ARTYKUŁ PRZEGLĄDOWY/REVIEW ARTICLE

INDEX COPERNICUS INTERNATIONAL

Nonspecific vaccines for immunostimulation in patients with recurrent respiratory infections

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Article history: Received: 29.11.2016 Accepted: 2.12.2016 Published: 21.12.2016

ABSTRACT: Recurrent respiratory tract infections in children are the most common cause of outpatient visits. Due to the necessity of treatment of chronic, frequent use of antibiotics and the dangers of complications are a major clinical problem. Big hopes are now with the possibility of the use of immunostimulation as prevention of these infections. The paper discusses the most important methods of stimulation of the immune system in children. In the light of previous reports were evaluated effects of this type of therapy.

KEYWORDS: recurrent respiratory tract infections, innate immunity, acquired immunity, immunostimulation

RECURRENT RESPIRATORY TRACT INFECTIONS AS A CLINICAL PROBLEM

Recurrent respiratory tract infections (RRTIs) are an important clinical problem, particularly within the pediatric population. The number of infections drops down as children mature and their immune systems develop. However, if a child falls ill too often, for too long, and presents poor response to antibiotic treatment, diagnostic examinations should be deepened. Recurrent respiratory tract infections are still difficult to define in an unambiguous manner, as it is difficult to determine the boundaries of "safe" course and incidence of these infections in this group of patients. According to the Italian Pediatric Society, the diagnostic criteria of RRTI in children are as follows: ≥ 6 respiratory tract infections in a year, or ≥1 upper respiratory tract infection in a month between September and April of ≥ 3 lower respiratory tract infections in a year [18].

According to data from the World Health Organization, RRTIs are the main cause of deaths in children below the age of 5. In countries with high mortality rates (e.g. in South-Eastern Asia and Africa), the percentage of deaths is as high as 23% and absolute numbers are estimated at 2 million individuals [12,13]. In the developed countries, RRTIs are the reason behind 20% of all physician visits and their treatment consumes 75% of global demand for antibiotics [12,13].

Compared to adults, majority of RRTI cases in children is due to the differences in the morphology and function of the respiratory tract as well as the immaturity of the immune system. Morphological and functional differences favor rapid transmission of infections, quick development of respiratory obstruction as well as restrictive ventilatory defects and impairment of the mechanisms responsible for the cleansing of airways and elimination of pathogens [40]. The efficiency of the immune system's protection against microbial pathogens is determined by the ontogenetic development of the system's organs and tissues as well as by the correct course of local and systemic immunoregulatory processes. Non-specific mechanisms for the protection of the respiratory tract include the anatomical barriers of the mucosal membranes as well as physicochemical membranes, most importantly including the secretion of mucus, mucociliary transport, air filtration, sneezing, coughing, epiglottic reflex, and lymphatic drainage. Elements of nonspecific (innate) immunity also include numerous cells and mediators such as macrophages, neutrophils, lactoferrin, fibrinonectin, collectins and nitric oxide (NO) [19,40].

 DOI: 10.5604/01.3001.0009.4819

The response of a child's immune system to pathogenic agents is not effective compared to that in adults, . The immunity deficits observed during the first years of life are determined by the degree of immune system's immaturity which is different for individual components thereof. The immaturity of the humoral immune system in neonates and infants is associated with the reduced ability to synthesize and release immunoglobulins. Reduced immunoglobulin levels are observed in younger children presenting with RRTIs: IgG in 57% of patients and IgA in 17% of patients [17]. Significant deficits in cellular immune responses are also observed in the neonatal period, infancy, and early childhood. The bone marrow reserve of lymphocytes is several times lower than in adults. Quantitative and functional immaturity of neutrophils may lead to disturbance of early anti-inflammatory response and higher probability of inflammation becoming generalized [17]. Low expression of adhesion molecules on antigen-presenting cells (APC) leads to w poorer response to chemotactic agents and reduced migration towards the inflammatory focus [14]. During the first months of a child's life, one may observe lower intensity of cytotoxic reaction of T cells, deficit in the adjuvant and suppressor activity of B cells, as well as reduced synthesis of pro- and anti-inflammatory cytokines[17,50].

Medical management of pediatric patients RRTI should follow a dual path. Firstly, it is important to eliminate the acute disease. The second stage consists of prevention to avoid recurrence. Of much importance here are the primary and supplementary vaccinations, climate therapy, education aimed at development of appropriate hygiene habits, appropriate nutrition, motor rehabilitation, hardening of the system and elimination of environmental hazards. Currently, an increasing importance is also attributed to immunomodulatory pharmacotherapy.

POSSIBILITIES FOR THE REGULATION OF THE IMMUNE SYSTEM

The role of the immune system is to protect the body from being attacked by pathogens such as bacteria, viruses, fungi, and parasites. The immune system consists of two parts of different origin which are responsible for non-specific and specific immunity, respectively. The immune system is equipped with very precise self-regulatory mechanisms supervised by various populations of cells and mediators secreted by these cells. The activity of the immune system is modulated according to the system's needs. In some cases, rapid stimulation of defense mechanisms against environmental factors (risk signals) in preferred whereas in other cases, immune responses should be suppressed after the risk has subsided. Disturbances of immune homeostasis may sometimes occur in circumstances that are not always clear. In these cases, some mechanisms of the system are enhanced while some others are suppressed. This is observed in patients with allergic, autoimmune, infectious and cancer diseases [17,50].

There are two possible ways to influence the immune system: immunosuppression or immunostimulation. Overly activated immune system that excessively responds to exo- and endogenous stimuli in a manner leading to systemic damage requires **immunosuppression**. The method is commonly used in patients after organ transplants or patients with life-threatening autoimmune diseases. Numerous groups of drugs are used in immunosuppressive treatment, including glucocorticosteroids, thiopurins (azathioprin, mycophenolate mofetil), alkylators (cyclophosphamide) and fungal isolates (cyclosporine, tacrolimus, syrolimus). In addition, methods to suppress the immune system include high doses of immunoglobulins and plasmapheresis.

Much more often, however, medical intervention in the immune system consists in its stimulation. Immunostimulatory treatment is sometimes referred to as **immunorehabilitation**, **immunopotentialization**, or **immunocorrection**. Treatment with thymus products is referred to as **immunoreconstruction**. Immunostimulants are administered in primary and secondary immunodeficits in cancer diseases. In pediatric population, RRTIs are the most common reason for the use of immunosuppression.

POSSIBILITIES OF IMMUNOSTIMULATORY TREATMENT

Numerous immunoactivating products available in the market are the result of research for methods to control and modulate the immune system responses. These include nonspecific vaccines, polysaccharides and peptides isolated from fungal organisms, products containing alcoxyglycerols or squalenes obtained from sharks, thymus preparation and antiviral drugs.

When selecting immunostimulatory treatment the physician should particularly consider the pediatric patient's age and medical history including the frequency, location, course and duration of infections. Quantitative and functional assessment of the immune system would also be optimal for the selection of an appropriate immunostimulant. However, assays of markers of humoral and cellular responses are rarely possible due to their financial costs.

Plant products

In worldwide literature, plant products are referred to as biological response modifiers (BRMs) [49]. The surface of nonspecific immune cells features receptors that recognize microbial molecular patterns; the most important group of these are the toll-like receptors (TLRs). TLRs are capable of recognizing numerous structural elements and specific features of the nucleic acids present within the microorganisms [17]. Following TLR activation, the cells produce and release cytokines that stimulate specific and nonspecific responses. Activation of TLRs is currently considered the main mechanism of action of natural immunostimulants obtained from fungal and bacterial organisms.

Immunotropic activity of plant-derived products is delivered by polysaccharides (heteroglycans containing galactose, xylose, rhamnose, arabinose and glucose), glycoproteins, including lectins, and a wide range of low-molecular weight compounds including alkaloids, polyphenols, or quinolines obtained from plant products [14,49]. Among the most common products used in the prevention of respiratory tract infections are those obtained from *Echinacea purpurea*, *Echinacea angustifolia*, or *Echinacea pallida*. The products have a demonstrated beneficial effect on nonspecific components of the immune system, mostly manifested by bactericidal activity; reduced incidence and severity of respiratory tract infections is reported, although reports showing no effect of this type were also published [5,17]. In 2015, the clinical activity of *Echinacea* was examined in a meta-analysis carried out by the research team headed by *Schapowal* [43]. The products were assessed for the efficacy in reducing the respiratory tract infections in adults and children. The meta-analysis included 6 studies characterized by the best methodology with the total of 2458 patients. *Echinacea* was confirmed to present with ability to reduce the incidence of upper and lower respiratory tract infections, alleviate their natural history and shortening their duration. Also demonstrated was a significantly less frequent incidence of post-infection complications such as pneumonia, otitis media, pharyngitis and tonsillitis.

Polysaccharides and peptides isolated from fungi

An increasing importance in the immunoprophylaxis of RTIs in children is ascribed to polysaccharides and peptides isolated from fungi. The isolated agents that activate the immune system are β-D-glucans that bind specific cell surface structures. Activation of the immune cells is effected by these substances via interactions with TLR2 and TLR4 receptors as well as via adhesion molecules such as CD11b/CD18, lactosylceramide, scavenger receptors, and Mac-1 [31]. The most common glucans used in medicine include: lentinan isolated from *Lentinus edodes*, crestin isolated from *Coriolus versicolor*, schizophyllane isolated from *Schizophyllum commune* and β-glucan isolated from *Pleurotus ostreatus*.

The main activity of glucans when administered in appropriate concentrations is focused on the activation of T cells. They increase the mitogen-activated proliferation of T cells and the phagocytic activity of phagocytes while reducing the activity of NK cells and the complement system. Due to the latter properties of the glucan, attempts were made at its application in oncology [31]. The studies of Japanese researchers suggest that lentinan elongates the survival of patients with nonsurgical gastric tumors after it is used in combination with chemotherapy [22,38].

Few studies conducted to date suggest a very good tolerance to β-glucans and positive effects of their application in children with RRTIs. *Jesenak* et al. studied the efficacy of long-term (more than 3 months) use of a product containing the glucan in 215 pediatric patients. They were able to demonstrate a significant reduction in the incidence of infections compared to the previous season. A decrease in incidence defined as a 50% reduction was observed in 71.2% of patients. A significantly lower number of infections was demonstrated in children receiving the β-glucan product as compared to the group of untreated children (3.6 vs. 8.9 infections per year/child, $p< 0.05$). No correlation was confirmed between the use of β-glucan and a reduction in the incidence of fever and in the need for antibiotic therapy [26]. Other reports point at reduced incidence of infections induced by physical effort in athletes following a long-term use of β-glucan products [37]. Randomized, double-blind studies were carried out to assess the effects of a three-months use of a β-glucan product on the incidence of infections and on selected immune markers in a group of 50 athletes. A significantly lower incidence of upper respiratory tract infection was demonstrated in athletes receiving the glucan as compared to the placebo group.

One of the potential uses for glucan products is based on their expected local effect on pharyngeal lymphatic tissue. According to the manufacturers, combination drugs containing glucan, vitamins C, B5, B6, and B12 as well as specific ions should alleviate the symptoms of the hypertrophy of pharyngeal tonsil and palatine tonsils in children. These disorders are the cause of RRTIs in these patients. To date,

no reports are available with regard to the clinical efficacy of these products and therefore it is difficult to compare their effects with those of other immunostimulants.

Synthetic drugs

Inosine pranobex (IP) antifungal is a synthetic drug containing a combination of 1 molecule of inosine with 3 molecules 1-dimethylamino-2-propyl 4-(acetylamino)benzoate. As shown by the *in vitro* and *in vivo* studies conducted to date, IP is an immunostimulant that activates the immune system to respond to the viral infection and thus to shorten its duration. Despite the fact that the main indication for the drug is the treatment of viral infections, only after many years of market presence was it discovered that its primary effect consists in immunostimulation. The activating effect was demonstrated for IP with regard to the synthesis and release of cytokines including IL-1, IL-2, IL-10, TNF-α, IFN-γ, , as well as IgG by the stimulated immune cells [17,18]. Studies published to date suggest that IP is an efficient immunostimulant in children with respiratory tract infections [30,47].

Nonspecific vaccines

Nonspecific vaccines (intranasal, oral, and injectable) are composed of combinations of extracts from various bacterial species (lyophilized extracts, lysates or inactivated bacteria, ribosomes, cell membrane proteoglycans), most commonly being the etiological factors responsible for respiratory tract infections. The mechanism of action of non-specific vaccines should be based on nonspecific stimulation of innate immune system elements by interacting with gastrointestinal mucose and by activation of the immune system of the mucosal membranes within the respiratory tract. The activity of gut-associated lymphoid tissue (GALT) enhances lymphocytic presentation of bacterial antigens contained in vaccines and induces the production and secretion of IgA antibodies that subsequently immunize the mucosal membranes of the gastrointestinal or respiratory tract [14]. Bacterial lysates of nonspecific vaccines are also capable of stimulating antibacterial resistance via activation of nonspecific immunity mechanisms, particularly toll-like receptors (TLRs) [14,50].

Bacterial lysates used in Poland include such products as Luivac, Broncho-Vaxom, IRS-19, Polyvaccinum, Ismigen, Buccaline, and bacterial ribosome-containing Ribomunyl.

Most of these products is characterized by non-specific activity that triggers the components of innate immune system by stimulating phagocytosis (IRS-19, Polyvaccinum, Ismigen) and production of interferon-gamma (Luivac, Ismigen) or lysosyme (IRS-19); however, one may not rule out possible activation of specific immunity against the bacteria contained in the vaccines and thus the development of specific antibodies (Ribomunyl). Demonstrated findings included the increase in the number of IgA-producing cells in Peyer's patches, increase in IgA levels within the secretions and serum (Luivac, Ribomunyl, IRS-19, Ismigen), activation of T-cells (Broncho-Vaxom, Ribomunyl, Ismigen), stimulation of B-cells and production of antibodies (Broncho-Vaxom, Ribomunyl), activation of neutrophilic activity (Broncho-Vaxom), increase in the activity of monocytes, macrophages, and NK cells (Ribomunyl), and stimulation of the synthesis of IL-1 and IL-6 (Ribomunyl) [50].

Experimental and clinical studies of nonspecific vaccines

The studies include the results of basic research using the material obtained from experimental animals as well as the results of preclinical, clinical, and post-registration studies.

One of the oldest products, registered and used in multiple countries, is Broncho-Vaxom (Broncho-Munal, Imocur, Ommunal). *In vitro* studies demonstrated that the drug activates aerobic metabolism within the peritoneal macrophages of mice, enhances intracellular inactivation of bacteria, stimulates the synthesis of IL-1 in bronchial macrophages, enhances phagocytosis and degradation of mumps virus antigens, enhances the cytotoxic activity of human NK cells, and production of IL-2 and TNFa; in combination with PHA, it leads to an increase in the production of IFNg, selectively activates the transcription and intracellular production of IL-6 and IL-8 in human pulmonary fibroblast cultures, and stimulates the expression of adhesion molecules on phagocytes [21,27,32]. *In vivo* studies conducted in animal models demonstrated that the drug caused an increase in IgA levels in serum, GI tract, had and lungs in mice as well as in serum, salivary glands, and BAL in rats, had a protective effect against *Klebsiella pneumoniae* and *Streptococcus pneumoniae* infections in mice, stimulated *in vivo* bacterial killing, led to an increase in IgA levels in BAL of patients with chronic bronchitis, an increase in IFN-g levels in BAL, and normalization of the CD4/CD8 ratio [3,9,21]. The efficacy of the product was suggested by the results of clinical studies. Randomized, double-blind multicenter studies were conducted *Collet* et al. in 423 pediatric patients with recurrent respiratory tract disorders. Significant reduction in the incidence or recurrent upper respiratory tract infections and good drug tolerance were demonstrated [15]. In

their study conducted in 116 children with RRTI observed that 180 days after the treatment 39.5% of patients remained free of subsequent infections (as compared to 16% of patients in the control group where no drug was administered). Reduced consumption of antibiotics and mucolytics was also confirmed [41]. Similar results were obtained in a studies conducted in a group of 155 children (69% vs. 38% remaining infection-free 180 days after the treatment) [1]. Positive effects of Broncho-Vaxom on the incidence and course of infections were demonstrated in studies conducted in adult patients, for example in 60 Polish patients with recurrent bronchitis and bronchial asthma [16], 284 patients with recurrent purulent sinusitis [25], as well as in other studies conducted in respectively 1218 and 350 patients with chronic bronchitis [39].

Luivac (*Paspat oral*) is an oral immunostimulant available on the market from 1992. Currently, it is used in 25 countries worldwide. Animal model revealed an increase in the number of IgA-producing cells Peyer's patches within the intestines of mice as the result of exposure to antigens contained in Luivac [34]. As confirmed by other studies, this observation correlated with enhanced migration of lymphocytes from the intestinal basal membrane and Peyer's patches to the lungs, increased proliferation of mesenteric lymph node cells, and production of IL-2 and IFN-γ within mesenteric lymph node cells as the response to the product administration [34,39]. Clinical studies revealed an increase in total and antigen-specific IgA levels within the saliva of pediatric patients after administration of the vaccine [44]. Other studies demonstrated that the saliva of patients treated with Luivac inhibited the adhesion of *Haemophilus influenzae* to nasal mucosal epithelial cells in *in vitro* studies [44]. The clinical efficacy of Luivac was confirmed numerous times in randomized, prospective, placebo-controlled clinical studies (PIROL, SIGA, PAIS, LUISUISSE, PASPORT) and open-label studies (PIROL II, PIROL M, SALUD) conducted in a total population of 7000 pediatric and adult patients with recurrent respiratory tract infections. The cited studies demonstrated a reduction in the incidence of inflammations within thee respiratory tract, shorter duration of these infections, reduced consumption of antibiotics, and reduced numbers of days off school or kindergarten [23]. The drug was well tolerated, with no changes in laboratory analyses and no adverse interactions with other drugs being observed. Post-registration studies were performed in a total population of more than 6000 patients. Of note are the recent study conducted in 9 countries in a total of 1615 patients (LUIPAS), including 242 patients in 25 centers in Poland. The study showed the plausibility of use of Luivac for prevention of recurrent infections as well the possibility of savings in relations to the costs of health care provided to frequently ill patients [28].

Broadly used Ribomunyl (Immucytal, Biomunil, Biomunyl, Ribovac) has been confirmed as efficient in the prevention of RRTIs. Numerous studies demonstrated the effects of Ribomunyl on the components of specific and nonspecific immune system. Experiments in animal models were indicative of the product's impact on increased activity of macrophages and cytotoxic cells. Following oral administration, an increase in concentrations of main classes and subclasses of immunoglobulins was observed, as was a reduction in the mortality rates of mice treated with Ribomunyl against *Klebsiella pneumoniae* infection [28]. Also observed in the *in vitro* studies was the stimulating effect of Ribomunyl on the activity of natural killer cells and the secretion of IL-6 and IL-8 from monocytes isolated from human blood [2,28]. Numerous studies determined the effects of Ribomunyl on the activity of neutrophils, demonstrating activation of adhesion, chemotaxis and phagocytosis of cells obtained from patients with recurrent purulent bronchopulmonary infections [24]. Recent studies by *Villa-Ambriz* et al. confirm an increase in the expression of adhesion molecules CD11c and CD103 on neutrophils incubated with Ribomunyl over a period of 4 hours [45].

In Ribomunyl-treated patients, particularly in pediatric patients RRTIs, increase in the serum levels of specific antibodies against the bacterial components of the product was observed, as was the increase in the quantities of secretory IgA within bronchial mucosa [33]. Likewise, the number of antibody-producing cells in tonsillar tissues was higher in children treated with Ribomunyl prior to tonsillectomy procedure [7]. The efficacy of the product observed *in vitro* an in the animal models was confirmed in clinical studies. A group of Italian researchers carried out a multicenter, double-blind, placebo-controlled study in a group of 164 children below the age of 5. After six months of product use, the researchers confirmed a reduction in the incidence, duration, and severity of respiratory tract infections as compared to the groups not receiving Ribomunyl [20].

Several comparative studies were conducted in children with recurrent rhinosinusitis and pharyngitis. In the study by *Laccome* et al., children treated with Ribomunyl were characterized by lower incidence of upper respiratory tract infections and lower number of days off school [29]. In two randomized, double-blind studies, a three month-long treatment with Ribomunyl was more efficient than placebo in children with recurrent respiratory tract infections. The treatment led to reduced incidence and severity of infec-

tions, shorter duration of pyrexia, as well as increased production of IgA and IgG [4,8]. Satisfactory results of Ribomunyl treatment were observed in children with recurrent serous otitis media [48]. Beneficial effects of Ribomunyl in recurrent infections of the respiratory tract and middle ear in children [48] as well as in patients with respiratory tract inflammation with bronchospastic reaction [10] were also confirmed in the studies conducted by Polish researchers. *Mora* et al. demonstrated improvement in clinical status, reduction in the number of infections and improvement in the humoral immune system markers after 60 days of treatment in a group of 60 children with recurrent tonsillitis [35].

A number of open-label or comparative studies were conducted in adults with RRTIs, demonstrating the plausibility of the use of bacterial ribosomes in the prevention of infection recurrence. Efficacy of Ribomunyl was demonstrated in a study conducted in 1000 adult patients with laryngopharyngeal reflux by *Mora* et al. Besides the observed clinical improvement, improved humoral immunity markers were observed in laboratory studies as measured by the concentrations of the major classes of immunoglobulins. Studies conducted in children and adults were suggestive of good tolerance of the drug and a low risk of adverse reactions.

Beneficial effects of bacterial ribosome treatments were also confirmed in meta-analyses. In 2000, an analysis was conducted on 28 clinical studies on the use of Ribomunyl in 14,213 children and adults with NZDO. Reduction in the incidence of infections and in the use of antibiotics was observed in patients after three months of treatment [11]. Another meta-analysis of 19 European clinical studies (randomized, double-blind, placebo-controlled) encompassing more than 2000 adult and pediatric patients with recurrent upper and lower respiratory tract infections demonstrated that Ribomunyl reduced the duration and incidence of these infections, synergistically interacts with anti-flu vaccinations and reduces the need for antibiotic therapy [6].

Can immunostimulants be used without fear?

Based on numerous presented studies, the use of nonspecific vaccines was demonstrated to play a potential role in the treatment or prophylaxis of recurrent infections of the respiratory tract and ears in children and adults. Specific mechanisms of action were established for numerous products with regard to their involvement in activation of regulation of immune processes. The use of immunostimulants is not accepted by all physicians and remains a controversial problem; highlighted issues include the unfeasibility of expectations and placebo effect.

One must keep in mind that not all questions may be answered with regard to the risks associated by excessive stimulation of the immune system: whether or not it would cause allergic reactions, whether or not the products would lead to an unfavorable direction of changes in the immune system and, most of all, of what importance is the stimulation of the immune system in the particular disorder. When considering interventions in the maturing immune system of children, it is particularly important to ask oneself the question whether the use of immunostimulants without the possibility to assess the immune status of the patient would not increase the risk of autoimmune processes.

Despite the widespread, worldwide use of nonspecific vaccines, no convincing evidence was found for the induction of autoimmune processes, no proof was found for the formation of autoantibodies as the response to the treatment, no induction of allergic processes was observed, nor were pathological changes in lymphocyte activation or any adverse effects of the products.

SUMMARY

The search for the methods to control the reactions of the immune system has been one of the most important aims of experimental and clinical research in recent years. The studies led to the development and introduction of ever newer groups and generations of agents which, according to their manufacturers, are characterized by immunoactivating properties. The expected effect of the treatment is often obtained after chronic use, frequently serial and based on specific use algorithms. The sometimes contradictory reports regarding the efficacy of treatment with individual products as well as controversies regarding the therapeutic regimens result in the need for the treatment to be revised individually for every patient. In pediatric patients, particularly in children attending day care centers and kindergartens, good effects obtained after a single cycle of immunostimulatory treatment predisposes the patients for subsequent cycles of the same product due to the high probability of infections being transmitted. Failure of the treatment as associated with increased incidence and severity of infections or with the occurrence of any side symptoms warrants immediate discontinuation of the particular product. The physician should exercise care when choosing the immunostimulatory agent and the therapeutic regimen due to the lack of data on the effects of immunopharmacological intervention in the maturing immune systems. An additional risk is also posed by the high and constantly growing market availability of dietary supplements that are beyond the restrictions imposed by the Pharmaceutical Law.

The effective and expansive advertising of these products as efficient "immunoboosting agents" introduces much chaos into the very young discipline of immunotherapy while also being associated with the risk of adverse reactions. These reactions may be due to the use of large doses of the dietary supplements, their interactions with other drugs and foods, or patient's hypersensitivity to the particular components of the supplement. This requires that the physicians remain vigilant and react to unnecessary polypragmasia which is particularly dangerous in small children.

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Word count: 4400 Tables: – Figures: – References: 50

Access the article online: DOI: 10.5604/01.3001.0009.4819 Table of content: http://otolaryngologypl.com/resources/html/articlesList?issueId=9414

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Competing interests: The authors declare that they have no competing interests.

Cite this article as: Paśnik J.: Vaccines nonspecific – immunostimulation in patients with recurrent respiratory infections; Otolaryngol Pol 2016; 70 (6): 32-40