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*Article*

# Epidemiology and Genotype Distribution of Hepatitis C Virus in Russia

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**Abstract:**

Hepatitis C virus (HCV) causes both acute and chronic disease of the liver that can lead to liver cirrhosis, cancer and liver failure. HCV is characterized by high genetic diversity and substantial variations in prevalence of specific HCV genotypes in different countries of the world. Many effective regimens of direct-acting antivirals (DAAs), including pan-genotypic, can successfully treat HCV infection. However, genotype-specific treatments for HCV are being actively employed in the national plans for elimination of HCV infection around the world. Evaluation of HCV genotype prevalence in a country is mandatory for successful implementation of the national plans for elimination of HCV infection and allocation of financial resources to DAAs most effecting for specific HCV genotypes prevalent in a country. Here, we analyzed HCV genotypes, subgenotypes and recombinants in 10,107 serum samples from patients with chronic HCV infection from all Federal districts of Russia collected in 2015-2017. This is the first, largest evaluation of HCV genotypes performed on samples from all territories of Russia, from its Central Federal district to the Far East. Moreover, we have updated retrospective epidemiological analysis of chronic and acute HCV infection in Russia in 2001-2021. We demonstrate that the incidence of acute HCV infection in Russia reduced from 16.7 cases per 100,000 population in 2001 to 0.6 cases per 100,000 population in 2021. The number of cases of chronic HCV infection decreased from 29.5 to 16.4 per 100,000 population during



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this period. HCV genotype analysis indicated that HCV genotype 1 dominates in Russia (53.6%). Genotypes 3 and 2 were detected in 35.4% and 7.8% of patients respectively. These proportions are virtually identical in all regions of Russia except for Far East, where HCV genotype 2 amounts only to 1%. HCV genotypes 1 and 2 are more widespread in women, while HCV genotype 3 in men. The highest frequency of identification of genotype 3 was found in the age group of 31-40 years old (44.9%, respectively), and genotype 1 was more prevalent in a group of over 70 years old (72.2%). The proportion of HCV genotype 2 is predominant among HCV-infected persons older than 40 years. Discriminating HCV genotype 2 and recombinant RF1_2k/1b, which are frequently misclassified, is important for successful antiviral treatment of such patients. For the first time, we demonstrate the countrywide prevalence of HCV RF1_2k/1b in different regions of Russia. HCV RF1_2k/1b amounts to 3.2% in the structure of HCV genotypes, reaching 30% among samples classified as genotype 2 by some commercial genotyping tests. The highest proportion of HCV RF1_2k/1b was detected in the north-west (60%), southern (41.6%) and central (31.6%) federal district. Its frequency in Far Eastern and North Caucasus Districts was ~ 14.3%. HCV RF1_2k/1b was not detected in the Volga, Ural and Siberian districts.

To conclude, this is the first and most complete evaluation of HCV epidemiology and genotype/subgenotype distribution in Russia.

**Key words:** hepatitis; HCV; epidemiology; genotype; subgenotype; recombinant; RF1_2k/1b; direct-acting antivirals

## 1. Introduction

Hepatitis C infection (either acute or chronic) is caused by hepatitis C virus (HCV) infecting the liver and inducing liver inflammation. HCV infection can lead to a severe liver disease, including liver cirrhosis (LC) and cancer (hepatocellular carcinoma, HCC). It is a global health problem and, along with hepatitis B virus infection, is the leading cause of cirrhosis and liver cancer in the world [1]. In 2015, 71 million people worldwide were estimated to live with HCV infection, while the global prevalence of infection was 1% [2]. According to the latest WHO estimates, 58 million people have chronic hepatitis C, with about 1.5 million new infections occurring every year. There are an estimated 3.2 million adolescents and children with chronic hepatitis C (CHC). In 2019, approximately 290 000 people died due to consequences of HCV infection , mostly cirrhosis and hepatocellular carcinoma [3].

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To eliminate hepatitis as a threat to public health, the Sixty-ninth World Health Assembly adopted the first global health sector strategy, aiming at the 90% reduction of new HBV and HCV infection cases by 2030 and the 65% reduction of deaths from HBV and HCV infections compared to 2015 [4, 5]. WHO Regional Office for Europe approved the Action plan for the health sector response to viral hepatitis. According to the goals adopted in the WHO European Region by 2020, 50% of all people living with chronic viral hepatitis B, C, and D and 75% of those with LC or HCC should be diagnosed, 75% of HCV patients meeting the criteria for treatment should receive antiviral therapy, and at least 90% of them should be completely cured of the infection [6].

HCV displays a high genetic diversity, and is currently classified into 8 genotypes (GTs), with varying geographic prevalence in different regions of the world [7]. Globally, genotype 1, 3 and 4 are the most common, representing 44%, 25% and 15% of all cases, correspondingly. Genotype 1 is dominant (60%) in high- and middle-income countries, genotype 3 (36%) is most common in middle-income countries, and genotype 4 (45%) prevails in low-income countries [8].

For many years, various direct-acting antiviral drugs (DAA) have been successfully used to treat HCV infection. Pangenotypic and genotype-specific treatment regimens for HCV infection were developed [9]. Although HCV can currently be cured with new DAAs, many countries are facing challenges associated with late diagnosis of HCV infection and low access to treatments. As a result, HCV infection is diagnosed at late stages of the disease, when liver damage is severe [10].

HCV infection was registered in all regions of the world, but about 80% of infected persons live in just 30 countries [8]. A large number of HCV infected persons live in Russia [11]. The current population of Russia is more than 146 million people (ninth place in the world and the most populated country in Europe). The average age in Russia is 39 years. The average population density is 8.6 people/km$^2$ (the largest in Moscow is 4950 people/km$^2$, the smallest in the Chukchi autonomous district is 0.1 people/km$^2$). The share of the urban population is 74.6% [12]. There are 8 federal districts in Russia (Central, Northwestern, Volga, Ural, North Caucasian, Southern, Siberian, Far Eastern) with highly diverse ethnic, geographic, cultural features and different migration and travel history which all may affect prevalence of HCV genotypes [12]. The high prevalence of HCV infection, along with the unique geographical and demographic features of Russia, creates many challenges for analyzing distribution of HCV infection in the country and meeting the goal for eliminating HCV infection as a serious public health threat by 2030. Despite the reduction of HCV infection in Russia, chronic infection

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remains a serious healthcare problem. To provide medical assistance to patients with chronic HCV infection in Russia and develop a strategy for treating such patients with modern antivirals, it is necessary to understand the epidemiology of HCV infection in a country.

Up to now, HCV genotypes distribution in all regions of Russia has never been studied. Only several reports related to HCV genotypes on small sample groups and with specific groups of patients were published previously [13–16]. These studies demonstrated the major prevalence of HCV 1b genotype (68.9% to 76% according to different reports) and, along with that, circulation of HCV genotype 1a, 2 and 3.

The aim of our study was to evaluate the current epidemiology of HCV infection in Russia and determine the distribution of HCV genotypes and clinically relevant HCV subgenotypes (1a, 1b) and recombinant (RF1_2k/1b). Understanding HCV genotype distribution is extremely important for the rational use of DAAs and strategic planning of medical healthcare needs to ensure successful implementation of the HCV elimination program in the country. Along HCV genotyping, we analyzed distribution of HCV recombinant RF1_2k/1b, which is frequently misclassified as genotype 2 by some commercially available test kits affecting the choice of DAAs and treatment outcomes. RF1_2k/1b recombinant or «chimera» was first discovered in St. Peterburg by O. Kalinina et al. [17]. In particular, the sustained virologic response (SVR for  Recommended treatment regimens are substantially higher for HCV genotype 2 patients than for patients with HCV RF1_2k/1b strain [18].

Although recombination in HCV genome is extremely rare and plays a minor role in HCV evolution, this particular recombinant spread widely and represents the most frequent HCV recombinant, generally not exceeding 3% of other genotypes. RF1_2k/1b likely represents the recombination event in HCV genome that occurred in the Soviet Union (between 1923 and 1956) [19] and then spread across the world: the prevalence of RF1_2k/1b is 1.2% in Germany, 2.6% in Cyprus, 3% in Netherlands, 0.5% in Estonia [20], 1% in Uzbekistan [21]. RF1_2k/1b was identified in many other countries, including Moldova [22]. Recent reports confirmed the distribution of RF1_2k/1b to Italy [23], Greece [24] and Austria [25]. The highest reported incidence of RF1_2k/1b was recently identified in Georgia, reaching ~ 20% [26]. Previous assessments at a limited sample size (285 samples) reported 2% prevalence of RF1_2k/1b in Russia [27]. In general, little is known about the prevalence of RF1_2k/1b in the world and in Russia, in particular. This is the first study providing country-wide estimation of RF1_2k/1b recombinant distribution in Russia.

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## Materials and Methods

**Retrospective epidemiological analysis**. To estimate the incidence of AHC and CHC in Russia, we analyzed the official statistical data from 2001 to 2021 [28]. The analysis included incidence of AHC/CHC in different age and sex groups.

**Collection and storage of serum samples**. 10,107 HCV positive serum samples were collected during routine epidemiological monitoring from 2015 to 2017. HCV isolates were obtained from patients from all 8 federal districts (35 regions in total) of Russia, and stored in -80 °C before use. All patients gave a voluntary informed consent before participating in the study.

**Isolation of HCV RNA**. RNA isolation was carried out using commercial kits "RIBOSORB" (AmpliSens Biotechnologies), "MAGNO-sorb" (AmpliSens Biotechnologies) and "RIBOSOL E" (AmpliSens Biotechnologies) according to manufacturer's instructions. Reverse transcription was performed using "REVERTA-L" variant 100 kit (AmpliSens Biotechnologies), designed to obtain cDNA on an RNA matrix according to the manufacturer's instructions.

**PCR analysis and genotyping of HCV**. PCR amplification of HCV cDNA was performed using proprietary primers and reagents for amplification. HCV genotype was determined using commercially available test kit "AmpliSens HCV-Genotype-FL" (AmpliSens Biotechnologies). All samples classified as genotype 2 were subsequently sequenced for confirmation purposes. "Rotor Gene Q" (Qiagen, Germany) machine was used for real-time PCR analysis.

**Sanger sequencing**. The RF_2k/1b HCV recombinant was determined by sequencing of Core and NS5B region of viral isolates classified as genotype 2 by commercially available genotyping test. . Sequence results were analyzed using Geneious software version 7.1.7 (Biomatters Limited, New Zealand) and NCBI information resources (Viral genotyping tool and BLAST).

**Epidemiological characterization of samples from HCV infected people**. The study group included 5,780 (57.2%) men and 4,327 (42.8%) women aged 0 to 83 years (median 41 years). All patients were divided into 8 age groups: under 15 years old, 16-20 years old, 21-30 years old, 31-40 years old, 41-50 years old, 51-60 years old, 61-70 years old and over 70 years old.

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**Statistical analysis.** Data analysis was performed in SPSS software (SPSS 21.0.0.0). The Chi-Square Test was used to determine a statistically significant difference between variables.

## Results

*Epidemiology of HCV infection in Russia*

The dynamics of AHC incidence since the early 2000s showed a pronounced downward trend in Russia. The incidence rate of AHC in 2001 amounted to 16.7 per 100,000 population, and by 2019 it was reduced to 1 by 100,000 population (Fig. 1). Trends in the dynamics of CHC cases during this period of time are multidirectional. From 2001 to 2009, the incidence rate increased, then it stabilized in 2010-2014 and turned down after 2015. In 2015, 55,596 cases of CHC were detected in Russia (38.1 per 100,000 population), and decreased to 45,376 cases in 2019 (30.9 per 100,000 population). A sharp reduction in the incidence of CHC in 2020 and 2021 was most likely the result of low diagnosis and detection rates during the COVID-19 pandemic.

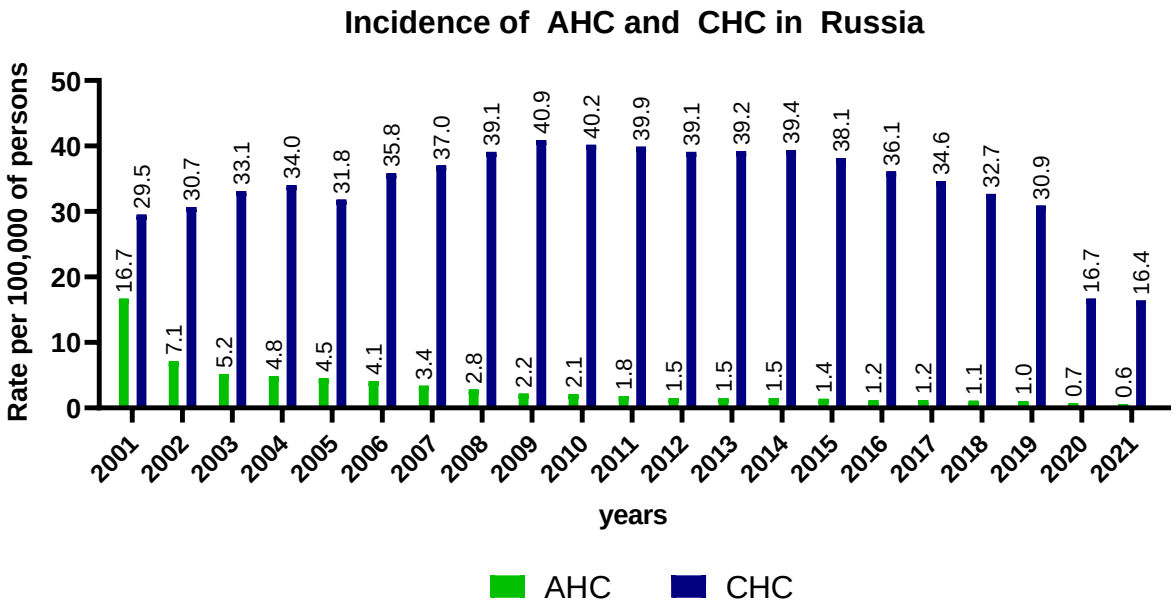


**Figure 1. Incidence of acute and chronic hepatitis C in Russia in 2001-2021.** The incidence rates are provided for AHC (green bars) and CHC (blue bars) per 100,000 of people.

There are differences in the incidence rates between Federal districts. In 2019, the highest number of CHC cases was registered in the Northwestern Federal district (48.1 per 100,000 population), and the lowest one in the North Caucasian District (12.9 per 100,000

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population). The highest CHC incidence rates are registered among persons aged 30-39 years (94.4 per 100,000 population in 2015).

*HCV genotype and subgenotype distribution*

The study showed that genotype 1 dominates in Russia (53.6%) (Table 1, Fig. 2A). Subtypes 1a and 1b were detected in 7.8% and 92.2%, respectively. Genotype 3 was detected in 35.4% of infected patients and genotype 2 in 7.6% of patients. Genotypes 4 were extremely rare (0.2% and 0.1%, respectively). There were no patients with genotype 5 among studied samples. There were no significant differences in the distribution of genotypes 1, 2 and 3 between federal districts, the proportions of HCV genotypes remained virtually the same across Russia except for the Far East district where the genotype 2 was the lowest, reaching only 1% (Fig. 2B). A mixt of two HCV genotypes was detected in 12 patients (0.1%) (Fig. 2B).

**Table 1. Prevalence of HCV genotypes, subgenotypes and recombinant RF1_2k/1b in Russia.**

| Age groups | Genotype (subtype) total value (percentage %) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | | 2 | 3 | 4 | 5 | 6 | RF1_2k/1b | Mixt |
| | 1a | 1b | | | | | | | |
| <15 | 7 (5,4) | 66 (50,8) | 4 (3,1) | 46 (35,4) | 0 (0,0) | 0 (0,0) | 0 (0,0) | 7 (5,4) | 0 (0,0) |
| 16-20 | 3 (4,1) | 46 (63,0) | 2 (2,7) | 19 (26,0) | 0 (0,0) | 0 (0,0) | 0 (0,0) | 2 (2,7) | 1 (1,4) |
| 21-30 | 83(7,7) | 463 (43,2) | 82 (7,7) | 412 (38,5) | 2 (0,2) | 0 (0,0) | 0 (0,0) | 29 (2,7) | 0 (0,0) |
| 31-40 | 188 (5,3) | 1493 (41,8) | 129 (3,6) | 1604 (44,9) | 8 (0,2) | 0 (0,0) | 6 (0,2) | 134 (3,8) | 7 (0,2) |
| 41-50 | 54 (2,4) | 1078 (47,4) | 189 (8,3) | 866 (38,1) | 5 (0,2) | 0 (0,0) | 0 (0,0) | 81 (3,6) | 1 (0,0) |
| 51-60 | 9 (0,5) | 1107 (62,2) | 202 (11,3) | 409 (23,0) | 0 (0,0) | 0 (0,0) | 0 (0,0) | 51 (2,9) | 2 (0,1) |
| 61-70 | 19 (2,2) | 570 (66,0) | 116 (13,4) | 145 (16,8) | 1 (0,1) | 0 (0,0) | 0 (0,0) | 12 (1,4) | 1 (0,1) |
| >70 | 55 (23,9) | 111 (48,3) | 31 (13,5) | 31 (13,5) | 0 (0,0) | 0 (0,0) | 0 (0,0) | 2 (0,9) | 0 (0,0) |
| **Total** | **418 (4,2)** | **4934 (49,4)** | **755 (7,6)** | **3532 (35,4)** | **16 (0,2)** | **0 (0,0)** | **6 (0,1)** | **318 (3,2)** | **12 (0,1)** |

Differences in the distribution of genotypes 1, 2 and 3 HCV were found in different gender and age groups ($p<0.05$) (Fig. 2A, B, Fig. 3, Table S1). The ratio of HCV genotypes 1, 2 and 3 is 49%, 6% and 45% in men and 58%, 9% and 33% in women, respectively (Fig. 3, Table S1).

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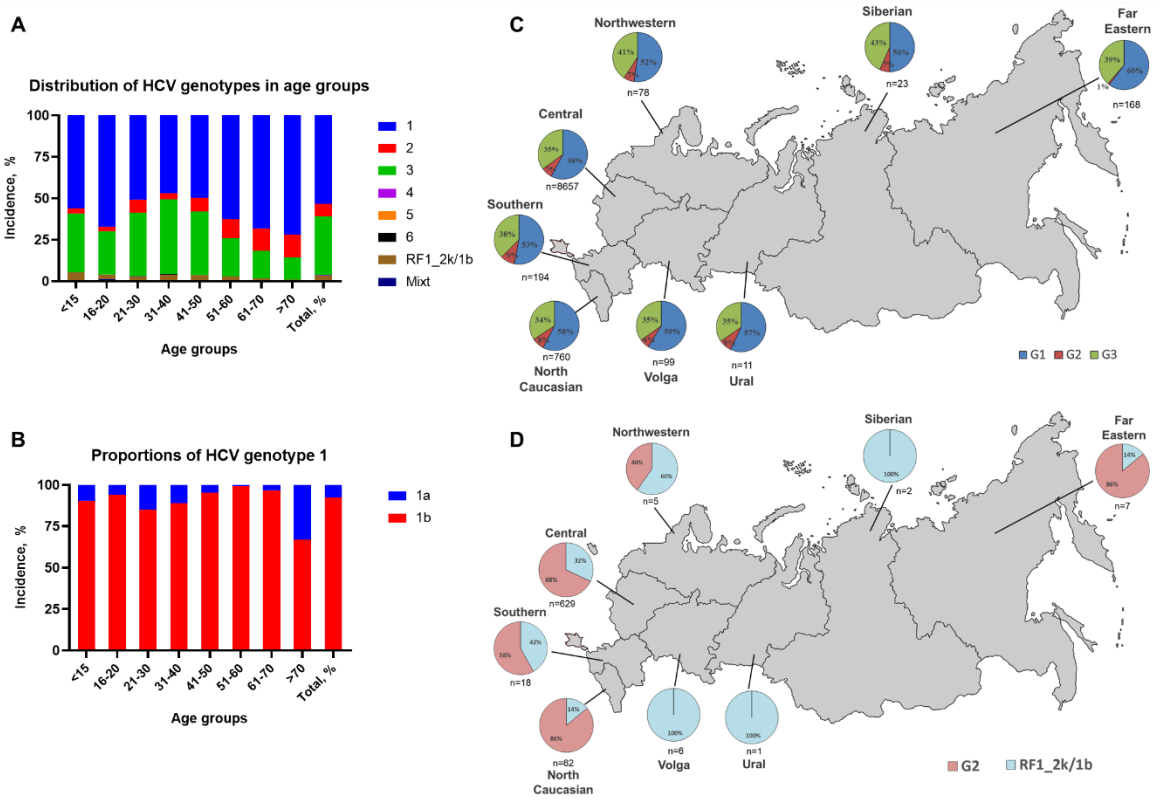


**Figure 2. Molecular epidemiology of HCV in Russia.** (A) Prevalence of HCV genotypes, recombinant, mixt genotypes and (B) subgenotypes in different age groups. (C) Geographic distribution of HCV genotypes and (D) RF1_2k/1b recombinant.

In all age groups, the proportion of genotype 1 was the largest. In the age group 31-40 years, the proportion of genotype 1 was 47.1%, the share of the genotype 3 - 44.9%. In the group of 41-50 years, the frequency of genotype 3 was 38.1% decreasing in older groups. On the contrary, the proportion of genotype 1 in the age group of 41-50 years was 49.8% and increased in each older age group, reaching 72.2% among people over 70 years. The proportion of genotype 2 was the smallest among people aged 16-20 years (2.7%) and increased in each subsequent age group, reaching the maximum value in the group 61-70 years (13.5%).

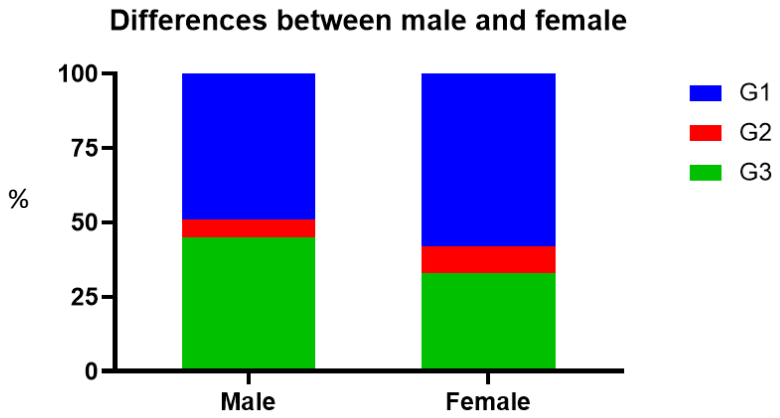

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**Figure 3. Proportion of HCV genotypes in males and females.**

*Distribution of RF1_2k/1b recombinant*

The RF1_2k/1b recombinant, the most prevalent HCV recombinant, was found in 312 infected patients, which amounted to 3.2% in the total structure of genotypes and 30% among isolates classified as genotype 2 by commercial genotyping test (putative genotype 2). (Table 1, Fig. 2A). The proportion of RF1_2k/1b recombinant among all age groups ranged from 0.9% to 5.4% (Table 1). There were substantial differences observed in the geographical distribution of the recombinant (Figure 2D) with the highest incidence of RF1_2K/1B in the North-West (60% of putative genotype 2), Southern (41.6% of putative genotype 2) and Central (31.6% of putative genotype 2) federal districts (Figure 2D). In the Far Eastern and North Caucasus Districts, the frequency of detection of the recombinant amounted to 14.3% and 14.4% of HCV genotype 2, respectively. Although the recombinant was not detected in the Volga, Ural and Siberian districts, this may rather be related to a small number of samples collected from these regions, and rare cases of genotype 2 identified (n=6, n=1 and n=2, correspondingly).

The highest prevalence of the recombinant was identified among persons under 15 years (5.4%), but generally was similar in all age groups, descending from 3.6% in a group of 41-50 years old to 0.9% in >70 years old (Table 1). The frequency of detection of the RF1_2K/1B recombinant among men (3.9%) and women (2.4%) were different ($p<0,05$).

## Discussion

The high incidence of AHC in Russia in the early 2000s was related to a large number of injection drug users, most of them were young men [11]. Moreover, there were no standard methods for determining the cases as acute or chronic HCV infection. Therefore, many cases of chronic infection were falsely diagnosed as acute hepatitis C. In the following years, as the prevalence of intravenous drug abuse in Russia was decreasing, the incidence of AHC was also reduced. In contrast, there was an onward trend in the incidence of CHC until 2009, then it stabilized and only after 2015 started to decline. Until 2020, more than 40 thousand of CHC cases were recorded annually in the country. In 2020-2021, when the COVID-19 pandemic began and quarantine measures were introduced, the number of new cases of CHC decreased (~24 000 cases per year). In total, for 2001-2021, more than 1 million cases of hepatitis C in Russia were identified. A large number of new cases of CHC have led to a large prevalence of CHC in the country [11].

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According to the World Health Organization Guidelines pangenotypic treatment regimens are prioritized for people with CHC. Genotype-specific modes are recommended in countries where certain viral genotypes are more prevalent [18]. The Russian national CHC guidelines include both pangenotypic regimens (velpatasvir + sofosbuvir; glecaprevir + pibrentasvir; daclatasvir + sofosbuvir) and various regimens for the treatment of patients with subtypes 1a, 1b, genotypes 3 and 4 [29]. The use of genotype-specific regimens in Russia is justified as HCV genotype 1b strain is the most prevalent.

According to our study, HCV genotype 1 dominates in Russia (53.6%). Genotypes 3 and 2 were detected in 35.4% and 7.8% of patients respectively (Table 1). Over 92.1% of all HCV genotype 1 samples were of subtype 1b (Table 1). Distribution of HCV genotypes is very uniform across the country with similar proportions of three major genotypes (Figure 2C). This is the refined, and the most complete evaluation of HCV genotypes distribution performed across all regions in Russia with the largest set of patients' samples.

Genotypes 1 and 2 HCV were more often detected in women, and genotype 3 in men. The highest frequency of identification of genotype 3 was found in the age group 31-40 years (44.9%, respectively), and genotype 1 in a group over 70 years (72.2%). The proportion of genotype 2 is increased among infected older than 40 years. HCV RF1_2k/1b prevalence was 3.2%, which is higher than previous estimation of 2% made in 2008 [21].

The Russian Ministry of Health has prepared a national plan for HCV elimination, which represents a comprehensive program that covers all aspects ranging from HCV prevention to the treatment and control of HCV infection with a final goal to substantially reduce the incidence and mortality of HCV infection by 2030. Thus, the data obtained during the study on the distribution of HCV genotypes in the country became the basis for meeting the needs for genotype-specific therapeutic regimens.

To achieve the goals of WHO elimination, 2030, further work is needed to expand testing and treatment. All patients with CHC should be provided with DAAs to reduce significantly the prevalence of CHC and mortality from liver cirrhosis and primary liver cancer. A comprehensive treatment program will reduce the socio-economic burden of hepatitis C and achieve the targets of the WHO strategy for the elimination of the infection in Russia by 2030.

Although the incidence of AHC and CHC in Russia has been declining in recent years, a large number of patients with CHC need antiviral treatment in accordance with modern national guidance. In Russia, a comprehensive national hepatitis C plan has been prepared, which includes all aspects from prevention to the treatment and control of diseases to reduce incidence and mortality from the HCC infection by 2030.

**Conflict of interest**: the authors declare no competing interests related to this work

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