

Collective Immunity of the Population from Endemic Zones of Hemorrhagic Fever with Renal Syndrome in Kosovo

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SUMMARY

Hemorrhagic fever with renal syndrome (HFRS), also known as mice fever, is an acute viral zoonosis and it appears in the natural focus after the human contact with Hantaan virus infected mice. The objective (purpose) of this project is: to determinate the rate of Morbidity (Mb), Mortality and Lethality (Lt); to investigate the collective immunity in endemic focus. In this project we applied the epidemiological method of studying with retrospective-perspective, the serological method for determination and detecting antibodies from the persons of epidemical focus and statistical methods. The disease diagnosis is based on the epidemiological, clinical and serological records. The collected samples have been sent to referral laboratory in Medical Faculty-Institute of Microbiology Ljubljana for laboratory confirmation. From the results we came to conclusion that in the territory of Republic of Kosovo, the HFRS is still a serious health, economic and biological problem. The lethality rate from HFRS in 1986 was 15.4%, 1986-89 10.8%, from 1995-2006 8.70%. The lowest rates of morbidity, mortality and lethality of HFRS compared with the previous periods of time, prove collective immunity growth in Dukagjini valley. For collective immunity research and to conduct the persistence of antibodies for viral corresponding (relative) antigen, after the disease, the samples were collected in the time period of May-June 2008, with 203 persons that were tested with serological method IIF (Indirect immune fluorescence) from which 187 cases (92.1%) resulted sero-negative and 16 cases (7.9%) resulted sero-positive with HFRS. This proves the collective immunity increase for HFRS. Out of the total number of sero-positive persons with HFRS (16 cases) the highest number resulted in persons of first contact with 12 cases (75%) sero-positive with HFRS, while the lowest number in persons with hemodialysis with only 1 case (6.3%); (high level of antibody for HTN and DOB, with level 1:1024). The collected samples in the period May – June 2008, have been tested with serological method IIF in health workers and 20 healthy persons (control group). Antibodies for viral antigen were not found in any of the cases (HTN, PUU

and DOB). From 13 recovered patients previously diagnosed with HFRS (1986-1989-1995), levels of antibodies were screened in 2008 with IIF. Out of 13 persons, positive antibodies were found in 10 cases, while 3 cases were negative for antibodies (HTN, PUU, and DOB). After 13, 19 and 22 years HTN, PUU and DOB antibodies persisted in level (1:16-1:512). Based on the gathered results, we came to conclusion that it is necessary to compile the National Strategy of Surveillance for the Kosovo Health System for a 5 year period, for avoiding this high risk disease.

Keywords: HFRS, collective immunity, HTN PUU DOB antibodies, IIF, Republic of Kosovo

1. INTRODUCTION

Haemorrhagic Fever with Renal Syndrome (HFRS), or else known as 'mice fever', is an acute viral zoonosis, that appears in natural hearths after the humans get in contact with some sorts of mice infected with the Hantaan virus (ARN virus).

HFRS – is a zoonosis with viral ethiology, with various clinical manifestations, and has more than 150 synonyms, appears in many countries of the world. ^(1, 4)

This disease has a wide geographical spread, and it is present in almost all European countries, especially in Balkans, and Kosovo is not excluded from attacks.

There are diseases and natural hearths of two sorts of viral haemorrhagic fever in Kosovo: haemorrhagic fever with renal syndrome (HFRS) and Crimean Congo Haemorrhagic Fever (CCHF).

Viral Haemorrhagic Fevers (CCHF and HFRS) are diseases that started manifesting very early in our country; HFRS was officially registered since 1986, either in sporadic or epidemic forms. Consequently, the epidemics

of these diseases in Kosovo appeared several times starting in 1986, and then in 1995, 2001, 2004 and 2005. ^(1, 3, 4)

Natural hearths of HFRS in Kosovo are: Bjeshkët e Nemuna, Mountains of Peja, Deçan, Junik, Gjakova, Istog and Kashtanjeva in Ferizaj. The scale of resistance of a population towards a particular communicable disease is determined with **collective immunity**. This is with high importance for epidemiology, since from the scale of collective immunity depends also the epidemiological situation with particular diseases (HFRS). With the increase of the collective immunity, comes also the decrease of the scale of morbidity, mortality and lethality from the particular diseases (HFRS) and vice versa.

The finding of the antiviral antibodies in human serums and the rodent serums in various places out of this geographical dissemination offers possibility for appearance of the same diseases anywhere where there is contact between humans and rodents. ^(1, 2)

Sensitivity towards HFRS is general. All those who are in contact with the disease virus become ill, but most vulnerable are: farmers, mountain trackers, campers, shepherds, mountain rangers and collectors of natural fruits.

After the recovery from the disease, comes the decrease of the antibodies, which shows the possible existence of re-infection with other types of Hantaan viruses. Various authors have found traces of specific antibodies against the Hantaan virus, even 34 years after the disease. Other researches show that in natural hearths, seropositivity in Hantaan is 2-29%, while in Europe it's in 2.1% of population. ^(1, 4, 10)

2. AIMS OF THE RESEARCH WORK

To research the presence of specific antibodies in the persons of the first and second family circle, in diseased persons that undergo haemodialysis from the endemio-zootic hearths, health personnel that attends to the hospitalized patients and in healthy persons that do not belong to endemic hearths (control groups).

To investigate the persistence of specific antibodies in HFRS, in convalescent persons (collective immunity in endemic hearths).

3. METHODOLOGY AND WORKING MATERIALS

Epidemiological method of study was used, retrospective-perspective component, serologic method and statistical method.

For explication of this study were analysed the cases of the diseased with HFRS, that were treated in Infectious Disease Clinic, respectively in UCCK, and in the secondary level of the health care, as well as the field collection of the samples from convalescents (that have passed the acute disease), from the persons of the first and second family circle, ill persons that undergo haemodialysis from endemic-enzootic hearths, from persons that could have been infected in the epidemic hearth, health workers that treated the patients with HFRS as well as from the control group (healthy persons) that come from areas in Kosovo that had no diagnosed cases of this disease.

Diagnosis of the disease was done based on the epidemiological, clinical and serological data. For verification of the HFRS disease cases, laboratory research – serological testing was done, with the following methods: IIF (Indirect immune fluorescence) and the modern method of PCR (polymerase chain reaction) for acute cases.

The collected samples (serums) were sent to the referent laboratory in the Faculty of Medicine – Institute of Microbiology- Ljubljana, for their laboratory confirmation. The research on the collective immunity scale on HFRS was achieved with: Serological Tests – detection of antibodies (Ab) in serum with IIF method (Indirect Immune Fluorescence) that has diagnostic character and research of collective immunity. Detection of antibodies, from the blood of persons that live in HFRS endemio-epidemiological hearths, for the purposes of verification of the contact with specific antibodies, respectively verification of the fact if the tested person was in contact with the causes of HFRS.

For the epidemiological research, we have used the continuous epidemiological surveillance in the field, case research, data collection on the movement of the disease, health indicators, like: scale of morbidity, mortality and lethality.

Results' testing was done with T-test and Spearman's correlation for the parametric data, X2-test, and Fishers test for the non-parametric data. Test verification was done for credibility 95% and 99%. Tables and graphs were used for presentations.

4. RESULTS

For researching the **collective immunity** and follow up on **antibodies persistence** for respective viral Ag (HTN, PUU, DOB), during the period **may-June 2008**, the following was done: blood samples (serums) were taken from 203 persons and after the testing made with serological method IIF, the following results came out: 187 serums or 92.1% were negative on HFRS and 16 serums or 7.9% were positive on HFRS, as well as the follow up of health indicators like: morbidity, mortality and lethality scale for HFRS during the period 1995-2006.

Table 1. Movement of average morbidity, mortality and lethality scale of HFRS, in Kosovo, 1995-2006

Time Period	Mb/100.000	Mt/100.000	Lethality (%)
1996-2006	0.16	0.02	8.70

This was proved even during our research, 1995-2006 in Kosovo, where a low scale of morbidity, mortality and lethality of HFRS was registered, compared to other earlier time periods, which results in high scale of collective immunity on HFRS in Kosovo during the time of our research. (tab.1)

Table 2. Movement of Lethality scale (%) of HFRS in Kosovo, during different time periods

Time Period	Lethality (%)
1986	15.40%
1986-1989	10.80%
1995-2006	8.70%

Table 3. Detection of immune fluorescent Antibodies in population living in the natural hearths characteristically with HFRS, 2008, Kosovo

Tested	HFRS – IIF				Total	
	Seronegative	%	seropositive	%	N	%
Contact 1*	43	23.0	12	75.0	55	27.1
Contact 2**	79	42.2	3	18.8	82	40.4
Haemodialysis Pat.	29	15.5	1	6.3	30	14.8
Health Personnel	16	8.6	0	0.0	16	7.9
Control Group	20	10.7	0	0.0	20	9.9
Total	N	187	100.0	16	100.0	203
	%	92.1	-	7.9	-	100.0

*Contact 1 or the first family circle – means close family members that live with the patient with HFRS

** Contact 2 or the second family circle – means members of the family that live together in the endemic zones characteristic with HFRS

Out of the total number of positive serums (16 seropositive) on HFRS, the highest number of positive serums has resulted in persons of the **first contact** with 12 or 75% of positive serums on HFRS, then the persons of the **second contact** with 3 or 18.8% of positive serums, while the lowest number of positive serums resulted in patients with haemodialysis with 1 or 6.3% of positive serums. While the other groups that were tested: health personnel and control group have resulted with negative serums on HFRS. (tab.3).

With the IIF method, **55 collected serums** were researched from persons of the **first contact** (first family circle) and 43 persons resulted negative on HFRS, positive were 12 persons. Afterwards, in 82 collected serums from persons of the **second contact** (or the second family circle), 79 resulted negative, while 3 resulted positive. This proved the presence of the positive level of immune fluorescent antibodies for respective viral Ag (HNT, PUU, DOB), (see tab. 3)

Research of the tested serums from 30 ill patients that were hospitalized in the haemodialysis centre at the Peja Regional Hospital (HD 1-10 years), due to **Chronic Renal Insufficiency (CRI)** with unknown etiology, only one patient that is hospitalized in haemodialysis centre, has resulted positive in HFRS (high level of immune fluorescent Ab for HTN and DOB virus with levels 1 : 1024). (tab.3)

Research (with the IIF method) of 16 serums collected from health personnel that were nursing the patients with HFRS in the Infectious Disease Clinic in Pristina. None of the cases showed positive level of immune fluorescent Antibodies for respective viral Ag (HNT, PUU, and DOB). (tab.3)

Research (with IIF method) of 20 serums collected from healthy persons (voluntary blood donors), that do not

live in natural hearths characteristic with HFRS, which in fact serves as control group (see tab.3). None of the cases showed positive levels of immune fluorescent Antibodies for respective viral Ag (HNT, PUU, and DOB).

During May-June 2008, with the serological method IIF, research of 203 samples (serums) was done, where 187 serums or 92.1% were negative on HFRS and 16 serums or 7.9% were positive on HFRS. **This proves the increase of the collective immunity scale of the population of endemic zones characteristic with HFRS.** (graph.1).

Through the Fisher's test, we have gained difference with important statistical significance between the scale of serums positivity from persons of the first and second contact ($p < 0.001$). Relative risk shows that the persons of the first contact are approx. 6 times more endangered compared to persons of the second contact (95%, CI 1.7 – 20.1). (tab.4).

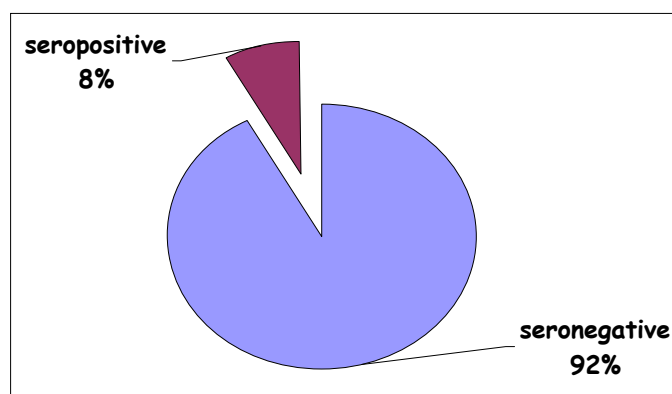
Out of 13 convalescents (that have undergone the acute disease during 1986, 1989, and 1995), we have determined

Table 4. Serpositivity scale of serums from persons of the first and second contact.

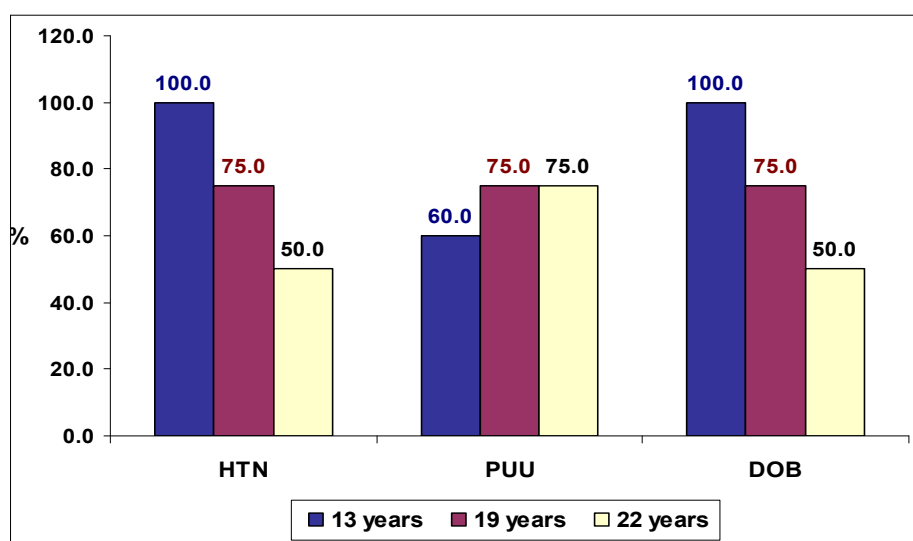
Contact	Seropositive		Seronegative		Total	
	N	%	N	%	N	%
First	12	21.8	43	78.2	55	100
Second	3	3.7	79	96.3	82	100
Total	15	10.9	122	89.1	137	100
Fisher's test	$p < 0.001$					
Relative Risk	5.96					
95% CI	1.7–20.1					

Table 5. Table presentation showing persistence levels of antibodies of viral Ag (HTN, PUU, DOB), during various time periods, 13, 19 and 22 years after the disease.

Nr.	(Convalescents) ex patients with HFRS	Municipality	Contact	Antibodies level of HFRS 2008			Time period
				HTN	PUU	DOB	
1	1986	Deçan	first	1:256	1:64	1:256	1986-2008 (22 years)
2	1986	Pejë	first	1:32	neg	1:64	
3	1986	Pejë	first	neg	neg	neg	
4	1986	Pejë	first	neg	neg	neg	
5	1989	Pejë	first	1:128	1:16	1:256	1989-2008 (19 years)
6	1989	Gjakovë	first	1:512	1:32	1:512	
7	1989	Pejë	first	1:32	1:16	1:64	
8	1989	Deçan	first	neg	neg	neg	
9	1995	Deçan	first	1:256	1:32	1:128	1995-2008 (13 years)
10	1995	Pejë	first	1:32	neg	1:64	
11	1995	Klinë	first	1:64	1:32	1:128	
12	1995	Istog	first	1:32	neg	1:64	
13	1995	Gjakovë	first	1:128	1:16	1:64	
Spearman's correlation				$r = -0.300$ $p > 0.05$	$r = -0.16$ $p > 0.05$	$r = -0.21$ $p > 0.05$	-



Graph 1. Graphical presentation expressed in percentage of the seronegative persons with HFRS, 2008, Kosovo.



Graph 2. Graphic presentation of the positivity scale of levels of Antibodies for viral Ag (HTN, PUU, and DOB) during various time periods 13, 19, and 22 years after the disease.

the level of antibodies for the viral Ag (HTN, PUU, DOB), in 2008, with the indirect immune fluorescent method (IIF). Out of all these convalescents, persistence of antibodies was found in 10 persons, while in 3 others we did not find antibodies persistence for respective viral Ag.

In 4 convalescents (ex acute patients in 1986), testing with indirect immune fluorescent method (IIF) was done in 2008 (after 22 years); in two of them were found levels of antibodies for viral Ag HTN, PUU, DOB (from 1:32 to 1:256), while in the other two, levels of antibodies for respective viral Ag were not found.

Also, in 4 other convalescents (ex acute patients in 1989), testing was done with indirect immune fluorescent method (IIF), in 2008 (after 19 years), and in 3 of them, levels of antibodies of viral Ag HTN, PUU, DOB were found (from 1:16 to 1:512), while in one case, levels of antibodies for respective viral Ag were not found.

In 5 convalescents (ex acute patients in 1995) testing was done with indirect immune fluorescent method (IIF), in 2008 (after 13 years), and in all of them, levels of antibodies of viral Ag HTN, PUU, DOB were found (from 1:16 to 1:256). (tab.5, graph.2)

At the patients, in which the acute disease (HFRS) has passed before 13, 19, and 22 years, we did not gain any significant difference in the levels of antibodies for viral Ag: for HTN ($r = 0.3000$, $p > 0.05$); for PUU ($r = 0.16$, $p > 0.05$), and DOB ($r = 0.21$, $p > 0.05$). (Tab.5 and Graph.2).

5. DISCUSSIONS

Lethality scale of HFRS was higher in Kosovo in 1986, with 15.4%, compared to other neighbouring countries (average Lethality in ex YU was 5.2%) and Balkans. Similar Lethality was not registered anywhere else in Europe, with exception of Bulgaria and Albania, and in the Far East. ^(1, 4, 10) This is explained with the heavy forms of the illness as well as with the lack of sufficient experience in curing of these illnesses, in the first year of epidemics.

Lethality scale of HFRS during various time periods marks a decrease as follows: in 1986 it was 15.4%, afterwards during 1986-1989, it was 10.8%, in a way that it continuously decreases; even also during the period 1995-2006 it was lower (8.70%); This is explained due to the fact that after the 1986 epidemics, sufficient experience was gained, not only in curing, but also in diagnosing, which explains why the lethality has decreased from 15.3% (1986) to 8.7% (1995-2006). This means that the increasing scale of resistance of population or the collective immunity on HFRS, results with the decrease of these health parameters, respectively, decrease of Mb, Mt and Le. According to

the foreign literature, the lethality scale of HFRS varies: in Soviet Union Le- 3-22%, then decreases to 10-15%, Korea Le - 5-20%; Greece Le - 13%; Albania Le - 28.1%; Scandinavia and Western Europe Le - 0.5-1%. ^(1, 4, 10) This shows that the Lethality scale in Kosovo is much lower compared to other countries.

Humans get infected in direct contact with rodents (catching them with traps, while harvesting, etc), with water and food contaminated with mice excreta or in the form of aerosols. Infected rodents do not manifest signs of the illness, but they eliminate the virus of the disease in external ambience through faeces, urine or saliva, for 1 to 12 months after the infection. ^(1, 4, 10) The information that for infection with HFRS, it is necessary to be in direct contact with rodents or their secretions, is proved also during our work while obtaining the serums from the control group (total of 20 serums), where after the testing with the serological method (IIF), in Ljubljana, the positive levels of Antibodies for respective viral Ag (HNT, PUU, and DOB) was not found in any of the cases. **Absence of antibodies for viral Ag (HNT, PUU, and DOB) at the population out of the natural hearths (control group) shows the necessity**

of the direct contact with rodents or their excreta and secretions for causing this illness.

HFRS is an illness with heavy gravity, with kidney damages up to their insufficiency, but it is not transmitted human to human (no such cases in our practice until now), which is a relieving circumstance compared to CCHF. ^(1, 4,10) *The information that there is no transmission of HFRS from human to human, is proved also during our research while collecting serums from health personnel (total of 16 serums), where after the testing with serological method IIF in Ljubljana, non of the cases proved positive levels of antibodies for respective viral Ag (HNT, PUU and DOB).*

During our research, **May-June 2008**, we have collected blood samples (serums) from 203 persons and after testing with serologic method IIF, we had the following results: out of 203 samples (serums) tested, 187 serums or 92.1% were negative on HFRS and 16 serums or 7.9% were positive on HFRS. This means that specific HTN antibodies were found in 7.9% of the population from the natural hearths of HFRS. *This proves the increase of the scale of collective immunity on HFRS.*

Based on the data from foreign literature, specific antibodies on HNT were found in 1.9-29.1% of population from the natural hearths of this disease; In Europe, in 2.1% of population.

During our research, **May-June 2008**, **30 patients with haemodialysis** were tested with serologic method IIF, and only one resulted positive serum (high level of antibodies for HTN and DOB, 1:1024);

In our research, finding the antibodies for viral Ag (HNT, PUU and DOB) in a patient with Chronic Renal Insufficiency (CRI) with unknown etiology, shows the possibility of chronic damage of the kidneys during HFRS, therefore in all the cases with CRI with unknown etiology, especially when these patients are on dialyses come from natural hearths characteristic with HFRS, we should also consider this illness (HFRS). Chronic damage of kidneys during HFRS were researched and verified by other authors also. (tab.19).

During May-June 2008, with serological method IIF, were tested 16 serums from health personnel. None of the cases showed positive levels of antibodies for respective viral Ag (HNT, PUU and DOB).

The absence of antibodies for viral Ag (HNT, PUU and DOB) in health personnel that has treated and cured the patients with HFRS, proves once again the known fact that there is no way of human to human transmission of this illness.

During period May-June 2008, with serological method IIF, were tested **20 healthy persons (control group)**. In none of the cases the positive level of antibodies for respective viral Ag (HNT, PUU and DOB) was found.

The absence of antibodies for viral Ag (HNT, PUU and DOB) in population outside of the natural hearths (control group) shows the necessity of direct contact with rodents or with their excreta and secretion for causing the HFRS illness.

Out of all these convalescents, the persistence of Antibodies was found in 10 persons, while in 3 others we did

not encounter any persistence of antibodies for the respective viral Ag. After 22 years (1986-2008), with the serologic method (IIF), the persistence of the levels of antibodies for viral Ag HTN, PUU, and DOB was found (with levels from 1:32 to 1:256). After 19 years (1989-2008), with the serologic method (IIF), the persistence of the levels of antibodies for viral Ag HTN, PUU, and DOB was found (with levels from 1:16 to 1:512). After 13 years (1995-2008), with the serologic method (IIF), the persistence of the levels of antibodies for viral Ag HTN, PUU, and DOB was found (with levels from 1:16 to 1:256).

After the illness, comes the decrease of the levels of antibodies, which shows the existence of possibility for re-infection with other types of Hantaan viruses.

Various authors have found traces of specific antibodies against the Hantaan virus, even up to 34 years after the disease. ^(1, 4,10)

During our research, we found persistence of antibodies for viral AG HTN, PUU and DOB (with levels from 1:16 up to 1:512), even after 13, 19 and 22 years after the illness. ⁽¹⁰⁾

Good results have been achieved in defining of natural hearths, defining the reservoirs and sources of infection as well as in curing of the patients, which has influenced the decrease of the Morbidity, Mortality and Lethality scale. All this was achieved thanks to the hard work of the experts from NIPHK and regional IPH's, health personnel of the Infectious Disease Clinic and other personnel of UCKK, regional hospitals and primary health care; but it was missing at it is still missing the authentic governmental programme, which would prevent any future appearance and new deaths from this disease. ^(1, 4,10)

6. CONCLUSIONS

Based on the research work done, we can conclude that:

- Lethality scale from HFRS in 1986, was 15.4%, then in 1985-89 it was 10.8%, while from 1995-2006 it was lower, 8.70%;
- **Low Morbidity, Mortality and Lethality scale form HFRS** compared to earlier time periods, results with **increase of the collective immunity in the population from natural hearths of HFRS;**
- During **May-June 2008**, with the serological method IIF, the testing of 203 samples (serums) was done, where 187 serums or 92.1% were negative on HFRS and 16 serums or 7.9% were positive on HFRS. **This proves the high scale of increase of collective immunity in population from natural hearths with HFRS;**
- Out of the total number of positive serums (16 seropositive) in HFRS, the highest number of positive serums resulted in persons from the **FIRST** contact with 12 positive serums in HFRS, while the lowest number of positive serums in patients with haemodialysis, with 1 positive serum;
- During the period **May-June 2008**, with the serologic method IIF, there were **55 serums** tested, collected from persons of the **first contact**, out of which 43 persons resulted negative in HFRS, while

- 12 persons were positive on HFRS;
- With the serological method IIF, 82 collected serums from persons of the **second contact** were analysed and 79 resulted negative in HFRS, while 3 resulted positive in HFRS;
- Collected serums during period May-June 2008, were tested with the IIF method; 30 **patients with haemodialysis**, only one patient has resulted with positive serum (high level of antibodies for HTN and DOB, with level 1:1024);
- Serums collected during **May-June** 2008, were tested with IIF method health personnel: None of them showed positive level of antibodies for respective viral Ag (HNT, PUU and DOB);
- Serums that were collected during the period May-June 2008, tested with IIF method, 20 healthy persons: there were no cases with positive levels of antibodies for viral Ag (HNT, PUU and DOB);
- **Out of 13 convalescents** (that have undergone the acute disease during 1986, 1989 and 1995), with the immune fluorescence method IIF, **the level of antibodies was determined for antibodies of viral Ag (HTN, PUU and DOB) in 2008**, where the persistence of antibodies was found in 10 persons, while in 3 of them we did not encounter any persistence of antibodies for respective viral Ag;
- After 22 years (1986-2008), the persistence of the levels of antibodies for viral Ag HTN, PUU, and DOB was found (with levels from 1:32 to 1:256);
- After 19 years (1989-2008), the persistence of the levels of antibodies for viral Ag HTN, PUU, and DOB was found (with levels from 1:16 to 1:512);
- After 13 years (1995-2008), the persistence of the levels of antibodies for viral Ag HTN, PUU, and DOB was found (with levels from 1:16 to 1:256).

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