F.S. Kharlamova[1], V.F. Uchaikin[1], O.V. Kladova[1], E.M. Sergeeva[2], V.G. Nesterenko[2]
[1] Pirogov Russian National Research Medical University, Health Ministry of Russia, Moscow
[2] Gamaleya Research Institute of Epidemiology and Microbiology RAMN, Moscow

Clinical and Prophylactic Efficacy of Interferon Inducer in Viral Respiratory Infections in Children From 3 Years Old

Consistently high level of morbidity in acute respiratory infections (ARI) is currently present among all age groups. Flu is particularly dangerous one among them, and is characterized by severe course, especially in children, high risk of complications during any period of starting from the onset of the disease; this places flu among the most relevant problems of pediatrics. In this paper the results of studying the efficacy and safety of a domestic immune modulatory drug with an interferon-inducing effect are demonstrated in children older than 3 years.

***Key words**: acute respiratory infections, immune system, interferon, treatment efficacy, safety, and children.*

Received on: 26.09.2011, accepted for publication: 15.01.2012 г

Acute respiratory infections (ARI) are among the most relevant public health problems worldwide. In recent years new variants of viruses are not only appearing, but also returning into circulation: Influenza A virus (H5N1), Pandemic California 0409-H1N1-new, Metapneumovirus, bocavirus, coronaviruses (CoVNL63, CoVHKU1, CoV SARS) and enterovirus (EV71). In 2009 the World Health Organization (WHO) declared a 6th phase Californian Influenza 0409-H1N1-new pandemic caused by a reassertant of bird, pig and human influenza viruses. The new influenza infection where high mortality occurs mainly among risk groups (children and patients with chronic diseases), is registered in more than 140 countries. According to the WHO the influenza A (H1N1) 09 pandemic will continue to dominate together with the co-circulation of seasonal influenza viruses H1N1, A (H3N2) and B in the epidemic season of 2011-2012 in the northern hemisphere.

Comparative analysis of epidemic situation of Pandemic Influenza A (H1N1) California 0409 and seasonal influenza in 2009-2010 showed that children of preschool age and younger were the least involved in the epidemic process of influenza pandemic. However, if in this age category during a seasonal flu, the causes of severe illness were, with the same frequency, pneumonia and bronchitis, during pandemic influenza the disease severity in two thirds of cases was due to pneumonia, mainly in children with uncomplicated premorbid background [1].

In children high susceptibility to influenza and acute respiratory pathogens is due to the absence of any immunologic memory of previous contacts with the pathogens. Due to the immaturity of the immune system no inadequate restoration of the functional characteristics of the immune system happens during repeated acute respiratory viral infections; at the same time the severe impairment of interferon (IFN) determines the severity of the disease, its duration and promotes the development of bronchopulmonary and other complications.

In cases of mass infection, together with a reduced resistance of the organism (which often occurs during the physiological immunodeficiency period in children in the first years of life, or due to defect of the interferon system and cellular immunity), unfavorable environmental conditions, and stress the disease progression is accompanied by suppression of the interferon system, which ensures high efficiency of viral mRNAs translation. This can be illustrated by the influenza infection.

Nonstructural protein of influenza virus NS1 blocks the splicing of pre-mRNA in infected cells and inhibits the nuclear export of cellular RNA into the cytoplasm, which leads to the cessation of synthesis of proteins which are necessary for cell activity. In addition, the influenza virus contains trigger mechanisms of apoptosis, to which the mitochondria are central and are thus turned into a target for another virus-specific genomic protein PB1-F2 - a pathogenecity factor of the influenza A virus [2]. In case of effective viral suppression of protein synthesis and the IFN system, cell death occurs within 20-40 hours after the onset of virus replication. The RS-virus occupies a special place among respiratory viruses in the mechanism of suppression of early cytokine responses and IFN type 1. This virus blocks intracellular signaling from the IFN1 receptors and 2nd types of transcriptional activators into the system of STAT1, 2, which leads to a complete blockage of the signal from the receptors α / β-IFN and does not inhibit signal transduction from the receptor γ-IFN [3].

Thus, the pathogenic viral impact is carried out against interferon, its receptors, IFN-producing cells (including dendritic), IFN signal transduction pathways within cells, transcription factors that ensure the activation of IFN genes and those genes that encode proteins induced by IFN, and provide specific ways to protect cells from viral infection.

Epithelial lung cells respond poorly to viral infection, producing α / β-IFN, interleukins (IL) 1, 6, and tumor necrosis factor (TNF) α at a low level in response to viral impact. This may explain the pulmonary tropism of influenza and other respiratory viruses in the epithelium to the respiratory tract. With the weakness of the protective pulmonary epithelia, monocytes-macrophages of the respiratory tract act as the compensatory mechanism of protection and cytokine production with the alveolar macrophages having the greatest potency. Dendritic cells are responsible for the production of IL 12 acting through the toll-receptors. Dendritic cells are essential to the system's response to viral infection and are a major source of circulating IFN type 1.

With SARS or moderate flu, as the accumulation of viruses in the body tissues increases, so does the induction of IFN, and the non-specific innate immune response inhibits virus replication at early stage at the cellular level, allowing to "win" the time and to activate in a short time the adaptive immune response, which is required to eliminate the infection. There is a critical period in this process. The time span between the growth of the virus titer, the cytotoxic activity of NK-cells, non-specific protection and synthesis of specific antibodies and cytotoxic lymphocytes is very small. Particularly during this period the fate of the infection process is being decided: whether there would be a rapid elimination of the viral agent, or life-threatening complications would develop. With the rapid development of the infectious process the effect of "lag" of the non-specific and specific immune responses in patients with severe inhibition of early cytokine

responses by highly pathogenic viruses is observed; it can also occur in the background of the initial immune deficiency [4].

During the XX century numerous studies were devoted to studying the weakening of immune system in children with recurrent respiratory infections. As a result, it was shown that the most common causes of depression are immune deficiency of immunoglobulin (Ig) A; the slow recovery of the number of T lymphocytes after acute viral infection; decreased chemotaxis of neutrophils and macrophages; cytokine changes leading to increased concentrations of IL-4, 8, 10 and reducing the content of IFN-γ which causes a weak response to the viral invasion of the body [5].

It is known that resistance to infection depends on genetically determined reaction of human immunocompetent cells (ICC) to the production of interferon. The development of an infectious process with acute respiratory infections (ARI) happens in case of an existing deficit of synthesis of interferon and other cytokines, which are humoral products of ICCs. The immune system of children is characterized by high proliferative activity of lymphocytes with the predominance of undifferentiated "naive" lymphocytes, reduced cytotoxic and IFN-producing activity of ICCs [3-6].

76,7-90,0% of the examined patients with pathology, including CHBD, having a burdened allergic anamnesis and / or a chronic foci of infection, have a decreased activity of all indicators of IFN-performance status [6].

One of the major problems in treating influenza and other viral respiratory infections in children is to find the most optimal, effective and safe means of causal, immune modulatory therapy compliable with the child.

Etiotropic drugs should combine the properties of an inhibitor of viral reproduction and an effective stimulator of the immune defense to eliminate the inertia of the specific antiviral immune response in children.

According to the developed criteria, IFN drugs and their inductors are appointed for patients with flu and other ARI, with moderate levels of serum IFN α and γ, as well as with initially low rates of spontaneous production of IFN α and γ, but with a high index of stimulation of IFN-α and γ in immunocompetent cells, in children aged 1 to 6 years, and with an allergy in their history[6].

Two types of prevention, classic and target, are part of the arsenal of preventive measures against frequent respiratory infections.

Classical prevention involves taking immunomodulatory drugs by a healthy patient with the risk of recurrent respiratory infections during the period of maximum epidemic risk (October-March) in order to reduce the possible risk of the disease.

Target prevention, by contrast, involves the use of immune modulators in the acute phase of illness, if necessary, together with antibiotic therapy, in order to shorten the duration of the disease and compensate for the immunosuppression caused by the infection.

Both types of prevention are aimed at reducing the number of respiratory infections; especially classical prevention, which, while preventing from infection beforehand, is demonstrating the best economic effect [7].

Domestic interferon inducer Kagocel (active ingredient - Kagocel) has worked well in a number of experimental and clinical studies in adults and children.

In 2006 in the Ivanovskiy Institute of Virology (Moscow) antiviral activity of kogatsel was studied in cell cultures infected with highly pathogenic influenza A (H5N1) [8]. A little later in the same institute, the FMBA Institute of Immunology (2008-2009), in GOU VPO RGMU Roszdrav on the Department of infectious diseases (2007-2009) studies on the clinical and preventive efficacy in children older than 6 years were carried out. In 2009 its high efficiency was proved in the pandemic of influenza A (H1N1) / California/04/09 [9-12].

In addition, in the course of these investigations it was noted that the new drug is not toxic even when used in the culture of human cells in very high doses [13].
The product is a high molecular compound, synthesized on the basis of sodium salt of carboxyl methylcellulose and a low molecular weight natural polyphenol derived from plants (cotton) through chemical synthesis.

The Russian-made interferon inducer triggers the synthesis of endogenous IFN α and β in close to physiological titres with a peak of activity after 24-48 h, followed by circulation of up to 5 days. Kagocel is an insoluble substance, which acts at the level of the small intestine, is safe, non-toxic, and without side effects [14].

The brand (proprietary) name of the drug is Kagocel (Kagocel) (JSC "NEARMEDIC PLUS", Russia, registration number R № 002027/01-19.11.07). It's available in tablets containing the active substances Kagocel 12 mg. The main mechanism of action of the drug is its ability to induce the so-called late-interferon production (a mixture of α - and β-IFN) in the human body, which has a high antiviral activity. The drug causes the production of interferon in virtually all populations of cells involved in the antiviral response of the body: T-and B lymphocytes, macrophages, granulocytes, fibroblasts, and endothelial cells. After taking in one dose of the antiviral drug, the titre of interferon reaches a maximum after 48 hours in the serum. The body's interferon response on the induction of the drug is characterized by a prolonged (4-5 days) interferon circulation in the blood stream. The dynamics of accumulation of IFN in the gut while taking the drug do not match the dynamics of circulating interferon titers: serum interferon production reaches high values only after 48 h, whereas in the intestine - after 4 hours. Therapeutic doses are not toxic; the drug is not accumulating in the body. It also does not have any mutagenic or teratogenic effects; it doesn't have any carcinogenic or embryotoxic effects. It is removed from the body mainly through the intestines: after 7 days after admission 88% of the administered dose is being removed, 90% in the feces and 10% in the urine. In exhaled air the drug is not detected [7].
The listed properties became the support for the possible use of new antiviral agents for children from 3 years.
The aim of the study was to evaluate the clinical and preventive efficacy and safety of the Russian-made interferon inducer in a blind placebo-controlled comparative study in the presence of flu and other acute respiratory viral infections in children aged 3 to 6 years.
60 children aged 3 to 6 years old, who at the time of admission had clinical signs of acute

respiratory viral infection in the form of stenosing laryngotracheitis with stenosis of the larynx of the 1st (n = 41) and 2nd degree (n = 13); laryngitis with no signs of stenosis (in 6) in 4 children in the form of laryngotracheobronchitis, 2 - with signs of bronchial obstruction, took part in the investigation.

The following patients were excluded from the study: those who participated in other clinical studies over the past 4 weeks, patients with hypersensitivity to any component of the antiviral agent; chronic renal, endocrine, hematological, immune, neurological, psychiatric, cardiovascular diseases or other diseases / conditions , which, according to the doctor's decision, could affect the results of the study; children receiving treatment for any other immune modulators within 28 days preceding the first day of the study.

Patients were randomized into two groups: Group 1 - subjects and Group 2 - control group, 30 children in each group. Children in the groups were comparable according to age, sex and clinical manifestations of SARS.

In group 1 there were 12 girls and 18 boys; laryngeal stenosis of the 1st degree was diagnosed in 19 patients, 3 of whom had it with bronchial obstruction; 2nd degree was found in 7 patients, 4 had only the symptoms of laryngitis without signs of stenosis. 6 patients had a recurrent croup.

Comorbidities were: otitis media (in 4 patients), conjunctivitis (1), goiter (3), asthma (1), and gastroenteritis (1).

Antibiotic therapy was carried out in 11 patients due to otitis and bronchitis of viral and bacterial etiology.

In group 2 there were 12 girls and 18 boys. The manifestations of laryngeal stenosis of the 1st grade was found in 22 patients, one of whom had signs of bronchial obstruction; 6 were diagnosed with 2nd degree; 6 with stenosing laryngotracheobronchitis, 2 with laryngitis without the signs of stenosis, 4 with the recurrent croup.

Comorbidities were: otitis media (4), conjunctivitis (1), goiter (3), reactive pancreatitis (2), and candidiasis (1).

Antibiotic therapy was prescribed for 9 patients due to otitis and bronchitis of viral and bacterial etiology.

Patients in Group 1 received the estimated safe and effective dose (as recommended by the Russian manufacturer) of interferon inducer: 1 tablet twice a day during the first 2 days, then 1 tablet once a day for the next two days. The total dose of the drug had been 72 mg (6 tablets) for 4 days. In order to achieve the therapeutic effect, the drug intake should have been started no later than on the fourth day of the onset of disease.

The 2nd group of patients had been receiving placebo the same way for 4 days.

All groups received full symptomatic treatment (inhalation, cough medicine, nose drops, fever, and desensitizing agents) except antivirals and immune modulators. Broad spectrum antibiotics (cephalosporin and macrolides) were assigned for bronchitis and otitis..

Main clinical symptoms in accordance with the individual patient's card were recorded before taking the drug (day 0) and daily for 5 days, and if necessary, on the 7th and 9th days of treatment. All participants had to undergo a complete blood analysis, urine analysis, and blood chemistry on the 1st (before treatment) and the 5th (after treatment) days.

Virus studies were fulfilled in all patients at entrance of the study before the appointment of therapy, i.e., on the first day (using the polymerase chain reaction, PCR).

Clinical efficacy of the drug was assessed on the basis of frequency and duration of the main

symptoms and the dynamics of laboratory studies. The following parameters were observed: normalization of body temperature , disappearance of intoxication; deadlines of catarrhal symptoms normalization, the onset of dry cough and sputum production, laryngitis , laryngeal stenosis and bronchitis, and the occurrence of complications during the treatment.
Probability of adverse events, changes in red blood cells and neutrophils, elevated liver enzymes evidenced as safety indicators.
The following grades served as antiviral agent's effectiveness criteria:

- «good" - 2-3 days after medicine withdrawal while common condition improved, intoxication and catarrhal symptoms disappeared;
- «satisfactory" – In more than 4-5 days after drug withdrawal common condition improved, the respiratory distress disappeared;
- «no effect" – There has been an absence of dynamics by the 7th day of the illness while patients are receiving the medicine.

The results of the research and discussion

The etiology of the disease was spelled out by using PCR method in 59 (96.7%) patients with parainfluenza-5 (6.8%), influenza B - 31 patients (50.3%), influenza A (H3N2) - 3 (4, 5%), influenza A (H1N1) - 7 (12.4%), influenza A (H1N1 California, 0409 - Pandemic) - 10 (16.8%), adenovirus infection - 12 (19.5%), respiratory syncytial (RS) infection - 7 (12.4%); bocavirus infection - 7 (12.4%); metapneumovirus - 12 (20.3%), Rhinovirus - 3 (4.5%), mixed infection - 26 (43.3%) examined patients and a monoinfection - 33 (56.7%) (Tables 1 and 2).
A characteristic feature of influenza clinics, including pandemic, were: more prolonged fever, symptoms of intoxication, joined acute otitis media; metapneumo- and bocavirus infections (mono-and mixed variants) damaged upper and lower respiratory ways causing the phenomena of laryngobronchial obstruction. The manifestations of conjunctivitis were typical for mono-and mixed versions of the adenovirus infection.
The group of children that was receiving the antiviral agent and symptomatic therapy, the signs of intoxication and fever were brought to a stand by the 4th day of treatment, while the duration of the fever in this group was on average 2,5±0,4 day. In the control group receiving placebo, in 17 patients (56.7%) intoxication symptoms persisted until the 5th day of therapy, with an average duration 2,75 ± 0,2, and fever - 2,8 ± 0,3 days (Table. 3).

The persistence of catarrhal symptoms was significantly shorter in the main group as compared to the placebo group, which on average drew up to 4,2 ± 0,2 vs. 5,9 ± 0,3 days ($p \leq 0,001$), respectively (see Table 3).
Dry cough disappearance rate and the rate of sputum production varied significantly; the symptoms of laryngitis, laryngeal stenosis disappeared more rapidly in Group 1. In patients taking antiviral drug, dry cough disappeared significantly faster in comparison with patients receiving placebo (4,4 ± 0,1 vs. 5,4 ± 0,3 days, $p < 0.001$, see Table. 3).
The therapy with Kagocel decreased the number of hospital days spent by children in the hospital and formed about 4, 7 ± 0, 3 vs. 6, 3 ± 0, 3 days ($p < 0.001$) in the placebo group (see Table 3).
The influence of the tested drug compared to the placebo on antibiotics in the treatment against otitis and bronchitis are shown in Table 4, showing authentic shortening deadlines of antibiotics in patients receiving domestic interferon inducer compared with children in the placebo group.
The results of therapeutic efficacy are presented in Fig. 3. There was no significant relation

between the rate of flu and SARS relieves with mono or mixed etiology and an antiviral drug.

In the course of treatment all patients tolerated drug well, side effects were not fixed, as confirmed by the absence of negative changes in the status of patients, peripheral blood, blood chemistry and general urinalysis checked during follow-up.

Thus, the example of antiviral drugs effectiveness is able to show its impact on the infection process of different etiological variants of SARS in children from 3 years old occurring with a syndrome of larynx obstruction, indicating the source of immunopathology in a deficit of interferon and cytokines, with a shift in T cell immunity toward Th2-type response, as well as deficits in the system of mononuclear phagocytes [15].

In children older than 3 years old the flu and SARS prevention before an outbreak comes with the estimated safe and effective dose of domestic interferon inducer according to manufacture recommendation which is 1 tablet a day, once in the first 2 days, 5 days off (7-day cycle), and then rehearsal of cycle. Endurance of preventive course lasts from one week to several months. The drug is well combined with other antiviral agents, immune modulators, and antibiotics (additive effect).

To assess the preventive efficacy and safety of the new domestic inducer of interferon, we conducted another study that included 100 children 3 to 6 years old, receiving Kagocel whereby 50 patients out of 100 were in a study group while the rest 50 were in placebo (control group). In the group of children who received the studied medication was 30 (60%) of children aged 3 to 5 years, 20 (40%) - aged 5-6 years. In the group of children who received a placebo - 33 (66%) of children aged 3 to 5 years, 17 (34%) - aged 5-6 years. Early departure from studied patients was not registered in both groups.

All children included in the study suffered from recurrent bacterial and viral upper respiratory tract infections (at least 6 times over the previous year).

In the main group children were observed with the following concomitant diseases: 10 with chronic tonsillitis, 7 with atopic dermatitis, 9 with adenoiditis, 5 with urinary tract infection, 1 with recurrent obstructive bronchitis, 1 with angiomatosis of larynx, 1 with Epstein-Barr virus infection, 1 with reactive pancreatitis, 3 with intestinal misbalance, 1 with gastroduodenitis, 8 with food allergies, 3 with biliary dyskinesia, and 2 with bronchial asthma.

In the comparison group a number of patients had: 11- chronic tonsillitis, 5 - atopic dermatitis, 9- adenoiditis, 3 - urinary tract infection, 7 - recurrent bronchitis, 8 - recurrent croup, 5 - biliary dyskinesia, 2 - chronic gastritis, 1 - reactive pancreatitis, 1 - gastritis, 2 - dysbiosis, 5 - food allergies, and 2 – hypertensive hydrocephalic syndrome.

In the study group during the 4 weeks of preventive drug administration 9 children (18%) suffered from SARS once. Among them the disease was mild in 6 (66.7%), moderately - in 3 (33.3%) patients occurring with complications: viral and bacterial conjunctivitis - in 1, bronchitis - in 1, acute otitis media - in 1 patient; which was an indication for antibiotic therapy (Table 5). In the comparison group SARS had been registered in 21 (42%) children, 17 (34%) of them had had one episode of illness, and 4 (8%) had 2 or more episodes of the disease for 4 weeks. Total 25 cases of the disease were fixed with 10 complicated by bacterial infection.

Mild form of acute respiratory viral infections was in 15 (60%) cases of the disease and moderately - in 10 (40%). 10 children with viral respiratory infections had a bacterial infection (3-bronchitis adenoiditis, 3-tonsil pharyngitis, 4-otitis adenoiditis), therapy of which was carried out with broad-spectrum antibiotics.

All patients, regardless of the observed group, were receiving symptomatic treatment of SARS (medicine for cough, nasal drops, fever, and desensitization means Erespal, etc.) except for

immune modulators.
Studies indicate that during the 4-week course of preventive medication, the number of children suffering from SARS decreased to 2.3, and the frequency of episodes was 2.8 times less in comparison with the same parameters in the comparison group. The index of the effectiveness of taking antiviral was 2.8 and the coefficient of efficiency - 64% (see Table. 5).
Over the next 4 months of children supervising, 38 patients from the study group suffered from ARI (76%); 25 (50%) once, and 13 (26%) - recurrent.
55 cases of the disease were registered in total. 46 of the last had mild form (83.6%), 9 moderate (16.3%) with the following complications: 1-adenoiditis, 4-bronchitis, 2-acute otitis media, 1-laryngotracheitis, 1-tonsillopharyngitis, treated by antibiotic therapy (Table 6).
In the comparison group ARI were recorded in 49 (98%) children, one episode was in 6 (12%) children, and 2 or more illnesses were in 43 (86%). Total was 132 cases of the disease (18 of them were complicated by bacterial infection).
Mild form was in 114 (86.3%) cases of the disease, and moderately - in 18 (13.6%). In 18 children acute respiratory viral infection were complicated by bacterial infection (bronchitis adenoiditis - 8, tonsils pharyngitis-2, otitis adenoiditis -7, laryngotracheitis - 1); the therapy was complied with broad-spectrum antibiotics (see Table. 6).
The number of mild SARS cases in the study group was 2.5 times lower and moderate forms of the disease were 2 times less than in the comparison group.
Application of Kagocel didn't cause any single case of side or adverse events. The drug was well tolerated by children.
Thus, the studies found that use of the drug Kagocel for prevention of influenza and other acute respiratory infections in children aged 3 to 6 years old with frequently recurrent bacterial and viral upper respiratory tract infections (at least 6 times over the previous year) was effective.

Conclusions:

1. The therapy of Kagocel significantly reduced the duration of intoxication symptoms, fever, catarrhal symptoms in the nasal-oropharynx, and the main symptoms of stenosing laryngotracheitis (bronchitis) in children 3 years old with SARS and flu, regardless of the etiology and clinical manifestations of disease.
2. The interferon inducer didn't cause any side effects in children.
3. The drug is well tolerated by 3 years old children, reduces the period of antibiotic therapy, hospital stay and can be recommended for use in pediatric patients for the treatment of influenza and SARS in the early stages of the disease in children from 3 years old.
4. The drug is recommended for prevention of influenza and other acute respiratory diseases, regardless of their cause in children from 3 years old.
5. Receiving the drug as a preventive measure contributes to a significant reduction in the incidence of SARS in sick children.
6. The data obtained allow recommending the prescribing the drug into prevention programs of immune rehabilitation of SARS in frequently ill children from the age of 3.

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Table 1.Varianty combinations of mixed infections in children aged 3 to 6 years who received Kagocel (n = 14)

Etiology	**Number of patients**
Bocavirus+ RS virus	1
Adenovirus+metapneumovirus	1
RS virus + metapneumovirus (2)	2
Adenovirus+ rhinovirus	1
Adenovirus+ RS virus	1
Adenovirus+ Bocavirus	1
H1N1 influenza virus, adenovirus	1
H1N1 influenza virus +B	1
H1N1 influenza virus +H3N2	1
The flu B virus+ Parainfluenza B	1
H1N1 influenza virus+ Parainfluenza	1
Adenovirus +Para flu	1
Metapneumovirus + rhinovirus	1

Table 2.Diverse combinations of mixed infections in children aged 3 to 6 years who received placebo (n = 12)

Etiology	**Number of patients**
Influenza viruses AN3N2 + B	1
H3N2 influenza virus+ adenovirus	1
Metapneumovirus + RS virus	1
Adenovirus+ RS virus	1
The flu virus + meta pneumonia virus B	1
Adenovirus + RS virus	1
Metapneumovirus + rhinovirus	1
Bocavirus + rhinovirus	1
Flue Virus H1N1 + + adenovirus+ Parainfluenza	1
Flue virus H1N1 + H3N2	1
Bocavirus + rhinovirus	1
Influenza A H1N1 + adenovirus	1

Table 3: The continuation of SARS symptoms while treated with Kagotsel and Placebo in children 3-6 years old (n=40)

Symptoms:	Continuation in days	
	Kagosel + symptomatic therapy	Placebo + symptomatic therapy
Fever	1,7 ± 0,4*	2,8 ± 0,3
Intoxication	1,3 ± 0,4	2,75 ± 0,2
Catarrhal conditions	4,2 ± 0,2**	5,9 ± 0,3
Dry cough	4,4 ± 0,3**	5,4 ± 0,3
Laryngitis	3,2 ± 0,1**	5,2 ± 0,2
Stenosis of larynx	1,8 ± 0,4	2,4 ± 0,2
Number of bed days	4,7 ± 0,3**	6,3 ± 0,3

*Differences are significant * — $p < 0,05$; ** — $p < 0,001$

Table 4. The continuation of SARS symptoms while treated with Kagotsel and Placebo in children taking antibiotics 3-6 years old (n=20)

Symptoms:	Continuation in days	
	Kagosel + symptomatic therapy	Placebo + symptomatic therapy
Fever	2,9 ± 0,6*	4,3 ± 0,3
Intoxication	3,8 ± 0,3	5 ± 0,7
Catarrhal conditions	5,7 ± 0,4*	6,9 ± 0,5
Dry cough	5,7 ± 0,3*	6,8 ± 0,4
Laryngitis	3,0 ± 0,2**	4,8 ± 0,3
Stenosis of larynx	2,4 ± 0,1**	3,2 ± 0,2
Number of bed days	6,1 ± 0,3*	7,3 ± 0,4

*Differences are significant * — $p < 0,05$; ** — $p < 0,001$

Table 5. Performance indicators of the study drug for the prevention of influenza and other viral respiratory infections in children aged 3 to 6 years during a 4-week course

Indicators	Main group **n=50**	**Comparison group** **n=50**
Children's age 3−5 years old 5−6 years old	 30 20	 33 17
Frequency of event (illness)	 9*	 21
The incidence of the disease	9*	25
The number of children that experienced SARS: once multiple	9 9* -	21 17 4
Index of efficiency	I=P2:P1 I=25:9=2,77	
Coefficient of efficiency	E=(P2-P1): P2×100 E= (25-9):25×100=64%	
The severity of flow of SARS: Light moderate	 6 3	 15 10
Number of complications	3	10
Complications of SARS: viral and bacterial conjunctivitis Acute Bronchitis otitis media tonsillopharyngitis	 1 1 1 -	 - +Adenoiditis in 3 +Adenoiditis in 4 3

Notice * - Differences are significant ($p < 0.001$).

Table 6 Performance indicators of the study drug for the prevention of influenza and other viral respiratory infections in children aged 3 to 6 years in 4 months after treatment

Indicators	Main group, **n=50**	**Comparison group, n=50**
Frequency of event (illness)	38*	49
The incidence of the disease	55*	132
The number of children that experienced SARS: once multiple	38 25* 13*	49 6 43
Index of efficiency	I=P2:P1 I=132:55=2,4	
Coefficient of efficiency	E=(P2-P1): P2×100 E= (132-55):132×100=58%	
The severity of flow of SARS: Light moderate	 46* 9*	 114 18
Number of complications	9	18
Complications of SARS: Acute Bronchitis otitis media prolonged tonsillopharyngitis adenoiditis	 1 4 2 1 1	 - +adenoiditis in 8 +adenoiditis in 7 1 2

Notice * - Differences are significant ($p < 0.001$)