of resistance *S. pneumoniae* to penicillin reached 40-60% [21, 15].

Studies on determining the level of antibiotic resistance conducted in Uzbekistan showed that the resistance level of clinical and nasopharyngeal *S. pneumoniae* isolates to penicillin averaged 27,7%, to macrolides from 15,1% to 36,2%, and trimethoprim/sulfamethoxazole within 53.3–69.5%, which indicates an unfavorable trend associated with the spread of resistant strains among children [6, 7].

It has been established that antibiotic resistance is characteristic for certain serotypes of pneumococcus: 6B, 9V, 14, 19F, 23F, 6A and 19A. Respectively, with mass routine immunization with vaccines containing the above pneumococcal serotypes, predicted a decreasing the incidence of PI caused by antibiotic-resistant strains [13, 16].

Risk factors for the development of invasive pneumococcal diseases. Cases of invasive pneumococcal diseases are high in the age group under the age of 2 years and among people over 60, in the age group of often suffering from acute respiratory viral infections, and during autumn-winter period [2, 6]. The development of IPD and mortality closely related to the socio-economic level of the population and from the development of the healthcare structure [4, 18]. In people with normal immune defenses, the risk of developing IPD increases with alcohol abuse, during the epidemic rise of the influenza, with diabetes mellitus, asthma, and cigarette smokers. Also, the risk of developing IPD is increased among patients with primary and secondary immunodeficiency conditions (sickle cell anemia, HIV infection, cancer, asplenia, organ transplant recipients). The frequent development of pneumococcal resistance to penicillin and co-trimoxazole in HIV-infected patients is probably associated with prolonged use of these drugs for prophylactic purposes [1, 21].

The relevance of monitoring the incidence and prevalence of IPD is determined by the potentially high mortality rate from this form of infection – from 20% for septicemia to 50% for meningitis in developing countries. So, in Europe, a fatal outcome in outpatient adults with CAP is observed with a frequency of 1:30, among patients hospitalized in a hospital - 1:15, among hospitalized in the intensive care unit - 1:3. The

risk of fatal outcome in pneumonia in young patients is 3-5 times lower than in the elderly, and it is 1-5% [21].

Pneumococcal infection (PI), as a rule, proceeds as sporadic cases. However, outbreaks of pneumococcal disease are also possible, outbreaks occurs among adults in crowded living conditions. In this regard, at risk group are military personnel, students, the elderly living in nursing homes, and patients undergoing long-term inpatient treatment. Numerous publications in the world indicate that pneumococcal infection is a significant problem for the military medical service of different countries [11, 12, 14, 23]. This leads to special attention to monitoring PI in military personnel.

Thus, according to one of the largest studies of the US military medical service, which included 3,367 recruiting sailors, among whom, in November 2000, was recorded an outbreak of pneumonia - 25 cases, 12 of which were caused by *S. pneumoniae* serotypes 4 and 9B. In order to eliminate the outbreak, sick sailors were isolated, and carried out prevention with azithromycin and PPV-23 vaccination [23]. The outbreak was successfully eradicated, no new cases of PI were reported, which indicates the effectiveness of the prevention.

In 2005, were published data on the onset of pneumococcal pneumonia outbreak in the Israel army [24]. The overall morbidity of pneumonia was 5,5%. *S. pneumoniae* (serotype 5) was isolated from 4 patients with CAP and 30 healthy contact persons. The indicated serotype was characterized by high virulence and a short period of carriage. Further spread of the infection was stopped thanks to vaccination with PPV-23 and antibiotic therapy with azithromycin (2 doses). According to studies conducted in Russia, the main risk factors for pneumonia in young men in organized groups are: lack of vaccination against pneumococcal infection and influenza virus, weight loss, chronic diseases of upper respiratory tract, repeated pneumonia, acute respiratory viral infections, smoking [12, 26].

Thus, based on international literature data, pneumococcal infections are of particular importance, the issues of its prevention and reduction of fatal outcomes are important. WHO characterizes PI as the most dangerous infection among vaccine preventable diseases. In this regard, adults who are at risk of developing PI are recommended to receive pneumococcal vaccination.

Prevention of pneumococcal diseases in adults. Prevention of invasive pneumococcal diseases among adults depends on ongoing epidemiological surveillance, the widespread introduction of vaccination programs, access to health care, promotion of the dangers of smoking, and compliance with standard guidelines for the diagnosis and treatment of diseases. In Uzbekistan, vaccination against pneumococcal infection of children according to the scheme of 2 months - 3 months - 12 months included in the National Immunization schedule of Uzbekistan since 2015 [3].

It is important to note that the approach to vaccination of the adult population should be differentiated depending on the presence of chronic somatic diseases and the absence or presence of immunocompromising conditions. That is, the approach to vaccinating a patient with a chronic somatic disease, but without immunocompromising

conditions (i.e., hematological and oncohematological diseases, nephrotic syndrome, chronic renal failure, HIV infection), differs from the approach to vaccinating a patient with an immunocompromising condition.

Today the WHO position on vaccination against pneumococcal infection: vaccination is the only way to significantly affect the incidence and mortality from pneumococcal infection. According to the recommendations, it is optimal to start vaccination with a pneumococcal conjugate vaccine (PCV), which causes a pronounced secondary immune response, which confirms the presence of immune memory and the possibility of long-term protection. All adults over the age of 65 must be vaccinated. Vaccination with a polysaccharide vaccine (PPV23) is used as booster after the primary immunization of PCV and to expand the coverage of serotypes [13, 17, 25].

Pneumococcal polysaccharide vaccine (PPV23) became available in 1983, it was an antigen-dependent vaccine and it was not immunogenic enough to be effective in the main risk group for children under the age of 2 years. On the other hand, the PCV7, PCV10, PCV13 vaccine dependent on the T-cell immunity effectively protected against all serotypes that usually caused invasive diseases and was 100% effective against diseases caused by pneumococcal serotypes included in the vaccine (7/10/13 serotypes) [1, 4]. As mentioned above, the prevention of pneumococcal infection and diseases in children leads to a decrease in the burden of pneumococcal diseases in adults [19].

Today for the prevention of pneumococcal diseases in children over 2 years of age and in adults, with Prevenar13 vaccine can be used the Pneumovax vaccine. PIV13 and Pneumovax are used to vaccination people aged 65 years and older, as well as people aged from 2 to 64 years with an increased risk of pneumococcal infections [1, 13].

In the United States and in some European countries recommendations for the use of vaccines to prevent IPD include vaccination of adults in the vaccination program that currently smokes cigarettes and adults with asthma. The recommendations are that persons aged from 19 to 64 years: smokers of cigarettes should receive a single dose of PPV23/PCV13 and counseling on smoking cessation; and / or those suffering from bronchial asthma, a single dose of PPV23 / PCV13 should be obtained [1, 13, 17].

The use of pneumococcal vaccines for people who have a history of hypersensitivity reactions with the introduction of pneumococcal vaccines is contraindicated. Immunization is not carried out for patients with hyperthermia, acute diseases of infectious and non-infectious etiology, as well as during the recurrence of chronic diseases (vaccination is allowed only after a stable remission or complete recovery). Pneumococcal infection (regardless of the reliability of the diagnosis) is not a contraindication in vaccination against pneumococcal infection of both PPV and PCV.

PPV23 - pneumococcal polysaccharide 23-valent vaccines designed to prevent bacteremic (invasive) pneumococcal pneumonia and invasive pneumococcal infections caused by *S. pneumoniae* serotypes present in the vaccine in people at risk from 2 years of age.

PCV13 - pneumococcal conjugated 13-valent vaccine (Prevenar13), is a capsular polysaccharide of 13 pneumococcal serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A,

19F and 23F, individually conjugated to diphtheria protein CRM197 and adsorbed on aluminum phosphate.

PCV13 is indicated for the prevention of pneumococcal diseases, including invasive infections (including meningitis, bacteremia, sepsis), pneumonia and otitis media caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F from 2 months of life onwards without age restriction. The Prevenar 13 vaccine includes up to 90% of all serotypes that cause IPD, including resistant strains to antibiotic treatment.

The immunogenicity and safety of the Prevenar 13 vaccine has been confirmed for older people. The most common adverse effects were reactions at the injection site, fever, irritability, decreased appetite, and disturbed sleep. In older children, during primary vaccination with Prevenar 13, a higher frequency of local reactions was observed than in children of the first year of life. In general, the frequency of adverse effects was the same in patients aged 18-49 years and in patients older than 50 years. This adverse effect in patients aged 18-49 years was more common than in patients over the age of 50 years. In people 65 years of age and older showed fewer side effects, regardless of previous vaccinations, but the frequency of reactions was the same as in a younger population. When immunized simultaneously with an inactivated influenza vaccine, the number of local adverse reactions did not increase [4].

Thus, in risk groups, there are certain prospects for the simultaneous use of pneumococcal and influenza vaccines, such a vaccination strategy, according to studies, is accompanied by a decrease in the risk of death from pneumonia in adults with chronic respiratory diseases [20].

In conclusion, it should be noted that invasive pneumococcal diseases represent a significant public health burden. The widespread vaccination program has led to a reduction in invasive diseases due to vaccination of the population and the formation of the immune layer in the population, but the effectiveness is limited by the possibility of replacing serotypes and the formation of resistant strains of pneumococci. The ongoing development of new vaccines against pneumococcal infection is encouraging, but it is very important to focus on preventive measures, such as adequate medical treatment and education of the population (especially those with high risk factors), the study of epidemiology, and strict adherence to standard recommendations for antibiotic therapy.

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