

Regional Review

Epidemiology of hepatitis C in the Republic of Moldova: achievements and remaining challenges in prevention and control

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Abstract

Viral hepatitis, especially those with parenteral and sexual transmission, still remain a major problem of public health, both globally and for the Republic of Moldova, due to wide spreading, endemicity, increased morbidity and mortality and high rate of invalidity following the chronization of infection, but usually neglected by population and public health authorities. This paper describes the epidemiology and preventive and control measures of hepatitis C in Moldova.

Epidemiological analysis of the surveillance data on hepatitis C incidence in the Republic of Moldova was conducted. The data were obtained from the national reporting system of infectious diseases and serosurvey studies.

Epidemiological particularities of acute and chronic hepatitis C in general Moldovan population and specific risk groups were evaluated. National hepatitis policies for prevention and control were analyzed.

Only consolidation of all the actions stipulated in the national and international normative documents on the prevention and control of hepatitis, will help to reduce the morbidity of viral hepatitis C and probably to eliminate the new cases of disease in some regions.

Key words: hepatitis C infection; epidemiology; risk group; prevention and control; national programme.

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Introduction

Viral hepatitis, especially those with parenteral and sexual transmission, still remain a major problem of public health, both globally and for the Republic of Moldova, due to wide spreading, endemicity, increased morbidity and mortality and high rate of invalidity following the chronization of infection, but usually neglected by population and public health authorities.

Globally two billion people have been exposed to hepatitis B virus, of which 240 million have become chronic carriers and, potentially, have a high risk of infection with hepatitis D virus, about 170 million are infected with hepatitis C virus, and more than 10 million - hepatitis D virus. Every year in different geographical areas occur, over 100,000 cases of fulminant hepatitis, 400,000 cases of chronic hepatitis, 700,000 cases of liver cirrhosis and 300,000 cases of primary liver carcinoma [1,4].

In comparison with other public health problems (HIV, TB, STIs, malaria) viral hepatitis is usually neglected by population and authorities. Most people with chronic hepatitis B or C are unaware of their

infection and are at serious risk of developing cirrhosis or liver cancer, contributing to global increases in both of those chronic diseases [2,4].

Viral hepatitis is now responsible for 1.4 million deaths every year compared to 1.5 million deaths from HIV/AIDS and 1.2 million deaths from each of malaria and tuberculosis. In high endemic countries for hepatitis like Republic of Moldova, where about 9,000 people live with HIV and about 40,000 are infected with viral hepatitis this problem becomes the most important. At the same time high co-infection rates of HIV/ hepatitis C and HIV/hepatitis B in viral hepatitis endemic countries (in the Republic of Moldova 10% of HIV infected people have hepatitis B and 37% - hepatitis C) can present an important reason of deaths among HIV infected people [1,3].

Viral hepatitis is responsible for 78% of cases of primary liver cancer – the second cause of cancer mortality globally. While hepatitis C is not preventable by vaccination, current treatment regimens offer high cure rates that are expected to further improve with upcoming new treatments; and that although hepatitis B

is preventable with a safe and effective vaccine, there are 240 million people living with hepatitis B virus infection and available effective therapies could prevent cirrhosis and liver cancer among many of those infected and reduce liver cancer mortality rates [1].

Actually, Republic of Moldova may be qualified as an area with moderate endemicity of viral hepatitis B (frequency of HBsAg detection varies around 2-7%, risk of infection on lifetime is 20-60% for all groups of population) [5,4]. In order to reduce the morbidity of acute viral hepatitis and the decreasing prevalence of chronic hepatitis, cirrhosis and primary liver cancer the Ministry of Health in cooperation with the National Center for Public Health of the Republic of Moldova has developed National Programme for control of viral hepatitis B, C and D for the years 2012 - 2016 [9].

Methodology

Epidemiological analysis of the official surveillance data on hepatitis C infection incidence in the Republic of Moldova was conducted. The data were obtained from the national reporting system of infectious diseases. Data for acute hepatitis were collected in the aggregated format by type of hepatitis, district, age group, type of residence (urban or rural) etc. Reports of acute cases of hepatitis C were sent on a monthly basis. Primary data were reported by infectious diseases hospitals and general practitioners to the territorial Center for Public Health and from there to the National Center for Public Health. The national standard case definitions according to the European Union case definitions were established and approved in 2007.

We also used materials and the results of research over many years obtained in National Center for Public Health (NCPH) in the laboratory of viral hepatitis epidemiology. During period of 2010-2014 we studied prevalence of Anti-HCV antibodies in different risk population: women of reproductive age (1,182), injective drug users (181), haemodialysis patients (460), health care workers from hospitals (1,149), dentists (292), TB infected patients under treatment (110). The Moldova National Ethics Committee approved these surveys. After surveys participants completed the questionnaire, they were asked to provide five milliliters of venous blood, collected by a trained phlebotomist, and tested for anti-HCV. These infections are included as part of the national second generation surveillance system and testing is based on national algorithms developed by the Republic of Moldova National Center for Public Health. Antibodies to HCV were detected using registered tests. Estimates

and 95% confidence intervals (CI) were calculated with Mccallum Layton Stats Calculator (www.mccallum-layton.co.uk).

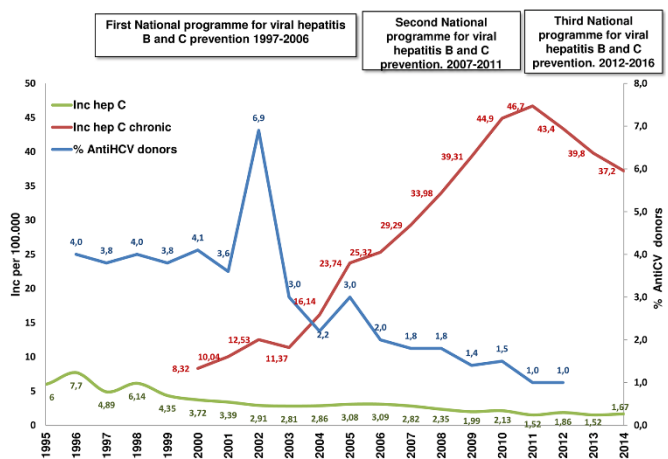
Also we analyzed published data of different surveys among population at risk: Men who have sex with men (MSM), female sex workers, HIV infected patients and blood donors in goal to compare the results [6,7,10]. To evaluate preventive and control measures, the National Programme for Control of Hepatitis B, C and D monitoring data were analyzed.

Results

Viral hepatitis C (VHC) epidemiological data for the general population in the Republic of Moldova are available from routine epidemiological surveillance system which includes registration of all acute and chronic infections. A new case definition of hepatitis C has been established in 2012 and approved by Ministry of Health order. All newly diagnosed hepatitis C cases are notifiable unless they are already known to be chronic. Beside this, prevalence of chronic hepatitis C is registered. Also results of different studies on seroprevalence are available especially in risk groups. Clinical diagnosis is based on elevated transaminases, and confirmed by laboratory specific diagnosis through detection of viral ARN in serum or of HCV antibodies in ELISA test.

The incidence of acute hepatitis C in the Republic of Moldova declines from one year to another and in 2014 was about 1,67 cases per 100.000 inhabitants. In 1995-1998 when VHC lab based epidemiological surveillance was started the incidence was about 6-8 cases of acute infection per 100,000 population (figure 1). The most affected population is between 25-49 years of age and there is no difference in viral hepatitis C

Figure 1. VHC morbidity in 1995-2014: incidence of acute VHC, incidence of chronic VHC and Anti-HCV positivity in blood donors.



morbidity in male and female. In possible ways of transmission structure in acute VHC morbidity prevails transmission during medical interventions (27.7 %), sexual transmission in 11.9% of cases and IDU – 6,5 %, rest of the cases are without determined way of infection (Figure 1).

Registered incidence of chronic hepatitis C increased from year 2000 to 2011 (from 8.32 to 46.7 cases per 100.000 citizens), probably due to accessibility of diagnostic tests and from 2011 to 2014 this incidence decreased to 37.2 cases per 100.000 inhabitants.

Blood donors

Most epidemiological studies on HCV infection were conducted among blood donors. Routine screening of anti-HCV has been implemented in all blood centers in the Republic of Moldova since 1996. An increase in blood donor seropositivity was seen in 2002 and can be related to the using of a not high specific ELISA test (see figure 1). The annual anti-HCV seroprevalence among whole blood donors at Blood Transfusion Centers decreased from 4.0% in 1996 to 1,0 in 2012. The mean anti-HCV seropositivity reported in blood donors in 2007-2012 was 1,44%. Overall, prevalence rates among blood donors in different parts of the country were similar, although some regional variations were observed.

Health care workers

The average anti-HCV positivity in health care workers (HCW) was higher in comparison to blood donors and similar to rates in other regional countries. The average prevalence in HCW reported by an epidemiological study in 2011-2014 was 4,4%. Also the high level of Anti-HCV was highlighted in dentists (7,8%). Several studies conducted between 1994 and

2014 have shown that prevalence of HCV among HCWs has fallen from 5,9% to 4.4% [8]. This is probably due to introduction of single use medical devices, improved hygiene measures and increased awareness. However, the HCV prevalence rate remains higher in HCW than in the blood donors. Effective preventive measures against blood borne pathogen transmission to HCW were implemented in the Republic of Moldova since 1998, such as screening, education and hepatitis B vaccination of all HCW, students and residents. However, these measures are not enough, all HCW should respect standard precautions, including hand washing, the use of protective barriers and care in the use and disposal of needles, and other sharp instruments. Written protocols for prompt reporting, evaluation, counselling, treatment and follow-up procedures should be implemented in all medical facilities. In the Republic of Moldova guidelines are in place to restrict HBV and HCV infected HCW from performing exposure prone procedures, where the HCW's gloved hands may be in contact with sharp instruments, based on HBV DNA, and HCV RNA presence.

Risk groups

The results of serosurveys of different populations are presented in Table 1. The average anti-HCV prevalence in haemodialysis patients, based on studies conducted across the country decreased from 85.7% during the period 1995-1997 to 43.2% between 2011 and 2013. At regional level, prevalence rates among these patients are highly variable, with levels of 32,4% in the south up to 49,1% in the northern part of the country. The anti-HCV IgM was detected in 68,4% of cases in anti-HCV positive patients. Multiple transfusion and HC procedures appeared to have an impact on anti-HCV seroprevalence in haemodialysis

Table 1. Anti-HCV positivity in different population groups.

population	year	N (total)**	n (%) AntiHCV + [#]	95% Cis ^{##}
Blood donors (first time)*	2007-2012	397438	5731 (1.44 %)	1.4% to 1.48%
Women of reproductive age	2010	1182	30 (2,5%)	1.61% to 3.39%
IDU	2014	181	97 (53,6 %)	46.33% to 60.87%
MSM	2010	397	10 (2.5 %) ⁶	0.96% to 4.04%
Sex workers (female)	2010	658	149 (22.6 %) ⁷	19.4% to 25.8%
Haemodialysis patients	2013	460	199 (43.2 %)	38.67% to 47.73%
Health care workers (hospitals)	2011-2014	1149	51 (4.4 %)	3.21% to 5.59%
Dentists	2013	292	15 (7.8%)	4.72% to 10.88%
TB infected patients	2012	110	9 (8.1%)	3% to 13.2%
HIV infected patients	2003-2013	2491	855 (34.2 %) ^{10, 8}	28.81% to 39.59%

Source: In table are presented results of serosurveys in different populations obtained in different periods at National Center for Public Health of the Republic of Moldova in the laboratory of viral hepatitis epidemiology during 2010 – 2014; ^{6,7,8,10} The data obtained from published sources cited at the same number in the bibliography; * Results obtained in National Center of Blood Transfusion of the Republic of Moldova; ** Total number of investigated persons; [#] Absolut number and percentage of positive for AntiHCV persons; ^{##} 95% Confidence intervals.

patients: 85,1% of infected patients had transfusions and 89,7% - have performed in past parenteral medical procedures. It has been established that duration of haemodialysis treatment (more than 5 years) and procedure frequency are important risk factors in VHC transmission in this patients.

Seroprevalence is also higher in TB infected patients (8,1% anti-HCV positive), female sex workers (22,6%) [7] and injection drug users (53,6%). Among HIV positive individuals, the rate of HCV co-infection in 2011-2013 is 34,2% - lower than rates in 2003-2010 (66,4%) [10,11]. The most affected group in co-infection HIV/VHC was adult male blood drug users.

Molecular epidemiology of HCV

HCV genotype 1b is the predominant type in Republic of Moldova, while HCV types 2, 3 and 4 viruses also circulate in the country at lower frequencies (1%- 2%), however, a systematic review is needed to confirm this.

Discussion

In most of the developed and developing countries control and response measures to the spread of infectious disease are stipulated in policy documents that are approved at different levels, for example: strategy plans, framework and national or special programmes. Viral hepatitis is not excluded from these approaches. In Moldova traditional prevention and control measures are stipulated in the National Programme for Control of Hepatitis B, C and D approved by Government Decision. This document consists of a general descriptive part, national complex plan and financial support description of all included measures.

The first National Programme for Control of Hepatitis B, C and D was approved by Government Decision 507 of June 2, 1997. The purpose of this Programme was the creation of a basic organizational system in order to reduce the morbidity of viral hepatitis B, C and D and to decrease the medical, social and economic impact of hepatitis on the population of Moldova. For the first time this programme included the main measures to prevent and combat parenteral viral hepatitis: specific and nonspecific prophylaxis of viral hepatitis, specific diagnosis and rehabilitation of patients, social mobilization of the population and medical professionals. As a result of the implementation of measures such as: testing donated blood for markers of viral hepatitis, sterilization improvement and information of population, these objectives were successfully achieved.

In 2007 by Government Decision 1143 the second National Programme for control of hepatitis B, C and D for 2007-2011 was approved [5].

This program was aimed at further reducing the incidence of acute and chronic viral hepatitis to the morbidity indices of most of the European countries. Basically, the second program included all main compartments and measures of the previous program. For the first time scientific research of epidemiology of viral hepatitis was included in the national plan. It was also planned and organized in the National Center for Public Health a reference laboratory for viral hepatitis and HIV infection. It is important to note that the National Programme for Control of Hepatitis B, C and D for 2007-2011 was not fully and regular funded, only the costs related to HBV vaccination of high risk groups were covered.

On 21 May 2010 the 63rd World Health Assembly Resolution WHA63.18 was issued on viral hepatitis. In this resolution, priorities were set relating to prevention, surveillance and control of viral hepatitis in the member countries of World Health Organization (WHO). Recommendations included: improving epidemiological surveillance and laboratory capacity; multisectoral collaboration between medical and educational institutions, non-governmental organizations (NGOs) and civil society to prevent viral hepatitis; providing vaccination strategies, infection control measures for injection safety; development and implementation of monitoring and evaluation tools in order to analyze progress in reducing viral hepatitis morbidity and strategies to guide evidence-based policy decisions about the activities of prevention, diagnosis and treatment. July 28 was designated as World Hepatitis Day in order to provide an opportunity for education and a better understanding of viral hepatitis as a global public health problem and to stimulate the strengthening of prevention and control measures in Member States.

In order to implement the resolution mentioned above and other appropriate international documents, the Government of Moldova has initiated a process of developing the National Programme for Control of Hepatitis B, C and D for 2012-2016. This strategic document was approved by the Government on 13.02.2012 [9].

Reducing of the morbidity, disability and mortality due to acute and chronic viral hepatitis B, C and D, cirrhosis caused by these viruses is the main objective of the Programme. The third Programme included all actual control and prevention measures on viral hepatitis but for the first time specific antiviral

treatment. A special attention is given to the prevention of chronic viral hepatitis and early diagnosis of the diseases.

The programme provided six specific activities:

1. Scientific research, which regulates the priority directions of scientific development: studying etiology, epidemiology, clinical diagnosis and treatment; molecular mechanisms of development and progression of virus resistance to antiviral drugs, methods of rehabilitation and prevention of viral hepatitis, chronic liver cirrhosis.

2. Specific prophylaxis of viral hepatitis B included risk population immunization and catch up vaccination of population under 35 years of age.

3. Nonspecific prophylaxis of viral hepatitis B, C and D can be performed successfully through a complex of nonspecific prophylactic measures in medical and non-medical institutions, in condition of habitat, which limits the transmission of pathogens from the source of infection to others (blood transfusion safety, guaranteed sterilization of medical and paramedical equipment and active detection and treatment of the patients etc.).

4. Informing and raising the awareness level in the population. The main purpose is to inform people in particular risk groups on the epidemiological situation and the serious consequences of illness, about the effectiveness of specific and nonspecific prophylaxis.

5. Specific diagnostic: optimization of the laboratory diagnostic of viral hepatitis and strengthening of capacities in order to provide comprehensive screening of population and specialized clinical diagnosis of the patients.

6. Detection and antiviral treatment of the patients with viral hepatitis B, C and D. Annual number of eligible patients which antiviral treatment is covered by Government was established.

In addition to the six specific priority activities described above, the programme contains other sections: responsible organizations for implementation of the programme and their tasks; programme budget and estimated funds; programme implementation mechanism; expected result; monitoring and evaluation of the programme.

The National Programme for Control of Hepatitis B, C and D for 2012 - 2016 has the specific complex plan that includes a detailed description of each activity including financial coverage.

Currently the program is implemented and due to stipulated activities the epidemic process in parenteral viral hepatitis has a decreasing trend, but it is very important to note that to achieve the programme objectives sustainable funding is required.

Negative economic impact of viral hepatitis morbidity in the Republic of Moldova during period of 1997-2014 amounted to 74.9 million USD. Prevented economic damage as a result of national programmes implementation in this period was 60.2 million USD, while the budget of the National Programmes during 1997-2014 was only 6 million USD. In other words, one dollar invested in hepatitis prevention saves 10 USD [9].

In conclusion it is important to note that the consolidation of all the actions stipulated in the national and international normative documents on the prevention and control of hepatitis, will help to reduce the morbidity of viral hepatitis C and probably to eliminate the new cases of disease in some regions.

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