NJSC "Medical University of Karaganda"

**ANNOTATION**

Dissertation work for the PhD degree

specialty 6D110100 "Medicine"

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**Clinical, immunological and microbiological**

**characteristics of community-acquired pneumonia in children vaccinated with pneumococcal vaccine**

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**Relevance of the study**

Respiratory diseases occupy one of the leading places in the structure of child morbidity. Respiratory diseases occupy the third place in the structure of causes of infant mortality, following perinatal pathology and congenital malformations. The total number of deaths of children under the age of 5 years per 1000 births is 12.16 cases. The mortality rate of children under the age of 1 year per 10,000 live births in 2015 was 93.7, of which 6.5 (6.9%) – from respiratory diseases, including 5.6 (5.9%) - from pneumonia [1,2]. Pneumonia accounted for 13% of the causes of infant mortality under the age of 5 in 2016 - 10.79 cases per 1,000 births [1,2]. Currently, at the initiative of WHO, programs have been implemented in the country to improve the diagnosis and treatment of childhood diseases, including pneumonia, the most common causative agent of which in children is Streptococcus pneumonia [3,4]. Streptococcus pneumoniae is the main cause of morbidity and mortality from respiratory infection worldwide, which contributed to an increase in mortality in 2016- 1,189,937 cases to a greater extent than all other etiologies combined [5]. In this regard, in order to create a specific immunity, the prevention of pneumococcal infection is vaccination [6, 7]. In May 2020, the IOM, once again, published a warning about the importance of immunization coverage [8], considering vaccination to be the only way to significantly affect the incidence of pneumococcal infection. At the same time, since 2010, it has been recommended to include routine vaccinations against pneumococcus in the national calendars of all countries. As a result of a cohort study in western Australia in the period from 1996 to 2012, which included 469,589 children, it was found that the use of pneumococcal vaccine reduces the incidence of pneumonia caused by viruses [9]. Of the CIS countries, Kazakhstan is the first country to introduce vaccination against pneumococcal infection in the National Calendar of Preventive Vaccinations for all children aged 2 months to 5 years [10, 11]. And already during this time of immunization, the epidemiological situation in the regions has improved significantly. So, in 2015, the incidence fell from 63.7 per 1,000 children of the first year of life to 33.3, and mortality decreased from 24.8 to 16.41 cases per 10,000 live births [1, b.235]. At the same time, there is currently a problem of a disrupted vaccination schedule associated with various factors, including insufficiently substantiated medical contraindications to its implementation. This circumstance, along with other reasons, could not but affect the incidence of pneumonia in children. In connection with the above, this problem requires its study, especially in the conditions of the emerging negativism of the population to vaccinate children, in order to compile a causal relationship between the incidence of children from controlled infections. Due to the unfavorable infectious situation, the governments of a number of countries in Europe, the USA and Australia have made changes to the mandatory vaccination programs, which made the refusal of parents from vaccination more difficult legally [12]. However, in other states, there remains a significant proportion of parents who refuse to vaccinate children for non-medical reasons, which may affect the health level of the population as a whole [13]. In these conditions, it is important to take into account the modern development of clinical pulmonology, its progressive movement for a deeper understanding of the essence of diseases based on knowledge of morphology, physiology, immunology. Fundamental sciences, providing full knowledge of the structure and function of the lungs, create real prerequisites for understanding the exhaustive pathogenesis of diseases of the respiratory system.

 In this regard, it is important to study the regulatory role of cytokines in the immune response in pneumonia in children against the background of vaccination with pneumococcal vaccine. The main properties of cytokines and the functioning of the cytokine network are presented in recent publications [14-16]. There are studies in which the cellular mechanisms of nonspecific protection in the respiratory department of the lungs have been studied [17]. At the same time, it was found that with massive bacterial aggression, leukocytes, labrocytes, eosinophils and macrophages release chemokines such as IL-8, TNF-α, IL-10, MCP-1, components of the complement system.The content of IL-1, IL-4, IL-6, IL-8, IL-10 has been sufficiently studied in community-acquired pneumonia. At the same time, the works highlighting the importance of the study of such proinflammatory cytokines as MCP-1 (monocytic chemoattractant protein-1) in community-acquired pneumonia in children have not been studied, and the information available in the literature is insufficient. Currently, publications are mainly devoted to the problems of diabetes, systemic connective tissue diseases, glomerulonephritis [18-23].

 Taking into account the high incidence rates of community-acquired pneumonia in children, as well as in the structure of mortality of young children, the difficulties of predicting its complications in the early stages of the disease determine the need for further improvement of the diagnosis of this disease. In this regard, the study of the relationship between the content of MSP-1 and will give the most in-depth understanding of the state of the local inflammatory response in the lungs in children with community-acquired pneumonia, with an assessment of the criteria for the severity of the disease.

 Thus, the study of the features of the clinical course of community-acquired pneumonia, depending on the vaccination with pneumococcal vaccine, seems relevant, especially taking into account the indicators of the immunological status and the microbiological picture of the disease. It is promising to study the features of community-acquired pneumonia in children vaccinated with pneumococcal vaccine to determine the criteria for the severity of the disease.

**Аim:** To study the effect of pneumococcal vaccination on the clinical course of community-acquired pneumonia in vaccinated children from 2 months to 3 years on the basis of clinical, microbiological and immunological factors.

 **Research objectives:**

1. To identify the causes of impaired immunization with pneumococcal vaccine in children from 2 months to 3 years.

2. To determine the structure of pathogens of community-acquired pneumonia in children from 2 months to 3 years on the background of timely and disrupted vaccination schedule with pneumococcal vaccine.

3. To identify the features of the clinical course of community-acquired pneumonia in children against the background of timely and disrupted vaccination schedule with pneumococcal vaccine.

4. To identify the relationship between the level of proinflammatory cytokines MSR-1 and the severity of community-acquired pneumonia in children vaccinated with pneumococcal vaccine from 2 months to 3 years.

5. To develop a mathematical model for predicting the severity of community-acquired pneumonia in children from 2 months to 3 years with a disrupted vaccination calendar.

 **Scientific novelty**

This work is a prospective modern scientific study, new data have been obtained on the structure of pathogens of community-acquired pneumonia in hospitalized children vaccinated with pneumococcal vaccine from 2 months to 3 years in the Karaganda region, depending on the severity of the disease.

A comprehensive assessment of the health status of children vaccinated with pneumococcal vaccine with community-acquired pneumonia based on WHO clinical recommendations and the impact of impaired immunization on morbidity, clinical course features were studied.

Depending on the features of the course of community-acquired pneumonia, in children vaccinated with pneumococcal vaccine, the relationship between the level of proinflammatory cytokines MSP-1 and the severity of the course of community-acquired pneumonia was established for the first time.

A model for predicting the severity of community-acquired pneumonia in children from 2 months to 3 years with a disrupted vaccination calendar has been developed.

**Materials and methods of research**

The study was conducted on the basis of the departments of young children with respiratory pathology of the Regional Children's Clinical Hospital of Karaganda, the Children's Hospital of Karaganda, Temirtau, using general clinical, instrumental, immunological, microbiological and statistical research methods, there is informed consent of parents for the research.

To analyze the reasons for refusals of vaccination, individual child development cards (f112/y), vaccination cards (f 063), a journal of preventive vaccinations (form 064/y), an outpatient patient's medical card (form No. 025/y), a sheet of voluntary informed consent or refusal to carry out preventive vaccinations were studied.

In accordance with the tasks set, we examined 162 sick children with an established diagnosis of community-acquired pneumonia. Of these, 82 (50.6%) vaccinated children and 80 (49.3%) children with impaired immunization aged 2 months to 3 years and the control group vaccinated healthy children (n=20). Distribution of children by age, as well as by the severity of the course of community-acquired pneumonia.

The content of cytokines MSR-1 was determined in a portion of morning urine by enzyme immunoassay. Statistical processing of the obtained data was carried out using the "STATISTICA 7" application software packages.

**The main provisions submitted for protection:**

1. Violations of immunization with pneumococcal vaccine in children from 2 months to 3 years old are accompanied by a predominance of refusals of parents / legal representatives from vaccination related to distrust of vaccination, insufficient information of parents and the imposition of contraindications to vaccination.

2. The microbiological structure in severe forms of community-acquired pneumonia in children with impaired immunization with pneumococcal vaccine is characterized by the predominance of Streptococcus Pneumoniae, in children vaccinated with pneumococcal vaccine - mixed infection: such as Streptococcus pneumoniae + Staphylococcus aureus, Haemophilus influenza + Streptococcus pneumoniae, Klebsiella pneumoniae + Streptococcus pneumoniae.

3. The clinical picture of community-acquired pneumonia in children from 2 months to 3 years is characterized by a more severe course against the background of a disrupted vaccination schedule with pneumococcal vaccine.

4. The study of the immune response in community-acquired pneumonia in children from 2 months to 3 years old against the background of vaccination with pneumococcal vaccine according to the indicators of the proinflammatory cytokine MSP -1 is characterized by its activation depending on the severity and is manifested by a pronounced imbalance in the level of cytokines in children with severe.

5. The use of a mathematical model of community-acquired pneumonia in vaccinated children based on the analysis of the results of clinical, immunological and microbiological studies makes it possible to assess the severity of community-acquired pneumonia against the background of vaccination with pneumococcal vaccine in the early stages of the disease.

**Practical significance of the work**

Based on the available results of clinical, immunological and microbiological studies, severity criteria were determined in children vaccinated with pneumococcal vaccine from 2 months to 3 years with community-acquired pneumonia.

The results of the study of proinflammatory cytokines in community-acquired pneumonia in children vaccinated with pneumococcal vaccine will significantly improve the accuracy of diagnosis and predict the severity of the disease.

The developed mathematical model of community-acquired pneumonia in children vaccinated with pneumococcal vaccine allows assessing the severity of the disease at the early stages of diagnosis.

The results obtained are included in the training programs of students, interns, residents, doctors of various specialties, which will increase vaccination coverage, reduce the incidence of community-acquired pneumonia and increase the economic efficiency of preventive measures.

**Implementation into practice**

The act of implementing the results of the research "Mathematical modeling of the severity of community-acquired pneumonia" dated 10.03.2020 (Appendix A).

Certificate No. 24680 dated 03/31/2022 on the topic "The role of cytokine MSR-1 in the development of community-acquired pneumonia in children vaccinated with pneumococcal vaccine" was obtained from the state registration of copyright rights (Appendix B).

**Approbation of the work**

The main provisions of the study were published and reported: at the scientific and practical conferences of residents, undergraduates and doctoral students "Young researcher: challenges and prospects for the development of modern pediatrics and pediatric surgery", (Almaty, Kazakhstan, 2019); at the 10th International Conference "Science and Technology" held by SCIEURO in London (2018); at the VII and IX Annual International Scientific and Practical Conference "Topical Issues of Medicine" "Satellite Forum on Healthcare and Health Policy" (Baku, Azerbaijan 2018, 2020); at the meeting of the Department of Pediatrics and Neonatology of NJSC MUK (2020).

**Publications**

Based on the materials of the dissertation, 9 scientific papers were published, including: 3 in scientific publications recommended by the Committee for Control in the Field of Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan; 2 publications in the international scientific publication included in the Scopus information base –"Revista Latinoamericana de Hipertensión", "Open Access Macedonian Journal of Medical Sciences"; 1 publications in materials of international conferences; 3 publications in materials of foreign conferences.

**Сonclusions**

1.The reasons for the violation of immunization of children from 2 months to 3 years with pneumococcal vaccine are medical contraindications from vaccination: PPEP, motor disorders syndrome 26%, ARVI - 24.6%, severe pneumonia - 10.9%, atopic dermatitis, infant form - 9.6%, moderate pneumonia- 8.2%, anemia of moderate severity - 6.16%, CHD- 5.4%, cerebral palsy, spastic diplegia - 4.1%, thymomegaly - 4.8%. The main reasons for refusal of vaccination are distrust of vaccines - 39.9%, religious reasons - 28.8%, insufficient information of parents - 17.8%.

2. In the structure of pathogens of community-acquired pneumonia randomly vaccinated with pneumococcal vaccine in children from 2 months to 3 years, a mix of infection prevails - 21.9%. The microbiological landscape is represented by a combination of pathogens Streptococcus pneumoniae + Staphylococcus aureus - 19.04%, Haemophilus influenza + Streptococcus pneumoniae -14.29%, Klebsiella pneumoniae + Streptococcus pneumoniae - 9.52%. Streptococcus pneumoniae dominates in the group of children with a disrupted vaccination schedule - 25%. The structure of gram-negative bacteria was dominated by Enterobacter aerogenes (8.6% of observations), Acinetobacter baumannii (6.2%).

3. The features of the clinical course of the disease in children from 2 months to 3 years had differences in the groups of timely and impaired vaccination and were most pronounced in the group of children from 2 months to 1 year. Thus, in the group of children with severe pneumonia, dyspnea occurred in 61.9% (95% CI 33.8;90), while in the group with impaired vaccination - 90% (95% CI 75.2; 100) (p<0.031). Febrile hyperthermia in severe pneumonia was observed in 66.67% (95% CI 40.39;92.95) of vaccinated children from 2 months to 1 year, and in children with impaired immunization in 90% (95% CI 75.2;100) of cases. Retraction of the lower chest was detected in 57.14% (95% CI 27.34; 86.94) of vaccinated children from 2 months to 1 year, in the group of children with impaired immunization, it occurred in 90% (95% CI 75.2; 100) (p<0.014).

4. Significant differences in the level of proinflammatory cytokines MSR-1 were revealed depending on the severity of the disease: in vaccinated children from 1 to 3 years of age with severe community-acquired pneumonia, it was 5.76 [4.03;9.07] pg/ml Me [Lq; Uq], which is 4 times higher than these indicators in the group of children with mild pneumonia– 1.30 [0.01;2.05] pg/ml Me [Lq; Uq. The highest rates were found in children from 2 months to 1 year with impaired immunization, where this indicator in children with severe community-acquired pneumonia is 11.73 [6.57;30.08] pg/ml Me [Lq; Uq] was 5 times higher than in non-severe -2.34 [0.02;3.63] pg/ml Me [Lq; Uq].

5. The developed mathematical model revealed the most significant indicators of predicting the severity of community-acquired pneumonia in children from 2 months to 3 years old against the background of vaccination with pneumococcal vaccine: cough - (68.75%) (p>0.000), shortness of breath - (71.25%) (p>0.003), the presence of crepitation - (72.5%) (p>0.002), pulse oximetry - (63.75%) (p>0.013), MCP – 1 - (88.9%) (p>0.004), ESR - (74.5%) (p>0.021), CRP - (88.75%) (p>0.003), leukocytes - (73.75%) (p>0.002). The used logistic model for assessing the severity of the disease has a high prognostic ability (89.1%) and is statistically significant (p<0.00001).