UDC [616.921.5:615.371]:612.017:616.21/.22-002.2-008.87-07 https://doi.org/10.26641/2307-0404.2021.4.248169

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# THE INFLUENCE OF PARENTERAL INFLUENZA VACCINATION ON LOCAL IMMUNITY INDICES AND MICROBIOTA OF OROPHARYNGEAL SECRETION IN PATIENTS WITH CHRONIC INFLAMMATORY DISEASES OF THE UPPER RESPIRATORY TRACT

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***Цитування: Медичні перспективи. 2021. Т. 26, № 4. С. 104-112***
***Cited: Medicni perspektivi. 2021;26(4):104-112***

**Key word:** *chronic inflammatory diseases of the upper respiratory tract, local immunity, microbiota, vaccination, influenza*
**Ключові слова:** *хронічні запальні захворювання верхніх дихальних шляхів, місцевий імунітет, мікробіота, вакцинація, грип*
**Ключевые слова:** *хронические воспалительные заболевания верхних дыхательных путей, местный иммунитет, микробиота, вакцинация, грипп*

**Abstract. The influence of parenteral influenza vaccination on local immunity indices and microbiota of oropharyngeal secretion in patients with chronic inflammatory diseases of the upper respiratory tract. Zabolotny D.I., Melnikov O.F., Timchenko S.V., Sambur M.B., Rylska O.G., Volosevich L.I., Zayets T.A., Timchenko M.D., Faraon I.V.** *When studying the effect of vaccines against influenza, attention is mainly paid to obtaining high titers of protective antibodies in the blood and reducing the incidence of respiratory infections among vaccinated people. At the same time, the changes occurring in patient,s body from the factors of local specific and innate immunity remain insufficiently studied. The aim of the study was to determine the effect of parenteral influenza vaccination on the state of local immunity, cytology and microbiota of oropharyngeal secretion (OS) in patients with chronic inflammatory diseases of the upper respiratory tract. The study of immunological and microbiological parameters was performed in 32 patients with chronic inflammatory diseases of the upper respiratory tract, including 11 diagnosed with chronic rhinosinusitis, 9 – with chronic tonsillitis, 12 – with chronic pharyngitis 3 and 12 weeks after vaccination with trivalent inactivated influenza-vaccine (PASTEUR, SA, France), which was administered intramuscularly. Single vaccination against influenza A and B has been shown to normalize reduced local humoral immunity indices, in particular sIgA and immune complexes concentrations, increase release of lymphocytes into oropharyngeal secretion and cause a significant decrease in the representation of OS transient microflora without affecting the overall level of bacterial contamination. In both periods after the vaccination the reduced content of interferon-α in the OS of patients with chronic inflammatory diseases of the upper respiratory tract did not change. The obtained data allow to recommend vaccination against influenza virus in the period up to 3 months before the the beginning of mass infections as an effective means of stimulating the protective reactions of local immunity of oropharynx and nasopharynx mucous membranes in patients with chronic inflammatory diseases of the upper respiratory tract.*

**Реферат. Влияние парентеральной вакцинации против гриппа на состояние локального иммунитета и микробиоту секрета ротоглотки у больных хроническими воспалительными заболеваниями верхних дыхальных путей. Заболотный Д.И., Мельников О.Ф., Тимченко С.В., Самбур М.Б, Рыльськая О.Г., Волосевич Л.И., Заяц Т.А., Тимченко М.Д., Фараон И.В.** *При исследовании эффективности вакцин против гриппа в основном внимание обращается на получение высоких титров протективных антител в крови и снижение частоты случаев заболевания респираторными инфекциями среди вакцинированных. При этом все еще недостаточно изученными остаются изменения, происходящие в организме пациента со стороны факторов местного специфического и врожденного иммунитета. Целью работы было определение влияния парентеральной вакцинации против гриппа на состояние локального иммунитета, клеточный состав и*

*микробиоту секрета ротоглотки (СР) у больных хроническими воспалительными заболеваниями верхних дыхательных путей. Исследование иммунологических и микробиологических показателей было проведено у 32 больных хроническими воспалительными заболеваниями верхних дыхательных путей, среди которых у 11 диагностировали хронический риносинусит, у 9 – хронический тонзиллит, у 12 – хронический фарингит, через 3 и 12 недель после вакцинации инактивированной трехвалентной противотивогриппозной вакциной Ваксигрипп (SANOFI PASTEUR, S.A., Франция), которую вводили внутримышечно. Показано, что одноразовая вакцинация против гриппа А и В способствует нормализации сниженных показателей локального гуморального иммунитета, в частности концентраций sIgA и иммунных комплексов, увеличивает выход лимфоцитов в секрет ротоглотки, вызывает значительное уменьшение численности транзиторной микрофлоры, не влияя на общий уровень бактериальной обсемененности. В оба срока после проведенной вакцинации сниженное у больных хроническими воспалительными заболеваниями верхних дыхательных путей содержание интерферона – α в СР не изменялось. Таким образом, полученные данные позволяют рекомендовать вакцинацию против вирусов гриппа в период до трех месяцев перед началом массовых инфицирований в качестве эффективного способа стимуляции защитных реакций локального иммунитета слизистых оболочек рото- и носоглотки у больных хроническими воспалительными заболеваниями верхних дыхательных путей.*

Recurrent acute respiratory infections of the upper respiratory tract (URT) are a global health problem [6, 8]. In developed countries, up to 25% of patients of all ages suffer from recurrent respiratory infections [7, 8], among which influenza is one of the first [6, 8].

Vaccination is one of the effective methods of prevention of respiratory viral infections, in particular influenza. It is known that parenteral administration of inactivated influenza vaccine induces the formation of specific immunity, which is realized by an increase of antiviral antibodies of different classes in blood [10].

Most of the observations are aimed at determining the effect of influenza vaccines on the level of protective antibodies in the blood and preventing new episodes of acute respiratory viral infections, as well as the number of inflammatory processes in the upper respiratory tract caused by bacterial infections [7, 14]. However, the importance of local factors of specific and innate immunity in the implementation of effective influenza protection remains insufficiently studied. It can be assumed that the systemic administration of influenza vaccine differently affects the factors of local immunity of the upper respiratory tract, especially in patients with chronic diseases, which determined the feasibility of this work.

The aim of the study was to determine the effect of parenteral influenza vaccination on the state of local immunity, cell composition and microbiota of the oropharyngeal secretion in patients with chronic inflammatory diseases of the upper respiratory tract.

**MATERIALS AND METHODS OF RESEARCH**

The study of immunological and microbiological parameters was conducted in 32 patients with chronic inflammatory diseases (CID) in the stage of clinical remission, among which 11 were diagnosed with chronic rhinosinusitis, 9 – chronic tonsillitis, 12 – chronic pharyngitis. All patients were not vaccinated for 1 year prior to the study. The control group consisted of 32 healthy individuals of the same age.

The study was conducted in accordance with the principles of bioethics set out in the Helsinki Declaration on Ethical Principles for Human-Based Medical Research and the Universal Declaration on Bioethics and Human Rights (UNESCO).

All patients signed an information agreement to participate in the study, the procedure for which was approved by the Committee on Medical Ethics and Deontology of the State Institution "Institute of Otolaryngology named after prof. O.S. Kolomiychenko National Academy of Medical Sciences of Ukraine" (Minutes No. 5/19-1 of March 20, 2019).

Vaccination of patients was performed with trivalent influenza inactivated split- vaccine Vaccigrip (SANOFI PASTEUR, S.A., France), which was administered intramuscularly in the shoulder according to the instructions for use of the drug.

All examined patients had a sanitized condition of the oral cavity. Samples of oropharyngeal secretion (OS) were obtained from each patient according to previously developed recommendations [3] and distributed into tubes for immunological parameters and sterile Petri dishes for microbiological studies.

The concentration of sIgA was measured using reagents from the company "Xema", α-interferon (IFN-α) – reagents from the company "Cytokine", and the content of immune complexes (IC) - by their precipitation with a solution of PEG-6000 according to Yu.A. Grinevich, A.N. Alferov [2] on the enzyme-linked immunosorbent assay Stat Fax-2100 (USA).

The relative number of cells in the OS was calculated by microscopic examination of smears of cell sediment according to a previously developed method [3].

The qualitative composition of the OS microflora of patients with chronic inflammatory diseases of the URT was determined by its morphological, tinctorial, cultural and biochemical properties according to standard methods [4].

The level of OS contamination with microorganisms was assessed by two parameters: a) the total content of microorganisms isolated from 1 ml of OS, which was defined as the decimal logarithm of the number of colony-forming units (CFU) – lg CFU/ml, and b) the percentage of pathogenic and opportunistic pathogenic (transient) microflora (TMF) from the total content of microorganisms isolated from OS. TMF included: *Staphylococcus haemolyticus, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus anginosus, Klebsiella pneumoniae, Enterobacter aerogenes, Pseudomonas aeruginosa, Haemophilus influenza, Moraxella catarrhalis,* different types *of Candida* in the amount ≥3 lg *CFU/ml*. Resident (non-pathogenic) were considered *Staphylococcus epidermidis, Streptococcus mitis, Streptococcus Salivarius, Enterococcus faecalis, Enterococcus faecium, Neisseria subflava, Neisseria lactamica, Neisseria mucosa, Neisseria flavescens, Neisseria sicca, Corynebacterium pseudodiphtheriticum, Actinomyces israelii, Lactobacillus, Candida* in the amount (1-2) lg *Staphylococcus epidermidis, Streptococcus mitis, Streptococcus salivarius, Enterococcus faecalis, Enterococcus faecium, Neisseria subflava, Neisseria lactamica, Neisseria mucosa, Neisseria flavescens, Neisseria sicca, Corynebacterium pseudodiphtheriticum, Actinomyces israelii, Lactobacillus, Candida* in the amount of (1-2) lg CFU/ml.

The results are processed by methods of variation statistics [1]. The reliability of the discrepancies obtained was determined using the one-sided non-parametric criterion "U"-Mann-Whitney and the criterion φ by Fisher's angular transformation method using the software package STATISTICA 6.0 (License - Free BSD). The results were given in the form of arithmetic mean (M), median (Me) and quartiles (Q25-Q75). The number of studies was denoted as n. Differences in Me values were considered statistically significant at $p<0.05$.

**RESULTS AND DISCUSSION**

The main protective factors of URT include sIgA and IFN-α, which have antiviral properties, manifested in the inhibition of virus replication and induction of antiviral response in the infected cell [5].

The results of the studies presented in Table 1 show that in the OS of patients with chronic inflammatory diseases (CID) of URT there was a significant decrease in the concentration of IFN-α compared with the control group, which remained the same at 3 and 12 weeks after vaccination, which may be a consequence of reduced production and depletion of the pool of this cytokine in chronic inflammatory diseases of the airways (Table 1).

*Table 1*

**Content of IFN-α in the oropharyngeal secretion of patients with chronic inflammatory diseases of the upper respiratory tract before and at different terms after vaccination against influenza**

| Statistical values | Content of IFN-α, ng/l | | | |
|---|---|---|---|---|
| | Patients with CID of URT | | | donors |
| | Terms of vaccination | | | |
| | before | in 3 weeks | in 12 weeks | |
| M | 34.47 | 32.03 | 30.42 | 50.14 |
| Me | 34.55 | 32.75 | 30.10 | 47.00 |
| Q25-Q75 | 27.00-39.70 | 25.80-37.10 | 24.50-40.60 | 40.80-53.50 |
| n | 30 | 30 | 30 | 19 |
| Significance of differences, $p_U$ | $p_{1/4}<0.001$ | $p_{2/4}<0.001$ | $p_{3/4}<0.001$ | |

The content of sIgA in the OS of patients with chronic diseases of URT in the stage of clinical remission before the introduction of influenza vaccine did not differ significantly from that in donors (Table 2).

The average values of this indicator did not change significantly in the dynamics of observation in 3 and 12 weeks after vaccination against influenza. However, an individual analysis of the concentration of sIgA in the OS of patients at

different times after vaccination revealed that among 14 people (43.8% of subjects) the content of sIgA in the OS, which before vaccination was less than average one in the group and significantly less than in donors – 171.17 mg/l, after 3 weeks it increased in 12 people (85.7%) and averaged 307.66 mg/l (79.8% significantly more than the initial), and after 3 months it increased in 9 of the 13 surveyed (69.2%) and made up 342.63 mg/l, which was by 100.2% significantly more than the initial (Table 3).

*Table 2*

**Content of sIgA in the oropharyngeal secretion of patients with chronic inflammatory diseases of the upper respiratory tract before and at different terms after vaccination against influenza**

| Statistical values | Content of sIgA, mg/l | | | |
|---|---|---|---|---|
| | patients with CID of URT | | | donors |
| | terms of vaccination | | | |
| | before | in 3 weeks | in 12 weeks | |
| M | 320.62 | 364.32 | 345.99 | 312.40 |
| Me | 342.85 | 370.30 | 380.50 | 316.95 |
| Q25-Q75 | 195.40-435.15 | 268.30-506.05 | 278.20-427.40 | 113.90-460.80 |
| n | 32 | 32 | 30 | 30 |

The data obtained indicate that vaccination with influenza vaccine in patients with chronic diseases of URT in the stage of clinical remission with low levels of this immunoglobulin contributes to a significant increase in levels of sIgA concentration in the OS to nearly normal.

Determination of the dynamics of the amount of immune complexes (IC) in the oropharyngeal secretion of patients with CID of URT after administration of influenza vaccine showed that, as compared with that of donors, the concentration of IC in the OS of patients before vaccination was significantly reduced (Table 4).

*Table 3*

**Concentration of sIgA before and at different terms after vaccination against influenza in the oropharyngeal secretion of patients with chronic inflammatory diseases of the upper respiratory tract with decreased content of sIgA**

| Statistical values | Content of sIgA, mg/l | | | |
|---|---|---|---|---|
| | patients with CID of URT | | | donors |
| | terms of vaccination | | | |
| | before | in 3 weeks | in 12 weeks | |
| M | 171.17 | 307.66 | 342.63 | 312.40 |
| Me | 184.10 | 316.95 | 387.20 | 316.95 |
| Q25-Q75 | 162.20-206.80 | 147.20-448.40 | 189.50-494.90 | 113.90-460.80 |
| n | 14 | 14 | 13 | 30 |
| Significance of differences, $p_U$ | $p_{1/4}<0.05$ | $p_{1/2}<0.05$ | $p_{1/3}<0.05$ | |

*Table 4*

**Content of immune complexes in the oropharyngeal secretion of patients with chronic inflammatory diseases of the upper respiratory tract before and at different terms after vaccination against influenza**

| Statistical values | Content of IC, u. of optical density | | | |
|---|---|---|---|---|
| | patients with CID of URT | | | donors |
| | terms of vaccination | | | |
| | before | in 3 weeks | in 12 weeks | |
| M | 18.03 | 27.90 | 16.31 | 28.11 |
| Me | 18.00 | 20.00 | 14.00 | 27.00 |
| Q25-Q75 | 5.00-29.00 | 12.00-41.00 | 8.00-20.50 | 12.00-42.00 |
| n | 31 | 31 | 29 | 28 |
| Significance of differences, $p_U$ | $p_{1/4}<0.05$ | | $p_{3/4}<0.05$ | |

However, 3 weeks after vaccination, it increased to the level of control values, while 12 weeks after it decreased again and became significantly lower than that of donors.

Due to the fact that one of the components of the normal immune response is the formation of IC, mainly due to binding and subsequent elimination of antigen, it can be assumed that increasing their concentration in OS is a manifestation of the stimulating effect of vaccination on humoral defense mechanisms of oral mucosa of URT in patients with CID of URT. In the context of immunity against influenza, this is especially relevant because it is known that vaccinal IC through FcγR on the immune cells can promote the formation of high-affinity antibody responses [15].

To date, little is known about the factors that affect the relative number of epitheliocytes and leukocytes in the OS, but studies of patients with dental pathology found that the number of these cells increases markedly in inflammatory processes in the oral cavity due to polymorphonuclear leukocytes (PNL) which have functional potential and can contribute to the maintenance of its ecosystem [12, 13].

A study of the relative cell composition of OS in patients with CID of URT before and after parenteral administration of influenza vaccine showed a significant increase in lymphocytes in the OS of patients 3 and 12 weeks after vaccination compared with those to control values. and with their level before vaccination (Table 5).

This result is likely to be associated with a nonspecific local response to the introduction of antigens of vaccine strains of influenza viruses, aimed at enhancing the protection of the mucous membrane of the upper respiratory tract from the impact of pathogens of infectious nature. Significant changes in the relative content of PNL and epitheliocytes in the OS of patients after vaccination were not observed.

The study of local immunity in the patients examined was performed simultaneously with the determination of the qualitative and quantitative composition of the microbiota in the OS both before and 3 and 12 weeks after vaccination. According to the qualitative analysis of the microflora of clinically healthy donors, 209 strains of obligate flora were identified, including: *Staphylococcus epidermidis, Streptococcus mitis, Streptococcus salivarius, Enterococcus faecalis, Enterococseis nea Cossa, Neisseria flavescens, Neisseria sicca, Corynebacterium pseudodiphtheriticum, Actinomyces israelii, Lactobacillus, Candida albicans*, which accounted for 83.6% of the total microflora (250 strains). 16.4% were representatives of TMF (41 strains), among which in the control group there were determined *Staphylococcus aureus (6.2%), Strepto-coccus pneumoniae (2.4%), Haemophilus influenzae (3.8%), Moraxella catarrhalis (0.4%), Klebsiella pneumoniae (1.6%), Candida albicans (2.0%)*.

*Table 5*

**Content of cells in the oropharyngeal secretion of patients with chronic inflammatory diseases of the upper respiratory tract before and at different terms after parenteral introduction of vaccine against influenza**

| Cells | Statistical values | Content of cells, % | | | |
|---|---|---|---|---|---|
| | | patients with CID of URT | | | donors |
| | | terms of vaccination | | | |
| | | before | in 3 weeks | in 12 weeks | |
| Epitheliocytes | M | 86.78 | 86.09 | 84.93 | 89.74 |
| | Me | 91.50 | 88.50 | 89.00 | 93.00 |
| | Q25-Q75 | 84.00-98.00 | 80.50-96.00 | 81.00-94.00 | 84.00-96.00 |
| | n | 32 | 32 | 30 | 31 |
| | Significance of differences, $p_U$ | | | | |
| PNL | M | 10.00 | 9.22 | 9.43 | 8.16 |
| | Me | 6.00 | 8.00 | 6.00 | 5.00 |
| | Q25-Q75 | 1.50-14.50 | 2.00-14.50 | 3.00-11.00 | 2.00-15.00 |
| | n | 32 | 32 | 30 | 31 |
| | Significance of differences, $p_U$ | | | | |
| Lymphocytes | M | 3.25 | 4.69 | 5.60 | 1.81 |
| | Me | 1.00 | 2.50 | 3.50 | 1.00 |
| | Q25-Q75 | 0-3.50 | 1.00-5.50 | 2.00-7.00 | 0-2.00 |
| | n | 32 | 32 | 30 | 31 |
| | Significance of differences, $p_U$ | | $p_{2/1}<0.05$<br>$p_{2/4}<0.01$ | $p_{3/1}<0.01$<br>$p_{3/4}<0.01$ | |

Before vaccination, there was a probable increase in the frequency of detection of microorganisms in the transient group to 26.6% ($p\varphi<0.01$) (67 strains) of all isolated microflora (252 strains), including: *Haemophilus influenza – 22.4%, Streptococcus pneumoniae – 21.0% Streptococcus pyogenes – 3%, Staphylococcus aureus – 16.4%, Moraxella catarrhalis – 9.6%, Enterobacter aerogenes – 1.5%, Klebsiella pneumoniae – 6.0%, Candida albicans* – 20.1%.

3 weeks after vaccination, the frequency of TMF secretion decreased from 26.6% to 18.3% ($p\varphi<0.05$). *Streptococcus pneumoniae, Haemophilus influenza* and *Staphylococcus aureus* were less frequent.

The total number of microorganisms in the oropharyngeal secretion of patients with CID of URT before and at different times after administration of influenza vaccine did not differ significantly from that of donors (Table 6).

At the same time, the relative content of TMF in the composition of all microorganisms in the OS of patients with CID of URT before vaccination on average was higher than that of donors, although there was no significant difference between them (Table 7). After 3 weeks of observation, the relative content of TMF in the OS regarding that in patients before vaccination was significantly reduced and remained significantly lower and 12 weeks after vaccination (Table 7), i.e. the reproduction of bacterial pathogens in the OS did not occur.

*Table 6*

**Content of microorganisms in the oropharyngeal secretion of patients with chronic inflammatory diseases of the upper respiratory tract before and at different terms after vaccination against influenza**

| Statistical values | Content of microorganisms, lg CFU/ml | | | |
|---|---|---|---|---|
| | patients with CID of URT | | | donors |
| | terms of vaccination | | | |
| | before | in 3 weeks | in 12 weeks | |
| M | 47.15 | 47.87 | 48.76 | 45.04 |
| Me | 48.46 | 48.36 | 47.35 | 48.05 |
| Q25-Q75 | 38.03-55.15 | 38.86-57.39 | 40.00-58.65 | 35.92-54.11 |
| n | 28 | 17 | 27 | 31 |

The obtained data indicate that vaccination of patients with CID of URT against influenza significantly corrects local microecological disorders with the approximation of the values of the average content of TMF in the OS to those in almost healthy individuals of the control group.

*Table 7*

**Relative content of transitory microflora in the oropharyngeal secretion of patients with chronic inflammatory diseases of the upper respiratory tract before and at different terms after vaccination against influenza**

| Statistical values | Content of transitory microflora, % | | | |
|---|---|---|---|---|
| | patients with CID of URT | | | donors |
| | terms of vaccination | | | |
| | before | in 3 weeks | in 12 weeks | |
| M | 21.30 | 11.69 | 15.10 | 16.16 |
| Me | 24.15 | 15.90 | 16.27 | 14.00 |
| Q25-Q75 | 12.40-32.16 | 0-19.25 | 9.79-19.00 | 8.35-27.96 |
| n | 28 | 17 | 27 | 31 |
| Significance of differences, $p_U$ | | $p_{2/1}<0.01$ | $p_{3/1}<0.05$ | |

It is known that influenza can be complicated by secondary bacterial infections, which are caused by both external pathogens and changes in the structure of the microbiome of the URT and the lack of stable relationships between it and the host organism [9]. Due to the current unmet need for alternative conservative methods of treatment of respiratory diseases, efforts are focused on preventive strategies, including nonspecific immunostimulation or immunomodulation, which are also recommended for a number of chronic diseases of the respiratory tract [11]. Recent literature data indicate the ability of influenza vaccination in some cases to show nonspecific effect and reduce the number of secondary bacterial infections after the disease [14], which led us to study the state of local immunity and microbiota structure of OS in patients with CID of URT and after the introduction of inactivated influenza vaccine.

The results confirm that vaccination is accompanied by a significant reduction in the content of TMF in the mixed saliva of patients, which indicates a reduced risk of bacterial infection in such patients or exacerbation of existing chronic infectious and inflammatory disease. In particular, the constant content of PNL in the OS of patients is most likely due to the lack of activation of inflammatory phenomena after vaccination in the mucous membrane of the URT. The active role of local immune factors in patients was also indicated by the temporary increase in the content of IC in the oropharyngeal secretion and the steady increase in the number of lymphocytes characteristic of the vaccinal process. The immunocorrective effect of vaccination was manifested in the stimulation of sIgA production in patients who had low levels of this immunoglobulin before vaccination. At the same time, no changes in innate antiviral immunity were detected in vaccinated individuals, as evidenced by the absence of stimulation of IFN-α-suppressed IFN-α production in patients with CID of URT during the follow-up period. Thus, parenteral administration of inactivated split vaccine against influenza at the earliest date after vaccination stimulates a number of important factors of anti-infective protection of the mucous membranes of URT in patients with CID of URT. This is accompanied by changes in the composition of the microbiota of OS, which is near the to normal values and due to this the protection of such patients increases, the risk of exacerbations of the underlying disease and respiratory infections of bacterial and viral nature decreases.

**CONCLUSIONS**

1. In patients with chronic inflammatory diseases of the upper respiratory tract, there is a decrease in the content of interferon-α in the oropharyngeal secretion, the level of which does not change after parenteral administration of influenza vaccine.
2. One-time vaccination against influenza A and B is accompanied by normalization of reduced local humoral immunity, in particular the concentration of secretory IgA and immune complexes, increases the release of lymphocytes to the oropharyngeal secretion.
3. Parenteral administration of influenza split vaccine to patients with chronic inflammatory diseases of the upper respiratory tract at the earliest date to vaccination causes a significant reduction in the presence of transient microflora in the secretion of the oropharynx, not affecting the overall level of bacterial contamination.
4. The obtained data allow to recommend vaccination against influenza virus in the period up to 3 months before the onset of mass infections as an effective means of stimulating protective reactions of local immunity of the mucous membranes of the mouth and nasopharynx in patients with CID of URT.

Conflict of interest. The authors declare no conflict of interest.

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The article was received
2021.08.11