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**CHRONIC HEPATITIS, LIVER CIRRHOSIS AND PRIMARY
LIVER CANCER IN THE REPUBLIC OF MOLDOVA:
EPIDEMIOLOGY, PROGNOSIS AND COMBAT STRATEGY**

331.01 – EPIDEMIOLOGY

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LIST OF ABBREVIATIONS

CFD - Center for Family Doctors
CHB - Liver Cirrhosis of B virus
CHC - Liver Cirrhosis of C virus
DAAs - Antiviral drugs with direct action
DSV - Dasabuvir
DTP - Diphtheria, tetanus, pertussis
EASL - European Association for the Study of the Liver
EBR - Elbasvir
EMA - European Medicines Agency
HBc - Hepatitis B core antigen
HBsAg - hepatitis B surface antigen
HBV - Hepatitis B Virus
HCB - Chronic hepatitis B
HCV Ag - Viral hepatitis C antigen
HCV RNA - Ribonucleic acid of viral hepatitis C
HEV - Hepatitis E virus
HIV - Human Immunodeficiency Virus
HVBC - Chronic viral hepatitis B
HVCC - Chronic viral hepatitis C
ICD - International Classification of Diseases
IDU - Injecting drug users
IgM - Immunoglobulin M
LPA - Local Public Administration
MLHSP - Ministry of Labor Health and Social Protection
MSM - Men who have sex with men
NAPH - National Agency for Public Health
NCBT - National Center for Blood Transfusion
NCP - National Control Program
NGO - Non-governmental organizations
NIP - National Immunization Program
NMIC - National Medical Insurance Company
OBV - Ombitasvir
PHC - Public Health Center
RDD - Development Region
RM - Republic of Moldova
SSSSP - State Public Health Surveillance Service
STI - Sexually Transmitted Infections
SVR - Sustained viral response
SW - Sex workers
TMA - Territorial Medical Assistance
WHO - World Health Organization

CONCEPTUAL RESEARCH FRAMEWORK

The relevance and significance of the research study

The burden of chronic liver pathologies presents a major public health problem determined by their medical, social and economic impact both at national and global levels [1-8]. Worldwide, it is estimated that about 1.5 billion people have chronic liver diseases, with 2 million deaths annually, including 1 million from complications caused by liver cirrhosis and 1 million from viral hepatitis and hepatocellular carcinoma [9-13]. These pathologies can be compared with other major public health problems such as diabetes mellitus, estimated at 422 million cases, including 1.6 million deaths, lung diseases - 650 million cases, with 6.17 million deaths, and cardiovascular diseases - 540 million cases, with 17.7 million deaths [10, 14].

Hepatic pathology represents a public health problem for the Republic of Moldova as well, causing a high morbidity and mortality rate [15].

Among the most common chronic pathologies of the liver are chronic hepatitis, liver cirrhosis, alcoholic hepatitis and hepatic steatosis. In Europe, the rate of new cases of chronic liver diseases is about 6%, which is about 29 million people, of which chronic viral hepatitis B and C are more frequently reported [16-19].

The global spread of these pathologies is determined by the high epidemic potential of hepatotropic viral infections , their ubiquity and susceptibility, with a predominance of subclinical forms , and the reduction of symptoms [20].

In terms of growth rate and prevalence, hepatotropic viral infections significantly exceed the incidence of AIDS and tuberculosis [21-24]. About 2.9 million people living with HIV are co-infected with hepatitis C virus and 2.6 million with hepatitis B virus [22].

However, while mortality from tuberculosis and HIV is decreasing, that from viral hepatitis is increasing. Thus, in 2015, most deaths in case of viral hepatitis were caused by its complications – liver cirrhosis and primary liver cancer [23]. Chronic viral hepatitis B and C are the main cause of chronic liver disease, liver cirrhosis and primary liver cancer, which more frequently leads to the need for liver transplantation [24, 25, 26, 27].

According to the medical and socioeconomic characteristics, viral hepatitis is among the ten most common infectious diseases both in the Russian Federation and in the Republic of Moldova [21].

Annually, in different geographical regions, more than 100 thousand cases of fulminant hepatitis, 700 thousand cases of chronic hepatitis, 400 thousand cases of liver cirrhosis and approximately 300 thousand cases of primary liver carcinoma are registered. The main complications of chronic hepatitis are cirrhosis and hepatocellular carcinoma . According to WHO estimates, about 20-30% of patients with chronic hepatitis develop liver cancer. Approximately 780 thousand people die annually due to hepatitis B infection, of which 650 thousand from the complications of chronic hepatitis B - liver cirrhosis and liver cancer, and 130 thousand from acute hepatitis B [28-30] .

Worldwide, about 257 million people are infected with chronic viral hepatitis B and around 71 million with chronic viral hepatitis C, mainly in economically less developed countries [22, 23, 31, 32]. The diagnosis rate of viral hepatitis B and C is very low, only 11% of cases [31]. Chronic hepatitis B is defined as the persistence for six months or more of hepatitis B surface antigen – HBsAg [33, 34].

In 2020, over 73 thousand patients with chronic hepatitis and about 10 thousand with cirrhosis of the liver were registered in the republic, and 70% of patients with cirrhosis developed

primary liver cancer [20, 35-38]. According to literature data, in 94–96% of cases, the source of infection of patients with acute viral hepatitis is people with chronic forms of these infections. It should also be mentioned that most of the deaths in recent years have been recorded in patients with chronic viral hepatitis and not acute [24, 58]. Not even half of the patients with chronic viral hepatitis B and C are registered because, in addition to newly diagnosed patients with these forms of hepatitis, there is an impressive cohort of "carriers" of these undiagnosed asymptomatic causative agents [24, 39, 40].

In the Republic of Moldova, a continuous increase in the incidence of primary liver cancer was recorded , and during the years analyzed in the present study, the number of cases practically doubled, reaching around 400 cases in 2020 [41].

The purpose of the study:

Studying the epidemiological features and risk factors in the development of chronic hepatitis, liver cirrhosis and primary liver cancer, with the elaboration of the prognosis and the strategy to eliminate morbidity through these pathologies at the national level.

Research objectives :

1. Assessment of the epidemiological situation through chronic hepatitis, liver cirrhosis and primary liver cancer in the Republic of Moldova.
2. Determination of epidemiological features and risk factors responsible for the chronicity of hepatitis and the development of cirrhosis and primary liver cancer.
3. Determination of the medical and socio - economic impact in chronic hepatitis, liver cirrhosis and primary liver cancer.
4. Prognosis of the epidemiological situation in the Republic of Moldova regarding chronic hepatitis, liver cirrhosis and primary liver cancer according to the evolution of risk factors.
5. Elaboration of the strategy for the elimination of morbidity through chronic hepatitis, liver cirrhosis and primary liver cancer in the current conditions of the Republic of Moldova.

Research hypothesis: pathologies are an acute health problem worldwide. Cirrhosis is the final stage of chronic liver disease and is characterized by an asymptomatic or compensated phase and a progressive or decompensated phase. The development of complications such as ascites, gastrointestinal bleeding, encephalopathy and spontaneous bacterial peritonitis marks the beginning of the decompensated phase, which has a survival of approximately 2 years compared to a median survival of over 12 years in compensated cirrhosis. Currently, there is little data on the epidemiology of these conditions in developing countries, including the Republic of Moldova.

In this context, a complex study, that will include chronic hepatitis, liver cirrhosis and primary liver cancer in order to determine the epidemiological features and risk factors that contribute to the unfavorable evolution of the disease, and at the same time, the development of a strategic plan to eliminate viral hepatitis in the Republic of Moldova, is necessary.

Synthesis of the scientific research methodology and justification of the chosen research methods. The study was carried out within the Epidemiology Discipline, Department of Preventive Medicine of Nicolae Testemitanu Univeersity. To carry out the study, a longitudinal retrospective study and analytical study were applied to determine the risk factors involved in the occurrence of complications of chronic hepatitis caused by liver cirrhosis and primary liver cancer. The results of the research allowed the determination the epidemiological peculiarities of the manifestation of the epidemic process through chronic hepatitis, liver cirrhosis and liver cancer, including the epidemiological surveillance system in these pathologies. Morbidity and mortality data from chronic hepatitis, liver cirrhosis, and malignant tumors of the liver and intrahepatic bile

ducts were collected from the National Public Health Agency. In the first stage of the study, the epidemiological situation of chronic hepatitis, liver cirrhosis and primary liver cancer in the Republic of Moldova was assessed based on the epidemiological surveillance indicators of chronic hepatitis, liver cirrhosis and liver cancer.

At the same time, to collect the data disaggregated by different epidemiological indicators, the "Questionnaire for the collection of epidemiological data, prevention and treatment in viral hepatitis B, C, D" was developed, to collect the data from the Territorial Public Health Centers, including the laboratories involved in the diagnosis laboratory of viral hepatitis, public and private medical institutions, republican, departmental, municipal and district hospitals, TMA (Territorial Medical Assistance), CFD (Center for Family Doctors), NBTC (National Blood Transfusion Center) in accordance with the provisions of MLHSP no. 218 of 07.04.2021 "Regarding the collection and presentation of epidemiological data, treatment and laboratory diagnosis in viral hepatitis B, C and D". In order to collect data on laboratory testing and diagnosis of viral hepatitis, the "Laboratory Evaluation Questionnaire on Laboratory Testing and Diagnosis of Viral Hepatitis B, C and D" was developed. The data were presented by public and private laboratories, in accordance with MLHSP provision no. 218 of 04.07.2021 "Regarding the collection and presentation of epidemiological data, treatment and laboratory diagnosis in viral hepatitis B, C and D".

The obtained results were used to analyze the epidemiological situation with chronic hepatitis, liver cirrhosis and liver cancer, to estimate the real morbidity due to these conditions at the country level and to develop the Strategic Plan for the elimination of viral hepatitis from the territory of the republic.

These results were discussed at the work sessions by specialists in the field, the existing impediments in the national surveillance system of viral hepatitis B, C and D being determined.

Novelty and scientific originality of the obtained result. For the first time, the morbidity of chronic hepatitis, liver cirrhosis and primary liver cancer was analyzed in complexity as a nosoform, given the fact that liver cirrhosis and primary liver cancer are the complications of chronic hepatitis. For the first time, the epidemiological peculiarities of the evolution of the epidemic process in each nosological form and the determination of the risk factors that contribute to the development of complications caused by liver cirrhosis and primary liver cancer were studied in a complex way. The multifactorial regression analysis allowed the identification of risk factors, which contribute to the unfavorable evolution of chronic hepatitis and the development of complications.

It was estimated the social, medical and economic impact allows determining the burden of liver disease, caused by high morbidity through chronic hepatitis, which subsequently lead to the development of liver cirrhosis and liver cancer. Chronic hepatitis and its sequelae caused by liver cirrhosis and primary liver cancer impose considerable direct costs on public healthcare services.

At the same time, the disaggregated analysis of the data on the morbidity of chronic hepatitis, liver cirrhosis and liver cancer contributed to the development of the national strategic plan for the elimination of viral hepatitis for the Republic of Moldova, which is a strategic priority for our country, and provides a normative framework for the elimination of viral hepatitis. Elimination of viral hepatitis is defined by the World Health Organization (WHO) as a 90% reduction in new chronic infections and a 65% reduction in mortality compared to the baseline in 2015. The national strategic plan for the elimination of viral hepatitis focuses on hepatitis

parenteral viruses: viral hepatitis B and C, which make up about 64% of all chronic hepatitis, and also have a significant impact on the health of the population. The strategic plan for the elimination of viral hepatitis provides 6 strategic directions, which frame more specific objectives and strategic activities, including monitoring and evaluation indicators. It is based on international recommendations, including WHO, CDC, ECDC, and at the same time, it will serve as methodological support for the implementation of the National Program to eliminate viral hepatitis B, C and D for the period 2022-2026.

The research problem solved in this paper: Epidemiological features of the manifestation of morbidity through chronic hepatitis, liver cirrhosis and primary liver cancer were analyzed in complexity, which allowed the determination of the gaps in the epidemiological surveillance system at the level of the public health service and as a result the elaboration of the National Plan for the Elimination of Viral Hepatitis in the Republic of Moldova.

New research directions in science and practice. Chronic hepatitis presents a public health problem, driven by the high morbidity and mortality caused by the sequelae it causes, including liver cirrhosis and primary liver cancer. In most cases, people infected with the liver virus do not show clinical signs, and the disease proceeds asymptotically and as a result is detected quite late, being already in the stage of liver cirrhosis. Thus, based on these considerations, it was necessary to determine the real situation regarding the number of patients with chronic hepatitis at country level and the epidemiological particularities, including the risk factors in these pathologies. The officially reported indicators do not allow the assessment of the real level of morbidity and the risk factors that determine the chronicity of these pathologies. In this context, a questionnaire was developed for the evaluation of epidemiological features and risk factors in chronic hepatitis, liver cirrhosis and primary liver cancer. The data obtained allowed the estimation of the population infected with HVB and HCV in different groups at increased risk of infection and in the general population and the determination of the medical, social and economic impact for the country.

At the same time, the estimation of the social impact allowed the determination of the years of life lost as a result of the premature deaths of patients with chronic hepatitis, liver cirrhosis and liver cancer. The estimated calculations show economic losses for the country in the period 2009-2020 determined by chronic hepatitis, liver cirrhosis and liver cancer of 5,611,635,005.34 lei or 5.6 billion lei.

Based on the results obtained, a strategic plan for the elimination of viral hepatitis was proposed, reflecting the main strategic directions recommended by international bodies, which frame specific objectives and strategic activities, including monitoring and evaluation indicators.

The theoretical significance and the applied value of the study

The results of the research allowed determining the directions of action in order to detect and reduce the risk of the formation of these pathologies; determining the economic and social impact, estimating the real morbidity, developing the national strategic plan for the elimination of hepatitis, developing indicators for monitoring the implementation of the plan. At the same time, the contemporary visions about the epidemiological peculiarities and the causes of the evolution of chronic hepatitis towards liver cirrhosis and primary liver cancer were broadened ; the real morbidity due to chronic hepatitis at the national level was estimated, the epidemiological situation was predicted and the strategic plan for the elimination of chronic hepatitis in the Republic of Moldova was developed, which, for the first time, foresees the reduction of cases of liver cirrhosis and primary liver cancer.

Major scientific results submitted for the defence:

1. The epidemiological situation of chronic hepatitis, liver cirrhosis and primary liver cancer in the last 20 years (2000-2020).
2. Epidemiological peculiarities and predominant risk factors, responsible for the unfavorable evolution of these pathologies.
3. Results of the evaluation of the current epidemiological surveillance system for the monitoring of acute and chronic hepatitis, including liver cirrhosis and primary liver cancer.
4. Estimation of the real number of cases by carrying out the study to estimate the real morbidity due to chronic hepatitis compared to those officially reported.
5. Burden of liver disease determined by potential years of life lost due to chronic hepatitis, liver cirrhosis and liver cancer.
6. The medical, economic and social impact of chronic hepatitis, liver cirrhosis and liver cancer on the country's economy.
7. Expenses required for the treatment of the case of HVB and HCV.
8. The national strategic plan for the elimination of hepatitis, which includes six strategic directions: prevention of new viral liver infections; strengthening and strengthening the testing and diagnosis of viral hepatitis; ensuring the treatment, care and monitoring of people with viral hepatitis; reducing health disparities caused by viral hepatitis; strengthening the system of epidemiological surveillance of viral hepatitis and data quality assurance; integrated multisectoral collaboration between decision-makers interested in addressing viral hepatitis and its consequences.

Implementation of scientific results. The results were implemented within the ANSP, the Discipline of Epidemiology and Microbiology Nicolae Testemitanu University, 3 workshops were carried out through the Provision of the Ministry of Health, including the Provision 148-d of 12.03.2021 regarding the organization of the workshop on the pre-testing of questionnaires for data collection in viral hepatitis; Provision of MS 457-d of 15.06.2021 Regarding the organization of the workshop on situational analysis in viral hepatitis B, C and D and control and response measures; Provision of Ministry of Health no. 653-d of 06.09.2021 regarding the organization of the workshop on the development of the Action Plan for the elimination of viral hepatitis for the period 2022-2030.

Approval of scientific results. The results of the study were presented and discussed at scientific forums Nation and international : Межрегиональной научно-практической international conferences _ with the participation of "Virusnye ". infections and society : problematic questions diagnostics , treatment , prevention and supervision ». Yekaterinburg , October 17-18 , 2018; The annual scientific conference devoted to the days of N.Testemitanu University . Chisinau, October 15-19, 2018; Annually Всероссийского Congress по infectious I'm sick with international participation « Actual problems epidemiology infectious and not infectious болезней » Moscow , October 18-19 , 2018; XI Annual Всероссийского Congress по infectious I'm sick with international participation . Moscow , April 1-3 , 2019; UMF days in Craiova. XLIXth Edition. June 7-8, 2019; 12th National Conference of Microbiology and Epidemiology 2019. November 14-16, 2019, Bucharest, Romania; The annual scientific conference devoted to the days of N.Testemitanu University . Chisinau, October 15-18 , 2019; VIII Congress of Specialists in the field of Public Health and Health Management. Chisinau, October 24-25, 2019; VIII Congress of Specialists in the field of Public Health and Health Management. Chisinau, October 24-25, 2019; Annual всероссийская научно-практическая conference with international participation . "

Actually problems epidemiology infectious and non- infectious болезней ", 21—23 October 2020, Moscow ; Conference annual scientific meeting of N.Testemitanu University Chisinau, October 17, 2019; The congress devoted to the 75th anniversary of the founding of Nicolae Testemitanu University, October 22, 2020, Chisinau. Всероссийской научно-практической conferences « Actual problems epidemiology infectious and non- infectious diseases : epidemiological , organizational and hygienic aspects » . 20-22 October 2021, Moscow. Also, the results were presented at the following invention salons, the works being mentioned with distinctions : The 22nd international exhibition of inventica 2018. Iasi, Romania 27-29.06.18; PROINVENT XVII Edition (Cluj-Napoca, Romania, 2019 – diploma of excellence); International Salon of Scientific Research, Innovation and Invention, XVII Edition, Cluj-Napoca , March 20-22, 2019, International Salon of Scientific Research, Innovation and Invention, XVII Edition, Cluj-Napoca , March 20-22, 2019; ; Inventica 2019 (Iasi , Romania, 2019 – gold medal); Infoinvent XVI edition (Chisinau , Republic of Moldova, 2019 – bronze medal); Specialized International Exhibition "MOLDMEZIN & MOLDENT" XXV edition, September 11-13, 2019; International Specialized Exhibition Infoinvent 2019

Publications on the research topic. The results of the study were published in 49 scientific papers, including 2 monographs, 4 articles in journals from the Web of Science and SCOPUS databases , including 2 with impact factor, four articles in recognized foreign scientific journals, 17 articles in scientific journals from the National Register of professional journals, 12 articles and theses in international scientific collections of medical congresses and exhibitions, 2 abstracts at national conferences in the republic, an invention patent, a copyright registration certificate, five innovations. The scientific results of the thesis were presented at 18 scientific forums international and at 3 scientific forums national with international participation.

Summary of thesis compartments. The thesis manuscript is presented in Romanian, on 209 computer-edited pages. Structured in accordance with the rigors of preparing a doctoral thesis, the manuscript includes the title page, the copyright page, table of contents, list of tables and figures, annotation in Romanian, English and Russian, introduction, seven chapters, general conclusions, recommendations and the bibliography that includes 225 bibliographic references , 12 appendices, the statement regarding the assumption of responsibility and the author's CV. The illustrative material includes 46 tables and 105 figures.

The general conclusions and practical recommendations are based on the evidence obtained in the research and correspond to the purpose and objectives outlined.

Key words : chronic hepatitis, liver cirrhosis, primary liver cancer, risk factors, epidemiological surveillance, prevention and control measures.

THESIS CONTENT

1. ANALYSIS OF THE EPIDEMIOLOGICAL SITUATION ON CHRONIC HEPATITIS, LIVER CIRRHOSIS AND PRIMARY HEPATIC CANCER WORLDWIDE

Worldwide, it is estimated that about 2 billion people are infected with HBV. According to WHO data, 1/3 of the world's population is infected with HBV, 350 million people are chronic carriers of this infection, and 170 million are infected with HCV, which is about 3% of the world's population. Of the more than 300 million HBV carriers, approximately 17 million are also infected with HDV.

The overall global prevalence of HCV is 1.6% (1.3–2.1%), which corresponds to 115 million people. The majority, 104 million, are adults over 15 years of age, with a HCV infection rate of 2.0% (1.7-2.3%). The prevalence of RNA-positive viremia is estimated at 1.1% (0.9–1.4%), which corresponds to 80 million people with viremic infections .

Recent data published internationally show a decrease in the spread of liver infection caused by a single virus and an increase in the share of infection caused by virus associations. Chronic hepatitis, induced by an association of several viruses, differs from mono-infection by the development of more serious clinical signs and a tendency for rapid worsening, extrahepatic clinical manifestations , hemorrhage in the upper digestive tract and the activation of the autoimmune process. According to evidence-based evidence, patients who acquire multiple hepatitis viruses are at risk of developing fulminant hepatitis with rapid progression to liver cirrhosis and primary liver cancer.

The economic impact caused by chronic viral hepatitis, consisting of direct and indirect costs, was estimated at 4,677 euros for hepatitis B, 12,798 euros for hepatitis C and 8,277 euros for hepatitis D.

Globally, most hepatitis deaths were caused by chronic liver disease, including 1 million cirrhosis and 470,000 hepatocellular carcinoma .

For 2019, according to the ranking of the top 10 causes of death, mortality from liver cirrhosis ranks 11th worldwide, and third in the Republic of Moldova.

The World Health Organization estimates the burden of liver cirrhosis in terms of disability-adjusted life years DALYs, the sum of years of life lost due to premature death and years of life lived with disability. The more DALYs attributable to a disease, the greater its public health burden. In 2019, liver cirrhosis caused 26.8% fewer DALYs than in 1990, a fact determined by the implementation of measures to eliminate hepatitis worldwide. It has been estimated that viral hepatitis C causes 26% of DALYs, alcohol 24%, and hepatitis B 23%, the contribution to the global burden of liver cirrhosis being close.

The global annual incidence of hepatocellular carcinoma is over 500,000 cases and ranges from 2% to 5%.

Hepatocellular carcinoma, the most common primary liver cancer, is the fifth most common tumor worldwide and the second leading cause of cancer death, behind lung and gastric cancer. Currently, hepatocellular carcinoma is responsible for 9.1% of cancer deaths worldwide. The incidence of new cases of hepatocellular carcinoma is estimated at 500,000–1,000,000 per year, causing 600,000 deaths annually globally.

2. MATERIALS AND RESEARCH METHODS

The study was carried out within the Department of Epidemiology of Nicolae Testemitanu State University of Medicine and Pharmacy, and the National Agency for Public Health, *Toma Ciorba* Clinical Hospital for Infectious Diseases, *Sfanta Treime* and, *Timofei Mosneaga* Clinical Hospitals and Oncological Institute.

In order to achieve the objectives, standardized research methods adapted to the requirements of the applied study were used. The following methods were applied:

1. *Epidemiological analysis of the data* - was based on careful observation and description of the health phenomena studied in the research;
2. *The observation method* - tracking the development of detected phenomena in order to be able to analyze them dynamically, compare them, and later synthesize the essential characteristics

of the evolution of the epidemic process and the particularities of the manifestation of morbidity in chronic hepatitis, liver cirrhosis and primary liver cancer.

3. *The epidemiological method* - allowed the synthesis of what was highlighted by the observation method and the further realization of the correlative study of the phenomena detected in the study, including the risk factors that determine the evolution of chronic hepatitis into liver cirrhosis and primary liver cancer.
4. *The historical method* - was applied to compare the same phenomena reported to the different categories of the population according to signs such as sex, age, territories, localities studied in the analyzed period 2000-2020.
5. *The economic method* – was applied to determine the economic and social impact determined by morbidity and mortality from chronic hepatitis, liver cirrhosis and primary liver cancer.
6. *The method of extracting information from a statistical form* - data were collected from statistical reports on the number of diseases registered in patients and from the medical records of inpatients .
7. *The bibliographic - analytical, logical* - method was applied for the theoretical study of the bibliographic sources, concepts and theoretical approaches existing at the current stage in chronic hepatitis, liver cirrhosis and primary liver cancer.

The study was grouped into several research stages:

Stage I – included the collection of data on morbidity and mortality from chronic hepatitis, liver cirrhosis and malignant tumors of the liver and intrahepatic bile ducts , presented by the National Agency for Public Health. Data were collected from statistical registration and reporting forms. For the collection of disaggregated data on different epidemiological indicators, a "Questionnaire for collection of epidemiological data, prevention and treatment in viral hepatitis B, C, D" was developed. The data from the territorial Public Health Centers, including the laboratories involved in the laboratory diagnosis of viral hepatitis, public and private medical and sanitary institutions, republican, departmental, municipal and district hospitals, AMT, CMF, CNTS were collected in accordance with the provisions of MSMPS no. 218 of 07.04.2021 "Regarding the collection and presentation of epidemiological data, treatment and laboratory diagnosis in viral hepatitis B, C and D".

The collected data were used to analyze the epidemiological situation of chronic hepatitis, liver cirrhosis and liver cancer, to estimate the real morbidity of these diseases at the country level and to develop the plan to eliminate viral hepatitis from the territory of the Republic of Moldova. Based on these data, the existing impediments in the national system of epidemiological surveillance of viral hepatitis morbidity were identified and the National Strategic Plan for the elimination of viral hepatitis B, C and D in the health sector at the national level was developed.

In the second stage, the "Questionnaire for the evaluation of epidemiological features and risk factors in chronic hepatitis, liver cirrhosis and primary liver cancer" was developed. The questionnaire was applied to respondents hospitalized at Toma Ciorba Clinical Hospital for Infectious Diseases, Sfanta Treime and Timofei Mosneaga Clinical Hospitals and IMSP Oncological Institute.

The clinical-epidemiological data about the patient were collected from the observation sheets of the patients in the period aa.2010-2018, later starting from a.2018 they were collected from the automated information system for hospital medical assistance SIA AMS. Data on risk factors, harmful habits, disease knowledge and practical skills were collected by interviewing patients with chronic hepatitis, liver cirrhosis and liver cancer.

For the calculation of the sample for the purpose of determining the epidemiological characteristics and risk factors, the formula applied in determining the sample in descriptive studies was used.

Stage 3 – Epidemiological data were collected from patients with chronic hepatitis, liver cirrhosis and liver cancer from the observation sheets and the automated information system for hospital medical assistance SIA AMS.

In order to achieve the set objectives, *the descriptive study was applied* with the description of the epidemiological peculiarities of the manifestation of morbidity through chronic hepatitis, liver cirrhosis and liver cancer, and *the analytical case-control study* that allowed us to determine the probability of the existence of a cause-effect relationship based on the risk factors determined in the research study.

The data from the questionnaire were statistically processed by the EPI INFO program version 7.2 which is a reliable software for epidemiological research. In the same context, in addition to the basic statistical indicators regarding the frequency rate of the studied phenomenon, confidence and error limits, linear and logistic regression analysis was carried out, which allowed the determination of Odds Ratio and hierarchical systematization of the implications of risk factors in the development of complications in chronic hepatitis, determined by liver cirrhosis and primary liver cancer.

The 4th stage . Determining the social impact by determining the AVPP indicator (Potential Years of Life Lost) which is applied in order to determine the burden of the disease and the systematization of pathologies with an impact on public health. Determining the economic impact was carried out based on the indicators included in the Government Decision 1460/2016 of 30.12.2016 regarding the medical-sanitary tariffs. Healthcare costs were included here: in-patient: the cost of a bed-day, the cost of an operation, the cost of an anesthesia, the cost of a medical examination or investigation service; in outpatients - the cost of a visit the cost of a medical examination or investigation service.

3. ANALYSIS OF THE EPIDEMIOLOGICAL SITUATION ON CHRONIC HEPATITIS, LIVER CIRRHOSIS AND PRIMARY LIVER CANCER IN THE REPUBLIC OF MOLDOVA, FOR THE PERIOD 2000-2020

3.1 Morbidity due to chronic hepatitis, liver cirrhosis and liver cancer in the Republic of Moldova, period 2000-2020

At the national level, the state policy in the field of viral hepatitis was implemented through the fourth National Program to combat viral hepatitis B, C and D for the period 2017-2021. At the current stage, in the Republic of Moldova, a plan of measures to combat/eliminate viral hepatitis B, C and D has not been developed and approved, and the existing epidemiological surveillance system must be adjusted to allow the comprehensive and disaggregated collection of data on acute viral hepatitis and chronic liver cirrhosis, primary liver cancer and deaths associated with viral hepatitis B, C and D. Since in most patients chronic viral hepatitis B, C and D degenerate into liver cirrhosis and primary liver cancer, these pathologies must be analyzed in complex to be able to assess their impact on our country.

The morbidity due to chronic hepatitis, liver cirrhosis and liver cancer in the Republic of Moldova for the last 21 years (2000-2020) does not reflect an improvement in the epidemiological situation due to these conditions. Thus, in 2020 the morbidity from these conditions was 83,229 cases, of which from chronic hepatitis – 73,431 cases or 88.23±0.11%, p<0.001, from liver

cirrhosis – 9,408 cases or $11.30 \pm 0.32\%$, $p < 0.001$ and by liver cancer – 390 cases or $0.47 \pm 0.34\%$, $p > 0.05$. Thus, out of seven patients with chronic hepatitis, one developed liver cirrhosis, the ratio being 7:1, and out of 24 patients with liver cirrhosis, one developed liver cancer, the ratio being 24:1. A large number of people do not know that they are infected, having already been diagnosed in the stage of liver cirrhosis or primary liver cancer.

According to the officially registered data in the Republic of Moldova, the prevalence of chronic hepatitis during the analyzed period increased approximately twice, from $1092.2 \pm 5.02\%$ cases in 2000, to $2218.34 \pm 7.82\%$ cases in 2019, with a slight decrease in 2020 to $2071.32 \pm 7.57\%$ cases, a fact determined by the reduction in the diagnosis of cases due to the COVID-19 pandemic. In 2000, the prevalence indices of liver cirrhosis morbidity increased 1.72 times, from 7 206 cases or $168.6 \pm 1.98\%$ cases to 10 246 cases or $289.02 \pm 2.85\%$ cases in 2019, and in 2020 there was a slight decrease to 9,408 cases or $265.38 \pm 2.73\%$ cases (Figure 1).

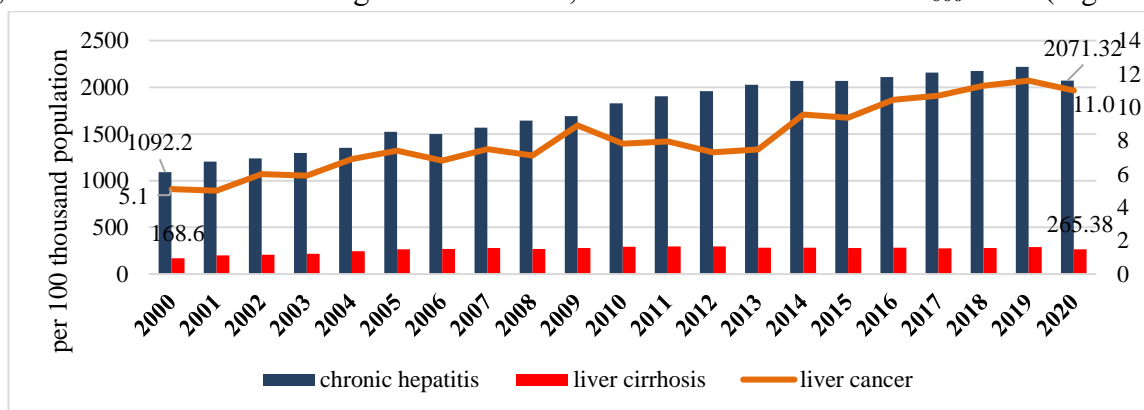


Figure 1. Multiannual dynamics of cumulative morbidity due to chronic hepatitis, liver cirrhosis and liver cancer in the Republic of Moldova, period 2000-2020 (per 100,000 population)

Along with the increase in cases of chronic hepatitis and liver cirrhosis, the number of patients diagnosed with liver cancer also doubled – from 186 cases or $5.1 \pm 0.35\%$ cases in 2000 to 412 cases or $11.6 \pm 0.57\%$ cases in 2019. In 2020 there was a decrease in the number of people diagnosed with cancer up to 390 cases or $11.0 \pm 0.56\%$ cases, as a result of the COVID-19 pandemic.

In 2020, 3,575 new cases of chronic hepatitis and 1,246 new cases of liver cirrhosis were registered in the Republic of Moldova, which is 100.84 and 35.15% cases. The prevalence indices of chronic hepatitis and liver cirrhosis registered a clear increase in the analyzed period (2000-2019), while the incidence indices of the last eight years indicate a decrease in morbidity from these conditions. Thus, in the multi-year dynamics of chronic hepatitis morbidity, two periods of evolution of the epidemic process are highlighted. In the first period (2000-2011) there was an increase in the incidence of chronic hepatitis from 100.9% cases to 228.79% cases, showing an increase of 2.26 times compared to the first year taken as the base (a. 2000). The year 2020 was not taken into account, in order to exclude the misinterpretation of the epidemiological situation during the COVID-19 pandemic.

In the second period (2011-2019), an improvement in the epidemiological situation with chronic hepatitis was attested, with the morbidity decreasing to 153.99% cases in 2019, down 1.48 times compared to 2011, when the highest incidence index in viral hepatitis. Unlike the incidence, the prevalence indices in chronic hepatitis were increasing throughout the analyzed

period, reaching 2218.34‰ cases in 2019. The share of new cases of chronic hepatitis in the cumulative morbidity was 6.94% in 2019 and 4.86% in 2020 (Figure 2).

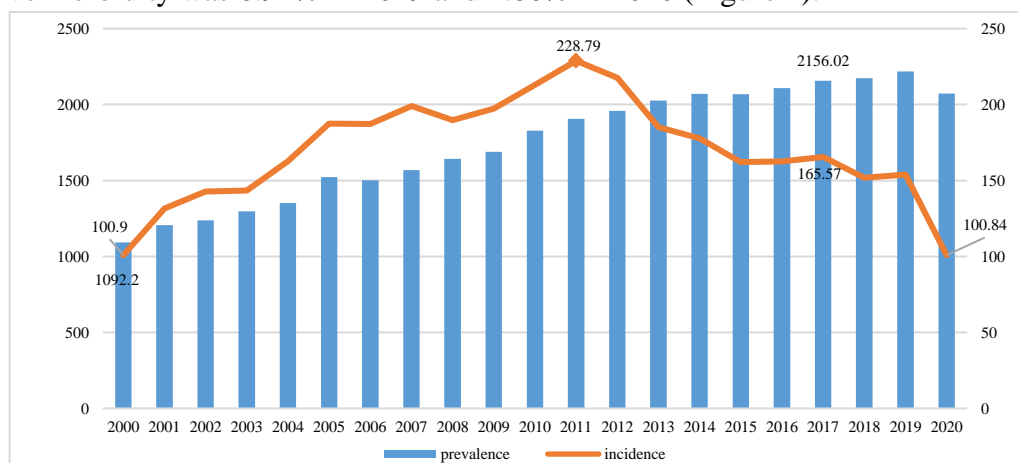


Figure 2. Dynamics of the prevalence and incidence of chronic hepatitis, for the period 2000-2020 (per 100,000 population)

A similar situation, the decrease in incidence and the continuous increase in prevalence, was also recorded in the case of liver cirrhosis morbidity. In the multiannual dynamics, the incidence of liver cirrhosis shows an uneven periodicity, highlighting a cyclicity of 2-4 years. Thus, in the first period (2000-2005) there was the highest increase in new cases of liver cirrhosis from 33.7‰ cases in 2000 to 65.21‰ cases in 2005, the morbidity being 1.79 times higher than in the first year studied (Figure 3). In the same period, the incidence of liver cirrhosis increased by 27.51‰ cases. In the following years, the dynamics of the epidemic process was characterized by a stable situation of the incidence of liver cirrhosis, with a variation of 62.24 - 52.9‰ cases, the lowest index being recorded in 2005 - 52.9‰ cases .

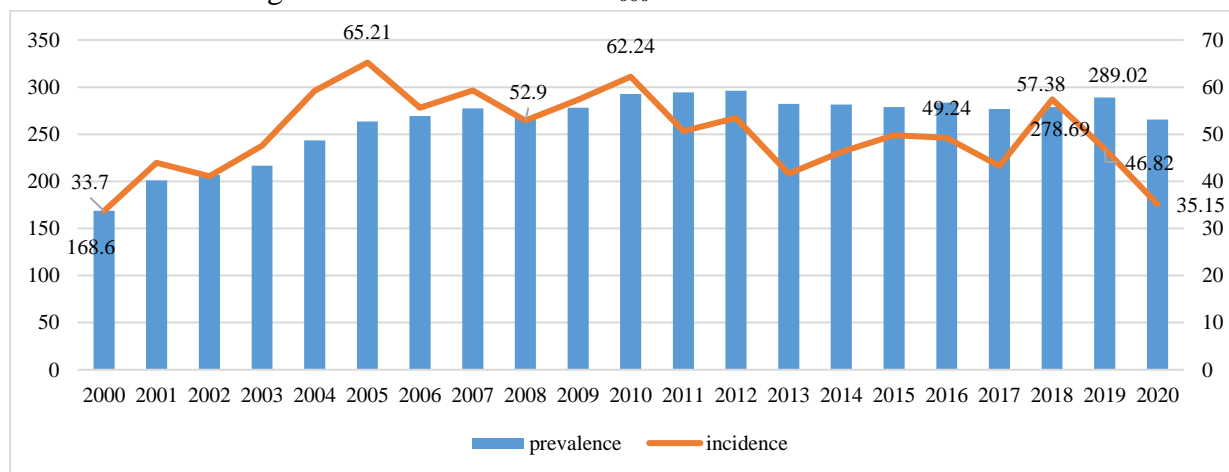


Figure 3. Dynamics of the prevalence and incidence of liver cirrhosis for the period 2000-2020 (per 100,000 population)

The medical, social and economic impact of viral hepatitis is determined by the chronic evolution of this disease towards liver cirrhosis, and some patients end up being diagnosed with primary liver cancer. Most patients diagnosed with viral hepatitis die in the liver cirrhosis phase and only a very small percentage of primary liver cancer. Thus, most patients either die of liver cirrhosis and do not develop primary liver cancer, or do not know they have liver cancer. This state of affairs is determined by the gaps in the surveillance of the given category of patients and the absence of screening of patients with liver cirrhosis. In the Republic of Moldova, statistical reports do not provide for the reporting of hepatocellular carcinoma cases , according to international recommendations. The epidemiological situation of liver cancer in the country can only be

assessed based on the registration reports of malignant tumors of the liver and intrahepatic bile ducts . Since there is a lack of data disaggregated by categories of liver tumors, especially those caused by hepatitis B, C and D viruses, it is not possible to assess the impact of these pathologies and develop health policies in order to reduce their morbidity.

The epidemiological situation in the republic with malignant tumors of the liver and intrahepatic bile ducts for the period 2000-2020 was also analyzed.

Cumulative morbidity from liver cancer increased from 186 cases or 4.34±0.32%⁰⁰⁰ cases in 2000 to 11.0±0.56%⁰⁰⁰ cases in 2020. An increase in the incidence of new tumor cases was also attested malignant liver and intrahepatic bile ducts from 174 cases or 4.06±0.31%⁰⁰⁰ cases in 2000 to 314 cases or 8.83±0.50%⁰⁰⁰ cases in 2016, in 2020 registering a decrease to 6.2±0.42%⁰⁰⁰ cases (Figure 4). Thus, the prevalence indices indicate a continuous increase in new cases of liver cancer, and the incidence indices a decrease of 2.01%⁰⁰⁰ cases.

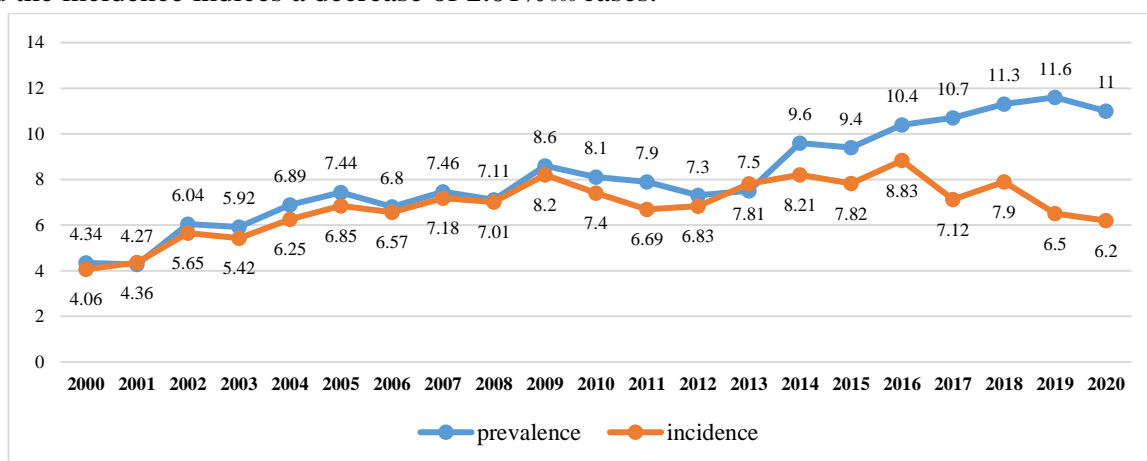


Figure 4. **Prevalence and incidence of morbidity from malignant tumors of the liver and intrahepatic bile ducts, for the period 2000-2020**

Morbidity from chronic hepatitis and liver cirrhosis is higher in adults compared to children. Thus, in 2020, 73,057 cumulative cases of chronic hepatitis were registered in adults or 2,543.45%⁰⁰⁰ cases, compared to 374 cases in children (0-17 years 11 months and 29 days), which constitutes 55.59%⁰⁰⁰ cases. This result is largely determined by the introduction of vaccination of newborns against viral hepatitis B according to the National Program of Immunizations, which provides for the administration of four doses (at 0, 2, 4 and 6 months). Another cause is the large number of patients with asymptomatic or occult forms, diagnosed late. Among them are both children and adolescents, a potential source of infection. The revaccination of children vaccinated between 1998-2012 was carried out in 2016, therefore at the current stage the level of the anti-HVB immune blanket after this revaccination is not known.

The analysis in multi-year dynamics of morbidity through chronic hepatitis and liver cirrhosis in children and adults showed a significant decrease in illnesses among children. Thus, the morbidity rates of chronic hepatitis and liver cirrhosis among children decreased by 8.43 times, making up respectively 0.51% and 0.03% in the general structure of chronic hepatitis and liver cirrhosis. During the 21 years analyzed in the study, the risk of children contracting chronic hepatitis decreased by 413.51%⁰⁰⁰ cases, and the average annual rate of decrease was 22.86. The prevalence indices of chronic hepatitis in children have decreased from 469.1 cases registered in 2000 to 55.59%⁰⁰⁰ cases in 2020. In adults, on the contrary, a double increase was recorded, compared to the first year taken into account study (2000), of chronic hepatitis morbidity from 42 065 cases or 1277.9%⁰⁰⁰ cases in 2000 to 76 576 cases or 2 543.45%⁰⁰⁰ cases in 2020 (Figure 5).

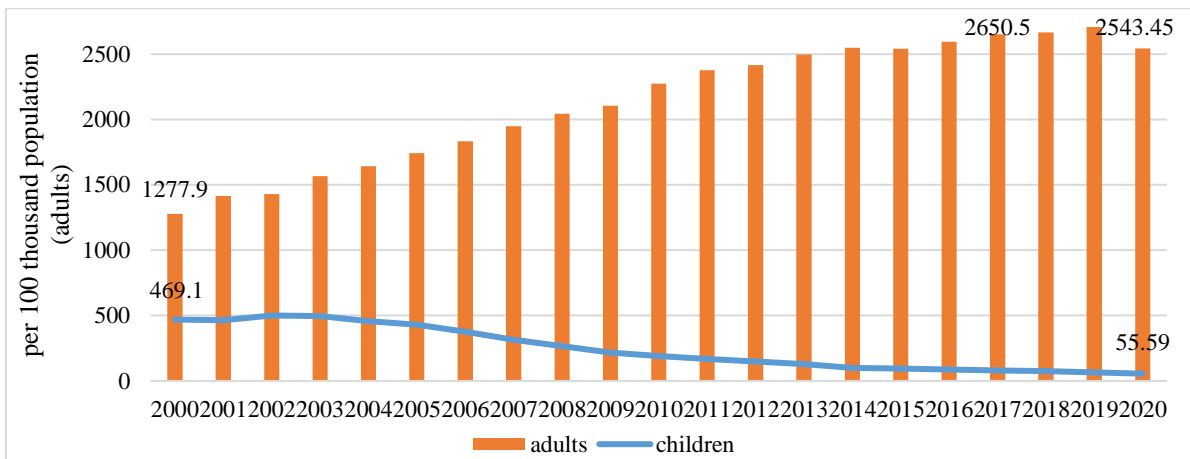


Figure 5. Evolution of cumulative morbidity due to chronic hepatitis in children and adults, for the period 2000-2020 (per 100,000 population)

The decrease in morbidity due to chronic hepatitis in children is due, in large part, to the achievements of the national public health system and the effectiveness of specific and non-specific prophylactic measures applied.

A similar situation can be seen in the case of liver cirrhosis. Prevalence indices in liver cirrhosis among children decreased by 6.35‰ cases, and the average annual rate of decrease was 0.36. According to the data presented in Table 3.7, during the 21 years analyzed, the prevalence indices in liver cirrhosis in children decreased from 67 cases or 6.8‰ cases in 2000 to 3 cases or 0.45‰ cases in 2020. In adults the situation is the opposite, the prevalence indices in liver cirrhosis are continuously increasing from 7 139 cases or 216.9‰ cases in 2000 to 9 405 cases or 327.43‰ cases in 2020 (Figure 6).

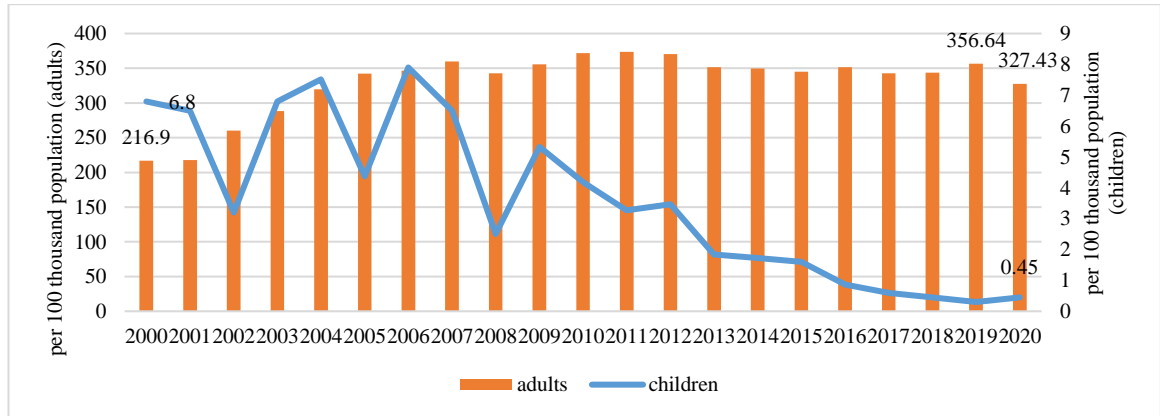


Figure 6. Morbidity prevalence rates due to liver cirrhosis among children and adults for the period 2000-2020 (per 100,000 population)

Chronic hepatitis has an uneven distribution on the territory of the republic. The analysis of morbidity according to development regions (RDD) determined a higher average cumulative morbidity in the regions of RDD "Centre" - 2,835.01‰ cases and RDD "Gagauzia ATU" - 2,639.70‰ cases. A lower level of morbidity due to chronic hepatitis was recorded in the RDD "municipality of Chisinau" - 1,369.49‰ cases, the "North" RDD - 1799.26‰ cases and the "South" RDD - 2,089.39 (‰) cases (Figure 7).

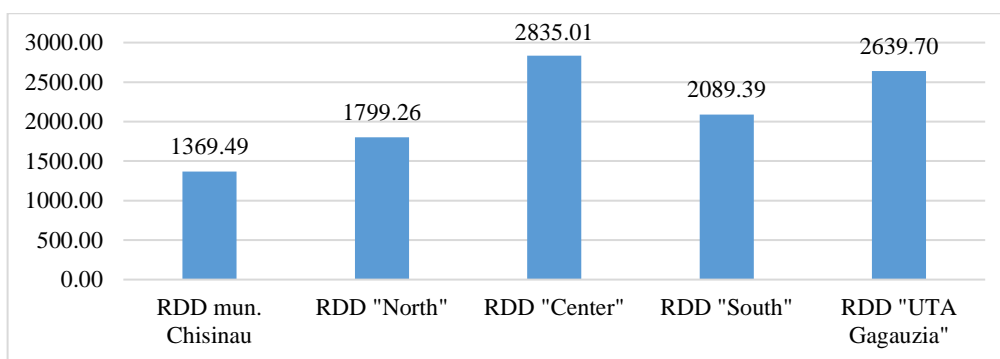


Figure 7. Cumulative morbidity average of chronic hepatitis morbidity in the administrative regions of the Republic of Moldova, period 2003-2020 (per 100,000 population)

In multiannual dynamics, chronic hepatitis morbidity was increasing in all development regions for the period 2003-2020. The exception is the year 2020, in which the epidemic process was influenced by the COVID-19 pandemic. A more pronounced increase in morbidity due to chronic hepatitis was recorded in RDD "Centre", from 1 662.66‰ cases in 2003 to 2 808.95‰ cases in 2020, being the highest morbidity recorded in 2020. In RDD "Găgăuzia ATU", in 2020 there was a reduction in morbidity due to chronic hepatitis compared to 2000. Thus, the prevalence indices due to chronic hepatitis decreased from 2,723.1‰ cases in 2003 to 2,610.64‰ cases in 2020. In the "South" DRR, chronic hepatitis morbidity increased from 1,284.46‰ cases in 2003 to 2,070.23‰ cases in 2020. "North" DRR records an increase in chronic hepatitis morbidity from 973.34‰ cases in 2003 up to 1749.63‰ cases in 2020. The increase in chronic hepatitis morbidity was also attested in the RDD " municipality of Chisinau ", from 860.4‰ cases in 2003 to 1275‰ cases in 2020 , the lowest morbidity due to chronic hepatitis during the analyzed period.

The analysis of the geographic distribution of morbidity through chronic hepatitis allowed the determination of the territories with the highest prevalence for the analyzed period. Thus, a significant cumulative morbidity due to chronic hepatitis was attested in Calarasi (3454.56‰ cases), Soldanesti (3347.12‰ cases) and Ceadir Lunga (3196.70‰ cases). The territories with the lowest cumulative morbidity rate due to chronic hepatitis are recorded in Briceni (1223.88‰ cases), Sangerei (1190.38 ‰ cases) and Cantemir (1035.98‰ cases), being territories with the lowest morbidity index.

The same epidemiological situation is attested in the case of liver cirrhosis. During the period 2003-2020, a higher average cumulative morbidity due to liver cirrhosis was recorded in the regions of RDD "Centru" - 386.84‰ cases and RDD "Gagauzia ATU" - 316.93‰ cases, years 2003-2020. Lower rates of average cumulative morbidity were recorded in the "South" RDD - 262.49‰ cases, the "North" RDD - 248.55‰ cases and the lowest level recorded is in the " Chisinau municipality " RDD - 170 ,17‰ cases (Figure 8).

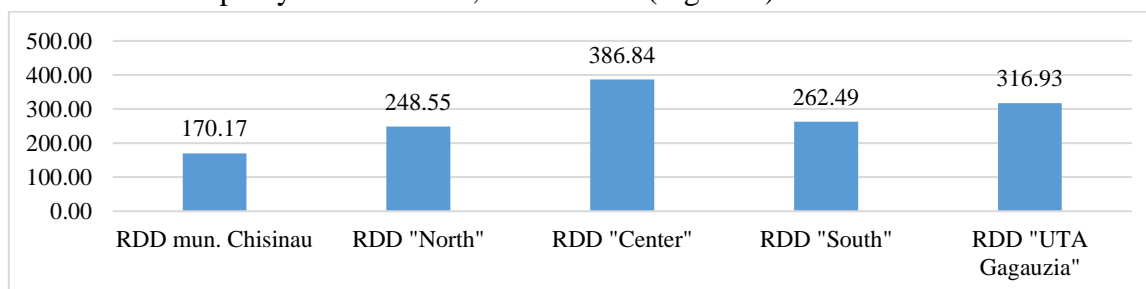


Figure 8. Average cumulative morbidity of liver cirrhosis morbidity by regions of the Republic of Moldova, period 2003-2020 (per 100,000 population)

When analyzing the geographical distribution of the average cumulative morbidity from liver cirrhosis in the Republic of Moldova, more affected territories were highlighted, such as Strășeni (588.09%₀₀₀ cases), Calarasi (528.23%₀₀₀ cases) and Telenesti (460.01 %₀₀₀ cases). Fewer cases were registered in Vulcanesti (167.64%₀₀₀ cases), Ocnîța (136.80%₀₀₀ cases) and Dondușeni (136.80%₀₀₀ cases), being the territory with the lowest morbidity due to liver cirrhosis.

Compared to chronic livers and liver cirrhosis, malignant tumors of the liver and intrahepatic bile ducts are predominantly registered in the RDD "Centre", constituting on average 14.20%₀₀₀ cases in the period yy.2010-2020. In the other development regions average cumulative indices vary between 7.37-7.66%₀₀₀ cases (Figure 9).

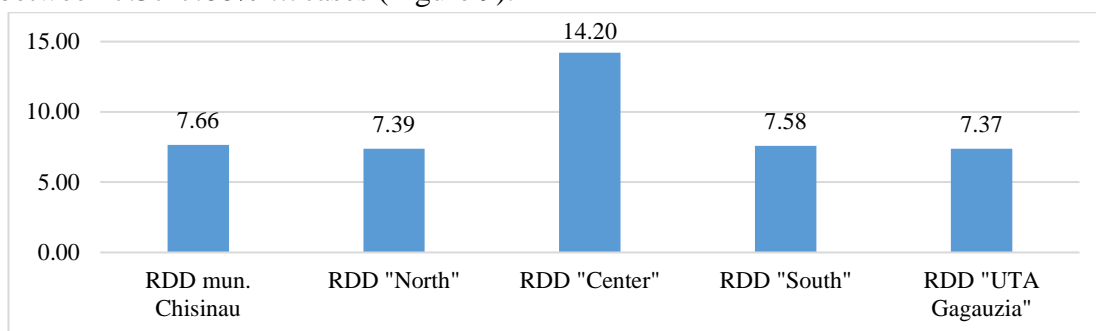


Figure 9. Cumulative average morbidity due to malignant tumors of the liver and intrahepatic bile ducts in the administrative regions of the Republic of Moldova, year 2010-2020

The average cumulative morbidity from malignant tumors of the liver and intrahepatic bile ducts remained at a high level throughout the period analyzed in the study, showing an increase from 11.94 %₀₀₀ cases in 2010 up to 14.67 %₀₀₀ cases in 2020. A continuous increase in morbidity from these conditions was witnessed in most of the development regions, with the exception of RDD "Gagauzia ATU" where the morbidity from malignant tumors of the liver and intrahepatic bile ducts was sharply decreasing from 12.98 %₀₀₀ cases in 2019 up to 8.65 %₀₀₀ cases in 2020. This fact is determined by the reduction of diagnosed cases in 2020 due to the COVID-19 pandemic, patients not having access to quality diagnostic services. Dubasari territories were more affected (38.81 %₀₀₀ cases), Criuleni (27.47 %₀₀₀ cases) and Donduseni (20.54 %₀₀₀ cases), and less affected Ceadar Lunga (3.40 %₀₀₀ cases), Glodeni (2.59 %₀₀₀ cases) and Briceni (1.34 %₀₀₀ cases).

3.2 Analysis of the epidemiological situation of chronic hepatitis and liver cirrhosis of viral etiology in the Republic of Moldova, year 2000-2020

The analysis of the etiological structure of cumulative morbidity through chronic hepatitis and liver cirrhosis in the Republic of Moldova for the years 2000-2020 shows the predominance of those of viral etiology. In the multi-year dynamics, we observe an increase in the share of viral hepatitis from 36.33±0.36% of the total number of chronic hepatitis cases registered at the beginning of the analyzed period (year 2000), up to 64.34±0.58% in 2020.

During the same period, the share of chronic non-viral hepatitis decreased from 29,712 cases or 63.67±0.27% in 2000 to 26,185 cases or 35.65±0.25% in 2020 (P_{1.2}<0.001) .

During the 21 years analyzed, the number of cases of viral hepatitis increased from 1 655 cases or 396.8%₀₀₀ in 2000 to 47 246 cases or 1332.70%₀₀₀ in 2020, compared to non-viral ones, in the case whose morbidity index decreased from 695.4%₀₀₀ in 2000 to 738.62%₀₀₀ in 2020 (Figure 10). Chronic hepatitis of non-viral etiology was increasing until 2010, when the highest level of morbidity was recorded (948.62%₀₀₀), after which a decrease followed with an average annual rate

of decrease (Δ) of 18 cases per 100,000 population . This fact can be explained by reducing the level of morbidity due to alcoholic and allergic hepatitis, and maintaining a constant level of morbidity due to toxic hepatitis. Cumulative morbidity from chronic viral hepatitis increased 3 times during 21 years, the average absolute increase (Δ) being 40.95. It should be noted that the increase in morbidity due to chronic hepatitis of viral etiology during this period coincides with the implementation of the Ministry of Health Order of 08/05/2011 Regarding the modification of the Donated Blood Testing Algorithm no. 220 of 04/02/2010.

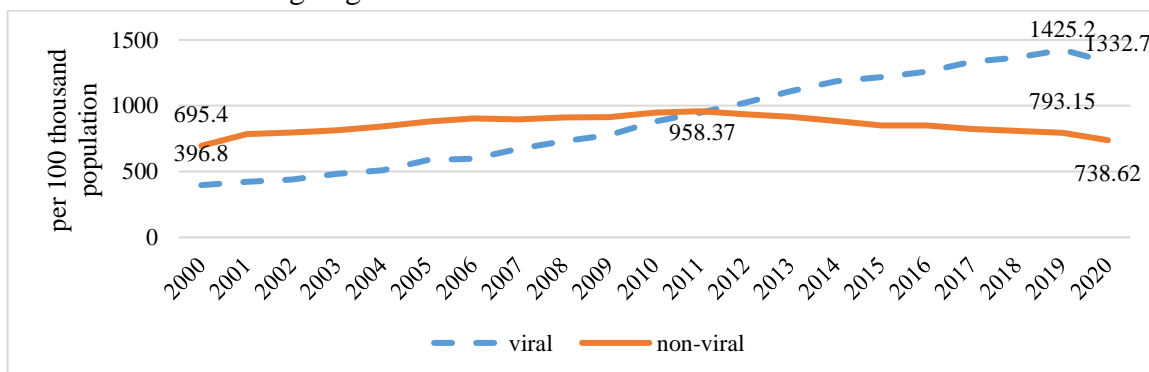


Figure 10. Evolution of the morbidity due to chronic viral and non-viral hepatitis in the Republic of Moldova in the multiannual dynamics, period 2000-2020

A similar situation can be seen in the case of liver cirrhosis, the rate of those of viral origin increasing from $22.05 \pm 1.04\%$ in 2000 to $53.25 \pm 0.68\%$ in 2020, compared to those of non-viral origin, whose share decreased from 77.94% in 2000 to 46.75% in 2020. Morbidity prevalence rates due to liver cirrhosis of non-viral etiology at the beginning of the analyzed period (a.2000) were 3.53 times higher compared to those of viral origin, constituting 5617 cases or 131.5 cases per 100 thousand population compared to 1589 cases or 37.2 cases per 100 thousand population respectively for a.2020 (Figure 11).

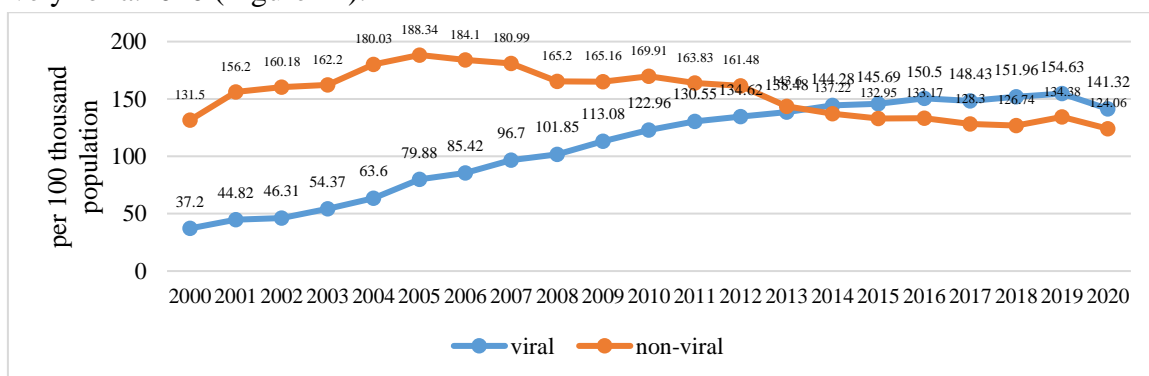


Figure 11. Evolution of viral and non-viral liver cirrhosis morbidity in the Republic of Moldova in multiannual dynamics, period aa . 2000-2020

Compared to the morbidity from chronic hepatitis of non-viral etiology, the morbidity from non-viral liver cirrhosis has been persistently decreasing since 2005, when it constituted 188.34 cases per 100,000 population, being the highest during the analyzed period. In parallel with the reduction of morbidity due to non-viral liver cirrhosis, there is a 4-fold increase in morbidity due to viral liver cirrhosis, with the substitution of those of non-viral etiology in the last 6 years (2014-2020). So, the prevalence indices of viral liver cirrhosis morbidity are continuously increasing from 37.2‰ in 2000 to 154.63‰ in 2019, followed by a slight decrease in 2020 to 141.32‰. The average annual rate of absolute increase (Δ) of viral liver cirrhosis morbidity was 7.49 cases.

Cumulative morbidity due to chronic viral hepatitis did not show any dynamic variability during the analyzed period. In multi-year dynamics, the morbidity from chronic viral hepatitis is continuously increasing, except for 2020, when there was a slight decrease due to the pandemic caused by the SARS-CoV-2 virus that led to a reduction in the number of tests performed in the country.

In the multi-year dynamics, morbidity from chronic viral hepatitis showed a significant increasing trend during the years 2000-2011, from 1675 cases or 39.2 ‰ to 4340 cases or 121.89 ‰. Later, with the implementation of prevention and control programs in viral hepatitis at country level, new cases of chronic viral hepatitis show a reduction up to 2166 cases or 61.10 ‰ in 2020 (Figure 12).

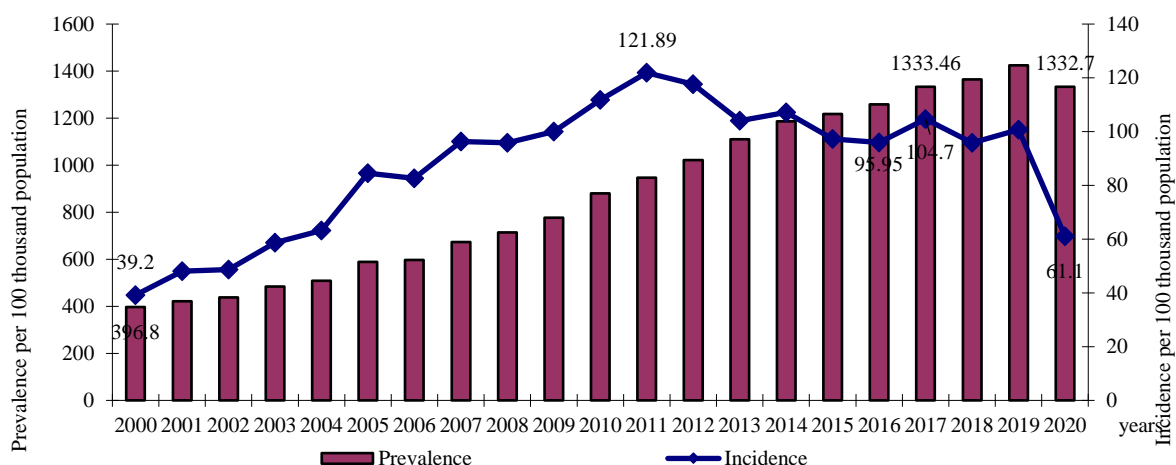


Figure 12. Evolution of the prevalence and incidence of chronic viral hepatitis morbidity in the Republic of Moldova, period 2000-2020

The same situation can be seen in the morbidity of liver cirrhosis of viral etiology. The incidence of liver cirrhosis of viral etiology increased in the period 2000-2009 by about 4 times, from 238 cases or 5.6 ‰ to 854 cases or 23.93 ‰. After 2009, new cases of liver cirrhosis began to decrease, reaching the value of 562 cases or 15.85 ‰ in 2020 (Figure 13).

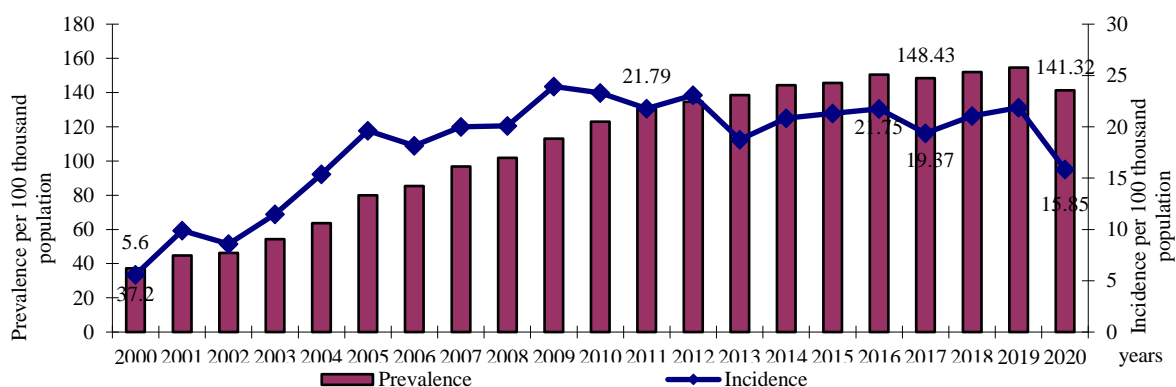


Figure 13. Evolution of the prevalence and incidence of viral liver cirrhosis morbidity in the Republic of Moldova, period 2000-2020

In the etiological structure of chronic viral hepatitis, HVBC predominates, accounting for 61.53% of all chronic viral hepatitis registered during the analyzed period. Over the period, CVD morbidity was stable, with a slight increase in share from 52.0% in 2000 to 61.53% in 2020.

During the analyzed period, there was a significant increase in the cumulative infection rate with HCV from 10.94% in 2000 to 31.6% in 2020. According to data from the literature, the risk of chronicity of both viral hepatitis and viral liver cirrhosis is higher in patients infected with HCV

compared to HBV. The share of chronic hepatitis caused by VHD increased from 2.7% in 2000 to 3.35% in 2020. During the same period, the share of chronic hepatitis of undetermined etiology decreased from 34.32% in 2000 to 3.52 % in 2020. This fact demonstrates the strengthening of the capacity of laboratories in testing and etiological diagnosis of chronic viral hepatitis.

Epidemiological analysis of chronic viral hepatitis morbidity in multi-year dynamics shows a significant increase in HVBC and HVCC. In the analyzed period, the prevalence indices of HVBC increased 4 times, from 206.4‰ in 2000 to 819.97‰ cases in 2020. It should be noted that the morbidity due to HCV has increased exponentially during the 21 analyzed years by about 10 times, from 1855 cases or 43.4 cases per 100 thousand population in 2000 to 14928 cases or 421.09 cases per 100 thousand population in 2020. Morbidity due to chronic hepatitis caused by VHD is also increasing from 10.9‰ cases in 2000 to 44.71‰ cases in 2020. A significant reduction in etiologically undiagnosed chronic hepatitis cases is attested from 110,0‰ cases in a.2000 to 46.94‰ cases in a.2020 (Figure 14).

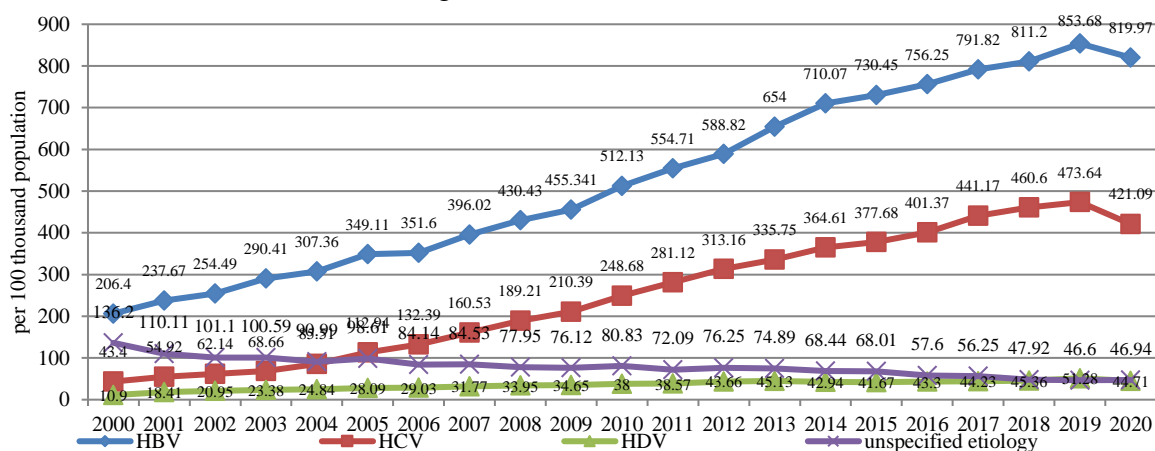


Figure 14. Multiannual dynamics of morbidity due to chronic viral hepatitis caused HBV, HCV, HDV and of unspecified etiology

In the etiological structure of liver cirrhosis, the same epidemiological peculiarity similar to chronic hepatitis is attested. Thus, in most cases HBV was the predominant etiological factor throughout the analyzed period. In 2020, the share of liver cirrhosis caused by HBV constituted 2221 cases which constitutes 44.15%, HCV – 1960 cases or 39.12%, VHD – 362 cases or 7.23%, and those with unspecified etiology – 476 cases or 9.5% of all viral liver cirrhosis . In the multi-annual dynamics, the share of liver cirrhosis caused by HBV is relatively constant throughout the analyzed period, varying between 41.22%-44.15% during the 21 years analyzed. A slight increase is recorded in the case of liver cirrhosis caused by HCV from 34.96% in a.2000 to 40.86% in a.2019, then it decreases to 39.12% in a.2020. Morbidity due to liver cirrhosis caused by HVD decreased from 11.52% in 2000 to 7.23% in 2020. A significant reduction of about 3 times can be seen in the case of viral liver cirrhosis of unspecified etiology from 32.85% in 2000 to 9.5% in 2020.

In the analyzed period, the prevalence of liver cirrhosis caused by HBV increased from 655 cases or 15.3 cases per 100 thousand population recorded in 2000 to 2221 cases or 62.40 cases per 100 thousand population in 2020 (Figure 15) . It should be noted that the morbidity during this time period increased by 4.1 times compared to the year 2000, and compared to the average for the republic (M=44.04) by 1.42 times, A significant increase in morbidity was also determined in the case of liver cirrhosis caused by HCV. This increased from 229 cases or 5.4 per 100 thousand cases registered in the year 2000 to 1960 cases or 55.29‰ in the year 2020, being 11.2 times higher compared to the first year studied (the year 2000). In the same period of time, the morbidity

of liver cirrhosis caused by VHD increased 2.65 times, from 183 cases or 4.3 cases per 100 thousand registered population in 2000 to 362 cases or 10.21‰ in 2020. At the same time, morbidity increased 1.37 times compared to the average for the republic ($M=8.27‰$). There is a slight decrease in morbidity due to viral liver cirrhosis of unspecified etiology. During the analyzed period, their prevalence varies between 522 cases or 12.2‰ recorded in 2000 to 476 cases or 13.74‰ in 2017, the highest level being recorded in 2007, where the prevalence was 18.59 cases per 100,000 population. Thus, there is a slight decrease in the cases of liver cirrhosis with undetermined etiology by 1.12 times compared to the first year studied (year 2000). On average, 13.43 cases per 100,000 population are recorded in the republic in 2020.

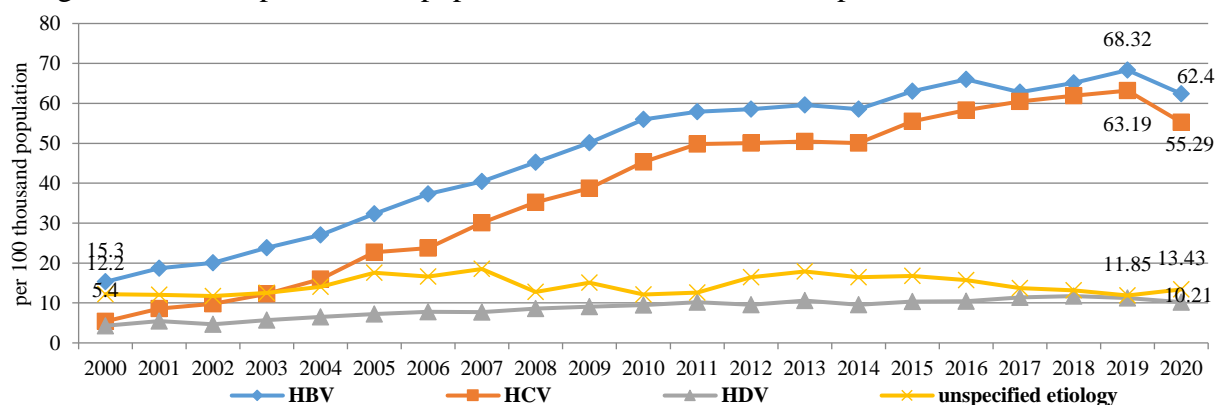


Figure 15. Multiannual dynamics of viral liver cirrhosis morbidity caused by HBV, HCV, HDV and of unspecified etiology in the Republic of Moldova, period 2000-2020

The territorial distribution of chronic HBV morbidity in the Republic of Moldova was analyzed in 2 time periods: 2003-2010 and 2011-2020. Thus, in the second period (2010-2020), the cumulative number of people infected with chronic HBV practically doubled, constituting 727.2 cases per 100 thousand population compared to 2003-2010 where the prevalence was 374.1 cases per 100 thousand population. Most cases are registered in RDD "Gaguzia ATU" and RDD "Centru". In the multiannual dynamics, the prevalence of chronic HBV is increasing in all administrative territories. The DDR region "Gaguzia ATU" being the most affected region at country level. In these territories, morbidity increased during these 18 years from 934.8 cases per 100 thousand population in 2003 to 1334.07 cases per 100 thousand population in 2020. A lower level of chronic HBV morbidity is recorded in the northern regions of the country. Morbidity in the northern regions increased from 163.07 cases per 100 thousand population in 2003 to 504.24 cases per 100 thousand population in 2020. The analysis of the official statistical data recorded in the Republic of Moldova, highlights the average morbidity per country for a.2020 of 819.97 cases per 100 thousand population. The most affected territory at country level turned out to be Telenești with 2222.35 cases per 100 thousand population, being 2.7 times higher than the average for the republic. Higher prevalence indices were also found in Causeni (1791.35‰) and Ceadir -Lunga (1662.58‰). Lower morbidity rates were recorded in the municipalities of Balti (325.09‰), Cantemir (268.54‰), and Briceni (256.67‰).

Epidemiological surveillance of HVBC carried out at the country level, vis -à-vis the level of morbidity in different territories, allowed the highlighting of gaps in case reporting and misinterpretation of the case definition.

The analysis of cumulative morbidity through CHBV for 2020 according to the development regions of the country showed that the most affected were: RDD "Gaguzia ATU" - 1313.07‰ cases, RDD "Centru" - 1081.53‰ cases and RDD "South" - 1080.93‰ cases.

HCV morbidity in the "North" RDD constituted only 504.24%₀₀₀ cases, being below the average level of HCV morbidity with 315.73%₀₀₀ cases.

A similar situation was noted in the case of morbidity due to HVCC. In the analyzed period (2003-2020), the prevalence indices are increasing in all the administrative territories of the country, with the exception of the RDD "mun. Chisinau" where there is a significant decrease in cumulative morbidity from HCV starting from 2017. This fact can be determined by the discovery of treatment against HCV. If until 2017, the RDD of Chisinau recorded the highest cumulative morbidity due to HCV, after the discovery of the treatment, this region recorded lower values compared to the north and center. The lowest values of the prevalence indices are recorded in the southern region of the country – 265.02%₀₀₀ and Gagauzia ATU – 286.84%₀₀₀. In 2020, a cumulative morbidity through HCV higher than the average for the republic (421.09 %₀₀₀) was recorded in the "North " RDD - 460.33%₀₀₀ and the "Center " RDD - 454.50%₀₀₀. The prevalence of HVCC was higher in the districts of Rascani - 867.49%₀₀₀, the morbidity due to HVCC being here 2 times higher compared to the average for the republic, Edineț - 743.96%₀₀₀ and Șoldănești - 727.58%₀₀₀. The least affected territories with HVCC were Cantemir - 63.47%₀₀₀ and Sangerei - 130.98%₀₀₀.

3.3 Analysis of the epidemiological situation by chronic hepatitis and liver cirrhosis of non-viral etiology in the Republic of Moldova, period 2000-2020

In 2020, the share of chronic hepatitis of non-viral etiology in the general structure of chronic hepatitis was 35.65%, with 26 185 cases or 738.62%₀₀₀ cases being registered. In the period 2000-2020, the etiological structure of non-viral chronic hepatitis underwent significant changes. Thus, if in the first year analyzed (2000), chronic hepatitises of non-viral etiology constituted 63.67%, the absolute values being 29,712 cases and a prevalence of 695.4%₀₀₀, then in 2020 their share was reduced to 35, 65%. Since during 21 years the morbidity due to chronic non-viral hepatitis decreased by only 3527 cases, and by viral hepatitis it increased by 30 291 cases, we can state that the reduction of cases of chronic non-viral hepatitis is not determined by national programs to combat them, but improving the testing and detection of cases of hepatitis of viral etiology.

The same situation was found in the case of liver cirrhosis. In 2000, in the general structure of liver cirrhosis, the share of non-viral ones was 77.94%, the absolute values being 5617 cases or 131.5%₀₀₀. By 2020 this was reduced to 46.75%, with absolute values of 4398 cases or 124.06%₀₀₀. Thus, in 2020, liver cirrhosis morbidity is determined, in 53.50% of cases, by viral forms. At the same time, in the 21 years analyzed, the number of cases of non-viral liver cirrhosis decreased by only 1219 cases, and of viral liver cirrhosis increased by 3421 cases. Thus, the change in the etiological structure of liver cirrhosis is not determined by the reduction of cases of non-viral liver cirrhosis, but by the increase of cases of chronic viral hepatitis and, as a result, of cases of liver cirrhosis of the same etiology.

In the multi-year dynamics, the morbidity from chronic non-viral hepatitis is relatively constant, with a slight increase from 695.4%₀₀₀ cases in 2000 to 738.62%₀₀₀ cases in 2020. During the analyzed period, the morbidity from chronic non-viral hepatitis decreased insignificant, with a rate of 43.22 %₀₀₀ cases. At the same time, the incidence of non-viral chronic hepatitis cases practically doubled, from 61.7%₀₀₀ cases in 2000 to 39.74%₀₀₀ cases in 2020 (Figure 16).

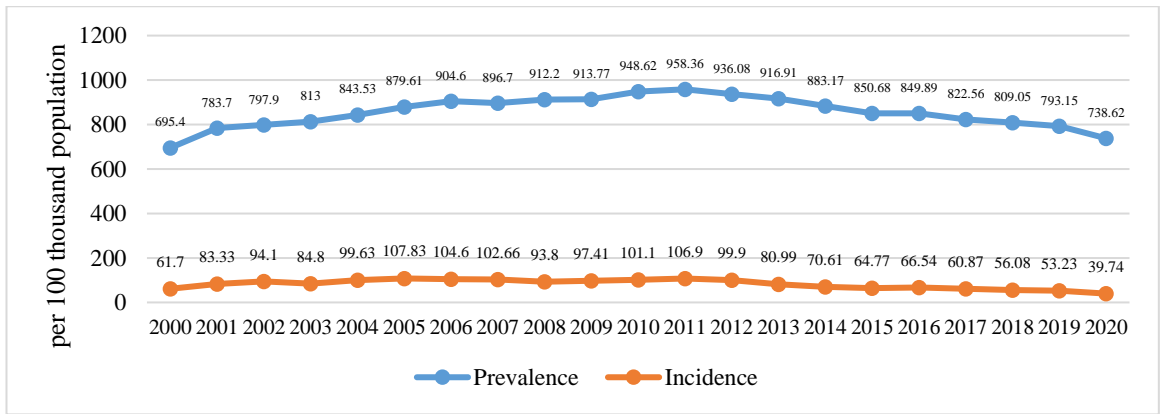


Figure 16. **Multiannual dynamics of prevalence and incidence of chronic non-viral hepatitis, 2000-2020**

A similar situation emerged in the case of liver cirrhosis morbidity. The prevalence indices of non-viral liver cirrhosis during this period decreased from 131.5%⁰⁰⁰ cases in 2000 to 124.06%⁰⁰⁰ cases in 2020, with a rate of decrease of 7.44%⁰⁰⁰ cases. New cases of non-viral liver cirrhosis also decreased from 28.1%⁰⁰⁰ cases in 2000 to 19.29%⁰⁰⁰ cases in 2020, with a tempo of 8.81%⁰⁰⁰ cases (Figure 17).

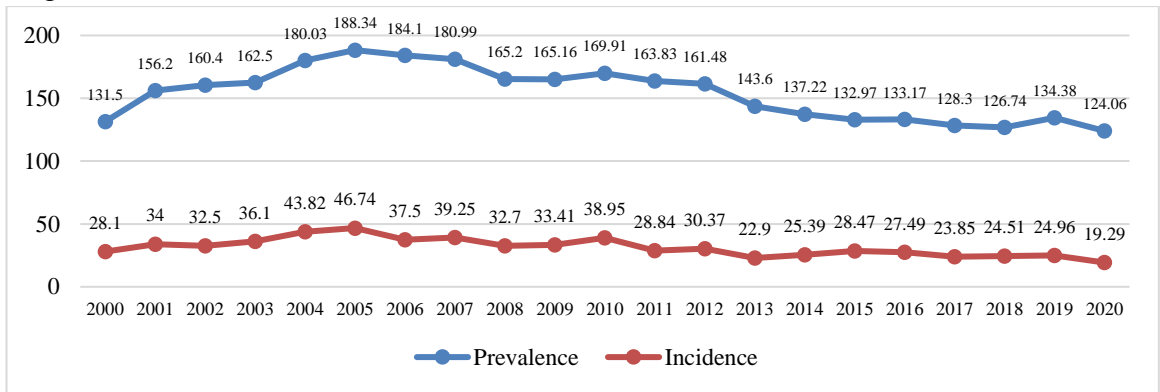


Figure 17. **Multiannual dynamics of prevalence and incidence of non-viral liver cirrhosis, 2000-2020**

During the analysis of the morbidity caused by chronic non-viral hepatitis and the prevalence indices of chronic viral hepatitis, it was found that in the period 2000-2020 the number of cases of viral hepatitis increased throughout the analyzed period by 3.3 times, from 396.8%⁰⁰⁰ cases in 2000 up to 1332.7%⁰⁰⁰ cases in 2020, and those of non-viral etiology only until 2011, when the highest prevalence index of chronic non-viral hepatitis was recorded - 958.36%⁰⁰⁰. In the following years, the rates of morbidity from chronic non-viral hepatitis gradually reduced to 738.62%⁰⁰⁰ cases in 2020. Thus, the significance of viral hepatitis in relation to non-viral ones changed essentially in 2011, when viral ones reached a significant share in the general structure of chronic hepatitis.

In the case of liver cirrhosis, the change in the overall structure occurred later, in 2013, when non-viral liver cirrhosis was replaced by viral liver cirrhosis. In the multi-year dynamics, morbidity from non-viral liver cirrhosis registers an increase in prevalence indices from 131.5%⁰⁰⁰ cases in 2000 to 188.34%⁰⁰⁰ cases in 2005, being the highest in the analyzed period. In subsequent years, the morbidity of non-viral liver cirrhosis decreased to 124.06%⁰⁰⁰ cases in 2020.

According to the data officially registered at ANSP, Statistical Form 29, a significant number of cases of unspecified etiology are registered. In 2020, according to the morbidity data from chronic non-viral hepatitis in relation to the etiological factor, the majority of cases of chronic

non-viral hepatitis are of unspecified etiology, with an absolute value of 21,592 cases or 83.27%, the prevalence indices being 609.06%₀₀₀ cases. Thus, the etiological factor was determined only in 16.58% of cases, including chronic alcoholic hepatitis with an average of 1829 cases or 5.48%, with a prevalence index of 42.65%₀₀₀ cases, chronic toxic hepatitis – 3112 cases or 10.17%, prevalence index 79.94%₀₀₀ cases, chronic allergic hepatitis – 230 cases or 10.93%, prevalence index 7.81%₀₀₀ cases (Figure 18).

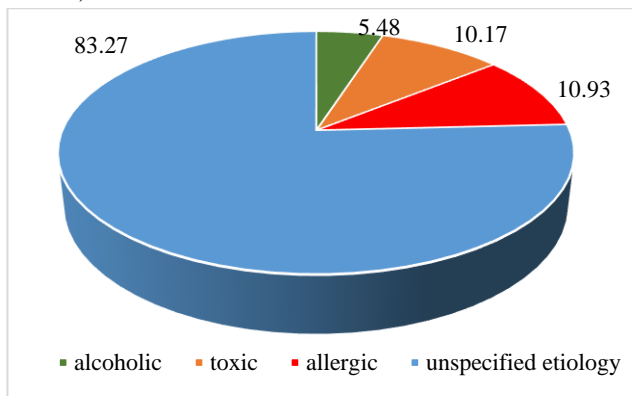


Figure 18. The average share of non-viral chronic hepatitis according to the etiological factor, period 2000-2020

During the analyzed period, in multi-year dynamics, no variability was found in the etiological structure of non-viral chronic hepatitis.

The analysis of prevalence rates of non-viral chronic hepatitis morbidity highlights the deficiencies of testing and diagnostic capacity in the field of liver pathology. It is regrettable that in the Republic of Moldova morbidity from chronic non-viral hepatitis is dominated by those of unspecified etiology. This fact points to a series of gaps in the epidemiological and clinical monitoring of patients with these pathologies, including not allowing the identification of the causal factor for the development of measures to prevent and control them.

In multi-year dynamics, the prevalence indices of morbidity from chronic hepatitis of unspecified etiology were not decreasing, but on the contrary, they increased from 560.6%₀₀₀ cases in 2000 to 609.06%₀₀₀ cases by 2020. A slight increase it is also evident in the case of chronic toxic hepatitis morbidity, from 56.6%₀₀₀ cases in 2000 to 75.54%₀₀₀ cases in 2020, and allergic, from 7.9%₀₀₀ cases in 2000 to 11.57 %₀₀₀ cases in 2020. During the same period, the morbidity of chronic alcoholic hepatitis practically doubled, from 70.2%₀₀₀ cases in 2000 to 42.45%₀₀₀ cases in 2020.

etiological structure of non-viral liver cirrhosis was stable and uniform throughout the analyzed period, with the predominance of liver cirrhosis of unspecified etiology. As a result, for 21 years, the establishment of the clinical diagnosis of the manifestation of liver cirrhosis did not improve, patients being treated only based on the signs.

The analysis of the prevalence indices of non-viral liver cirrhosis revealed the same epidemiological peculiarities. The high level of morbidity due to non-viral liver cirrhosis is maintained at the expense of those with unspecified etiology. Their share increased from 94.5%₀₀₀ cases in 2000 to 142.02%₀₀₀ cases in 2005, reducing in 2020 to 85.98%₀₀₀. The second place in the etiological structure of non-viral liver cirrhosis is occupied by alcoholic ones whose prevalence index has slightly decreased from 23.17%₀₀₀ cases in 2000 to 18.48%₀₀₀ cases in 2020. Compared with liver cirrhosis and alcoholic cirrhosis, the prevalence rates in toxic liver and biliary cirrhosis are increasing from 12.4%₀₀₀ cases and 0.8%₀₀₀ cases respectively in 2000 to 17.21%₀₀₀ cases and 2.4%₀₀₀ cases respectively in 2020.

Since chronic hepatitis and alcoholic liver cirrhosis are determined by alcohol consumption in the general population, we aimed to analyze the epidemiological situation through these pathologies in relation to the prevalence indices of alcoholism and alcoholic psychoses. According to the data published by the National Bureau of Statistics, the number of officially registered cases of alcoholism and alcoholic psychoses is decreasing from 49,346 cases in 2000 to 46,346 cases in 2020. However, the prevalence indices of morbidity from alcoholism and alcoholic psychoses in relation to the number of the population denotes an increase in the incidence of these pathologies from 1356.8%₀₀₀ cases in 2000 to 1768.6%₀₀₀ cases in 2020. We assume that this fact depends on the denominator used. Until 2014, the total number of the population, which was 3.5 million, was used in this capacity, and after this year the number of the population with regular residence, which constituted about 2.6 million.

3.4 Epidemiological analysis of the data collected from the Territorial Public Health Centers

In the Republic of Moldova, in addition to the serious situation with acute and chronic viral hepatitis, liver cirrhosis and primary liver cancer, there are also deficiencies in the implementation of prevention and control measures. Thus, in the republic there is an insufficient epidemiological investigation of cases of chronic hepatitis and chronic carriage of HBV and HCV, non-compliance with the standard laboratory diagnostic algorithm, inadequate examination of contacts from outbreaks for markers of viral hepatitis, insufficient coverage with vaccine against hepatitis B of contingents with increased risk of infection, etc.

In order to determine the ways of transmission of chronic hepatitis, the data from Form no. 362-2/e of the investigation of cases of acute hepatitis, because cases of chronic hepatitis are not investigated. The analysis of the epidemiological investigation sheets of the case of acute viral hepatitis B, C and D (Form no. 362-2/e) showed that out of 86 cases of acute HBV registered, the epidemiological investigation, with the completion of the mentioned form, was carried out only in 65 cases, which is 75.58%. The route of transmission of the infection was established only in 24 cases or 36.92%, in 63.08% of cases it was declared as unknown/other (Table 1).

Table 1. **Pathways of transmission in acute HBV based on epidemiological survey sheets**

Ways of transmission	2016	2017	2018	2019	2020	TOTAL	%
Total acute BVD reported in Form 2	26	2.3	25	7	5	86	
TOTAL researched Form no. 362-2/e	22	2.3	25	6	5	65	
% of investigated cases	84.62	100.00	100.00	85.71	100.0	94.1	
From the 65 cases investigated:							
<i>Use of injectable drugs</i>	3	1	0	0	0	4	6.15
<i>Unprotected sex</i>	5	6	5	2	0	15	23.08
<i>From mother to child</i>	3	1	2		0	5	7.69
<i>Unknown, others</i>	11	15	18	4	5	41	63.08
TOTAL	22	2.3	25	6	5	65	100

According to the data of the epidemiological investigation sheet (Form no. 362-2/e) of acute HBV cases, the sexual route of transmission remains dominant. Thus, of the 65 investigated cases, the sexual route of transmission of acute HBV was established in 15, which constitutes 23.08%. Transmission of acute HVB from mother to fetus remains a problem, determined in 5 cases or 7.69%. Acute HBV transmission through injection drugs was established in 4 cases or 6.15%. In the last 2 years, no cases of acute HBV transmitted by this route have been registered (Figure 19).

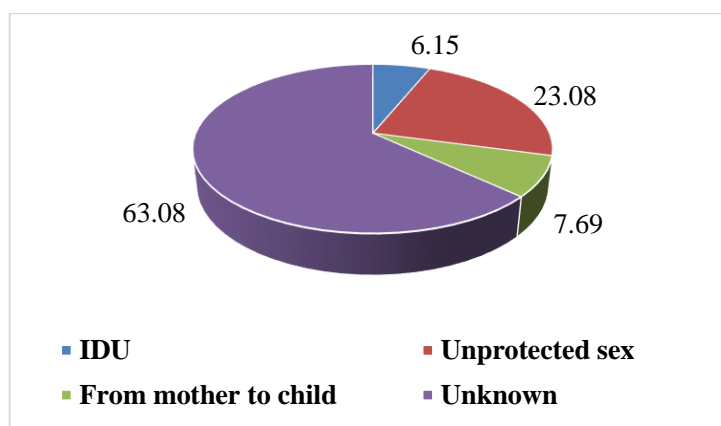


Figure 19. **The share of transmission routes of acute HBV, period 2016-2020**

Of the 197 cases of acute CVD detected in the period 2016-2020, the epidemiological investigation was carried out in 172, which constitutes 87.31% (Table 2). Although the research rate of acute HCV cases is higher compared to acute BVD, the problem of identifying the routes of transmission of the liver virus remains a priority. Thus, of the 172 investigated cases, only in 34 cases or 19.23% was the transmission route identified, and in 138 cases or 80.23%, it remained unknown/others.

Table 2. **Pathways of transmission in acute HVC based on epidemiological survey sheets**

Ways of transmission	2016	2017	2018	2019	2020	TOTAL	%
Total acute BVD reported in Form 2	49	53	42	35	18	197	
TOTAL researched Form no. 362-2/e	46	44	36	29	17	172	
% of investigated cases	93.88	83.02	85.71	82.86	94.44	87.31	
From the 197 investigated cases:							
<i>Use of injectable drugs</i>	1	0	1	0	0	2	1.16
<i>Unprotected sex</i>	7	8	7	3	1	26	15.12
<i>Nosocomial infection</i>	3	2	0	0	1	6	3.49
<i>Unknown, others</i>	35	34	28	26	15	138	80.23
TOTAL	46	44	36	29	17	172	100

The analysis of the data on the routes of transmission of acute HCV shows a predominance of HCV transmission through the sexual route, determined in 26 cases (15.2%). In 6 cases (3.49%), transmission was nosocomial, and in 2 cases (1.16%) through injectable drugs (Figure 20).

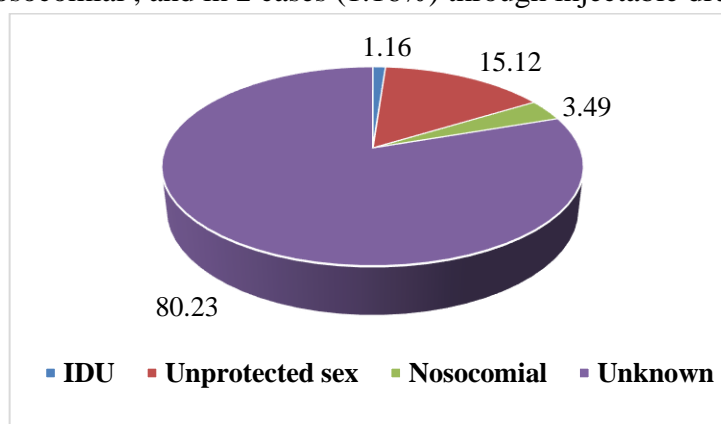


Figure 20. **The share of transmission routes in patients with acute HCV, period 2016-2020**

New cases of HVBC are not subject to epidemiological research. In the period 2016-2020, of the total of 2192 newly registered cases of chronic HBV, the routes and factors of transmission were selectively determined in only 194 cases (8.85%). The analysis of the transmission routes of

chronic HBV showed that the sexual route prevails, identified in 185 cases, which constitutes 8.44%. Transmission from mother to fetus was found in 8 cases (0.36%), and with injectable drugs in 1 case (Table 3).

Table 3. Pathways of transmission in chronic HBV

Routes of chronic HBV transmission	2016	2017	2018	2019	2020	Total	
						abs	%
<i>Use of injectable drugs</i>	1	0	0	0	0	1	0.05
<i>Unprotected sex</i>	17	36	47	65	20	185	8.44
<i>From mother to child</i>	0	0	3	1	4	8	0.36
<i>Unknown, others</i>	264	468	547	440	279	1998	91.15
TOTAL	282	504	597	506	303	2192	100.00

Cases of chronic HCV are also not subject to epidemiological research. Out of the total of 2604 cases of HVCC, registered in the period 2016-2020, the route of transmission was selectively determined in only 116 cases (4.45%). According to the data presented, sexual transmission remains dominant also in HVCC, being detected in 115 cases (4.42%). Transmission of HVCC with injection drugs was identified in only one case (0.04%) in 2019 (Table 4).

Table 4. Routes of transmission of chronic HCV

Routes of transmission of chronic HCV	2016	2017	2018	2019	2020	Total	
						abs	%
<i>Use of injectable drugs</i>	0	0	0	1	0	1	0.04
<i>Unprotected sex</i>	11	33	25	22	24	115	4.42
<i>Unknown, others</i>	585	590	525	540	248	2488	95.55
TOTAL	596	623	550	563	272	2604	100

The lack of collection of epidemiological data for chronic cases of viral hepatitis B and C based on an approved form, presents an impediment in determining the conditions of contamination and at the same time implementing prevention and control measures at the country level .

3.5 Mortality due to chronic hepatitis, liver cirrhosis and liver cancer in the Republic of Moldova, period 2000-2020

To ensure a health system that is adequately aligned with the real health challenges of the population, policy makers must be able to compare the effects of different diseases that kill people prematurely and cause health problems. One of these public health problems is chronic hepatitis which, in turn, leads to the development of liver cirrhosis and liver cancer. When analyzing mortality from these pathologies, it was found that in the period 2009-2020 there were 37,629 deaths, most of them caused by liver cirrhosis - 32,065 deaths or 85.21±0.15%, CI 95% 84.88-85.59 (P<0.00001). The second cause of death was liver cancer - 5354 deaths, which is 14.23±0.47%, CI95% 13.89-14.59 (P<0.001). Thus, patients either do not know the stage of evolution of the disease, or they die prematurely.

Fewer deaths are caused by chronic hepatitis. During the analyzed period (2009-2020), 210 people died from chronic hepatitis, which is 0.56±1.01% CI 95% 0.45-0.6 (P<0.000001). Per year, an average of 16.42±2.10 CI95% 11.80-21.03 people die from chronic hepatitis, from liver

cirrhosis – 2670.9 CI95% 2466.5-52875.29 people, and from cancer hepatic – 446.16 CI 95% 466.29-426.03 (Figure 21).

Standardizing the indices to 100,000 population demonstrates the same legitimacy. The average incidence of deaths determined by chronic hepatitis is $0.47 \pm 0.05\text{‰}$ deaths, by liver cirrhosis - $75.14 \pm 2.5\text{‰}$ deaths CI95% 69.47-80.80, and by liver cancer - $12.55 \pm 0.25\text{‰}$ deaths CI95% 11.98-13.12.

In the multi-year dynamics, the number of deaths due to chronic hepatitis has practically halved, from 31 cases in 2000 (0.87‰) to 14 cases (0.4‰) in 2009, due to liver cirrhosis - from to 3117 deaths (87.42‰) in 2000 to 2370 deaths (66.9‰) in 2020. At the same time liver cancer mortality was increasing from 424 deaths (1.89‰) in 2000 up to 450 deaths (12.7‰) in 2020 (Figure 21).

The analysis of mortality from chronic hepatitis, liver cirrhosis and liver cancer indicates a higher fatality rate in the case of liver cirrhosis – 26.53% on average for the analyzed period. In the multi-year dynamics, the fatality rate due to liver cirrhosis decreased from 31.41% in 2009 to 25.15% in 2020. The fatality rate in chronic hepatitis is very low, constituting an average of 0.46% for the entire analyzed period, and in the multiannual dynamics it has remained relatively stable, with a slight decrease from 0.87% in 2000 to 0.7% in 2020.

The analysis of officially registered statistical data at the country level highlights the fact that in the Republic of Moldova the number of people who died from liver cancer is higher than those who remained alive with this diagnosis. This situation prevails throughout the analyzed period, the fatality rate due to liver cancer being on average 135.7%. Thus, in 2020 there were 390 people on record with liver cancer, and 450 people died from the same pathology. In this context, we can mention deficiencies in the early diagnosis of liver cancer in patients with liver cirrhosis, determined by the insufficient clinical monitoring of this category of patients. At the same time, patients do not know the stage of evolution of the disease, the diagnosis of liver cancer being established after the death of the patients.

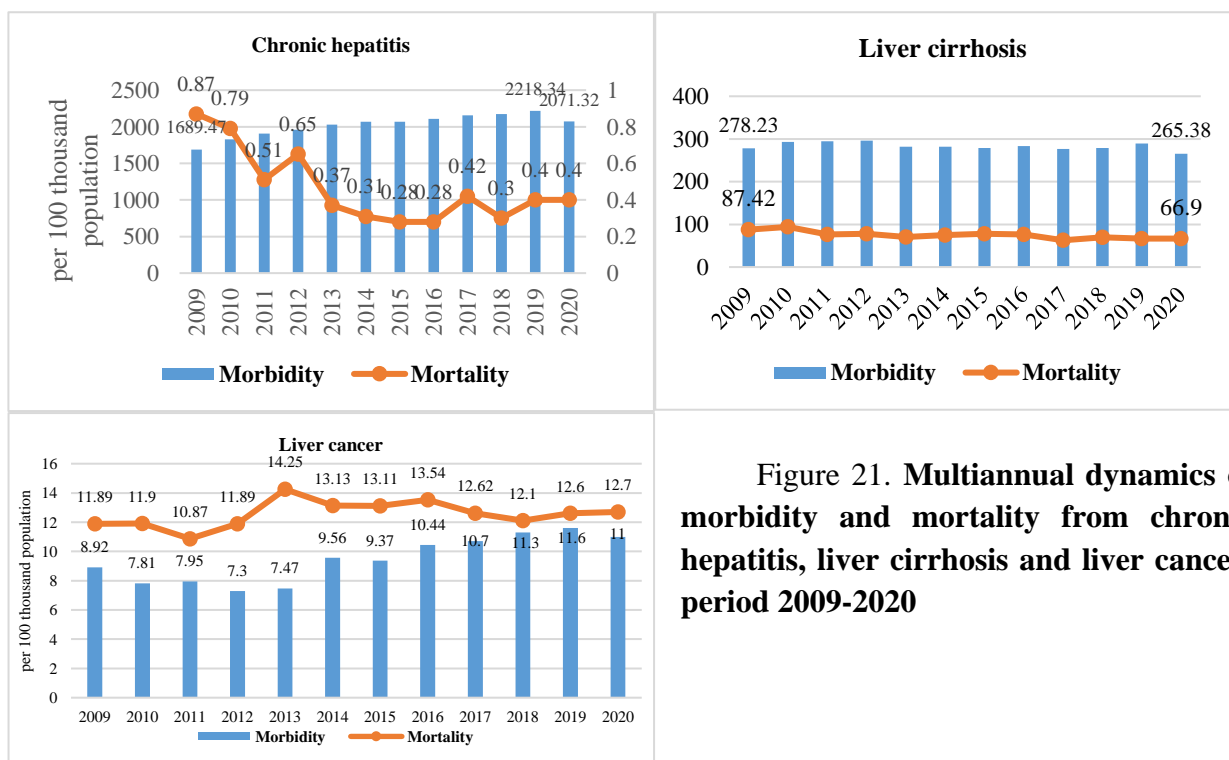


Figure 21. Multiannual dynamics of morbidity and mortality from chronic hepatitis, liver cirrhosis and liver cancer, period 2009-2020

The following results were obtained when evaluating mortality from chronic hepatitis, liver cirrhosis and liver cancer depending on the gender of the patients and their age. During the analyzed period, 37,629 people died of chronic hepatitis, liver cirrhosis and liver cancer, of which 20,144 (53.53%) were men, and 17,485 (46.47%) were women.

Most women died of chronic hepatitis, 107 cases (50.95%) compared to 103 (49.05%) cases among men. The highest share of deaths among men was recorded in the case of liver cirrhosis and liver cancer: 16,597 men died of liver cirrhosis (51.76%), and women – 15,468 (48.24%), of liver cancer 3,444 of men (64.33%), and women – 1,910 (35.67%).

Deaths caused by chronic hepatitis, liver cirrhosis and liver cancer are more common after the age of 60. According to the data presented in Annex 4, the average age at which patients with chronic hepatitis die is 66.06 ± 1.8 years CI 95% 62.35-69.76 years, those with liver cirrhosis – 61.51 ± 0.15 years CI 95% 61.21-61.80, and with liver cancer - 65.33 ± 0.37 years, CI 95% 64.59-66.06 years.

The distribution of the structure of morbidity through the prism of the population pyramid of deaths from chronic hepatitis, liver cirrhosis and liver cancer allowed highlighting the share of deaths caused by these pathologies in relation to the gender and age of the deceased. Thus, in the case of chronic hepatitis, more frequent deaths among women were recorded at the age of 80-89 years, $26.17 \pm 4.24\%$ ($P < 0.001$), and 60-69 years, $22.43 \pm 4.03\%$ ($P < 0.001$), and among men aged 60-69, $23.3 \pm 4.16\%$ ($P < 0.001$). For liver cirrhosis, the most affected age was found to be 50-69 years for both men and women. However, if in women the younger age of 50-59 years prevails, $32.23 \pm 0.63\%$ ($P < 0.001$) of the general morbidity due to liver cirrhosis in women, then in men the age of 60 was more affected -69 years, $30.38 \pm 0.67\%$ ($P < 0.001$) % in the general structure of liver cirrhosis morbidity in men.

In the case of liver cancer, the predominant age was older compared to chronic hepatitis and liver cirrhosis. Thus, in men, the most liver cancer deaths were registered in the age group 70-79 years, constituting $33.40 \pm 1.87\%$ ($P < 0.001$) of the overall mortality from liver cancer among men for the whole the analyzed period, and in women - 60-69 years, constituting $34.04 \pm 1.39\%$ ($P < 0.001$) of the general mortality due to liver cancer in women.

3.6 Challenges identified following the analysis of the epidemiological surveillance system in the Republic of Moldova

Until 2010, chronic parenteral viral hepatitis was not included in the list of communicable diseases, mandatory for records and reporting. Thus, the territorial CSP received urgent information only in case of detection or suspicion of acute viral hepatitis, and the data on cases of chronic hepatitis were presented in aggregate form in the Reporting of chronic hepatitis and liver cirrhosis (Statistical report no. 29-breast) of the Center of Public Health Management at the end of the year. As a result, chronic parenteral viral hepatitis was practically not reported and, respectively, epidemiologically investigated, and the principle of the surveillance system that provides for the collection of data to undertake response actions was not respected. This situation contributed significantly to the increase in the incidence and prevalence of chronic hepatitis in the Republic of Moldova.

The epidemiological surveillance system of acute viral hepatitis B, C and D includes the reporting of cases in accordance with ICD 10 (International Classification of Diseases). Currently, the record-keeping and reporting system includes the declaration of cases of acute and chronic viral hepatitis. According to statistical form no. 2 "Infectious and parasitic diseases", approved in 2011, the viral hepatitis section includes: viral hepatitis A; acute viral hepatitis B (total cases),

including acute viral hepatitis B with Delta antigen and separately acute superinfection with Delta antigen in chronic HBsAg carriers and patients with chronic HBV; acute viral hepatitis C; viral hepatitis E; other acute viral hepatitis; chronic viral hepatitis B with detected primary antigen Delta; chronic viral hepatitis B without detected primary antigen Delta; primary chronic viral hepatitis C detected; other primary detected chronic hepatitis and primary detected chronic carriers of HBsAg .

Another official statistical document, which allows us to analyze the data, is Report no. 29-breast "Regarding patients with chronic hepatitis and liver cirrhosis" which includes the prevalence and incidence of these pathologies according to age, only children and adults (without the disaggregation of age categories), the number of people on record at the end of the year managed with chronic hepatitis and liver cirrhosis, and the fullness of coverage through surveillance of patients with chronic hepatitis.

This reporting form does not allow a more detailed analysis of the epidemiological situation according to the disaggregated age of the affected persons, gender, risk categories, risk factors, etc. It should be noted that the data presented on paper and those in the information system for the surveillance of communicable diseases do not correspond, which determines the need to strengthen the electronic reporting system, with the inclusion of the possibilities of evaluating and monitoring the epidemiological situation, but also with risk estimation and the prognosis for the implementation of countermeasures, depending on the outcome of the assessment. When registering a case of acute and chronic parenteral viral hepatitis, the epidemiological investigation must be carried out by collecting the epidemiological anamnesis at the patient's bedside, in order to establish the source, the mechanism and the factors of transmission of the infection , as well as the investigation of the source of infection with the establishment of contact persons and the undertaking of measures prophylactic and anti- epidemic measures to limit the spread and liquidate the outbreak.

Currently, the epidemiological investigation of the case of acute viral hepatitis B, C and D is carried out by epidemiologists from the territorial CSP with the completion of the " Epidemiological investigation sheet of the case of acute viral hepatitis B, C and D" no. 362-2/ e (approved by Ministry of Health order no. 828 of 31.10.2011 "Regarding the approval of primary record forms") Newly registered chronic cases are not subject to epidemiological research, which leads to a lack of data on the factors and ways of transmission for the respective forms of the disease. All cases of acute and chronic viral hepatitis or carriers of HBsAg are registered in the register of infectious diseases (Form 60), with the assignment of the epidemiological number. The public medical and sanitary institution, the Doctors' Center, is informed about the registered case of Family at the place of residence (record) and territorial CSP (in case it is not in the territory supervised by the CSP that received the information about the case of the disease), which records it in its records and carries out the examination and testing of contacts, medical surveillance of the patient or chronic carrier, with repeated testing every 6 months for the presence of markers of viral hepatitis and biochemical blood analysis.

All declared cases of acute and chronic viral hepatitis B, C and D are notified at the territorial CSP level, then reported in Form 2 "Regarding infectious diseases and parasites" monthly and annually at the national level to ANSP. An important aspect is the reporting both at the national and international level, according to the standard case definition, approved at the international level. The case definitions for viral hepatitis, used in the Republic of Moldova, do not correspond to those recommended by the WHO. Thus, following the analysis of the

epidemiological surveillance system of hepatitis, cirrhosis and liver cancer, the following challenges were established:

1. There is a National Program to combat viral hepatitis B, C, and D, but a plan of measures to combat/eliminate viral hepatitis B, C, and D is not implemented in the Republic of Moldova.
2. There are divergences between the case definitions for viral hepatitis used in the Republic of Moldova and those recommended by the WHO.
3. Viral hepatitis, liver cirrhosis and liver cancer surveillance indices are insufficiently disaggregated for country-level estimation, modeling, monitoring and evaluation.
4. There is no integrated database that would allow the analysis of morbidity data in complexity.
5. The data presented in Statistical Form no. 2 are disaggregated by age (children 0-2 years, 3-6 years and 0-17 years, and adults; urban and rural residence), not by gender.
6. The statistical report no. 29-bread Regarding patients with chronic hepatitis and liver cirrhosis does not include disaggregated data on age categories, gender, profession, risk group, form of liver cirrhosis (compensated or decompensated), degree of fibrosis, virus genotype.
7. There are data discrepancies regarding chronic viral hepatitis in form no. 2 "Infectious and parasitic diseases" and statistical report no. 29-bread Looking at patients with chronic hepatitis and liver cirrhosis, which creates a lack of clarity regarding the actual number of patients with viral hepatitis under medical supervision.
8. It is not determined how to report cases of simultaneous infection with two or three liver viruses. Thus, in some territories they are reported as a single infection, in others as two or three infections in the same person.
9. Epidemiological data on cases of chronic viral hepatitis and chronic carriage of hepatitis B and C viruses are insufficiently collected due to the lack of a standardized form , which does not allow a complex analysis to be carried out, estimating the economic and medical impact.
10. Prophylactic and anti-epidemic measures are insufficiently implemented in chronic viral hepatitis outbreaks (examination for viral hepatitis markers and vaccination against viral hepatitis of people-contacts from the outbreak).
11. Complex, effective, targeted monitoring, oriented towards the assistance of patients with chronic viral hepatitis, the family, the community is not carried out by the family doctor.
12. Screening for hepatocellular carcinoma is not indicated for all patients with HCV/CCV or cirrhosis.
13. Informing the general population and groups at increased risk of infection about the epidemiological situation through viral hepatitis and the serious consequences of these infections, about preventive measures is insufficient and is not focused on different population groups with increased risk of infection (medical workers, people who come into contact with patients with viral hepatitis, key populations, people with diabetes, STIs, etc.).
14. There is no coordination unit of the National Program to combat viral hepatitis B, C and D.

4. EPIDEMIOLOGICAL FEATURES AND RISK FACTORS IN CHRONIC HEPATITIS, CIRRHOSIS AND PRIMARY HEPATIC CANCER BASED ON THE ANALYZED QUESTIONNAIRES

4.1 Sociodemographic characteristics of patients with chronic hepatitis, liver cirrhosis and primary liver cancer

The evolution of chronic hepatitis into liver cirrhosis and primary liver cancer is conditioned by a series of epidemiological peculiarities and risk factors associated with the basic diagnosis. In this context, the observation sheets were analyzed and 3666 patients were questioned, of which with chronic hepatitis - 1528 patients (41.68±1.26%), liver cirrhosis 1891 patients (51.58±1.14%) and cancer hepatic – 247 patients (6.74±1.59%), to establish the risk factors that contribute to the evolution of chronic hepatitis into liver cirrhosis and primary liver cancer (Table 5).

Table 5. General characteristics of the researched lots

TOTAL (n=3666)	Witness lot (n=153)	Chronic hepatitis Batch I (n=1528)	Liver cirrhosis Lot II (n=1891)	Liver cancer Lot III (n=247)	P-value	
	1	2	3	4		
%		41.68±1.26 [95%,CI:41.71-46.36]	51.58±1.14 [95%,CI:49.96-53.20]	6.74±1.59 [95%,CI:5.97-7.60]	P _{2,3} <0.001 P _{2,4} <0.001 P _{3,4} <0.001	
AGE						
Average age, years	55.5±10.18	54.74±11.22	56.21±10.17	59.05±10.94	P _{2,3} <0.0001 P _{2,4} <0.001 P _{3,4} <0.001	
age, min (years)	20	17	2, 3	18		
age, max (years)	79	87	87	84		
Gender						
Female	abs	114	873	923	91	P _{1,2} <0.001 P _{2,3} <0.001 P _{2,4} <0.001 P _{3,4} <0.01
	%	74.51 [95%, CI: 66.84-81.20]	57.13±1.67 [95%,CI:54.64-59.59]	48.81±1.64 [95%,CI:46.56-51.06]	36.84±5.05 [95%,CI:30.81-43.19]	
Male	abs	39	655	968	156	
	%	25.49 [95%, CI:18.80-33.16]	42.87±1.93 [95%,CI:40.41-45.36]	51.19±1.60 [95%,CI:48.94-53.44]	63.16±3.86 [95%,CI:56.81-69.19]	

More often, chronic hepatitises have been recorded in women, but their evolution into liver cirrhosis and liver cancer is more common among men. Thus, chronic hepatitis in women was recorded in 873 cases or 57.13±1.67% [95%, CI:54.64-59.59], compared to men – 655 cases or 42.87±1.93% [95%, CI:40.41-45.36] (P<0.001). The ratio between men and women was 1.33 (873:655), representing 968 cases or 51.19±1.60% [95%, CI:48.94-53.44] and respectively 923 cases or 48.81±1.64% [95%, CI:46.56-51.06]. A higher proportion of affected men was found to be among patients with primary liver cancer. Men, with primary liver cancer, constituted 156 cases or 63.16±3.86% [95%, CI:56.81-69.19], compared to women – 91 cases or 36.84±5.05% [95%, CI: 30.81-43.19]. The average age at diagnosis of patients with chronic hepatitis was 54.74 years.

Liver pathologies have been recorded in patients aged between 10 and 90 years, with the frequency increasing with age. More frequently, chronic hepatitis and liver cirrhosis are recorded in patients with an average age of 50-59 years (37.50% and 39.56%), who develop primary liver

cancer after an average age of 60 years (49.80%). At the same time, it should be mentioned that chronic hepatitis, liver cirrhosis and liver cancer were also recorded in children aged 10 years.

analysis of chronic liver pathologies showed that although chronic hepatitis occurs more frequently in women, their evolution to liver cirrhosis and liver cancer occurs more frequently among men. Thus, 873 women or $57.13 \pm 1.67\%$ [95%, CL:54.64-59.59] and 655 men or $42.87 \pm 1.93\%$ [95%, CL:54.64-59.59] were diagnosed with chronic hepatitis, CI;40.41-45.36] ($P < 0.001$), male:female ratio being 1.33 (873:655); with liver cirrhosis 968 men or $51.19 \pm 1.60\%$ [95%, CI;48.94-53.44] and 923 women or $48.81 \pm 1.64\%$ [95%, CI;46, 56-51.06], and with liver cancer 156 men or $63.16 \pm 3.86\%$ [95%, CI;56.81-69.19] and 91 women or $36.84 \pm 5.05\%$ [95%, CI; 30.81-43.19].

It should be noted that the share of patients with liver pathologies increases with age, reaching maximum values at the age of 60. At an older age, there is a decrease in the number of patients with liver pathologies as a result of the evolution of chronic hepatitis to liver cirrhosis and liver cancer, which causes approximately 2700 deaths annually.

The most affected age was found to be 50-59 years with a higher share in men compared to women, this being 38.67% versus 37.31% respectively **Eroare! Fără sursă de referință.**

The analysis of chronic hepatitis morbidity according to the gender and age of the patients shows that among women, the most affected age was 50-59 years, making up a share of 37.11% of the total number of women with chronic hepatitis. Analysis of the same indicator among men determined a higher share of cases in the same age group, making up 38.02% of all men with chronic hepatitis.

The same epidemiological situation is recorded in patients with liver cirrhosis. In most cases, patients with liver cirrhosis, both in women and in men, were in the 50-59 age group, the share being 38.79% and 40.29%, respectively. A slightly higher share is evident among men compared to women.

It is worth noting that the complications caused by chronic hepatitis and liver cirrhosis, respectively, are evident at an older age. Thus, if chronic hepatitis and liver cirrhosis are registered more frequently at the age of 50-59 years, then primary liver cancer determined by these pathologies is registered more frequently at the age group of 60-69 years in both women and men, the share being of 47.25% and 51.28% respectively.

Most of the patients undergoing inpatient treatment were from the rural regions of the republic. The comparative analysis of the data on chronic liver pathologies allowed us to find that the patients with chronic hepatitis from the rural region constituted $65.71 \pm 1.49\%$ compared to those from the urban region who constituted $34.29 \pm 2.07\%$ ($P < 0.001$). We found the same peculiarity in the case of patients with liver cirrhosis, who were found in the vast majority from the rural region - $66.90 \pm 1.32\%$ compared to those from the urban region - $33.10 \pm 1.88\%$ ($P < 0.001$). Patients with primary liver cancer from rural areas constituted $63.56 \pm 3.84\%$ compared to those from the urban region - $36.44 \pm 5.07\%$ ($P < 0.001$). These particularities denote the fact that people from rural regions get sick more frequently from chronic hepatitis, a fact determined by low access to medical assistance, and as a result they develop liver cirrhosis and primary liver cancer.

4.2 The etiological and clinical particularities of chronic hepatitis, liver cirrhosis and liver cancer

Of the total cases of chronic liver disease analyzed, 80% were of viral etiology, 1352 cases or $88.48 \pm 0.86\%$ against 176 cases or $11.51 \pm 2.40\%$ ($P < 0.001$) of non-viral etiology. In the case of liver cirrhosis, the legitimacy was the same: 1501 cases or $79.38 \pm 1.04\%$ of viral etiology versus

359 cases or 20.62±2.04% (P<0.001) of non-viral etiology. Liver cancer of viral etiology was diagnosed in 192 cases or 77.73±3.0%, and non-viral in 55 cases or 22.44±22.44% (P<0.001) (Figure 22).

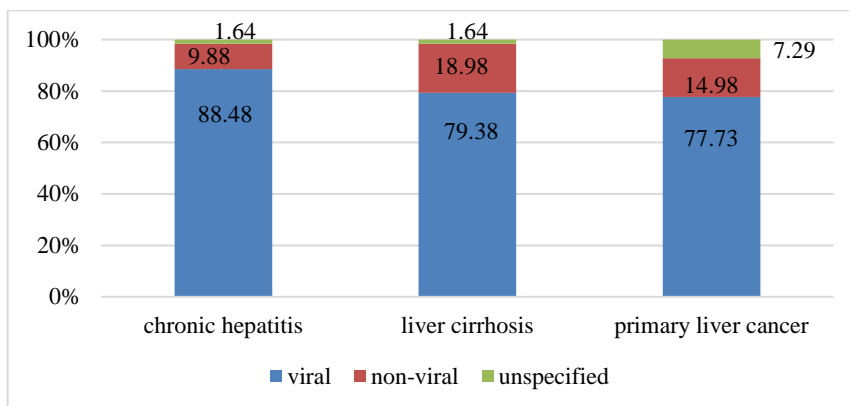


Figure 22. Structure of liver pathologies according to viral/nonviral etiology

When analyzing the etiological structure of liver pathologies with viral etiology, the predominance of HBV was found, identified in 679 cases or 50.22±1.91%, 95% CI 47.56-52.88%, compared to 423 cases or 31.29±2.25, 95% CI 28.87-33.81% of which HCV was found to be responsible; 249 cases or 18% were determined by mixed infection: HBV+VHD – 139 cases or 10.28±2.57%, 95%CI 8.77-12.01%, HBV+HCV – 105 cases or 7.77±2.61%, 95% CI 6.46-9.32%, HBV+BVC+VHD – 4 cases or 0.30%, 95% CI 0.16-0.86% (Figure 23).

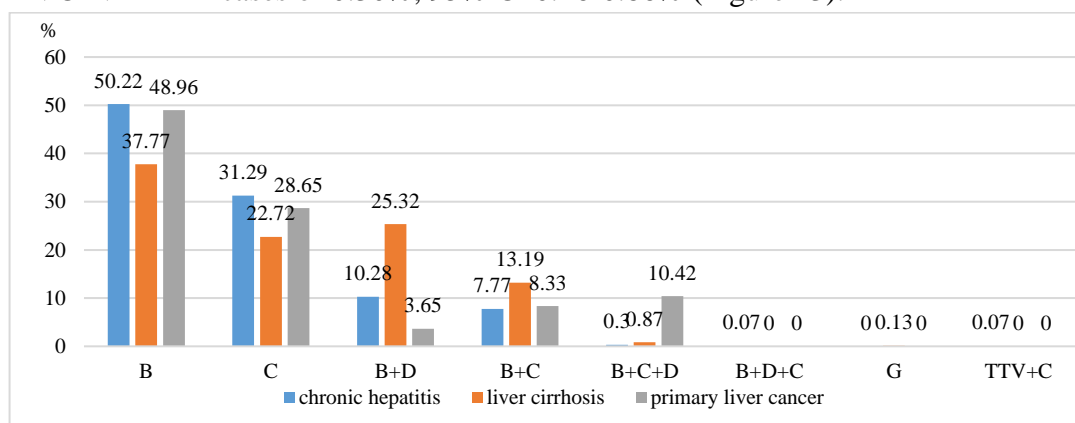


Figure 23. The structure of liver pathologies of viral etiology in the research groups

4.3 Analysis of risk factors in chronic hepatitis, liver cirrhosis and primary liver cancer

The unfavorable evolution of chronic hepatitis and the development of liver cirrhosis and primary liver cancer is determined by a number of risk factors. One of these factors is concomitant pathologies that worsen the patient's health. 61 Clinical diagnoses secondary to the basic diagnosis were established. As a result of the analysis of the data from the collected questionnaires, the most important pathologies were identified, which prevailed in more than 40% of the patients. It should be noted that in most cases the patients had 5 or more pathologies simultaneously. Thus, both in the case of patients with chronic hepatitis and in the case of those with liver cirrhosis and primary liver cancer, they simultaneously had 5-9 secondary diagnoses, making up 65.14%, 71.92% and 79.35% respectively, compared to the control group that showed up to 4 concurrent pathologies in about 99%.

Among patients with chronic hepatitis, 966 or 65.14±1.53%, 95% CI 62.72-67.49% (P<0.001), had from 5 to 9 secondary diagnoses. Up to 4 concomitant pathologies were determined in 277 patients or 18.18±2.31%, 95%CI 16.33-20.19% (P<0.001); 255 patients were diagnosed

with 10 to 24 pathologies secondary to the basic diagnosis, including 10-14 secondary diagnoses – 229 cases or 14.98±2.35%, 95% CI 13.28-16.85% (P<0.001), 15-19 secondary diagnoses – 24 patients or 1.57±2.59, 95% CI 1.06-2.33% (P>0.05), and 20-24 secondary diagnoses – 2 cases or 0.13±3.6%, 95% CI 0.04-0.48%.

The vast majority of patients with liver cirrhosis, 1360 patients or 71.92±1.21%, 95% CI 69.85-73.90% (P<0.001), were also diagnosed with 5 to 9 secondary diagnoses. Up to 4 secondary pathologies were determined in 22 patients with liver cirrhosis, which represents 1.16±2.33%, 95%CI 0.77-1.76% (P>0.05). With 10-14 pathologies secondary to the basic diagnosis, 506 patients or 26.76±1.96%, 95% CI 24.81-28.80% (P<0.001), with 15-19 secondary diagnoses were identified – 3 patients or 0.16±2.82, 95% CI 0.005-0.47% (P>0.05).

The majority of patients with liver cancer, 196 patients or 79.35±2.89%, 95% CI 73.76-84.22% (P<0.001), had 5 to 9 diagnoses secondary to the basic one; 41 patients or 16.60±5.81%, 95% CI 12.18-21.84% (P<0.01) – from 10 to 14 secondary diagnoses; 8 patients or 3.24±6.69%, 95%CI 1.41-6.28% (P<0.005) – up to 4 secondary diagnoses, and two patients or 0.81%, 95% CI 0.10 -2.89% – 15-19 secondary diagnoses.

Next, the selected pathologies were analyzed by means of logistic regression and the 2x2 table, which allowed the determination of the Odds index Ratio and confidence interval. Based on this analysis, the pathologies with the highest risk influencing the evolution of patients in liver cirrhosis and liver cancer were highlighted . Thus, for patients with chronic hepatitis, these constituted pancreatitis, gastritis, portal hypertension , gastroduodenitis and cholecystitis. In the case of patients with liver cirrhosis, these were chronic liver failure, liver fibrosis, toxic-dysmetabolic encephalitis , esophageal varices, obesity, cholecystitis and gastroduodenitis . For patients with liver cancer, these have proven to be: esophageal varices, ascites, anemia, toxic-dysmetabolic encephalitis , pancreatitis, obesity and liver failure.

The study of risk factors in chronic hepatitis, liver cirrhosis and primary liver cancer allowed the identification of parenteral medical procedures performed by patients during their lifetime. Thus, in the case of patients with chronic hepatitis, 1080 patients or 70.68% underwent surgical interventions, 95 CI 68.35-72.91%, OR constituted 1.89 (95% CI 1.28-2, 77), and gynecological interventions – 839 patients or 54.91%, 95% CI 52.49-57.39%, OR – 1.55 (95% CI 1.06-2.27). Although blood transfusions mentioned a smaller number of patients with chronic hepatitis - 285 which constitutes only 18.65% of the total patients with chronic hepatitis, the risk factor analysis by the 2X2 contingency table demonstrated that the OR is the highest namely in this type of parenteral operation, OR=2.72, 95% CI 1.36-5.44.

Patients with chronic hepatitis were diagnosed on average 8.81±6.24 years ago, with a minimum duration of 2 years and a maximum of 50 years. The average period from the diagnosis of chronic hepatitis until the diagnosis of liver cirrhosis was 11.29±4.49 years, the minimum duration was 2 years and the maximum was 24 years, and the duration of the disease in patients with liver cancer was mean 3.66±1.15 years, minimum 1 year and maximum 7 years (Table 6).

Table 6. Average duration of disease in patients with chronic hepatitis, liver cirrhosis and primary liver cancer (years)

Pathology	Total	Average duration of illness	Std dev	Min	MAX
Chronic hepatitis	1455	8.81	6.24	2	50
Liver cirrhosis	1891	11.29	4.49	2	24
Primary liver cancer	247	3.66	1.15	1	7

In 1095 of the patients with chronic hepatitis or 75.26%, 95% CI 72.98-77.41%, the duration of the disease was at most 10 years, and in 25% more than 10 years. In 973 (51.45%) of the patients with liver cirrhosis, more than 10 years passed from the diagnosis of chronic hepatitis to the development of liver cirrhosis. In 918 or 48.55%, 95% CI 46.30-50.80% of patients with liver cirrhosis the duration of the disease was up to 10 years, in 938 or 49.60%, 95% CI 47.35-51, 86% – 11-20 years, and at 35 or 1.85%, 95% CI 1.33-2.56% – 21-30 years.

Table 7. Duration of disease in patients with chronic hepatitis, liver cirrhosis and primary liver cancer

Duration of illness	abs	%	How. Percent	Wilson 95% LCL	Wilson 95% UCL
Chronic hepatitis					
1 - 10 years	1095	75.26	75.26	72.98	77.41
11 - 20 years	280	19.24	94.50	17.30	21.35
21 - 30 years	60	4.12	98.63	3.22	5.27
30 and more	20	1.37	100	0.89	2.11
TOTAL	1455	100	100		
Liver cirrhosis					
1 - 10 years	918	48.55	48.55	46.30	50.80
11 - 20 years	938	49.60	98.15	47.35	51.86
21 - 30 years	35	1.85	100.00	1.33	2.56
TOTAL	1891	100	100		
Liver cancer					
15 years	234	94.74	94.74	91.17	97.17
6 - 10 years	13	5.26	100.00	2.83	8.83
TOTAL	247	100	100		

The duration of the disease in patients with liver cancer was found to be the shortest, they died within the first ten years of the disease. Thus, in 234 of the patients with liver cirrhosis or 94.74%, 95% CI 91.17-97.17% the duration of the disease was up to 5 years. The short duration of the disease in patients with liver cancer is determined by the fact that most are not diagnosed and die in the stage of liver cirrhosis or are diagnosed late.

In order to determine the behavior of patients in the family after confirming the diagnosis of liver pathology, vis -a-vis the probability of infection of its members, the attitudes and practices used in the family were introduced in the questionnaire . According to the data obtained, patients with chronic hepatitis, liver cirrhosis and liver cancer do not comply with measures to prevent infection of family members.

Thus, when analyzing the questionnaires of patients with chronic hepatitis, it was found that 90.18% practiced unprotected sex, 60.54% shared sharp objects, of which 55.3% – scissors, and 49.54% – needles. Cases of shared use with family members of razor blades (2.81%), toothbrushes (0.50%), and syringes (2.42%) were also determined.

The same situation was found in patients with liver cirrhosis. Unprotected sexual intercourse was mentioned by 96.83% of patients with liver cirrhosis, the use of shared sharp objects – 71.81%, including scissors – 41.46%, needles – 52.67, razor blades – 5 .29%, toothbrush – 0.79%, syringes – 0.69% (Figure 24).

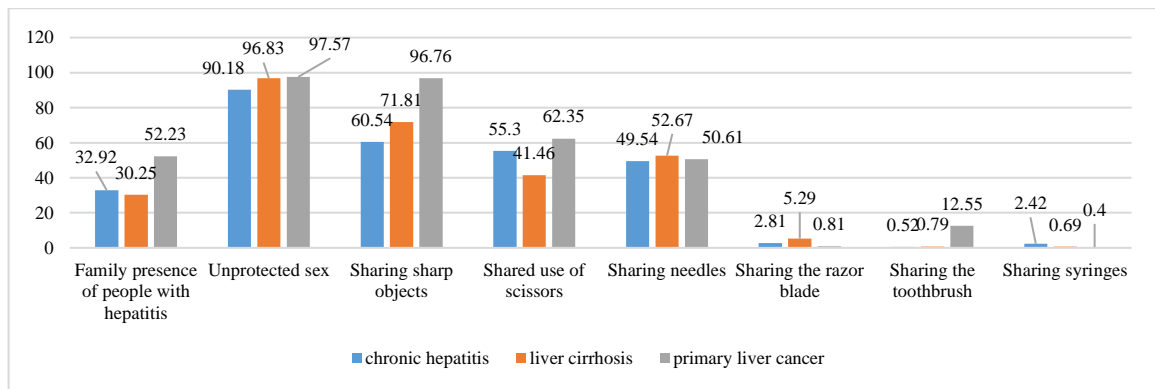


Figure 24. **The share of patients with chronic liver pathologies according to behavioral risk factors in the family**

When analyzing the probability of the risk of infection among family members, it was found that in all analyzed pathologies, the OR is higher when practicing unprotected sexual relations. Depending on the nosology, the risk of infection is higher in patients with liver cancer, OR=25.91 (95% CI 10.82%-62.01%), followed by patients with liver cirrhosis OR=19.68 (95% CI 13.01%-29.78%) and those with chronic hepatitis – OR= 5.92 (95% CI 4.11%-8.54%).

At the same time, based on the determination of the OR risk probability, the main risk factors were highlighted. Thus, for chronic hepatitis, the behavioral risk factors in the family proved to be unprotected sexual relations - OR=5.92 (95%CI 4.11%-8.54%), the use of shared sharp objects OR=1.91 (95% CI 1.3%-2.68%), sharing syringes OR=1.24 (95% CI 0.37%-4.07%) and sharing scissors OR= 1.15 (95% CI 0.83%-1.61%).

The analysis of behavioral risk factors in the family in patients with liver cirrhosis revealed the same legitimacy as in the case of those with chronic hepatitis. Behavioral risk factors in the family of patients with liver cirrhosis were proven to be unprotected sexual relations - OR=19.68 (95%CI 13.01%-29.78%), shared use of sharp objects - OR=3.15 (95% CI 2.25%-4.4%), including the razor – OR=1.36.

In the case of patients with liver cancer, behavioral risk factors in the family were unprotected sexual relations - OR=25.91 (95%CI 10.82%-62.01%), shared use of sharp objects - OR=37.34 (95% CI 17.23%-80.91%) and of the toothbrush – OR=5.34 (95% CI 1.84%-15.46%).

The prognosis of the evolution of liver pathology is also determined by the patients' compliance with the diet, alcohol and tobacco consumption.

According to the data from the specialized literature, reflected in the bibliographic data analysis chapter, several authors mention that some behaviors of patients with chronic hepatitis such as non-compliance with the diet, alcohol and tobacco consumption favor its degeneration into liver cirrhosis and primary liver cancer. In this context, we aimed to analyze the compliance with the diet by patients with chronic liver pathologies, the consumption of alcohol and tobacco by them.

Irregular and unbalanced diet is part of the risk factors that aggravate some forms of liver pathology. Non-compliance with the diet was highlighted in all research groups, with a considerable share in patients with liver cirrhosis - 89.05% (95% CI 87.57-90.38%), less in patients with liver cancer - 86.23% (95% CI 81.30%-90.28%) and in those with chronic hepatitis – 54.65% (95% CI 52.14%-57.13%).

Alcohol abuse is a major risk factor in the development of liver and extrahepatic diseases. Among the patients with liver pathology, 605 patients with chronic hepatitis or 39.59% (95% CI

37.17%-42.07%), 723 or 38.23% (95% CI 36) admitted the consumption and /or abuse of alcohol .07%-40.45%) with liver cirrhosis and 164 or 66.40% (95% CI 60.13%-72.26%) with liver cancer.

Smoking, another risk factor in the evolution of liver pathologies , was recognized by 210 patients with chronic hepatitis or 13.74% (95% CI 12.11%-15.56%), of 620 or 32.79% (95 % CI 30.71%-34.94%) with liver cirrhosis and 77 or 31.17% (95% CI 27.74%-39.87%) with liver cancer.

Non-compliance with the diet is the risk factor with the highest OR in patients with chronic hepatitis - OR=1.43 (95% CI 1.01%-2.02%), and alcohol consumption in patients with liver cirrhosis - OR= 3 .06 (95% CI 2.57%-3.64%) and in those with liver cancer – OR=3.19 (95%CI 2.41%-4.22%). In addition to alcohol consumption, in patients with liver cancer, non-compliance with the diet is also a risk factor - OR= 1.29 (95% CI 0.87%-1.91%).

In the same vein, the rate of risk factors was analyzed in relation to the gender of the patients. Thus, it should be noted that these risk factors were recorded more frequently among women than among men.

Patients with chronic hepatitis mentioned in a uniform proportion the observance of the diet, highlighting a rate of 46.39% (95% CI 43.11%-49.71%), and among men 43.97% (95% CI 40 .21%-47.79%). However, more than half of patients with chronic hepatitis, both among men and among women, do not follow the diet. Alcohol consumption was more frequent among men with a rate of 49.01% (95% CI 45.20%-52.83%). However, the rate of alcohol consumption proved to be quite high also among women, constituting 32.53% (95% CI 29.51%-35.71%). Tobacco use among men constituted 24.43% (95% CI 21.29%-27.86%), and among women 5.73% (95% CI 4.37%-7.47%) (Figure 25).

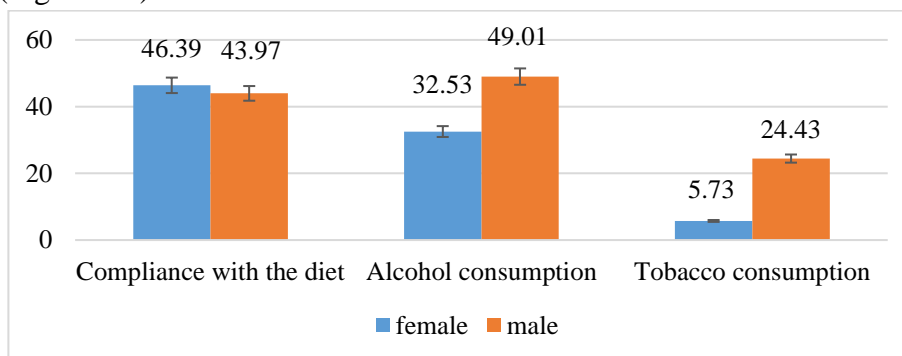


Figure 25. **The share of risk factors in the evolution of chronic hepatitis according to the gender of the patients**

Among the patients with liver cirrhosis, the diet was observed only by 14.73% (95% CI 12.59%-17.17%) of women and 7.33% (95% CI 5.86%-9.15 %) among men. Alcohol consumption was recorded in 27.41% (95% CI 24.63%-30.38%) of women and at a higher rate in men - 48.55% (95% CI 45.42%-51 .70%). Tobacco use among women was quite low – 6.93% (95% CI 5.47%-8.76%), compared to men where the rate of tobacco use was quite high – 57.44% (95% CI 54.30%-60.52%) (Figure 26).

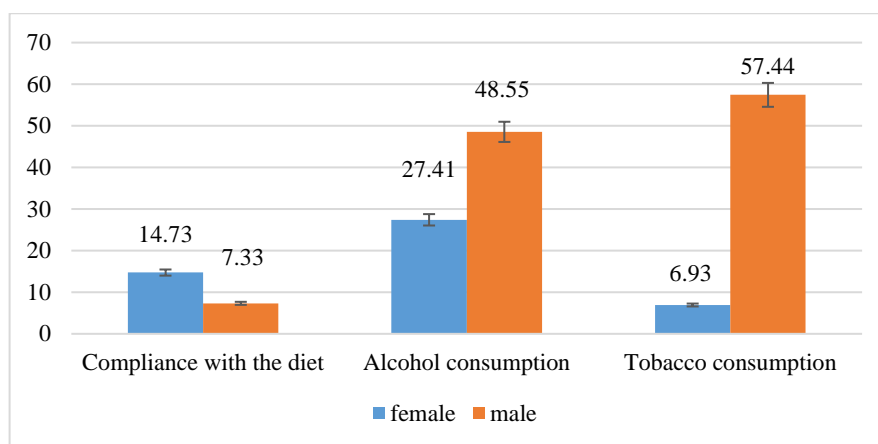


Figure 26. The share of risk factors in the evolution of liver cirrhosis according to the gender of the patients

Regarding patients with liver cancer, the dietary regime was observed by 15.38% (95% CI 8.67%-24.46%) of women and 12.82% (95% CI 8.01%-19.10 %) among men. Alcohol consumption was confirmed by 29.67% (95% CI 20.55%-40.16%) of women with liver cancer and by 87.82% (95% CI 81.64%-92.51%) among men with this pathology. Tobacco consumption was recorded at a higher rate in patients with liver cancer than in those with chronic hepatitis and liver cirrhosis - 34.07% (95% CI 24.45%-44.75%). In men with liver cancer, the rate of tobacco consumption was lower than in women with the same pathology – 29.49% (95% CI 22.47%-37.31%). The data obtained when examining the risk factors in the evolution of liver pathologies (compliance with the diet, alcohol and tobacco consumption) were analyzed in terms of the probability of the risk of developing liver cirrhosis and liver cancer in relation to these factors and the gender of the patients. The probability of OR risk and the ratio of risk factors and patient gender are shown in Table 4.16. According to the data in this table, both in chronic hepatitis and liver cirrhosis and in primary liver cancer, the analyzed factors demonstrated a higher OR risk in men than in women. Both men and women who do not follow the diet are exposed to a higher risk of chronic hepatitis. The risk of developing liver cirrhosis is much higher in men – OR=9.91 (95% CI 7.44-13.21%) than in women – OR = 5.01 (95% CI 3.99%-6.27%). In the case of patients with liver cancer, the risk was higher in men who consume alcohol - OR= 7.64% (95% CI 4.65%-12.54%). Among women with liver cancer, 6.93% (95% CI 4.19%-11.46%) were alcohol consumers.

The administration of long-term antiviral treatment can prevent the progression of HVBC and HVDC to liver cirrhosis and hepatocellular carcinoma , thus improving the quality of life of patients with chronic viral hepatitis.

In the Republic of Moldova, for the treatment of patients with HCV and HVDC, in 2019 the national clinical protocol "Chronic hepatitis with hepatitis B virus with or without delta antigen in adults" was approved. This protocol was developed in accordance with the current international guidelines regarding chronic viral hepatitis B and Delta in adults and serves as a basis for the development of institutional protocols . According to the Protocol, antiviral treatment for HBV lasts 48 weeks (more than 48 weeks for HVD). For the treatment of patients with HCV, in 2019 the national clinical protocol "Chronic hepatitis with the hepatitis C virus in adults" was approved , developed in accordance with current international guidelines : European Association for the Study of the Liver (EASL) - 2018, American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) - 2018 and the World Health

Organization (WHO) - 2017 on chronic viral hepatitis C in adults and which serves as a basis for the development of institutional protocols . The goal of treatment for HCV infection is to cure HCV infection - achieving sustained viral response (SVR), assessed more than 12 weeks after completion of antiviral therapy = SVR12 and more than 24 weeks after completion of antiviral therapy = SVR24, which corresponds to definitive cure of HCV infection HCV in over 95% of cases.

The analysis of the data collected by means of the questionnaire from 1528 patients with chronic hepatitis, 1891 patients with liver cirrhosis and 247 patients with liver cancer allowed the determination of the number of days/bed in hospital for treatment. On average, patients with chronic hepatitis were treated in the hospital for 8.73 ± 2.80 days/bed, minimum 1 day and maximum 51 days, with liver cirrhosis – 9.43 ± 2.55 days/bed, minimum 3 days and maximum 35 days, and those with primary liver cancer – 10.51 ± 4.94 days/bed, minimum 3 days and maximum 48 days. Thus, the length of stay of patients in the hospital increases when chronic hepatitis progresses to cirrhosis and primary liver cancer, but, at the same time, it does not correspond to the recommendations specified in the national clinical protocols. This fact proves that the treatment of these patients is insufficient for healing, being applied only to remove the clinical signs that appeared at the time. The majority of patients with chronic hepatitis – 1289 or $84.36 \pm 1.01\%$, 95% CI 82.45-86.09% ($P < 0.001$) – were treated in the hospital for 1-10 days. 239 patients with chronic hepatitis were treated for more than 10 days, of which 231 or $15.12 \pm 2.35\%$, 95% CI 13.41-17.0% were hospitalized for 11-20 days, 4 or $0.26 \pm 2.9\%$, 95% CI 0.10-0.67% ($P > 0.05$) – 21-30 days, 3 or $0.20 \pm 3.15\%$, 95 % CI 0.07-0.58% ($P > 0.05$) – 31-40 days. One patient, or 0.07%, was hospitalized for more than 50 days.

A similar situation was also evident in the case of patients with liver cirrhosis. 1437 or $75.99 \pm 1.12\%$, 95% CI 74.01-77.86% ($P < 0.001$) of patients with liver cirrhosis were inpatient for up to 10 days. The number of patients with liver cirrhosis treated in the hospital for 11-20 days was higher than those with chronic hepatitis - 442 patients, which is $23.37 \pm 2.01\%$, 95% CI 21.53-25.33% . For 21-30 days, 11 patients with liver cirrhosis were treated or $0.58 \pm 2.40\%$, 95% CI 0.33-1.04% ($P > 0.05$), and 31-40 days a patient, 0.05%, 95% CI 0.01-0.30%.

The majority of patients with primary liver cancer were under inpatient treatment for up to 10 days – 153 patients or $61.94 \pm 3.92\%$, 95% CI 55.57-68.02% ($P < 0.001$). A duration of 11-20 days was determined in 82 cases or $33.20 \pm 5.20\%$, 95% CI 27.36-39.45% ($P < 0.001$), 21-30 days – 9 cases or $3.64 \pm 6.62\%$, 95% CI 1.68-6.80% ($P > 0.05$), 31-40 days – 2 cases or 0.80%, 95% CI 0.10-2.23 % , and more than 50 days – 1 case or 0.40%, 95% CI 0.01-2.23%.

4.4 Anti-epidemic measures undertaken within family members

The system of anti-epidemic measures includes measures aimed at all 3 links of the epidemic process. These include: measures aimed at neutralizing the source of infection, the mechanism of transmission and the receptivity of the population. In this context, we proposed the evaluation of the measures taken by the family doctor during the primary detection of the patient with chronic hepatitis, liver cirrhosis or primary liver cancer. The anti-epidemic measures carried out in the outbreak were analyzed in relation to liver pathology. Thus, in outbreaks with chronic hepatitis, anti-epidemic measures were implemented only in 15.03% cases, liver cirrhosis – 17.59% cases, and in liver cancer outbreaks – only 10.18% cases.

According to the collected data, 98.52% of HVBC patients were not previously vaccinated against HBV, the share of those vaccinated being only 1.48%. The majority (96.34%) of HVBC patients followed home treatment, but were not monitored by their family doctor. 95.75% of

patients with chronic hepatitis did not receive relevant information about the consequences of the disease if they do not treat it in time. 67.28% of HVBC patients did not go to the family doctor when the first clinical signs appeared, being diagnosed in advanced stages of the disease.

When evaluating the interventions applied to family members who had direct contact with the HBV patient, it was found that only 6.36% were vaccinated against HBV, and 25.79% were investigated for the presence of liver markers .

Compared to the outbreaks of chronic hepatitis, in the outbreaks with liver cirrhosis, anti-epidemic measures were carried out in a proportion of about 17.59%. In 99.04% of patients with HBV cirrhosis, they were not previously vaccinated against B virus, and only 0.96% of respondents mentioned that they had been vaccinated against HBV in the past. In most cases (94.98%) the patients underwent treatment at home, but were not monitored by the family doctor. It is worth noting that more than half of patients with liver cirrhosis (58.75% of cases) received relevant information about the consequences of the disease if they do not treat it in time. At the same time, patients do not go to the family doctor at the appearance of the first clinical signs, which constitute a proportion of 69.06 % of cases, thus being detected in advanced stages of the disease. In the same context, we analyzed the interventions applied to family members who have direct contact with the patient. Thus, the patients diagnosed with liver cirrhosis with HBV mentioned that family members were not vaccinated against HBV, investigations for the presence of liver markers were carried out only in 22.53%, and the other 77.47% of cases were not investigated for the presence liver markers.

On average, anti-epidemic measures were carried out in a proportion of about 10.18%. It should be noted that no patient with liver cancer caused by HBV was previously vaccinated against HBV. In 98.38% of cases, the patients underwent treatment at home, but were not monitored by the family doctor. It is worth noting that, in 94.33% of patients with liver cancer, they did not receive relevant information about the consequences of the disease if they do not treat it in time. At the same time, patients do not go to the family doctor at the appearance of the first clinical signs, which constitute a proportion of 95.95 % of cases, thus being detected in late stages, and some die without knowing the status of liver cancer. Thus, according to official statistics , more cases of death are recorded than cases of illness detected in the first instance. The family members who have direct contact with the patient with liver cancer caused by HBV were not vaccinated against HBV, and investigations for the presence of liver markers were carried out only in 18.62%, and the other 81.38% of cases were not investigated for the presence of liver markers.

5. ESTIMATION OF REAL MORBIDITY DUE TO CHRONIC VIRAL HEPATITIS IN POPULATION AT HIGH RISK OF INFECTION AND THE GENERAL POPULATION.

The prevalence of acute viral hepatitis B and C, HCV and HCV was estimated by collecting data from the national statistical forms of the ANSP, the Republican Blood Transfusion Center, statistical yearbooks of the National Bureau of Statistics of the Republic of Moldova, seroprevalence studies carried out by the ANSP and Integrated study of biological and behavioral surveillance among sex workers, injecting drug users and men who have sex with men in the Republic of Moldova.

To estimate the prevalence of viral hepatitis in different population groups, they were divided into:

MSM – *men who have sex with men.*

SW – *sex workers.*

IDU - *injecting drug users*

HBV "+" blood donors – *the number of blood donors who were diagnosed with chronic HBV infection*

HCV "+" blood donors - *the number of blood donors in whom chronic HCV infection was detected*

The general population with a low risk of infection - *the population with an increased risk of infection was excluded from the adult population over 15 years of age with usual residence according to the Statistical Yearbook for a.2020, the National Bureau of Statistics of the Republic of Moldova.*

In 2020, a total of 29,069 cases of chronic HBV infection were registered, which constitutes 1.03% of the total population with regular residence in 2020 on the right bank of the country (2640.4 thousand people). These cases were identified, mainly, at the appearance of clinical signs, specific to viral hepatitis, especially pain in the right rib cage.

Therefore, the official statistics do not reflect the real situation of viral hepatitis morbidity in the country. A large number of people, who do not show clinical signs of the disease, remain undiagnosed, as they are not tested for the presence of antibodies against viral hepatitis. Worldwide, WHO has estimated the prevalence of HBV infection to be 3.7%. Based on this finding, we could estimate that in the Republic of Moldova the real number of BV cases would be 97,694, compared to 29,069 officially registered. Therefore, 70% of cases remain undiagnosed. In the same period, 14,928 cases of chronic HCV infection were registered, which constitutes 0.56% of the total population of the country .

In order to determine the estimated number of people infected with HCV and HCV in the territories on the right bank of the Republic of Moldova, it was proposed to carry out an estimation exercise in the population at increased risk of infection and in the general population to determine the real situation of viral hepatitis morbidity B and C, necessary for the planning, monitoring and evaluation of activities and interventions for screening, treatment, management of infected persons.

Such an exercise to estimate the real number of HCV and HCV cases in the Republic of Moldova has not been carried out before. In order to estimate the seroprevalence of HCV and HCV in the territories on the right bank of the Republic of Moldova, the data of the seroprevalence studies carried out within the ANSP were collected, data presented by public and private laboratories that carry out tests for the purpose of establishing the diagnosis of HCV and HCV, and the data presented by public medical and sanitary institutions, including the Republican Blood Transfusion Center. Based on data on viral hepatitis B and C testing carried out in public and private laboratories for a.2020, together with data on the seroprevalence of HVB and HVC in populations at increased risk of infection (SW, MSM, IDU) and other categories that have a low risk of infection among blood donors, the seroprevalence of HBV and HCV was determined.

Thus, the data collected from 72 public and private laboratories in the country were used based on the "Laboratory Evaluation Questionnaire regarding the testing and laboratory diagnosis of viral hepatitis B, C and D" with the presentation of the number of persons investigated and persons positive to markers of HBV and HCV infection.

According to the collected data, from 87 199 investigated persons, HBsAg was determined in 1787, which is 2.05% (95% CI 1.95-2.14 P<0.0000001).

HBsAg seroprevalence of 2.05% was used to estimate HCV seroprevalence in the general population (Table 8).

Table 8. Risk group-specific HBsAg prevalence , population size and estimated number of chronic HBV infections

The group at risk	% BVD prevalence (minimum-maximum estimate)	The population in the Republic of Moldova	Estimating people with CVD
MSM	3.2 (95% CI 2.9-3.5 P<0.0000001)	12 965	415
IDU	3.1 (95% CI 2.8-3.3 P<0.0000001)	22 780	706
SW	3.4 (95% CI 3.1-3.7 P<0.0000001)	13 450	457
HIV+	4.4 (95% CI 4.05-4.8 P<0.0000001)	10,596	470
Blood donors	0.59 (95% CI 0.53-0.65, P<0.0000001)	59 603	354
Pregnant women	0.46 (95% CI 0.39-0.54 P<0.0000001)	30 118	140
General population at low risk of infection	2.05 (95% CI 2.03-2.07 P<0.0000001)	2 001 488	41 031
TOTAL	2.03 (95% CI 2.0-2.04 P<0.0000001)	2 151 000	43 573

Based on these data, the seroprevalence in the low-risk population of 41,031 HCV cases was estimated, relative to the seroprevalence of 2.05% (95% CI 2.03-2.07 P<0.0000001, and in general population – 43 573 cases of HVBC, the seroprevalence being 2.03% (95% CI 2.0-2.04 P<0.0000001). In the same vein, the seroprevalence for HVCC was estimated. According to the data presented by public and private laboratories, it was determined that out of 69,844 people investigated for anti HCV in a.2020, a positive result was determined in 1,418 cases, which is 2.03% (95% CI 1.92-2.13 P<0.0000001). (Table 9). HCV-RNA testing was performed in 47,993 people, of which a positive result was determined in 64 cases, which is 0.13% (95% CI 0.13-0.16 P<0.0000001). Thus, according to the data presented, the anti-HCV seroprevalence is 2.03%. If we relate this seroprevalence to the number of people at low risk of infection, then the estimated number of people infected with HCV in the population at low risk of infection is 40,630 people, and in the general population – 55,834 people, the seroprevalence being 2.60% (95% CI 2.57-2.61 P<0.0000001).

Table 9 . HCV prevalence specific to risk group, population size, and estimated number of chronic HCV infections

The group at risk	% HCV prevalence (minimum-maximum estimate)	Population in Moldova	Estimating people with CVD
MSM	4.7 (95% CI 4.34- 5.07 P<0.0000001)	12,965	609
IDU	49.3 (95% CI 48.65-49.95 P=0.03)	22,780	11,231
SW	8.6 (95% CI 8.13- 9.08 P<0.0000001)	13,450	1,157
HIV+	16.7 (95% CI 16.0-17.42 P<0.0000001)	10,596	1,770
Blood donors	0.72 (95% 0.65-0.79 CI P<0.0000001)	59,603	430
Pregnant women	0.02 (95% CI 0.009-0.04 P<0.0000001)	30,118	7
Population at low risk of infection	2.03 (95% CI 2.01-2.05 P<0.0000001)	2,001,488	40,630
TOTAL	2.60 (95% CI 2.57-2.61 P<0.0000001)	2,151,000	55,834

6. MEDICAL AND SOCIO-ECONOMIC IMPACT IN CHRONIC HEPATITIS, LIVER CIRRHOSIS AND PRIMARY LIVER CANCER

Chronic hepatitis and its consequences, caused by liver cirrhosis and primary liver cancer, involve considerable direct costs for public healthcare services. At the same time, premature deaths due to these pathologies cause the loss of years of healthy life, estimated on the basis of the indicator of potential years of life lost (APVP). The average number of years lost in case of death before the age of 70 highlights the fact that the higher the value of the APVP index, the higher the number of deaths at a younger age. Deaths recorded in people over 70 years old were not taken into account. Thus, according to the officially registered data, a greater number of deaths at a younger age were recorded in the case of patients with liver cirrhosis - on average 23 731 APVP years, compared to liver cancer - 2708 years and chronic hepatitis - 127.03 APVP years. Since the number of patients with liver cancer is small, on average 400 cases annually, respectively, the APVP index is lower compared to liver cirrhosis. Thus, most patients die in the stage of liver cirrhosis.

Patients with chronic hepatitis lose an average of 13.1 years of life, those with liver cirrhosis – 11.5 years and those with liver cancer – 9.5 years until the age of 70, the average age of life expectancy. In the multi-annual dynamics, the number of years potentially lost prematurely, up to the age of 70, is stable both in the case of liver cirrhosis and liver cancer, compared to chronic hepatitis, where an uneven dynamic was revealed throughout the analyzed period, with a significant increase in 2018, when it constituted 19.8 years. This considerable rise is determined by the death of a child in the age group 0-4 years in the Briceni region, which determined 66 years of life lost until the age of 70. Throughout the analyzed period, 2009-2020, deaths from chronic hepatitis were recorded starting from the age of 20-29, with the exception of the child who in 2018 developed fulminant hepatitis, resulting in death.

At the same time, the APVP indicator related to the total number of deaths regardless of life expectancy of 70 years was calculated. Thus, the average number of potentially lost years is reduced in all the pathologies analyzed in this study. This fact is determined by the large number of deaths registered after the age of 70. In this context, the APVP index related to the total number of deaths recorded from chronic hepatitis, on average was 7.3 years, liver cirrhosis – 8.9 years, and liver cancer – 6.1 years.

The analysis of the data shows a stable situation regarding the years potentially lost throughout the analyzed period both in liver cirrhosis and in liver cancer. Thus, patients with liver cirrhosis lost 7.7 potential years of life in a.2009, subsequently an increase of up to 10.2 years was recorded in a.2018 with a decrease until a.2020 of up to 8.4 years of life potentially lost relative to the total number of liver cirrhosis deaths for the same time period. Patients with liver cancer have a lower number of potential years of life lost. In this group of patients, APVP increased from 5.8 years in 2009 to 7.2 years in 2020, which proves that the age at which patients die from liver cancer is lower compared to the period in 2009. If in the case of liver cirrhosis and liver cancer the number of potential years lost is relatively stable throughout the analyzed time period, then in the case of patients with chronic hepatitis we observe an uneven dynamic, with an increase in 2010, where 6 cases of deaths were recorded chronic hepatitis at the age of 30-39 years, the most cases in relation to the other years analyzed, and a. 2018, the year in which the death of the child aged 0-4 years was determined in the Briceni region.

In the same context, the impact of chronic hepatitis, liver cirrhosis and liver cancer on the country's economy caused by costs in the form of added value that a deceased person could have

contributed by being employed in the labor field was determined. Thus, taking into account the value of the gross domestic product for one person - 17,602 lei and the potential years of life lost for each pathology separately, we can estimate the economic impact for our country determined by the death of these patients. So , the economic impact for the year 2009-2020 caused by the death of patients with chronic hepatitis constituted $1524.36 \text{ years} \times 17602.0 \text{ lei} = 26831784.72 \text{ lei}$, liver cirrhosis – $284777.6 \text{ years} \times 17602.0 \text{ lei} = 5,012,655,315.2 \text{ lei}$, and liver cancer $32504.71 \text{ years} \times 17602.0 \text{ lei} = 572147905.42 \text{ lei}$. In total, the economic losses for the country in the period 2009-2020 determined by chronic hepatitis, liver cirrhosis and liver cancer constituted **5,611,635,005.34 lei or 5.6 billion lei.**

Along with the increase in the number of patients with chronic hepatitis, liver cirrhosis and liver cancer, the expenses borne by both the state and the patient for the treatment of these patients are also increasing. The expenses in viral hepatitis were classified into three groups: expenses for the clinical and paraclinical investigations necessary to establish the diagnosis and the phase of the evolution of the disease, including the genotyping of the virus; the costs of treatment and medical assistance, including periodic outpatient visits ; cost per day/bed and endoscopy.

In total, a patient with HVB needs 9,558 lei for public IMS and 15,807 lei for private IMS, and a patient with HCV – 11,378 lei for public IMS and 16,337 lei for private IMS. Currently, in the country, 29,064 patients with HVBC and about 10 thousand patients with HVCC are recorded. Thus, the expenses for patients with these pathologies are very high. Since 2017, due to the implementation of the National Program to combat viral hepatitis B, C and D for the years 2017-2021, considerable progress has been achieved in the treatment of patients with viral hepatitis. Until 2016, approximately 180 patients with HCV and 50 patients with HVBC benefited annually from antiviral treatment with interferons and ribavirin . Following the approval of new antiviral treatment regimens, at the end of 2020, 17,820 patients with HCV received DAA treatment, of which more than 90% eliminated HCV, and in 4,372 patients with chronic HVB/HVD, treatment with interferons and nucleoside inhibitors stopped the progress of the disease (Table 10) .

Table 10. DAA treatment in the Republic of Moldova, period 2016-2020

No. patients	2016	2017	2018	2019	2020	Total
HVC	920	6664	5267	3537	1432	17820
HVB/HVD	-	1064	1411	1191	706	4372
Total	920	7728	6678	4728	2138	22192

At the same time, it should be mentioned that, in 2020, a total of 14,928 cases of chronic HCV were officially reported in the Republic of Moldova, but according to the officially presented data, in total, until today, 17820 patients have been treated and have fully recovered from this pathology. Based on these considerations, it was found that patients who eliminated HCV are not removed from the ANSP statistical record, and at country level the epidemiological situation through chronic HCV continues to present a public health problem. In this context, it is mandatory to review the mechanism for removing from the record patients who have eliminated HCV and are considered cured.

Patients with chronic hepatitis were hospitalized for treatment for an average of 8.73 days, and the cost of a bed day according to the Single Catalog of rates in the hospital medical assistance service is 249.0 lei. Thus, only for the cost of days/bed in chronic hepatitis, the expenses reach 2173.77 days/bed per patient. It should be noted that during 2018 in SCR " Timofei Moșneaga ",

519 patients with chronic hepatitis were hospitalized, which causes expenses in the amount of $519 \times 2173.77 \text{ lei} = 1,128,186.63 \text{ lei}$ only for days/bed during one year.

Patients with liver cirrhosis were hospitalized for an average of 9.43 days, compared to the cost of a day/bed of 249 lei, resulting in expenses of 2348.07 lei per patient. In the same period of time (2018) in SCR " Timofei Moşneaga " 1237 patients received treatment. Thus, the expenses only for days/bed in liver cirrhosis constitute $1237 \times 2348.07 = 2,904,476.0 \text{ lei}$ for days/bed during one year. Liver cancer patients were on average 10.51 days/bed, the cost of one day/bed being 254 lei. Thus, for the entire duration of inpatient stay, the expenses for days/bed are on average 2669.54 lei per patient. Also in the same period of time (2018) in SCR " Timofei " Moşneaga " 11 patients received treatment for primary liver cancer, so compared to this number of patients, the costs determined by days/bed in the hospital are $11 \times 2669.54 = 29,364.94 \text{ lei}$ per year. If we calculate the summary impact of these pathologies, determined only by the costs related to the days/bed, we can mention that over the course of a year for patients with chronic hepatitis, liver cirrhosis and primary liver cancer, an average of 6,969,156.63 lei were spent per year .

The economic impact was also evaluated in relation to other expenses incurred for the treatment of inpatients. Thus, the expenses related to inpatient clinical investigations for patients with chronic hepatitis constituted 1,921 lei, liver cirrhosis – 1,847.0 lei, and liver cancer 2,905.0 lei. Also included here were the costs related to treatment , which turned out to be more expensive in the case of liver cirrhosis, which was estimated on average at 1847.0 lei per patient, compared to chronic hepatitis - 470.0 lei and liver cancer – 827.50 lei. Thus, a total of 4903.77 lei were spent on chronic hepatitis per patient, liver cirrhosis - 5703.10 lei, and liver cancer - 6746.04 lei. It should be mentioned that the estimation of these expenses did not include the costs related to the patients' nutrition, and other indirect costs related to the salary of the medical staff, expenses for ambulatory and primary care services, social subsidies determined by disability, etc.

pathologies was estimated in relation to the number of hospitalized patients during a year on the SCR " Timofei " model Old lady ". Thus, in the context of the previously mentioned vis-a-vis days/beds in the resort, the cost of expenses per total patients hospitalized in the period of 2018 in the hepatology department was similarly calculated. So, expenses for patients with chronic hepatitis constituted 2,545,056.63 lei, liver cirrhosis - 7,054,734.7 lei and liver cancer 74,206.44 lei. In total , 9,673,999.04 lei were spent for the treatment of these pathologies for one year, reported for 1767 patients .

7. STRATEGIC PLAN FOR THE ELIMINATION OF CHRONIC HEPATITIS, LIVER CIRRHOSIS AND LIVER CANCER IN THE REPUBLIC OF MOLDOVA

7.1 Strategic plan to eliminate chronic hepatitis, liver cirrhosis and liver cancer in the Republic of Moldova

The strategic plan for the elimination of chronic hepatitis is a strategic priority in the Republic of Moldova. This plan provides a regulatory framework for eliminating chronic hepatitis, and at the same time reducing the impact determined by the consequences of these pathologies, such as liver cirrhosis and primary liver cancer. The elimination of viral hepatitis is defined by the World Health Organization (WHO) as a 90% reduction in new chronic infections and a 65% reduction in mortality compared to the baseline in 2015. The national strategic plan focuses on the elimination of parenteral viral hepatitis: viral hepatitis B and C, which make up about 64% of all chronic hepatitis, and also have a significant impact on the health of the population. It is based on international recommendations, including WHO, CDC, ECDC, and will also serve as

methodological support for the implementation of the National Program to combat viral hepatitis B, C and D for the years 2022-2026.

Viral hepatitis B can be prevented by vaccination, and viral hepatitis C is curable with a short course of treatment. Reducing the rates of viral hepatitis B and C, preventing new infections and improving care and treatment requires a strategic and coordinated approach by decision makers in collaboration with the Ministry of Health and the National Public Health Agency. The national strategic plan for the elimination of parenteral viral hepatitis provides well-defined objectives, strategies and indicators, which can be implemented through the participation of all stakeholders from different levels and sectors, both public and private as well as non-governmental organizations, affected communities, etc.

Primary, secondary and tertiary prevention measures implemented in the National Hepatitis B, C and D Control Programs include safe and effective vaccines against viral hepatitis B, accurate diagnostic tests that can detect viral hepatitis B and C infections long before symptoms of the disease appear, the treatment of viral hepatitis that significantly lowers the risk of mortality, including direct-acting antiviral (DAA) treatment, and can cure viral hepatitis C with an effectiveness rate of more than 95%. Despite the availability of these intervention tools, viral hepatitis B and C infections remain a priority problem that needs to be addressed.

State policy in the field of viral hepatitis is implemented through the National Program to combat viral hepatitis B, C and D for the years 2017-2021. This is the fourth national program implemented for the prevention and control of viral hepatitis at the country level. However, although it exists, at the current stage in the Republic of Moldova, a Plan of measures for the elimination of viral hepatitis has not been developed and approved, and the existing epidemiological surveillance system needs to be strengthened to allow the comprehensive and disaggregated collection of data on acute viral hepatitis and chronic diseases, but also data on liver cirrhosis, hepatocellular cancer and deaths associated with viral hepatitis B, C and D.

Up to the current stage, a National Strategic Plan for the elimination of viral hepatitis has not been developed. At the same time, it is important to develop indicators for monitoring the progress of eliminating viral hepatitis in the Republic of Moldova. The development of such a National Strategic Plan, with the inclusion of indicators for monitoring and evaluating progress regarding the elimination of viral hepatitis in the country, is of major importance for public health.

Following the analysis of the epidemiological surveillance system of viral liver infections, the following challenges and opportunities were identified in its operation:

- the lack of a national strategic plan to eliminate viral hepatitis in the country;
- divergences between the case definitions used in the Republic of Moldova and those recommended by the WHO;
- gaps in the system for detecting and reporting cases of viral hepatitis and the lack of disaggregated data on viral hepatitis, liver cirrhosis and liver cancer, which does not allow to make estimates, modeling, monitoring and evaluations at the country level;
- the lack of an integrated database that would allow the analysis of morbidity data in complexity;
- lack of screening for hepatocellular carcinoma ;
- the lack of a complete and effective, targeted monitoring, oriented towards the assistance of the patient with chronic viral hepatitis, his family and the community by the family doctor;

- insufficient collection of epidemiological data on cases of chronic viral hepatitis and chronic carriage of hepatitis B and C viruses, which does not allow complex analysis, estimating the economic and medical impact of chronic viral hepatitis;
- insufficient prophylactic and anti-epidemic measures in outbreaks of chronic viral hepatitis (examination for markers of viral hepatitis and vaccination against viral hepatitis B of contacts in the outbreak);
- inadequate information and awareness of the general population and groups at increased risk of infection regarding viral hepatitis and their serious consequences, about preventive measures, including the lack of information and awareness activities focused on different population groups at increased risk of infection (medical workers, people in contact with people with viral hepatitis, key populations - people with UDI, LS, BSB, people with diabetes, STIs, etc.);
- lack of financial resources to carry out activities to raise awareness among the population regarding viral hepatitis;
- reduced coverage with vaccination against viral hepatitis B of people from risk groups;
- reduced HVB and HVC testing of key populations/GRSI in NGOs providing risk reduction services;
- national electronic record and monitoring register of patients with viral hepatitis and liver cirrhosis of viral etiology (B, C and D);
- the precarious situation regarding the development and implementation of screening services and laboratory diagnosis of viral hepatitis B, C and D;
- lack of capabilities to determine mutations of liver viruses associated with resistance to antiviral preparations;
- the reporting mechanisms and the incomplete content of the data in the existing reporting forms do not ensure the correctness and veracity of information about the volume of laboratory investigations per country, including in the private sector, in the case of viral hepatitis;
- the lack of a national registry for the record of the network of laboratories involved in the diagnosis of viral hepatitis, and their level does not allow the establishment of key links between testing and other support services and, accordingly, the periodic evaluation of the programmatic performance of the diagnosis;
- the lack of a national reference laboratory in viral hepatitis that would ensure the evaluation of the quality of supervision and training assistance, as well as other aspects in the monitoring and management of HV testing.

Taking into account the challenges in combating viral hepatitis, a National Strategic Plan for the elimination of viral hepatitis in the Republic of Moldova was developed. The implementation of this plan requires the active participation of state structures at national and territorial level, public health institutions, primary health care, specialized ambulatory health care and hospital care, the private sector, the academic environment, non-governmental organizations and affected communities. The strategic directions, objectives and activities are designed to help focus efforts and resources to achieve the elimination of viral hepatitis and its consequences.

The analysis of the epidemiological situation with viral hepatitis at the country level and the determination of deficiencies in the management of cases of chronic hepatitis, liver cirrhosis and primary liver cancer allowed the development of strategic directions of activity to be included in the National Strategic Plan for the elimination of viral hepatitis.

In support of this plan, six strategic directions were established:

1. Prevention of new viral liver infections.
2. Strengthening and strengthening viral hepatitis testing and diagnosis.
3. Ensuring the treatment, care and monitoring of people with viral hepatitis.
4. Reducing health disparities caused by viral hepatitis.
5. Strengthening the system of epidemiological surveillance of viral hepatitis and ensuring data quality.
6. Integrated multisectoral collaboration among decision makers interested in addressing viral hepatitis and its consequences.

For each strategic direction and strategic activities for each objective. These strategic objectives and activities will help guide stakeholders in achieving the strategic directions and purpose of this Plan. The objectives for each strategic direction set an overall directed course. Activities strategies specify approaches or methods to help achieve goals. Numerous strategic goals and activities could fit across multiple strategic directions. However, each objective has been placed under the strategic direction in which it best fits.

Strategic direction 1: prevention of new viral hepatitis infections

Strategic objectives and activities in the prevention of new viral hepatitis infections describe effective ways to deliver key prevention services. Awareness of the population and health care providers about viral hepatitis and training on prevention strategies are essential to decrease the incidence of viral hepatitis. Information, education and awareness of the population will contribute to the minimization of risky behaviors and will increase the access and application of prevention interventions, such as referral for vaccination against viral hepatitis B. Implementation of information and awareness campaigns about viral hepatitis, the need for vaccination and the benefits of testing and treatment need to be carried out annually at territorial and national level.

Objectives:

- 1.1 Increasing the population's awareness of viral hepatitis;
- 1.2 Increasing the vaccination coverage of newborns and the inclusion of vaccination of groups at increased risk of infection against viral hepatitis B;
- 1.3 Elimination of perinatal transmission of viral hepatitis B and C;
- 1.4 Provision of viral hepatitis prevention services for people from GRSI (UDI, LS, BSB people);
- 1.5 Strengthening the capacities of public health institutions, primary, secondary and tertiary healthcare institutions in the prevention of viral hepatitis;
- 1.6 Ensuring the control of healthcare-associated infections in order to prevent viral hepatitis;
- 1.7 Ensuring blood transfusion safety .

Strategic direction 2: Strengthening viral hepatitis testing and diagnosis

Objectives:

- 2.1 Strengthening diagnostic capacities in viral hepatitis
- 2.2 Ensuring the testing and diagnosis of viral hepatitis
- 2.3 Consolidation of the national laboratory network in the testing and diagnosis of viral hepatitis.
- 2.4 Development of a quality management system in viral hepatitis testing and diagnosis

Strategic direction 3: Ensuring treatment, care and monitoring of people with viral hepatitis

Objectives:

- 3.1 Increasing the quality and accessibility of healthcare services for people with viral hepatitis, liver cirrhosis and liver cancer, including people who use drugs and people in penitentiary institutions;

- 3.2 Strengthening the knowledge of specialists in the field of public health, primary, secondary and tertiary medical care regarding the treatment and medical care of patients with viral hepatitis, liver cirrhosis and hepatocellular carcinoma ;
- 3.3 The adaptation of new antiviral drugs in the treatment of viral hepatitis and the implementation of methods for detecting resistance to antiviral preparations;

Strategic direction 4: Reducing health disparities caused by viral hepatitis

Objectives:

- 4.1 Reducing stigma and discrimination of people at increased risk of hepatitis virus infection.
- 4.2 Providing support in status awareness and adherence to treatment and ongoing care

Strategic direction 5: Strengthening the epidemiological surveillance of viral hepatitis and ensuring qualitative data

Objectives:

- 5.1 Strengthening the epidemiological surveillance of viral hepatitis at territorial and national level;
- 5.2 Ensuring the reporting, analysis, evaluation, and dissemination of viral hepatitis data;
- 5.3 Strengthening the capacities of public health specialists regarding routine epidemiological surveillance, data analysis on viral hepatitis;

Strategic direction 6: integrated multisectoral collaboration between decision-makers involved in the approach Viral hepatitis and their consequences

Objectives:

- 6.1 Integration of policies regarding the prevention and combating of viral hepatitis, HIV infection, STIs and illicit drug use;
- 6.2 Consolidation and strengthening of collaboration and coordination of the implementation of the National Program to combat viral hepatitis B, C and D between public and private medical and sanitary institutions and non-governmental organizations, civil society, etc.;
- 6.3 Ensuring scientific research in the field of policies to prevent and combat viral hepatitis, liver cirrhosis and hepatocellular carcinoma ;
- 6.4 Strengthening mechanisms for monitoring, evaluating, reporting and disseminating progress in eliminating viral hepatitis at local and national levels.

For the monitoring and evaluation of the global strategy of the health sector on viral hepatitis in the world, the World Health Organization (WHO) proposes a monitoring and evaluation framework, which facilitates the collection and analysis of the standardized data necessary to evaluate the progress of elimination of viral hepatitis at the national level. The national strategic plan for the elimination of viral hepatitis includes the basic indicators recommended by the WHO, which will allow determining the degree of its achievement. At the same time, it identifies basic monitoring and evaluation criteria for each indicator and sets targets for 2025 and 2030.

According to international recommendations indicators are classified into context indicators (e.g. resources, infrastructure), process indicators (e.g. training, logistics systems) that translate into outcomes (e.g. availability of services and interventions), outcome indicators (e.g. intervention coverage) and, finally, impact indicators (e.g. mortality) that allow us to assess the success of the National Strategic Plan for the elimination of viral hepatitis B and C and are the basis for measuring national progress in the elimination of viral hepatitis.

Thus, based on the 10 basic indicators, the monitoring and evaluation indicators of the elimination of viral hepatitis towards 2030 were developed .

7.2 Viral hepatitis C elimination model based on the mathematical simulation exercise

The modeling exercise on the elimination of viral hepatitis C was carried out with the technical support of the Global Alliance "Task Force for Global Health" USA and the Global Coalition for the Elimination of Hepatitis in collaboration with the National Agency for Public Health. In order to carry out this exercise, a series of data were collected: the morbidity due to viral hepatitis C in the Republic of Moldova, the degree of progression of the disease, the therapeutic methods used, the screening policy applied in the Republic of Moldova, diagnostic methods, the costs of care and treatment, risk factors and the population's access to health services. The application of the modeling exercise allows the determination of the morbidity trend for the next years, the care cascade, the number of people who need to be tested and included in the treatment to eliminate HCV, the costs for the elimination of HCV, the budget saved due to the application of a correct HCV elimination strategy .

WHO's HCV elimination goal includes reducing HCV incidence by 80% and HCV mortality by 65%, increasing the HCV diagnosis rate to 90%, and including 80% of people diagnosed with HCV in treatment .

The data obtained from the epidemiological analysis, which includes the HCV seroprevalence rate of 2.28 in the Republic of Moldova, the proportion of the population infected with HCV, were calibrated by the Global Alliance "Task Force" and adjusted to the HCV elimination simulation exercise.

There are 28 strategy options, defined by different levels of intervention (screening and treatment rates), which meet or exceed the elimination targets set by 2030 or earlier. The screening rate included the percentage of the entire adult population that should be tested. The treatment rate includes the percentage of the population that is diagnosed and needs to be included in treatment. Next, the results of the following two strategies are presented. Two strategies are presented in this case study: the strategy that requires a slower HCV phase-down and the strategy that will result in the lowest total cost between 2022-2050. The following results are based on the antibody test and the PCR test.

Thus, for the gradual strategy to eliminate viral hepatitis C, the testing of the population was selected in a proportion of 10%, which would constitute about 300,000 people, out of the total of 2,600,000 in the republic, and the treatment of 50% of the people confirmed positive for HCV.

In relation to the gradual strategy to eliminate HCV in the Republic of Moldova, the number of people diagnosed positive for HCV will increase to 8,000 cases in 2023 and subsequently decrease to about 5,000 cases in 2030 (Figure 7. 3). The increase in the number of people diagnosed with HCV requires their inclusion in treatment in a proportion not less than 50%. Thus, the gradual strategy modeled the increase in the number of people included in treatment by 2026 to about 7,000 people, with a decrease of up to 6,000 people in 2030, as a result of the elimination of the virus after treatment.

For 2030, it is predicted that 100% of people with HCV will be diagnosed, of which 97% will know their infection status, and 86% will be nonviremic after treatment .

Using the HCV phase-out strategy provides for higher implementation costs in the early years, around \$8 million, which will gradually decrease to around \$6 million. These include both the indirect costs of disease management and the costs of population-level treatment, confirmation and screening .

Costs may be lower if only treatment, confirmation of HCV patients, and population screening are considered. About \$1 million is requested for these measures, including \$700,000

for population screening , \$200,000 for diagnostic confirmation, and \$200,000 for treatment. These calculations were made based on the current costs required for HCV patients in RM .

At the same time, for the elimination of HVC, the strategy is proposed that would use low costs, a much more efficient method from the economic point of view, but with a positive impact on the public health interventions applied for the elimination of HVC.

The second HVC removal strategy, although involving lower costs, is equally effective and can be applied under RM conditions. This strategy assumes the inclusion in screening of 30% of the country's population and an 80% rate of inclusion in treatment .

In the context of the low-cost HCV elimination strategy, the number of people tested is expected to increase to around 500,000 in 2022 and to over 800,000 in 2023. Thus, it will be possible to detect all people who do not know their infection status, with the reduction their number up to 100,000 annually as a result of detecting all those infected in a maximum proportion in the period 2022-2023. A higher number of people confirmed with HCV can be reached in the period 2022-2024, about 30 000 people in 2023 and a decrease to 10 000 people in 2025. At the same time, this fact will allow us to establish the positive diagnosis in a number more people in a shorter period of time, including inclusion in treatment.

Thus, according to the data obtained, we can mention that by applying the low-cost HCV elimination strategy for a.2030 we can achieve the identification of all HCV-infected people, 99% of them will know their infection status and 98% of them will be treated with non-viremia status.

9,000,000 is needed by 2022, increasing to \$10,000,000 in 2023. By 2030 costs will drop to \$3,000,000. Higher costs are required for disease management, which includes indirect costs.

Higher costs are required for population screening , approximately \$1 million for 2022 and \$2 million for 2023 and 2024, respectively. Starting from 2026, a considerable decrease in costs for screening is observed due to the reduction in the number of people who do not know their infection status. Costs for treatment are about \$300,000 in 2022 and rise to \$1.5 million in 2023, and by 2030 they will drop considerably.

So, eliminating HVC in RM is feasible. The Global Alliance Task Force and ANSP, analyzing the two strategies to eliminate HVC, came to the conclusion that for the Republic of Moldova the most relevant is the strategy with lower costs, but very effective in eliminating HVC. According to this strategy, RM needs **USD 8.61 million** for HCV testing from 2022 to 2030 and **USD 3.33 million** for HCV treatment to eliminate HCV (costs are calculated based on private sector rates) .

GENERAL CONCLUSIONS

9. The epidemiological situation through chronic hepatitis, liver cirrhosis and primary liver cancer is alarming and presents a pressing public health problem, determined by the continuous increase in cumulative morbidity. In the last 20 years (2000-2020), the prevalence due to chronic hepatitis has increased approximately 2 times, from $1092.2 \pm 5.02\%_{000}$, to $2071.32 \pm 7.57\%_{000}$, due to liver cirrhosis $168,6 \pm 1.98\%_{0000}$ to $265.38 \pm 2.73\%_{0000}$, and by liver cancer from $5.1 \pm 0.35\%_{0000}$ to $11.0 \pm 0.56\%_{0000}$.
10. As a result of the epidemiological analysis, the predominant risk factors responsible for the unfavorable evolution of these pathologies were found, including the viral etiological factor determined by the B and C virus, age 50-59 years, pathologies concurrent with the basic diagnosis, non-compliance with the diet by patients, tobacco and alcohol consumption, short duration of treatment – 10 days on average, insufficient application of prevention and control

measures in the outbreak, unprotected sexual relations, shared use of sharp objects – 60.54%, etc.

11. The current epidemiological surveillance system includes the monitoring of acute and chronic hepatitis without considering liver cirrhosis and primary liver cancer as a complex pathology, which makes it impossible to determine the real complex impact and consequence of these pathologies.
12. Officially registered data at the national level do not reflect the real situation regarding the number of people who know their infection status. The realization of the study to estimate the real morbidity due to chronic hepatitis allowed the finding of the real number of cases of chronic viral hepatitis B - 43573 cases compared to 29069 cases registered in the national statistical forms, and 53834 cases of chronic viral hepatitis C compared to the 14928 official cases reported.
13. The evaluation of the epidemiological surveillance system for the morbidity of chronic hepatitis, liver cirrhosis and primary liver cancer allowed the identification of gaps in the investigation of outbreaks. Out of the total number of patients with chronic viral hepatitis B detected, the transmission route was determined only in 8.85%, and among those with chronic viral hepatitis C – in 4.45%. Thus, in over 90% of cases, the route of infection of the patients is unknown, which prevents the application of prevention and control measures in the outbreak.
14. analysis of mortality due to chronic hepatitis, liver cirrhosis and liver cancer highlights the fact that mortality in chronic hepatitis constitutes $0.47 \pm 0.05\text{‰}$ deaths, liver cirrhosis - $75.14 \pm 2.5\text{‰}$ deaths, and liver cancer - $12.55 \pm 0.25\text{‰}$ deaths. The average age at which deaths were recorded in patients with chronic hepatitis was 66.06 ± 1.8 years (CI 95% 62.35-69.76 years), liver cirrhosis - 61.51 ± 0.15 years (CI 95% 61.21-61.80), and liver cancer - 65.33 ± 0.37 years (CI 95% 64.59-66.06 years).
15. The burden of liver pathology is also determined by the large number of APVP caused by chronic hepatitis which constitutes 127.03 years, liver cirrhosis - 23731 years and liver cancer - 2708 years. On average, patients with chronic hepatitis lose 13.1 years of life, those with liver cirrhosis – 11.5 years and those with liver cancer – 9.5 years.
16. The impact of chronic hepatitis, liver cirrhosis and liver cancer on the country's economy, caused by costs in the form of added value that a deceased person could have contributed by being employed in the labor field, is considerable. Thus, taking into account the value of the gross domestic product for a person and the potential years of life lost for each pathology separately, the economic impact at country level determined by the death of these patients, constituted 5.6 billion lei in the analyzed period.
17. In the study, the necessary expenses for a BVD patient receiving healthcare in public and private IMS were calculated. Thus, for a patient with CVD, an amount of 9558 lei is required for public IMS and 15807 lei for private IMS, and for patients with HCV – 11378 lei in public IMS and 16337 lei in private IMS. At the same time, the analysis of inpatient expenses shows that only 4903.77 lei were spent for a patient with chronic hepatitis, liver cirrhosis - 5703.10 lei and liver cancer - 6746.04 lei.
18. Based on the results of the study, the National Strategic Plan for the elimination of hepatitis was developed, which includes six strategic directions: prevention of new viral liver infections; strengthening and strengthening viral hepatitis testing and diagnosis; ensuring the treatment, care and monitoring of people with viral hepatitis; reducing health disparities caused by viral hepatitis; strengthening the system of epidemiological surveillance of viral hepatitis and data

quality assurance; integrated multisectoral collaboration between decision-makers interested in addressing viral hepatitis and its consequences.

PRACTICAL RECOMMENDATIONS

Based on what was analyzed and in order to solve the problems highlighted in this study, we propose the following recommendations:

For decision makers:

1. Implementation of the communication mechanism between health sector institutions to strengthen the epidemiological surveillance of liver pathologies .
2. The implementation of the integrated monitoring system for viral hepatitis, liver cirrhosis and liver cancer, which will allow estimating the impact of sequelae developed by patients infected with liver viruses, must be based on three main directions:
 - a. detecting outbreaks, monitoring incidence trends and identifying risk factors for new infections;
 - b. estimating the prevalence of chronic liver viral infections and monitoring trends in the general population;
 - c. estimating the burden of sequelae of chronic hepatitis, including liver cirrhosis and liver cancer.
3. Providing medical facilities with BVD and HCV rapid diagnostic tests for testing key populations/GRSI through mobile units and social events, with the organization and implementation of BVD and HCV rapid diagnostic test campaigns in the general population.
4. development of an automated information system "Hepatitis Registry", which would allow the registration and monitoring of cases of viral hepatitis.
5. Creation of the PNC HV coordination and monitoring unit to ensure its technical management .

For the public health surveillance system:

1. Updating the National Program to combat viral hepatitis B, C and D for the years 2022-2026 in accordance with WHO recommendations.
2. Development of standardized indicators for monitoring viral hepatitis, liver cirrhosis and liver cancer at the national level in accordance with the recommendations of international organizations - WHO, CDC, ECDC.
3. Staff training on data collection and continuous evaluation of surveillance and monitoring indicators of liver pathologies .
4. Estimation of the real morbidity due to viral hepatitis in the Republic of Moldova based on epidemiological studies, including surveillance of viral hepatitis biomarkers .
5. The collection of disaggregated data, which will allow the epidemiological analysis of liver pathologies according to age, gender and some risk factors.
6. Elaboration of the plan of measures for the elimination of viral hepatitis B, C and D in the Republic of Moldova.
7. Perfecting the hepatitis B vaccination planning and reporting forms with disaggregations of people at increased risk of infection, in order to monitor their vaccination by group of people at risk.
8. Development of epidemiological data collection forms for the case of chronic viral hepatitis B and C and its application in the routine surveillance system to ensure the

collection of complete and objective data on the incidence and prevalence of viral hepatitis B and C.

9. Making estimates and mathematical modeling to ensure the planning, implementation, monitoring and evaluation of strategies, policies, programs and plans in viral hepatitis.

For primary and hospital care:

1. Organization and implementation of interventions to promote BVD and HCV testing among key populations/GRSI at community and general population levels, in order to increase detection of infected persons.
2. Develop informational materials on HVB and HVC testing for the key population/GRSI and the general population and ensure their distribution.
3. Carrying out information, education, communication activities regarding HVB and HCV, and prevention measures among key populations/GRSI, including person-based communication and information interventions.
4. Application of anti-epidemic measures in the outbreak according to the legislation in force.

Suggestions for the future research

1. The results of this study allowed the determination of the priority problems faced by the public health service in the context of the epidemiological surveillance of chronic hepatitis, liver cirrhosis and primary liver cancer.
2. The given study did not provide for the study of the epidemiological peculiarities of chronic viral hepatitis depending on the groups with increased risk of infection (BSB, LS, UDI). In this context it is necessary to continue research in that direction.
3. Further research is needed into the effectiveness of hepatitis B vaccination in the general population and in groups at increased risk of infection.
4. It is necessary to carry out an epidemiological study on the seroprevalence of HVB and HVC among medical personnel and other categories with increased risk of infection.

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- 3.2.10 PARASCHIV, A. ș.a. *Hepatitele virale parenterale și cirozele hepatice – epidemiologia, clinica, diagnosticul, tratamentul, prevenirea și controlul*. Salonul internațional al cercetării științifice, inovare și inventicii, ediția XVII. Cluj-Napoca, România, 2019, 20-22 martie, p.169. ISBN 978-606-737-356-1
- 3.2.11 Spînu, C. ș.a. *Metodă de identificare a markerului virusului hepatitei virale C în sângele uman*. Salonul internațional al cercetării științifice, inovare și inventicii, ediția XVII, Cluj-Napoca, România, 2019, 20-22 martie, p.159. ISBN 978-606-737-356-1.
- 3.3 în lucrările conferințelor științifice naționale**
- 3.3.1 PARASCHIV, A. Problema hepatitelor cronice, ciroze hepatice și cancer hepatic în Republica Moldova. În: Abstract book Congres consacrat aniversării a 75-A de la fondarea USMF „Nicolae Testemițanu”, 2020, 21-23 septembrie, p.164.
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- 3.4.1 SPÎNU, C. ș.a. *Metodă de identificare a markerului virusului hepatitei C în sângele uman*. Brevet de invenție înregistrat cu nr.1844 din 14.11.2018
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ADNOTARE

Paraschiv Angela

Hepatita cronică, ciroza hepatică și cancerul hepatic primar în Republica Moldova: epidemiologie, pronostic și strategie de combatere

Teza de doctor habilitat în științe medicale, Chișinău, 2022

Structura tezei: Teza este expusă pe 209 pagini text de bază ce include introducere, șapte capitole și concluzii. Lucrarea citează 225 de surse bibliografice și este ilustrată cu 46 de tabele, 105 figuri și 12 anexe. Rezultatele obținute sunt publicate în 49 de articole științifice, dintre care 18 monoautor.

Cuvintele cheie: hepatite cronice, ciroze hepatice, cancer hepatic primar, strategie de combatere, factori de risc, impact socio-economic.

Domeniul de studii: 331.01.Epidemiologie

Scopul lucrării: studierea particularităților epidemiologice și factorilor de risc în dezvoltarea hepatitelor cronice, cirozelor hepatice și cancerului hepatic primar, cu pronosticarea morbidității prin aceste patologii la nivel național și elaborarea planului strategic de eliminare.

Obiectivele cercetării: Aprecierea situației epidemiogene prin hepatită cronică, ciroze hepatice și cancer hepatic primar în Republica Moldova. Determinarea particularităților epidemiologice și a factorilor de risc responsabili de cronicizarea hepatitelor și dezvoltarea cirozelor și cancerului hepatic primar. Determinarea impactului medical și socio-economic în hepatitele cronice, cirozele hepatice și cancerul hepatic primar. Elaborarea pronosticului situației epidemiogene în Republica Moldova prin hepatite cronice, ciroze hepatice și cancer hepatic primar în funcție de evoluția factorilor de risc. Elaborarea strategiei de eliminare a morbidității prin hepatite cronice, ciroze hepatice și cancer hepatic primar în condițiile actuale ale Republicii Moldova.

Noutatea și originalitatea științifică: Pentru prima dată a fost studiată problema hepatitei cronice, cirozei hepatice și cancerului hepatic primar în complex, ținând cont de legătura strânsă dintre ele, și totodată determinat impactul social și economic în ansamblu. Pe baza rezultatelor estimării morbidității reale prin hepatite cronice a fost pronosticată situația epidemiogenă prin hepatite cronice, ciroze hepatice și cancer hepatic primar și elaborat planul strategic de eliminare a hepatitelor la nivel național.

Problema științifică soluționată: au fost stabilite particularitățile epidemiologice ale morbidității prin hepatita cronică, ciroza hepatică și cancerul hepatic primar ceea ce a permis determinarea lacunelor în supravegherea epidemiologică a acestor afecțiuni la nivelul serviciului de sănătate publică și elaborarea planului strategic de eliminare a hepatitelor cronice în Republica Moldova.

Semnificația teoretică: au fost lărgite viziunile contemporane despre particularitățile epidemiologice și cauzele evoluției hepatitei cronice către ciroza hepatică și cancerul hepatic primar; a fost estimată morbiditatea reală prin hepatite cronice la nivel național, pronosticată situația epidemiogenă și elaborat planul strategic de eliminare a hepatitelor cronice în Republica Moldova care, pentru prima dată, prevede reducerea cazurilor de ciroze hepatice și cancer hepatic primar.

Valoarea aplicativă a lucrării: Rezultatele cercetării au permis determinarea direcțiilor de acțiune în scopul depistării și reducerii riscului de formare a acestor patologii; determinarea impactului economic și social, estimarea morbidității reale, elaborarea Planului strategic național de eliminare a hepatitelor, elaborarea indicatorilor de monitorizare a realizării planului.

Implementarea rezultatelor științifice: Au fost implementate în cadrul ANSP, Disciplina de epidemiologie și Microbiologie USMF „Nicolae Testemițanu”, realizate 3 ateliere de lucru prin Dispoziția MS, inclusiv Dispoziția 148-d din 12.03.2021 cu privire la organizarea atelierului de lucru privind pretestarea chestionarelor pentru colectarea datelor în hepatite virale; Dispoziția MS 457-d din 15.06.2021 Cu privire la organizarea atelierului de lucru privind analiza situațională în hepatită virală B, C și D și măsurile de control și răspuns; Dispoziția MS nr.653-d din 06.09.2021 cu privire la organizarea atelierului de lucru privind elaborarea Planului de acțiuni pentru eliminarea hepatitelor virale pentru perioada 2022-2030.

ANNOTATION

Paraschiv Angela

Chronic hepatitis, liver cirrhosis and primary liver cancer in the Republic of Moldova: epidemiology, prognosis and control strategy"

Thesis of doctor habilitat in medical sciences, Chisinau, 2021

Thesis structure: The paper is exposed on 209 pages, includes 46 tables, 105 figures, 12 annexes and 7 chapters, 225 specialized bibliographic sources, published 49 scientific articles, of which 18 are single authors,

Keywords: chronic hepatitis, liver cirrhosis, primary liver cancer, control strategy.

Field of study: 331.01. Epidemiology

The aim of the thesis: to study the epidemiological features and risk factors in the development of chronic hepatitis, liver cirrhosis and primary liver cancer, with the elaboration of the prognosis and strategy for reducing morbidity through these pathologies at the national level.

Research objectives: Assessment of the epidemiological situation by chronic hepatitis, liver cirrhosis and primary liver cancer in the Republic of Moldova. Determination of epidemiological features and risk factors responsible for chronic hepatitis and the development of cirrhosis and primary liver cancer. Determining the medical and socio-economic impact of chronic hepatitis, cirrhosis of the liver and primary liver cancer. Elaboration of the prognosis of the epidemiogenic situation in the Republic of Moldova regarding chronic hepatitis, liver cirrhosis and primary liver cancer depending on the evolution of risk factors. Development of a strategy to reduce morbidity from chronic hepatitis, liver cirrhosis and primary liver cancer.

Scientific novelty and originality: For the first time, the problem of chronic hepatitis, liver cirrhosis and primary liver cancer in the complex was studied, taking into account the close link between them, and also determined the social and economic impact as a whole. Based on the obtained results, the prognosis of the epidemiogenic situation by chronic hepatitis, liver cirrhosis and primary liver cancer was elaborated, as a result of the estimates regarding the real morbidity by chronic hepatitis and the strategy of elimination of chronic hepatitis at national level was elaborated.

The scientific problem solved: the epidemiological features of chronic hepatitis morbidity, liver cirrhosis and primary liver cancer in complexity have been established, which has identified gaps in epidemiological surveillance in the public health service and the development of the plan for the elimination of chronic hepatitis in Moldova.

Theoretical significance: Contemporary views on the epidemiological features and causes of the evolution of chronic hepatitis in liver cirrhosis and primary liver cancer have been completed. The paper contributed by estimating the actual morbidity from chronic hepatitis at the national level and developing the prognosis of the epidemiogenic situation and developing a plan to eliminate chronic hepatitis in the Republic of Moldova, which included for the first time reducing cases of liver cirrhosis and primary liver cancer.

The applicative value of the work: The results of the research allowed to determine the directions of action in order to detect and reduce the risk of formation of these pathologies; determined the economic and social impact, estimated the real morbidity regarding chronic hepatitis, developed the National Strategic Plan for the elimination of hepatitis, developed indicators for monitoring and evaluation of the implementation of the plan, including developed indicators of context, process and impact that need to be obtained by 2030, updated National Clinical Protocols.

Implementation of scientific results: The results were implemented within ANSP, Epidemiology and Microbiology Discipline Nicolae Testemitanu SUMPh, conducted 3 workshops by the Order of the MH, including from 12.03.2021 Pre-testing questionnaires for data collection in viral hepatitis; Disposition of MH 457-d of 15.06.2021 Regarding the organization of the workshop on situational analysis in viral hepatitis B, C and D and control and response measures; Disposition of the MH no. 653-d of 06.09.2021 regarding the organization of the workshop on the elaboration of the Action Plan for the elimination of viral hepatitis for the period 2022-2030.

АННОТАЦИЯ

Параскив Анжела

Хронический гепатит, цирроз печени и первичный рак печени в Республике

Молдова: эпидемиология, прогноз и стратегия борьбы

Диссертация доктора медицинских наук. Кишинев, 2022 г.

Структура диссертации: Статья изложена на 209 страницах, включает 46 таблиц, 105 рисунков, 12 приложений и 7 глав, 225 библиографических источников, опубликовано 49 научных статей, из них 18 один автор,

Ключевые слова: хронический гепатит, цирроз печени, первичный рак печени, стратегия борьбы.

Область исследования: 331.01.Эпидемиология.

Цель работы: изучение эпидемиологических особенностей и факторов риска развития хронического гепатита, цирроза печени и первичного рака печени с разработкой прогноза и стратегии снижения заболеваемости этими патологиями на национальном уровне.

Задачи исследования: Оценка эпидемиогенной ситуации хронического гепатита, цирроза печени и первичного рака печени. Определение эпидемиологических особенностей и факторов риска, ответственных за хронический гепатит и развитие цирроза и первичного рака печени. Определение медицинских и социально-экономических последствий. Разработка прогноза эпидемиогенной ситуации в отношении хронического гепатита, цирроза печени и первичного рака печени в зависимости от эволюции факторов риска. Разработка стратегии снижения заболеваемости хроническим гепатитом, циррозом печени и первичным раком печени.

Научная новизна и оригинальность: Впервые изучена проблема хронического гепатита, цирроза печени и первичного рака печени в комплексе с учетом тесной связи между ними, а также определен социально-экономический эффект в целом. На основании полученных результатов разработан прогноз эпидемиогенной ситуации по хроническому гепатиту, циррозу печени и первичному раку печени, в результате проведена оценка реальной заболеваемости хроническим гепатитом и разработана стратегия ликвидации хронического гепатита на национальном уровне. проработанный.

Решенная научная задача: установлены эпидемиологические особенности заболеваемости хроническими гепатитами, циррозом печени и первичным раком печени в комплексе, что позволило выявить пробелы в эпидемиологическом надзоре в системе здравоохранения и разработке плана ликвидации хронических гепатитов.

Теоретическая значимость: завершены современные представления об эпидемиологических особенностях и причинах эволюции хронического гепатита к циррозу печени и первичному раку печени. В работе проведена оценка фактической заболеваемости хроническим гепатитом на национальном уровне, разработан прогноз эпидемиогенной ситуации и разработан план ликвидации хронического гепатита, который впервые включал снижение случаев цирроза печени и первичных раков печени.

Практическое значение работы: Результаты исследования позволили определить направления действий по выявлению и снижению риска формирования данных патологий; определил экономический и социальный эффект, оценена реальная заболеваемость хронического гепатита, разработал Национальный стратегический план по ликвидации гепатита, разработаны индикаторы для мониторинга и оценки реализации плана, индикаторы контекста, процесса и воздействия, обновленные национальные клинические протоколы.

Внедрение научных результатов: Результаты внедрены в НАОЗ, Дисциплины эпидемиологии и микробиологии ГУМФ «Николае Тестемицану», проведены 3 семинара по Приказу МЗ 148-д от 12.03.2021 Тестирование вопросников для сбора данных при вирусных гепатитах; Распоряжение МС 457-д от 15.06.2021 Об организации семинара по ситуационному анализу вирусных гепатитов В, С и D и мерах контроля и реагирования; Распоряжение Минздрава от 06.09.2021 № 653-д об организации рабочего совещания по разработке Плана мероприятий по ликвидации вирусных гепатитов на период 2022-2030 гг.

PARASCHIV ANGELA

**CHRONIC HEPATITIS, LIVER CIRRHOSIS AND PRIMARY LIVER
CANCER IN THE REPUBLIC OF MOLDOVA: EPIDEMIOLOGY,
PROGNOSIS AND COMBAT STRATEGY**

331.01 – EPIDEMIOLOGY

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