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Article

Epidemiology of hepatitis C in the Moscow Region: data from the Moscow Regional Registry and screening for HCV antibodies

P.O. Bogomolov[1] • A.O. Bueverov[1, 2] • M.V. Matsievich[1] • M.Yu. Petrachenkova[1] • N.V. Voronkova[1] • S.V. Koblov[1] • K.Yu. Kokina[1] • V.D. Beznosenko[1] • E.V. Fedosova[1]

Pavel O. Bogomolov – MD, PhD, Head of Department of Hepatology, Head of the Moscow Regional Hepatology Center[1]

Aleksey O. Bueverov – MD, PhD, Leading Research Fellow, Department of Hepatology[1]; Professor, Chair of Medical and Social Expert Assessment and Out-Patient Therapy of the Postgraduate Medical Training Faculty[2]; Leading Research Fellow, Department of Research on Innovative Therapy, Research Center[2]

✉ 61/2–8 Shchepkina ul., Moscow, 129110, Russian Federation. Tel.: +7 (495) 631 72 90.
E-mail: hepatology@monikiweb.ru

Mariya V. Matsievich – MD, PhD, Senior Research Fellow, Department of Hepatology; Hepatologist, Hepatology Department, Consultative and Diagnostics Department[1]

Mariya Yu. Petrachenkova – MD, Gastroenterologist, Hepatology Department, Consultative and Diagnostics Department[1]

Natal'ya V. Voronkova – MD, PhD, Senior Research Fellow, Department of Hepatology; Specialist in Infectious Diseases, Hepatology Department, Consultative and Diagnostics Department[1]

Sergey V. Koblov – MD, Gastroenterologist, Hepatology Department, Consultative and Diagnostics Department[1]

Kseniya Yu. Kokina – MD, Gastroenterologist, Hepatology Department, Consultative and Diagnostics Department[1]

Valeriy D. Beznosenko – MD, Specialist in Infectious Diseases, Hepatology Department, Consultative and Diagnostics Department[1]

Ekaterina V. Fedosova – MD, Gastroenterologist, Hepatology Department, Consultative and Diagnostics Department[1]

[1] Moscow Regional Research and Clinical Institute (MONIKI); 61/2 Shchepkina ul., Moscow, 129110, Russian Federation

[2] I.M. Sechenov First Moscow State Medical University; 8/2 Trubetskaya ul., Moscow, 119991, Russian Federation

Background: Epidemiological characteristics of chronic hepatitis C virus (HCV) infection presented in the literature are not representative for the real situation with its incidence and prevalence in the Russian Federation. In the Moscow Region, which is the second largest population in the Russian Federation (7.2 million people), the Moscow Regional Registry of patients with hepatic disorders has been continuously maintained since 2010, as well as screening programs for anti-HCV positive individuals. Analysis of this data allows for generalization of the results obtain to the general population and for description of the prevalence of the infection among adult population of the Russian Federation. **Aim:** To analyze the epidemiological situation with chronic hepatitis C in the Moscow Region. **Materials and methods:** We analyzed data from the Moscow Regional Registry of patients with hepatic disorders as per April 2016, as well as the results of large scale screening of the population of the Moscow Region with oral express test for anti-HCV antibodies (OraQuick HCV Rapid Antibody Test). Based on the registry, we assessed the following parameters of the patient cohort with chronic HCV infection (n = 17 182): age, gender, HCV genotype, grade of liver fibrosis, allele variants of interleukin 28B. Within the large scale screening program among the population of the Moscow Region, 1447 individuals from 6 districts of the region were screened for anti-HCV antibodies. **Results:** As per April 2016, the proportion of patients with chronic viral hepatitis in the Registry was 75.3% (n = 12 938 of 17 182). The vast majority of them (80.3%, or n = 10 393) had chronic hepatitis C, with 84% (n = 8726) of referrals were patients of productive age (from 20 to 50 years). 8.4% (n = 873) of all HCV infected patients had liver cirrhosis. Although the proportion of patients with cirrhosis was negligibly low (< 1.5%) in patients below 30 years of age, it was progressively increasing with age, with a maximum of 23.8% in those above their 50-es. As far as the HCV genotype distribution is concerned, it was as follows: genotype 1, 54.1% (n = 5622) of patients, genotype 2, 7.2% (n = 747), genotype 3, 38.4% (n = 3990). According to the results of assessment of IL28B genetic polymorphisms (n = 3212), CC rs12979860, which is associated with the most favorable sensitivity to interferon α, was found in 27.5% (n = 883), CT allele, in 58.4% (n = 1876), and TT in 14,1% (n = 453). Prevalence of HCV infection in the Moscow Region, assessed by the screening program, is 1.38% of adults, or 77 200 anti-HCV positive persons, whereas estimated number of patients with chronic hepatitis C may amount to 54 000 to 61 700. **Conclusion:** HCV infection is the most prevalent among other viral hepatites in the Moscow Region (80.3%), and the largest numbers of infected individuals are of productive age. Almost three quarters of these patients are referred for medical care at the stage of minimal liver injury, and antiviral therapy can be used on an elective basis. Knowing the proportion of patients with liver cirrhosis (8.4%) allows for planning of the need in emergency treatments. The true prevalence of HCV infection estimated from the results of the screening program is at least 5-fold higher than that in the Registry. This indicates the necessity to upgrade the system of primary assessments. In particular, it seems reasonable to include detection of anti-HCV antibodies into the list of obligatory screening laboratory tests.

Key words: chronic hepatitis C, prevalence, Moscow Region, anti-HCV antibodies, screening, oral express test, registry

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The numbers of hepatitis C virus (HCV) infected worldwide are estimated as 130 to 200 million; however, true prevalence of the disorder has not been established. So, among 3.2 million of HCV-carriers in USA, from 50 to 70% are unaware of their disease [1–3]. According to the World Health Organization, annually more than 700,000 people die of HCV-associated liver disorders [4].

In addition to late liver complications, such as live cirrhosis and hepatocellular carcinomas, which are seen in 10 to 25% and 4% of patients, respectively, after 20 years of infection, chronic hepatitis C is associated with higher rates of cardiovascular disorders, B cell lymphoma, type 2 diabetes mellitus and other disorders of various organs and systems [5–7]. There is emerging data on accelerated progression of other existing disorders, type 1 and type 2 diabetes in particular, in patients with chronic HCV infection [6, 8].

In Russia, formal registration of HCV infection has been performed since 1994; however, there is no accurate statistical data on the prevalence of chronic hepatitis C, because patient registries exist only in few regions. According to some estimations, total number of cases of chronic hepatitis C exceeds 1.94 million. As there is no reliable data, this does not include patients with chronic hepatitis C who with sustained virological response after anti-viral treatment, as well as hepatitis C-related mortality [9].

With this in mind, it is interesting to analyze the epidemiological situation with chronic hepatitis C in the Moscow Region, which is the second largest population in the Russian Federation (7,318,647 people) and where the registry of such patients has been maintained since 2010.

Materials and methods

Analysis of the epidemiological situation was performed based on the data from the Moscow Regional Registry of patients with liver disorders (hereinafter, the Registry) and on the results of the wide-scale program for population screening for anti-HCV antibodies with an oral express test in the Moscow Region. The following assessments were extracted for patients with chronic hepatitis C from the Registry: age, gender, HCV genotype, stage of liver fibrosis, allele variants of interleukin 28B. The wide scale screening program for anti-HCV antibodies recruited 1447 persons from 6 districts of the Moscow Region. Their mean age was 44.5 ± 14.4 years. Slightly above two thirds of all screened persons were of female gender (1013 women and 434 men).

The oral express test for anti-HCV antibodies (OraQuickHCV Rapid Antibody Test, OraSureTechnologies, Inc., USD) was used with the indirect horizontal-flow immune analysis for detection of antibodies to recombinant core antigen, as well as to non-structural antigens NS3 and NS4 with synthetic viral peptides. The tests were done according to the instruction from the manufacturer. Within 15 minutes before the saliva sampling, the subjects did not eat or drink anything, including drinking water. If mouth care products had been used, saliva was sampled at least 30 minutes later. Saliva samples were taken by passing with a sampling pad on the external surface of upper and lower gums (it was allowed to use both sides of the pad). The testing device was put into the vial with developer solution. Results were analyzed at 20 to 40 minutes; the reliability of each test was confirmed by a built-in control device. If only one line in the C zone developed, the result was considered negative, if two lines (in the C zone and in the T zone) were seen, the result was considered positive and indicated the presence of anti-HCV antibodies.

Results

According to the Registry as per April 2016, total number of patients with liver disorders was 17,182, with 75.3% of them (n = 12,938) having chronic viral hepatic disorders. Of those, 10,392 had been referred for medical care because of chronic HCV infection; in 873 of cases liver cirrhosis was diagnosed (8.4% of all patients with chronic hepatitis C) (Fig. 1).

Age distribution of patients demonstrated obvious predominance (> 80%, n = 8,726) of those in their productive age, namely, from 20 to 50 years (Fig. 2). The highest numbers of HCV infected individuals were 30 to 39 years of age (n = 4,359).

There was no significant gender difference in patients with chronic hepatitis C in the Registry, with slightly more men (53.5%, n = 5,559). Separate analysis of men and women by age group showed that the largest number of male patients belonged to the age group from 26 to 39 years, while the largest proportion of females were above their 40-es (2,878 and 3,103, respectively).

HCV genotypes demonstrated the following distribution. Genotype 1 was found in more than half of patients – 54.1% (n = 5,622), genotype 2, in 7.2% (n = 747), genotype 3, in 38.4% (n = 3990). In 0.3% of cases (n = 33) genotype was not determined (Fig. 3). There were only sporadic cases of HCV infection genotypes 4, 5, and 6 in the Registry. It is of interest, that HCV genotype 1 is more frequent in women, than in men: 48.8% (n = 2,743) vs 36.8% (n = 1,468), whereas HCV genotype 3 is more frequent in men (63.2%, n = 2,522) than in women (51.2%, n = 2,879).

Fig. 4 shows patient groups with various grades of liver fibrosis, assessed by liver elastography. In the

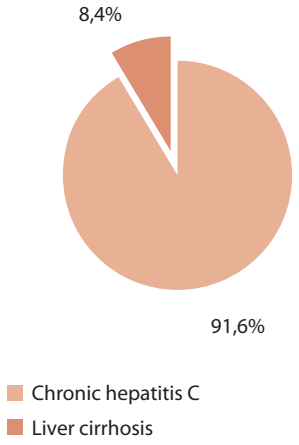

Fig. 1. Distribution of types of liver disorders associated with HCV, according to the Moscow Regional Registry of patients with hepatic disorders (n = 10,392), as per April 2016

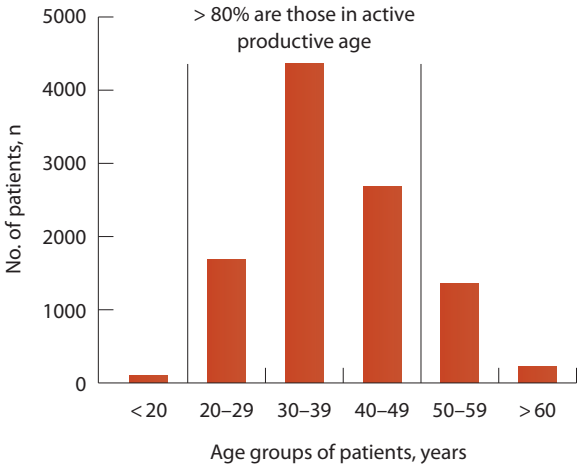

Fig. 2. Age characteristics of patients with chronic hepatitis C (n = 10,392)

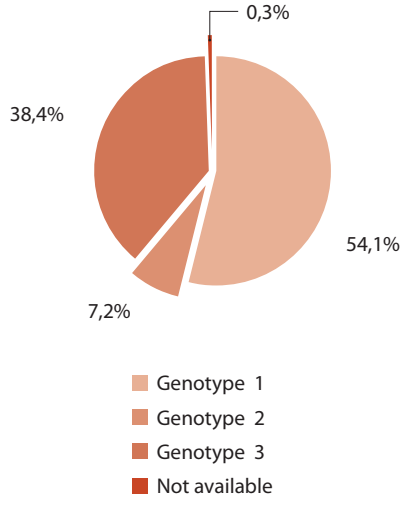

Fig. 3. Genotypes distribution of HCV in patients with chronic hepatitis C (n = 10,392)

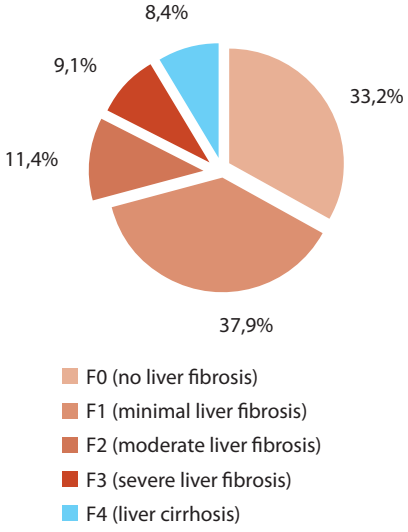

Fig. 4. Distribution of HCV-infected patients (n = 10,392) by stages of liver injury (assessed with METAVIR score)

vast majority of patients (71.1%, n = 7,389) no fibrosis was found or it was minimal (METAVIR score F 0–1). Histological examination of liver biopsy samples (total, n = 4,157) showed minimal liver fibrosis (Ishak score 1–2) in 86.9% of patients (n = 3,612) (Fig. 5). The proportion of patients with liver cirrhosis diagnosed by elastography was 8.4% (n = 873), and at liver biopsy, 2.9% (n = 121). The difference is to be explained by quite frequent contraindication to invasive assessments in patients with liver cirrhosis, such as thrombocytopenia and coagulation disorders.

Age distribution of patients with liver cirrhosis (as calculated from total number of patients with chronic hepatitis C) is shown in Fig. 6. The proportion of cirrhotic patients is negligibly low in those under 30 years of age (1.4%, or 26 / 1791), and progressively increases with age, achieving the maximum in those above 50 years (23.8%, or 492 / 2,065).

Taking into account that majority of patients with chronic hepatitis C that are on file in the Moscow Regional Center of Hepatology had been treated with interferon α and ribavirin, it was of a certain interest to analyze interleukin 28B allele variants that play a role

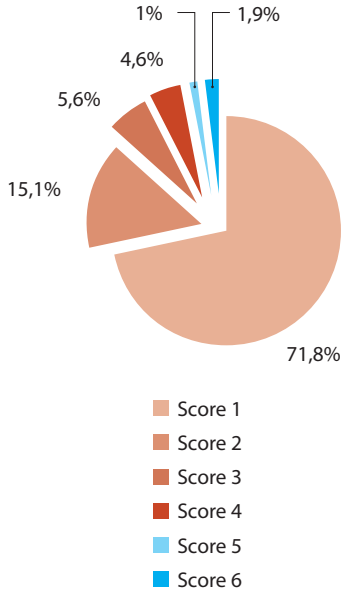

Fig. 5. Stages of liver disease based on histological assessment (Ishak staging system) in patients with chronic hepatitis C (n = 4,157)

in predicting the treatment response (Fig. 7). Genetic assessments were performed in 3,212 patients, most of them being infected with HCV genotype 1. The rs12979860 CC, which confers the most favorable sensitivity to interferon α, was found in less than one third of patients (n = 883), CT, in 876, and TT, in 453 patients.

Total population of the Moscow Region as per January 1, 2016 (data from the Rosstat agency) is 7,318,647 people, 5.6 million of them being adults. As mentioned above, the Registry includes 10,392 patients with chronic hepatitis C. Screening for anti-HCV antibodies with the oral express test (n = 1,447) showed that the true prevalence of HCV infection is much higher than the official data. For example, in the city of Klin the rate of HCV infection is 2.4% (6 positive test results of 250 individuals tested), in Domodedovo, 1.6% (5 of 313), in Dubna and Mytishchi, 1.2% (2 of 170 and 2 of 160, respectively), in Medvezhyi Ozyora, 1.1% (2 of 182), in Kolomna, 0.8% (3 of 372) (Fig. 8). The last value is significantly lower than in other towns of the Moscow Region and can be explained by a relatively low proportion of the population tested. The estimated number of anti-HCV positive people was 77,200 (1.38% of adult population). This number may include patients who had had acute hepatitis C with subsequent recovery and cure of hepatitis. However, according to the published data and our own studies, the first group has the leading position. Hence, from 70% to 80% HCV carriers (or from 54,000 to 61,700 people) have chronic hepatitis C.

Discussion and conclusion

The Moscow Regional Registry of patients with liver disorders has been maintained since 2010 and is the largest regional registry in Russia. That is exactly why its detailed analysis may help to understand the epidemiological situation with chronic hepatitis C in the Russian Federation.

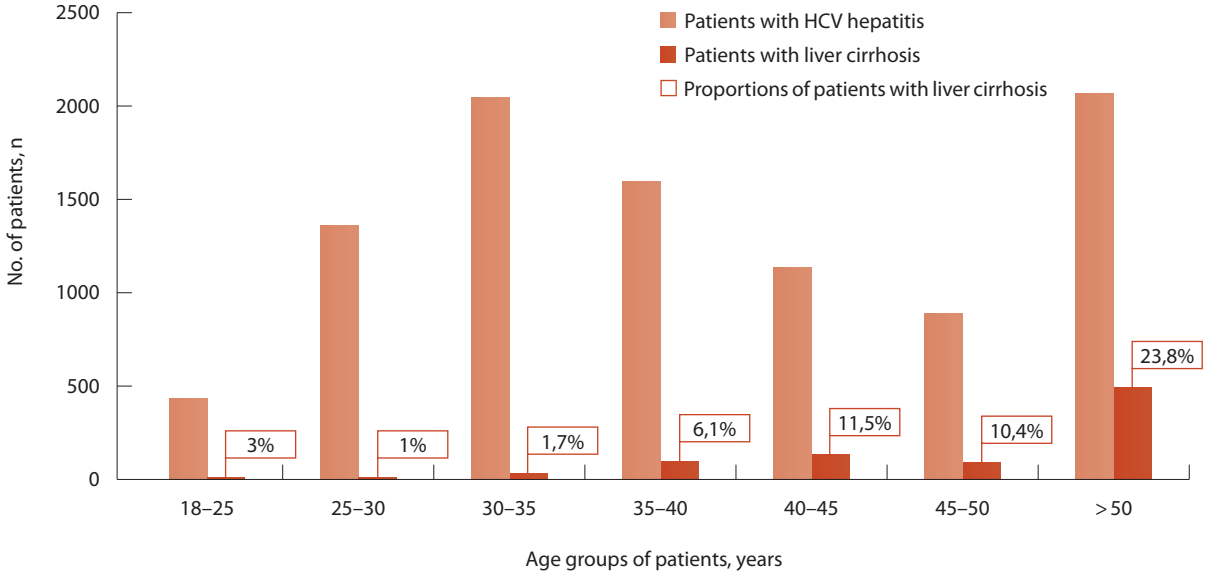

Fig. 6. Proportions of patients with liver cirrhosis in various age groups of patients with chronic hepatitis C (n = 10,392)

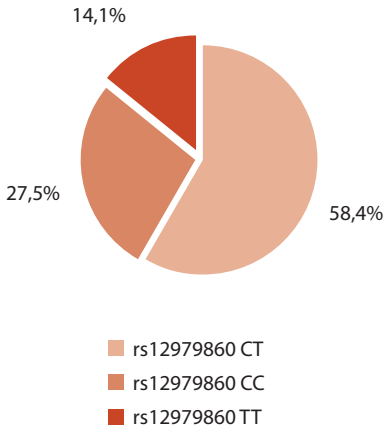

Fig. 7. IL28b gene polymorphisms as per results of the oral express test in patients with chronic hepatitis C on antiviral treatment with interferon α and ribavirin (n = 3,212)

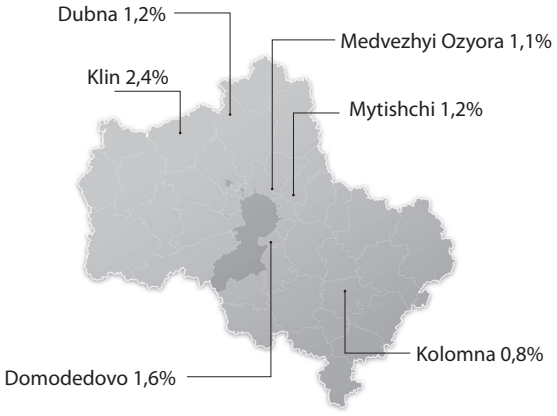

Fig. 8. Prevalence of HCV infection in some districts of the Moscow Region, as per results of the screening for anti-HCV antibodies (n = 1,447)

In the Moscow Region, HCV infection prevails among other viral hepatites and amounts to 80.3% (n = 10,392 from 12,938 patients with viral liver disease). It is crucial to stress that the majority of them are in their productive age that highlights the social importance of HCV hepatitis.

Formerly, at the end of 1990-es and the beginning of 2000-es, HCV genotype 1 was most prevalent in all Russian regions. In the recent years, the prevalence of genotype 3 has been constantly on the rise, with some decrease of the prevalence gap between genotypes 1 and 3. This situation can be explained by a significant improvement of control over the quality of blood transfusions and sterilization of medical instruments. Putting together the results obtained and prevalence of genotype 3 in men, one can assume an increasing role of intravenous drug addiction as a source of HCV infection.

In all patients included into the Registry, the stage of liver fibrosis had been determined by elastography; in a proportion of patients (n = 4,157) the diagnosis had been confirmed by liver biopsy. Biopsy samples were assessed with a 6-score Ishak scale. Minimal or mild liver fibrosis was found in the majority of liver samples. Ishak fibrosis score 5–6 indicating the formation of and well-established liver cirrhosis, was diagnosed in 2.9% of patients (121 / 4,157 patients who underwent liver biopsy). We merged these results with the data on patients with HCV-associated cirrhosis confirmed by liver elastography (they had contraindications to liver biopsy due to hypocoagulation). In total, the number of patients with chronic hepatitis C at the stage of cirrhosis was 8.4% (n = 873).

We found no major differences comparing the data of histological examination with that of elastography in the main patient groups. However, it should be taken into account that the pooled assessment was based on a 4-score METAVIR tool. In more than 70% of patients, there was no or only minimal fibrosis (n = 7,389). Therefore, antiviral treatment in these patients could be postponed by several years. On the contrary, patients with F3 (9.1%, n = 946) and F4 (8.4%, n = 873) should be treated in the nearest future.

Calculating the percentage of patients with HCV-associated liver cirrhosis from the total number of patients with chronic hepatitis C, one can find minimal prevalence of cirrhosis among those younger than 30 years of age. In patients aged from 30 to 35, the rate was 1.4% (26 / 1,791), with further geometrical increase up to maximal rate of 23.9% (493 / 2,065) in the age group of ≥ 50 years. Such distribution of cirrhosis prevalence is quite understandable, if we consider natural course of chronic hepatitis C. Therefore, HCV-infected individuals of the middle age and the elderly should be assessed more frequently, and finding of symptoms of severe fibrosis or cirrhosis should prompt the beginning of etiotropic therapy.

The analysis of polymorphism of interleukin 28B, which plays an important role in predicting of success of interferon α treatment, showed that a significant proportion of patients with chronic hepatitis C that are filed in the Registry, have the CC/TT allele variant (rs12977860/rs8099916). As it is known, this variant of interleukin 28B associated with the highest probability of successful treatment of HCV genotype 1. Taking into consideration, that in the Moscow Region

patients with chronic hepatitis C and minimal/mild fibrosis are treated with interferon α and ribavirin, determination of interleukin 28D polymorphism is on the list of obligatory tests for those being included into the Registry.

Although screening for HCV infection is performed in medical establishments, one can be sure that there is a significant proportion of the population that has been infected but is unaware of it [10]. With that in mind, a wide implementation of a simple and reliable method of diagnosis of hepatitis C is pressing for identification of latent patients and prevention of development of severe late complications. The development of oral express tests for salivary anti-HCV antibodies is seen as one of the most promising in this area.

In the study by Cha et al., sensitivity and specificity of OraQuick test was 97.8% (95% confidence interval (CI) 93.2–99.4%) and 100% (95% CI 98.4–100%), respectively. No cross-reactivity with interfering factors (bilirubin, hemoglobin, lipids, rheumatoid factor, other viruses, etc) was found [11]. Other authors showed similar results [10, 12, 13]. Moreover, a recently published regression meta-analysis demonstrated the highest sensitivity and specificity of OraQuick test, compared to other express tests [12].

Residents of the Moscow Region who participated in the screening program considered themselves to be healthy and were unaware of having any markers of HCV infection. The screening results helped to establish that the main group of risk for HCV infection was represented by men of productive age. Based on the data obtained, we can indirectly speculate a higher rate of intravenous drug addition among younger men that is one of the most important ways of transmission of the infection.

Thus, implementation of screening programs for anti-HCV antibodies would help to obtain objective information on the prevalence of the disease and the scale of infection in certain districts of the Moscow Region and the region as a whole. The projected number of patients with chronic hepatitis C is estimated as 54,000 to 61,700 (compared to already known 10,392 cases), which is at least one fifth from all patients. This indicates the necessity of modernization of the primary assessment system, including detection of anti-HCV antibodies into the obligatory screening list of laboratory parameters. In addition, the prevalence rates found in this study seem to be decisive for predicting of the amounts of medications needed for the population of the Moscow Region within the program of global elimination of infection and prevention of life-threatening complications. It is especially important because treatment of these complications in the future can substantially more expensive that financial expenses needed for implementation of this program.

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