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# FEATURES OF HAEMOPHILUS INFLUENZAE TYPE *b* VACCINE IN PATIENTS WAITLISTED FOR LUNG TRANSPLANTATION

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**Objective:** to evaluate the immunological efficacy of *Haemophilus influenzae* type b (*Hib*) vaccine in patients with severe bronchopulmonary condition waitlisted for lung transplantation. **Materials and methods.** 16 patients (age 22–61 years) with severe bronchopulmonary diseases were vaccinated once against *Hib* infection. IgG antibody concentrations to *Hib* capsular polysaccharide before vaccination and 1 month after was measured by ELISA using a test system developed at Mechnikov Research Institute of Vaccines and Sera. Statistical data processing was carried out using stats (v.3.6.2), lme4 (v.1.1 – 21), and lmerTest (v.3.1 – 1) packages. **Results.** *Hib* vaccine in patients with severe bronchopulmonary condition did not elicit any local or systemic reactions. The proportion of patients whose antibody (Ab) concentrations to *Hib* capsular polysaccharide exceeded the long-term protection threshold was 69% and 100% before and after vaccination, respectively (p = 0.02). There were differences in the formation of post-vaccination immunity depending on the nosological forms of patients' diseases. In the group of patients with obstructive pulmonary diseases, the geometric mean level of antibodies to the *Hib* capsular polysaccharide after vaccination increased as compared to the baseline value – from 1.3 [0.6–2.8] to 5.5 [1.9–15.4] AU/mL, (p = 0.05). In the group of patients with restrictive lung diseases, the level did not change – 2.8 [0.6–14.1] AU/mL before vaccination and 3.4 [1.3–8.5] AU/mL 1 month after vaccination. In the group of patients taking glucocorticosteroids, there was no increase in the level of antibodies to *Hib* capsular polysaccharide (2.7 [0.8–9.3] AU/mL before and 2.8 [1.2–6.5] AU/mL after vaccination). In the group of patients who did not take hormones, antibody concentrations to *Hib* capsular polysaccharide increased from 1.2 [0.7–2.1] AU/mL to 4.8 [2.2–10.1] AU/mL (p = 0.006). **Conclusion.** *Hib* vaccination of waitlisted patients with severe bronchopulmonary disease is safe and immunologically effective.

*Keywords: Haemophilus influenzae type b, IgG, vaccine prophylaxis, adults, bronchopulmonary diseases.*

*Haemophilus influenzae* type b (Hib) vaccination is a good example of the efficacy of this method in preventing infectious diseases. The introduction of vaccination using first a polysaccharide and later a conjugate vaccine significantly reduced the incidence of Hib infection, especially in children younger than 5 years old. It was in this age group that severe invasive forms of the disease, such as meningitis and pneumonia, were most often noted, which in many cases ended in death or disability [1–3]. WHO is currently recommending the inclusion of Hib vaccination in routine prevention programs for children. In 2018, vaccination against this infection was included in national vaccination calendars across 191 countries around the world [4, 5].

Healthy adults usually do not receive Hib vaccine, since most of them are carriers of the bacteria, or the disease proceeds as acute respiratory infections, mainly in mild and clinically not pronounced forms. The risk group for invasive Hib infection primarily includes patients with functional and anatomic asplenia. However, according to a study by D.C. Cassimos et al., out of 42 European countries, only 5 have included Hib vaccination for adults at risk in their national vaccination policies; the vaccination is recommended in 3 countries and is compulsory in 2 countries [6]. This being said, the risk groups for severe Hib infection in some countries include patients with HIV infection, patients with malignant tumors, and solid organ recipients [7].

The aim of the study was to evaluate the immunological efficacy of Hib vaccination in patients with severe bronchopulmonary condition waitlisted for lung transplantation.

## MATERIALS AND METHODS

The study included 16 patients with severe bronchopulmonary diseases aged 22 to 61 years (median 42 [41–47] years). Among those examined were 81.3% (13/16) women and 18.8% (3/16) men. There were 44%

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(7/16) of patients with chronic obstructive pulmonary diseases (COPD, lymphangioleiomyomatosis, emphysema), 31% (5/16) with restrictive lung disease (idiopathic pulmonary fibrosis, fibrosis resulting from exogenous allergic alveolitis, nonspecific interstitial pneumonia), 3 patients had pulmonary vascular diseases (pulmonary hypertension of various origins) and one with cystic fibrosis. Patients with obstructive diseases received therapy with bronchodilators, mucolytics, while the patient with cystic fibrosis also received antibiotic therapy. Patients with idiopathic pulmonary fibrosis were treated with fibrostatics. In other types of interstitial lung diseases (fibrosis resulting from exogenous allergic alveolitis, nonspecific interstitial pneumonia), the patients received small doses of systemic glucocorticoids. Patients with pulmonary hypertension were on PAH-specific therapy with endothelin receptor antagonists, guanylate cyclase stimulants, and prostacyclin drugs. At the time of vaccination, 38% (6/16) of patients were taking glucocorticoids. The patients had not previously been vaccinated against Hib.

Hib vaccination was carried out in the absence of an exacerbation of the underlying disease and signs of respiratory infection. A single 0.5 mL intravenous Hiberix vaccine (manufactured by GlaxoSmithKline) was administered. Before vaccination and 1 month after, there was blood sampling, followed by measurement of the IgG antibody (Ab) concentrations against the Hib capsular polysaccharide.

The serum Ab concentrations (IU/mL) in the examined were determined by enzyme-linked immunosorbent assay (ELISA) using a test system developed at the Mechnikov Research Institute of Vaccines and Sera, Moscow [8]. A ≥0.15 IU/mL concentration was conventionally regarded as the antibody concentration providing short-term protection, while ≥1 IU/mL was considered the threshold for long-term protection.

## STATISTICAL ANALYSIS

Descriptive statistics of quantitative features were represented by the geometric mean and 95% confidence interval (95% CI) for Ab, and for median and interquartile range for the age of the subjects. Qualitative traits were represented by the proportion with 95% CI, calculated by the Clopper-Pearson method, and the absolute number of subjects with the trait under study in the total group population (n/N). Initial quantitative data were pre-logarithmized and checked for compliance with normal distribution (Shapiro-Wilk test was used). The check showed that all the logarithmic features corresponded to normal distribution. All calculations were performed on the transformed data, with reverse transformation of results obtained.

Two related samples (before/after vaccination) were compared based on quantitative criteria by the Student's t-test for related samples, and based on qualitative criteria by McNemar's test. Two independent samples were compared under qualitative criteria by Fisher's exact test. A mixed-effects model was used to analyze the change in Ab levels depending on the period and study group. The prerequisites for use were tested by the Levene's test (homoscedasticity of residuals) and the Shapiro-Wilk test (normal distribution of standardized residuals). Post-hoc tests were performed using Tukey Test. The relationship between the two quantitative traits was calculated using Spearman's correlation. All calculations were performed in free statistical environment R (v.3.6, GNU GPL2 license). Packages stats (v.3.6.2), lme4 (v.1.1 – 21), and lmerTest (v.3.1 – 1) were used.

## RESULTS

Administration of the Hib vaccine in patients with severe bronchopulmonary disease was not accompanied by local and systemic reactions, although in childhood immunization, it can rarely lead to such phenomena.

In all patients enrolled in the study, antibody concentrations against the Hib capsular polysaccharide before vaccination exceeded 0.15 IU/mL. The proportion of subjects with Ab concentrations exceeding the long-term protection threshold before and after vaccination was 69 [41–89]% (11/16) and 100 [79–100]% (16/16) respectively, the differences tending to be statistically significant (p = 0.06 – McNemar's exact test).

The geometric mean of Ab concentrations against the Hib capsular polysaccharide before and after vaccination was 1.7 [1.0–2.8] IU/mL and 3.9 [2.3–6.6] IU/mL respectively. So, the indicator increased 2.3 [1.2–4.6] times, and this increase was statistically significant (p = 0.02) (Fig. 1).

Among the patients enrolled in the study, 7 had obstructive pulmonary disease, 5 had restrictive lung disease, 3 had vascular pulmonary disease and one had cystic fibrosis. Among patients with vascular pulmonary disease, 2 out of 3 people had a protective threshold for Ab concen-

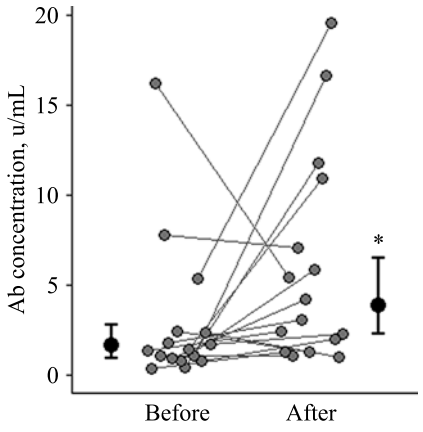


Fig. 1. Geometric mean of antibody concentrations against the Hib capsular polysaccharide before and after vaccination. Individual values, geometric mean and 95% CI are shown

trations against the Hib capsular polysaccharide, which is necessary for long-term protection against infection. Before vaccination, 2 out of 3 people had protective Ab concentrations while after vaccination, all 3 patients had protective Ab levels. In a patient with cystic fibrosis, the baseline antibody concentrations against the Hib capsular polysaccharide exceeded the threshold required for long-term protection against infection. The proportion of subjects with Ab concentrations against the Hib capsular polysaccharide required for long-term protection against infection among patients with obstructive and restrictive lung diseases before and after vaccination is shown in the table (Table 1).

The study revealed an increase in the proportion of patients with Ab concentrations against the Hib capsular polysaccharide in both groups at the necessary long-term protection levels. This increase was not statistically significant, probably due to the small sample size.

A linear mixed effect model was used to analyze the change in the Ab concentrations against the Hib capsular polysaccharide depending on the period and study group. The study period and the group were the fixed effects, individual changes for each subject were considered as random effects. The prerequisites for application of the method were met: homoscedasticity of residuals was tested by the Levene's test ($p = 0.15$), while the normality of distribution of standardized residuals was tested by the Shapiro-Wilk test ($p = 0.59$). The analysis revealed that the average Ab concentrations against the Hib capsular polysaccharide did not differ between patients with obstructive and restrictive lung diseases ($p = 0.22$). The study period (before/after vaccination) had a statistically significant effect ($p = 0.01$), and the change in Ab concentrations against the Hib capsular polysaccharide resulting from vaccination may differ between groups of subjects with different diseases ($p = 0.07$, trending toward statistical significance). The geometric mean Ab concentrations against the Hib capsular polysaccharide in the study groups before and after vaccination, as well as post-hoc test results, are shown in Table 2.

Individual data on the dynamics of Ab concentrations against the Hib capsular polysaccharide before and after vaccination in vaccinated patients are clearly presented in Fig. 2.

In the group of patients with obstructive pulmonary diseases, the geometric mean Ab concentrations against the Hib capsular polysaccharide after vaccination increased by 4.1 [1.1–14.7] times compared with the baseline: from 1.3 [0.6–2.8] IU/mL to 5.5 [1.9–15.4] IU/mL, the increase is statistically significant ($p = 0.05$). In the group with restrictive diseases, the geometric mean Ab concentrations against the Hib capsular polysaccharide did not change statistically significantly after vaccination ($p = 0.99$) – 2.8 [0.6–14.1] IU/mL before vaccination and 3.4 [1.3–8.5] IU/mL 1 month after the procedure. There were no statistically significant differences between the study groups with different lung diseases, both before vaccination ($p = 0.63$) and after vaccination ($p = 0.89$).

The next stage of the study was to evaluate the effect of taking glucocorticoid on changes in Ab to the Hib capsular polysaccharide during vaccination. A mixed-effects model was used, with the study period and the presence/absence of hormones used as fixed factors, individual changes for each subject were taken as random factors. The prerequisites for application of the method were met (Levene's test – $p = 0.94$, Shapiro-Wilk test – $p = 0.22$). As a result, it was found that, on average, Ab concentrations against the Hib capsular polysaccharide

Table 1

**Percentage of patients with Hib capsular polysaccharide antibodies required for long-term protection against infection, before and after vaccination, depending on the study group**

| Study groups | Before vaccination | | 1 month after vaccination | | Dynamics analysis[1] |
|---|---|---|---|---|---|
| | Abs. | % | Abs. | % | |
| Obstructive diseases | 4 | 57.1 [18–90] | 7 | 100 [59–100] | p = 0.25 |
| Restrictive diseases | 4 | 80.0 [28–99] | 5 | 100 [48–100] | p = 1.00 |
| Differences between groups[2] | p = 0.58 | | p = 1.00 | | – |

Note: [1] – McNemar's test was used; [2] – Fisher's exact test was used.

Table 2

**Geometric mean of IgG antibody concentrations against the Hib capsular polysaccharide before and after vaccination, depending on the study group**

| Study groups | Geometric mean of antibody concentrations and 95% CI | | Dynamics analysis[1] |
|---|---|---|---|
| | Before vaccination | 1 month after vaccination | |
| Obstructive diseases | 1.3 [0.6–2.8] | 5.5 [1.9–15.4] | p = 0.05 |
| Restrictive diseases | 2.8 [0.6–14.1] | 3.4 [1.3–8.5] | p = 0.99 |
| Differences between groups[2] | p = 0.63 | p = 0.89 | – |

Note: [1, 2] – Tukey's post hoc test was used.

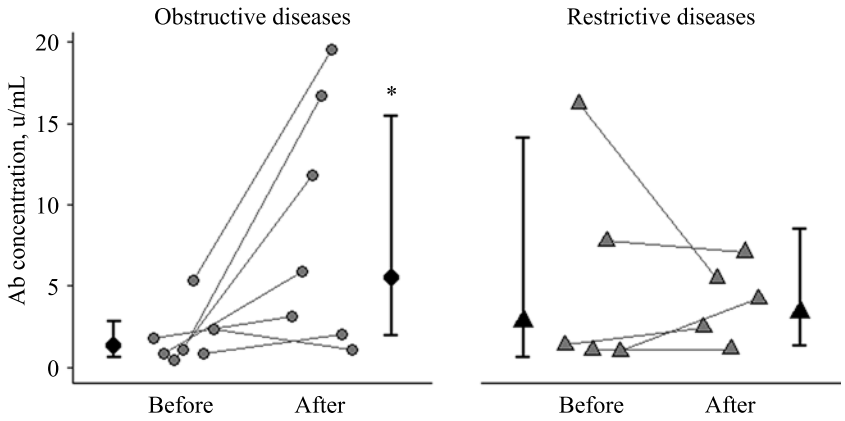


Fig. 2. Antibody concentrations against the Hib capsular polysaccharide before and after vaccination, depending on the disease. Individual values, geometric mean and 95% CI are shown

is independent of hormone intake (p = 0.12), and the Ab concentration changes statistically significantly after vaccination (p = 0.002), but the intensity of this change differs depending on hormone intake (p = 0.03). The geometric mean of Ab concentrations against the Hib capsular polysaccharide before and after vaccination, depending on hormone intake, as well as the results of post-hoc tests, are given in Table 3.

Individual data on changes in Ab concentrations in vaccinated patients with and without hormone therapy are shown in Fig. 3.

There was no statistically significant increase in Ab concentrations against the Hib capsular polysaccharide in the group of patients taking glucocorticoid, the geometric mean level was 2.7 [0.8–9.3] IU/mL before vaccination and 2.8 [1.2–6.5] IU/mL after (p = 1.00). Whereas in the hormone-free patient group, the geometric mean Ab concentration increased 3.9 [1.7–9.0] times as a result of vaccination: from 1.2 [0.7–2.1] IU/mL to 4.8 [2.2–10.1] IU/mL, the change is statistically significant (p = 0.006). There were no statistically significant differences between the study groups, either before vaccination (p = 0.39) or after (p = 0.73).

Table 3

**Geometric mean of antibody concentrations against the Hib capsular polysaccharide before and after vaccination, depending on hormone intake**

| Took hormone | Geometric mean of antibody concentrations and 95% CI | | Dynamics analysis[1] |
|---|---|---|---|
| | Before | After | |
| No | 1.2 [0.7–2.1] | 4.8 [2.2–10.1] | p = 0.006 |
| Yes | 2.7 [0.8–9.3] | 2.8 [1.2–6.5] | p = 1.00 |
| Differences between groups[2] | p = 0.39 | p = 0.73 | – |

Note: [1, 2] – Tukey's post hoc test was used.

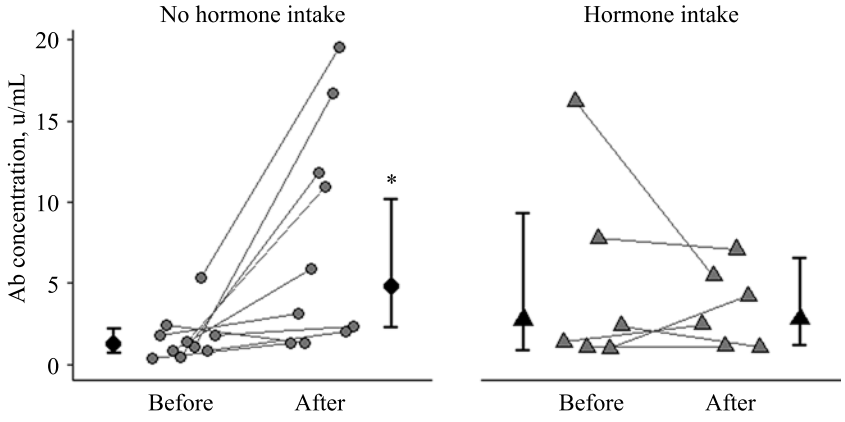


Fig. 3. Antibody concentrations against the Hib capsular polysaccharide before and after vaccination, depending on GCs intake. Individual values, geometric mean and 95% CI are shown

It should be noted that hormone intake is very strongly associated with restrictive lung diseases: 83% (5/6) of all cases of hormone intake occur in the patients of this group.

Next, we analyzed the effect of the age of the subjects on changes in Ab concentrations against the Hib capsular polysaccharide during vaccination. A mixed-effects model was used, the study period and the subject's age were the fixed factors, while the individual changes for each subject were taken as random factors. The prerequisites for applying the method were met (Levene's test – p = 0.83, Shapiro-Wilk test – p = 0.51). Regression curves characterizing the dependence of Ab concentrations against the Hib capsular polysaccharide on the subject's age, estimated using the linear mixed effects models (LMEM), are shown in Fig. 4.

There was a statistically significant increase in concentrations of Hib capsular polysaccharide antibodies after vaccination (p = 0.02), and the intensity of the increase was independent of age (p = 0.84). The relationship between the Ab concentration and age of the subject (p = 0.02) was also established. This relationship manifests itself only after vaccination (correlation coefficient of age and Ab concentrations – rs = 0.48, p = 0.05), before vaccination the relationship was weak and statistically insignificant (rs = 0.26, p = 0.34). This may be a consequence of the different immune response to vaccination in subjects with different lung diseases, as well as the fact that the group of subjects with obstructive diseases is somewhat older than restrictive diseases: 43 [41–49] years versus 32 [32–43] years (differences were not statistically significant p = 0.25).

Subsequently, we analyzed the relationship between the age of vaccinated patients and changes in Hib capsular polysaccharide antibody concentrations after vaccination within certain groups of lung diseases. For the analysis, a mixed-effects model was applied separately for patients with obstructive and restrictive diseases. The period and age of the subjects were the fixed factors; individual changes of each member of the group served as random factors. The prerequisites for application of the method were met in both groups (p = 0.16 – Levene's test, p = 0.41 – Shapiro-Wilk test in the obstructive pulmonary disease group; p = 0.45 – Levene's test, p = 0.52 – Shapiro-Wilk test in the restrictive lung disease group). Regression curves characterizing the dependence of Hib capsular polysaccharide anybody concentrations on the subject's age, estimated using the linear mixed effects model (LMEM) separately for each group of lung diseases, are shown in Fig. 5.

Analysis found no relationship between age and Ab concentrations against the Hib capsular polysaccharide in any of the groups (p = 0.29 in the obstructive pulmonary disease group, p = 0.15 in the restrictive lung disease group). In the group with restrictive lung diseases, there were no statistically significant changes in Hib capsular polysaccharide antibody concentrations after vaccination (p = 0.14). At the same time, the absence of changes in Ab concentrations is characteristic of all ages (no correlation between age and intensity of change, p = 0.16). While in the group of subjects with obstructive pulmonary diseases, there is a statistically significant increase in the Ab concentration after vaccination (p = 0.02), the intensity of increase was independent of age (p = 0.82).

## DISCUSSION

Lung transplantation is the only treatment for end-stage lung diseases. The lung transplantation waiting list includes patients with severe bronchopulmonary conditions, for whom all other treatments have proved ineffective. The main nosologies of waitlisted candidates are obstructive pulmonary diseases, cystic fibrosis,

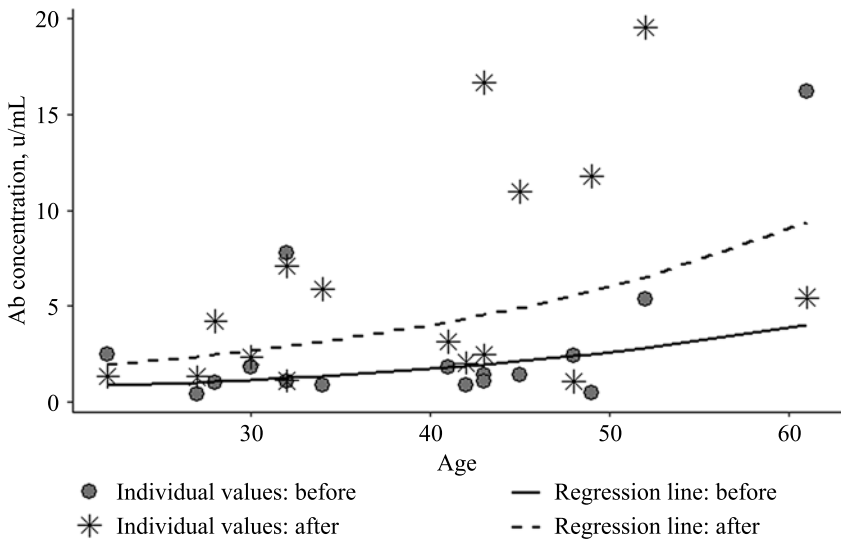


Fig. 4. Antibody concentrations against the Hib capsular polysaccharide before and after vaccination, depending on the age of the subjects. Individual values and regression curves estimated using the LMEM are shown

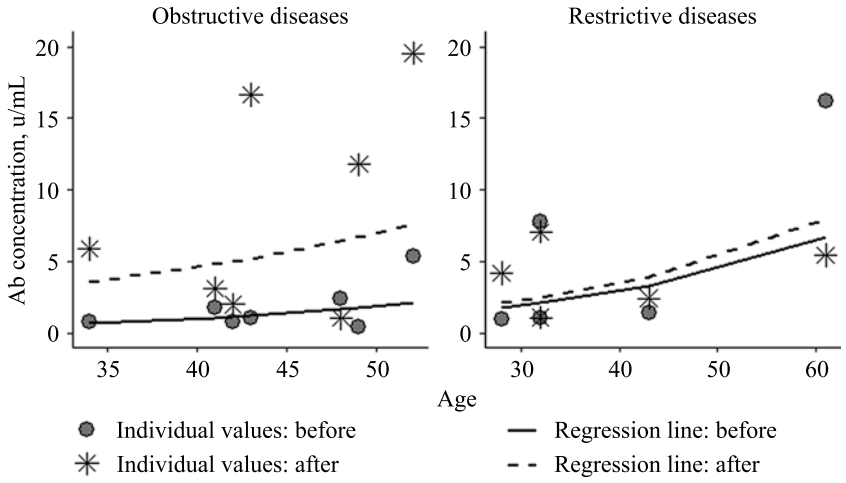


Fig. 5. Antibody concentrations against the Hib capsular polysaccharide before and after vaccination, depending on the age of the subjects and their disease. Individual values and regression curves estimated using the LMEM are shown

restrictive diseases and pulmonary vascular disease. After lung transplantation, patients undergo lifelong immunosuppressive therapy, in most cases including calcineurin inhibitors, glucocorticoids and antimetabolites, which dramatically increases the risk of infectious complications [9]. In addition, the predisposing factors for development of infectious processes in this category of patients are constant exposure of the allograft on environmental factors and violation of natural defense mechanisms (impaired mucociliary clearance, allograft denervation, inhibition of cough-reflex sensitivity [10]. As a result, infectious complications occur 2 times more often after lung transplantation than after heart transplantation. The most common site of infection is the transplanted lung itself [11–12]. All this points to the importance of prevention (vaccine-preventable, primarily respiratory) of infections in terms of management of waitlisted patients. Vaccination should be started as early as possible, since immunosuppressive therapy, initiated after transplantation, disrupts innate and acquired immunity mechanisms, and reduces the effectiveness of post-vaccination immunity [13–16].

Together with pneumococcal, meningococcal infections and influenza, Hib is one of the infections posing a danger to patients with lung diseases [16–22]. In the pre-vaccination era, the most vulnerable age group was children younger than 5 years old. The disease overwhelmingly proceeded in the form of meningitis [23–25]. At present, after the introduction of childhood vaccination against Hib into the national vaccination calendars of most countries, invasive forms of infection are increasingly described in adults, while the clinical disease in most cases proceeds in the form of pneumonia. Unencapsulated types of the pathogen prevail [26]. Nevertheless, the proportion of Hib in invasive forms of disease is 1.6% of all isolated *Haemophilus influenzae* strains, while over 60% of adult patients have chronic diseases [27].

Undoubtedly, invasive forms of *Haemophilus influenzae* infection are particularly severe in immunocompromised patients, which include waitlisted patients, primarily for lung transplantation. It should be noted that in COPD patients, about 75–80% of exacerbations of the disease are infectious in nature, with bacterial pathogens isolated from the sputum or bronchial secretions of patients in 40–50%, of which 13–46% are found in the culture of *Haemophilus influenzae* [28, 29]. At the same time, most patients with restrictive lung diseases receive glucocorticoids in the course of therapy even before transplantation, as well as, in some cases, cytostatic therapy, i.e. they are immunosuppressed, which significantly increases the risk of developing infectious complications. Hib vaccination in these patients can reduce the risk of infectious complications and increase the chances of remaining alive till transplantation.

Literature data on antibody concentrations against the Hib capsular polysaccharide in healthy individuals vary. In a study by Ladhani S.N. et al. in a cohort of persons aged 25 to 85 years, Ab concentrations exceeding the short-term and long-term protective thresholds were noted in 41–57% and 8–21% of cases, respectively [30]. These figures differ from those obtained by Nix E.B. et al., who noted Ab concentrations exceeding the short-term protective threshold in 97% of healthy controls [31]. In our study, all patients had Ab concentrations against the Hib capsular polysaccharide that exceeded the short-term protective threshold, while the proportion of patients with Ab concentrations exceeding the long-term protective threshold was 69%. This data can be compared with the results obtained by Nix E.B. et al. showing that the proportion of patients with a protective Ab level (≥0.15 μg/mL) among patients with COPD was 86%; among patients with chronic renal failure, 71% had protective antibody concentrations, 80% with diabetes, and 45% with melanoma [31].

One month after vaccination, the proportion of patients with long-term Ab protective levels was 100%. There was a statistically significant increase (by 2.3 times) in the geometric mean Ab concentrations against the Hib capsular polysaccharide as compared to the initial values ($p = 0.02$). Moreover, in 7 patients (44.8%), Ab concentrations exceeded 5 IU/mL, which also protects against bacterial carriers. Similar data were obtained during Hib vaccination in both adults and children with various bronchopulmonary conditions. Thus, during combined vaccination of COPD patients against influenza, pneumococcal and hemophilic type b infections, concentrations of post-vaccination antibodies to the Hib capsular polysaccharide remained significantly higher than the initial values at 3, 6 and 12 months after vaccination [32]. Similar data were obtained for vaccination of children with pulmonary malformations and bronchial asthma [33–35].

We found that a more pronounced increase in Ab concentrations against the Hib capsular polysaccharide was noted in the group of patients with obstructive pulmonary diseases as compared to the group with restrictive diseases. This is probably due to ongoing therapy, since patients in this group received hormonal therapy. In this regard, it is necessary to once again note the importance of early vaccination, since with progression of the disease, hormone dose increases, and this negatively affects formation of post-vaccination immunity. It is possible that this patient group needs to be re-vaccinated against Hib. A similar approach is used in the Serbian national guidelines on vaccination against Hib for at-risk groups. Under these guidelines, patients vaccinated against Hib before surgery are given the drug once, and 2 or more times in the post-transplant period (i.e., in immunosuppressive therapy) [7].

The study did not reveal any correlation between the age of the patients and antibody concentrations against the Hib capsular polysaccharide. Consequently, formation of antibodies is influenced by the ongoing therapy, which is in direct proportion to the severity of the disease.

So, Hib vaccination should be considered as an integral part of prevention of infectious complications in patients with severe bronchopulmonary diseases. The vaccine is not only safe, but also immunologically effective in lung-transplant waitlisted candidates with severe bronchopulmonary conditions.

*The authors declare no conflict of interest.*

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