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Blood-borne viral infections among blood, organ and tissue donors

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The article presents an actual information on the detection rate of blood-borne viral infections (BBVI) among blood donors, potential organ and tissue donors in Russia and other countries. The causes of differences in BBVI prevalence between blood donors and potential organ and tissue donors have been analyzed. The BBVI prevalence among potential organ donors was proved to be much higher than among blood donors due to their medical-and-social characteristics.

Keywords: blood borne viral infections (BBVI), blood donor, potential organ donor.

Transfusion has passed a long way of development. Sporadic experiments in blood transfusion were made as early as in the Middle Ages. [1] However, until the beginning of the XX-th century blood transfusions remained an extremely risky method of therapy and were primarily empirical. After the discovery of the ABO blood group system, blood preservation techniques, immune doctrine development, the blood component therapy firmly came into clinical practice. However, its wide use in various fields of medicine has always been hampered by the shortage of donors [2].

Dr. S.S.Yudin was the first who tried to solve the problem of donor blood shortage at the Sklifosovsky Research Institute for Emergency Medicine in 1930, using the blood of a suddenly died person as a blood donation [2]. At that time, taking as an example the existing risk of syphilis transmission from a deceased donor to a recipient via blood transfusion, S.S.Yudin raised the issue of infectious safety of transfused blood. But the solution of the problem was difficult as there was the risk of testing the donors for syphilis in the so called “serological window period”. However, while the use of cadaver donor blood mandated the donor autopsy section in addition to mandatory serological study, it made possible to investigate thoroughly all other organs for syphilis that considerably reduced the risk of disease transmission.

Currently, the issue of the infectious safety of blood and its components has not lost its relevance. Testing for syphilis has been complemented with tests for BBVIs that include the infection caused by the human immunodeficiency virus (HIV), hepatitis B virus (HBV), and C virus (HCV). These infections were included in donor screening because of their medical and social relevance due to high prevalence and complication rates. According to WHO [3], in 2014 more than 36 million people worldwide were infected with HIV; more than 240 million, and 150 million had chronic HBV, and HCV infection, respectively [4]. There are from 3 to 5 million inhabitants in Russia who have chronic HBV infection, and from 1.5 to 3 million having chronic HCV infection; an extremely unfavourable epidemiologic situation still remains with HIV infection [5, 6]. The incidence of acute and chronic forms of BBVI in Russia exceeds those in many countries of Western Europe and the United States [7, 8].

Infectious safety of blood and its components is a fundamental principle for blood bank services worldwide. A modified donor screening algorithm, improved serological screening test systems, the implementation of innovative BBVI-testing technologies (gene-amplification testing), and the quarantine and virus inactivation of blood components allowed a significant decrease of the transfusion-transmission infection risk.

However, the risk of BBVI transmission still exists if the blood for transfusion has been taken from the infected individuals during the "serological window period" or from those with "latent" infection, specifically with hepatitis B infection.

A high prevalence of BBVIs among the Russian population and their mostly asymptomatic course pose a great risk of epidemics spreading, especially among donors [9]. Much attention in literature has been paid to studying the behavioural pattern of a modern blood donor and the factors influencing potential donors so that to predict the organ donation development in the nearest future [10]. However, given the high prevalence of BBVIs among population, no less important is to study the infection incidence rates in donor populations, and the medical and social characteristics of such populations to predict medical withdrawals from donation and to increase an infectious safety of blood and its components.

Blood-borne viral infections in blood donors in Russia

In accordance with the RF current legislation, the blood donor screening shall be performed using the enzyme-linked immunosorbent assay (ELISA) or chemiluminescence immunoassay (ChLIA) that includes testing for HIV markers (HIV Ag/Ab), HBV (HBsAg), HCV (anti-HCV), and for syphilis. Blood donation shall additionally be tested for gene material of

BBVI pathogens using biomolecular techniques (RF Government Resolution No. 1230 of December 31, 2010, "On approval of examination rules and methods of blood sampling to apply and strictly follow the technical regulations on the requirements for the safety of blood, its products, blood-substituting solutions, and equipment used in transfusion-infusion therapy". This allows a maximum minimization of the risk of BBVI transmission to a recipient.

The routine activities of blood bank service institutions functioning in the Russian Federation were studied based on the data of their official statistical reports as per Form No. 39 "Report of the blood bank station, the blood transfusion department, the hospital engaged in donor blood procurement". The study made it possible to assess the incidence of detecting the BBVI markers in donors (in primary and repeated blood donations, and among regular blood donors) (Table 1). The findings suggest the presence of divergent trends in the incidence of detecting BBVI markers in the donor population for the study period:

- Decrease for HBV and HCV infection;

- Increase for HIV infection due to a generally worsened epidemic situation with this infection in the Russian Federation [6].

Table 1. Changes in BBVI detection rates over time in blood donors in the Russian Federation in 2007-2014, %

Year / Infection	HIV	HBV	HCV	Reference
2007	0.07	0.90	1.60	E.A. Selivanov et al., 2009 [11]
2008	0.08	0.80	1.30	

2009	0.09	0.60	1.20	E.A. Selivanov et al., 2010 [12]
2010	0.20	0.60	1.10	E.A. Selivanov et al., 2011 [13]
2011	0.10	0.60	1.00	E.A. Selivanov et al., 2012 [14]
2012	0.11	0.47	0.77	A.V. Chechetkin et al., 2014 [15]
2013	0.10	0.41	0.79	
2014	0.10	0.34	0.81	A.V. Chechetkin et al., 2015 [16]

Meanwhile, the incidence rates of HCV infection were found to be higher that those of HIV and HBV infection in the donor population. It should be noted that the incidence of BBVI detection in blood donors as assessed per Form No. 39 Statistical Report constitutes the average for the whole of the Russian Federation and may not reflect true differences in the infection rates among blood donor populations between Russian regions. HIV, HBV, and HCV infection detectability varies between different regions of the Russian Federation (Table. 2).

Table 2. Detectability of BBVI markers in the donors of blood and blood components in the regions of Russia, %

Region / Infection	HIV	HBV	HCV	A source
Perm Territory	0.42	0.07	0.44	L.V. Reneva et al., 2011 [17]
Mari El Republic	0.014	0.34	0.42	E.Yu. Zangerova et al., 2013 [18]
Krasnodar Territory	0.0272	0.42	0.75	A.T. Kodenev et al., 2010 [19]

Sakhalin Region	-	-	2.3	A.V. Baranov et al., 2008 [20]
Khabarovsk Territory	-	3.0	3.0	S.N. Slobodyanyuk et al., 2008 [21]
Moscow	0.03	0.04	0.3	M.Sh. Khubutiya et al., 2014 [23]

Note: "-" data unavailable.

Causes of varied BBVI detection rates in donors may be related to:

- Epidemiological characteristics of the study area with regard to BBVIs;

- Medical and social characteristics of various subpopulations becoming blood donors;

- The quality and completeness of the programs aimed at BBVI spread prevention;

- The medical screening algorithm for potential blood donors;

- Using BBVI diagnostic methods of different sensitivity and specificity.

Despite the national trends to reduced overall incidence of BBVI detected in blood donors [15], there is an increased number of persons deferred from donation in some regions because of detected HIV infection. E.Kudinova et al. [22] reported a 1.3-fold increase in the absolute number of deferred donors as a result of identified HIV infection at the Regional Blood Transfusion Station in Samara in the period from 2008 to 2011. A similar situation is documented among blood donors in the Tver and Yaroslavl Regions, the Altai Territory, and the Republic of Karelia. The increment of new diagnosed HIV infection cases in these areas made 3, 4.5, 1.6, and 3 times, respectively, in 2013 versus 2012 [24].

In Russia, the number of discarded blood donations still remains high as a result of identifying or obtaining questionable test results for BBVI. For example, among the causes of discarding the preserved donor blood in 2014, the detection of HBsAg, anti-HCV, and HIV Ag/Ab made 3.64%, 8.90%, and 1.18%, respectively. Other causes, including questionable test results for BBVI, made 34.66% [16]. The significant amount of discarded defective blood as a result of questionable test results for BBVI may apparently be explained by using test-systems of inadequate quality [9]. The rate of blood discards as a result of false positive test results for BBVI in Russia is over twice higher that in the USA [25].

Blood-borne viral infection in blood donors in other countries

The problem of BBVI prevalence in blood donors is quite acute, not only in Russia but also in many other countries. It is accepted worldwide to calculate the data on infection in donors per 100 000 population. So, the annual reports on the activities of blood banks and transfusion services in many countries contain the measuring parameters of incidence and prevalence. The prevalence of infection is defined as the ratio of the primary donors with obtained positive results at screening to the total number of primary donors. The incidence is defined as the ratio of repeat donors with revealed positive results at screening to the total number of repeat donors. Data on the prevalence and incidence of BBVIs in blood donors in other countries are presented in Table. 3.

Table 3. Prevalence and incidence of BBVIs in blood donors in Europe (per 100 000 population) [26]

Country / Infection	HIV		HBV		HCV	
	Prevalence	Incidence	Prevalence	Incidence	Prevalence	Incidence
Iceland	0	0	71.53	0	0	25.65
Luxembourg	0	0	0	0	220.51	0
Malta	0	0	173.91	9.99	43.48	0
Norway	0	0	27.87	0	33.44	1.07
Finland	0	0	0	0.65	33.92	1.16
Ireland	0	0	38.76	0	7.75	0
Denmark	0	0.45	15.6	1.34	15.6	0
Slovakia	2.49	1.06	72.25	3.18	24.91	6.35
Netherlands	2.84	0	34.12	1.64	19.91	0
Bulgaria	2.94	-	3224.29	-	341.57	-
Belgium	3.74	0	76.6	0.41	39.23	0
United Kingdom	5.09	0.95	37.95	0.47	37,49	0.39
Hungary	5.3	1.09	8.83	1.09	158.92	8.21
Switzerland	6.79	1.01	145.9	3.02	50.9	1.01
Germany	7.37	2.46	116.3	0.83	61.93	1.47
Czech Republic	8.14	0.58	59.04	3.76	215.79	8.1
Croatia	11.63	1.03	232.59	1.03	139.55	2.05
Italy	15.19	4.87	167.89	2.54	94.2	2.26

Latvia	33.32	16.61	-	-	-	-
Lithuania	47.76	8.39	560.04	16.77	1536.86	150.97
Estonia	53.3	3.47	266.52	6.93	959.49	20.8
Greece	54.39	6.36	1373.68	64.57	1201.75	55.66
Sweden	-	0	-	0.25	-	0.74

Note: "-" data unavailable.

The obtained results have shown a higher incidence of HIV infection and viral hepatitis in the donor population among the inhabitants of eastern and southern Europe [26]. These data are consistent with the results of the European Centre for Disease Prevention and Control (ECDC) and have been attributed to different dominant ways of pathogen transmission. The predominant way of HIV infection transmission is through homosexual intercourse in Western Europe, and through injected drug abuse in the countries of Eastern Europe [8]. Hepatitis B in the European Union (EU) is transmitted primarily through heterosexual contact and nosocomial infection, and hepatitis C is transmitted through intravenous administration of psychotropic substances. On the whole, in the EU countries, the BBVI infection transmission disproportionately affects socially marginalized groups (especially migrants), the people whose way of life is subjected to social stigmatization (men who have sex with men), and those whose behaviour is associated with law violations in any way [8, 27 28].

Blood-borne viral infections in potential organ and tissue donors in the Russian Federation

When considering the need for transplantation, one should minimize transplant contraindications associated with the risk of transmitting infection pathogens to the recipient via donor organs and tissues. The risk of such a transmission from a potential organ donor to the recipient is attributed to the biological characteristics of BBVI pathogens, and also to inability of a deferred examination or a quarantine of the donor organ because of its short lifetime after the retrieval.

In Russia, the laboratory screening of potential organ donors for BBVI is limited to the tests for serological markers only: HIV Ag/Ab, HBsAg, anti-HCV, using the test systems recommended by the Russian Healthcare Ministry for screening the donors of blood, human organs and tissues (the RF Healthcare Ministry Order No. 336 of 07.09.2000 "On the case of kidney transplantation from a donor infected with HIV and hepatitis C in Yekaterinburg Regional Clinical Hospital No.1").

The data on the prevalence of infectious markers among potential organ donors in Russia are limited because there are few publications on the causes of medical deferrals from organ and tissue donation, and because of the lack of a unified statistical report form, as is the case with Form No.39 for blood donors, in regional coordination centres of organ donation.

According to M.G. Minina, the Head of the Moscow Organ Donation Coordination Centre, the proportion of potential donors with medical contraindications in Moscow is higher than in the EU countries. In 2009, the loss of the donor pool due to the detection of BBVI laboratory markers accounted for 19%, reaching 25% in some years of the study period [29]. Similar results (17.0-21.2%) were obtained by a research working group

headed by M.Sh. Khubutiya [23]. The authors reported of the detection rates of HCV infection laboratory markers in potential organ donors significantly exceeding those of HIV and HBV infection ($p<0.01$). The changes in BBVI detection rates over time in potential organ donors in Moscow in 2008-2014 are shown in Table. 4.

Table 4. The BBVI detection rates in potential organ donors in Moscow in 2008-2014, %

Year / Infection	HIV	HBV	HCV	Reference
2008	2.2	3.7	11.0	M.Sh. Khubutiya et al., 2014 [23]
2009	2.8	2.4	12.2	
2010	1.8	2.6	13.3	
2011	2.1	4.4	14.7	
2012	2.4	4.1	14.4	
2013	2.7	3.7	15.4	M.Sh. Khubutiya et al., 2015 [30]
2014	1.9	2.5	13.0	

Blood-borne viral infections in potential organ and tissue donors in other countries

The studies conducted abroad to assess the BBVI prevalence among potential organ donors have revealed that it varies between the infection types as in case with blood donors (Table 5).

Table 5. The BBVI prevalence in potential organ and tissue donors abroad, %

Country / Infection	HIV	HBV	HCV	Reference
USA	0	0.3	18.3	L.M. Kucirka et al., 2009 [31]
United Kingdom	0.04	0.02	0.08	Public Health England, 2012 [32]
France	-	0.6	-	D. Challine et al., 2008 [33]
Brazil (Municipality of Passo Fundo)	-	-	7.0	B. Dutra Roos et al., 2014 [34]
Portugal (District of Coimbra)	-	6.1	-	F. Judas et al., 2005 [35]

Note: "-" data unavailable.

In 2004, a research group headed by S.Zou retrospectively reviewed the data on BBVI detection rates in US tissue donors. The results for HIV, HBV, and HCV infection made 0.09%, 0.23%, and 1.09%, respectively. The estimated incidence was 30.12, 18.33, and 12.38 per 100 000 population per year. The prevalence of infection markers in tissue donors was lower than in general population. However, despite the obtained results, the authors suggested that the assessed probability of undetected BBVI viremia in tissue donors was higher than that in the primary blood donors [36].

In 2007, G. Zahariadis et al. [37] retrospectively reviewed the detectability of BBVI laboratory markers in potential organ donors, tissue donors, and primary blood donors in the Canadian Province of Northern Alberta. The prevalence of HIV, HBV, and HCV infection laboratory

markers in organ and tissue donors was 0%, 0.09%, and 0.48%, respectively; the incidence rates for HBV and HCV infection were 24.2 and 11.2 per 100000 population per year, respectively. The authors noted that the prevalence of HCV infection markers in potential organ donors (10.34%) was higher than that in live donors of bone tissue (0.60%), and in primary blood donors (0.13%). In Australia, the prevalence of HIV, HBV, and HCV infection among the cornea donors was 0.11%, 2.88%, and 5.04%, respectively [38]. Meanwhile, the incidence of BBVI markers in such donors was higher than that in the primary blood donors: 0.35, 1.29, and 3.02 vs. 0.30, 1.13, and 2.40 per 100 000, respectively, as was noted above.

Having analyzed the test results for laboratory markers of HIV and HCV infection markers in potential organ donors in 17 treatment and prevention US institutions, K. Ellingson at el. found the infection prevalence in donors being at the level of 0.10%, 3.45%, and 0.50%, 18.20% for donors with standard and high risk of being infected with BBVI (according to PHS/CDC 1994 Guidelines for preventing transmission of HIV through transplantation of human tissue and organs), respectively. The identified differences in the degree of BBVI vulnerability among potential organ donors were predetermined by their medical and social behaviour [39].

Discussion

WHO has defined three types of blood donation [40]: voluntary unpaid, family/replacement, and paid. Voluntary unpaid blood donation is the most common type in many industrialized countries. The social and economic reforms that have taken place in Russia in two recent decades resulted in changing the ratio of blood donor types, namely in the redistribution of unpaid and paid proportion of donors towards increasing

the number of the latter [10]. Stimulating remuneration makes the blood donation attractive for various population segments including those from high risk social populations who often do not have complete information about their health status, or try to hide data about previous illnesses.

The BBVI prevalence is known to be lower among voluntary unpaid donors who give blood for altruistic reasons compared to the people who donate blood for family members or for a fee. WHO data demonstrate that the higher are the standard of living and financial well-being of the population, the lower is the prevalence of HIV infection in blood donations [40]. Among the volunteer donors there is a high proportion of those from socially secured sectors of the population who are well-considered and motivated to become donors. In 2013, the Russian Public Opinion Research Centre (VTsIOM) published the results of the donation survey in the Russian Federation [41]. More than half (57%) of the respondents reported their desire to help people as the main reason for voluntary blood donation. According to the survey, a particularly high proportion (43%) of those wishing to become non-remunerated blood donors was among young people aged 18-24 years. Only 4% of respondents have indicated getting an additional income as the leading reason of blood donation. Regular donors give blood and blood components many times and, therefore, they are tested on a regular basis. In this subset, not only medical, but also the social status of those who want to donate blood shall be studied with revealing their bad habits (alcoholism, drug addiction), signs of antisocial behaviour. If a donor is suspected of a psychoactive substance addiction or of the behaviour leading to the risk of BBVI infection, the donor is deferred.

Primary blood donors constitute the source of an increased risk of BBVI transmission. The incidence of detecting the BBVI markers in their

donations is 5-10 times higher than that among regular active donors (who donate blood 5-6 times per year) [42, 43]. Among the primary donors, the BBVIs are most frequently detected in males [18, 43].

The existing differences in the procedures of documenting and record-keeping BBVIs in blood donors between Russia and other countries make the comparative evaluation of obtained results hardly possible. Thus, E.B. Zhiburt et al. [44] calculated the incidence and prevalence of BBVI markers in donors in Tula Region in accordance with the EU requirements to blood donation and blood transfusion safety surveillance and found that HBV and HCV infection prevalence are respectively 163% and 632% higher than in the general population; and the HIV and HCV infection incidence exceeded their rates among the general population by 1539% and 491%, respectively. However, the obtained results raised doubts of their veracity in the authors because of lacking the HBV infection detection in regular donors.

The most common type of organ donation in Russia is the use of organs from a deceased person [45]. And an individual can become a potential donor only if he/she is a patient of the Intensive Care Unit (ICU) who has the clinical signs of the brain death or the cardiac arrest recorded [46].

People become organ donors as a result of events or circumstances that resulted in personal injury incompatible with life, for example, as a result of falls, hetero-aggressive actions, etc. At first sight, such injuries may seem to be sustained accidentally. However, very often such injuries may be predetermined by a peculiar social behaviour that deviates from the accepted social norms and is evaluated by sociologists as a deviant (marginal) behaviour that does not fall under the criminal liability and does not require psychiatrist’s special intervention. Often, these individuals are prone to

antisocial and risky lifestyle (persons of no fixed abode, those from the criminal sectors of society or those going in for high-risk traumatic sports, aggressive driving, etc.), alcoholism, substance abuse, and constitute the high-risk groups of BBVI transmission [47].

In many cases the injuries may be sustained due existing mental disorders. According to Moscow Branch of Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor), the rates of mental and behavioural disorders due to the alcohol abuse, and a nervous system degeneration caused by alcohol, as causes of death for the period from January to March 2015, were 61.3% and 28.0%, respectively [48]. The incidence of detecting BBVI markers in blood of ICU patients has been demonstrated to be several times higher than in patients of other clinical departments of health care facilities [49].

A high incidence of BBVI in potential organ donors is an evidence of the existing high risk of infection for recipients. This risk arises from the threat of direct transmission of infection agents via donor organs and tissues to a recipient [50]. Some authors consider the high prevalence of BBVI in potential organ donors to be the result of laboratory overdiagnosis. Having reviewed 56 (0.45%) samples initially reactive for HIV infection as detected by ELISA and polymerase chain reaction (PCR), T.J. Shafer et al. [51] could confirm the obtained initial results only in 8 cases (14.3%) when used subsequently the last generation tests, Western-blotting, and a repeated PCR assay of the biomaterial. While testing for BBVIs the serum samples from 487 cornea donors, I. Wilkemeyer et al. [52] obtained false positive results in 3.5% of cases (n=17) and false negative results in 0.8% (n=4). Obtaining false-positive and false-negative results may often be attributed to using the immunoassay test systems not intended for testing blood from deceased

patients [52, 53]. There is no consensus on the use of nucleic acid amplification testing (NAT) for BBVIs in routine screening of potential organ donors, and on the interpretation of data in case of obtaining questionable results [54].

The main problem for transplantation in Russia is a low level of the donor organ pool and a large number of donors with expanded criteria [55]. The causes for this include the lack of readiness to post-mortem donation among the Russian population, the high demand for donor organs, and inconsistencies in the existing legal and regulatory base on the issue of the "presumed consent" for organ retrieval (Art. 8 of RF Law No. 4180-1 "On transplantation of human organs and (or) tissues"; Art. 47 of Federal Law No. 323-FZ "On the basics of public health protection in the Russian Federation" and Art. 5 of Federal Law No. 8-FZ "On the burial and funeral business").

The development of medical technologies in situation of existing donor organ shortage enables physicians to use a pool of patients who were previously considered unsuitable for donation, i.e. expanded criteria donors (ECDs), including marginal donors with identified behavioural risk factors [55]. However, the use of organs from such donors is associated with a higher incidence of postoperative complications in recipients, and with an increased risk of infection transmission [56]. We should also mention the problem of infectious safety in orthopedics and ophthalmology where bone and cornea allografts are used. Despite the fact that the allografts are mechanically and chemically processed for sterilization (exposure to gamma-irradiation, ethylene oxide) and preservation (cool storage, cryogenic preservation, freeze-drying or lyophilization), yet, the risk of

BBVI transmission from the donor to a recipient is not completely excluded [57].

Xenotransplantation could be a possible solution to the problem of donor organ shortage. However, its widespread use is limited by a number of unresolved issues related, as in the case of allotransplantation, to a xenograft humoral and cellular rejection, and the existing risk of infection transmission from animals to humans, specifically, the pig endogenous retrovirus (PERV) [58]. Transplantologists confer great expectations on the achievements in immunology and biotechnology related to the study of the mechanisms to induce and control immune tolerance in transplant recipients, and on the development of cellular approaches in parenchymal organ engineering [59, 60]. However, all these studies are far from ideal and require further research. Today the risk of donor-derived infection in organ transplant recipients can be decreased through improving the existing selection of potential organ donors with regard to their medical and social characteristics, and the introduction of new improved laboratory testing algorithms, primarily using gene amplification techniques. These measures will significantly reduce the risk of infection transmission from the donor to a recipient.

Conclusion

Infectious safety in transfusion and transplantation is a topical global problem and is directly dependent on the quality of donor screening and laboratory testing of blood donations. Numerous studies in Russia and abroad have convincingly shown that BBVI prevalence among donor population vary between countries, being higher among potential donors of organs and tissues than among blood donors. The differences are due to

medical and social characteristics of subpopulations who become blood donors and potential organ donors. The study of BBVI incidence in donors is of great scientific and practical interest and could actually reveal the prevalence of infectious diseases and their trends making possible the predictions on the development of organ donation in the short term.

The Russian Federation is one of the leaders in the implementation and use of innovative technologies in the field of infectious safety of blood and its components, and in medical screening of donors. However, the infectious safety of organ donation needs more attention in our country. Until now the issues of legal regulation related to the concept of "presumed consent" have not been completely resolved; there is no relevant level of the state policy regulating the promotion of post-mortem donation. An earlier solution of these problems in the nearest future would raise the number and quality of transplantations being so vital in clinic nowadays.

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