# Causes of delayed immunization with pneumococcal vaccine and aetiological patterns of pneumonia in young children

***Causas de la inmunización tardía con la vacuna neumocócica y los patrones etiológicos de neumonía en niños pequeños***

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## Abstract

To analyze the causes of delayed immunization with pneumococcal vaccine, as well as the impact of vaccination on the aetiology and severity of pneumonia in young children. Individual health records (f112/u) and vaccination records (f 063) of 309 children with delayed pneumonia vaccination were studied. The children were divided into two groups. The first group includes children (n=163) with vaccination refusals, the second group includes those with temporary medical contraindications (n=146). Additionally, retrospective study of health records of 71 children aged 0 days to 1.5 years was conducted. They were divided into 2 groups: the first included vaccinated children (n=36), the second – unvaccinated (n=35). To compare the data of 2 groups, IBM SPSS Statistics 20 was used for the calculation of CI (Confidence interval) for the ratio with the specified p-level – 0.05. Vaccination refusals in the described cases amounted to 52.7%, temporary medical contraindication was 47.2%. Among the main reasons for vaccination refusals, distrust of the vaccine is a prevailing one – 39.9%. Severe pneumonia in unvaccinated children was 42.9% (CI 95%, 26.5-59.3) of the total number of cases. In vaccinated children, the proportion of severe pneumonia was 22.2 % (CI 95%, 8.6 – 35.8) of the total number of cases. Thus, cases of severe pneumonia development in unvaccinated children are 20.7% more than in vaccinated children, p>0.05. It should be noted that the applied for the comparison 95 % CI did not show statistically significant differences in the two groups, which indicates the need for further study of the issue of increasing the sample size.

**Keywords**: pneumococcal pneumonia, pneumonia causative agents, vaccination refusal, Streptococcus pneumonia, delayed vaccination

## Resumen

Analizar las causas de la inmunización tardía con la vacuna neumocócica, así como el impacto de la vacunación en la etiología y la gravedad de la neumonía en niños pequeños. Se estudiaron los registros de salud individuales (f112/u) y los registros de vacunación (f 063) de 309 niños con neumonía retardada. Los niños fueron divididos en dos grupos. El primer grupo incluye niños (n=163) con rechazos de vacunación, el segundo grupo incluye a aquellos con contraindicaciones médicas temporales (n=146). Además, se realizó un estudio retrospectivo de los registros de salud de 71 niños de 0 días a 1,5 años. Se dividieron en 2 grupos: el primero incluía a los niños vacunados (n=36), el segundo no vacunado (n=35). Para comparar los datos de 2 grupos, se utilizó IBM SPSS Statistics 20 para el cálculo de CI (Intervalo de confianza) para la relación con el nivel de p especificado - 0.05. El rechazo a la vacunación en los casos descritos ascendió a 52.7%, la contraindicación médica temporal fue de 47.2%. Entre las principales razones de los rechazos de vacunación, la desconfianza de la vacuna es una prevalente - 39.9%. La neumonía grave en niños no vacunados fue del 42.9% (IC 95%, 26.5-59.3) del número total de casos. En los niños vacunados, la proporción de neumonía grave fue del 22,2% (IC 95%, 8,6-35,8) del número total de casos. Por lo tanto, los casos de neumonía grave en niños no vacunados son un 20,7% más que en niños vacunados, p> 0,05. Cabe señalar que el IC del 95% aplicado para la comparación no mostró diferencias estadísticamente significativas en los dos grupos, lo que indica la necesidad de un estudio adicional sobre el tema del aumento del tamaño de la muestra.

**Palabras clave:** neumonía neumocócica, agentes causantes de neumonía, rechazo de la vacunación, neumonía por estreptococos, vacunación diferida

The morbidity of the child population, as a leading criterion of public health, depends on the interaction of a number of factors. The dynamics of morbidity indicators enables to identify problem situations, develop and evaluate specific organizational, preventive and therapeutic measures.

Pneumonia accounted for 12 % of the causes of mortality of children under five years of age in 2017 (United Nations Children's Fund, World Health Organization, World Bank and United Nations 2018). Streptococcus pneumoniae is the leading cause of morbidity and mortality from respiratory infection around the world, and it contributed to an increased mortality in 2016 more than all other aetiologies combined (Begaidarova et al., 2018). Streptococcus pneumoniae is one of the most widespread bacteria causing a wide range of infections, the high social significance of which requires the development and implementation of preventive measures (Lobzin et al., 2013; Dogan et al., 2016).

Pneumonia is one of the main causes of infant mortality in Kazakhstan; in 2008, it accounted for 31.5 % of all deaths among children under one year of age. In 2010, Kazakhstan became the first CIS country where vaccination against pneumococcal infection was introduced into the national preventive vaccination schedule (Karibayeva et al., 2015).

For the first time pneumococcus was described by Edwin Klebs, who in 1875 isolated it from the pleural fluid of patients with pneumonia. Louis Pasteur in France and George Miller Sternberg in the United States, working independently, in 1880 and 1881 accidentally discovered pneumococcus during a series of experiments relating to the study of mechanisms of rabies transmission. Pasteur found a bacterium in the saliva of a rabies patient, which prompted him to assume the involvement of pneumococcus in this disease. However, this hypothesis had to be abandoned, because similar bacteria were determined in healthy people. In 1882, Carl Friedlander isolated pneumococci from lung tissue in patients with pneumonia, and then identified them as causative agents in most cases of acute pneumonia. In 1884, Friedlander described the pneumococcus capsule and revealed the morphological features of pneumococci, contributing to their colonization, and in 1886 for the first time isolated the pathogen from the blood of patients with pneumonia, and later gave it the name – pneumococcus. Over the next few years, the aetiological significance of pneumococcus has been proven in all currently known infections, including meningitis and otitis media. By 1890, most studies have identified pneumococcus as the leading cause of pneumonia development (Abaturov et al., 2016).

At the very beginning of pneumococci studies, scientists discovered the ability of serum obtained from animals immunized to pneumococcus to provide protection from experimental pneumococcal infection. Historically, the use of serums to treat patients prior to the discovery of antibiotics has been very effective. Simultaneously with the introduction of anti-pneumococcal serum into clinical practice, studies were conducted in the field of the creation and study of the efficacy of pneumococcal vaccines. Although attempts to create effective pneumococcus vaccines began in parallel with the introduction of serum, vaccination was not available until 1945 (Abaturov et al., 2016; Günay et al., 2018).

The German bacteriologist Fred Neufeld at the beginning of the 20th century for the first time divided the pneumococci into serotypes using type-specific antisera. This observation laid the foundation for subsequent studies aimed at fighting pneumococcal infection, including the discovery of the nature of the type-specific capsule antigens of pneumococcus (polysaccharides) and the creation of effective pneumococcal polysaccharide vaccines. Pneumococci are oval or lance-shaped cocci, arranged in pairs, gram-positive, with a size of about 1 micron. Each pair of bacteria is surrounded by a thick capsule, which performs a protective function. The capsule consists of polysaccharides and is the main virulence factor. It inhibits complement-dependent bacteriolytic activity of blood and phagocytic activity of leukocytes. Unencapsulated strains of pneumococcus are practically avirulent, they are rarely found. The pool of anti-pneumococcal antibodies consists mostly of antibodies to the antigens of the capsule (Mayanskiy et al., 2014).

The availability and efficacy of penicillin and other antibiotics have led to some decline in researchers' interest in vaccine development. This attitude to pneumococcal vaccines lasted until appeared the information about the development of antibiotic resistance of many clinically significant strains of pneumococci, which showed the need to continue research in the field of prevention of pneumococcal infection (Abaturov et al., 2016). The emergence and spread of resistant strains of pneumococci are associated with various factors, but one of the most important is the irrational use of antibiotics. The level of resistance of pneumococcus to penicillin is usually proportional to the level of antibiotic consumption (Mayanskiy et al., 2014; Mardani et al., 2014).

In addition to pneumonia, pneumococcus causes a number of diseases — from severe, life-threatening meningitis, sepsis, bacteraemia (invasive forms) to upper respiratory tract infections, otitis and sinusitis (non-invasive forms). Carriers of pneumococcus are a reservoir of infection and contribute to the spread of pneumococcal diseases in the community. The frequency of pneumococcal carrier state increases during the first year of life. In preschool institutions it is especially high (can reach 50 %).

Another fact makes pneumococcal infection one of the most currently important, it is the growth of resistance

of pneumococcal strains to penicillins, macrolides and other antibacterial agents (Tsarkova, Kuznetsova & Kupreeva, 2011).

According to modern ideas, most pneumococcal infections are endogenous in nature. This explains the rarity of epidemics of these diseases. If the normal processes of nasopharyngeal secretion clearance are disturbed, for example, as a result of chronic bronchitis or acute viral infection, pneumonia may develop when pneumococcus enters the lower respiratory tract. During an epidemic of pneumococcal pneumonia, the infection can have airborne transmission from person to person. The body's natural defense mechanisms usually filter out harmful foreign microorganisms before they reach the alveoli. Both physical clearance and alveolar macrophage activity are important for the removal of any aspirated bacteria. The disease occurs when local and/or systemic immune mechanisms are compromised, such as in case of respiratory viral infections or chronic bronchitis, pneumococcus reaches loci that are normally sterile (Dvoretskiy & Danilina, 2004).

A serious problem is the growing worldwide resistance of pneumococci to the main classes of antimicrobials, the emergence and spread of multi-resistant strains. Thus, the resistance of pneumococci to penicillin in some countries reaches 50 %, and sometimes 80 %. The incidence rate, severity of clinical manifestations of pneumococcal infection, high mortality, despite the ongoing antibiotic therapy, as well as an increase in the prevalence of pneumococcal strains resistant to antimicrobial agents, determine the need for continuous monitoring of pathogens and expansion of researches in the treatment and prevention of pneumococcal infection (Abaturov et al., 2016).

Along with Moraxella catarrhalis, Haemophilus influenzae, Neisseria meningitidis, Staphylococcus aureus and various hemolytic streptococci, pneumococci colonize the nasopharynx. Colonization is often asymptomatic, but in some cases a local or systemic infection may develop. Any pneumococcal infection is preceded by colonization of the nasopharynx by a homologous strain. In addition, the pneumococcal carrier state is an important source of horizontal pathogen transmission in the population. The gathering of people, for example in hospitals, children's institutions or barracks contributes to the transmission of pneumococci. Given the fact that in children's communities there is the highest frequency of carrier state and close communication, this age group is the main reservoir and vector of horizontal transmission of pneumococci (Mayanskiy et al., 2014). Streptococcus pneumoniae can cause acute, invasive bacterial infections, such as meningitis, bacteriemia and pneumonia, as well as less invasive diseases, such as sinusitis and otitis media (Souter, 2014).

Measures to prevent pneumonia, according to the WHO, are vaccination, exclusive breastfeeding and reduction of indoor air pollution. Scheduled vaccination has been introduced in many developed countries to prevent pneumococcal diseases. There are two types of vaccines –pneumococcal polysaccharide (PPV) and pneumococcal conjugate vaccines (PCV). PCV are used from the first years of life, PPV - from the age of two. The reduction of deaths of children under 5 years of age is one of the priorities for the health system of the Republic of Kazakhstan. In 2008, there were 33,774 cases of pneumonia in children under 5 years of age in Kazakhstan. The total number of deaths of children under 5 years in 2008 amounted to 8,225 children, of which about 1.5 thousand children died from pneumonia (Karibayeva et al., 2015).



In developed countries Streptococcus pneumoniae, being the most frequent causative agent of bacteriemia, community-acquired pneumonia, otitis media, also causes serious damage to public health. The wide spread of this infection is associated with an abundance of serotypes: 91 types of capsular antigens determining the serotype of pneumococcus have been described. About 20 of these serotypes are associated with more than 80 % of pneumococcal diseases worldwide. It is a polysaccharide capsule that protects pneumococcus from phagocytosis, being its main virulence factor. However, the protective effect of the capsule can be neutralized by antibodies to capsular antigens, mainly opsonizing ones (Tatotchenko & Namazova-Baranova, 2012).

Pneumococcal infection occupies a leading position among the diseases leading to fatal cases regardless of age, especially among children of the first year of life and in the age group above 55. According to the WHO new strategy, the vaccination against this infection should be included in national vaccination schedules covering above-mentioned categories of persons. Polysaccharide pneumococcal vaccine, being introduced for quite a long time, has shown its efficacy in children above two years and adults, but the clinical and immunological effect was marked by hyporesponsivity. With the introduction of pneumococcal conjugate vaccines, the prevention of this infection in young children became real, which made it possible to include these vaccines in the national vaccination schedules of 113 countries (Kostinov, Chuchalin & Korovkina, 2015).

It is clear that, since the preventive effect can only cover the infections caused by bacteria belonging to serotypes included in vaccines, the most important requirement for PCV is the ability to "cover" the maximum number of serotypes circulating in specific geographical regions. The first conjugate vaccine, which included 7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), was PCV7. The massive use of this vaccine in the United States in 2007 resulted in a 78 % decrease of invasive pneumococcal infections among children in the first 2 years of life and a 45 % decrease in the incidence among the population as a whole, with the incidence of invasive infections caused by serotypes covered by vaccine decreasing by 94 %. Against this background, however, there has been some increase in the incidence of infections caused by non-PCV7 serotypes. Data on the pneumococci serotypes are needed both for the

initial selection of the vaccine for inclusion in the vaccination schedule, and to assess the vaccination efficacy and timely adjustment of the serotype composition of vaccines (Lobzin et al., 2013).

In countries, where 7-valent vaccine was applied in mass vaccination, the switch to 13-valent vaccine was implemented by replacing the next dose. Children older than one year of age that were fully vaccinated with 7-valent vaccine were additionally vaccinated with 2 (1-2 years) or 1 (3-5 years) doses of 13-valent vaccine to expand the protective spectrum. Contraindications for vaccination is hypersensitivity to the components of the vaccine, including diphtheria toxoid, as well as severe acute diseases (in non-severe forms of pathology, such as ARVI, vaccination is not postponed) (Tatotchenko & Namazova-Baranova, 2012).



World history and long-standing practice of vaccination enable us to recognize the priority of preventive vaccination as the most effective, economical and accessible to the general population method of preventing common infectious diseases and improving the quality of life. This is confirmed by the eradication of smallpox, the course for elimination of poliomyelitis, measles, rubella, mumps, a sharp reduction (to sporadic cases) of diphtheria, HBV, as well as the impact of vaccination on the increase in life expectancy. To prevent pneumococcal infection with a 100-year history, two types of vaccines are used across the world: polysaccharide and conjugated polysaccharide ones. In children's practice conjugate vaccines are far more preferred. Meanwhile, the experience of foreign countries demonstrates the efficacy of scheduled vaccination of children, which significantly reduces the incidence of invasive forms of pneumococcal infection and pneumonia, not only in children but also in adults and the elderly (Sabitov et al., 2012). It is essential to monitor vaccination coverage regularly and identify reasons that contribute to delay or non-vaccination at local levels, in order to develop appropriate strategies to address the needs of susceptible populations (Pavlopoulou et al., 2013).

According to the WHO, more than 12 million children die each year under the age of five (2013), 2 million of these deaths are caused by diseases that can be prevented by means of vaccination. New generations of vaccines save millions of children's lives each year. The whole world experience shows that vaccination is the most effective method of infectious diseases control. If we compare the cost of treatment with the cost of vaccines, vaccines are more cost-effective. Vaccination in Kazakhstan is free for population. To date, there is no alternative to immunization (Terekhova et al., 2013).

Newborns receive antibodies from their mother to many types of pneumococcus. But as the levels of antibodies decrease, pneumococcal incidence significantly increases from the 2nd half of the first year of life. Up to 3 years, the level of antibodies to Streptococcus pneumoniae remains low, reaching the level of adults only at school age. After reducing the level of maternal antibodies, children aged 3 to 24 months are most susceptible to invasive infections caused by encapsulated bacteria, so immunization of this age group against pneumococcal infection is of high priority. Polysaccharide vaccines consist of whole capsular polysaccharides and are thymus-independent, that is, the proliferation of B cells and the production of antibodies does not involve the participation of T cells, which induces the production of low-avidity antibodies with insufficient bactericidal activity, while there is no formation of immune memory. Therefore, 23-valent pneumococcal polysaccharide vaccine is intended only for older children and adults with a high risk of pneumococcal infection. However, the solution was found: polysaccharides that did not show immunogenic properties in infants and young children, when binding (conjugation) with a protein carrier, turned into T-dependent antigens with long-term protection and immune memory (Tsarkova, Kuznetsova & Kupreeva, 2011). Full immunization coverage during infancy is essential to ensure prevention against childhood life-threatening infections. However, this is not sufficient alone and delivering vaccines within the deadline is also essential. Immunization status is more often evaluated by up-to-date vaccination coverage rather than timeliness of vaccination (Poorolajal et al., 2012). Treatment and rehabilitation of patients with pneumonia are costly both at economic and social level. It is proved that primary prevention of pneumonia and pneumococcal infection by vaccination is economically feasible. According to the WHO, vaccination is the only way enabling to significantly affect the incidence of pneumococcal infection. The increase in antibiotic resistance emphasizes the importance of vaccination (Kostinov, Chuchalin & Korovkina, 2015).

Pneumococcal vaccine provides protection against invasive pneumococcal infections (sepsis, bacteraemia, meningitis, pneumonia and acute otitis media), which are caused by 13 serotypes of Streptococcus pneumoniae in children aged 6 weeks to 5 years. The general permanent medical contraindications in Kazakhstan include: a strong reaction developed within 48 hours after the previous vaccine administration (fever up to 40 -C and above, long-term, unusual crying syndrome for 3 or more hours, febrile or afebrile convulsions, hypotonic-hyporeactive syndrome); complication of previous administration of this vaccine (anaphylactic shock developed within 24 hours after vaccination, immediate allergic reactions, encephalitis or encephalopathy developed within 7 days after administration of the vaccine), increased sensitivity to auxiliary substances and/or diphtheria toxoid (Terekhova et al., 2013). Because death from pneumococcal pneumonia, even in absence of invasive disease, is more frequent in patients with underlying chronic pulmonary conditions, appropriate and timely vaccination against pneumococcus is an essential component of preventative care in this population (Berical et al., 2016).

Diagnosis of pneumonia in children, despite a fairly clear list of clinical symptoms of the disease, can be serious problem in practice. According to the recommendations of experts of the WHO, the most important diagnostic

signs of pneumonia are cough, shortness of breath, as well as tachypnea; the respiratory rate should be assessed in accordance with the age of the child. Since cough and difficulty / rapid breathing can be observed in other diseases of the lower respiratory tract, the consequences of diagnostic errors with CAP can be excessive and inadequate appointment of X-ray and laboratory tests, unwarranted antibiotic therapy and child's hospitalization. However, in many cases it is not possible to clearly distinguish the indications for hospitalization, because the differentiation of the disease severity is not accurate enough, or because it is difficult to distinguish between viral and bacterial pneumonia. In addition, it is not always possible to assess the ability of parents to cooperate and to provide adequate treatment of the child at home. As a result, unwarranted hospitalization of children with CAP is not uncommon, because pediatricians prefer not to risk and ensure close supervision to the child (Namazova-Baranova et al., 2012).

Unfortunately, the monitoring of pneumococcal infections, in particular pneumonia, is complicated by insufficient sensitivity and specificity of diagnostic tests, especially since sputum analysis is not carried out in a routine manner, not to mention the blood tests. In the future, the problem of verification of pneumococcus is expected to be solved by determining the pneumococcal antigen or DNA in the blood or urine of the patient. The risk of drug resistance and its increase require new measures to control the potential increase in morbidity in general, complicated diseases, mortality, the cost of treatment of pneumococcal disease. A number of researchers believe that widespread monitoring is necessary for a detailed understanding of the problem and timely provision of clinicians with information about the level of local resistance to select the optimal empirical therapy. The microbiology laboratory needs to keep track of all pneumococcal isolates and to determine the minimum inhibitory concentration of resistant strains. The results of the research should be analyzed in reference laboratories. The ratio of the distribution of pneumococcus serotypes among carriers and patients is of considerable importance (Dvoretskiy & Danilina, 2004).

According to the WHO, the use of pneumococcal vaccine, started in 2000, significantly reduces the children's mortality from pneumonia caused by Streptococcus pneumoniae (Wahl et al., 2018). In addition, the use of a 10-valent pneumococcal polysaccharide vaccine conjugated with D-protein nontypeable Haemophilus influenzae also significantly reduces the incidence of pneumonia caused by Streptococcus pneumoniae in infants and young children (Kilpi, 2018). It was also found that the use of pneumococcal vaccine reduces the incidence of pneumonia caused by viruses (Fathima, 2018). Pneumonia is an important cause of influenza-associated morbidity and mortality. Influenza vaccination has been shown to reduce morbidity and mortality during influenza seasons. Protection from severe pneumonia may contribute to the beneficial effect of influenza vaccination. Prevention or attenuation of the predisposing viral illness through vaccination should reduce the risk for more severe secondary pneumonia (Tessmer et al., 2011).

Due to the unfavorable infectious situation, the governments of several countries in Europe, the USA and Australia have made amendments to mandatory vaccination programs, which made parents' refusal to vaccinate more problematic in legal terms (Attwell, 2018). However, there remains a significant percentage of parents who refuse to vaccinate their children for non-medical reasons, which may affect the health of the population as a whole (Damnjanović et al., 2018).

However, along with significant advances in the organization of preventive measures, currently a "delayed" vaccination also occurs, which has insufficiently substantiated contraindications to its implementation. A cohort study of primary health care practices in London during the 2016-2017 influenza season showed that in a number of cases there is an unreasonable negative attitude towards vaccination associated with excessive expectations of side effects, which adversely affects the intention to be vaccinated in the future (Smith, 2018). This fact, along with other reasons, has affected the level of morbidity of children with community-acquired pneumonia. Despite the achievements in pediatrics, the incidence of respiratory diseases shows no sign of decreasing (for 2016 – 1143.3 cases, for 2017 – 1468.3) (Statistikalyk zhynak, 2018). The study of the incidence of community-acquired pneumonia in Kazakhstan is currently of particular importance in connection with the introduction of vaccination against pneumococcal infection in 2010 to the national preventive vaccination schedule for all children aged 6 weeks to 5 years with 13-valent pneumococcal polysaccharide vaccine (Decree of the Government of the Republic of Kazakhstan no. 2295, 2009).

The aim of this study is to analyze the causes of delayed immunization with pneumococcal vaccine, as well as the impact of vaccination on the etiology and severity of pneumonia in young children.

## Materials and methods

The individual health records (f112/u) and vaccination records (f 063) of 309 children with delayed pneumonia pneumococcal vaccination were studied. The analysis of documents of informed consent or motivated refusals to vaccination from children legal representatives was conducted.

The children records were divided into two groups. The first group includes children (n=163) with vaccination refusals, the second group includes those with temporary medical contraindications (n=146). CI was calculated with specified 0.05 p-level.

Additionally, authors conducted retrospective study of health records of 71 children aged 0 days to 1.5 years that had incidences of pneumonia with verified causative agent. They were divided into 2 groups: the first included vaccinated children (n=36), the second – unvaccinated (n=35). Pneumonia incidents were divided by severity and types of causative agent. To compare the data of 2 groups, IBM SPSS Statistics 20 was used for the calculation of CI for the ratio with the specified p-level – 0.05.

1. Among other reasons of vaccination refusal, prevails the distrust of applied vaccines of the children's legal representatives (39.9%) and religious grounds (28.8%), as is shown in Table 1.

Among the diseases indicated as temporary contraindications to vaccination, ARVI occupied the leading position (Table 2). At the same time, during the analysis of clinical signs, in some cases, individual health records (f112) contained no clear data indicating a significant decrease in children's well-being. This was the case with other diseases, where there was also insufficient data (or grounds) for contraindications to vaccination.

Comparative analysis of the causes of delayed vaccination showed that the amount of vaccination refusals is more than cases of temporary contraindications (52.7% and 47.2% respectively).

As a result of the study, we obtained data on the ratio of severe pneumonia in vaccinated and unvaccinated children. Table 3 demonstrates that the proportion of severe pneumonia among unvaccinated children is nearly twice higher than in vaccinated children (42.9 % and 22.2 % respectively), p>0.05.

According to our data, non-severe pneumonia significantly prevails among vaccinated, whereas the ratio of both types of pneumonia is nearly equal among unvaccinated children, which almost doubles the proportion of severe forms.

Streptococcus pneumonia prevails among severe pneumonia causative agents in unvaccinated children – 46.7 % (CI 95 % 25.2; 71.9) of all cases. Streptococcus pneumonia was a pneumonia causative agent in 12.5 % of cases in vaccinated children (CI 95 % -10.4; 35.4), as is shown in Table 4.

Streptococcus pyogenes was a non-severe pneumonia causative agent in 20% of all cases in unvaccinated children (CI 95 % 2.5; 37.6), Staphylococcus aureus in 20% of all cases (CI 95% 2.5; 37.6).

Streptococcus pneumoniae was non-severe pneumonia causative agent in vaccinated children in 17.9 % (CI 95 % 3.7; 32.1), Streptococcus pyogenes in 17.9 % of cases as well (CI 95% 3.7;3 2.1) as is shown in Table 5.

**Table 1. Reasons for the preventive pneumococcal vaccination refusal.**

| no. | Reasons for refusals | Number of vaccination refusals, n=163 | Relative proportion (CI 95%), % |
|---|---|---|---|
| 1 | Distrust of vaccines | 65 | 39.9 (32.4-47.4) |
| 2 | Insufficient information for parents (parents questionnaire) | 29 | 17.8 (11.9-23.7) |
| 3 | Religious grounds | 47 | 28.8 (21.9-35.8) |
| 4 | Other reasons | 22 | 13.5 (8.3-18.7) |
| | Total | 163 | 100 |

**Table 2. Reasons for medical contraindications to vaccinations.**

| no. | Reasons for medical contraindications | Number of contraindications to vaccination (n=146) | Relative proportion (CI 95%), % |
|---|---|---|---|
| 1 | ARVI | 36 | 24.7 (17.7-31.7) |
| 2 | Moderate severity pneumonia | 12 | 8.2 (3.8-12.7) |
| 3 | Severe pneumonia | 16 | 10.9 (5.8-16.0) |
| 4 | Congenital heart defect | 8 | 5.5 (1.8-9.2) |
| 5 | Infantile cerebral palsy, spastic diplegia | 6 | 4.1 (0.9-7.3) |
| 6 | Neonatal encephalopathy, movement disorders | 38 | 26 (18.9-33.1) |
| 7 | Moderate anaemia | 9 | 6.2 (2.3-10.1) |
| 8 | Atopic dermatitis | 14 | 9.6 (4.8-14.4) |
| 9 | Thymomegaly | 7 | 4.8 (1.3-8.3) |
| | Total | 146 | 100 |

**Table 3. The ratio of severe to non-severe pneumonia in vaccinated and unvaccinated children.**

| Severity of pneumonia | Vaccinated children, n=36 | | Unvaccinated children, n=35 | |
|---|---|---|---|---|
| | Absolute number | Relative proportion (CI 95 %), % | Absolute number | Relative proportion (CI 95%), % |
| Non-severe | 28 | 77.8 (63.9-91.7) | 20 | 57.1 (40.7-73.5) |
| Severe | 8 | 22.2 (8.6-35.8)* | 15 | 42.9 (26.5-59.3) |

**Table 4. Patterns of causative agents of severe pneumonia in children.**

| Causative agent | Unvaccinated children, n=15 | | Vaccinated children, n=8 | |
|---|---|---|---|---|
| | Absolute number | Relative proportion (CI 95 %), % | Absolute number | Relative proportion (CI 95 %), % |
| *Streptococcus pneumoniae* | 7 | 46.7 (25.2-71.9) | 1 | 12.5 (-10.4-35.4) |
| *Haemophilus influenzae* | 2 | 13.3 (-3.9-30.6) | 1 | 12.5 (-10.4-35.4) |
| *Pseudomonas aerogenosa* | 2 | 13.3 (-3.9-30.6) | 0 | 0 |
| *Acinetobacter baumannii* | 0 | 0 | 1 | 12.5 (-10.4-35.4) |
| *Streptococcus pyogenes* | 1 | 6.7 (-6.0-19.4) | 0 | 0 |
| *Stenotrophomonas maltophilia* | 0 | 0 | 1 | 12.5 (-10.4-35.4) |
| *Klebsiella oxytoca* | 0 | 0 | 0 | 0 |
| *Enterobacter aerogens* | 0 | 0 | 0 | 0 |
| *Klebsiella pneumoniae* | 1 | 6.7 (-6.0-19.4) | 1 | 12.5 (-10.4-35.4) |
| *Staphylococcus aureus* | 1 | 6.7 (-6.0-19.4) | 1 | 12.5 (-10.4-35.4) |
| *Escherichia coli* | 0 | 0 | 0 | 0 |
| *Mycoplasma pneumoniae* | 1 | 6.7 (-6.0-19.4) | 2 | 25 (-5.0-55.0) |



**Table 5. Pattern of causative agents of non-severe pneumonia in children.**

| Causative agent | Unvaccinated children, n=20 | | Vaccinated children, n=28 | |
|---|---|---|---|---|
| | Absolute number | Relative proportion (CI 95 %), % | Absolute number | Relative proportion (CI 95 %), % |
| *Streptococcus pneumoniae* | 1 | 5.0 (-4.6-14.6) | 5 | 17.9 (3.7-32.1) |
| *Haemophilus influenzae* | 1 | 5.0 (-4.6-14.6) | 2 | 7.1 (-2.4-16.6) |
| *Pseudomonas aerogenosa* | 0 | | 0 | |
| *Acinetobacter baumannii* | 2 | 10.0 (-3.1-23.1) | 1 | 3.6 (-3.2-10.4) |
| *Streptococcus pyogenes* | 4 | 20.0 (2.5-37.6) | 5 | 17.9 (3.7-32.1) |
| *Stenotrophomonas maltophilia* | 1 | 5.0 (-4.6-14.6) | 2 | 7.1 (-2.4-16.6) |
| *Klebsiella oxytoca* | 1 | 5.0 (-4.6-14.6) | 1 | 3.6 (-3.2-10.4) |
| *Enterobacter aerogens* | 2 | 10.0 (-3.1-23.1) | 3 | 10.7 (-0.7-22.1) |
| *Klebsiella pneumoniae* | 0 | | 1 | 3.6 (-3.2-10.4) |
| *Staphylococcus aureus* | 4 | 20.0 (2.5-37.6) | 4 | 14.3 (1.3-27.3) |
| *Escherichia coli* | 3 | 15.0 (-0.6-30.6) | 2 | 7.1 (-2.4-16.6) |
| *Mycoplasma pneumoniae* | 1 | 5.0 (-4.6-14.6) | 2 | 7.1 (-2.4-16.6) |

## Discussion

Vaccination refusals in cases described amounted to 52.7%, while a temporary contraindication amounted to 47.2%. In our studies, the percentage of vaccination refusals was higher. Among the main reasons for vaccination refusals the prevailing one is a distrust of the vaccine that was 39.9%. In addition, a significant proportion in this choice is represented by: insufficient information for parents – 17.8%, religious grounds – 28.8%, other reasons – 13.5 %. The study conducted by Chephra McKee and co-authors (McKee, 2016) identified 4 main reasons for refusal of vaccination in the United States: religious grounds, distrust of vaccination, concerns about the safety of vaccination and lack of awareness on the part of health workers, which corresponds to the reasons for vaccination refusals in our study. Among the reasons for the temporary contraindications for vaccination, ARVI amounted to 24.6%, moderate severity pneumonia was 8.2%, severe pneumonia was 10.9%, congenital heart defect was 5.4%, Infantile cerebral palsy, spastic diplegia was 4.1%, neonatal encephalopathy, movement disorders was 26 %, moderate anemia was 6.16%, atopic dermatitis amounted to 9.6%, and thymomegaly was 4.8%. Comparative analysis of the causes of delayed vaccination showed that number of the vaccination refusals prevails over the temporary contraindications (52.7% and 47.2% respectively). For comparison, according to the retrospective study of 14,232 medical records in Israel, the parents' refusal caused a disruption in the vaccination schedule in 44.3% of cases (Aharon, 2018). It should be noted that among the temporary contraindications listed in the Decree of the Ministry of Health and Social Development of the Republic of Kazakhstan no. 636 (2008; Decree of the Minister of the Nation Economy of the Republic of Kazakhstan no. 190, 2015) there are: 1) acute communicable and non-communicable diseases, regardless of body temperature; 2) the use of steroids for various diseases, as well as other drugs with immunosuppressive properties; 3) acute central nervous system diseases (meningitis, encephalitis, meningoencephalitis) – vaccination is postponed for one year from the date of recovery; 4) acute glomerulonephritis – vaccination is postponed until 6 months after recovery; nephrotic syndrome – immunization is postponed until the end of treatment with corticosteroids; 5) exacerbation of chronic diseases. Thus, in most cases, temporary contraindications in cases studied were not justified.

## Conclusions

Severe pneumonia in unvaccinated children was 42.9% (CI 95%, 26.5-59.3) of the total number of cases. In vaccinated children, the proportion of severe pneumonia was 22.2% (CI 95%, 8.6-35.8) of the total number of cases. Thus, cases of severe pneumonia in unvaccinated children are 20.7% more than in vaccinated children, p>0.05. Non-severe pneumonia in unvaccinated children was 57.1% (CI 95%, 40.7-73.5) of the total number of cases. In vaccinated children, the percentage of non-severe pneumonia was 77.8 % (CI 95%, 64.2-91.4) of the total number of cases. Streptococcus pneumoniae was the predominant causative agent of severe pneumonia in unvaccinated children – 46.7% (CI 95%, 25.2-71.9). Among the unvaccinated children, there were 2 cases of pneumonia caused by Pseudomonas aerogenosa (13.3%; CI 95%, 3.9-30.6), both cases were severe pneumonia, among the vaccinated cases, Pseudomonal infection was not identified. It should be noted that the applied comparison of CI 95% did not show statistically significant differences in the two groups, which indicates the need for further study of this issue focusing on the increasing the sample size. However, given the practical experience and literature data, it is necessary to continue to study the cause of delayed immunization with pneumococcal vaccine in young children, which will increase vaccination coverage, reduce the incidence of community-acquired pneumonia and improve the cost-effectiveness of preventive measures.



## References


1. Abaturov, A. E., Bolbot, Yu. K., Alifanova, S. V., Bordiy, T. A., Agafonova, E. A., & Nikulina, A. A. (2016). Pneumococcal infection in children. Khmelnitskiy: FLP Storozhuk.
2. Aharon, A. A. (2018). Social-economic-demographic differences in reasons not to comply in time with routine childhood vaccinations. Harefuah, 157(1), 16-20.
3. Attwell, K. (2018). Recent vaccine mandates in the United States, Europe and Australia: A comparative study. Vaccine, 410X(18), 31371-31379.
4. Begaidarova, R. Kh., Alshynbekova, G. K., Asenova, L. Kh., Diusembayeva, N. I. & Talipbakova, Kh. D. (2018). Epidemiological situation of ARVI and pneumonia in Karaganda region for 2012-2016. Meditsina i Ekologiya, 4, 20.
5. Berical, A. C., Harris, D., Dela Cruz C. S., & Possick, J. D. (2016). Pneumococcal Vaccination Strategies. An Update and Perspective. Ann Am Thorac Soc, 13(6), 933-44. DOI: 10.1513/AnnalsATS.201511-778FR.
6. Damnjanović, K., Graeber, J., Ilić, S., Lam, W. Y., Lep, Ž., Morales, S., Pulkkinen T., & Vingerhoets, L. (2018). Parental Decision-Making on Childhood Vaccination. Front Psychol, 9, 735.
7. Decree of the Government of the Republic of Kazakhstan no. 2295 from December 30, 2009 "National preventive vaccination schedule."
8. Decree of the Minister of Health of the Republic of Kazakhstan no. 636 from December 4, 2008 "On medical contraindications to immunization, reporting and investigation of post-vaccination complications."
9. Decree of the Minister of the Nation Economy of the Republic of Kazakhstan no. 190 from March 6, 2015 "On approval of Health Regulation 'Sanitary and Epidemiological Requirements for Public Preventive Vaccination'"
10. Dogan, S., Yildirim, A., Erbakirci, R., Okur, A., Cagli, S., Mavili, E. ... Ozturk, M. (2016). The Role of Ultrasonography for Differentiating and Management of Malignant Cervical Lymph Nodes. European Journal of General Medicine, 13(1), 7-15. https://doi.org/10.15197/ejgm.01416
11. Dvoretskiy, L. I. & Danilina, V. A. (2004). Clinical significance of resistant pneumococcus. Infektsii i Antimikrobnaya Terapiya, 6(4), 126-133.
12. Fathima P. (2018). The impact of pneumococcal vaccination on bacterial and viral pneumonia in western Australian children: record linkage cohort study of 469589 births, 1996-2012. Clin Infect Dis, 66, 1075–1085.
13. Günay T, Yardımcı OD, Polat M, Sandal K, Şeneldir H. Evaluation of Malignancy Risk in Patients Who Underwent Hysteroscopy for Preliminary Diagnosis of Endometrial Polyp. J Clin Exp Invest. 2018;9(2):95-9. https://doi.org/10.5799/jcei.433819
14. Karibayeva I. K., Aimbetova G., Amireev S., Yeraliyeva L., Kyzayeva A., Akanov A. A., Tulebayev K. A., Turdaliyeva B. C., Grjibovski A. M. (2015). Assessment of the pneumococcal vaccination programme in Mangistau Region, Kazakhstan. Ekologiya cheloveka, 3, 32-39.
15. Kilpi, T. M. (2018). Effectiveness of pneumococcal Haemophilus influenzae protein D conjugate vaccine against pneumonia in children: A cluster-randomised trial. Vaccine, 36(39), 5891-5901.
16. Kostinov, M. P., Chuchalin, A. G., & Korovkina, E. S. (2015). The innovative vaccine against pneumococcus infection as prevention of exacerbations of chronic diseases in adults. Zdravookhranenie Rosiyskoy Federatsii, 59(5), 49-53.
17. Lobzin Yu. V., Sidorenko S. V., Kharit S. M., Belanov S. S., Volkova M. O., Gostev V. V. et al. (2013). Serotypes of Streptococcus pneumoniae, a leading cause nosological forms of pneumococcal infections. Zhurnal Infektologii, 5 (4), 35-41.
18. Mardani, M., Lavasani, S. M., & Omidvari, M. (2014). An investigation into DOW and MOND indices with fuzzy logic based on fire and explosion risk assessment in Iran oil refinery, UCT Journal of Research in Science, Engineering and Technology, 2(3): 126-137.
19. Mayanskiy, N. A., Alyabieva N. M., Lazareva A. V., Katosova L. K. (2014). Serotype diversity and antimicrobial resistance of Streptococcus pneumonia. Vestnik RAMN, 69(7-8), 38-45.
20. McKee, C. (2016). Exploring the Reasons Behind Parental Refusal of Vaccines. J Pediatr Pharmacol Ther, 21(2), 104–109.
21. Namazova-Baranova L. S., Kulitchenko T. V., Malakhova A. E., Starovoytova E. V., Bakradze M. D., Tchashchina I. L., Mityushin I. L. (2012). Pneumococcal infection in children: everyday practice. Voprosy Sovremennoy Pediatrii, 11(4).
22. Pavlopoulou, I. D., Michail, K. A., Samoli, E., Tsiftis, G., Tsoumakas, K. (2013). Immunization coverage and predictive factors for complete and age-appropriate vaccination among preschoolers in Athens, Greece: A cross - Sectional study. BMC Public Health, 13, 908.
23. Poorolajal, J., Khazaei, S., Kousehlou, Z., Bathaei, S., & Zahiri, A. (2012). Delayed Vaccination and Related Predictors among Infants. Iran J Public Health, 41(10), 65-71.

24. Sabitov, A. U., Kharitonov, A. N., Budalina, S. V., & Rozhkova, L. V. (2012). From the pneumococcal infection vaccination of the risk-group children to the universal vaccination. Zhurnal Infektologii, 4(4S), 35-36. Received from: https://doi.org/10.22625/2072-6732-2012-4-4S-35-36

25. Smith L. E., Weinman J., Amlôt R., Yiend J., & Rubin G. J. (2018). Parental expectation of side effects following vaccination is self-fulfilling: a prospective cohort study. Ann Behav Med, 1-16.

26. Souter, J. (2014). An update on pneumococcal vaccination in children and adults. S Afr Pharma J, 81(2), 15–8.

27. Statistikalyk zhynak (2018). Public health and activity of health care organizations in Kazakhstan in 2017. Astana

28. Tatotchenko, V. K., Namazova-Baranova L. S. (2012). 13-valent pneumococcal conjugate vaccine. Voprosy Sovremennoy Pediatrii, 11(2).

29. Terekhova, T. I., Mukametzhanova, K. A., Alimbekova, A. L., Burbayeva, A. P., Makarova, O. A., Tsypkunova, E. V., Burgucheva, I. Yu., Gurianova, G. M. & Goosen, E. A. (2013). Topikal issues of childhood pneumococcal infection prevention. Nauka i Zdravookhranenie, 1, 39-42.

30. Tessmer, A., Welte, T., Schmidt-Ott, R., Eberle, S., Barten, G., Suttorp, N., Schaberg, T. (2011). Influenza vaccination is associated with reduced severity of community-acquired pneumonia. European Respiratory Journal, 38, 147-153. DOI: 10.1183/09031936.00133510

31. Tsarkova S. A., Kuznetsova P. V., Kupreeva N. G. (2011). Pneumonia in children: old challenges and new opportunities. Pediatricheskaya farmakologiya, 8(1), 12-16.

32. United Nations Children's Fund, World Health Organization, World Bank and United Nations (2018). Levels & Trends in Child Mortality. Report 2017. Estimates developed by the UN Inter-agency Group for Child Mortality Estimation. New York (NY): United Nations Children's Fund.

33. Wahl, B., O'Brien K. L., Greenbaum A., et al. (2018). 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. The Lancet Glob Health, 6(7), PE744–E757.