
Epidemiology of Hepatitis C Infection and its Public Health Implications in Puerto Rico

CYNTHIA M. PÉREZ, PhD; ERICK SUÁREZ, PhD; ESTHER A. TORRES, MD, FACG*

Hepatitis C infection is the most common chronic blood-borne pathogen in the United States associated with liver cirrhosis and hepatocellular carcinoma and is the leading reason for liver transplantation. It has been estimated that hepatitis C infection may lead to a substantial health and economic burden over the next 10 to 20 years. The prevalence of hepatitis C virus (HCV) infection varies worldwide, with an estimated overall prevalence of 3%. However, the only available data of hepatitis C in the general population of Puerto Rico suggest an elevated prevalence of hepatitis C infection in the municipality of San Juan (6.3%) in comparison with estimates for the adult population residing in the United States (0.9%-3.9%).

Much of the inter-region variability in the prevalence of hepatitis C can be attributable to the frequency and extent to which different risk factors have contributed to the transmission of the virus. Established risk factors for infection include injection drug use, transfusion of blood and solid organ transplantation from infected donors prior to July 1992 and blood clotting products before 1987, occupational injury, vertical transmission, sex with an HCV infected partner,

and multiple sexual partners. Other potential exposures for infection that have been investigated in epidemiologic studies include history of intranasal cocaine use, sharing of contaminated equipment and personal care items, tattooing, body piercing, imprisonment, acupuncture, and use of contaminated healthcare instruments. The high incidence of AIDS in Puerto Rico and the large prevalence observed in Puerto Rican inmates and in adults residing in the municipality of San Juan indicate that HCV infection is an emerging public health concern.

From a public health perspective, potential targets for intervention to decrease the spread of HCV infection, ongoing surveillance, increased clinician awareness of disease reporting systems and the epidemiology and management of hepatitis C, availability of diagnosis and treatment facilities, and recognition of the need for local resources will be of paramount importance to face this silent infection in Puerto Rico.

Keywords: Hepatitis C infection, Prevalence, Mortality, Risk factors, Puerto Rico

Since the discovery of HCV in 1989 and the introduction of tests to detect antibodies to the virus in 1990, significant advances have been made in our understanding of the natural history, prevalence, and modes of transmission; however, much remains to be learned in all these areas. HCV is the most common chronic blood-borne pathogen in the United States associated with liver cirrhosis and hepatocellular carcinoma and is the leading reason for liver transplantation (1-5). Using data from the United Network for Organ Sharing, the

number of patients with HCV who underwent liver transplantation in the United States increased nearly five-fold from 1991 (343 patients) to 2000 (1,679 in 2000) (2). On July 27, 2000, the Assistant Secretary for Health and Surgeon General of the United States, Dr. David Satcher, along with members of the Congress alerted the American public concerning the "silent epidemic" of hepatitis C (6). Towards this end, they distributed a letter explaining the transmission routes of HCV and actions to be taken by individuals at risk.

Using available clinical and epidemiologic data, mathematical models have been used to estimate the overall burden of HCV infection. The number of persons at risk of chronic liver disease and the number of deaths attributed to hepatocellular carcinoma in the United States over the next two to three decades is projected to increase (2,7). Using a Markov computer simulation model, Wong and colleagues estimated future HCV-related morbidity,

From the Department of Biostatistics and Epidemiology, Graduate School of Public Health and the *Department of Medicine, School of Medicine, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico.

Address correspondence to: Cynthia M. Pérez, PhD, Department of Biostatistics and Epidemiology, Graduate School of Public Health, P.O. Box 365067, San Juan, Puerto Rico 00936-5067. E-mail: cperez@rcm.upr.edu Phone: 787-758-2525 extension 1470.

mortality and costs resulting from hepatitis C (7). This model projected 165,900 deaths from chronic liver disease, 27,200 deaths from hepatocellular carcinoma and \$10.7 billion in direct medical expenditures for hepatitis C. These projections suggest that HCV may lead to a substantial health and economic burden over the next 10 to 20 years. More recently, Salomon and colleagues employed an empirically calibrated model to project the future course of HCV infection in the United States (8). Their results indicate that the rates of progression to advanced liver disease may be lower than previously assumed.

Prevalence

The prevalence of HCV infection varies worldwide, with an estimated overall prevalence of 3% or 170 million infected individuals (9,10). It has been reported that the prevalence of HCV infection is lowest in the United Kingdom and Scandinavia (0.01-0.1%), marginally higher in the Americas, Western Europe, Australia, and South Africa (0.2-0.5%); intermediate in Brazil, Eastern Europe, the Mediterranean, the Mideast, and the Indian subcontinent (1-5%); and highest in Egypt where prevalence rates range from 17% to 26%.

According to a recent large-scale epidemiologic survey of the non-institutionalized, civilian population aged 6 years or older conducted in the United States, 1.8% or 3.9 million (95% CI: 3.1 million-4.8 million) persons have been infected with HCV, of which, 2.7 million (95% CI: 2.4 million-3.0 million) have chronic viral infection (11). This prevalence was significantly higher among individuals with the following characteristics: age 30-49 years old, African Americans, males, those below the poverty level, and those

who had completed 12 or fewer years of education (Figure 1). Although this survey included Mexican Americans, it excluded other Hispanic populations that are believed to be at increased risk for HCV infection. Puerto Ricans constitute the third largest Hispanic group in the United States and have been characterized by high rates of human immunodeficiency virus (HIV) infection/AIDS, hepatitis B virus (HBV) infection, tuberculosis, and other sexually transmitted infections (12-14). Serologic surveys conducted in Puerto Rico have been limited to allogeneic blood donors, patients at hemodialysis units, and women attending publicly funded prenatal clinics in San Juan (Table 1)(15-18). These investigations have reported anti-

Table 1. Prevalence of Hepatitis C Infection in Various Population Subgroups, Puerto Rico

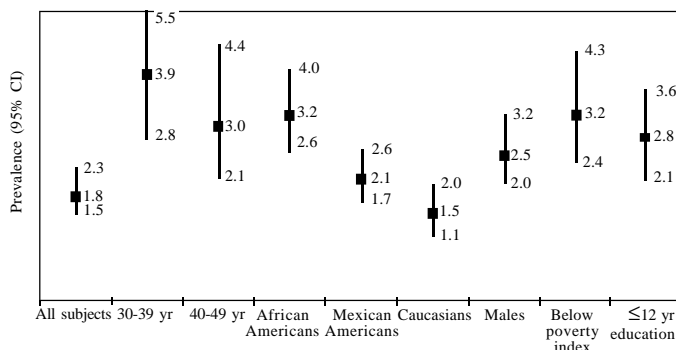
Study	Population	Prevalence
Martínez et al., 1992 (15)	Blood donors	0.79%
Martínez-Díaz et al., 1997 (16)	Blood donors	1.0%
López-Navedo et al., 1999 (17)	Patients attending three hemodialysis units in the western region of Puerto Rico	2.0%
Deseda et al., 1995 (18)	Women attending four public prenatal clinics in San Juan, Puerto Rico	1.9%
	Women with past or current HBV infection	7.7%

HCV prevalence estimates within the values found for the United States population. The only available data of hepatitis C in the general population of Puerto Rico was gathered from a seroprevalence study recently conducted in the municipality of San Juan (19). This study found a prevalence of HCV antibody of 6.3% (95% CI: 5.4%-7.4%)

among adults aged 21 to 64 years, higher than that reported for the non-institutionalized, adult population of the United States (11). A higher prevalence was observed among individuals with the following characteristics: age 30-49 years, male sex, 12 or fewer years of education, and those with public or no health insurance coverage (Figure 2).

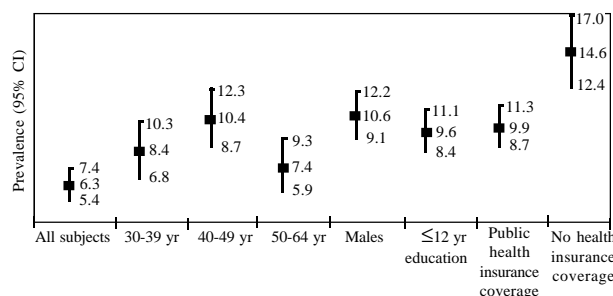
A study conducted among the correctional inmate population in Puerto Rico during 1998 revealed that the prevalence of hepatitis C infection among 11,530 inmates who volunteered for hepatitis C testing was 49.3% (20). The majority of HCV seropositive individuals were males aged 20-29 years (49%) and 30-39 years (36.7%) who reported a history of tattooing practices (80.1%) and injection drug use (68%) as possible routes of transmission. Of 5,686 HCV seropositive inmates, 10.5% were co-infected

Figure 1. Prevalence of Hepatitis C Virus Infection According to Selected Demographics: NHANES III, United States, 1988-1994 (n=21,241)*



*Alter MJ et al. The prevalence of hepatitis C virus infection in the United States, 1998 through 1994. NEJM 1999;341:556-562.

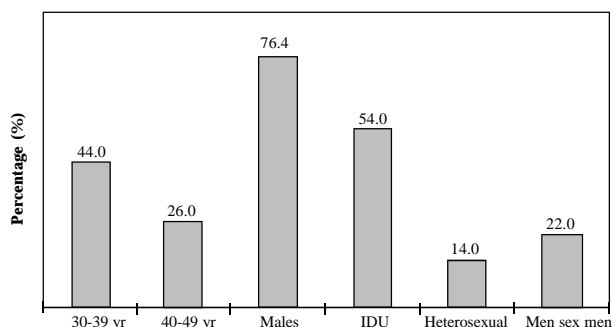
Figure 2. Prevalence of Hepatitis C Virus Infection According to Selected Demographics: San Juan, Puerto Rico, 2001-2002 (n=964)



with HIV. The prevalence of inmates observed in this study is higher than figures reported from other correctional institutions. For example, serologic surveys conducted in inmates of the United States, United Kingdom and Ireland report rates of anti-HCV of 25.2% to 39.4% (21-27). Hammet and colleagues developed estimates of the burden of selected infectious diseases among correctional inmates and releasees during 1997 in the United States (28). This study suggests that 29% to 43% of people with HCV infection in the United States passed through a correctional facility. Appropriate control measures to help reduce continued transmission in this setting are warranted since these individuals represent a source of infection to their communities.

Among 170 patients attending the Liver Transplant Evaluation Clinic at the Puerto Rico Medical Center from 1999 to 2002, the etiology of their liver disease was chronic hepatitis C in 33% of patients and chronic hepatitis C and alcohol abuse in 16% of the patients (29). One would expect a higher prevalence of hepatitis C infection in settings where rates of HIV infection and high-risk behaviors are elevated. For example, Puerto Rico has been disproportionately affected by the HIV epidemic. As of January 30, 2004, 29,055 AIDS cases have been reported to the AIDS Surveillance System of the Puerto Rico Department of Health, of which, 18,249 (63%) have died (13). The majority of the cases were aged 30-39 (44%) and 40-49 (26%) years and the most common exposures were injecting drug use (54%), homosexual contact (22%) and heterosexual contact (14%) (Figure 3). In 2001, Puerto Rico ranked fourth in the incidence rate of AIDS with an annual rate of 32.3 per 100,000 population; this rate was preceded by Washington, DC (152.1 per 100,000), New York (39.3 per 100,000) and Maryland (34.6% per 100,000) (30). Male and female adults and adolescents in Puerto Rico had the third and the sixth largest AIDS rate per 100,000 inhabitants (65.4 per 100,000 and 21.1 per 100,000, respectively) in 2001, respectively, among all states and territories of the United States.

Figure 3. Selected Characteristics of AIDS Cases Reported Through January 30, 2004 to the Puerto Rico AIDS Surveillance System (n=29,055)*



*Puerto Rico Department of Health, Division of Epidemiology, AIDS Surveillance System, 2004

Incidence

HCV initial infection may be asymptomatic in more than 90% of the cases. The asymptomatic and mild nature of the infection in addition to the inability of available serologic tests in distinguishing acute from chronic infection limit the accurate estimation of the incidence of HCV.

Estimates of acute infection derive from a sentinel surveillance system based on selected counties in the United States. After adjusting for under-reporting and asymptomatic infections, the annual incidence of HCV infection in the United States has decreased from an estimated 230,000 cases per year during the decade of the 1980's to 36,000 cases in 1996 (1). This sharp reduction in the number of new cases correlates with a decline in the number of cases among injecting drug users and to testing of blood donors for HCV with a more sensitive test (1).

Risk Factors

Much of the inter-region variability in the prevalence of HCV can be attributable to the frequency and extent to which different risk factors have contributed to the transmission of HCV. Established risk factors for infection include injection drug use, transfusion of blood and solid organ transplantation from infected donors prior to July 1992 and blood clotting products before 1987, nosocomial and occupational exposures (inadequate infection control techniques or disinfection's procedures), vertical transmission, sex with an infected partner, and multiple sexual partners (1,31 - 42). Other potential exposures for infection that have been investigated in epidemiologic studies include history of intranasal cocaine use, sharing of contaminated equipment and personal care items, tattooing, body piercing, imprisonment, acupuncture, and

use of contaminated healthcare instruments (1,37,43-49).

HCV seropositivity has been strongly associated with drug use, and rates of infection among injection drug users are four times higher than rates among the general population. The strongest predictor of hepatitis C infection among injection drug users appears to be duration of injecting. For example, Garfein and colleagues found that HCV seroconversion was significantly associated with injecting for less than two years of experience (49). Díaz and colleagues also found that HCV antibody was associated with having injected for more than three years (44). Thorpe and colleagues found that sexual behaviors were unrelated to seropositivity, and independent drug-related risk factors included frequent injection, heavy crack smoking, injecting in a shooting gallery, and syringe-mediated sharing (47).

Frequency of injection has been consistently found to be higher among Puerto Rican injection drug users than among other groups of injection drug users, and they do so relatively often in high-risk settings in which sterile injecting equipment and cleaning materials are often scarce (50-55). Various researchers have suggested that differences in high-risk behaviors among Puerto Rican injection drug users who reside in the island of Puerto Rico compared with those who reside in New York City may be partially explained by environmental structural differences, including greater availability of needle exchange programs and drug treatment programs and greater access to methadone maintenance treatment programs (54-56). These findings may support the hypothesis that the prevalence of HCV infection may be higher in Puerto Rico and becomes a critical issue in view of the extensive migration and travel to the United States. A probabilistic household survey of substance abuse disorders in the San Juan municipality conducted in 2001-2002 showed that the lifetime prevalence among subjects aged 15-64 years old was 18.1% for illicit drug use, 6.4% for cocaine use, and 1.9% for heroin use (57). Another survey conducted in a probability sample of 14,849 students in grades 7-12, selected from all public and private schools in Puerto Rico during 2000-2002, indicate a 13.1% (95% CI: 11.1%-15.1%) lifetime prevalence of drug use (marihuana, inhalants, cocaine, heroin, and crack)(58). This prevalence increased to 19.1% (95% CI: 17.0%-21.3%) among students in the 10th through 12th grades.

Evidence for transmission of HCV through sexual or household contact has been less clearly defined. Epidemiologic studies that have attempted to estimate the magnitude of an individual's risk of HCV acquisition by sexual contact have suffered methodological flaws including incomplete risk ascertainment in partners and failure to exclude nonsexual sources of transmission such

as injection drug use (59). In addition, a limited number of studies have performed virological analyses to confirm that anti-HCV concordant sexual partners were infected with the same virus. Halfon and collaborators reported virological confirmation of male-to-female sexual transmission of HCV after vaginal and anal intercourse after excluding nonsexual sources of HCV (60). Alter and colleagues found that 10-15% of non-A non-B hepatitis patients had no identifiable risk factor except for sexual or household contact with a patient who had hepatitis C in the past (31). Higher seropositivity for anti-HCV antibodies among high-risk groups such as prostitutes, homosexual men, and heterosexual men attending sexually transmitted disease clinics may support the sexual route as a mode of HCV transmission.

Feldman and colleagues reported evidence of heterosexual transmission of HCV in a sample of inner-city women with no history of injecting drug use (61). Similarly, Hershov et al. found that although injection drug use was the strongest predictor of hepatitis C, sexual risk factors were independently associated (62). This difference in HCV infection rates may reflect differences in sexual risk behaviors or different rates of exposure to nonsexual sources of HCV, including drug use practices and other potential risk factors for infection.

High-risk drug use behaviors and high-risk sexual behaviors further increase the risk of transmission of blood-borne pathogens. These high-risk sexual behaviors include unprotected anal, vaginal, or oral sex, multiple partners, and lack of treatment of sexually transmitted infections, especially those with ulcerative lesions. Zeldis and collaborators reported that 72% of injection drug users in their study were reactive for anti-HCV, 71% were positive for anti-HBV, and 1% for HIV-1 antibody (63). However, more than 85% of subjects infected with HCV or HBV were co-infected with the other virus.

Page-Shafer and colleagues found that women infected with HCV were more likely to have a history of injection and non-injection drug use and to have sexually transmitted infections (64). HCV was independently associated with a history of herpes simplex virus type 2 infection. Dhopes and colleagues found that 80% of injection drug users in an addiction treatment unit had antibodies to HBV and 90% had antibodies to HCV (65). After injection drug users begin to use drugs, they acquire HCV infection more rapidly than other viral infections including HBV and HIV (66). Garfein and colleagues determined that individuals who had been injecting drugs for less than six years had higher seroprevalence rates of HCV and HBV (67). Des Jarlais and collaborators found a low HIV incidence and moderate-to-high HBV/HCV incidence among young injection drug users at two sites

in New York City - Harlem (predominantly African Americans and Hispanics) and Lower East Side, an ethnically diverse, with large transient population of young Whites (68). Friedman and colleagues found evidence to support the hypothesis that hierarchically higher drug use was related to infection among young adults in a high-risk neighborhood (predominantly African Americans and Hispanics) for HIV, hepatitis C, and herpes simplex type 2; and, among young women, for hepatitis B and syphilis (69).

HIV co-infection is associated with higher rates of anti-HCV in persons engaged in higher-risk sexual practices (62,66,70,71). In addition, sexual practices that may traumatize the mucosa are more frequent in HCV seropositive individuals than seronegative, suggesting that these factors increase the sexual transmission of HCV (62,64,66,67). Since these infections share similar risk factors, assessment of HCV co-infection with HIV, HBV, and other sexually transmitted pathogens requires adjustment for potential confounding effects, making sample size estimation an important consideration.

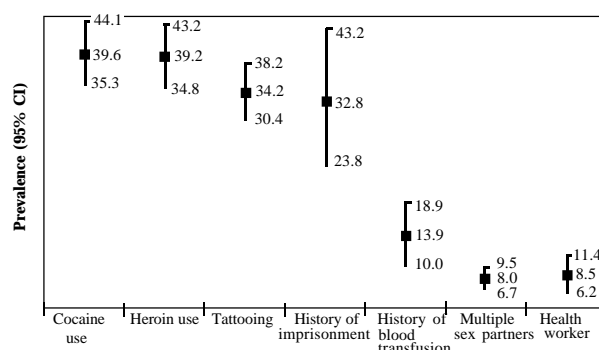
It is estimated that approximately 25%-30% of HIV-infected patients are co-infected with HCV (72). However, the prevalence of HCV infection varies depending on the HIV exposure category. For example, it has been estimated that 50% to 90% of individuals who acquired HIV through injection drug use are co-infected with HCV infection. HIV appears to affect the natural history of HCV infection by accelerating the rate of liver fibrosis and cirrhosis (72,73).

Sharing of injection equipment other than syringes may be an important cause of HCV transmission among injection drug users (47). Among injection drug users who do not share syringes, an important proportion of HCV infections may be attributable to cooker or cotton sharing (45). Although some studies have found an association between tattooing and HCV infection in highly selected populations (42-44,74-77), it is not known if these results can be generalized to the general population. One community-based seroepidemiologic survey of hepatitis C in Catalonia (Northeastern Spain) found that tattoos were significantly associated with infection (78). Other potential modes of unapparent blood contact include body piercing and folk medicine (79). Further studies are needed to determine if these types of exposures, and the settings in which they occur, are risk factors for HCV infection. Many of the studies reported in the literature have been performed in special populations such as sex workers, homosexual and bisexual men, and injection drug users and their partners. Therefore, it is not possible to determine whether the study groups differ from other segments of the population with regard to the exposures of interest.

Analysis of correlates of HCV infection among Puerto

Rican adults revealed that those who reported a history of cocaine or heroin use, tattooing practices, history of imprisonment, history of blood transfusion prior to 1993, multiple sex partners, and health workers had a significantly larger prevalence than those without such history (Figure 4) (19). Among drug users, the prevalence of hepatitis C infection was significantly higher in individuals who reported sharing cookers and filter cotton and in individuals who reported injection with a syringe previously used by another injector (data not shown).

Figure 4. Prevalence of Hepatitis C Virus Infection According to HCV Correlates: San Juan, Puerto Rico, 2001-2002 (n=964)



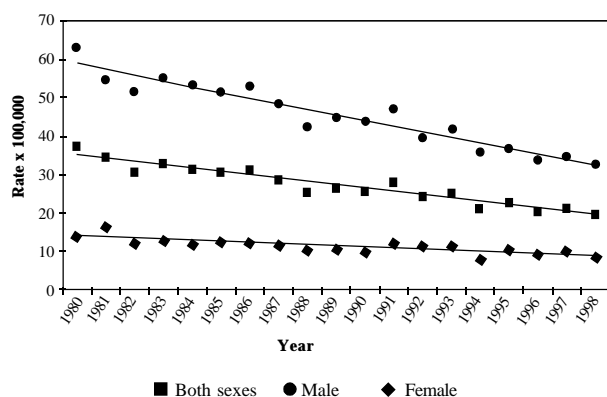
Mortality

The Centers for Disease Control and Prevention estimates that HCV causes approximately 8,000 to 10,000 deaths each year and predicts that the number of deaths in the United States due to hepatitis C complications may double or triple over the next 20 years (1,80). In 1998, liver disease and cirrhosis (ICD-9 571) was the tenth leading cause of death in the U.S., responsible for 1.1% (25,192) of all deaths reported (80). When other diagnoses related to liver disease (viral hepatitis, primary liver cancer, intrahepatic bile duct cancer, esophageal varices, fulminant liver disease, hepatic coma, portal hypertension, hepatorenal syndrome, other sequelae of chronic liver disease, hepatitis – unspecified, other specified disorder of the liver and unspecified disorder of the liver) are taken into account, the number of deaths attributable to liver disease and cirrhosis in the United States increases from 25,192 to 44,677 for 1998, ranking as the eighth leading cause of death. Liver disease and cirrhosis have accounted for nearly 2.2% to 3.1% of all deaths reported in Puerto Rico for the past two decades, ranking between the eighth and eleventh cause of death (81). In 1998, liver disease and cirrhosis was also the tenth leading cause of death in Puerto Rico but ranked as the fifth leading cause of death among individuals aged 35-39 years and fourth leading

cause of death among subjects aged 40 to 64 years.

Analysis of vital registration data for the years 1980 through 1998 in Puerto Rico revealed that there has been a steady decline in the age-adjusted death rates due to liver disease and cirrhosis, from 37.2 per 100,000 in 1980 to 19.6 per 100,000 in 1998 (Figure 5). Similar trends were seen among males (from 63.0 x 100,000 in 1980 to 32.8 x 100,000 in 1998) and females (from 13.9 x 100,000 in 1980 to 8.4 x 100,000 in 1998). This pattern is consistent with that observed for the United States, where age-adjusted death

Figure 5. Age-Adjusted Mortality Rates Due to Chronic Liver Disease and Cirrhosis (ICD-9=571) in Puerto Rico, 1980-1998*



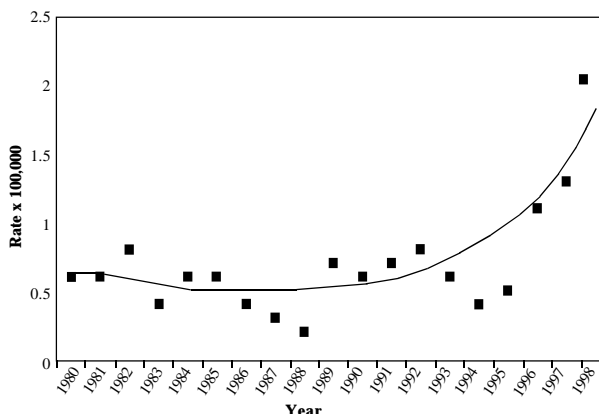
*Age-adjusted to the U.S. 2000 population census. Locally weighted polynomial regression curves were employed to describe the trend in mortality rates.

rates from liver disease and cirrhosis have decreased in the past two decades (80). However, a small increase in the age-adjusted death rate during the 1990s (from 16.1 per 100,000 in 1991 to 16.7 in 1998) was noted in the United States, and this increase has been mainly attributed to viral hepatitis and hepatocellular carcinoma. In fact, the age-adjusted death rate for hepatocellular carcinoma in the United States has increased from 1.8 per 100,000 during the time period 1979-1983 to 3.1 per 100,000 during the time period 1994-1998(3). Using an expanded definition of chronic liver disease, Vong and Bell also found that mortality declines of chronic liver disease during the early 1990s were not sustained after 1994 (82). Of the deaths reported during this period, 39% were alcohol related, 15% were attributed to HCV infection, and 4% were attributed to HBV infection, and age-adjusted rates were higher among males and among Hispanics.

The annual number of deaths in Puerto Rico for which viral hepatitis (ICD-9 070) was the underlying cause of death on death certificates in 1980 increased six-fold in 1998. Throughout most of the 1980s, the age-adjusted death rate remained relatively constant; however, there has been a marked increase after 1995 (Figure 6), reaching a rate of 2.1 per 100,000 in 1998. A similar pattern has been

observed in the United States, where the age-adjusted death rates due to viral hepatitis increased from 0.4 to 1.8 deaths per 100,000 during the period 1980-1999 (2). Vong

Figure 6. Age-Adjusted Mortality Rates Due to Viral Hepatitis (ICD-9=070) in Puerto Rico, 1980-1998*



*Age-adjusted to the U.S. 2000 population census. Locally weighted polynomial regression curves were employed to describe the trend in mortality rates.

and Bell evidenced that the number of chronic liver disease deaths and proportion attributable to viral hepatitis during the time period of 1990 to 1998 increased by 23% and 19%, respectively (82).

Preventive Measures

Two objectives of the Healthy People 2010 are directed towards preventing disease, disability, and death from hepatitis C (14-9) and identifying persons with chronic hepatitis C (14-10)(83). In addition, the National Institutes of Health have developed a strategic plan to reduce and ultimately eliminate health disparities among racial and ethnic minorities (84). One of the major areas of disparity is hepatitis C since it is estimated that 44.3% of HCV-infected individuals are minorities; however, efforts of the National Institute of Allergy and Infectious Diseases are being focused on the promotion of liver wellness and prevention of hepatitis C, especially among African-Americans. In view of the growing body of information regarding the management and treatment of hepatitis C, an update of the Consensus Development Conference on Management of Hepatitis C was held June, 2002(85). One of the recommendations of the Consensus Panel was to expand research aimed at understanding the natural history, prevention and treatment of hepatitis C, particularly in special populations such as incarcerated persons, individuals of low socioeconomic status, the elderly, the homeless and ethnic minorities (86).

Education of the general public regarding hepatitis C

and improved awareness among individuals who received blood products before July 1992 and those exposed to high-risk behaviors should be enhanced. Health care providers should also review the current state of knowledge on hepatitis C prevention, diagnosis and medical management so that disease prevention, counseling, testing and follow-up can be delivered effectively.

Surveillance is a critical component of any public health program. Public health surveillance has been defined as the ongoing, systematic collection, analysis, interpretation, and dissemination of data regarding a health-related event for use in public health action to reduce morbidity and mortality and to improve health (87). Surveillance provides the basis for determining the public health priorities and for planning and implementing prevention and control programs. In July 1998, the Centers for Disease Control and Prevention (CDC) staff and field experts developed recommendations for the prevention and control of HCV infection and its related complications (1). To reduce the burden of hepatitis C, preventive measures must be implemented to reduce the risk of acquiring the infection and to reduce the risk of chronic liver disease and other complications. In addition, surveillance and evaluation activities should also be taken to examine the potential impact of various interventions aimed at reducing disease incidence, identifying individuals infected with HCV, and providing appropriate treatment, counseling and follow-up (1). To accomplish the objectives of hepatitis C surveillance, the following approaches were recommended:

- Surveillance for hepatitis C - Hepatitis C is one of the 72 notifiable diseases mandated by the Puerto Rico Department of Health for reporting (See Executive Order #177 of January 1, 2003. (Appendix 1 p.23) using standard case definitions (88-90). All health care providers are required to report all cases of hepatitis C to the Epidemiology Division of the Puerto Rico Department of Health within five working days after being suspected or diagnosed (Category I Reporting). The CDC recommends that as hepatitis C prevention and control programs are implemented, federal, state and local agencies must determine the best methods to monitor disease trends, in view of the limited resources to determine if a laboratory report represents acute infection, chronic infection, repeated testing or a false-positive result (1).
- Development of a registry of HCV infection can provide information regarding the disease burden, more specifically, estimation of prevalence/incidence, mortality, morbidity, and direct and

indirect health care costs. For example, laboratory reports constitute an important source for determining the proportion of infected individuals who require counseling and medical management (1).

- Conduct of periodic serologic surveys in Puerto Rico are needed to provide critical information on the magnitude and changing patterns of the infection and to evaluate preventive strategies (1). Until recently, no island-wide serologic surveys have been conducted. To address this issue, a group of investigators of the University of Puerto Rico, Medical Sciences Campus has taken the initiative to seek federal funds to conduct a cross-sectional survey aimed at estimating the seroprevalence of hepatitis C, assessing patterns of co-infections and determining risk factors for infection for the Puerto Rico household, adult population and for specific population groups defined by age, sex, and geographic stratification regions. Such study is critical to understand the epidemiology of HCV infection and to develop appropriate prevention programs; this effort is consistent with the NIH Strategic Research Plan to Reduce and Ultimately Eliminate Health Disparities for the fiscal years 2002-2006 (84). Questions concerning the epidemiology of hepatitis C that remain unanswered primarily concern the magnitude of the risk attributable to sexual transmission, illegal non-injecting drug use, sexually transmitted infections as cofactors for sexual transmission of HCV, tattooing and body piercing. Therefore, additional efforts to seek funds to conduct epidemiologic studies aimed at answering these questions must be undertaken.
- Surveillance of chronic liver disease can provide information on the burden of disease, determine the natural history and risk factors for HCV infection, and evaluate the effect of therapeutic interventions on the incidence and severity of disease (1). A sentinel surveillance pilot program for physician-diagnosed chronic liver disease is under way in the United States. This network is expected to provide baseline data and a model for a comprehensive sentinel surveillance system for chronic liver disease.

In addition to these efforts, analysis of other data sources must be performed. For example, insurance claims of patients who have received services for chronic HCV infection could provide an estimate of the economic impact of treatment and health services utilization of the insured population. Moreover, continued analysis of mortality

data due to hepatitis C and related complications should be conducted to facilitate the planning of public health services in this population. In addition, the underlying factors associated with the apparent increase in hepatitis C mortality merit further investigation.

Conclusions

The high incidence of AIDS in Puerto Rico and the large prevalence observed in Puerto Rican inmates and in adults residing in the municipality of San Juan indicate that HCV infection is a public health concern. Efforts to enhance awareness of local laws requiring health care providers and laboratories to report hepatitis C to public health authorities is a key element to an effective surveillance.

From a public health perspective, potential targets for intervention to decrease the spread of HCV infection, ongoing surveillance, increased clinician awareness of disease reporting systems and the epidemiology and management of hepatitis C, availability of diagnosis and treatment facilities, and recognition of the need for local resources will be of paramount importance to face this emerging infection in Puerto Rico.

Resumen

La infección con el virus de hepatitis C es la causa principal de cirrosis, cáncer hepático y trasplante de hígado en los Estados Unidos. Se ha estimado que la infección con el virus de hepatitis C puede acarrear un impacto sustancial en el estado de salud y la economía en las próximas dos décadas. La prevalencia de hepatitis C es alrededor de 3%, pero varía a nivel mundial. Sin embargo, los únicos datos disponibles en la población general de San Juan, Puerto Rico revelan que la prevalencia (6.3%) es mayor que la informada en la población adulta de los Estados Unidos (0.9%-3.9%). La variabilidad geográfica observada en la prevalencia de hepatitis C se puede atribuir a la frecuencia y la extensión de los factores de riesgo. Entre los factores de riesgo establecidos para hepatitis C se encuentran el uso de drogas inyectables, transfusiones de sangre y trasplantes de órganos de donantes infectados antes de julio de 1992 y productos sanguíneos antes de 1987, exposiciones ocupacionales, transmisión vertical, relaciones sexuales con una pareja infectada, y múltiples parejas sexuales. Otras exposiciones investigadas incluyen historial de uso de cocaína intranasal, compartir equipo contaminado e ítemes de cuidado personal, prácticas de tatuajes y perforaciones corporales, historial de prisión, acupuntura y uso contaminado de instrumentos utilizados en el cuidado de salud. La alta incidencia de SIDA en Puerto Rico y la alta prevalencia de hepatitis C en

las cárceles y en la población adulta de San Juan indican que la hepatitis C es un problema emergente de salud pública. Desde una perspectiva de salud pública, métodos de intervención para disminuir la transmisibilidad del virus, vigilancia eficiente, mayor conocimiento de los profesionales de la salud en las áreas de notificación obligatoria de enfermedades y la epidemiología y el manejo de hepatitis C, disponibilidad de facilidades para el diagnóstico y el tratamiento, y reconocimiento de la necesidad de recursos locales son de gran importancia para enfrentar esta infección silente en Puerto Rico.

References

1. Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *MMWR* 1998;47:1-39.
2. Kim WR. The burden of hepatitis C in the United States. *Hepatology* 2002;36:S30-S34.
3. El-Serag HB. Hepatocellular carcinoma and hepatitis C in the United States. *Hepatology* 2002;36:S74-S83.
4. Kim WR. Global epidemiology and burden of hepatitis C. *Microbes Infect* 2002;4:1219-1225.
5. Tanaka Y, Hanada K, Mizokami M, Yeo AE, Shih JW, Gojbori T, Alter HJ. A comparison of the molecular clock of hepatitis C virus in the United States and Japan predicts that hepatocellular carcinoma incidence in the United States will increase over the next two decades. *Proc Natl Acad Sci* 2002;99:15584-15589.
6. Satcher D. The letter from the Surgeon General. Washington, DC: Office of the Surgeon General. Retrieved March 26, 2004 from www.surgeongeneral.gov/topics/hepatitisc/letter.htm.
7. Wong JB, McQuillan GM, McHutchison JG, Poynard T. Estimating future hepatitis C morbidity, mortality, and costs in the United States. *Am J Public Health* 2000; 90: 1562-1569.
8. Salomon JA, Weinstein MC, Hammit JK, Goldie SJ. Empirically calibrated model of hepatitis C virus infection in the United States. *Am J Epidemiol* 2002;156:761-773.
9. World Health Organization. Global surveillance and control of hepatitis C. Report of a WHO consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. *J Viral Hepat* 1999;6:35-47.
10. Wasley A, Alter MJ. Epidemiology of hepatitis C: Geographic differences and temporal trends. *Semin Liver Dis* 2000;20:1-16.
11. Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, Kaslow RA, Margolis HS. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med* 1999;341:556-562.
12. Therrien M, Ramírez R. The Hispanic population in the United States: March 2000. *Current Population Reports*, P20-535. U.S. Census Bureau, Washington, DC, 2000.
13. Puerto Rico Department of Health, Division of Epidemiology, AIDS Surveillance System, 2004.
14. Estrada AL. Epidemiology of HIV/AIDS, hepatitis B, hepatitis C, and tuberculosis among minority injection drug users. *Public Health Reports* 2002;117:S126-S134.
15. Martínez J, Rubio CE, Oharriz JJ, et al. Hepatitis C antibody in healthy Puerto Rican blood donors: Prevalence, hepatic functional and histological abnormalities. *Bol Asoc Med PR* 1992;84:94-96.
16. Martínez-Díaz H, Frye-Maldonado AC, Climent-Peris C, Vélez-

- Rosario. Evaluation of serologic markers for transfusion transmitted infectious diseases in allogeneic blood donors in Puerto Rico. *P R Health Sci J* 1997;16:255-258.
17. López-Navedo PJ, Lebrón-Rivera R, González-Trápaga J et al. Prevalence of hepatitis C virus infection at three hemodialysis units in the western region of Puerto Rico. *Bol Asoc Med PR* 1999;91:100-102.
 18. Deseda CC, Sweeney PA, Woodruff BA, et al. Prevalence of hepatitis B, hepatitis C and human immunodeficiency virus infection among women attending prenatal clinics in San Juan, Puerto Rico, from 1989-1990. *Obstet Gynecol* 1995;85:75-78.
 19. Pérez CM, Suárez E, Román K, Colón V, Torres EA. Seroprevalence of hepatitis C virus antibody in adults of Hispanic origin. Poster session presented at the annual meeting of the American Public Health Association. November 2002, Philadelphia, PA. 20.
 20. Colón-Renta M. Perfil histórico del tratamiento del VHC en el Programa de Servicios de Salud Correccional. *El Nuevo Día* 2003 May 16; Suplementos, p. 7.
 21. Vlahov D, Nelson KE, Quinn TC, Kendig N. Prevalence and incidence of hepatitis C virus infection among male prison inmates in Maryland. *Eur J Epidemiol* 1993;9:566-569.
 22. Spaulding A, Greene C, Davidson K, Schneidermann M, Rich J. Hepatitis C in correctional facilities. *Prev Med* 1999;28:92-100.
 23. Ruiz JD, Molitor F, Sun RK, Mikanda J, Facer M, Colford JM, Rutherford GW, Ascher MS. Prevalence and correlates of hepatitis C virus infection among inmates entering the California correctional system. *West J Med* 1999;170:156-160.
 24. Solomon L, Flynn C, Muck K, Vertefeuille J. Prevalence of HIV, syphilis, hepatitis B, and hepatitis C among entrants to Maryland correctional facilities. *J Urban Health* 2004;81:25-37.
 25. Skipper C, Guy JM, Parkes J, Roderick P, Rosenberg WM. Evaluation of prison outreach clinic for the diagnosis and prevention of hepatitis C: Implications for the national strategy. *Gut* 2003;52:1500-1504.
 26. Baillargeon J, Wu H, Kelley MJ, Grady J, Linthicum L, Dunn K. Hepatitis C seroprevalence among newly incarcerated inmates in the Texas correctional system. *Public Health* 2003;117:43-48.
 27. Long J, Allwright S, Barry J, Sheilagh RR, Thornton L, Bradley F, Parry J. Prevalence of antibodies to hepatitis B, hepatitis C, and HIV and risk factors in entrants to Irish prisons: A national cross sectional survey. *Br Med J* 2001;323:1-6.
 28. Hammett TM, Harmon MP, Rhodes W. The burden of infectious disease among inmates of and releasees from US correctional facilities, 1997. *Am J Public Health* 2002;92:1789-1794.
 29. Guzmán A, Vázquez M, Just E, Torres EA. Perfil de una clínica de evaluación para trasplante de hígado de Puerto Rico. Poster session at the annual meeting of the *XVII Congreso Bienial de la ALEH y XXIX Congreso Chileno de Gastroenterología. Diciembre 2002, Santiago de Chile, Chile.*
 30. Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report, 2002;13:1-44.
 31. Alter MJ, Purcell RH, Shih JW, Melpolder JC, Houghton M, Choo QL, Kuo G. Detection of antibody to hepatitis C in prospectively followed transfusion recipients with acute and chronic non-A, non-B hepatitis. *N Engl J Med* 1989;321:1494-1500.
 32. Aach RD, Stevens CE, Hollinger FB, Mosley JW, Peterson DA, Taylor PE, Johnson RG, Barbosa LH, Nemo GJ. Hepatitis C virus infection in post-transfusion hepatitis: An analysis with first-and second-generation assays. *N Engl J Med* 1991;325:1325-9.
 33. Pereira BJ, Milford EL, Kirkman RL, Levey AS. Transmission of hepatitis C virus by organ transplantation. *N Engl J Med* 1991;325:454-460.
 34. Pereira BJ, Milford EL, Kirkman RL, Quan S, Sayre KR, Johnson PF, Wilber JC, Levey AS. Prevalence of hepatitis C virus RNA in organ donors positive for hepatitis C antibody and in the recipients of their organs. *N Engl J Med* 1992;327:910-915.
 35. Pereira BJ. Hepatitis C in organ transplantation: Its significance and influence on transplantation policies. *Curr Opin Nephrol Hypertens* 1993;2:912-22.
 36. Alter MJ, Gerety RJ, Smallwood LA, Sampliner RE, Tabor E, Deinhardt F, Frosner G, Matanoski GM. Sporadic non-A non-B hepatitis: Frequency and epidemiology in an urban United States population. *J Infect Dis* 1982;145:886-893.
 37. Puro V, Petrosillo N, Ippolito G for the Italian Study Group on Occupational Risk of HIV and Other Blood-borne Infections. Risk of hepatitis C seroconversion after occupational exposures in health care workers. *Am J Infect Control* 1995;23:273-277.
 38. Yeung LT, King SM, Roberts EA. Mother-to-infant transmission of hepatitis C virus. *Hepatology* 2001;34:223-229.
 39. Lanphear BP, Linnemann CC, Cannon CG, DeRonde MM, Pandy L, Kerley LM. Hepatitis C virus infection in healthcare workers: Risk of exposure and infection. *Infect Control Hosp Epidemiol* 1994;15:745-750.
 40. Roberts EA, Yeung L. Maternal-infant transmission of hepatitis C virus infection. *Hepatology* 2002;36:S106-S113.
 41. Matsubara T, Sumazaki R, Takita H. Mother-to-infant transmission of hepatitis C virus: A prospective study. *Eur J Pediatr* 1995;154:973-978.
 42. Balasekaran R, Bulterys M, Jamal MM et al. A case-control study of risk factors for sporadic hepatitis C virus infection in the southwestern United States. *Am J Gastroenterol* 1999;94:1341-1346.
 43. Haley RW, Fischer RP. Commercial tattooing as a potentially important source of hepatitis C infection: Clinical epidemiology of 626 consecutive patients unaware of their hepatitis C serologic status. *Medicine* 2001;80:134-151.
 44. Díaz T, Des Jarlais DC, Vlahov D, Perlis TE, Edwards V, Friedman SR, Rockwell R, Hoover D, Williams IT, Monterroso ER. Factors associated with prevalent hepatitis C: Differences among young adult injection drug users in lower and upper Manhattan, New York City. *Am J Public Health* 2001;9:23-30.
 45. Hagan H, Thiede H, Weiss NS, Hopkins SG, Duchin JS, Alexander ER. Sharing of drug preparation equipment as a risk factor for hepatitis C. *Am J Public Health* 2001;91:42-46.
 46. Thorpe LE, Ouellet LJ, Levy JR et al. Hepatitis C virus infection: Prevalence, risk factors, and prevention opportunities among young injection drug users in Chicago, 1997-1999. *J Infect Dis* 2000;182:1588-1594.
 47. Thorpe LE, Ouellet LJ, Hershov R, Bailey S, Williams IT, Williamson J, Monterroso ER, Garfein RS. Risk of hepatitis C virus infection among young adult injection drug users who share injection equipment. *Am J Epidemiol* 2002;155:645-653.
 48. Nishioka S, Gyorkos TW, Joseph L, Collet JP, Maclean JD. Tattooing and risk for transfusion-transmitted diseases: The role of the type, number and design of the tattoos and the condition in which they were performed. *Epidemiol Infect* 2002;128:63-71.
 49. Garfein RS, Doherty MC, Monterroso ER, Thomas DI, Nelson KE, Vlahov D. Prevalence and incidence of hepatitis C virus

- infection among young adult injection drug users. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;18:S11-S19.
50. Freeman RC, Williams ML, Saunders LA. Drug use, AIDS knowledge, and HIV risk behaviors of Cuban, Mexican, and Puerto Rican born drug injectors who are recent entrants into the United States. *Subst Use Misuse* 1999;34:1765-1793.
 51. Deren S, Robles R, Andía J, Colón HM, Kang SY, Perlis T. Trends in HIV seroprevalence and needle sharing among Puerto Rican drug injectors in Puerto Rico and New York: 1992-1999. *J Acquir Immune Defic Syndr* 2001;26:164-169.
 52. Colón HM, Robles RR, Deren S, Sahai H, Finlinson HA, Andía J, Cruz MA, Kang SY, Oliver-Vélez D. Between-city variation in frequency of injection among Puerto Rican injection drug users: East Harlem, New York, and Bayamón, Puerto Rico. *J AIDS* 2001;27:405-413.
 53. Deren S, Oliver-Vélez D, Finlinson A, Robles R, Andía J, Colón HM, Kang SY, Shedlin M. Integrating qualitative and quantitative methods: Comparing HIV-related risk behaviors among Puerto Rican drug users in Puerto Rico and New York. *Subst Use Misuse* 2003;38:1-24.
 54. Deren S, Kang SY, Colón HM, Andía JF, Robles RR, Oliver-Vélez D, Finlinson A. Migration and HIV risk behaviors: Puerto Rican drug injectors in New York City and Puerto Rico. *Am J Public Health* 2003;93:812-816.
 55. Finlinson HA, Oliver-Vélez D, Colón HM, Deren S, Robles RR, Beardsley M, Cant JGH, Andía J, Soto-López M. Syringe acquisition and use of syringe exchange programs by Puerto Rican drug injectors in New York and Puerto Rico: Comparisons based on quantitative and qualitative methods. *AIDS and Behavior* 2000;4:341-351.
 56. Robles RR, Colón HM, Matos TD, Finlinson HA, Muñoz A, Marrero CA, García M, Reyes JC. Syringe and needle exchange as HIV/AIDS prevention for injection drug users in Puerto Rico. *Health Policy* 1998;45:209-220.
 57. Puerto Rico Mental Health and Anti-Addiction Services Administration. Puerto Rico Substance Abuse Needs Assessment Program: 2002 Household Study Final Results. San Juan, 2002.
 58. Moscoso MR, Colón HM, Parrilla I, Reyes JC. El uso de substancias en los escolares puertorriqueños: Consulta Juvenil V, 2000-2002. Bayamón, Puerto Rico: Centro de Estudios en Adicción, Departamento de Medicina de Familia y Salud Comunal, Universidad Central del Caribe y Administración Auxiliar de Prevención y Promoción de la Salud Mental, Administración de Servicios de Salud Mental y Contra la Adicción, 2003.
 59. Terrault NA. Sexual activity as a risk factor for hepatitis C. *Hepatology* 2002;36:S99-S105.
 60. Halfon P, Riflet H, Renou C, Quentin Y, Cacoub P. Molecular evidence of male-to-female sexual transmission of hepatitis C virus after vaginal and anal intercourse. *J Clin Microbiol* 2001;39:1204-1206.
 61. Feldman JG, Minkoff H, Landesman S, Dehovitz J. Heterosexual transmission of hepatitis C, hepatitis B, and HIV-1 in a sample of inner city women. *Sex Transm Dis* 2000;27:338-342.
 62. Hershov RC, Kalish LA, Sha B, Till M, Cohen M. Hepatitis C virus infection in Chicago women with or at risk for HIV infection: Evidence for sexual transmission. *Sex Transm Dis* 1998;25:527-532.
 63. Zeldis JB, Jain S, Kuramoto IK, Richards C, Sazama K, Samuels S, Holland PV, Flynn N. Seroepidemiology of viral infections among intravenous drug users in northern California. *West J Med* 1992;156:30-35.
 64. Page-Shafer KA, Cahoon-Young B, Klausner JD, Morrow S, Molitor F, Ruiz J, McFarland W for the Young Women's Survey Team. Hepatitis C virus infection in young, low-income: The role of sexually transmitted infection as a potential cofactor for HCV infection. *Am J Public Health* 2002; 92: 670-676.
 65. Dhopes VP, Taylor KR, Burke VM. Survey of hepatitis B and C in addiction treatment unit. *Am J Drug Alcohol Abuse* 2000;26:703-707.
 66. Thomas D, Zenilman J, Alter MH, Shih J, Galai N, Carella A, Quinn T. Sexual transmission of hepatitis C among patients attending sexually transmitted diseases clinics in Baltimore: An analysis of 309 sex partnerships. *J Infect Dis* 1995;171:768-775.
 67. Garfein RS, Vlahov D, Galai N, Doherty MC, Nelson E. Viral infections in short-term injection drug users: The prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses. *Am J Public Health* 1996;86:655-661.
 68. Des Jarlais DC, Díaz T, Perlis T, Vlahov D, Maslow C, Latka M, Rockwell R, Edwards V, Friedman S, Monterroso E, Williams I, Garfein RS. Variability in the incidence of human immunodeficiency virus, hepatitis B virus, and hepatitis C virus infection among young injecting drug users in New York City. *Am J Epidemiol* 2003;157:467-471.
 69. Friedman SR, Flom PL, Kottiri BJ, Zenilman J, Curtis R, Neaigus A, Sandoval M, Quinn T, Des Jarlais D. Drug use patterns and infection with sexually transmissible agents among young adults in a high-risk neighbourhood in New York City. *Addiction* 2003;98:159-169.
 70. Filippini P, Coppola N, Scolastico C, Rossi G, Onofrio M, Sagnelli E, Piccinino F. Does HIV infection favor the sexual transmission of hepatitis C? *Sex Transm Dis* 2001;28:725-729.
 71. Ndimbie OK, Kingsley LA, Nedjar S, Rinaldo CR. Hepatitis C virus infection in a male homosexual cohort: Risk factor analysis. *Genitourin Med* 1996;72:213-216.
 72. Thomas DL. Hepatitis C and human immunodeficiency virus infection. *Hepatology* 2002; 36: S201-S209.
 73. Mohsen AH, Easterbrook PJ, Taylor C, Portmann B, Kulasegaram R, Wiselka M, Norris S. Impact of human immunodeficiency virus (HIV) on the progression of liver fibrosis in hepatitis C virus infected patients. *Gut* 2003;52:1035-1040.
 74. Brandao AB, Fuchs SC. Risk factors for hepatitis C virus infection among blood donors in southern Brazil: A case-control study. *BMC Gastroenterol* 2002;2:18.
 75. Gyarmathy VA, Neaigus A, Miller M, Friedman SR, Des Jarlais DC. Risk correlates of prevalent HIV, hepatitis B virus, and hepatitis C virus infections among noninjecting heroin users. *J Acquir Immune Defic Syndr* 2002;30:448-456.
 76. Campello C, Polli A, Dal MG, Besozzi-Valentini F. Seroprevalence, viremia, and genotype distribution of hepatitis C virus: A community-based population study in northern Italy. *Infection* 2002;30:7-12.
 77. Haley RW, Fischer RP. The tattooing paradox: Are studies of acute hepatitis adequate to identify routes of transmission of subclinical hepatitis C infection? *Arch Intern Med* 2003 May 12;163:1095-1098.
 78. Domínguez A, Bruguera A, Vidal J, Plans P, Salleras L. Community-based seroepidemiological survey of HCV infection in Catalonia, Spain. *J Med Virol* 2001;65:688-693.
 79. MacDonald M, Crofts N, Kaldor J. Transmission of hepatitis C virus: Rates, routes, and cofactors. *Epidemiol Rev* 1996;18:137-147.
 80. Kim WR, Brown RS, Terrault NA, El-Serag H. Burden of liver disease in the United States: Summary of a workshop. *Hepatology* 2002;36:227-242.
 81. Informe Anual de Estadísticas Vitales de Puerto Rico, 1980-

- 1998, Departamento de Salud, SAPEE, División de Estadísticas, San Juan, Puerto Rico.
82. Vong S, Bell BP. Chronic liver disease mortality in the United States, 1990-1998. *Hepatology* 2004;39:476-483.
83. U.S. Department of Health and Human Services. *Healthy People 2010: Understanding and improving health*. 2nd edition. Washington, DC: U.S. Government Printing Office, November 2000.
84. National Institute of Allergy and Infectious Diseases, National Institutes of Health. *NIAID Strategic Plan for Addressing Health Disparities: Fiscal Years 2002-2006*.
85. National Institutes of Health Consensus Development Conference. *Management of hepatitis C*. *Hepatology* 2002;36:S3-20.
86. Strader DB. Understudied populations with hepatitis C. *Hepatology* 2002;36:S226-S236.
87. Thacker SB. Historical development. In: Teutsch SM, Churchill RE (eds.). *Principles and practice of public health surveillance*, 2nd edition. New York, NY: Oxford University Press, 2000.
88. Departamento de Salud, Estado Libre Asociado de Puerto Rico. Orden Administrativa #177, 1 de enero de 2003. Retrieved April 5, 2004 from <http://www.salud.gov.pr>
89. Centers for Disease Control and Prevention. Hepatitis C virus infection (past or present): 2003 case definition. Retrieved April 7, 2004 from <http://www.cdc.gov/epo/dphsi/casedef/hepatitiscurrent.htm>
90. Centers for Disease Control and Prevention. Acute Hepatitis C: 2004 case definition. Retrieved April 7, 2004 from <http://www.cdc.gov/epo/dphsi/casedef/hepatitiscacutecurrent.htm>
-
-