Contents available at **PubMed**
www.clinicalandtranslationalinvestigation.com

PERMANYER

Rev Inves Clin. 2015;67:104-8 ORIGINAL ARTICLE

Hepatitis C Screening in the General Population

Clara Corona-Lau[1], Linda Muñoz[2], Enrique Wolpert[3], Luz María Aguilar[4], Margarita Dehesa[3], Concepción Gutiérrez[5] and David Kershenobich[4*]

[1]Laboratorio Biomedica de Referencia, México, D.F., Mexico; [2]Liver Unit, Hospital Universitario, Universidad Autónoma de Nuevo León, Monterrey, N.L., Mexico; [3]Fundación Mexicana para la Salud Hepática, México, D.F., Mexico; [4]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México, D.F., Mexico; [5]Universidad Autónoma Metropolitana, México, D.F., Mexico

ABSTRACT

Background: A significant number of patients infected with hepatitis C virus remain unaware of their infection, as this is a silent disease for many years. Patients are frequently detected at advance stages of the disease. **Objective:** To identify the prevalence and viremic stage of hepatitis C among a general population cohort. **Methods:** Anti-hepatitis C virus detection and viral RNA were offered without cost to individuals who voluntarily considered it relevant to be examined, as part of the World Hepatitis Day annually from 2007-2014. **Results:** A total of 32,945 individuals were analyzed; 57% were female and 43% male. Of them, 75.7% were between 21-50 years old. In 59%, the sample was obtained at their work place and in 41% at the facilities of 12 private laboratories. Anti-hepatitis C virus was positive in 194 patients (0.58%), of which 129 (66%) were confirmed positive by polymerase chain reaction. The overall prevalence of viremic cases in the sample was 0.39%. **Conclusions:** Adequate estimation of the prevalence of anti-hepatitis C virus and viremic population, not only among high-risk groups but also in the general population, is central to the allocation of resources in an effort to reduce the consequences of the disease. (REV INVES CLIN. 2015;67:104-8)
Corresponding author: David Kershenobich, kesdhipa@yahoo.com

Key words: Hepatitis C. Screening. Epidemiology. Direct acting antiviral.

INTRODUCTION

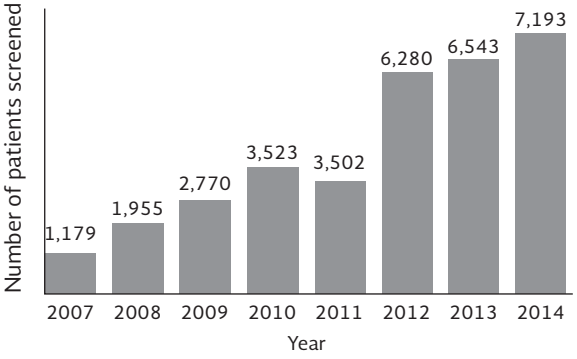
The diagnosis of hepatitis C virus (HCV) infection is commonly made through the detection of antibodies (anti-HCV) against recombinant proteins of the virus using chemiluminescence or enzyme immunoassays. A positive anti-HCV test may indicate: (i) current infection of HCV, (ii) infection with HCV that has resolved, or (ii) may be a false positive[1,2]. Quantitative and qualitative methods that allow the detection of viral nucleic acid in serum using polymerase chain reaction techniques (PCR) are used to confirm the presence of active infection (viremic cases)[3].

Hepatitis C represents an important global epidemiological disease and it is responsible for a significant number of chronic liver diseases, including chronic active hepatitis, liver cirrhosis, and hepatocellular carcinoma[4-6]. The burden of chronic infection is critical

Corresponding author:
*David Kershenobich
Manager Director
Instituto Nacional de Ciencias Médicas y Nutrición
Salvador Zubirán
Vasco de Quiroga, 15
Col. Belisario Dominguez, Sección XVI, Del. Tlalpan
C.P. 14080, México, D.F., México
E-mail: kesdhipa@yahoo.com

Received for publication: 30-01-2015
Accepted for publication: 25-02-2015

Figure 1. Yearly distribution of 32,945 individuals screened for hepatitis C.



for developing strategies to manage or eliminating HCV infection. In a study that included 87 countries, the global total of viremic HCV infections was estimated at 80 (64-103) million. Globally, genotype 1 was the most common (46%) followed by genotype 3 (22%) and genotype 2 (13%)[7].

The epidemiology of HCV infection has changed over the past decades[8,9]. In the 1970s and early 1980s, blood-acquired infections were the main source of infection, prompting for example the recommendation of the Centers of Disease Control and Prevention in the USA that all individuals born between 1945 and 1965 undergo one-time screening for HCV regardless of risk factors[10]. The introduction of screening essays in blood banks has significantly reduced the risk of transmitting HCV via blood products[11-13]. Other populations at risk have emerged, such as prisoners[14], intravenous drug addicts[15], and migrants[16], and new routes of infection are being recognized such as nosocomial acquired infections derived from unsafe invasive medical and surgical procedures such as endoscopy, invasive radiological procedures, hemodialysis, use of multidose vials, tattooing, and pedicure/manicure[17,18].

Most hepatitis C prevalence studies in the past were performed in selected populations of blood donors, in vulnerable groups, or as part of national surveys of health. A significant number of infected patients remain, however, unaware of their infection as this is a silent disease for many years. In fact a great majority of people infected worldwide are unaware of their status and are frequently detected at advance stages of the disease[19-21]. This may be caused, among other factors, by lack of testing opportunities. The objective of the present research is to identify the prevalence and viremic stage of hepatitis C among a general population cohort. To this end, anti-HCV detection and, if positive, determination of the viral DNA were offered without cost to individuals who voluntarily considered it relevant to be examined.

MATERIAL AND METHODS

Laboratory tests were offered free of charge by Laboratory Biomedica de Referencia as part of the World Hepatitis Day, organized annually from 2007 to 2014 by the Fundación Mexicana para la Salud Hepática. The offer was made through posters, brochures, and online promotion. A sample of 10 cc of blood was drawn in each patient. The determination of HCV was made by chemiluminescence enzyme immunoassay, utilizing the VITROS Anti-HCV Reagent Pack and the VITROS Calibrator in the immunodiagnostic system VITROS® 3600 and VITROS® 5600 (Intellicheck®. Ortho Clinical Diagnostics, Raritan NJ, USA). Viral load was determined using the Abbott RealTime PCR assay, with a cutoff point of < 12 UI/ml. All individuals turned up voluntarily for the examination. Each individual was examined only once during the period of the study. The results of the test were given in a written confidential report to each individual. Viremic patients were referred for medical care.

Results

A total of 32,945 individuals were analyzed over a period of eight years. As can be seen in figure 1, the number of individuals accessing the examination increased yearly from 1,179 in 2007 to 7,193 in 2014. In 19,437 (59%) the sample was obtained at their work place in 27 facilities (banks, food and bread factories, sport centers, government offices) and 13,507 (41%) were tested at the facilities of the clinical laboratories.

Of the total sample, 18,778 (57%) were female and 14,166 (43%) male. Their age range was 10 to 90 years, most of them (24,939, 75.7%) being from individuals between 21-50 years of age (Fig. 2). The determination of anti-HCV was positive in 194 patients (0.58%), of which 129 (66%) were confirmed positive by PCR.

Figure 2. Age distribution of 32,945 individuals screened for hepatitis C.

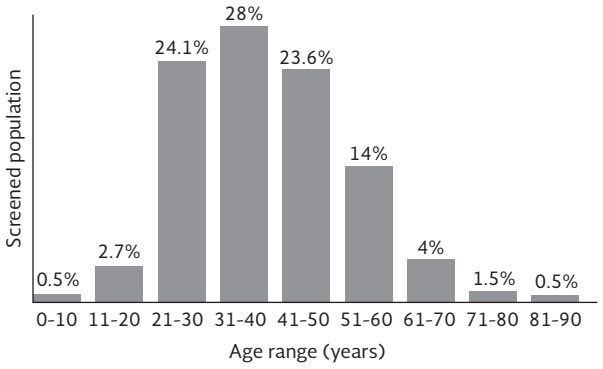


Table 1. Number of HCV+ and confirmed viremic individuals

Year	Total	HCV+	Confirmed +by PCR	
2007	1,179	17	7	0.59%
2008	1,955	24	13	0.66%
2009	2,770	23	20	0.72%
2010	3,523	29	22	0.62%
2011	3,502	24	13	0.37%
2012	6,280	36	23	0.37%
2013	6,543	28	20	0.31%
2014	7,193	13	11	0.15%
Total	32,945	194	129	0.39%

The overall prevalence of viremic cases in the sample was 0.39%. During the period 2007 to 2010 the proportion of viremic cases was 0.65%; between 2011 and 2013 it decreased to 0.35%, and in 2014 it further diminished to 0.15% (Table 1).

DISCUSSION

The screening program herein reported has several noteworthy characteristics: it is free of cost, it does not use a prescreening selection based on HCV risk factors, or elevated ALT as indicators for HCV screening. It is a long-term screening program that was carried out annually as part of World Hepatitis Day. The yearly increase in the examined individuals could correspond to an improvement in the announcing and promotion of the event and/or an increase in disease awareness. A significant proportion of the samples (59%) was obtained at the work place, an important determinant for being tested that may have attracted a different risk population that otherwise would not have been screened and that may not have perceived themselves as at risk of hepatitis C (hidden population). We acknowledge the difficulties to compare this with other strategies of screening for hepatitis C, but it undoubtedly contributes to the estimation of the burden of the disease by estimating the prevalence of hepatitis C and particularly the percentage of viremic cases among the general population, observations that may be of great relevance when deciding on the allocation of resources in the era of the new oral direct-acting antiviral agents free of interferon and ribavirin.

Certainly the epidemiology of HCV infection has undergone substantial changes over the past two decades, with the implementation of screening programs for hepatitis C in blood banks. In Latin America, the donor prevalence has remained relatively stable at 0.65%[11]. In Brazil, the incidence of hepatitis C dropped from 0.12 to 0.06 per 1,000 donor-years, and residual risk decreased more than threefold after blood screening implementation[22].

A significant number of infected patients are, however, unaware that they may be carriers of the virus C as this is a silent disease for many years. In fact about 90% of people infected with viral hepatitis are unaware of their status[23]. Screening for HCV among the general population is not a widespread practice. Even in high-income countries such as the USA, less than 20% of individuals are screened for HCV infection. In a controlled population study carried out at the Kaiser Permanente clinics over a period of 10 years among 444,594 patients, only 15.8% of the cohort was ever screened for HCV. Adult primary care and obstetrics and gynecology providers performed 75.9% of all screening. The overall test positivity rate was 3.8%. Screening was more frequent in younger age groups and in those with a documented history of illicit drug use. Patients missing drug use history were least likely to be screened[24].

These epidemiological variations are accompanied by relevant changes in the clinical presentation of the disease. A recent publication in the USA comparing the characteristics of newly referred HCV

patients in 2011-2012 (Era-2) compared to those seen in 1998-1999 (Era-1), identified that Era-2 patients were older and had a longer interval between diagnosis and referral. They were more likely to have advanced disease, with an eightfold higher prevalence of hepatocellular carcinoma[25].

A diagnosis of hepatitis at present is more commonly established in older patients, above 30 years, peaking after age 70 years, with more advanced disease[26,27] facilitated by the accumulation of risk factors and progression of liver disease, as symptoms of chronic infection emerge 20 or more years after the initial infection, leading individuals to seek medical attention[28]. Age at diagnosis of hepatitis has been shown to correlate significantly with fibrosis[29].

In the present study, the population accessing the screening program was composed mainly of individuals between 21 to 40 years of age, in part due to the fact that 44% of the samples correspond to the working population. On the other hand, 57% of the individuals that responded to the call were women. In Mexico the prevalence of hepatitis C has been estimated to a large extent by data from the National Survey of Health 2000. This study was carried out in a sample of 90,916 individuals, representative of non-institutionalized populations, of which 21,272 sera were randomly selected for analysis. The reported prevalence of hepatitis C was 1.4%, with a range from 0.8% in Mexico City to 2.0% in the north of the country. The percentage of viremic cases was 0.51%[30]. Similar results have been found in different cities in the country, mainly in the context of blood donors, high-risk populations, hospitals, and primary care centers, with similar results[31-34]. The prevalence of anti-HCV positivity that we herein report is lower. Most of the population that we screened was younger (below 50 years), however the benefit of screening blood products since 1992 could only explain changes in prevalence and viremia in those individuals 22 years old or younger. Another factor is a lower percentage of illicit use of drugs in Central Mexico compared with the northwest region of the country[35]. In Argentina, reported rates of HCV prevalence in the general population have decreased from 1.5% in 2004 to 0.32%[36]. A review carried out in Europe analyzing 260 epidemiological studies found that the prevalence of HCV globally varied from 0.13 to 3.26%[23].

Viremic prevalence estimates also differ widely between countries, ranging from 0.3% in Austria, England, and Germany to 8.5% in Egypt[37]. In the present study the number of viremic patients was lower at 0.39%. This finding, although unexpected, is not exclusive to our study, as similar tendencies have more recently been identified. Data from the National Health and Nutrition Examination survey in the USA indicate that the prevalence of anti-HCV decreased from 1.9% in 2001-2002 to 1.3% in 2005-2006, and remained stable up to 2010. Of these patients, 0.87% was viremic[38]. These findings suggest that there is a great window of opportunity to intervene earlier, particularly as new antiviral treatments emerge.

The importance of screening a younger population, mostly asymptomatic, has the advantage of intervening earlier and trying to avoid the burden of advanced liver disease. Considering viremic patients when designing new treatment policies relies on the fact that in this group of patients, the replication of the virus is active, denoting that the virus gets into the bloodstream, signifying a population at increased risk of transmission with a high impact on public health compared to non-viremic patients. As new HCV therapies emerge, their use in many countries will be limited in great part by economic barriers for access to screening and the use of direct-acting antiviral agents. Adequate estimation of the prevalence of anti-HCV and the viremic population, not only among high-risk groups but also in the general population, is central to the allocation of resources in an effort to reduce the consequences of the disease.

In summary, screening for hepatitis C among the general population demonstrated a lower prevalence and viremic rates in contrast to that previously described in studies based on risk factors. Identification and earlier treatment would contribute to decrease the impediments of chronic liver disease.

REFERENCES

1. Alter MJ, Kuhnert WL, Finelli L. Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus. Center for Disease Control and Prevention. MMWR Recomm Rep. 2003; 52:1-13.
2. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: An update. Hepatology. 2009;49:1335-74.
3. Gullett JC, Nolte FS. Quantitative nucleic acid amplification methods for viral infections. Clin Chem. 2015;61:72-8.

4. Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci. 2006;3:47-52.
5. Davis GL, Albright JE, Cook SF, Rosenberg DM. Projecting future complications of chronic hepatitis C in the United States. Liver Transpl. 2003;9:331-8.
6. Ward JW. The hidden epidemic of hepatitis C virus infection in the United States: occult transmission and burden of disease. Top Antivir Med. 2013;21:15-9.
7. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014;61(Suppl 1):S45-57.
8. Razavi H, Waked I, Sarrazin C, et al. The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm J Viral Hepat. 2014;21(Suppl 1):34-59.
9. Gane E, Kershenobich D, Seguin-Devaux C, et al. Strategies to manage hepatitis C virus (HCV) infection disease burden J Viral Hepat. 2015;22(Suppl 1):46-73.
10. Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Ward JW. Hepatitis C virus testing of persons born during 1945-1965: recommendations from the Centers for Disease Control and Prevention. Ann Intern Med. 2012;157:817-22.
11. Kershenobich D, Razavi HA, Sanchez-Avila JF, et al. Trends and projections of hepatitis C virus epidemiology in Latin America. Liver Int. 2011;31:18-29.
12. Selvarajah S, Busch MP. Transfusion transmission of HCV, a long but successful road map to safety. Antivir Ther. 2012;17: 1423-9.
13. Alter HJ, Houghton M. Clinical Medical Research Award. Hepatitis C virus and eliminating post-transfusion hepatitis. Nat Med. 2000;6:1082-6.
14. Arain A, Robaeys G, Stöver H. Hepatitis C in European prisons: a call for an evidence-informed response. BMC Infect Dis. 2014; 14(Suppl 6):S17.
15. Valdiserri R, Khalsa J, Dan C, et al. Confronting the emerging epidemic of HCV infection among young injection drug users. Am J Public Health. 2014;104:816-21.
16. Miners AH, Martin NK, Ghosh A, Hickman M, Vickerman P. Assessing the cost-effectiveness of finding cases of hepatitis C infection in UK migrant populations and the value of further research. J Viral Hepat. 2014;21:616-23.
17. Lee M-H, Yang H-I, Yuan Y, L'Italien G, Chen C-J. Epidemiology and natural history of hepatitis C virus infection. World J Gastroenterol. 2014;20:9270-80.
18. Cornberg M, Razavi HA, Alberti A, Bernasconi E, Buti M, Cooper C. A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. Liver Int. 2011;31(Suppl 2):30-60.
19. Loomba R, Rivera MM, McBurney R, et al. The natural history of acute hepatitis C: clinical presentation, laboratory findings and treatment outcomes. Aliment Pharmacol Ther. 2011;33:559-65.
20. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol. 2006;44:217-31.
21. Viner K, Kuncio D, Newbern EC, Johnson CC. The continuum of hepatitis C testing and care. Hepatology. 2015;61:783-9.
22. Kupek E1, Petry A. Changes in the prevalence, incidence and residual risk for HIV and hepatitis C virus in Southern Brazilian blood donors since the implementation of NAT screening. Rev Soc Bras Med Trop. 2014;47:418-25.
23. Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. J Hepatol 2013;58:593-608.
24. Linas BP, Hu H, Barter DM, Horberg M, Hepatitis C screening trends in a large integrated health system. Am J Med. 2014;127: 398-405.
25. Talaat N, Yapali S, Fontana RJ, Conjeevaram HS, Lok AS. Changes in characteristics of hepatitis C patients seen in a liver centre in the United States during the last decade. J Viral Hepat. 2015; 22:481-8.
26. Oliveira AC, Bortotti AC, Nunes NN, El Bacha IA, Parise ER. Association between age at diagnosis and degree of liver injury in hepatitis C. Braz J Infect Dis. 2014;18:507-11.
27. Wang L, Xing J, Chen F, et al. Spatial analysis on hepatitis C virus infection in Mainland China: From 2005 to 2011. PLoS One. 2014;9:e110861.
28. Schanzer DL, Paquette D, Lix LM. Historical trends and projected hospital admissions for chronic hepatitis C infection in Canada: a birth cohort analysis. CMAJ Open. 2014;2:E139-44.
29. Oliveira AC, Bortotti AC, Nunes NN, El Bacha IA, Parise ER. Association between age at diagnosis and degree of liver injury in hepatitis C. Braz J Infect Dis. 2014;18:507-11.
30. Valdespino JL, Conde-Gonzalez CJ, Olaiz-Fernández G, Palma O, Kershenobich D, Sepulveda J. Seroprevalence of hepatitis C in adults in Mexico: an emerging public health problem? Salud Pública Mex. 2007;49(Suppl 3):S395-403.
31. Cruz-Ruiz MA, López-Díaz F, González-Ibarra FP, Lara-Ortega C, Muñoz-Ledo Guzman AL, Patiño-Lopez GA. Prevalence of antibodies for the hepatitis C virus in the low land (bajio) region of Mexico. Arch Med Res. 2013;44:390-3.
32. Campollo O, Roman S, Panduro A, et al. Non-injection drug use and hepatitis C among drug treatment clients in west central Mexico. Drug Alcohol Depend. 2012;123:269-72.
33. Romero-Figueroa S, Ceballos-Salgado E, Santillan-Arreygue L, et al. Risk factors associated with hepatitis C virus infection in an urban population of the state of Mexico. Arch Virol. 2012;157: 329-32.
34. López-Colombo A, Meléndez-Mena D, Sedeño-Monge V, et al. Hepatitis C virus infection in patients and family members attending two primary care clinics in Puebla, Mexico. Ann Hepatol. 2014;13:746-52.
35. Medina-Mora ME, Borges G, Fleiz C, et al. Prevalence and correlates of drug use disorders in Mexico. Rev Panam Salud Publica. 2006;19:265-76.
36. Del Pino N, Oubiña JR, Rodríguez-Frías F, et al. Molecular epidemiology and putative origin of hepatitis C virus in random volunteers from Argentina. World J Gastroenterol. 2013;19:5813-27.
37. Bruggmann P, Berg T, Øvrehus AL, et al. Historical epidemiology of hepatitis C virus (HCV) in selected countries. J Viral Hepat. 2014;(Suppl 1):5-33.
38. Ditah I, Ditah F, Devaki P, et al. The changing epidemiology of hepatitis C virus infection in the United States: National Health and Nutrition Examination Survey 2001 through 2010. J Hepatol. 2014;60:691-8.