THE ROLE OF IMMUNOSTIMULANTS IN IMMUNOTHERAPY
AND IMMUNOPROPHYLAXIS

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ABSTRACT
Medical practice faces serious problems due to the constantly increasing bacterial poly-resistance to antibiotics, and the side effects of the latter, often including allergic and immunosuppressive reactions. One way to resolve this problem is the application of immunomodulators that increase resistance to bacterial and viral infections by stimulating non-specific immunity mechanisms. In the course of more than 20 years a number of oral immunomodulators have been developed and investigated in the NCIPD, Sofia: Respivax, Urostim and Dentavax which are widely and successfully applied in clinical practice for immunotherapy and immunomodulation.

Data about the effects of polybacterial immunomodulators demonstrate a pronounced stimulation of phagocytosis, synthesis of secretory IgA, surfactant, interferon and a number of Th1 type of cytokines. Numerous investigations, including double-blind studies, have proved their efficacy in the prevention and treatment of non-specific respiratory, uro-genital and periodontal infections as well as in the complex therapy of AIDS. Based on this, polybacterial immunostimulators seem a very promising tool for immunotherapy and immunoprophylaxis, allowing the modulation of immune responses in a most beneficial way.

Keywords: polybacterial immunomodulators, vaccines, immunotherapy, immunoprophylaxis, infections

Introduction
During the last two decades very intensive investigations are carried out on the preparation, experimental and clinical characteristics of one relatively new category biologically active substances - so called immunostimulators. They are products from natural or synthetic origin with different chemical characteristic and mechanism of action (1, 9, 13, 14, 16, 17, 18, 19, 23).

Immunostimulants:
- activate different elements and mechanisms of the immune system of humans and animals;
- they reinforce a body’s natural resistance in order successful to cope with various viral and bacterial infections or to help in the treatment of other pathogenically related with suppressed immune system conditions – cancer (malignant) diseases, AIDS, SARS etc. Immunostimulants created the base of the active and successful development and implementation in the clinical practice of the nonspecific immunotherapy and the nonspecific immunoprophylaxis by stimulating the main factors of the immune system:
  - the phagocytosis;
  - properdin and complement systems;
  - protective secretory IgA antibodies;
  - α- and γ- interferon release;
  - T- and B- lymphocytes;
  - synthesis of specific antibodies and cytokines;
  - synthesis of pulmonary surfactant.

Which are the factors determining the interest of the clinicians to use the immunostimulants in the control of different infectious diseases and the perspective for their large use in the medical practice?
- On the first place that is the increasing multi resistance of the bacteria to antibiotics, which creates in some regions in the world dramatic situation as more than 40% of the circulating bacterial strains are resistant to available antibiotics.
- Very serious problem in everyday clinical practice is frequently encountered allergic reactions to antibiotics and chemotherapeutics in patients and in medical personnel what restricts their use.
- It is very important to stress that practically the greatest part of the antibiotics have well proved immunosuppressive effect. They “kill” bacteria but in the same time diminish the natural resistance of the organism to cope with them.
- One has to have in mind also the lack of activity of the antibiotics in viral infections and finally the lack of specific treatment or vaccines for the greatest part of the viral infections, including HIV/AIDS, SARS, avian flu and some others newly immerging or intentionally spread bacterial and viral infections.

Undoubtedly all that grew into complex medical problem, placing physicians face to face with the difficult task to carry out the treatment of their patients to successful and safe completion what is particularly observed in the course of acute, chronic and frequently recurring non-specific diseases of respiratory tract, SARS and avian flu being typical examples in this respect.
The situation is getting worse nowadays because of:

- increasing air pollution
- increasing radiation

proved to affect negatively the different segments of the immune system and to increase the risk of sensitization of human organism to different allergens (22). As a result it is well known that nowadays not less than 10-15% of the human beings are so called *immunocompromized* persons with damaged immune system and not able to overcome or are easily exposed to common infectious diseases (7).

It is clear nowadays that naturally occurring epidemics (the flu epidemics and the following secondary bacterial infections for instance) as well as newly emerging and mainly – intentionally provoked infection diseases as a form of bioterrorism continually threaten the health of the people of the world. This explains the concerns of the National public health authorities and the international efforts for effective approaches to strengthen the capacities of the health system in order to minimize the risk for the population of deliberately caused disease outbreaks by different bacterial and viral pathogens.

Having all this in mind one can conclude that because of the lack of a specific treatment and a specific vaccine for these infection diseases, the time required for creation and clinical testing of any vaccine or specific drug it is quite reasonable to consider the *non-specific immunotherapy and the non-specific immunoprophylaxis* based on the use of some immunostimulants reinforcing the natural immune mechanisms as a very promising approach.

In Bulgaria more than 20 years we are working very intensively on the elaboration, experimental study and clinical application of different “targeted” *polybacterial immunostimulants* for per oral administration intended to stimulate the natural mechanisms of the immune system and to help in recovering and prevention of the infections of respiratory and urine systems, oral cavity and parodonte.

Why did we choose to work with polybacterial immunostimulants composed of Gram-negative and Gram-positive bacteria? That is because of their well proved mechanism of action in the organism:

- Gram-negative bacteria contain LPS, endotoxins, peptidoglycans, lipoproteins which stimulate macrophages, NK- cells, B- lymphocytes and antibody production and release of α- and γ- interferons and IL-2, IL-6.
- Gram-positive bacteria contain muramidilpeptide, lipoteichoic acids, peptidoglicans which stimulate also phagocytosis, T-cell and B-cell function.
- Absorption of these components occurs through gastrointestinal mucosa and on the base of the integral function of the immune system via GALT (Gut Associated Lymphoid Tissue) is stimulated BALT (Bronchial Associated Lymphoid Tissue) as a part of the whole MALT (Mucosal Associated Lymphoid Tissue).
- Bacterial species entering the preparations stimulate the synthesis of homologous specific protective IgG, IgA and IgM antibodies. That means the polybacterial immunostimulants act also like bacterial “vaccines”.
- Finally it is very important that polybacterial immunostimulants are natural products consist of the bacteria which are part of the normal flora of the body.

These per oral polybacterial immunostimulants are composed of freeze-dried lysates and killed bacterial bodies of microbial species with greatest importance for the occurrence of nonspecific respiratory infections (Respivax) or uro-genital (Urostim) or in oral cavity and parodont (Dentavax). Their advantage is that they contain not only lysates but in the body of the bacteria as in the cell walls are situated the greatest part of the antigens with well proved immunostimulating activity.

### TABLE 1

<table>
<thead>
<tr>
<th>Test groups of 8 white mice treated with:</th>
<th>Antibody titre after administration of the antigen (sheep erythrocytes)</th>
<th>7th day</th>
<th>14th day</th>
<th>7th day</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESPIVAX, perorally, 7 days before and 7 days after Ag</td>
<td>Primary antibody response</td>
<td>1:512</td>
<td>1:1024</td>
<td>1:2048</td>
</tr>
<tr>
<td>RESPIVAX, perorally, 7 days after administration of Ag</td>
<td></td>
<td>1:256</td>
<td>1:512</td>
<td>1:2048</td>
</tr>
<tr>
<td>RESPIVAX, s.c., 7 days before and 7 days after Ag</td>
<td></td>
<td>1:512</td>
<td>1:2048</td>
<td>1:4096</td>
</tr>
<tr>
<td>RESPIVAX, s.c., 7 days after administration of Ag</td>
<td></td>
<td>1:256</td>
<td>1:1024</td>
<td>1:2048</td>
</tr>
<tr>
<td>CONTROL GROUP - injected with Ag only</td>
<td></td>
<td>1:32</td>
<td>1:128</td>
<td>1:256</td>
</tr>
</tbody>
</table>

* - antigen - each mouse is injected i.v. with 0.2 ml of 50% suspension of sheep erythrocytes. On the 28-t day after the first administration the antigen is injected again in order the secondary immune response to be followed up. RESPIVAX is administered in a daily dose of 2 mg/0.5 ml of physiological solution perorally or s.c.
Of relevance to conditions with compromised immune system like HIV/AIDS, SARS, malignant diseases, avian flu etc. would be our polybacterial immunostimulant called RESPIVAX for per oral immunotherapy and immunoprophylaxis of non-specific infections of the respiratory system in adults and children in wide prescription and clinical use now over 20 years in Bulgaria and recently in several other countries. Because of its well proved stimulating capacity on different cells and mechanisms of the immune system Respivax is very convenient to be used as a general immunostimulant in treatment and prophylaxis of newly immuring and intentionally provoked infectious diseases, when we have to rely mainly on the natural resistance of the organism to cope with them in waiting for specific diagnosis and to be developed specific treatment and/or vaccine.

Some of our experimental and clinical data presented here demonstrate clearly the immunostimulating capacity of Respivax as an example of the activity of the polybacterial immunostimulants.

On Table 1 and Table 2 is seeing the stimulation of antibodies to sheep erythrocytes and to human serum albumin in mice treated with Respivax. This adjuvant effect of the polybacterial immunostimulant is very important as it can be used to provoke better immune response to bacterial or viral vaccines when is administered simultaneously with them. We observed this effect in a study of the immune response to routine revaccination against diphtheria in a group of 87 children (11). Paired sera were collected from 47 of them treated with Respivax 30 days before immunization (experimental group) and from 40 children treated with placebo (control group). The serum samples were taken before immunization and 45-50 days after the administration of the vaccine.

From results on Table 3 is seen that the children treated with Respivax demonstrate a considerably greater increase in GMT (8-fold) of anti-toxin antibodies and a higher percentage of re-immunized persons having a high level of this protective antibodies (85.1%).

On Table 4 is presented the protective effect of Respivax to a Staphylococcus aureus infection in mice (24). The results clearly reveal the immunostimulation activity of Respivax as it has favorable influence on non-specific immune mechanisms, which is manifested by the longer survival and lower mortality of the mice treated orally with the product in comparison with the control animals. It is seen that up to the 4th day of the experiment all control mice (treated with saline instead of Respivax) are dead. The Respivax treated mice demonstrate substantially longer survival time and on day 4 only 14 mice (50%) are dead. This indicates that the factors of natural resistance in the organism, contributing greatly to overcome the infection, are successfully stimulated by Respivax. One of this factors is obviously the phagocytosis which is stimulated strongly by Respivax as one can see from Fig. 1 where is shown that after the administration of Respivax the phagocytotic activity significantly is increased in guinea pigs (23). Three days after the end of the administration of Respivax the percentage of phagocytizing cells started to increase and reached a maximum of 50% at the 21st day. Up to 28th day the percentage of phagocytizing cells of the treated animals was 10 times higher than those of controls – 49.5% vs. 4.4% (p<0.001). These results clearly demonstrate that the oral administration of Respivax stimulates antibacterial functions of phagocytizing cells. This is obviously one of the factors explaining the demonstrative protective effect of Respivax in infected with Staph. aureus Sg 511 mice.

In support of the presented data are also the results of the immunomorphological studies, which demonstrate the material substrate of the changes in the immune system under the effect of Respivax (Fig. 2, 3, 4). It was established that after oral administration of the drug clearly expressed immunomorphological changes were observe, occurring in

<table>
<thead>
<tr>
<th>Test groups of 8 white mice treated with:</th>
<th>Antibody titre after administration of the antigen (human serum albumin)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary antibody response</td>
</tr>
<tr>
<td></td>
<td>7-th day</td>
</tr>
<tr>
<td>RESPIVAX, perorally, 7 days before and 7 days after Ag</td>
<td>1:64</td>
</tr>
<tr>
<td>RESPIVAX, perorally, 7 days after administration of Ag</td>
<td>1:32</td>
</tr>
<tr>
<td>RESPIVAX, s.c. 7 days before and 7 days after Ag</td>
<td>1:128</td>
</tr>
<tr>
<td>RESPIVAX, s.c. 7 days after administration of Ag</td>
<td>1:64</td>
</tr>
<tr>
<td>CONTROL GROUP - injected with Ag only</td>
<td>1:8</td>
</tr>
</tbody>
</table>

Ag - antigen - each mouse is injected i.v. with 0.2 ml of human serum albumin. On the 28-th day after the first administration the antigen is injected again in order the secondary antibody response to be followed up. RESPIVAX is administered in a daily dose of 2 mg/0.5 ml of physiological solution perorally or s.c. The antibody titre is determined by passive hemoagglutination with sheep erythrocytes treated with tannin.

TABLE 2
the lymphoid tissue associated with the intestines, bronchi, spleen and lungs – newly formed lymph nodes localized peribronchially, strongly activated lymphocytes and plasmocytes in mesenteron with well developed endoplasmic reticulum, but without any damaging effect on the intestines. As was mentioned a generalized immune response is unlocked which lays at the basis of stimulated non-specific and specific immune protection of the body (15, 20).

The large clinical studies (including two placebo controlled studies) of Respivax carried out the last 12-15 years clearly demonstrated its very positive effect on the different mechanisms of the immune system in humans and what is most important – on the clinical course of the non-specific respiratory diseases: chronic and recurrent bronchopneumonia, acute and chronic bronchitis and thraehitis, rinitis (2, 3, 5, 6, 8, 10). Especially favorable effect is observed during flu epidemics and in winter time when many other respiratory viruses are activated and Respivax is very convenient immunoprophylactic agent strengthening the natural resistance of the organism. From a double-blind controlled study carried out by Jossifov et al. (6) on 50 children with recurrent acute bronchopneumonia one can see the favorable effect of Respivax with significant reduction of total number of inflammatory episodes, days with antibiotic treatment, days of stay in hospital and increase of the secretory IgA in saliva (Table 5 and Table 6). The similar results – significant reduction in number and severity of respiratory episodes are received by Iliev et al. (5) in children with recurrent viral and bacterial pneumonia and bronchopneumonia treated with Respivax with demonstrative increase of phagocytic activity to the main bacterial strains responsible for development of respiratory diseases (Table 7).

In a study of 64 adults with chronic non-specific pulmonary diseases (CNPD) treated 20 days of each of 4 consecutive months with 50mg Respivax daily Kisyova et al. (8) find substantial reduction of number and severity of inflammatory episodes in comparison with the control group 3 months after the treatment (Table 8). These clinical changes were accompanied with the
increase of the titer of specific antibacterial antibodies (to the bacteria entering in Respivax) of IgG, IgA and IgM classes.

**TABLE 5**

IgA in the saliva in mg/ml

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>10th day</th>
<th>30th day</th>
<th>60th day</th>
<th>90th day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children treated with Respivax (n=47)</td>
<td>9.64</td>
<td>14.58</td>
<td>15.36</td>
<td>14.2</td>
<td>13.95</td>
</tr>
<tr>
<td>Control group (n=16)</td>
<td>8.92</td>
<td>10.18</td>
<td>10.18</td>
<td>10.18</td>
<td>10.18</td>
</tr>
</tbody>
</table>

**TABLE 6**

Diseases, antibiotic treatment and number of days of stay in hospital of the examined children for a 3-month period of the previous year and the period of observation - controlled study

<table>
<thead>
<tr>
<th>Studied patients</th>
<th>For previous year</th>
<th>For the period of observation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Respivax placebo</td>
<td>Respivax placebo</td>
</tr>
<tr>
<td>Inflammatory disease (total number)</td>
<td>95</td>
<td>65</td>
</tr>
<tr>
<td>Days of the antibiotic treatment (total number)</td>
<td>505</td>
<td>285</td>
</tr>
<tr>
<td>Number of days of stay in hospital</td>
<td>138</td>
<td>127</td>
</tr>
</tbody>
</table>

Kojuharova et al. (10, 11) in placebo control trial find that Respivax is strong interferon inductor. They have studied 56 children and 30 adults divided in two groups: experimental – treated 30 days with 25mg (children) and 50mg (adults) Respivax tablets daily and control- treated with placebo tablets. On the 3rd day after the treatment is assessed the level of the endogenous α- interferon and is observed four-fold increase of its titer in 86% of the treated with Respivax patients. These results demonstrate the capacity of one polybacterial immunostimulant in the treatment of viral diseases and in modulation of the immune reactivity based on interferon production.

The proved immunostimulating effect of Respivax on the cells of the immunocompent system was the reason to study its action in the complex treatment of patients with HIV/AIDS (21). Under the name Factor-R tablets we applied this polybacterial immunostimulant in 100 Americans from Texas (USA) with HIV/DADS for a period of 6 months. They received every day 60mg Factor-R per orally and were monitored every three months for clinical and laboratory variables of efficacy of Factor-R. It was found that Factor-R has a statistically significant stimulatory effect on different effector cells of host defence reactions. The increased or preserved level of monocytes and neutrophil granulocytes in 50 to 60% of the subjects contributes to the activation of phagocytosis against infectious agent. This resulted in an increase of non-specific resistance against secondary opportunistic infections, helped by the demonstrative increased of IgA secretory antibodies in 76% of all treated patients (Fig. 6). The tendency to maintain and to increase the red blood cells and platelets provides beneficial effect on stabilizing the haemostasis of AIDS sufferers and hence prevents them from haemorrhagies. The polybacterial immunostimulant practically has not any substantial effect on CD4 lymphocytes (Fig. 7), but its impact on CD8 cells is very demonstrative and important (Fig. 8) as these lymphocytes release a special factor suppressing the replication of HIV in

**TABLE 7**

Dynamics of the phagocytic index in the blood serum of the treated with Respivax and the control group children

<table>
<thead>
<tr>
<th></th>
<th>Before Treatment</th>
<th>10th day</th>
<th>30th day</th>
<th>60th day</th>
<th>90th day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated with Respivax</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Str. pneumoniae</em></td>
<td>0.720</td>
<td>1.060</td>
<td>1.120</td>
<td>1.100</td>
<td>1.040</td>
</tr>
<tr>
<td><em>Hem. influenzae</em></td>
<td>0.760</td>
<td>1.160</td>
<td>1.018</td>
<td>1.080</td>
<td>1.060</td>
</tr>
<tr>
<td><em>Staph. aureus</em></td>
<td>0.990</td>
<td>1.420</td>
<td>1.560</td>
<td>1.480</td>
<td>1.500</td>
</tr>
<tr>
<td>n = 50</td>
<td>n = 46</td>
<td>n = 44</td>
<td>n = 42</td>
<td>n = 39</td>
<td></td>
</tr>
</tbody>
</table>

p< 0.01

|                          |                  |          |          |          |          |
| Control group            |                  |          |          |          |          |
| *Str. pneumoniae*        | 0.790            | 0.820    |          |          |          |
| *Hem. influenzae*        | 0.770            | 0.930    |          |          |          |
| *Staph. aureus*         | 0.785            | 1.070    |          |          |          |
| n = 20                  | n = 18           |          |          |          |          |

p>0.05
RESPIVAX

Reg. No. 2001 0515 - 25 mg
Reg. No. 2001 0516 - 50 mg

COMPOSITION:
Each tablet contains 25 mg freeze-dried active substance for children and 50 mg freeze-dried active substance for adults, comprising freeze-dried killed bacterial cultures of the following microbial species: Streptococcus pneumoniae, Branhamella catarrhalis, Streptococcus pyogenes of group A, Haemophilus influenzae type b, Staphylococcus aureus and Klebsiella pneumoniae

INDICATIONS:
RESPIVAX is intended for oral immunotherapy and immunoprophylaxis of unspecific diseases of the respiratory system. It has a very good effect during treatment of children and adults, suffering from acute repeated and chronic respiratory infections:
♦ acute bronchitis and tracheobronchitis;
♦ chronic and relapsing bronchitis and tracheobronchitis;
♦ acute and chronic tonsillitis, pharyngitis and laryngitis;
♦ acute and chronic rhinitis, sinusitis and otitis;
♦ often repeated bronchopneumonia;
♦ infections of the respiratory system, resistant to antibiotic therapy;
♦ infections of the respiratory system, accompanied with hypersensitivity to antibiotics or other chemothapeutic agents;
♦ infectious bronchial asthma.

Its application is especially suitable for patients with allergies to antibiotics or with infections caused by bacteria, resistant to antibiotics. The application of RESPIVAX during the autumn-winter period is extremely appropriate before and during influenza epidemics, when its prophylactic and treatment effect regarding the developing secondary bacterial infections is distinctly favourable.

CONTRAINDICATIONS:
It is contraindicated in the cases of auto-immune diseases with an increased synthesis of antibodies.

UNDESIRABLE MEDICAL REACTIONS:
Till now no undesirable medicinal reactions after application of RESPIVAX were observed. Clinical results show very good tolerance by the organisms.

MEDICINAL INTERACTIONS:
No incompatibility with other medical preparations were observed.

RESPIVAX can be combined with any other treatment, including antibiotic therapy. It allows several fold application without gaining resistance.

PRECAUTIONS DURING ADMINISTRATION AND SPECIAL WARNINGS:
Application of the preparation during the first three months of pregnancy is not recommended.

DOSSAGE AND ADMINISTRATION:
For immunotherapy and immunoprophylaxis, RESPIVAX for adult at daily dose of 50 mg and for children from 3 to 14 years daily dose of 25 mg is applied.

RESPIVAX is administered in the following way:

TREATMENT:
Within 30 days, one tablet in the morning, before meal. For achieving long effect of the treatment 1 tablet RESPIVAX in the morning before meal within 20 successive days in three subsequent months is recommended. This course of treatment can be repeated again after 5 - 6 months.

In cases of significant suppression of immune system resulting from different diseases, including malignant ones, the doctor can prescribe a prolonged treatment and 1 tablet RESPIVAX is taken in the morning before meal without interruption of the treatment of the patients for 3 - 6 months.

PROPHYLACTIC COURSE:
One tablet RESPIVAX daily, in the morning before meal within 20 days in 3 subsequent months.

PRODUCER:
BB-NCIPD LTD.
BULGARIA
1504 Sofia, 26 "Yanko Sakazov" blvd.
Phone: **359 2 944 61 91
Fax: **359 2 943 30 75
e-mail: bulbio@bulbio.com

BB-NCIPD Ltd.
CD4 cells (4, 12). The substantial increased of CD8 cells of subjects with different duration of HIV positivity gives reason to consider that the treatment with Factor-R by means of its immunostimulating action, on the CD8 cell population, may lead to an extension and improvement of their life as well as contributes to transition of a number of subjects into so called “long-term non-progressors”.

**TABLE 8**

CLINICAL EFFECTIVENESS OF COMPLEX THERAPY INCLUDING RESPIVAX IN CNPD PATIENTS

<table>
<thead>
<tr>
<th>Endpoints recorded</th>
<th>With Respivax</th>
<th>Without Respivax</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No %</td>
<td>No %</td>
</tr>
<tr>
<td>Shortening of antibacterial treatment</td>
<td>51 82.25</td>
<td>11 36.6</td>
</tr>
<tr>
<td>duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence within six months</td>
<td>21 33.8</td>
<td>28 93.3</td>
</tr>
<tr>
<td>Treatment reduction</td>
<td>19 30.6</td>
<td>3 10.0</td>
</tr>
</tbody>
</table>

**Fig. 1.** Percentage of phagocytizing PMNC from guinea pigs treated with Respivax.

Days after treatment with Respivax or Saline (Control)

**Fig. 2.** Small intestine of a mouse 5 times treated per os with 1/10 dose (5mg) of RESPIVAX; on the 7th day after the last treatment. Well preserved brush border. Magnification – 40.000 X

**Fig. 3.** Lung of a mouse treated 5 times per os with 1/10 dose (5mg) of RESPIVAX; on the 7th day after the last treatment. New formed lymph nodes localized peribronchially. Staining – H.E. Magnification – 140 X

**Fig. 4.** Mesenterial lymph node of a rat 5 times treated per os with RESPIVAX (25 mg); on the 5th day after the last dose. Strongly activated lymphoid cells with numerous ribosomes in their cytoplasm and a plasmatic cell with strongly developed endoplasmic reticulum. Magnification – 16.000 X

**Fig. 5.** The impact of Respivax on α-Interferon synthesis in children and adults

**Children (29) with Respivax**

Before Treatment: 2.4

After Treatment: 37.8

**Placebo (20)**

Before Treatment: 5.2

After Treatment: 6.9

**Adults (17) with Respivax**

Before Treatment: 7

After Treatment: 42.6

BIOTECHNOL. & BIOTECHNOL. EQ. 21/2007/4
**Conclusions**

On the base of all presented experimental studies and clinical trials one can conclude that polybacterial immunostimulants, particularly Respivax, is convenient as a very prospective and scientifically proven meaning for prophylaxis and treatment of respiratory infections and in a complex therapy of some immunodeficiency diseases.

**REFERENCES**


