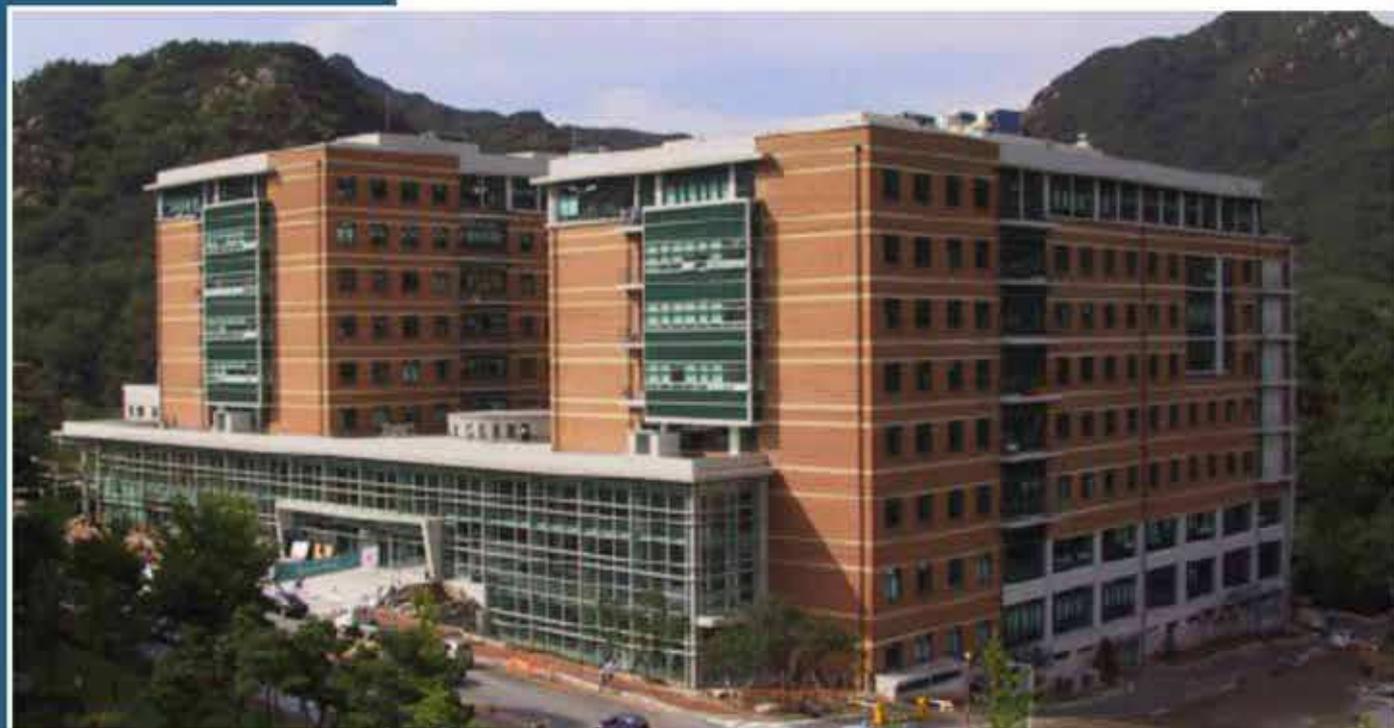
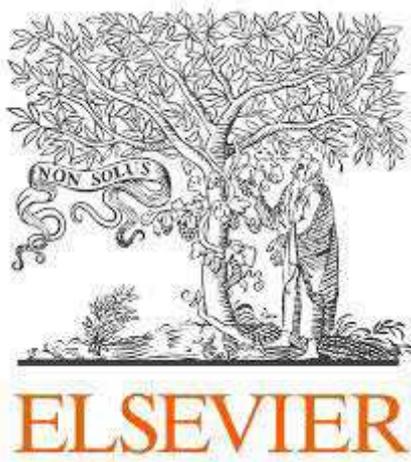


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***Meta-Analysis of clinical trials results of efficacy
and safety of the drug Proteflazid® in the treatment
and prevention of human herpesvirus infection in children***

Abstract: 18 publications involving 1400 children between 2003 and 2014 years in a meta-analysis of clinical trials evaluating the efficacy and safety of the drug in the treatment of children Proteflazid® with of human herpesvirus infection was included. The results show the high efficiency of application Proteflazid® drug for the treatment of children with of human herpesvirus infection – CMV, EBV. Treatment with the drug contributes to the positive dynamics of the main clinical symptoms of disease and elimination of herpes viruses from the body.

Keywords: meta-analysis, Epstein-Barr virus, cytomegalovirus, human herpesvirus infection, pediatrics, Proteflazid®, Flavozid®.

Rationale. Human herpesvirus (HHV) infection is among the most common human viral diseases and holds a special place in children's infectious pathology.

During childhood, infection contamination occurs most often in contact, airborne or vertical ways, and the age of 6 years about 80 % of children are infected with the herpes simplex virus 1 and 2 (HSV) [1].

At present we know 8 antigenic serotypes of herpes viruses: herpes simplex virus 1 and 2 (HSV-1, HSV-2), cytomegalovirus (CMV; human herpes virus 5), Epstein-Barr virus (EBV, human herpes virus 4), varicella zoster virus (herpes zoster, human herpes virus 3), and human herpes viruses 6, 7 and 8. Herpes viruses are characterized by multisystemic tropism. The ability of pathogens to persist for a long time in the body by causing severe, persistent, chronic and latent forms of infection with periodic exacerbations is common for the HHV infection [21].

The problem of persistent intracellular infection is among the important problems in pediatrics due to high prevalence, long persistence in the body of the child, possible pathogenetic involvement in the formation of secondary immune deficiencies, proved influence of persistent intracellular infection agents on the formation of a wide range of ante- and perinatal pathology [26].

A characteristic feature of modern infectious pathology is the growth of chronic infectious and inflammatory diseases, often emerging against the background of persistent infection process caused by following herpes viruses: HSV-1, HSV-2, CMV, EBV [27].

One of the most important forms of HHV infection is EBV caused infection. Antibodies to EBV have been found, according to published reports, in 40-60 % of children of the first three years of life, and in 80-90 % of adults [28].

In 90-95 % of cases, EBV causes the development of infectious mononucleosis (IM). IM in children, regardless of the pathogen and the age, is a symptom complex that includes long-term fever, systemic lymphadenopathy, acute tonsillitis, acute adenoiditis, hepatomegaly, splenomegaly, typical haematological changes in the blood in the form of leukocytosis, lymphocytosis, monocytosis, the presence of specific cells – atypical mononuclear cells or virocytes. The outcomes of IM according to different authors are recovery, asymptomatic carriage of viruses, persistent, latent, chronic form of infection, oncology lymphoproliferative process: lymphoma, nasopharyngeal carcinoma, leukoplakia of tongue, leukoplakia of mucous membranes of the oral cavity, stomach cancer, colon cancer, etc., autoimmune diseases: systemic lupus erythematosus (SLE), vasculitis, rheumatoid arthritis, Sjogren's syndrome, necrotizing enterocolitis (NEC), etc., chronic fatigue syndrome, splenic rupture, etc. [14].

In the human population CMV infection is widespread, it is a common factor for intrauterine fetal injury with the development of severe consequences and a cause of diseases in adults and children of different ages [7, 22, 29].

The variety of clinical manifestations of the disease is caused by the ability of CMV to replicate into almost all the body's cells: white blood cells, tissue macrophages, monocytes, endothelial, epithelial and neuronal cells, fibroblasts. CMV infection can occur acutely, chronically and latently, and manifest in congenital and acquired forms [29].

Long-term intracellular persistence of herpes viruses in the body of an infected child, multiple affinity to various organs and tissues and ability to reactivation lead to the need for treatment aimed to the suppression of infectious agent reproduction during acute manifestations, and the development of adequate immune response with long-term preservation [26].

One of the most effective means showing an expressed direct antiviral effect by inhibiting such virus specific enzymes as thymidine kinase (TK) and DNA polymerase, together with immunomodulatory action contributing to the induction of endogenous interferon, is the drug Proteflazid[®] (drops) and the drug Flavozid[®] (syrup) developed on the basis of drops and intended for use in the pediatrics (limited liability Scientific & Manufacturing Company "Ecopharm" Ltd, Ukraine). Active ingredients of the drug Proteflazid[®] are flavonoids that inhibit the synthesis of DNA viruses in infected cells through inhibition of activity of virus specific DNA polymerase and TK.

The drug Proteflazid[®] promotes the synthesis of endogenous interferons (IFN) such as α -IFN, γ -IFN to physiologically active level (without the occurrence of refractivity phenomenon), which increases nonspecific resistance to bacterial and viral infections, and normalizes immune status. The drug also prevents the accumulation of lipid peroxidation products (inhibits free radical processes) and is an apoptosis modulator, causing the death of infected cells [23, 28].

The drug Proteflazid[®] prevents the disease relapse and prolongs the period of remission.

It should be noted that the drug Proteflazid[®] shows high bioavailability, it is not toxic; it can be actively used in pediatrics and administered to children right after the birth and pregnant women.

Purpose of the trial. Conduct the meta-analysis of clinical trials and evaluation of the clinical efficacy of the drug Proteflazid[®] in children with HHV infection (CMV, EBV).

Materials and Methods. Data of clinical trials that examine the effectiveness of the drug Proteflazid[®] in the treatment of HHV infection in children were received with the help of the Internet information retrieval systems. The list of selected 18 pub-

lications reflecting the effectiveness of the drug Proteflazid® in the treatment of HHV infection in 1,400 children during the period from 2003 to 2014 is presented in Table 1.

Software: In order to ensure the greater reliability and the accuracy, the calculations were conducted simultaneously in the two specialized statistical programs RevMan and SPSS.

Inclusion criteria:

The studies to be included in the meta-analysis shall meet the following criteria:

1. Controlled studies allowing for the control or the control group and focused on the study of the clinical efficacy of the drug Proteflazid® (Flavozid®) in the treatment of HHV infection (CMV, EBV) in children.

Table 1

The list of publications reflecting the efficacy of the drug Proteflazid® (Flavozid®) in the treatment of HHV infection in children

Author	Year	Country	General number of patients	Scope of application of the drug Proteflazid®	Clinical study results
1. Publications reflecting the efficacy of the drug Proteflazid® (Flavozid®) in the treatment of EBV infection in children					
Usachova E.V. [5]	2005	Ukraine	38	Infectious mononucleosis caused by EBV	Significant reduction in clinical disease caused by EBV, positive dynamics of hemogram.
Chernyshova O.E. [24]	2007	Ukraine	30	Immune and cytokine status in children at the background of infections caused by EBV	Relief of symptoms of acute infection, transition of chronic recurrent herpes infection into a latent form.
Kharchenko Yu.P. [8]	2007	Ukraine	60	Infectious mononucleosis caused by EBV	Significant reduction in clinical disease caused by EBV
Kramarev S.A., Vigovskaya O.V. [2]	2008	Ukraine	55	Chronic active EBV infection in children	Positive dynamics of clinical symptoms of the disease caused by EBV, arresting viral activity
Kramarev S.A., Vigovskaya O.V. [25]	2008	Ukraine	35	Chronic EBV infection in children	Disappearance of markers of active viral replication from the blood: anti-EBV IgM VCA, EBV DNA after treatment

Krama- rev S.A., Vigovs- kaya O.V. [21]	2012	Ukraine	80	EBV and concurrent HHV infection in chil- dren in the process of activation	Positive dynamics of clini- cal manifestations of EBV and concurrent HHV in- fection in children.
Boriso- va T.P. [17]	2014	Ukraine	54	Hematuric form of chronic glomerulo- nephritis and related EBV infection in chil- dren	Positive dynamics of symptoms, improvement in cytokine status
Krama- rev S.A., Vigovs- kaya O.V. [14]	2014	Ukraine	243	Infectious mononucle- osis caused by EBV	Pronounced positive dynamics of indexes of T- and B-cell immunity, risk minimization of the transition of acute stage into a chronic stage
2. Publications reflecting the efficacy of the drug Proteflazid® in the treatment of CMV infection in children					
Usacho- va E.V. [7]	2005	Ukraine	23	Intrauterine CMV infec- tion in children	Positive dynamics of clinical symptoms of the disease, stabilization of specific immunological parameters
Reznichen- ko Yu.G. [15]	2007	Ukraine	65	CMV infection in children with glomerulonephritis	Normalization of the immunity parameters
Znamens- kaya T.K. [9]	2008	Ukraine	200	Newborn babies of moth- ers with herpes and CMV infections	Improved clinical status of newborns, positive dynamics of cellular and humoral immunity
Turlibeko- va S.S. [22]	2011	Kazakh- stan	48	Congenital CMV infection in children	Positive dynamics of clinical and laboratory data
3. Publications reflecting the efficacy of the drug Proteflazid® 4. in the treatment of mixed HHV infection (HSV-1, HSV-2, 5. CMV, EBV) in children					
Kruchko T.A. [1]	2006	Ukraine	62	HHV infection in children	Positive dynamics of clinical symptoms of the pathological process
Ershova I.B. [10]	2003	Ukraine	86	Clinical and immunologi- cal features of viral me- ningoencephalitis in children	Prevention of relapse and acceleration of functional activity of children.
Ovcharen- ko L.S. [13]	2006	Ukraine	50	HHV and CMV infections in children with second- ary immunodeficiency	Reduced antigenic load on the child with the pathology of immunity, reduction of virus-induced immunodeficiency
Kruchko T.O. [4]	2008	Ukraine	58	Prevention of viral fatigue syndrome in children with HHV infection	Restoring function of the affected organs, easier relapses

Antono- va N.M. [19]	2010	Ukraine	93	Acute oral herpes and prevention of relapses of HHV infection in children	Improved immunological status of children, positive dynamics of cellular and humoral immunity
Yulish E.I. [3]	2011	Ukraine	130	Prolonged low-grade fever in children with HHV infection	Significant reduction in clinical manifestations of concurrent infection, resistant anti-relapse effect

2. It is necessary to confirm the clinical diagnosis of diseases identified in children.

3. Published data on the effectiveness of the drug Proteflazid® (Flavozid®) are complete.

Studies that did not meet the stated criteria were excluded from the meta-analysis.

Taking into account the aforementioned criteria, the meta-analysis includes 18 controlled clinical studies of the effectiveness of the drug Proteflazid® (Flavozid®) involving 1400 children with HHV infection.

All children before the beginning of the treatment and after the treatment were thoroughly examined, including conventional clinical and laboratory tests, ultrasound study of cellular and humoral immunity. Enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) were used as main methods of diagnosis.

The meta-analysis of clinical trials reflecting the results of the effectiveness of the drug Proteflazid® (Flavozid®) in the treatment and prevention of HHV infection in children was conducted by the following statistically significant indexes:

1. Dynamics of EBV clinical symptoms in children after the treatment of HHV infection with the drug Proteflazid® (Flavozid®) at the completion of treatment:

- The detection rate of lymphadenopathy in children with EBV infection.
- The detection rate of hepatomegaly in children with EBV infection.
- The detection rate of splenomegaly in children with EBV infection.

2. Dynamics of CMV infection markers in the blood of children after a course of treatment with the drug Proteflazid®:

- The detection rate of CMV DNA by the use of the PCR in children with CMV infection.

Clinical trials results as for the aforementioned parameters are presented in tables 2-5.

Table 2

The detection rate of lymphadenopathy in children with EBV infection

Author	Experimental group		Control group	
	The number of children treated with Proteflazid® (Flavozid®) who showed lymphadenopathy	General number of patients	The number of children not treated with Proteflazid® (Flavozid®) who showed lymphadenopathy	General number of patients
Usachova O.V., 2005	3	17	11	21
Kharchenko Yu.P., 2007	2	30	10	30
Kramarev S.A., 2012	3	5	5	5
Kramarev S.A., 2014	30	60	44	60
Total	38	112	70	116

228 children with EBV infection were studied by the parameter “Detection rate of lymphadenopathy in children with EBV infection” after the treatment with the drug Proteflazid® (Flavozid®), 112 of them are from the experimental group, and 116 – from the control group.

Table 3

The detection rate of hepatomegaly in children with EBV infection

Author	Experimental group		Control group	
	The number of children treated with Proteflazid® (Flavozid®) who showed hepatomegaly	General number of patients	The number of children not treated with Proteflazid® (Flavozid®) who showed hepatomegaly	General number of patients
Usachova O.V., 2005	6	17	8	21
Kharchenko Yu.P., 2007	6	30	19	30
Kramarev S.A., Vigovskaya O.V., 2012	5	5	5	5
Kramarev S.A., Vigovskaya O.V., 2014	19	60	40	60
Total	36	112	72	116

228 children with EBV infection were studied by the parameter “Detection rate of hepatomegaly in children with EBV infection” after the treatment with the drug Proteflazid® (Flavozid®), 112 of them are from the experimental group, and 116 – from the control group.

Table 4

The detection rate of splenomegaly in children with EBV infection

Author	Experimental group		Control group	
	The number of children treated with Proteflazid® (Flavozid®) who showed splenomegaly	General number of patients	The number of children not treated with Proteflazid® (Flavozid®) who showed splenomegaly	General number of patients
Usachova O.V., 2005	7	17	13	21
Kharchenko Yu.P., 2007	2	30	18	30
Kramarev S.A., Vigovskaya O.V., 2012	4	5	5	5
Total	13	52	36	56

108 children with EBV infection were studied by the parameter “Detection rate of splenomegaly in children with EBV infection” after the treatment with the drug Proteflazid®, 52 of them are from the experimental group, and 56 – from the control group.

Table 5

The detection rate of CMV DNA detection by the use of the PCR in children with CMV infection

Author	Experimental group		Control group	
	The number of children treated with Proteflazid® who showed CMV DNA	General number of patients	The number of children not treated with Proteflazid® who showed CMV DNA	General number of patients
Reznichenko Yu.G., 2007	3	14	7	10
Turlibekova S.S., 2011	0	23	5	25
Total	3	37	12	35

72 children with EBV infection were studied by the parameter “Detection rate of CMV DNA detection by the use of the PCR in children with CMV infection” after the treatment with the drug Proteflazid®, 37 of them are from the experimental group, and 35 – from the control group.

Results and Discussion.

Assessment of the effectiveness of the drug Proteflazid® (Flavozid®) in the treatment of EBV infection in children.

Fig. 1 shows a Forest plot for the meta-analysis results on the basis of OR of the detection rate of lymphadenopathy in children with EBV infection after the treatment with the drug Proteflazid® (Flavozid®) in experimental and control groups.

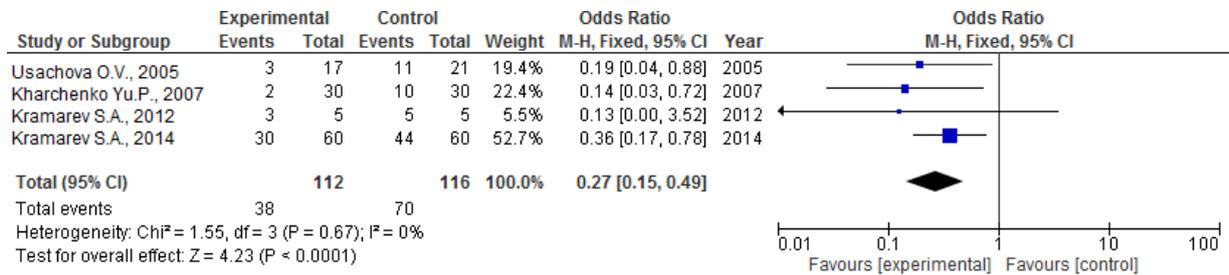


Fig. 1. The results of meta-analysis by indentifying the OR of detection rate of lymphadenopathy in children with EBV infection

χ -square criterion ($P=0.67$) and I^2 -test ($I^2=0\%$) indicate the homogeneity of these studies, so a model with fixed effect has been chosen. P-value of the Fisher test ($P=0.0001$) shows the importance of the selected effect.

Odds ratio ($OR=0.27$) indicates that the probability of the detection rate of lymphadenopathy in children with EBV infection after the treatment with the drug Proteflazid® (Flavozid®) in the experimental group is 3.7 times lower than in the control group.

The study conducted by Kramarev S.A., Vigovskaya O.V. (2014) has the greatest weight. They note that the drug Proteflazid® (Flavozid®) has a high clinical efficacy, an expressed immunocorrecting and antiviral activity in treatment of infectious mononucleosis of EBV etiology in children [14]. The study conducted by Kharchenko Yu.P. et al. (2007) indicates that the complex therapy with the drug Proteflazid® reduces the duration of the febrile period, the severity of infectious intoxication, the duration of symptoms of the lymphatic system damage [8].

Fig. 2 presents a Forest plot of the results of the meta-analysis by identifying the OR of the detection rate of hepatomegaly in children with EBV infection after treatment with the drug Proteflazid® (Flavozid®) in experimental and control groups.

χ -square test ($P = 0.11$) and I^2 -test ($I^2= 54\%$) indicate an insignificant heterogeneity of these studies, so a model with random effect has been chosen. P-value of the Fisher test ($P = 0.007$) shows the importance of the selected effect.

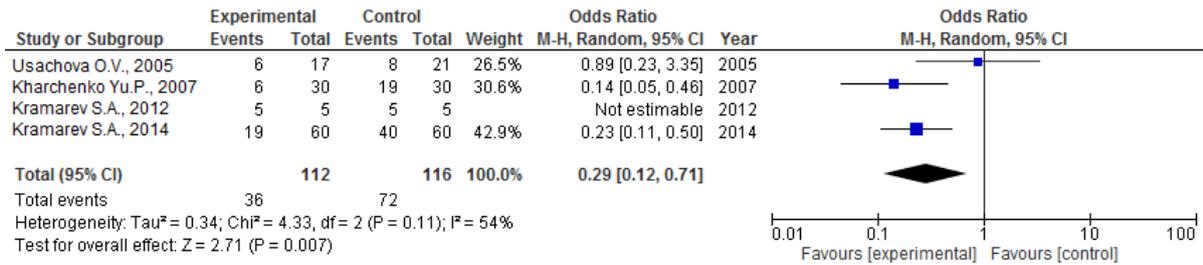


Fig. 2. The results of the meta-analysis by identifying the OR of the detection rate of hepatomegaly in children with EBV infection

Odds ratio (OR=0.29) indicates that the probability of the detection rate of hepatomegaly in children with EBV infection after treatment with the drug Proteflazid® in the experimental group is 3.45 times lower than in the control group.

The study conducted by Kramarev S.A., Vigovskaya O.V. (2014) has the greatest weight. They note that the drug Proteflazid® (Flavozid®) against the background of basic therapy of infectious mononucleosis in children increases the efficacy of treatment in the acute stage and minimizes the risk of progression of the disease in the acute phase into a protracted chronic disease [14]. The study conducted by Kharchenko Yu.P. et al. (2007) indicates that the complex therapy with the drug Proteflazid® reduces the frequency of hepatosplenomegaly [8]. Usacheva O.V. et al. (2005) noted a quicker arresting of hepatocyte cytolysis syndrome which is a manifestation of the complex course of infectious mononucleosis in children [5].

Fig. 3 presents a Forest plot of the results of the meta-analysis by identifying the OR of the detection rate of splenomegaly in children with EBV infection after treatment with the drug Proteflazid® (Flavozid®) in experimental and control groups.

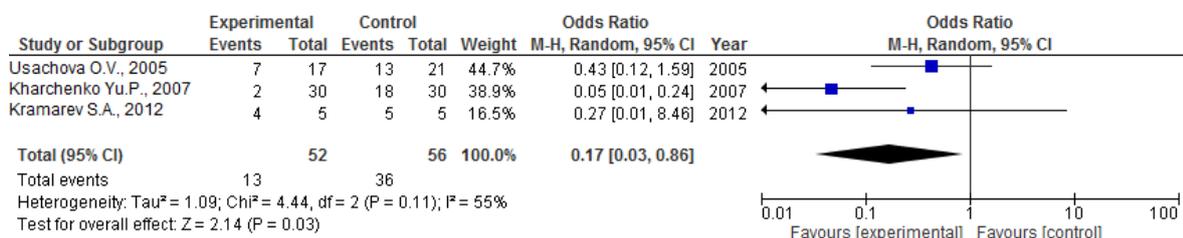


Fig. 3. The results of the meta-analysis by identifying the OR of the detection rate of splenomegaly in children with EBV infection

χ -square test ($P=0.11$) and I^2 -test ($I^2=55\%$) indicate an insignificant heterogeneity of these studies, so a model with random effect has been chosen. P-value of the Fisher test ($P=0.03$) shows the importance of the selected effect.

Odds ratio ($OR=0.17$) indicates that the probability of the detection rate of splenomegaly in children with EBV infection after the treatment with the drug Proteflazid® (Flavozid®) in the experimental group is 5.88 times lower than in the control group.

As for this sampling, the study conducted by Usacheva O.V. et al. (2005) demonstrated that the inclusion of the drug Proteflazid® in the complex therapy of infectious mononucleosis of EBV etiology in children leads to the positive dynamics of clinical symptoms of the disease and the blood count [5].

Assessment of the effectiveness of the drug Proteflazid® in the treatment of CMV infection in children.

Fig. 4 presents a Forest plot of the results of the meta-analysis by identifying the OR of the detection rate of CMV DNA in children with CMV infection by the use of the PCR after the treatment with the drug Proteflazid® at the completion of treatment in experimental and control groups.

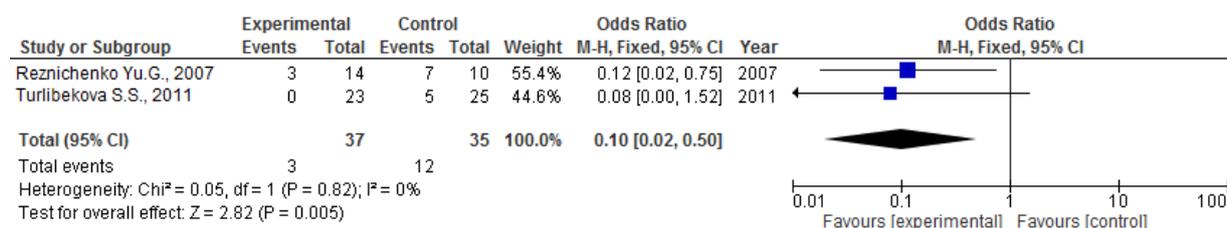


Fig. 4. The results of the meta-analysis by identifying the OR of the detection rate of CMV DNA in children with CMV infection by the use of the PCR

χ -square test ($P=0.82$) and I^2 -test ($I^2=0\%$) indicate the heterogeneity of these studies, so a model with fixed effect has been chosen. P-value of the Fisher test ($P=0.005$) shows the importance of the selected effect.

Odds ratio ($OR=0.10$) indicates that the probability of the detection rate of CMV DNA in children with CMV infection by the use of the PCR after the treatment with the drug Proteflazid® at the completion of treatment in the experimental group is 10 times lower than in the control group.

The study conducted by Reznichenko Yu.G. et al. (2007) has the greatest weight, it states that the use of the drug Proteflazid® in most cases ensures the CMV DNA elimination, improves the body's metabolism and the immune function [15]. Turlibekov S.S. (2011) concludes that the drug Proteflazid® enhances the innate immunity by increasing the level of endogenous interferon, which improves the resistance of the body not only against viruses but against bacteria as well [22].

Sensitivity Analysis. The sensitivity analysis was carried out in such a way as to assess the influence of each individual study on combined data by omitting individual research. The results of the sensitivity analysis showed that no individual study influenced significantly the combined data, which indicates statistically reliable results.

Assessment of publication bias. Funnel plot was used for assessing the bias of publications included into the study (Fig. 5-8). Almost all of the ES values in Fig. 5-8 are within the funnel, which indicates the absence of bias.

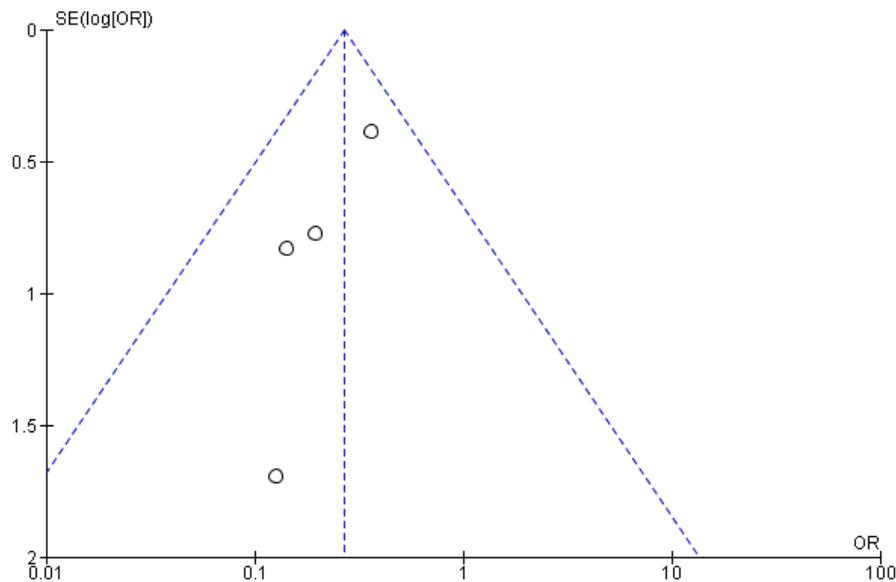


Fig. 5. Funnel plot for the index “The detection rate of lymphadenopathy in children with EBV infection”

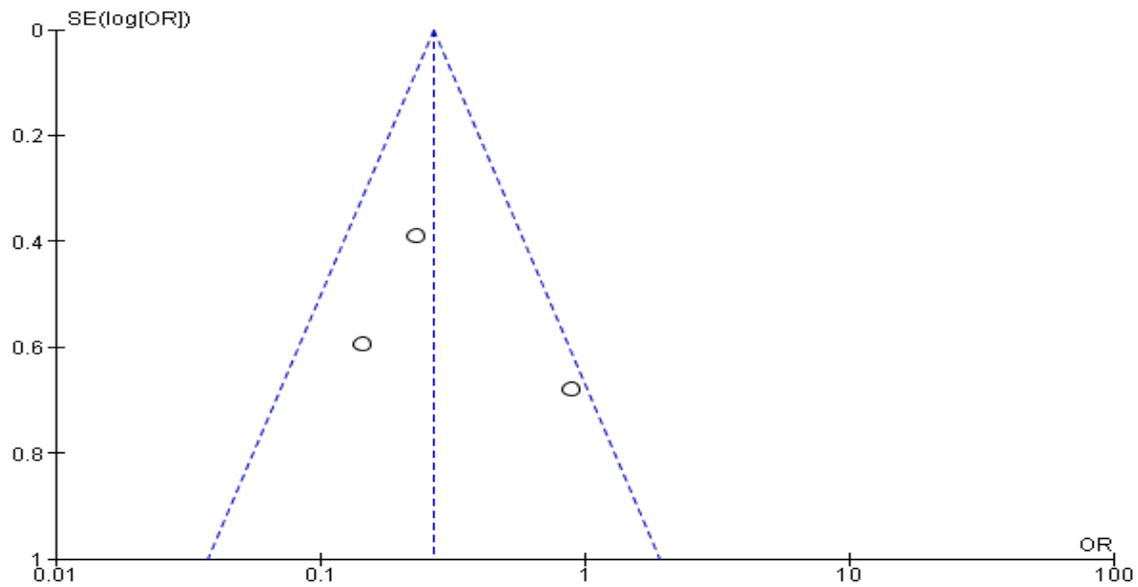


Fig. 6. Funnel plot for the index “The detection rate of hepatomegaly in children with EBV infection”

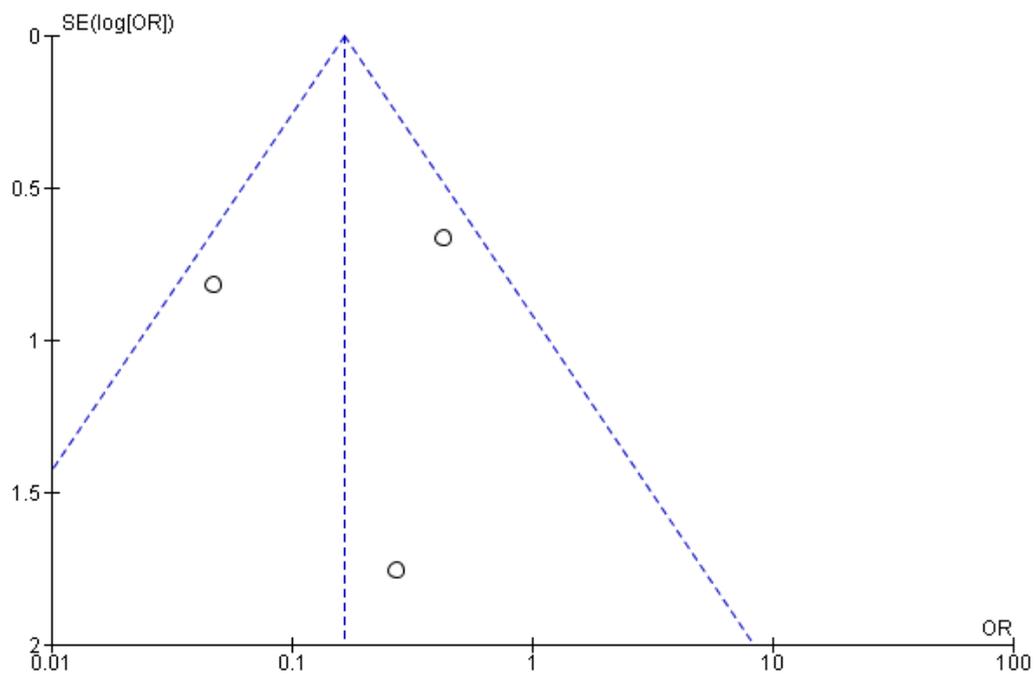


Fig. 7. Funnel plot for the index “The detection rate of splenomegaly in children with EBV infection”

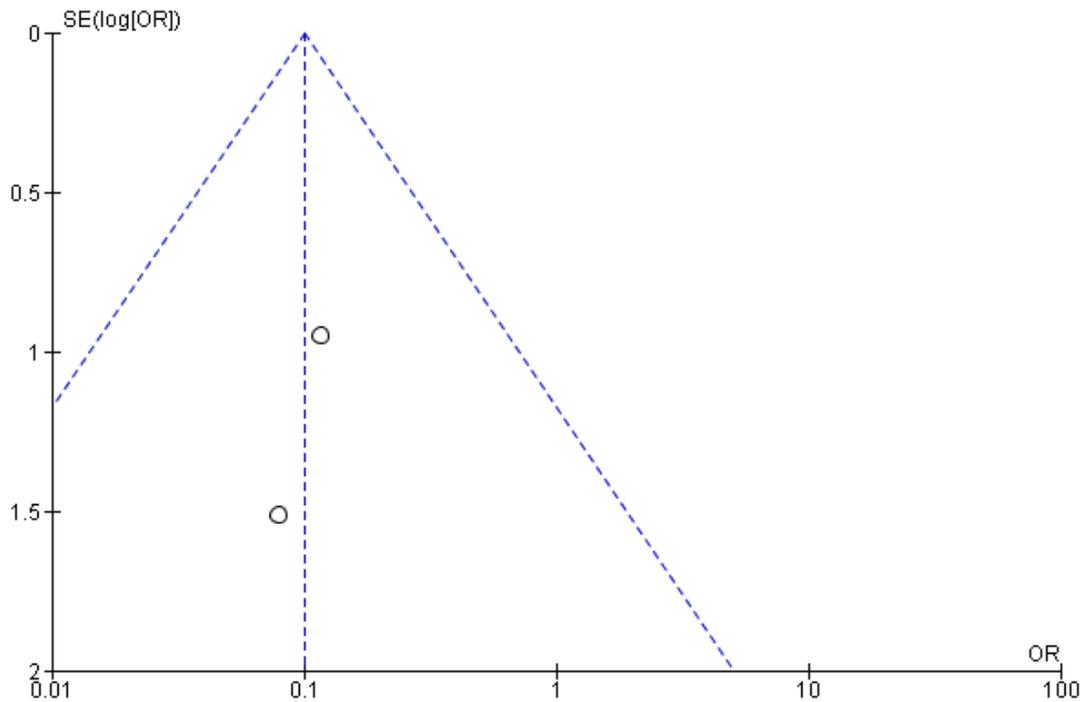


Fig. 8. Funnel plot for the index “The detection rate of CMV DNA detection by the use of the PCR in children with CMV infection”

Conclusion

This meta-analysis allowed increasing the evidence base for the effectiveness and the safety of the drug Proteflazid® for treatment of viral and concurrent infections in children.

The meta-analysis of clinical studies included 18 controlled clinical studies covering 1400 children for assessing the clinical effectiveness of the drug Proteflazid® in the treatment of children with HHV infection (CMV, EBV).

The meta-analysis has been conducted according to 4 indexes:

1. Detection of clinical symptoms of HHV infection in children after the treatment with Proteflazid® (Flavozid®) at the completion of treatment:

- The detection rate of lymphadenopathy in children with EBV infection.
- The detection rate of hepatomegaly in children with EBV infection.
- The detection rate of splenomegaly in children with EBV infection.

2. Dynamics of CMV infection markers in the blood of children after a course of treatment with the drug Proteflazid®:

- The detection rate of CMV DNA detection by the use of the PCR in children with CMV infection.

This meta-analysis confirms the effectiveness and the safety of the drug Proteflazid® in clinical use based on the following obtained results: in administering the drug Proteflazid® in children with EBV and CMV infection, (experimental group) positive dynamics of clinical symptoms of disease was observed at the stage of completion of the study:

- Reduction in the probability of detection rate of clinical symptoms of EBV infection: lymphadenopathy in the experimental group was 3.7 times lower than in the control group; hepatomegaly in the experimental group was 3.45 times lower than in the control group; splenomegaly in the experimental group was 5.88 times lower than in the control group.

- during treatment, the probability of the detection rate of CMV DNA in children with CMV infection by the use of PCR was 10 times lower than in children who did not take the drug Proteflazid® (control group).

Meta-analysis of clinical trials shows a high efficiency of the drug Proteflazid® in the treatment of children with HHV infection (CMV, EBV). The use of the drug in the treatment of HHV infection (including its mixed forms) contributes to the positive dynamics of the main clinical symptoms of disease – reduction in the detection rate of lymphadenopathy, splenomegaly and hepatomegaly and elimination of herpes viruses from the body of the child.

Given its high tolerability, high safety profile, combined effect on many elements of viral infections, the drug Proteflazid® can be recommended as an effective and safe antiviral agent for the treatment and prevention of diseases caused by HHV infection (CMV, EBV) in children.

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