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Immunoflazid in pediatrics: a systematic analysis of the effectiveness and safety of using

Resume

Based on the results of 12 clinical trials involving more than 800 children, conducted a systematic analysis of the efficacy and safety of domestic drug Immunoflazidum for the treatment of viral and viral-bacterial infections in children of different age groups on the background suppression of the immune system. Analyzed in this work, scientific publications support the clinical efficacy and good safety profile syrup Immunoflazidum when assigning children with therapeutic and prophy-lactic purposes.

Keywords: Immunoflazidum, flavonoids, children, spreading of respiratory desists, flu, immune system, clinical research.

Acute respiratory viral infections (ARVI), including influenza, are the most common infectious pathology of childhood, accounting for up to 90% of all infectious diseases. The cause of acute respiratory viral infections is more than 300 different types of viruses. High prevalence of acute respiratory viral infection is caused by a significant variety of pathogens: influenza (A, B, C), parainfluenza, adeno, respiratory syncytial, rhino, entero-and other viruses [1]. In addition to the direct etiologic causes of acute respiratory viral infection, a number of factors should be noted that contribute to the development of repeated episodes of respiratory infection in children, including an adverse premorbid background, perinatal lesions of the central nervous system, intrauterine infection, immaturity, prematurity, etc., which adversely affect the condition of all the systems of the developing body and, in particular, the full-fledged formation of immunity [2].

It is proved that the maturation and development of the immune system occurs during the entire period of childhood, in connection with which the so-called "critical" periods are distinguished characterized by its functioning features. Critical is the period of neonatality (infant's body is protected almost exclusively by maternal antibodies obtained through the placenta and breast milk); 4-6 months of life, when the child has a sharp decrease in the level of antibodies received from the mother; 2nd year of life (contacts of the child with the outside world and the causative agents of infection are significantly expanding); 6-7th years of life (low absolute and relative quantity of lymphocytes in the blood of the child, the level of immunoglobulin A, levels of immunoglobulins M and G in the blood are close to normal, the maximum content of immunoglobulin E) (Fig. 1); adolescence, when the growth spurt is combined with a relative decrease in the mass of lymphoid organs [3].

Among newborns, the group of high risk of infectious diseases is attributed to premature infants, as well as children born with low and extremely low body weight. They have a pronounced immaturity of the immune system.

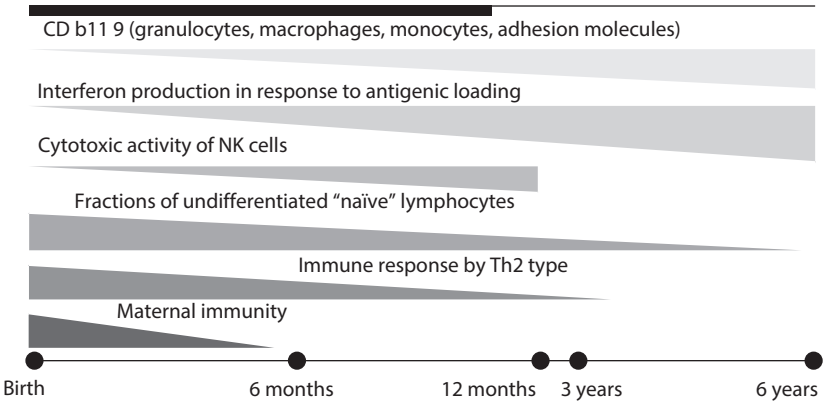

Fig. 1. Formation of anti-infectious protection in children

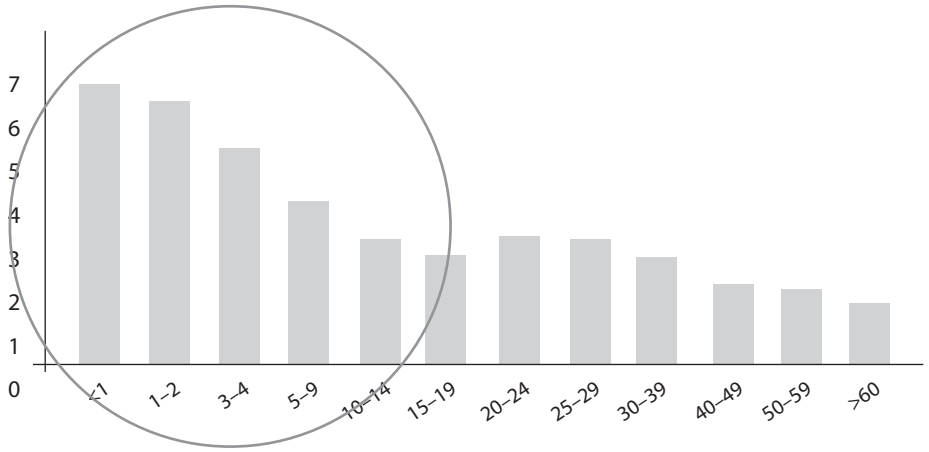

Fig. 2. The average incidence of respiratory infections per year, depending on the age of the patient (Heikkinen et al., 2003)

The second "critical" period is characterized by a weak synthesis of only immunoglobulins M and a lack of local protection of the mucous membranes in connection with the later accumulation of secretory immunoglobulin A. At the age of 1 to 6 years, a group of children of "late immunologically starting" is distinguished, characterized by recurrent acute respiratory viral infections. According to data from cohort studies conducted by Finnish scientists (Figure 2), it is precisely the age of 1-6 years that is characterized by the highest incidence of recurrent, up to 5-7 times per year. In terms of physiology it is reasonable, because in the presence of a large number of contacts of the child with infectious agents, frequent episodes of ARVI constitute the "price" that the child "pays" for the full maturation of the immune system. Thus, the age from 6 months until 6 years is characterized by an increased sensitivity of the child to ARVI and is a feature of its ontogeny. However, in the presence of a protracted and complicated course of acute respiratory viral infection, the immune system and, consequently, the mechanisms of anti-infective protection are inadequate when "the viruses give a sentence and bacteria execute it" [4].

It should be noted that clinical and laboratory markers of immunological "insolvency" in such children is a high incidence of recurrence of acute respiratory viral infection (more than 6 times per year) with prolonged or complicated course; a weak but long-term temperature reaction (prolonged subfebrile condition); low effectiveness of traditional treatment; presence of foci of chronic ENT organs infection; persistent leukopenia, neutrocytopenia, lymphocytopenia or unmotivated lymphocytosis; low ESR in the acute period of the disease, especially with bacterial infections. Immunological markers of infringements of anti-infectious protection include: deficiency of IgA (sIgA) and factors of cellular-mediated immunity; decreased activity of phagocytosis, NK and chemotaxis of neutrophils; insufficient synthesis of interferons.

Under the conditions of inflammatory process in ARVI an increased formation is observed of active forms of oxygen, ensuring bactericidal neutrophils, development of oxidative stress, which subsequently leads to depletion of the antioxidant system and cascade-like damage to the membranes of cells not only of the affected organ but also of the immune system [5]. Therefore, in addition to traditional methods of treatment and rehabilitation of ill children, it is often necessary to designate means that affect immunity and provide antioxidant action.

For a long period of time the world has been studying the antiviral, antioxidant and immunomodulating properties of flavonoids. Flavonoids are a group of natural biologically active compounds – benzopyrone derivatives, which are based on a phenylpropane skeleton consisting of C6-C3-C6 carbon units with an oxygen atom in a heterocyclic ring. Depending on the degree of oxidation and hydroxylation of the propane skeleton and the location of the phenyl radical, flavonoids are divided into several groups: flavones (chrysin, apigenin), isoflavones, flavonols, flavonones and flavononols.

Based on the results of experimental studies and clinical trials, the effectiveness has been proved of flavonoids in the prevention of respiratory, immune, oncological, neurodegenerative, cardiovascular and a number of other diseases.

Flavonoids are predominantly poorly soluble in water, able to accumulate in the lipid layer of the biological membranes. The mechanism of action of most flavonoids is explained by the interaction with various receptors and effect on their functioning. The flavonoids have an antioxidant effect through changing the cellular metabolism.

Recent studies suggest that complexes of flavonoids with transition metal cations participate in the formation of molecular assemblies, facilitate membrane adhesion, and fusion, protein-protein and protein-membrane binding, and other processes responsible for the regulation of cellular metabolism and protection against harmful environmental effects [6].

For the past 10 years, the effectiveness and safety of the domestic antiviral drug from the group of bioflavonoids – the Immunoflazid syrup ("SMC"Ecopharm", Ltd., Kyiv) has been actively studied. 100 ml of syrup contain 2 ml of the liquid extract of Proteflazid, obtained from the mixture (1:1) of tufted hair grass (Deschampsia cespitosa L.) and bush grass (Herba Calamagrostis epigeios L.). 1 ml of the extract contains at least 0.32 mg/ml of flavonoids in terms of rutin. Flavonoids, which are part of Immunoflazid, belong to the groups of flavone and flavonol glycosides.

Herba Deschampsia cespitosa L. and Herbaria Calamagrostis epigeios L. are native plants that are harvested in the clean ecological zones of Volyn, Ivano-Frankivsk, Lvov, and Zakarpattya oblasts (the purity of ecological zones is determined by the investigation of soils for the presence of herbicides, pesticides, and radiological pollution).

Table 1
Dosage regimen (ml) and frequency

Patient age (years)	Dosage regimen (ml) and frequency
from birth up to one year	0,5 ml BID
1-2 years	1 ml BID
2-4 years	3 ml BID
4-6 years	4 ml BID
6-9 years	5 ml BID
9-12 years	6 ml BID
over 12 years	9 ml BID

Vegetable raw materials are harvested in accordance with the GMP rules with the formulation of sanitary and hygienic certificates for each batch. The collection of raw materials is determined by the dynamics of replenishment of active substances during the vegetative period.

Extraction is carried out with no chemical and biological factors and with no use of intensive extraction methods (high-temperature extraction, extraction under pressure, extraction with CO2), but static trial maceration method.

Immunoflazid, having a high safety profile, is allowed for use in children from birth. Table 1 shows the dosing regimen of the syrup Immunoflazid for children, depending on age.

It has been proved that the flavonoids as part of Immunoflazid inhibit the replication of DNA and RNA of respiratory viruses, including influenza, both in vitro and in vivo. The mechanism of antiviral action of the drug is in the inhibition of virus-specific enzymes of DNA polymerase, thymidine kinase and reverse transcriptase; anti-influenza action – suppression of neuraminidase activity, induction of the synthesis of endogenous α- and y-interferons, inhibition of the synthesis of RNA viruses. By strengthening the effect of apoptosis-inducing substances the drug promotes faster elimination of virus-infected cells and prevention of chronic diseases against the background of latent viral infections.

In 2010, studies were conducted on the efficacy of flavonoids against a pandemic pathogen of influenza A on the model of influenza pneumonia in animals. The results of the study showed that the drug reduces 250-fold the infectious titre of the influenza virus (H1 F/California) in the lung tissue of infected animals [7].

The results of clinical studies have shown that under conditions of prolonged daily use of Immunoflazid, there is no inhibition of the activity of formation of IFN-α and -y, which normalizes the patient's immune status [8, 9, 28].

Immunoflazid protects the mucous membranes of the upper respiratory tract, normalizing the indices of local immunity (lactoferrin, sIgA and lysozyme); enhances the antioxidant status of cells by inhibiting free radical processes, which prevents accumulation of lipid peroxidation products, reduces intoxication, promotes recovery of the organism after the infection and adaptation to adverse factors surrounding the environment [9].

We analyzed the results of studies with drugs containing flavonoids, which are part of the Immunoflazid syrup, as active substances, in 12 clinical trials (including 10 randomized) in children. In total, the study involved more than 800 children who received flavonoids for therapeutic or prophylactic purposes (Table 2).

The preventive efficacy of Immunoflazid in influenza and ARVI was studied in 220 children aged from 1 to 6 years attending an organized children's group. Observed children were divided into two groups of 110 persons each [2]. The 14-day prophylactic course of Immunoflazid during seasonal morbidity allowed to reduce the incidence of acute respiratory viral infection in the main group of children by 2.2 times ($p < 0.05$). Diseases in children of the main group proceeded without complications. The number of absences in children's institution due to ARVI per child in the main group, decreased by 35%, i.e. almost by 2 days.

According to the results of the clinical study [10], the use of flavonoids for prophylactic purposes in children of middle and older groups of the kindergarten – residents of a large industrial center, makes it possible to reduce the incidence of ARVI by 1/3.

Analysis of the incidence of ARVI in the group of young children who received Immunoflazid with a prophylactic course compared to the control group showed that during the first week 6 (22.2%) patients had ARVI developed in the main group and 14 (56.0%) in the control group. In the main group the severe course of the disease was noted 2 times less than in the control group and 3 times shorter (on average 3.3 ± 0.7 days versus 9.7 ± 1.6 days) – duration [11].

Another study found that 67% of patients receiving Immunoflazid did not have influenza and ARVI developed during the epidemic period, and among children with a disease developed the children with mild and abortive forms of pathology without complications prevailed [12].

In young children with severe complications of acute respiratory viral infection who received additional treatment with Immunoflazid [1, 13], the serum level of thymulin increased by 53.6% ($p < 0.05$), while in the control group it decreased by 32.3% ($p < 0.05$). Children of the main group had normalized CD + lymphocytes (CD3 +, CD4 +, CD8 +, CD16 +) and immunoregulatory index CD4/CD8. Thus, the level of CD4 + T-helpers in the main group increased from $35.1 \pm 1.2\%$ to $42.7 \pm 1.2\%$ ($p < 0.05$). Also after the administration of Immunoflazid a significant increase in the cell-phagocyte defense coefficient and a decrease in the specific immune lymphocyte-monocyte potential (from 0.598 ± 0.05 to 0.701 ± 0.03 and from 0.832 ± 0.04 to 0.541 ± 0.05, respectively) <0.05), whereas in the control group no positive changes were noted.

In patients of the main group, in comparison with the control group, the length of stay in the hospital decreased 1.5-fold (6.02 ± 0.5 days vs 12.6 ± 0.7 days, $p < 0.05$); the disease progression was mild, temperature period was 2 times shorter (4.1 ± 0.6 days vs 8.7 ± 0.7 days, $p < 0.05$); symptoms of intoxication were less pronounced and resolved 2 times faster (4.6 ± 0.3 days vs 10.6 ± 0.7 days, $p < 0.05$) [1, 13].

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Source	Study subjects	Purpose	Efficacy	Tolerability
Yulish EI, Soroka Yu.A. et al. , 2009 [7]	110 children at the age of 1-6 years	Prevention of ARVI	Reduction in the incidence of ARVI in 2,2 times, absence of complications, a decrease of 35% in admissions of children's institutions	Good
Reznichenko Yu.G. et al. , 2008 [8]	30 children of preschool age	Prevention of ARVI	On 1/3 the incidence of preschool children in ARVI decreases	Good
Yulish E.I., Balychevtseva I.V. et al. , 2009 [9]	55 young children	Treatment and prevention of ARVI	Reduction in the incidence of 2.3 times, a decrease of 3 times the duration of the disease, the absence of its severe course	Good
Nazarenko V.I., Ovchinnikova N.M., 2009 [10]	218 children	Treatment and prevention of ARVI	67% did not fall ill during the epidemic period. Patients with abortive or mild form, without complications	Good
Tokarchuk NI, Starinets L.S., 2012 [11, 12]	25 young children	Treatment of ARVI	An increase of 53.6% in the level of thymulin, the coefficient of phagocyte protection. A 1.5-fold reduction in the length of stay in a hospital, a 2-fold duration of fever and intoxication	Good
Sichnenko P.I. et al., 2008 [13]	120 young children	Treatment of ARVI	Against the background of the therapy with Immunoflazid, a positive clinical effect was revealed in 90% of sick children	Good
Yulish E.I., Yaroshenko S.Ya., 2013 [14]	65 young children	Prevention of acute respiratory distress syndrome in frequently and long-term sick children with herpes virus infection	Reducing the incidence of ARVI during the year by 1.5 times (hereinafter 3 times), complications - 1.4 times, reducing the duration of the episode of the disease by 1.5 times	Good
Prokhorova M.P. et al., 2008 [16]	35 children at the age of 2-7 years	Treatment of ARVI with obstructive syndrome	Positive immunological dynamics, recovery came on the 5th day.	Good
Tokarchuk N.I. et al., 2011 [17, 18]	25 young children	Treatment of non-hospital pneumonia against a background of herpes-virus infection	The shortening was 6.6 ± 1.3 days. Length of hospital stay	Good
Tsimbalista O.L., Garidzhuk L.I., 2011 [19]	40 young children	Treatment of children with complicated pneumonia on the background of iron deficiency anemia	The level of proinflammatory cytokines decreased 2-6 times	Good
Mozar' V.V. et al., 2011 [20]	30 young children	Protein-energy insufficiency	The weight gain in the group of children receiving Immunoflazid is 2 times greater than in the comparison group	Good
Godovanets O.I., Rozhko M.M., 2007 [21]	48 young children	Prophylaxis and treatment of chronic catarrhal gingivitis in children living in nitrate contamination	In 2-3 times the intensity of clinical manifestations decreased, the probability of recurrence of the disease decreased 2 times	Good

With the inclusion of Immunoflazid into the complex treatment of young children with ARVI, a good clinical effect was noted in 90% of children – a decrease in respiratory symptoms, the temperature was steadily normalized by day 2-3 after drug administration. The average duration of treatment for children with ARVI was 6.5 days. At the end of the first week of treatment, signs of intoxication were noted in 2 patients only, but their general condition improved. Clinical manifestations of rhinitis, rhinopharyngitis decreased in all children observed; a rare productive cough remained only in 7% of children [14].

High antiviral efficacy of flavonoids was observed in treatment of 65 patients with recurrent respiratory diseases. According to the results of a 3-month course of therapy, they had an almost 1.5-fold decrease in the incidence of ARVI during the year and 1.4-fold decrease in the incidence of complications. In a year, along with the normalization of immunity indices, the incidence of ARVI was reduced by almost 3 times, their complications by 35%, and duration of the episode was reduced 1.5-fold. The authors substantiate the necessity of conducting a repeated course of complex etiopathogenetic therapy 2 times a year with a 6-month break [15].

The results of the flavonoids use indicate signs of activation of antiviral immunity, which is confirmed by an increase in the level of interferon-α after the course of therapy (from 10.25 ± 1.26 pg/ml to 39.89 ± 5.24 pg/ml, $p < 0.001$). The decrease in the activity of inflammation is confirmed by a decrease in the indices of proinflammatory cytokines, in particular TNF (from 84.37 ± 28.61 pg/ml to 4.20 ± 2.90 pg/ml, $p < 0.001$), which indirectly indicates a decrease in the antigen load due to inhibition of virus replication. The decrease in the concentration of IL-2 (from 187.34 ± 58.41 pg/ml to 28.17 ± 15.12 pg/ml, $p < 0.001$) and IL-6 (from 24.85 ± 4.65 pg/ml to 16.09 ± 8.45 pg/ml, $p < 0.001$) indicated the cytokine balance recovery and a decrease in the activity of inflammation. The normalization of the level of anti-inflammatory IL-4 (from 54.18 ± 13.25 pg/ml to 14.35 ± 7.98 pg/ml, $p < 0,001$) also, according to the authors, indicates the achievement of relative cytokine balance and remission of the inflammatory process, which from a smoldering (characteristic for the persistence of infection) acquires the features of acute, indicative of an adequate immune response to foreign agents [9].

The use of flavonoids (Immunoflazid) in 35 children aged 2 to 7 years with ARVI and bronchial obstructive syndrome showed a significant increase in the blood levels of CD4 +, CD8 +, CD16 + against the background of a decrease in CD22 + and IgG, IgM levels [16].

In non-hospital pneumonia in infants, the inclusion of Immunoflazid into complex treatment led to a decrease by 6.6 ± 1.3 days of hospital stay in patients compared with patients receiving only basic therapy [17, 18]. The use of Immunoflazid in combination with the standard treatment of complicated pneumonia against the background of iron deficiency anemia (IDA) contributed to a decrease in the proinflammatory cytokines blood count of patients: TNF (2.2-2.6 times); IL 6 (1.6-2.0 times) [19].

In the group of young children who were hospitalized for protein-energy deficiency caused by intrauterine infection, which inhibits the function of the thymus gland, lymphocytes and spleen, after 2 weeks of therapy with the inclusion of the drug Immunoflazid at the usual dose, the weight gain of more than 400.0 g was noted in 80% of patients, whereas in the comparison group – only in 43.3%. In 90% of children in the main group, the IgA blood level was normalized, while in the control group this value is 36.6% [20].

An increase was observed in the activity of the antioxidant defence system in cells of the oral mucosa and acceleration of the reverse development of clinical manifestations of chronic catarrhal gingivitis (HCG) after administration of Immunoflazid in infants [21-24]. The levels of diene conjugates and malonic dialdehyde in children of the main group with mild and moderate HCG were 12.5-11.1% and 19-24.6% lower, respectively, than in the comparison group. The activity of the antioxidant catalase enzyme in mild HCG was 30.8%, and at an average 47.2% higher in the observation group than in the control group. The level of HS-groups and glutathione was significantly higher after treatment in children of the main group vs patients of the comparison group (by 62.2% and 54.8% with mild HCG and 67.1% and 66.0% with moderate HCG), which was also reflected in the activity of glutathione-dependent enzymes: activity of glutathione reductase and glutathione transferase in the observation group was 40.2% and 67.7% higher for mild and 56.1% and 82.9% for moderate disease compared with the control.

After 1 month, in mild HCG, on days 2-3 of treatment a significant clinical improvement was observed and resolved signs of inflammation (the average duration of local treatment was 4.30 ± 0.26 days compared to 6.30 ± 0.23 days in the control); in moderate disease in children of the main group the hyperemia, edema and bleeding regressed from day 3-4 of treatment, and adjustment duration was 6.20 ± 0.21 days vs 9.30 ± 0.51 days with traditional treatment. Clinical examination of children after the course of therapy (14 days) showed complete elimination of the pathological process in the gums against the background of flavonoids use. In the comparison group, signs of inflammation persisted in 75.0% of children with mild and 100.0% of children with moderate disease.

After 1 month, in mild HCG in children of the main group, a recurrence was observed of the disease without bleeding gums in 41.7%, and in moderate disease – 50.0%. In the comparison group, recurrence of HCG was noted in 100.0% of children examined. The course of therapy with flavonoids reduced 2-3-fold the intensity of clinical manifestations with recurrence after 6-month follow-up in children with mild and moderate HCG, respectively.

For treatment of viral diarrhea Immunoflazid is used for 2 weeks. In case of bacterial complications, in order to bring to normal the immune system parameters, the drug is used for up to 4 weeks. For the prevention of viral diarrhea, for example, during the summer period or during an increased incidence of viral diarrhea, Immunoflazid is used 2 to 4 weeks at a dose corresponding to half the treatment dose [25].

Complex treatment of children with recurrent respiratory pathology, which included Immunoflazid, harmonizing adaptive reactions and improving the functions of the epithelial system reduces 7-fold the incidence and duration of ARVI in children [26].

Immunoflazid was studies in numerous clinical studies, the results of which are partially presented in a review of the literature prepared by N.P. Glyadelova [27]. The scientific publications analyzed in this work demonstrate the good clinical effectiveness of Immunoflazid and other medications containing similar flavonoids (Proteflazid, Flavozid) and high safety profile in prescribing them to children with a curative and prophylactic purpose in ARVI.

CONCLUSION

Immunoflazid syrup in the usual therapeutic doses has a direct antiviral effect and causes an immune modulating effect, reduces the level of pro-inflammatory cytokines, stimulates T-helper activity, increases the level of nonspecific defence, reduces the development of oxidative stress. The high efficiency of repeated courses of Immunoflazid therapy has been demonstrated in recurrent viral infections.

In the preventive use of syrup, Immunoflazid reduces the incidence of preschool children with influenza and ARVI by 1/3, minimizes by 35% the number of days passed by children in educational institutions, reduces 2.2-2.3-fold the incidence of ARVI in children, prevents the development of severe disease. When Immunoflazid is included into the treatment regimen, patients with severe acute respiratory viral infection and pneumonia have admission period reduced by 6.6 days and 2-fold decrease in the duration of intoxication and fever. Significant acceleration of condition improvement was noted with Immunoflazid included into the complex of treatment for children with protein-energy deficiency and chronic catarrhal gingivitis.

It is necessary to note the high profile of Immunoflazid syrup safety in children at a long-term daily use [8, 9, 28].

The therapeutic effect of Immunoflazid allows recommending it for widespread use in children with influenza and ARVI. Immunoflazid meets in full the requirements of prevention and treatment of ARVI in children [1, 13].

The results of all studies presented show that Immunoflazid syrup was well tolerated by patients with good compliance.

Thus, a systematic analysis of clinical trials (involving more than 800 children) demonstrate the efficacy and high safety profile of herbal medicinal product – Immunoflazid syrup for the prevention and treatment of influenza and ARVI, and their complications in children of different age groups and provides grounds to recommend it for extensive use.

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