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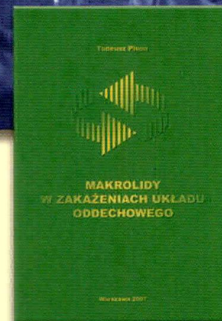
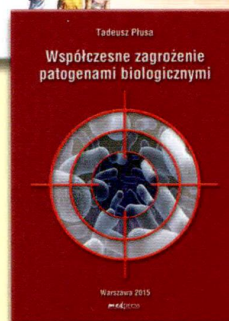
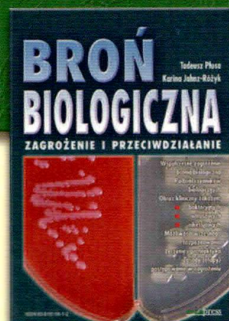
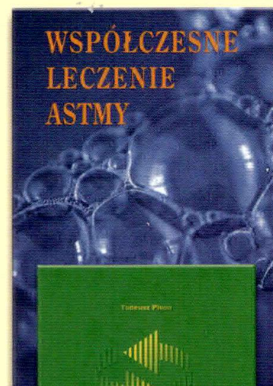
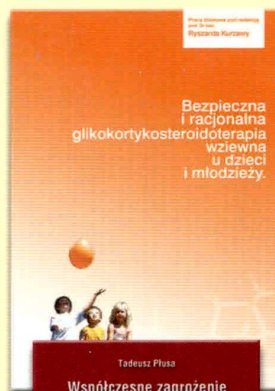
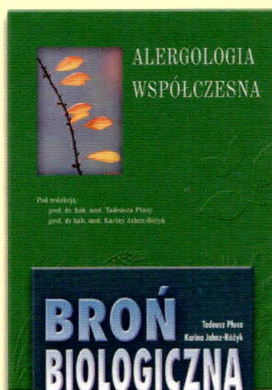
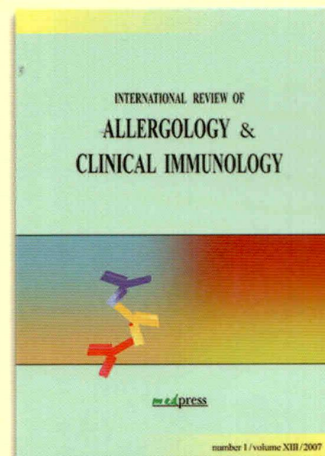
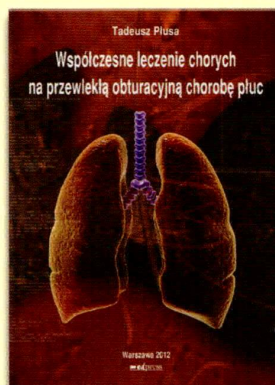
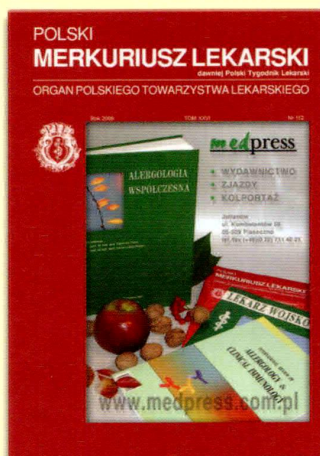
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Proteflazid®: Clinical experience in children of young and preschool age – systematic review of postmarketing surveillance

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Proteflazid®: Clinical experience in children of young and preschool age – systematic review of postmarketing surveillance

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Scientific literature data on the experience of use of Proteflazid® (drops) and Immunoflazid® (syrup) for the treatment of viral diseases in children of the first six years of life are analysed in the article. A systematic review was conducted on the basis of postmarketing comparative clinical trials and long-term follow-up (during the period of 2002 to 2016) that involved about 1500 children (the intent-to-treat population comprised more than 800 of them). The safety and efficacy of the Proteflazid® (drops) and Immunoflazid® (syrup) usage in children for the treatment of viral infections have been proven.

Key words: Proteflazid®, Immunoflazid®, herpetic infections, ARVI, treatment, children

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Proteflazid®: próby klinicznego zażywania przez niemowlęta i dzieci w wieku przedszkolnym – przegląd systematyczny obserwacji po rejestracji w odniesieniu do skuteczności i bezpieczeństwa

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W artykule przeanalizowano dane z piśmiennictwa o próbach zastosowania preparatów Proteflazid® (krople) i Immunoflazid® (syrup) w leczeniu chorób o etiologii wirusowej u dzieci w ciągu pierwszych 6 lat życia. Systematyczna ocena została przeprowadzona na podstawie badań post-marketingowych i porównawczych obserwacji klinicznych (w okresie od 2002 do 2016 roku), z udziałem około 1500 dzieci (ponad 800 z nich zażywało preparat). Potwierdzono bezpieczeństwo i skuteczność stosowania preparatów Proteflazid® (krople) i Immunoflazid® (syrup) u dzieci w leczeniu zakażeń wirusowych.

Słowa kluczowe: Proteflazid®, Immunoflazid®, zakażenia opryszczkowe, zakażenia górnych dróg oddechowych, leczenie, dzieci

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In clinical practice, the prophylaxis and treatment of viral infections take a special place due to their high prevalence in children as well as in adults. It is well known that 80-90% of population are infected with *Herpes simplex* viruses type I/II, *Ebstein-Barr* and *cytomegalovirus* – up to 70%, therefore herpetic pathology is one of the most important problems of modern paediatrics and neonatology [11]. Concerning the acute respiratory viral infections (ARVI), they have a persistently high level in the infectious morbidity pattern in both the whole world and Ukraine. Among children under 17 years of age, its level makes up more than 60,000 cases per 100,000 population (3.3 times higher than in adults, including influenza – 979, exceeding the level in adults by 2.8 times) [7]. In Poland over the last years, respiratory infections account for about 40% of all hospital admissions annually. This index reaches 90% in infancy and up to 70% for the initial four years of life [2]. For children who begin to visit pre-school facilities, repeated (recurrent) respiratory infections are specific characteristic. These particular children constitute a risk group for the development of chronic diseases of the nasopharynx and the bronchial asthma, since the immunity status post ARVI is species- and type-specific, which causes high incidence [2,9,39].

In management of viral infections, the elimination of pathogen and the host immune response have a great influence on the recovery. In the world practice it is considered that the shortest and most effective management of viral pathology is possible by affecting an aetiological agent. However, the aetiological therapy of such diseases often presents itself as challenging considering the enormous numbers of pathogens and the paucity of selective drugs with proven clinical efficacy and safety. Several product groups have been discovered to date, the ac-

tion of which is based on the suppression of viral replication. However, their application in paediatric practice is limited due to the high toxicity, since the metabolism of viruses' multiplying is closely related to the metabolism of the host's cells, and the effect on the virus almost inevitably affects the cells of the growing and developing child's organism. In addition, the certain challenges emerge in chronic viral infections management, which are as follows: it is not always possible to achieve a positive result with the help of aetiological therapy in the immunocompromised patients or in case of oxidative stress (OS). Consequently, a complex of treatment and rehabilitation measures should include drugs that normalize the immune system (IS) functioning and suppress the hyperactivity of free radical processes. It is known that aetiological agents destroy or inhibit the activity of the pathogen, while immunotropic therapy directly or indirectly increases the functional activity of phagocytes, enhancing their anti-infectious effect, stimulating the reaction of the cellular and humoral component of IS. OS control increases the degree of cell membranes protection improving the effectiveness of treatment and rehabilitation measures.

The problem solution of viral infection treatment efficiency improvement become possible now through the use in the general medical practice on a wide scale basis of the brand-name drug Proteflazid® (drops) (manufactured by the Ecopharm Research and Production Company, Ukraine), the active ingredient of which is derived from the plants *Deschampsia caespitosa* L. and *Calamagrostis epigeios* L. The major biologically active component of the active ingredient is a complex compound of O- and C-glycosidic flavones: tricine, luteolin and apigenin. For children, Proteflazid® is also recommended in the syrup dosage form, manufactured under the brand name Immunoflazid®.

The medicinal preparation Proteflazid® is characterized by a number of basic pharmacodynamic properties as follows:

- **etiotropic action:** a) inhibits the virus-specific enzymes synthesis of the RNA- and DNA-viruses (thymidine kinase, DNA- and RNA-polymerases, revertase), which is accompanied by impairment in ability or total block of the viral nucleic acids' replication and, as a result, makes the RNA- and DNA- viruses' reproduction impossible; b) inhibits the neuraminidase activity of influenza viruses, preventing them from entering the host through the respiratory tract mucous lining or the yield of viruses from the infected cells, reducing the risk of bacterial-associated complications (e.g. pneumonia) [4, 5, 9];
- **pathogenetic action:** a) it has an immunotropic mode of action, namely optimizes the endogenous α - and γ -interferons (IFN) synthesis, restores tissue immunity by increasing the secretory immunoglobulin A (sIgA) level; b) it has an antioxidative mode of action (in pre-clinical studies it has shown that the active ingredient of drug is an effective agent to speed control of the superoxide radicals generation by the normal and transformed cells, the agent at a dose of 5 mg/ml, nulls the superoxide cells generation). The drug reduces the lipid peroxidation activity and enhances the antioxidant defence activity, which results in reduced endotoxemia and increases the resistance of cells and tissue to damaging action of the free-radical oxidation products, the level of which is increased during the most pathological processes, especially in cases of inflammation and infection [9, 17, 27].

Polypharmacologic features (direct antiviral, immunotropic and antioxidant modes of action) of Proteflazid® provide both etiotropic and pathogenetic effects on both the viral infection and pathological processes in the host caused by this infection. The above mentioned properties of the medicinal preparation Proteflazid® are the basis for its wide application in various fields of medicine – prevention and treatment of a number of infectious diseases caused by such viruses as: *Herpes viruses* types I and II, *Epstein-Barr virus*, *human papilloma virus*, *hepatitis viruses*, *influenza virus*, *cytomegalovirus* (CMV) and others, as well as in the complex therapy for viral-bacterial and fungal infections [1, 3, 6, 9, 10, 22, 24, 26, 29]. The activity of drug is equally high in both the first hours of the disease, and the following days [3, 22, 24, 38].

Due to lack of a real opportunity in practical medicine to accurately determine the pathogen type of the infectious process in the first day of illness, physicians rely only upon their own experience in choosing etiotropic therapy, in both assessing the symptoms of the disease and using etiotropic antiviral agents [17].

Given the etiopathogenetic aspects of viral diseases (including influenza and ARVI), the routes and mechanisms of infection, the options for their treatment should have the following basic pharmacodynamic properties: – direct broad spectrum antiviral action (act on RNA- and DNA-viruses) at all stages of the viral infection development; – to suppress neuraminidase activity of influenza viruses; – the superior bioavailability to the upper respiratory tract mucosal lining; – detoxicative and antioxidant characteristics; – to show an immunotropic effect against a background of high-grade security, bioavailability and efficacy [17, 31].

Experimental studies with laboratory animals and cell cultures carried out at the stage of preclinical research have proved that the medicinal preparation Proteflazid® has specific antiviral activity against *influenza virus*, *Herpes simplex*, *Epstein-Barr virus*, *hepatitis virus*, *adeno-*, *papilloma* and *CMV*, *HIV*, no adverse and toxic effects, does not create a pharmacological loading on the detoxification and excretion organs; has a mild immune stimulating effect, on account of which it is recommended for paediatric use [5, 14]. However, despite the long-term experience of a line of medicines based on Proteflazid® in medical practice, the possibility of their use in children of early and preschool age raises a number of questions among many paediatricians, primarily regarding its safety and the po-

ssible impact on the child's postnatal development. We tried to answer such questions in the present systematic review.

On the basis of postmarketing comparative clinical trials and follow-ups, to conduct an analysis of scientific and practical data of the evidence base that confirms the efficacy and safety of the medicinal preparation Proteflazid® (drops) and Immunoflazid® (syrup) for the treatment of diseases of viral aetiology in children of the first 6 years of life.

MATERIALS AND METHODS

Scientific publications, clinical trial reports, systematic analysis were under evaluation in the study.

RESULTS AND DISCUSSION

In a systematic review, the results of studies of Proteflazid® (drops) and Immunoflazid® (syrup) in clinical practice published during the period of 2002 to 2016 were analysed.

A considerable part of the scientific data is devoted to the clinical experience of the medicinal preparation Proteflazid® for opportunistic infections, the development of which occurs in conditions of immune deficiency. *Herpes simplex viruses* types I and II, *CMV* and chlamydial infections rank high up among them. An infection level increase among women of fertile age with these pathogens leads to the fact that the infectious pathology of foetus and newborn becomes one of the most important issues of modern neonatology. The incidence of this pathology varies from 6% to 53% and tends to increase, while *CMV* takes the first position among its aetiological factors. In a newborn, along with the acute infection, a long-term persistence of pathogen can be noted with the formation of latent infectious disease, an immunodeficiency state, which, in subsequent years, may become one of the factors of the recurrent infectious morbidity. Ambiguity regarding the necessity and time frame of the toxic enough antiviral chemotherapy stimulates the scientists to search for effective mode therapy of this pathology. Thus, *Usachova Ye. V.* [35] has showed the effectiveness of Proteflazid® (drops) for the intrauterine *CMV* infection in infants. Evaluation of the results of the dynamic clinical and laboratory study demonstrated a nulling of the cytolytic syndrome, an achieved positive serological result, which manifested itself in the disappearance of IgM against *CMV* and a decrease of anti-*CMV* IgG. Such results are regarded as an evidence of an antigen load reduction, i.e., suppression of viral replication. In children with liquor hypertensive syndrome, according to the neurologist examination results and the control neurosonography data, stabilization of condition and the absence of a further enlargement of the third and lateral ventricles of cerebrum were noted.

The observation results made by *Znamenskaya T.K. et al.* [19] also showed the efficacy of Proteflazid® (drops) in the complex therapy of children with intrauterine infection, which was manifested by a positive dynamics of the clinical symptoms of the disease, a decrease in the duration of stay of newborns in intensive care unit, a decrease in the duration of invasive artificial lung ventilation, leading to reduction of treatment expenses of this category of patients. Neurosonography and Doppler ultrasound of the cerebral haemodynamics confirm the high treatment efficiency of intrauterine infection with Proteflazid® (drops).

To date it is known that among the newborns, the high risk group consists of premature neonates, and among them – small-for-date newborns, who have the most pronounced and persistent immunological defects [15]. Considering the important role of OS reactions in the formation of both compensatory and pathological mechanisms of postnatal adaptation of pretermatures, especially under conditions of hypoxia, the status of indices of pro-oxidant and antioxidant defence systems has been studied. *Godovanets Yu.D., Babintseva A.G.* [14] showed the effectiveness of the Proteflazid® (drops) in the complex treatment of an acute period of hypoxic-ischemic CNS

injury in premature neonates during the early neonatal period based on the antioxidant defence system and some immunological indices. The positive effect of drug on the postnatal adaptation, a significant decrease in the extra-neural manifestation rate of hypoxia was shown. The results of laboratory tests (complete blood cell count, pro-oxidant and antioxidant protection system indices) confirmed the efficacy of Proteflazid®.

Intrauterine infections are often responsible for child's disability due to congenital defects (CD) and background chronic diseases [8]. Nagornaia N.V., Vinogradov K.V. [27] presented the results of the study of the Proteflazid® (drops) effectiveness for various course of herpetic infections in children with congenital heart defects. It was shown that 3 and 12 months later after the treatment, which was conducted taking into account the differentiation according to the infection stage, in a significant proportion of children, who had an acute and / or an exacerbation of the chronic herpetic infections, the lack of activity laboratory markers, a significant decrease in specific IgG titres was revealed in more than 70% of patients with latent disease. The prospective follow-up during the first year after the treatment indicated a significant decrease in the incidence of ARVI, acute bronchitis, a decrease in the frequency and severity of complications of respiratory tract infections in patients who were administrated the agent.

The objective of the research of Veselyi S.V. and Klimanskii R.P. [12] was to study the effect of Immunoflazid® on the state of the IS activity in children with the gastrointestinal tract CD on condition of the different course of infection caused by persistent intracellular pathogens. A significant decrease in activity of proinflammatory cytokines (IL-1, IL-2, IL-6), INF- γ and TNF- α and the increase of anti-inflammatory cytokines (IL-10 and INF- α) activity served as a drug response rate. Immunoflazid® in the complex therapy, as well as in monotherapy, allowed to eliminate the IS imbalance in a shorter time period, induce the treatment terms reduction, without exerting a negative influence on the child's organism.

It has been proved that *Herpes simplex viruses*, *Ebstein-Barr virus*, *CMV* persist in organism for a long-term period and, in case of its reactivity decrease, they may affect the cardiovascular, digestive, nervous, lymphoid, respiratory systems, provoking frequent development of pneumonia. Ovcharenko L.S. et al. [28] showed a beneficial effect of Proteflazid® (drops) on intracellular pathogens (*CMV*, *Chlamydia*) for the treatment of ARVI and the prevention of bacterial complications in such children. Dynamics of immunological indicators confirmed the anti-inflammatory effect of Proteflazid® due to the infectious antigen loading decrease. Repeated course of treatment of the resistant forms of disease in 1.5-2 months allowed achieving normalization of laboratory parameters in 100% of cases.

The necessity and effectiveness of Immunoflazid® syrup usage in the complex treatment of community-acquired pneumonia in young children secondary to *CMV* and/or *Herpes virus* (types I, II) infections was investigated by Zalizyuk A.A. [18]. It was shown that the drug, as part of complex treatment, prevents the lingering disease, reduces hospital stay, restores the endocrine function of thymus, T-cell immunity parameters, and arrests the clinical manifestations of pneumonia along with lack of adverse effects.

Turlibekova S.S. [34] also showed that effective treatment of *CMV* infection can be provided only by applying in the complex therapy – etiotropic and pathogenetic. This approach grounds on a lifelong virus persistence in a host-organism. The authors have proved the clinical laboratory effectiveness of combined therapy that included Proteflazid® (drops) along with interferons.

Grigorchuk N.V. et al. [16] managed to arrest the acute herpetic infection in 58 children, and to prevent the formation of its clinically manifested relapses. All examined children had a twofold decrease in the number and duration of recurrent respiratory diseases and the frequency of their bacterial-associated complications.

A primary herpetic stomatitis is a widespread manifestation of primary Herpes simplex virus infection in children. Gerasimov S.V. et al. [13] showed that Proteflazid® (drops) taken in therapeutic dose reduces the duration of primary acute herpetic gingivostomatitis by 2-3 days, reduces the frequency of its recurrence in infants and young children, and is comparable in effectiveness to acyclovir.

Shamsiev F.M. et al. [32, 37] in their study confirmed the significant pathogenetic role of immune disorders in the formation of acute pneumonia associated with TORCH infection. The complexity of pathogenesis, the cascade of pathological processes and the variety of implementation mechanisms, as well as the deep of immune destruction, point out the necessity of including a drug with an antiviral and immunocorrecting effect in the treatment of pneumonia in such children. The authors proposed a new treatment regimen with a long-term intake of the drug for 5-6 months. Comparative analysis of the main parameters of the immune system showed that Proteflazid® (drops) as part of complex treatment under the new scheme promotes the faster improvement of clinical and immunological dynamics, increases the activity of immunoregulatory subpopulations of T-lymphocytes, non-specific factors of defence, for recurrent pneumonia in children with herpetic infection.

It is well known that early and preschool children's age (6 months – 6 years) is characterized by increased child's sensitivity to ARVI, which is their ontogenetic feature [9]. As a rule, at onset of disease, it is difficult to determine its viral aetiology. In this regard, the ability of an antiviral agent to be administered to influence both the RNA and the DNA viruses that cause the onset of ARVI acquires particular relevance [31].

In preclinical studies and in clinical practice, it has been found that Proteflazid® (drops) and Immunoflazid® (syrup) inhibit the replication of both RNA- and DNA-viruses via blocking the specific for all viruses enzymes (RNA- and DNA-polymerase, thymidine kinase, revertase), and also inhibit neuraminidase of influenza viruses. These properties of drugs are very important for the implementation of preventive and treatment measures in conditions where it is difficult to determine the aetiology of the disease [17].

The children of the infant orphanage are the most susceptible to ARVI category of the child population. The increased morbidity of this population is associated with multiple deviations in their health status and a violation of the host defences. The effectiveness and safety of the preparation Immunoflazid® for the prevention and treatment of ARVI among children in the orphanage was studied by Yulish Ye.I. et al. [38, 40]. The clinical effectiveness of the drug in the treatment and prevention of ARVI in children of early age is proved. Against the background of the drug usage, the incidence of the severe disease and its complications decreased, and from the third day of treatment a positive clinical dynamics was observed. In addition, the incidence of ARVI decreased 2.3 times that confirms the preventive effect of Immunoflazid®. Yulish Ye.I. et al. [41] recommend Immunoflazid® for use in healthy children and those with recurrent respiratory diseases for the purpose of non-specific prevention of ARVI during the seasonal increase of ARVI.

Zubarenko A.V. et al. [20] also confirmed the efficacy of Immunoflazid® in the prevention of infectious diseases in infants on the background of lack of allergic reactions and digestive tract disorders.

In children with recurrent infections, the IS is characterized by the intensity of the response processes and the inadequacy of reserve capacities, so the issues of their effective rehabilitation is a question of great importance. The purpose of research conducted by Zyuzina L.S., Myzgina T.I. [21] was to determine the clinical efficacy of Immunoflazid® in the complex therapy of young children with recurrent respiratory diseases. It was shown that in patients who were treated with the drug, compared with the control group, the disease course was mild. Clinical symptoms (intoxication, fever, bronchial obstruction) and general condition improved in a shorter period of time. The hospital stay of patients decreased by 1.2 times. In the catamnesis it was determined that the frequency of repeated

Table 1. Results of clinical trials on the efficacy and safety of the medicinal preparations Proteflazid® (drops) and Immunoflazid® (syrup) in young children during the period of 2002 to 2016

Tabela 1. Wyniki badań klinicznych dotyczących skuteczności i bezpieczeństwa preparatów medycznych Proteflazid® (krople) i Immunoflazid® (syrup) u małych dzieci w okresie od 2002 do 2016

No.	Authors, year, source	Pathology	Number of patients (total / intent-to-treat)	Main results of drug use in clinical practice
1.	Kryuchko T.A. et al., 2002 [25]	Neuroinfection	20 / 20	GP: 1* of intoxication, improvement of well-being, rapid arresting of meningeal syndrome, N of the CD4/CD8 correlation from 0.7 ± 0.21 to 1.3 ± 0.32 , ↑ of serum IgG from 3.8 ± 0.8 g/L to 8.4 ± 1.8 g/L; IgA from 0.1 ± 0.6 g/L to 3.3 ± 0.05 g/L.
2.	Godovanets Yu.D., Babintseva A.G., 2005 [14]	Hypoxic-ischemic CNS injury in premature neonates	54 / 22	GP: stabilization of general health status in 95.5% vs CG: 46.9% , $p < 0.05$. Peristalsis depression – 2.5% vs 43.8% , respectively, $p < 0.05$; hepar enlargement – 9.1% vs 65.6% , respectively, $p < 0.05$. The significant higher activity of plasma catalase (1.7 ± 0.11 U/min. 1 g protein and 1.2 ± 0.08 U/min. 1 g protein, respectively, $p < 0.05$), the ceruloplasmin level (46.8 ± 1.08 U/1 g protein and 25.2 ± 1.24 U/1 g protein, respectively, $p < 0.05$) and the level of sulfhydryl-groups of plasma (1.7 ± 0.03 μmol/1 g protein and 0.8 ± 0.05 μmol/1 g protein, respectively, $p < 0.05$). GP: ↓ in the intensity of oxidative modification of proteins was 70.6 ± 1.88 U/1 g protein vs CG: 106.9 ± 2.79 U/1 g protein, ($p < 0.05$) in.
3.	Usachova Ye.V., 2005 [35]	Intrauterine CMV infection	54 / 23	GP: ↓ ALT to normal limits at 8 ± 4.5 day of treatment. A positive serological effect in 52% cases: the disappearance of anti-CMV IgM and ↓ of anti-CMV IgG as an evidence of an antigenic burden reduction as a result of viral replication depression. Stabilization of children with liquor hypertensive syndrome and the absence of a further enlargement of the third and lateral ventricles of cerebrum.
4.	Ovcharenko L.S. et al., 2005 [28]	ARVI against a background of chronic persistence of intracellular pathogens (chlamydia and CMV)	60 / 30	GP: ↓ quantitative parameters of killer cells (CD8, CD16). Antioxidant action of the drug: ↓ (to normal values) of the tetrazolium test. ↑ IgG and IgA against ↓ IgM. After the course of treatment in 2 children with CMV, a high antibody titre of anti-CMV IgG 1:20, IgM 1:100 remained. After the repeated course of therapy: ↓ IgG titre to 1:4 and IgM to 1:10.
5.	Gerasimov S.V., 2006 [13]	Primary herpetic gingivostomatitis	34 / 17	GP: 2-3 days earlier rashes in the oral cavity disappeared, N the body temperature, appetite and salivation disappeared; the total number of doses of non-steroidal anti-inflammatory drugs was significantly less (GP: 12 ± 3 vs CG: 17 ± 5 , $p = 0.001$). Proteflazid® helps reduce the recurrence of disease: CG: 3/10 cases of recurrence, GP: no relapses.
6.	Nagornaia N.V., Vinogradov K.V., 2007 [27]	Herpetic infections in children with congenital heart defects	27 / 27	GP: In 3 months after treatment, there was lack of laboratory markers of herpetic infections. At the same time levels of HSV IgG remained high in 1 child with acute infections. ↓ the titre of specific IgG was observed more than 2-fold in 13 children. ↓ specific IgG in patients with latent herpetic infections. One year later after the treatment, the children had no signs of herpetic infections activity (ELISA, PCR). The diagnostically insignificant IgG titres were recorded in 10.0% of children with the exacerbation of chronic herpetic infection and in 100.0% with latent herpetic infections. ↓ the frequency of respiratory diseases (from 91.3 ± 5.8 to $43.4 \pm 10.4\%$) and acute bronchitis (from 56.5 ± 10.3 to $21.7 \pm 8.6\%$). ↑ the proportion of diseases with mild course ($69.5 \pm 9.5\%$) as compared with the baseline data. ↓ more than 2 times the number of complicated forms of respiratory infections, ↓ the frequency of antibacterial drugs administration ($52.1 \pm 10.4\%$), compared to the data before treatment ($82.6 \pm 7.9\%$).
7.	Grigorchuk N.V., 2008 [16]	Neonates with herpetic infections	100 / 100	GP: Acute manifestations of infection in 58 children were stabilized; the recurrent course of chronic herpetic infection was transferred to the latent infection. 2-fold ↓ the number and duration of recurrent respiratory diseases and the frequency of their bacterial-associated complications.
8.	Sagatova M., Shamsiev F.M., 2009 [32]	Recurrent pneumonia in children with herpetic infections	58 / 38	GP: ↑ CD3, CD4 and CD8 lymphocytes ($p < 0.001$) in 3 months from the initiation of the drug administration. N phagocytic activity and the concentration of IgG and IgM in the blood serum, compared with the baseline data ($p < 0.001$).
9.	Yulish Ye.I. et al., 2009 [41]	ARVI (prevention)	80 / 55	GI: the number of patients with ARVI was 22.2% ($n=6$) of children vs CG: 56.0% ($n=14$). Thus, during the epidemic season, the use of Immunoflazid® can protect against the disease 77.8% of young children. GI: ARVI course was mild, lack of severe forms, the average duration of ARVI was 3.3 ± 0.7 days, besides clinically they had catarrhal manifestations secondary to the low-grade temperature, which were arrested by the end of the fourth day vs CG: the duration of ARVI was 9.7 ± 1.6 days, which was due to the development of complications (otitis, bronchitis).
10.	Kinash Yu.M., 2010 [23]	Recurrent bronchitis	65 / 45	GP: in 3 months after treatment, ↑ the cellular and humoral components indices of immunity: ↑ the number of T-cells due to CD4 and CD8 ($p < 0.05$). 2-fold ↓ the IL-2, IL-10 values. The dynamics of local immunity indices showed ↑ of the lactoferrin and sIgA levels.
11.	Turlibekova S.S., 2011 [34]	Intrauterine CMV infection	48 / 23	GP: the significant positive dynamics of clinical symptoms (↓ temperature to normal values, arrest of dyspeptic syndrome, improvement of appetite and emotional tone of children).

12. Shamsiev N.Kh. et al., 2011 [37]	Bronchopulmonary pathology associated with TORCH infection	169 / 32	GP: ↑ the number of CD3-lymphocytes ($p<0.001$), CG: these values did not reach normal limits. GP: the performed immunocorrection contributed to ↓ in the number of CD16-cells. The parameters of humoral immunity component (the number of CD20+ cells, IgA, IgM and IgG levels), as well as the phagocytic activity of leukocytes were close to the control values.
13. Zalizyuk A.A., 2011 [18]	Community-acquired pneumonia in children secondary to CMV and/or Herpes simplex virus types I, II	50 / 25	GI: there was a reduction of terms of intoxication syndrome (6.67 ± 0.32 days vs CG: 10.7 ± 0.8 days) ($p<0.05$); GI: ↓ the duration of inpatient treatment by 6.6 ± 1.3 days against CG ($p<0.05$). GI: significant changes in the parameters of the immunological status in comparison with CG: N CD4+ T-lymphocytes in comparison with the initial levels. GI: N the thymulin level and prevention thymus mass reduction.
14. Tokarchuk N.I., Starinets L.S., 2012 [33]	ARVI and influenza	50 / 25	GI: N CD+ T-lymphocytes (CD3+, CD4+, CD8+, CD16+), immunoregulatory index CD4/CD8 ($p<0.01$), CD4+ T-helpers compared with baseline data ($35.1\pm1.2\%$ vs $42.7\pm1.2\%$, $p<0.05$); ↑ phagocytic protection and ↓ the specific immune lymphocyte-monocyte potential in comparison with baseline data ($p<0.05$) GI: N the thymulin level and prevention the thymus mass reduction: ↑ by 53.6% the thymulin level ($p<0.05$) vs CG: ↓ by 32.3% the thymulin level in the blood serum during the treatment ($p<0.05$).
15. Tsimbalista O.L., Garidzhuk L.I., 2013 [36]	Complicated community-acquired pneumonia secondary to iron deficiency anaemia	80 / 40	GI: ↓ the duration of inpatient treatment ($p<0.05$). ↓ pro-inflammatory cytokines level, i.e. ↑ the therapeutic effect by reducing the activity of inflammation at all degrees of concomitant iron deficiency anaemia.
16. Znamenskaya T.K. et al., 2013 [19]	Intrauterine infections	80 / 40	GP: ↓ the duration of the intensive care unit stay of newborns (13.4 ± 0.3 days vs CG: 17.5 ± 0.5 days), ↓ the artificial lung ventilation duration (8.4 ± 0.3 vs 11.2 ± 0.2 , respectively). GP: the rapid disappearance of jaundice: at the end of the first month of postnatal period, its incidence was 7.5% vs CG: 12.5%. At the 3 rd week of life, the signs of ventriculodilation (the ventricular index increase and the ventriculometry data) (neurosonography), which indicated a violation of haemocerebrospinal fluid circulation. GP: the above mentioned indicators were lower ($p<0.005$); interventricular asymmetry was less common; the width of the vascular plexuses was significantly less; the frequency of periventricular leukomalacia was lower. More intensive improvement of cerebral haemodynamics (doppler ultrasonography): significantly higher blood flow velocity, decrease of pulse and resistant indices ($p<0.05$).
17. Zubarenko A.V. et al., 2015 [20]	Infectious diseases in infants born from mothers who are TORCH infection carrier	75 / 39	GI: ↓ the incidence of disease: 17.94% of children vs CG: 83.33%. GI: the disease duration among children becoming ill was 6 ± 0.7 days vs CG: 8.25 ± 0.45 days.
18. Zyuzina L.S., Myzgina T.I., 2015 [21]	Children with respiratory recurrent diseases (prevention)	78 / 40	GI: the disease course was mild, compared with CG, the disappearance of intoxication symptoms, fever, obstructive syndrome and general condition improvement occurred in a shorter period. GI: ↓ by 1.2 times the hospital stay of patients, compared with CG.
19. Veselyi S.V., Klimanskii R.P., 2016 [12]	Congenital defects of the gastrointestinal tract, associated with the persistent intracellular pathogens	87 / 64	GI: ↓ the specific immunoglobulins level that before treatment exceeded the upper limit of normal by 8-9 times; ↓ activity pro-inflammatory cytokines (IL-1, IL-2, IL-6), INF- α , - γ and TNF- α ; ↑ the activity of anti-inflammatory cytokines IL-10 and INF- α . There was a lack of pathogens' markers of the persistent viral infections in the blood serum on completing the treatment.

*GP – group of children who were administered Proteflazid®; GI – group of children who were administered Immunoflazid®; CG – comparison group; ↓ – decrease; ↑ – increase; N – normalization.

hospital admission of children with complications of viral infection, who were administered the drug, was 3 times less than in the control group. The authors noted that Immunoflazid® is an effective, easy to use, well tolerated by children and has no adverse effects.

In the study of Tokarchuk N.I. and Starinets L.S. [33] it was shown that the preparation Immunoflazid® in children of early age with ARVI and influenza contributes to the restoration of the functional state of thymus (normalize thymulin level), and the T-cellular component of IS parameters, the integral coefficients of non-specific protective factors. The inclusion of Immunoflazid® in the treatment of ARVI in young children reduces the duration of hospital stay.

Kinash Yu.M. [23] confirmed that the underlying immune deviations in children with recurrent bronchitis relate mainly to thymus-dependent lymphocytes. There was a significant decrease in both the main T-cell pool and subpopulation of T-helpers CD4, as well as a decrease of T-suppressors CD8. Immunoflazid® contributed to normalization of those indicators levels.

Tsimbalista O.L., Garidzhuk L.I. [36] studied the levels of IL-4, IL-6, IL-8, IL-10, and INF- α in 90 young children with complicated community-acquired pneumonia secondary to iron deficiency anaemia (IDA). An increase of cytokines in pro-

portion to the iron deficiency degree was observed in the examined children. After clinical and radiological recovery, the active inflammation in lungs intensified to the extent of the iron level decrease. That was confirmed by an increase of the IL-6, IL-8 and TNF- α levels. The combination of basic therapy of pneumonia with the preparation Immunoflazid® improves the therapeutic effect by reducing the activity of inflammation at all levels of concomitant IDA. It has been shown that Immunoflazid®, due to its anti-inflammatory properties, is effective and safe for use in infants with complicated pneumonia on the background of IDA.

The results of the clinical management analysis confirm the effectiveness of the preparations Proteflazid® (drops) and Immunoflazid® (syrup) for the treatment of both the active viral infections and the latent diseases in children, providing direct antiviral, immunocorrecting and antioxidant actions. Mono- and complex therapy with these drugs, allow the elimination of pathogens within a short time period, normalize the IS imbalance, shorten the time of treatment and intake of concomitant medications; reduce the risk of repeated episodes and complications developing. The listed therapeutic effects give grounds for the wide use of Proteflazid® and Immunoflazid® in children with herpetic infections, ARVI and influenza, as they fully

correspond to the etiopathogenetic requirements for the prevention and treatment of these diseases.

It should be emphasized that the essential advantage of the preparations Proteflazid® (drops) and Immunoflazid® (syrup) over other drugs that are used in mono- and combination therapy of viral and viral-bacterial diseases is that these drugs under analysis have both etiotropic and pathogenetic potential, and in recommended doses they are safe and indicated for treatment in children from birth. The use of these drugs makes it possible to avoid unreasonable polypragmasy and save patients' financial resources.

The table presents the main results of 19 clinical trials in chronological order.

CONCLUSIONS

The analysis of scientific literature on the results of the clinical use of drugs derived from the active substance isolated from the plants *Deschampsia caespitosa* L. and *Calamagrostis epigeios* L. – Proteflazid® (drops) and Immunoflazid® (syrup) confirmed the availability of direct antiviral, immunomodulating and antioxidant properties. The use of drugs allow to eliminate the causative agent of the disease, normalises the imbalance of the child's immune system in a short time, reduces the timing of concomitant medications usage, thereby reducing the likelihood of adverse reactions of the child's organism. The high effectiveness of repeated courses of the drugs in children with recurrent diseases has been proved.

The results of systematic analysis of the scientific publications indicate a good clinical efficacy and a high profile of safety of Proteflazid® (drops) and Immunoflazid® (syrup) for the treatment of viral and viral-bacterial diseases in children, including of early age, which makes it possible to recommend these drugs for wide application in neonatology and paediatric practice.

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