

Prevention and control of viral hepatitis in Spain

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Part I Prevention and control of viral hepatitis in Spain – bibliography (in alphabetical order) –

Alvarez do Barrio M, Gonzalez Diez R, Hernandez Sánchez JM, Oyonarte Gomez S.

Residual risk of transfusion-transmitted viral infections in Spain, 1997-2002, and impact of nucleic acid testing. *Euro Surveill* 2005; 10:20-22.

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Estimates of the risk of bloodborne viral infections are essential for monitoring the safety of the blood supply and the impact of new screening tests. Incidence rates of seroconversion and the residual risk for HBV, HIV and HCV were calculated among Spanish repeat donors between 1997 and 1999 at 22 blood donation centres, and at 7 centres between 2000 and 2002. The residual risk per million donations was estimated to be 18.67 for HBV, 2.49 for HIV and 10.96 for HCV (between 1997 and 1999). For the 2000-2002 period, the residual risk per million donations was estimated to be 9.78 for HBV, 2.48 for HIV and 3.94 for HCV. Between 1999 and 2003, about 3.4 million donations were tested by NAT, mainly in pools of 44 donations, in 12 of the 22 Spanish blood donation centres participating in the study. Eight anti-HCV negative and HCV-RNA positive donations were found, which represent an approximate yield of 1/420,000, versus a projected yield of 1/240,000 obtained from 1995-1997 data. The residual risks of transfusion-transmitted viral infections in Spain were low, and with the implementation of NAT these risks are even lower.

Amela C, Pachón I, Bueno R, de Miguel C, Martínez-Navarro F. Trends in hepatitis A virus infection with reference to the process of urbanization in the greater Madrid area (Spain). *Eur J Epidemiol* 1995; 11:569-573.

National Centre of Epidemiology, Instituto de Salud Carlos III, Madrid, Spain.

Hepatitis A is an infection transmitted by the faecal-oral route. Endemicity within a specific country is directly related to sanitation and hygienic standards, while being inversely related to socioeconomic conditions. We studied how the process of urbanisation witnessed in Madrid had influenced the transmission of hepatitis A infection. In the Madrid Autonomous Region, this process first began in the early sixties and was not brought to a close until the late seventies. Catalytic models were used to estimate the annual infection rate, lambda, on the basis of seroprevalence data stratified by age. A cohort effect related to a fall-off in infancy-related hepatitis A virus (HAV) is to be observed in the results for the last few years. The model permits four birth cohort-based groups to be differentiated by lambda: individuals born pre-1960, lambda = 0.082 (95% CI 0.095-0.070); those born in the early sixties, lambda = 0.052 (95% CI 0.060-0.042); whose members were born in the late sixties, lambda = 0.033 (95% CI 0.041-0.025); and those born in the late seventies, lambda = 0.017 (95% CI 0.020-0.013). The first group includes those born before the urbanisation process had started. The second and third groups coincide with the development stage of that process, hence exhibiting transitional rates. The fourth group reflects the process in its consolidation stage. This reduction in the transmission of infection has changed the manner of presentation, so that while isolated cases or small outbreaks tend to be more common nowadays, occasionally epidemics may evolve explosively. The average age at presentation has risen and the likelihood of symptomatic infection is higher.

Arce Arnaez A, Rodero Garduno I, Inigo Martínez J, Burgoa Arenales M, Guevara Alemany E. Hepatitis A outbreak in a day care center and household transmission. *An Pediatr (Barc)* 2004; 60:222-227. [Article in Spanish]

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An outbreak of hepatitis A occurred in a day care center in Madrid between October 2002 and February 2003 and spread to the children's families. We performed a descriptive study of this outbreak and of the control measures adopted. The outbreak affected 23 people: eight children aged 1-3 years (attack rate = 8.7 %), two staff members (attack rate = 10.5 %), and 13 household contacts. Of the 23 cases, 17 were confirmed by serology and eight patients were hospitalised. The control measures were: (i) increasing general hygiene measures in the home and school and, in particular, those concerning diaper changing by staff, and (ii) vaccination of all pupils aged more than one year (92 children), staff members (16 adults) and family contacts of affected individuals. After vaccination, the epidemic curve showed intrafamilial transmission exclusively. Cases among familial contacts affected adults in contact with asymptomatic children. Vaccination was effective in controlling the epidemic outbreak within the day care center. However, when outbreaks occur, vaccination should be prescribed to close contacts of all the children, whether symptomatic or not, especially parents and siblings. The recommendation that day care center workers undergo vaccination on taking up their posts should be put into practice, since vaccination is not systematically performed. General vaccination would be the most effective measure for preventing outbreaks in educational centers.

Arenas MD, Muñoz C, Sánchez-Paya J, Jover R, Egea JJ, Gil MT, Martin F, Sarro F, Soriano A, Luna A, Olivares J, Reyes A, Muñoz del Bustillo E, del Pozo C, Valverde V, Perdiguer M, Araque A. Distribution of hepatitis C virus genotypes among the hemodialysis population in the province of Alicante. *Nefrologia* 2001; 21:581-758. [Article in Spanish]

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Hepatitis C virus (HCV) genotypes are irregularly distributed among the different geographic area and groups at risk. The aim was to study the different HCV genotypes and subtypes of haemodialysed patients from Alicante. We studied 640 patients on haemodialysis (HD) and we determined the RNA-HCV and the genotypes in the 120 patients with antibodies against HCV (HCV-Ab). We compared the results with the genotypes of 1,370 patients from other groups at risk in the same geographic area. RNA-HCV was not found in the serum in 15% (18/120) of the patients on HD who were HCV-Ab positive. Prevalence of the different genotypes in the 102 patients with positive viral RNA was the following: 1b: 56.8% (58/102), 1a: 19.6% (20/102), 3: 17% (17/102), 2a-2c: 1.9 (2/102), 2b: 0.9% (1/102) 4: 2.9 (3/102), 5: 0.9% (1/102). In conclusion, the genotype 1b was the most frequent in the patients studied in all these areas, and was the same as in the rest of the country. This genotype has been associated with the most severe hepatic disease and poor response to treatment, affecting the prognosis of these patients. The most frequent genotypes in HD in Alicante were 1b, 3 and 1a. HCV genotypes distribution among the HD units was not uniform in the different geographic areas. HCV genotypes distribution in the HD population is similar to other groups at risk from the same geographic area.

Arribas JR, González-García JJ, Lorenzo A, Montero D, Ladron de Guevara C, Montes, Hernandez S, Pacheco R, Pena JM, Vázquez JJ. Single (B or C), dual (BC or BD) and triple (BCD) viral hepatitis in HIV-infected patients in Madrid, Spain. *AIDS* 2005; 19:1361-1365.

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There are very limited data about the prevalence of multiple hepatitis virus infections in HIV infected individuals. In HIV uninfected individuals with triple BCD hepatitis, hepatitis D virus (HDV) appears to be the dominant virus. However, in HIV infected patients with triple hepatitis it is not known if HDV replication inhibits hepatitis B virus (HBV) and/or hepatitis C virus (HCV) replication. We calculated the prevalence of single (B or C), dual (BC) and triple (BCD) hepatitis in 423 HIV-infected patients with positive HCV serum antibodies and/or positive serum HBsAg. In patients with multiple infections we performed an evaluation of serum markers of HBV, HCV and HDV replication. The prevalence of multiple hepatitis was 4.7% (95% confidence interval, 2.7-6.7%). Multiple hepatitis occurred only among patients who acquired HIV through injection drug use. The most common multiple hepatitis was triple BCD. Patients with hepatitis BC and past or chronic hepatitis D were significantly more likely to have cirrhosis and a negative serum HBeAg and HCV PCR than patients with single hepatitis B or hepatitis C. Patients with chronic hepatitis D showed uniform suppression of HBV and HCV replication markers. In our geographic area approximately 5% of HIV infected patients with hepatitis suffer multiple hepatitis virus infection. In patients with triple hepatitis BCD virus infection, HDV appears to be the dominant virus causing inhibition of both HBV and HCV replication.

Asensio F, Bayas JM, Bertran MJ, Asenjo MA. Prevalence of hepatitis B infection in long-stay mentally handicapped adults. *Eur J Epidemiol* 2000; 16:725-729.

Hospital Sant Joan de Deu-Services of Mental Health, Sant Boi, Spain.

The objective was to determine the prevalence of hepatitis B virus (HBV) infection in long-stay institutionalised mentally handicapped adults and to develop a vaccination programme for them. The study was carried out in 1994. The subjects were 171 mentally handicapped adults aged 37-76 (median age 56) with a median hospital stay of 30 years (range 6-47). Markers for infection were determined using ELISA. Seronegative patients were vaccinated using the standard schedule, and the titre of antiHBs reached was determined later. The prevalence of seropositive subjects was 81.3%. Seropositive subjects had a longer hospital stay (median stay of 32 years, range: 15-47) than seronegative ones (median stay of 15 years, range: 6-33). A total of 43.3% of the vaccinated subjects developed antiHBs antibodies (GMT: 135 IU/l). The high prevalence of HBV exposure is probably a legacy of a past era which is reflected in patients with prolonged institutionalisation in a closed regime. The need for immediate vaccination of mentally handicapped subjects is of the utmost importance, as it has been shown that the response to the vaccine worsens with age.

Avellón A, Echevarría JM. Frequency of hepatitis B virus 'a' determinant variants in unselected Spanish chronic carriers. *J Med Virol* 2006; 78:24-36.

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The prevalence in the population of hepatitis B virus (HBV) surface antigen (HBsAg) variants that may impair diagnosis, or allow the virus to escape vaccine-induced immunity or passive immunoglobulin therapy is unknown. A genome fragment encoding HBsAg amino acids 112-212 was amplified and sequenced from the sera of 272 unselected DNA-positive, HBV-chronic carriers from Spain. The genotype and the HBsAg subtype were predicted from the sequences. Analysis of amino-acid positions 112-157 revealed single or multiple substitutions in 39% of the carriers studied. Mutations were not detected for residues 121, 135, 137, 139, 140, 141, 142, 146, 147, 148, 149, 151, 152, 153, 155, 156, and 157. Substitutions reported previously to be in association with failures of diagnostic tests or with vaccine or immunoglobulin therapy escape were found in 12.5%, 6.6%, and 9.2% of carriers, respectively. Met133Thr (2.2%); Gln129His, Met133Ile, Phe/Tyr134Asn (1.8%); Phe/Tyr134Leu, Gly145Ala (1.5%), and Pro120Thr (1.1%) were the most frequent. Other substitutions, including Gly145Arg (0.4%), were found at a frequency of less than

1%. Samples containing HBV mutants were tested with three commercial assays for HBsAg screening. Almost all the mutants reacted to the upper cut-off values of the assays, but six samples with weak reactivity with one or more of the methods were also found. Thus, HBV mutants with a potential impact on clinical and public health issues are moderately frequent among chronic carriers from Spain, although their influence on the performance of diagnostic tests seems to be slight.

Ayerbe MC, Perez-Rivilla A, on behalf of the ICOVAHB group. Assessment of long-term efficacy of hepatitis B vaccine. *Eur J Epidemiol* 2001; 17:150-156.

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In a healthy cohort of 462 subjects in which hepatitis B vaccine was administered between 1990 and 1992 a follow-up study was carried out to determine the duration of protection. Individuals with antibody against the hepatitis B virus surface antigen (anti-HBs) titer lower than 100 mIU/ml were administered a booster dose and antibodies determined 30 days later. The proportion of protection 6.5 years after vaccination was 85% (95% CI: 82-88). Only nine vaccinees seroconverted to anti-HBc positivity without becoming carrier or ill. In 125 subjects in which a booster dose was administered a significant increase in geometric mean of anti-HBs titer was observed (609 mIU/ml) as compared to late (13 mIU/ml) and early post-vaccination antibody levels (256 mIU/ml, Wilcoxon's test, $p < 0.001$) suggesting the existence of an anamnestic response. We conclude that in immunocompetent population it is not necessary to administer a booster dose 6.5 years after hepatitis B vaccination.

Barril G, Traver JA. Decrease in the hepatitis C virus (HCV) prevalence in hemodialysis patients in Spain: effect of time, initiating HCV prevalence studies and adoption of isolation measures. *Antiviral Res* 2003; 60:129-134.

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The effectiveness of isolation measures to prevent hepatitis C virus (HCV) infection in hemodialysis units is a controversial issue. Strict adherence to the universal infection control precautions has been deemed adequate to prevent nosocomial transmission of HCV. Subsequently, however, select isolation measures, such as the clustering of HCV-positive patients in a defined sector of the unit, have been adopted, specially for those units with a high HCV prevalence and when the personnel-patient ratio was such that it could involuntarily favor the break of the universal precautions. In this Multicenter Spanish Study on HCV in Dialysis, the importance of both time and isolation measures led to a decrease of HCV prevalence. Time was the most important factor (although interacting with the isolation measures) and was independent of the initial HCV prevalence.

Barril G, Trullas JC, Gonzalez-Parra E, Moreno A, Bergada E, Jofre R, Martínez-Ara J, de Sequera P, Oliver JA, Arrieta J, Miro JM. Prevalence of HIV-1-infection in dialysis units in Spain and potential candidates for renal transplantation: results of a Spanish survey. *Enferm Infecc Microbiol Clin* 2005; 23:335-339. [Article in Spanish]

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Patients with HIV infection and end-stage renal disease (ESRD) have improved their survival in the last few years. HIV infection is not considered a contradiction for renal transplantation, but

little experience exists in renal transplantation in HIV infected individuals. There is no information about the prevalence of HIV infection in Spanish patients under renal replacement therapies (RRT). A survey was performed in Spanish dialysis units during 2004. The objective was to study the prevalence and characteristics of HIV infection in patients under RRT in Spain. We also aimed to know how many of them met the Spanish criteria to be included on the renal transplantation waiting list. HIV prevalence was 1.15% (95%CI 0.85-1.45) of 4,962 patients who were under RRT, mostly under haemodialysis and, less commonly, peritoneal dialysis. The most frequent risk factor for HIV infection was parenteral drug use (58%). The most common causes of ESRD were glomerulonephritis (44%). The median time under RRT was 46 months. Coinfections with hepatitis C (60%) and B (7%) were found. Thirty-four percent of patients had a history of aids-defining events. Eighty-six percent were under HAART. The median CD4 cell count was 333 cells/ μ l and the viral load was undetectable in 68%. Of 40 patients with a completed clinical questionnaire, 9 (22.5%) met the Spanish criteria for renal transplantation. HIV prevalence in patients under RRT in Spain is 1.15% (0.85%-1.45%) and 22.5% percent of these patients met the Spanish criteria to be included on a renal transplantation waiting list.

Basaras M, Arrese E, Cabrera F, Ezpeleta C, Cisterna R. Detection of HGV in serum and peripheral blood mononuclear cells of maintenance haemodialysis patients. *J Hosp Infect* 1999; 42:155-159.

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The aim of the present study was to investigate the prevalence of hepatitis G virus (HGV) and also hepatitis C virus (HCV) infections in maintenance haemodialysis patients, and to identify extrahepatic sites as HGV reservoirs. HGV RNA was detected in the serum of 6/61 (10%) patients and in the peripheral blood mononuclear cells of 2/61 (3%) patients (one of whom was serum negative). These findings suggest that lymphoid cells constitute an extrahepatic HGV reservoir. HCV RNA was detected in 7/61 (11%) patients. Five of these patients (71%) were identified as carrying HCV genotype 1b. Co-infection with HCV and HGV was detected only in one patient. Haemodialysis patients are at risk for HGV infection, by nosocomial routes or via transfusions. HGV itself does not seem to be an important cause of hepatitis since all six HGV RNA positive patients not co-infected by HCV or HBV showed normal ALT values.

Bassani S, Toro C, de la Fuente L, Brugal MT, Jimenez V, Soriano V. Rate of infection by blood-borne viruses in active heroin users in 3 Spanish cities. *Med Clin (Barc)* 2004; 122:570-572. [Article in Spanish]

Servicio de Enfermedades Infecciosas, Hospital Carlos III, Madrid, Spain.

The objective of this paper was to determine the prevalence of human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV) and human T lymphotropic virus (HTLV) infections in active heroin users in Spain. A cross-sectional study was carried out in 440 heroin users in three different urban areas of Spain: Barcelona, Madrid, and Seville. Specimens were analyzed for the presence of anti-HIV, anti-HCV, anti-HBc, and anti-HTLV antibodies. The rate of anti-HIV antibodies was 20% (CI 95%, 16.3-23.7%); anti-HBc: 21.4% (CI 95%, 17.5-25.2%); anti-HCV: 59.1% (CI 95%, 54.5-63.7%); and anti-HTLV (HTLV-II in all cases): 3.4% (CI 95%, 1.7-5.1%). Barcelona and Madrid had similar rates for each virus, yet these were lower in Seville especially with regard to HCV (Barcelona: 59.7% [CI 95%, 53.1-66.3%]; Madrid: 63.8% [CI 95%, 56.7-70.9%]; Seville: 41.8% [CI 95%, 28.8-54.9%]). HCV is the most prevalent infection among active heroin users in Spain. The rate of infection by blood-borne viruses is higher in Madrid and Barcelona than in Seville (notably for HCV), most likely due to a lower rate of intravenous users in this city.

Bayas JM, González A, Vilella A, San-Martin M, Bertran MJ, Adell C. Cost analysis of two strategies for preventing hepatitis A virus infection in Spanish travellers to developing countries. *Epidemiol Infect* 2001; 127:347-351.

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Our objectives were to assess the prevalence of anti-hepatitis A (HAV) antibodies in Spanish travellers to developing countries and to carry out a cost analysis to allow the comparison of two vaccination strategies. Adult subjects were selected from among travellers to developing countries. Information was obtained on age, sex, destination, previous vaccination against HAV and having received immunoglobulin. Blood specimens were obtained for anti-HAV antibody determination. A total of 485 travellers were studied. The prevalence of anti-HAV antibody was 30.5% (95% CI 26-35). Antibody prevalence was inversely correlated with age: 9.8% in 18-25 years of age, rising to 75.4% in those 41-55 years of age. Cost analysis determined that the critical value of prevalence for vaccination with HAV vaccine was 37.5%. It was concluded that the youngest Spanish travellers lack anti-HAV antibodies. Vaccination without screening in those ≤ 35 years of age and screening before vaccination for those > 35 years, are the preferred alternatives.

Belza MJ, Clavo P, Ballesteros J, Menendez B, Castilla J, Sanz S, Jerez N, Rodriguez C, Sánchez F, del Romero J. Social and work conditions, risk behavior and prevalence of sexually transmitted diseases among female immigrant prostitutes in Madrid (Spain). *Gac Sanit* 2004; 18:177-183. [Article in Spanish]

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The objectives were to describe the sociodemographic characteristics, work conditions, sexual behavior, and prevalence of HIV, hepatitis B (HBV), and hepatitis C (HCV) infection and of other sexually transmitted infections among a group of female immigrant prostitutes in Madrid. We performed a descriptive study of a group of immigrant women who worked as prostitutes and who attended a sexually transmitted diseases (STD) clinic in Madrid in 1999 and 2000. Information was collected on sociodemographic characteristics, work conditions, use of injected drugs, and sexual practices with their clients and in their private lives. The services provided included screening for the main STDs and serological studies for HIV, HBV and HCV. A total of 579 female immigrants were analysed. The mean age was 28.7 years. Ninety-six percent were from Latin America. None reported having consumed injected drugs. They began to work as prostitutes at a mean age of 27.4 years and 93.3% of them began in Spain. In the previous month, 98% had always used condoms for vaginal and anal penetrations with their clients and 17.6% had used them in their private sexual relations. Thirty percent reported condom breakage during intercourse. The prevalence of HIV and HCV infection was 0.2 and 0.9%, respectively; 8.1% showed HIV anticore antibodies and 0.5% showed surface antigens. An ulcerative STD was diagnosed in 2.1% and a non-ulcerative STD was diagnosed in 16%. Condoms are generally used with clients although the frequency of breakage is high. Condom use in prostitutes personal lives is dramatically lower. The prevalence of markers for HIV, HBV and HCV is low and the frequency of STD is moderate.

Berbel Hernandez C, Morquecho Gil M, de La Puente Callejo J, Vina Simon M, Crespo Ilue E, García Montero I, Gonzalez Guillen M, Llorente Martinez M, Sanz López P. Documented immunization coverage in second-year primary schoolchildren from the province of Valladolid. *Gac Sanit* 2001; 15:224-922. [Article in Spanish]

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The objective was to estimate the documented immunisation coverage and degree to which schoolchildren's vaccination cards are kept up to date. Method: a transversal descriptive study of children in the second year of primary education in the province of Valladolid during the 1999-2000 academic year. The sample consisted of 698 children with a participation rate of 82%. The percentage of children whose immunisation schedule was up to date in accordance with their age, that of children with additional vaccinations and the accuracy of the vaccination cards was quantified. Information was collected through a questionnaire on vaccination cards or, for children without one, from their medical history. The documented immunisation coverage was 99.3% (95% CI: 98.6-99.9) for the first three dose of diphtheria toxoid, tetanus toxoid and pertussis vaccine and poliomyelitis vaccine, 98.9% (95% CI: 97.7-99.5) for the measles, mumps and rubella vaccine and 95% (95% CI: 93.4-96.7) for all doses up to the age of six. In addition, 7.2% (95% CI: 5.3-9.2) were immunised against hepatitis B, 14.4% (95% CI: 11.6-17) against *Haemophilus influenzae* type b and 90.3% (95% CI: 88-92.5) against meningococcal A + C. A total of 84.4% of vaccination cards were correctly filled in (95% CI: 81.7-87.2). Systematic immunisation coverage in the schoolchildren was high. Because of their accuracy, vaccination cards were a useful tool for determining immunisation coverage. Both the accuracy of the vaccination card and the incidence of non-systematic immunisation were higher in urban areas.

Bosch A, Sánchez G, Le Guyader F, Vanaclocha H, Haugarreau L, Pinto RM. Human enteric viruses in Coquina clams associated with a large hepatitis A outbreak. *Water Sci Technol* 2001; 43:61-65.

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An outbreak of hepatitis A, affecting 183 people, occurred in Valencia (Spain). Epidemiological evidence pointed to an association of the outbreak with consumption of Coquina clams (*Donax* sp), imported frozen from Peru. Shellfish were analysed for the presence of hepatitis A virus (HAV), enteroviruses, rotaviruses, astroviruses, caliciviruses and hepatitis E virus. HAV was detected in 75% of assayed shellfish samples. Other enteric viruses were occasionally found in the same samples. Molecular epidemiological analysis of fragments of the VP1/2A and the 5' end of the genome from shellfish and sera isolates, revealed the presence of six variants belonging to a single genotype.

Brown RE, De Cock E, Colin X, Antoñanzas F, Iloeje UH. Hepatitis B management costs in France, Italy, Spain, and the United Kingdom. *J Clin Gastroenterol* 2004; 38(10 Suppl):S169-S174.

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The goal was to estimate the costs associated with the management of chronic hepatitis B (CHB) and its sequelae in France, Italy, Spain, and the United Kingdom from the perspective of the healthcare payer. The World Health Organization estimates that the disease sequelae related to hepatitis B account for 1 million deaths annually worldwide. Northern Europe is a low endemic area, while Mediterranean regions are classified as intermediate endemic areas. The introduction of vaccination programmes in France, Italy, and Spain in recent years has lowered the hepatitis B incidence rates. The purpose of this study was to identify the medical management patterns of CHB patients in France, Italy, Spain, and the United Kingdom and estimate the economic burdens of CHB-related disease states for each country. A central questionnaire was used to collect data from specialist physicians in four countries, and responses were collated into management patterns for chronic active hepatitis, compensated and decompensated cirrhosis, and hepatocellular carcinoma. The average cost by disease state for each European country was found to increase across the identified disease states reflecting disease progression. Year-2001 average annual disease state costs per patient were estimated to be as follows: CHB, 1,093 Euro-3,396 Euro;

compensated cirrhosis, 1,134 Euro-3,997 Euro; decompensated cirrhosis, 5,292 Euro-8,842 Euro; hepatocellular carcinoma, 3,731 Euro-9,352 Euro; and, from published sources, liver transplant surgery, 25,165 Euro-84,568 Euro. The cost of CHB is variable both within and between European countries. The association of disease progression with increased cost of disease management suggests that measures to prevent or delay its progression would be economically beneficial.

Bruguera M, Forn X. Hepatitis C in Spain. *Med Clin (Barc)* 2006;127:113-117. [Article in Spanish]

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Spain has a medium endemicity of hepatitis C infection among central Europe countries and Italy. Prevalence of anti-HCV varies among regions and it ranges from 1.6 to 2.6%, which means that there may be between 480,000 and 760,000 people infected with hepatitis C virus in Spain. The prevalence is very low in people under 20 years of age and it increases from age 30 years. Prisoners and drug addicts have the highest infectious rates, between 40 and 98%. Some populations of immigrants also have a high prevalence of HCV infection, especially people from Asia and sub-Saharan countries, whereas people from Latin America have rates lower than those in the autochthonous population. Spanish people with chronic hepatitis C were mainly infected via blood transfusions, IV drug use, or during some medical and surgical hospitalisation. The reduction in the use of IV drugs and the programs of needle sharing, as well as the eradication of post-transfusional hepatitis, have led to a progressive reduction in the incidence of new infections (from 6.8 per 100,000 inhabitants in 1997 to 2.3 in 2003). Preliminary data suggest that an important rate of new hepatitis C cases owe to nosocomial transmission. Transmission is almost exclusively vertical in children. In spite of a two-third reduction of incident cases of hepatitis C in Spain in last few years, it is foreseeable that the number of patients with advanced HCV liver disease attended in the health-care system will increase in forthcoming years. This is due to the fact that many, still undiagnosed patients will be likely recognized for the first time as a result of some complication of the disease. All efforts to increase the screening of hidden cases of hepatitis C in primary health-care centers, allowing a prompt treatment before an advanced stage, will have a beneficial impact both in economic and social terms.

Bruguera M, Salleras L, Plans P, Vidal J, Navas E, Domínguez A, Batalla J, Taberner L, Espunes J. Changes in seroepidemiology of hepatitis A virus infection in Catalonia in the period 1989-1996. Implications for new vaccination strategy. *Med Clin (Barc)* 1999; 112:406-408. [Article in Spanish]

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The aim of this study was to investigate the prevalence of the risk factors of hepatitis A virus infection (HAV) in a representative sample of a Catalonian population obtained from 1995 to 1996 and the changes in the prevalence of this infection over the period of 1989-1996. The prevalence of anti-HAV was determined by an ELISA test in a randomised sample of 2,142 individuals, 884 from 6 to 14 years of age and 1,248 over the age of 15 years. The results were related to sociodemographic variables and multiple logistic regression analysis was performed to establish which variables were related to the risk of infection. The global prevalence of HAV infection was 67.8%. The prevalence of HAV infection increased from 3.5% in the group from 5-14 years of age to 99% in that over the age of 64 years ($p < 0.001$). A higher prevalence was observed in those born outside of Catalonia (odds ratio [OR] = 3.97; 95% CI, 2.4-6.4) and in those with a lower level of education (OR = 2.60; 95% CI, 1.9-3.5). In the period 1989-1996 the prevalence of the infection has decreased in the population under the age of 45, the differences being statistically significant in the age groups 10-14 ($p < 0.0001$) and 25-34 ($p < 0.0001$). The prevalence of HAV infection

has progressively decreased in Catalonia while it proportionally increases the susceptible population under the age of 45 years. These findings may be important in the design of strategies for the prevention of HAV infection with universal vaccination programmes against this disease.

Butí M, Clemente-Casares P, Jardi R, Formiga-Cruz M, Schaper M, Valdes A, Rodriguez-Frias F, Esteban R, Gironés R. Sporadic cases of acute autochthonous hepatitis E in Spain. *J Hepatol* 2004; 41:126-131.

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In industrialised countries hepatitis E virus (HEV) infection is rare and its diagnosis is difficult because the utility of available tests is not well established. We studied the presence of acute HEV infection markers in a cluster of 11 cases of acute hepatitis with IgG anti-HEV antibodies. Three cases were confirmed as acute hepatitis E and 8 as presumptive hepatitis E, two as a past HEV infection and one could not be determined. Three different HEV strains were identified in serum from 3 patients. Two strains belonged to genotype 3, the predominant genotype found in local urban sewage and the other strain belonged to genotype 1 and was considered an imported strain. Our findings demonstrate the presence of some autochthonous, sporadic acute hepatitis E cases as well as an imported case in our area and the transitory nature of virological and serological markers for HEV.

Butí M, Jardi R, Allende H, Cotrina M, Rodriguez F, Viladomiu L, Esteban R, Guardia J. Chronic delta hepatitis: is the prognosis worse when associated with hepatitis C virus and human immunodeficiency virus infections? *J Med Virol* 1996; 49:66-69.

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Eighty-six patients were followed for 6.5 years to study the epidemiological, virological, and histological course of chronic delta hepatitis and the relationship of this disease with HIV and HCV infection. Patients were classified into four groups according to simultaneous HCV and/or HIV infection: group 1, HDV infection (20 cases); group 2, HDV and HCV infection (11 cases); group 3, HDV and HIV infection (12 cases), and group 4, HDV, HCV, and HIV infection (43 cases). All but 14 patients were asymptomatic at presentation. Liver histology showed chronic active hepatitis in 53 cases and cirrhosis in 19 cases. During followup, 52 patients remained asymptomatic, 34 developed hepatic dysfunction, 28 died, and 1 received a liver transplant. Among the 28 patients who died, 4 had HDV infection; 3 HDV and HCV infection; 3 HDV and HIV infection; and 18 HDV, HCV, and HIV infection. Death was due to liver failure in 16 (57%), AIDS in 10 (36%), and was unrelated to liver disease in 2 (8%) cases. These results demonstrate that chronic delta hepatitis is a severe disease, especially among drug users with HIV and HCV infection. The high morbidity and mortality of chronic delta hepatitis justifies the use of antiviral therapy to modify the natural course of the disease.

Castell J, Gutierrez G. Outbreak of 18 cases of hepatitis C in a hemodialysis unit. *Gac Sanit* 2005; 19:214-220. [Article in Spanish]

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On September 30, 2001 we had notice of a probable outbreak of hepatitis C virus (HCV) infection in a hemodialysis unit in Ciudad Real (Spain). We conducted an investigation of the outbreak to determine its cause and implement control measures. We performed a descriptive study and another analytic study (retrospective cohort study). In the descriptive study, the incidence of HCV

infection in the unit between 01/01/98 and 09/30/01 was studied. In the cohort study, 86 subjects were included, of which 18 were infected with HCV during the outbreak. Virologic study was performed, including serology of anti-HCV antibodies, specific IgG avidity study, polymerase chain reaction and phylogenetic analysis of the viral subtypes found. In the study period, there were 86 patients under treatment in the haemodialysis unit, of which 27 (31.4%) were HCV-positive before 03/01/01. The epidemic curve suggested a common source with secondary cases. Since 1998 only one seroconversion had been documented (in 1999). Statistically significant differences were found only for the variable of dialysis shift. None of the patients who underwent dialysis on the Tuesday-Saturday-Thursday shift exclusively was infected. All cases were genosubtype 4d, which is uncommon in Spain (accounting for 3%), suggesting a common initial source for all cases. Most of the previous cases of HCV in the haemodialysis unit were 1b; three were 4c/4d and one was 1a. The IgG avidity study suggested that not all the cases were infected at the same time, supporting the hypothesis of a common source with secondary spread. The outbreak of HCV was confirmed, with 18 cases among dialysed patients in the central unit. The outbreak was caused by the same viral strain, probably due to a common source with secondary person-to-person transmission among the patients.

Cilla G, Perez-Trallero E, Artieda J, Serrano-Bengoechea E, Montes M, Vicente D. Marked decrease in the incidence and prevalence of hepatitis A in the Basque Country, Spain, 1986-2004. *Epidemiol Infect* 2006 Jul 19; 1-7 [Epub ahead of print]

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The aim of this study was to determine changes in the epidemiology of hepatitis A virus (HAV) infection in the Basque Country, Spain, and to evaluate their implications for vaccination strategies. A total of 1356 persons were enrolled in a study of the prevalence of anti-HAV in 2004 and compared with two previous studies (1986-1987 and 1992). The selection method and the characteristics of the population were similar in the three studies. A marked decline in the seroprevalence in all age groups ($P < 0.001$) and in the incidence of cases/100,000 inhabitants (from 38.0 in 1986-1988 to 2.9 in 2002-2004) were observed. The mean age of patients with hepatitis A increased from 17.7 years in 1986-1992 to 21.2 years in 1993-1998 and 25.3 years in 1999-2004 ($P < 0.001$). Between 1997 and 2004, 20% of patients were hospitalised. The changes observed have occurred rapidly causing a change in the epidemiological pattern from middle-high endemicity (1986) to low endemicity (2004).

Clemente-Casares P, Pina S, Butí M, Jardí R, Martín M, Bofill-Mas S, Gironès R. Hepatitis E virus epidemiology in industrialized countries. *Emerg Infect Dis* 2003; 9:448-454.

University of Barcelona, Barcelona, Spain.

To determine the prevalence of hepatitis E virus (HEV) in industrialised nations, we analyzed the excretion of HEV strains by the populations of Spain, France, Greece, Sweden, and the United States. Twenty of 46 (43.5%) urban sewage samples collected in Barcelona from 1994 to 2002 tested positive for HEV. We identified 15 HEV strains, which were similar to two HEV isolates previously described in Barcelona in clinical samples and to strains from diverse geographic HEV-nonendemic areas. We also identified two HEV strains in sewage samples from Washington, D.C., and Nancy, France; these samples were also positive for hepatitis A virus. In addition, we studied the role of pigs as a reservoir for HEV and identified one new swine HEV strain. Our results suggest that HEV may be more prevalent than previously considered in industrialised countries and that variants of the virus circulate simultaneously in one region.

Cotrina M, Butí M, Jardí R, Quer J, Rodríguez F, Pascual C, Esteban R, Guardia J. Hepatitis delta genotypes in chronic delta infection in the northeast of Spain (Catalonia). *J Hepatol* 1998; 28:971-977.

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Based on genetic analysis of variants obtained around the world, three genotypes of the hepatitis delta virus have been defined. Hepatitis delta virus variants have been associated with different disease patterns and geographic distributions. To determine the prevalence of hepatitis delta virus genotypes in the northeast of Spain (Catalonia) and the correlation with transmission routes and clinical disease, we studied the nucleotide divergence of the consensus sequence of HDV RNA obtained from 33 patients with chronic delta hepatitis (24 were intravenous drug users and nine had no risk factors), and four patients with acute self-limited delta infection. Serum HDV RNA was amplified by the polymerase chain reaction technique and a fragment of 350 nucleotides (nt 910 to 1259) was directly sequenced. Genetic analysis of the nucleotide consensus sequence obtained showed a high degree of conservation among sequences (93% of mean). Comparison of these sequences with those derived from different geographic areas and pertaining to genotypes I, II and III, showed a mean sequence identity of 92% with genotype I, 73% with genotype II and 61% with genotype III. At the amino acid level (aa 115 to 214), the mean identity was 87% with genotype I, 63% with genotype II and 56% with genotype III. Conserved regions included the RNA editing domain, the carboxyl terminal 19 amino acids of the hepatitis delta antigen and the polyadenylation signal of the viral mRNA. Hepatitis delta virus isolates in the northeast of Spain are exclusively genotype I, independently of the transmission route and the type of infection. No hepatitis delta virus subgenotypes were found, suggesting that the origin of hepatitis delta virus infection in our geographical area is homogeneous.

Cruz JM, Piera L, Bragg-Gresham JL, Feldman H, Port FK. Results of the international hemodialysis study DOPPS in Spain and Europe. *Nefrologia* 2003; 23:437-43. [Article in Spanish]

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The Dialysis Outcomes and Practice Pattern Study (DOPPS) is an international observational study of treatment conditions and medical outcomes in haemodialysis patients. Prospective sampling has yielded long-term observational data from randomly selected groups of patients receiving treatment at representative, randomly selected haemodialysis units in each country. The data shown were collected at 20 hemodialysis units/centers in Spain. The data pertaining to Spain – Sp – refers to 575 patients and their comparison with those of the Euro-DOPPS countries – Eu – (Germany, France, United Kingdom, Italy and Spain), which encompass 3,038 patients, represent the formal goal of this paper. Diabetes mellitus, at 21.5% in Eu and 21.7% in Sp, was the most common cause of renal insufficiency in dialysis and coronariopathy, as a concomitant disease, was present in 67.8% in Eu as opposed to 75.8% in Sp. Differences were observed in the incident of hypertension (73.4% in Eu vs 77.4% in Sp), hepatitis C (11.6% vs 19.5%), depression (12.7 vs 16.2%) and left ventricular hypertrophy (54.9% vs 62.3%). The patterns of vascular access were similar (79% vs 81% AV fistulas in Eu and Sp, and 10% synthetic grafts for both) and the mean applied dose of dialysis – Kt/V – smaller (1.19) in Sp than in Eu (1.24); likewise the duration of the dialysis (in minutes) was shorter (234 in Eu vs 217 in Sp) and the % of synthetic membranes used was smaller (60% in Eu vs 52% in Sp). There were no differences between the groups in the figures for urea, creatinine, albumin, nPCR, calcium, phosphate or PTH. There were also no differences in the mean values of Hb (10.7 for Eu vs 10.8 for Sp), given that the values of ferritin were noticeably lower in Sp (288 vs 355) and the dose of EPO/kg/week was higher to in Sp (115 vs 102); s.c. route was used in similar proportions (69% in Eu vs 67% in Sp). The level of medical care, understood as contact with the physician at all or almost all treatments, was noticeably better in Sp (90%) that in Eu (66%), whereas the number of patients per hour of specialised personnel

and % of specialised staff, were smaller. Mortality (death/100 patients-years) was one point lower in Sp than in Eu (15.4 vs 16.3). These data suggest that an increment in dialysis time and in the percentage of synthetic membranes used, as well as in the supply of intravenous iron, would be justified.

Dal-Re R, García-Corbeira P, García-de-Lomas J. A large percentage of the Spanish population under 30 years of age is not protected against hepatitis A. *J Med Virol* 2000; 60:363-366.

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A seroepidemiological study was conducted to assess the seroprevalence of hepatitis A (HAV) antibodies in the Spanish general population in 1992-93. A total of 2744 subjects (1337 men and 1437 women) in the 5-59 years age range were stratified by gender and age (5-12, 13-19, 20-29, 30-39, 40-49, 50-59 years). The presence of total anti-HAV antibodies was investigated using a commercial enzyme immunoassay. Fifty-five percent (95% CI: 53.5-57.2%) of the subjects were positive for anti-HAV antibodies, the age-standardised anti-HAV prevalence being 65.4%. Prevalence of seropositive subjects increased with increasing age ($\chi^2 = 996, 17; P < 0.0001$), being 11%, 25% and 54% for the 5-12, 13-19 and 20-29 age groups respectively. The results from this study showed a remarkable decline in seroprevalence rates among children, adolescents and young adults. The large number of susceptible subjects in these groups of the population has public health implications in a country with intermediate HAV prevalence.

de Juanes JR, Gonzalez A, Arrazola MP, San-Martin M. Cost analysis of two strategies for hepatitis A vaccination of hospital health-care personnel in an intermediate endemicity area. *Vaccine* 2001; 19:4130-4134.

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The aim of the study was to carry out a cost analysis to allow the comparison of the cost of two vaccination strategies against Hepatitis A in health-care personnel. A total of 423 health-care workers were recruited at one General Hospital of Madrid, Spain. Blood specimens were obtained for anti-HAV antibody determination. The prevalence of anti-HAV antibody was 40% (95% CI: 35-45) and it was directly correlated with age. Cost analysis determined that the critical value of prevalence for vaccination with HAV vaccine was 23%. In hospital health-care workers ≤ 30 years in age, vaccination with HAV vaccine (without screening) would be the less costly strategy. In those > 30 years in age, it would be less costly to screen for anti-HAV antibody first and vaccinate those who are antibody-negative.

del Olmo JA, Ornia E, Serra MA, García-Torres ML, Escudero A, Rodriguez F, Rodrigo JM. Changing prevalence, clinical features, and outcome of acute hepatitis in Spain (1982-2003). *J Gastroenterol Hepatol* 2006; 21:982-987.

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Diagnostic and preventive measures have contributed to a change in the epidemiology of acute hepatitis. The purpose of the present paper was to assess the changing prevalence of acute hepatitis from 1982 to 2003. Trends in the epidemiology, clinical findings, and outcome of acute viral hepatitis from 1982 to 2003 were examined. A total of 548 episodes of acute hepatitis diagnosed between 1982 and 2003, the clinical course of which was monitored up to the year 2003, were

included. Annual changes as well as for the intervals 1982-1992 and 1993-2003 were compared. Severe infections occurred in 1.3% of cases, with a mortality of 0.6%, with progression into chronicity in 25.1%. The annual incidences of acute hepatitis and the comparative intervals 1982-1992 and 1993-2003 showed a decline of parenterally -B, delta and C virus- transmitted infections, unchanged number of cases of acute hepatitis A, an increase in the number of cases of drug-induced hepatitis, increase in median ages, and a decrease in the proportion of hepatitis in injecting drug users. Ages of patients with hepatitis A tended to increase. A decline of parenterally transmitted acute hepatitis was documented throughout a 22-year period, while the number of cases of hepatitis A was unchanged and that of drug-induced hepatitis increased. Evaluation of the current targeted hepatitis A vaccination approach and adequate pharmacovigilance measures are required in the near future.

de Sanjose S, Nieters A, Goedert JJ, Domingo-Domenech E, Fernandez de Sevilla A, Bosch R, Herrera P, Domínguez A, Petit J, Bosch X, Kallinowski B. Role of hepatitis C virus infection in malignant lymphoma in Spain. *Int J Cancer* 2004; 111:81-85.

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Hepatitis C virus (HCV) has been implicated in the etiology of malignant lymphomas. We estimated the risk of lymphoma associated with detection of HCV infection. Cases (n = 529) were consecutive patients newly diagnosed with a lymphoid malignancy between 1998 and 2002 in 4 centers in Spain. Lymphomas were diagnosed and classified using the WHO Classification. Controls (n = 600) were hospitalised patients matched to the cases by 5-year age group, gender and study center. Several medical conditions associated with severe immunosuppression precluded the eligibility of controls. Patients underwent a personal interview and blood sampling. HCV positive subjects were considered those with antibody response to third generation ELISA or detection of HCV RNA with Amplicor 2.0. Cases were systematically tested for HIV antibodies. We used the χ^2 test and unconditional logistic regression to estimate the odds ratio (OR) and 95% confidence interval (95% CI) for lymphoma associated with HCV. HCV infection was detected in 40 cases (7.5%) and 23 (3.8%) control subjects. Six of 16 patients with HIV-related lymphomas and 4 of 8 organ-recipient-related lymphomas were HCV positive. The analysis, excluding HIV-infected subjects and organ recipients, led to a prevalence of HCV of 5.9% among cases and 3.8% among controls. The age-, gender- and center-adjusted OR for all lymphomas was 1.58 (95% CI = 0.89-2.79). Among all lymphoma categories, HCV was associated with an increased risk of low grade B-cell lymphomas not otherwise specified (NOS) (OR = 35.98, 95% CI = 4.70-275.4). A 2-fold excess risk associated to HCV was observed for marginal B-cell lymphomas, diffuse large B-cell lymphoma and lymphoma B NOS but the associations were not statistically significant. HCV infection is associated with an increased risk of a broad spectrum of lymphoid neoplasms among non severely immunocompromised subjects in Spain.

Domínguez A, Bruguera M, Plans P, Costa J, Salleras L. Prevalence of hepatitis A antibodies in schoolchildren in Catalonia (Spain) after the introduction of universal hepatitis A immunization. *J Med Virol* 2004; 73:172-176.

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The objective of this study was to investigate the prevalence of hepatitis A antibodies (anti-HAV) in schoolchildren in Catalonia and to compare it with the rates found in previous studies. Sera from a representative sample of 1,342 children aged between 6 and 15 years, recruited in 2001, were tested for anti-HAV. The results were related to sociodemographic variables and vaccination history. The overall prevalence of anti-HAV was 51.4%. The prevalence was 5.5% in non-

vaccinated children, similar to that found in a 1996 study, and 96.6% in vaccinated children. The prevalence of anti-HAV in non-vaccinated children increased significantly with age, reaching 11.6% in the 13-15 years age group. The prevalence of anti-HAV was higher in children born outside Catalonia than in those born in Catalonia (16.1% vs. 5.0%, $P = 0.02$). The expected continuation in the decline in the prevalence of anti-HAV in non-vaccinated schoolchildren, observed in Catalonia since 1986, was not found in 2001. The rate of anti-HAV in 2001 was slightly higher than in 1996, although the difference was not statistically significant (5.5 and 3.5%, respectively). This could be explained by the increased number of recent immigrant children born outside Catalonia, mainly in countries where hepatitis A is highly endemic.

Domínguez A, Bruguera M, Vidal J, Plans P, Salleras L. Changes in the seroepidemiology of hepatitis B infection in Catalonia 1989-1996. *Vaccine* 2000; 18:2345-2350.

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The objective of this study was to investigate the prevalence of hepatitis B markers in a representative sample of 2142 subjects in Catalonia, Spain, and to compare it with previous studies. Multiple logistical regression analysis was carried out to determine variables associated with the markers studied. The prevalence of anti-HBc and HBsAg was 9.1% and 1.2%, respectively. Male gender, urban habitat, birth place outside Catalonia and lower social class were associated with the presence of anti-HBc. Carrier status was only associated with male gender. Between 1989 and 1996 there was a decrease of 46% in the prevalence of serum HBV markers mainly in the 25-44 ($P < 0.0001$) and 35-64 year ($P = 0.0002$) age groups, in those born in Catalonia ($P = 0.003$) and in those in the higher social classes ($P < 0.0001$). These decreases can be explained by the improved socioeconomic conditions and, partially, by the routine pre-adolescent and risk group programmes of immunisation.

Domínguez A, Bruguera M, Vidal J, Plans P, Salleras L. Community-based seroepidemiological survey of HCV infection in Catalonia, Spain. *J Med Virol* 2001; 65:688-693.

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The objective of this study was to investigate the prevalence of antibodies against the hepatitis C virus (anti-HCV) and the associated risk factors in a representative sample of the population of Catalonia, Spain. Serum samples from 2,142 subjects aged between 5 and 70 years, selected at random from urban and rural habitats, were studied. Multiple logistic regression analysis was carried out to determine variables associated independently with the presence of HCV antibodies. The age and gender standardised prevalence of anti-HCV was 2.5% (95% confidence interval, 1.8-3.2). Prevalence increased significantly with age ($P < 0.001$), but no other sociodemographic variables were associated with HCV infection. Tattoos (OR: 6.2), blood transfusions (OR: 5.0) intravenous drug use (OR: 4.9) and antecedents of hospitalisation (OR: 2.3) were variables associated independently with infection. HCV infection affects mainly elderly people in Spain and spares children and adolescents. This suggests that major exposure to HCV may have occurred many years ago, when infection was more widespread than in recent years.

Domínguez A, Salleras L, Carmona G, Batalla J. Effectiveness of a mass hepatitis A vaccination program in preadolescents. *Vaccine* 2003; 21:698-701.

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A program of mass hepatitis A+B vaccination in preadolescents in schools was begun in the Catalonia in the last quarter of 1998. This study investigated the impact of the programme by comparing the incidence of hepatitis A in vaccinated and unvaccinated cohort. The greatest reduction of the incidence rate of hepatitis A was observed in the 10-14 years age group, from 10.3 per 100,000 persons-year in the period 1996-1998 to 1.8 per 100,000 persons-year in the period 1999-2001. The global incidence decreased from 6.2 to 2.6 per 100,000 persons-year. After analysis of cases occurring in the vaccinated and non vaccinated cohort, the effectiveness of the vaccination programme was estimated at 97.0% (95% CI: 78.6-99.6).

Echevarría JM, Avellón A. Hepatitis B virus genetic diversity. *J Med Virol* 2006;78(Suppl 1):S36-42.

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Hepatitis B virus (HBV) is a human DNA virus, which replicates through an RNA intermediate because of the reverse-transcriptase (RT) activity of its DNA polymerase. As a result, the mutation rate for HBV is higher than the rate observed for most DNA viruses. HBVs are classified into genotypes based on genomic sequencing, and antigenic subtypes based on the antigenic properties of its major surface glycoprotein, the HBV surface antigen (HBsAg). Subgenotypes have been identified within most of the HBV genotypes. The HBV groups defined by the different genotype-HBsAg subtype associations found over the world display characteristic geographical distributions, reflecting the movements of human populations and other epidemiologically significant events. Such HBV groups constitute genetically stable viral populations sharing a common evolutionary history, but additional stable changes, originating from mutation and mutant selection, are observed within all of them. These viral sub-populations are known as the HBV variants, and some of which have medical and public health relevance. Pre-core (pre-C) defective variants have been shown to make HBV infection much less susceptible to interferon treatment, and treatment failures with other antiviral drugs have been associated with selection of resistant variants that display specific mutations in the genome region encoding the viral RT activity. Since the RT region of the genome overlaps the sequence encoding the HBsAg molecule, selection of drug resistant variants involves, in some cases, the indirect selection of HBsAg variants. Viral variants displaying changes in HBsAg seem to be very common among chronic HBV carriers; and some of these variants may emerge under the pressure of the neutralizing antibody response, leading to vaccine resistance and resistance to immunotherapy. Mutations conferring resistance to immunotherapy are noted often among liver transplant recipients and among babies born to HBV-carrier mothers. In addition, some of these HBsAg variants have been associated with lack of detection by HBsAg tests used for the diagnosis of HBV infection, for the identification of chronic carriers, for screening of blood donations for transfusion, and in the manufacture of therapeutic blood products.

Echevarría JM, Avellón A, Magnius LO. Molecular epidemiology of hepatitis B virus in Spain: identification of viral genotypes and prediction of antigenic subtypes by limited sequencing. *J Med Virol* 2005; 76:176-184.

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The hepatitis B virus (HBV) genotypes were studied by a line probe assay (LiPA) and by direct sequencing of a 339 nucleotide fragment from the S region of the viral genome in samples from 269 carriers living in Spain, either native to Spain (231) or immigrants from Africa, Asia, and Eastern Europe (38). The sequences were also used to predict the HBV surface antigen (HBsAg) subtype on the basis of the amino acids specified at selected positions of the HBsAg molecule.

Agreement between the two genotyping methods was found in most cases (98.1%) and a HBV genotype could be assigned to all samples. The viral groups D/ayw2 (30.1%), D/ayw3 (28.6%), and A/adw2 (21.2%) were prevalent, with an additional participation of the groups D/ayw4 (4.8%), F/adw4q- (1.9%), A/ayw1 (1.9%), and D/adw3 (0.7%), all of them present among the autochthonous carriers. Strains from genotypes B and C were found exclusively among Chinese immigrants. Genotype E strains were found in immigrants from Central Africa and in one patient native of Spain. Point mutations leading to amino acid changes of residues involved in the expression of the HBsAg subtype determinants were found in 12 samples (4.5%). Some mutations would predict the putative novel genotype-subtype associations A/adw4q+, A/ayr, D/ayr, and E/ayw1, while others would suggest the loss of subtype-specific determinants. The finding of HBV strains characteristic for Africa among the autochthonous carriers confirms the emergence of African HBV strains in Spain.

Echevarría JM, Leon P. Hepatitis B virus genotypes identified by a Line Probe Assay (LiPA) among chronic carriers from Spain. *Enferm Infecc Microbiol Clin* 2004; 22:452-454.

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Genotypes A and D of the hepatitis B virus were found to be prevalent among 278 chronic carriers residing in Spain, and genotypes B, C, E and F were detected with significant frequency (9%). Two genotype E infections corresponded to carriers born in Spain who had never traveled to Africa. These results indicate that genotype E is beginning to circulate in the Spanish population in the same way that genotype F did in the past.

Echevarría JM, Leon P, Pozo F, Avellón A. Follow-up of the prevalence of hepatitis C virus genotypes in Spain during a nine-year period (1996-2004). *Enferm Infecc Microbiol Clin* 2006; 24:20-25.

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Recent data suggest that the prevalence of genotype 4 HCV strains among Spanish carriers is increasing. The objective was to assess changes in the prevalence of HCV genotypes in Spain during the last nine years. HCV RNA was amplified by the polymerase chain reaction from 3161 serum samples from unselected, anti-HCV-positive individuals, and the HCV genotype was identified by a reverse hybridisation assay (line probe assay, LiPA). Samples came from 17 different regions of Spain and were obtained between January, 1996 and December, 2004. The overall prevalence of HCV genotypes was: 1b, 41.3%; 1a, 24.1%; 3, 19.6%; 4, 11.6%; 2, 3.1%; and 5, 0.3%. The prevalence of genotypes 1a, 3 and 4 increased significantly among patients born after 1950, and that of genotype 1b decreased among them. These significant differences in regard to age were also observed among patients lacking notified high-risk factors. A main switch-up in prevalence of genotypes 1a and 3 was found when patients born in 1941-1950 were compared with those born in 1951-1960, but the same finding in genotype 4 was delayed to patients born in 1961-1970. Two separate epidemics of HCV seem to have occurred in Spain during the last 30 years. The former one involved the spread of HCV genotypes 1a and 3. The second was more recent, and involved the spread of genotype 4.

Eiras A, Sauleda S, Planelles D, Sedeno M, Ibarra A, Vesga MA, Franco E, Montoro JA, Hernandez JM, Villaescusa RG. HCV screening in blood donations using RT-PCR in mini-pool: the experience in Spain after routine use for 2 years. *Transfusion* 2003; 43:713-720.

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The aim of this study is to evaluate the feasibility of implementing a commercial HCV RNA RT-PCR screening method and provide data on the prevalence and incidence rates of hepatitis C in Spain. Five transfusion centers participated in the study, covering 34.1 percent of the country's total number of donations. All the centers evaluated the sensitivity and characteristics of a commercial RT-PCR reagent kit designed for pool testing (Cobas AmpliScreen HCV v2.0), for which serial dilutions of HCV WHO International Standard 96/790 and preseroconversion samples were used. The data obtained from this technique, employed routinely from May 1999 to June 2001 in 22- to 48-unit mini-pools, are presented in this study. An overall 95-percent detection limit was obtained either at 69 IU per ml when 0.2 ml volume of plasma was extracted (used to analyse individual units), or at 20 IU per ml, when viral particles were pelleted from 1 ml plasma (as used for screening in mini-pool). Three HCV-RNA-positive anti-HCV-negative donations were identified out of 1,015,482 screened donations. One of these had an initially undisclosed risk of HCV sexual transmission and carried a low viral load of 104.2 IU per ml HCV RNA. The analysis of first-time (FT) donations during the period of study (21.3% of the total) indicated an average prevalence rate of 2.05 per 103 FT donors (of which 1.55/103 FT donors were RNA positive); the residual risk calculated on repeat (RPT) donors was 3.91 per 106 donations (serology) or 0.59 per 106 donations (serology + NAT), and the predicted NAT yield estimate was 4.2 per 106 FT + RPT donations. The commercial RT-PCR reagent kit complies with the current European and FDA recommendations on sensitivity and can be easily implemented on a routine basis. The results obtained by the five transfusion centers on the predicted NAT yield (1/302,000 RPT donations or 1/237,000 FT + RPT donations) are very close to the published estimates corresponding to a larger area of our country (1/237,000 RPT donations) and are somewhat higher than, though in line with, the observed NAT yield (1/338,000 FT + RPT donations).

Espinosa M, Martín-Malo A, Alvarez de Lara MA, González R, Rodríguez M, Aljama P.
Natural history of acute HCV infection in hemodialysis patients. *Clin Nephrol* 2002; 58:143-150.

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Chronic liver disease develops in the majority of non-uraemic patients with hepatitis C virus (HCV) infection. The aim of this study was to analyse the evolution towards chronic hepatopathy in 19 cases of acute hepatitis C observed in haemodialysis patients from 1990 to 2001. A prospective follow-up study on HCV infection was conducted in 3 HD units from April 1990 to June 2001 to study clinical outcomes after acute hepatitis C. A total of 781 patients were tested monthly for alanine aminotransferase and anti-HCV in serum. In this period, 19 patients suffered from acute hepatitis C. Evolution to chronic liver disease in the follow-up was evaluated by means of biochemical (increased ALT) and virological criteria (HCV-RNA+). The transmission mechanism, the apparition of anti-HCV, clinical manifestations and mortality were also investigated. In 15 (78.9%) of the 19 patients, the viraemia remained positive (chronic viraemia) and 11 patients (57.8%) evolved to chronic liver disease (chronic viremia and high transaminase levels) with a median follow-up of 3 years (range 1 - 6). Five of them who underwent liver biopsies had histologic signs of chronic active hepatitis. One of them (5.2%) evolved to liver cirrhosis in the follow-up. In 4 out of 19 patients (21%) the HCV infection resolved. Although 7 (36.8%) of them died in the follow-up, acute hepatitis C infection was not a short-term independent risk factor of death. Three years after acute hepatitis C, 87.5% of the haemodialysis patients remained HCV-RNA positive and 56.2% evolved to chronic liver disease. It is important to stress that HCV infection spontaneously cleared in 4 out of 19 patients (21%).

Espinosa M, Martin-Malo A, Ojeda R, Santamara R, Soriano S, Aguera M, Aljama P.

Marked reduction in the prevalence of hepatitis C virus infection in hemodialysis patients: causes and consequences. *Am J Kidney Dis* 2004; 43:685-689.

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The prevalence of hepatitis C virus (HCV) infection in hemodialysis (HD) patients has decreased significantly in the course of the past decade in most HD units. The objective of this study is to analyse the causes of this reduction and obtain additional information for the near future that could be of use for health services planning. All patients who underwent HD in the Province of Córdoba, Spain, between January 1992 and December 2002 were studied. We analysed annual exclusions from the HD program of HCV-positive patients (deaths and kidney transplantations) and inclusions (predialysis patients, patients with chronic graft rejection, and HD patients with acute HCV infection). The trend in the time series of measurements was calculated by means of exponential smoothing with two parameters. In December 1992, the prevalence of antibody to HCV (anti-HCV) was 24% (n = 54), whereas by December 2002, it had decreased to 9.2% (N = 35). Of 657 predialysis patients included in the maintenance HD program, 2.8% (n = 19) were positive for anti-HCV. Annual mean incidence of acute HCV infection was 0.5%, and the median was 0.32%. Mean crude annual mortality rates were 12.2% for anti-HCV-positive patients versus 9.9% for anti-HCV-negative patients. The trend in this time series suggests that by 2006, the prevalence of anti-HCV in HD patients will be approximately 2.5%. Causes implicated in the reduction in prevalence of HCV infection in HD patients are a greater mortality rate, stabilisation of the incidence of acute HCV infection, and a low percentage of HCV infection in predialysis patients. By the end of 2006, the rate of HCV infection in HD patients will be very close to that of the predialysis population.

Espinosa M, Rodriguez M, Martin-Malo A, Alvarez de Lara MA, González R, López-Rubio F, de la Mata M, Aljama P. Interferon therapy in hemodialysis patients with chronic hepatitis C virus infection induces a high rate of long-term sustained virological and biochemical response. *Clin Nephrol* 2001; 55:220-226.

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The aim of the present study was to analyze the efficacy and tolerance of interferon (IFN) therapy in haemodialysis (HD) patients with chronic hepatitis C virus (HCV) infection. Specifically, we assessed whether the 'normalisation' of serum ALT levels was associated with the disappearance of the HCV-RNA. Thirteen haemodialysis patients with chronic hepatitis C were treated for one year with 3 µg of alpha-IFN. The primary end point was a sustained virological response defined as the absence of HCV-RNA in the last follow-up; the secondary end points were normalisation of the serum ALT levels and histological improvement. ALT was considered 'normal' below 27 IU/l. Ten patients completed the treatment, which was discontinued in the other 3 (23%). By the end of the treatment a virological response was observed in 8 of the 10 patients (80%) who completed the one-year IFN therapy. Biochemical response was associated with a virological response in 8 of the 9 patients in whom ALT levels became normal. Three patients had a biochemical and virological relapse in the follow-up. Two of them received a further year of IFN therapy, which resulted in a sustained biochemical and virological response. In all patients who underwent a liver biopsy (n = 5), the inflammation score improved. After a median follow-up of 5 years (range 2 - 7), a sustained response was observed in 6 (46%) of the 13 patients enrolled. Two patients with a sustained response received a kidney transplant and after more than 6 years still maintain a biochemical and virological response. Side effects included flu-like syndrome (n = 8), hemoglobin decrease (n = 8), thrombocytopenia (n = 3), depression (n = 1) and seizures (n = 1). IFN treatment over a one-year

period produces a high rate of long-term virological response in HD patients, associated to a biochemical response in all cases.

Feliu A, Carrion JA, Massaguer A, Martínez-Bauer E, García-Retortillo M, González P, Costa J, Sánchez-Tapias JM, Fornis X. Sensitivity to antiviral therapy may change after liver transplantation in patients with chronic hepatitis C virus infection. *J Viral Hepat* 2006; 13:544-551.

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In hepatitis C virus (HCV)-infected patients, it is generally assumed that the pattern of response to antiviral therapy remains unaltered after liver transplantation (LT). However, changes in the circulating HCV quasispecies and in the gene expression profiles of the graft might influence response to treatment after LT. We evaluated 22 HCV-infected patients who received antiviral treatment while awaiting LT and in whom HCV infection recurred. Eleven of these patients underwent a new antiviral treatment course. Our study analyses the early virological response to both treatment courses to assess the influence of the changes in HCV on the response to therapy. Patients were considered early virological responders (EVR) if viral load declined $> \text{or} = 2 \log_{10}$ during the first 12 weeks of therapy. The remaining individuals were considered nonresponders (NR). HCV sequences from hypervariable region 1 and nonstructural 5A (NS5A) region before both treatment regimens were compared. Of 11 patients, 8 (73%) showed identical early response to both courses of therapy (group A: five EVR-EVR, three NR-NR). Interestingly, the response changed in three patients (27%) (group B): two NR became EVR after transplantation, whereas one EVR became NR. Fixation of mutations within the NS5A occurred preferentially in group B (100%) compared with group A (37%) ($P = 0.12$). However, the number of fixed mutations was not significantly different between groups, suggesting that the changes in sensitivity to therapy after LT are not exclusively dependent on variations in HCV strains. In conclusion, in HCV-infected patients undergoing LT, the pattern of response to antiviral treatment may change after transplantation, and this possibility needs to be incorporated in clinical practice.

Fernandez-Arcas N, López-Siles J, Trapero S, Ferraro A, Ibanez A, Orihuela F, Maldonado J, Alonso A. High prevalence of hepatitis C virus subtypes 4c and 4d in Malaga (Spain): Phylogenetic and epidemiological analyses. *J Med Virol* 2006; 78:1429-1435.

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Hepatitis C virus (HCV) is a major aetiological agent of chronic hepatitis and it may lead to the development of liver cirrhosis and hepatocellular carcinoma. HCV has been classified into six clades as a result of high genetic variability. A commercial procedure to genotype HCV in 678 patients from Carlos Haya Regional University Hospital, Malaga was used to study the distribution of HCV genotypes in Malaga, southern Spain. A high prevalence of HCV-4 (10.2%) was found. This genotype is found more commonly in Egypt, Central Africa and the Middle East. The distribution of the different subtypes in the 69 patients with HCV-4 was as follows: 4.3% subtype 4e, 7.2% subtype 4a, 11.5% not subtypable, and 76.8% subtype 4c/4d. Of the 53 4c/4d patients, 69% were intravenous drug users and 31% non-intravenous drug users. In order to characterise further the HCV-4c/4d patients, sequences of the non-structural 5B gene (393 bp) were obtained from 36 HCV-4c/4d-infected untreated patients. Phylogenetic tree topologies distinguished clearly the two subtypes: 11 patients were infected by subtype 4c and 25 by 4d. This phylogenetic analysis, reinforced by the epidemiological characteristics, suggests the extension of the HCV-4c and -4d subtypes in the area of Malaga among both intravenous drug users and non-intravenous drug users.

Formiga-Cruz M, Hundesa A, Clemente-Casares P, Albinana-Gimenez N, Allard A, Gironés R. Nested multiplex PCR assay for detection of human enteric viruses in shellfish and sewage. *J Virol Methods* 2005; 125:111-118.

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Environmental samples and contaminated shellfish present frequently low concentrations of more than one viral species. For this reason, a nested multiplex RT-PCR was developed for the detection of adenoviruses, enteroviruses and hepatitis A viruses in different environmental samples such as urban sewage and shellfish. This assay will save time and cost for detection of these enteric viruses with a smaller sample volume, which otherwise can be a limiting factor in routine analysis. The limit of detection was approximately 1 copy for adenovirus and 10 copies for enterovirus and hepatitis A virus per PCR reaction using titrated cell-cultured viruses as template material. In shellfish and environmental samples, this multiplex PCR was optimised to detect all three viruses simultaneously when the concentration of each virus was equal or lower than 1000 copies per PCR reaction. This is the level found predominantly in the environment and in shellfish when the numbers of fecal bacterial and phage indicators are low. The detection of human adenoviruses by PCR has been suggested as a molecular index of fecal contamination of human origin in the environment and food and the multiplex assay developed may be a tool for evaluating the presence of viral contamination in shellfish and water and to expand microbiological control to include viral markers.

Formiga-Cruz M, Tofino-Quesada G, Bofill-Mas S, Lees DN, Henshilwood K, Allard K, Condén-Hansson AC, Hernroth BE, Vantarakis A, Tsibouxi A, Papapetropoulou M, Furones MD, Gironés R. Distribution of human virus contamination in shellfish from different growing areas in Greece, Spain, Sweden, and the United Kingdom. *Appl Environ Microbiol* 2002; 68:5990-5998.

Biology School, University of Barcelona, Spain.

Viral pollution in shellfish has been analysed simultaneously across a wide range of geographical regions, with emphasis on the concomitant variations in physicochemical characteristics and social features. The methods for sample treatment and for the detection of human enteric viruses were optimised by the participating laboratories. The second part of this study involves the selection of a protocol for virus detection, which was validated by analysing the distribution and concentration of human viral pathogens under diverse conditions during an 18-month period in four European countries. Shellfish-growing areas from diverse countries in the north and south of Europe were defined and studied, and the microbiological quality of the shellfish was analysed. Human adenovirus, Norwalk-like virus, and enterovirus were identified as contaminants of shellfish in all the participating countries. Hepatitis A virus was also isolated in all areas except Sweden. The seasonal distribution of viral contamination was also described. Norwalk-like virus appeared to be the only group of viruses that demonstrated seasonal variation, with lower concentrations occurring during warm months. The depuration treatments currently applied were shown to be adequate for reducing *Escherichia coli* levels but ineffective for the elimination of viral particles. The human adenoviruses detected by PCR correlate with the presence of other human viruses and could be useful as a molecular index of viral contamination in shellfish.

Forns X, Martínez-Bauer E, Feliu A, García-Retortillo M, Martín M, Gay E, Navasa M, Sánchez-Tapias JM, Bruguera M, Rodes J. Nosocomial transmission of HCV in the liver unit of a tertiary care center. *Hepatology* 2005; 41:115-122.

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Despite its medical and legal implications, there are no prospective studies analyzing the incidence and mechanisms involved in the nosocomial transmission of hepatitis C virus (HCV) in liver units. This study prospectively investigates the nosocomial transmission of HCV in the liver unit of a tertiary care center from August 2000 to October 2002. The median prevalence of HCV infection among hospitalised patients was 50%. Anti-HCV-negative patients admitted to the liver unit during the study period were prospectively followed, and serum markers of HCV infection were repeated 6 months after discharge. All known risk factors for HCV transmission (including the physical allocation of HCV-infected and noninfected patients during hospitalisation) were recorded. Complete follow-up data were available in 1301 (84.5%) of 1540 patients. Six patients (0.46%) acquired HCV infection (annual incidence: 0.27/100 admissions). Phylogenetic analyses of recovered HCV sequences identified the source of infection as an HCV-infected roommate (3 cases) and a patient receiving care by the same nurse team (1 case). The most relevant risk factors associated with HCV acquisition were duration of hospitalisation (> 10 days; OR, 35; 95% CI, 1.96-622) and hospitalisation with an HCV-infected roommate (> 5 days; OR, 12; 95% CI, 1.39-103). In fact, HCV infection occurred in 1.7% of the 357 patients hospitalised longer than 10 days. In conclusion, HCV nosocomial infection appears to occur via patient-to-patient transmission in liver units, particularly in individuals who require long hospitalisations. Continuous reinforcement of universal prevention measures and, when possible, isolation of patients at higher risk might further reduce nosocomial HCV transmission.

Franco E, Vitiello G. Vaccination strategies against hepatitis A in southern Europe. *Vaccine* 2003; 21:696-697.

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Hepatitis A virus (HAV) infection is decreasing in southern European countries, where epidemiological conditions vary among regions depending on the social and health-care system development. In high endemic settings, HAV infection has not heavy social and economic weight while in countries with a moderate/low degree of endemia there is a call for targeted vaccination policy. In countries, like Spain and in Italy, where several studies confirm an increase in susceptible adults, vaccination strategies have been applied and recommendations have been published about hepatitis A prevention. Universal hepatitis A immunisation seems economically unattractive and most evidences for targeted vaccination have not yet been sufficiently investigated. Vaccine should be used to protect travellers to countries where HAV infection is a major risk and in preventing secondary cases and outbreaks.

Gallego E, López A, Pérez J, Llamas F, Lorenzo I, López E, Illescas ML, Andres E, Olivas E, Gomez-Roldan C. Effect of isolation measures on the incidence and prevalence of hepatitis C virus infection in hemodialysis. *Nephron Clin Pract* 2006; 104:c1-6. Epub 2006 May 9.

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Nosocomial transmission of hepatitis C virus (HCV) in haemodialysis (HD) units is well established. In units with a high prevalence of HCV infection, the implementation of universal precautionary measures may not suffice in order to decrease the incidence and prevalence of HCV. In this setting strict isolation practices can be useful in order to achieve this goal. The incidence and prevalence of HCV infection amongst all HD and peritoneal dialysis (PD) patients from the province of Albacete, Spain, have been studied from 1992 to 2003. Through the 1993-1995 period

chronic HD patients were treated either in a room exclusively for HCV-patients or in a room shared by HCV+ and HCV- patients. Complete separation of HCV+ and HCV- patients was implemented in 1995. Acute patients have been separated since 1992. The implementation of universal precautions was applied throughout the period. There has not been a single seroconversion in the rooms where only HCV- patients were dialysed during the 11 years of follow-up. There were two seroconversions in the rooms shared for 3 years by both HCV+ and HCV- patients. In 1995 the prevalence of HCV+ cases in HD and PD was 21.6 and 23.2%, respectively. Since then it has decreased steadily and in parallel for both therapies, and the current prevalence is 6.8% in HD and 5.7% in PD. In HD units with a high prevalence of HCV+ patients, strict isolation in combination with implementation of universal prevention measures can eliminate nosocomial transmission and obtain a long-term reduction in prevalence.

García Ramos R, Ortiz Requena M, Garrido Villoldo A, Vera Chilet MJ. Results of a computerized vaccination database. *An Esp Pediatr* 2002; 56:510-515. [Article in Spanish]

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The aim was to analyse vaccine coverage in children from Picassent in Valencia (Spain) and to evaluate the effectiveness of a new computerised vaccine registration programme. A computer equipped with our self-made Babyvac-2000 programme, based on Microsoft Access was used. The 2,514 entries on children in our database were examined. The results were compared with those in other population groups. Uptake was high: 100 % in 12 of the 15 age groups (according to year of birth). Coverage was as follows: diphtheria-tetanus-pertussis (DTP)-oral polio vaccine was 100 % for 9 groups; the first dose of the triple virus vaccine was 100 % in 7 groups; full vaccination was between 96.2 % and 100 % for all age groups; vaccination at 6 years was between 91.6 % and 98.7 %, the second dose of the triple virus vaccine was between 72.2 % and 96.3 %; vaccination at 14 years was between 82.9 % and 87.7 %; hepatitis B vaccination in young children (from 1994 to 2000) was 100 % in 5 groups and was between 90 % and 98 % in teenagers; the *Haemophilus influenzae* type b vaccination rate was 100 % for children born between 1998 and 2001 and was between 74.3 % and 93.5 % for those born between 1994 and 1997; meningococcal group C conjugated vaccination was between 86.8 % and 100 % for children born between 1994 and 2001. This computer programme considerably increases uptake and vaccine coverage among children.

García-Samaniego J, Soriano V, Miro JM, Romero JD, Bruguera M, Castilla J, Esteban JI, González J, Lissen E, Moreno A, Moreno S, Moreno-Otero R, Ortega E, Quereda C, Rodríguez M, Sánchez-Tapias JM, on behalf of the Spanish Hepatitis-HIV Consensus Panel. Management of chronic viral hepatitis in HIV-infected patients: Spanish Consensus Conference. October 2000. *HIV Clin Trials* 2002;3:99-114.

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Co-infection by human immunodeficiency virus and hepatitis B and C viruses is quite common because they share similar routes of transmission. The introduction of highly active antiretroviral therapy has significantly improved the life expectancy of HIV-infected patients in the last few years. However, chronic viral hepatitis represents an emerging cause of morbidity and mortality in this population, either as a result of end-stage liver disease or as a consequence of hepatotoxicity induced by antiretroviral drugs. The main goal of the Consensus Conference was to establish specific recommendations for the management of chronic viral hepatitis B and C in HIV-infected patients. The role of orthotopic liver transplantation for co-infected individuals with end-stage liver disease was also assessed.

García-Torres ML, Zaragoza A, Giner R, Primo J, del Olmo JA. Incidence and epidemiological factors of hepatocellular carcinoma in Valencia during the year 2000. *Rev Esp Enferm Dig* 2003; 95:385-388, 381-384. [Article in English, Spanish]

Servicio de Hepatología. Hospital Clínico Universitario. Facultad de Medicina. Valencia, Spain.

The aim was to ascertain the incidence and epidemiological factors of hepatocellular carcinoma in the Province of Valencia, Spain. A prospective study was made of hepatocellular carcinoma during the year 2000 collecting all diagnosed cases from four hospitals during that year. A total of 64 cases of hepatocellular carcinoma with a male predominance (42/22) and a mean age of 73.4 years (range of 42-90) were diagnosed. Incidence rate was 8.2 per 100,000, and cirrhosis was known to pre-exist in most cases, half of which were Child-Pugh A. Anti-VHC positive, alone or alcohol or virus B related was detected in 3 of every 4 cases. In the majority of the cases the tumours were located in the right hepatic lobe and the size at first diagnosis was less than 3 cm in 37.3% of the cases. Alpha-fetoprotein levels only exceeded 200 mg/ml in 37.3% of the patients and bore a good size relation to the tumour ($R = 0.245$, $p = 0.003$). No relation vis-a-vis aetiology with age, sex, tumour location or Child-Pugh stage was found. The incident rate of hepatocellular carcinoma in Valencia province during 2000 was 8.2 per 100,000 individuals. This lesion appeared more frequently in men between the ages of 60-80. Hepatitis C virus was the main etiologic agent found.

Gisbert JP, García-Buey L, Arranz R, Blas C, Pinilla I, Khorrami S, Acevedo A, Borque J, Pajares JM, Fernandez-Ranada JM, Moreno-Otero R. The prevalence of hepatitis C virus infection in patients with non-Hodgkin's lymphoma. *Eur J Gastroenterol Hepatol* 2004; 16:135-138.

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Lymphomagenesis is a multifactorial process in which genetic, environmental and infectious factors can be involved. The aim of the present study was to assess the prevalence of hepatitis C virus (HCV) infection among patients with non-Hodgkin's lymphoma (NHL), and to compare it with that of a control group of voluntary blood donors. All consecutive patients with a histological diagnosis of NHL from January 1996 to December 2001 were included in this prospective study. As control group for HCV infection, voluntary blood donors recruited over the same time period from the same geographical area were considered. The presence of anti-HCV antibodies was investigated by ELISA-II and RIBA-II, and viraemia (HCV RNA) was tested by using a polymerase chain reaction (PCR). HCV genotyping was also performed. Ninety-nine patients (mean age 48 years) with NHL were diagnosed during the study period. Histological classification of NHL was high-intermediate grade (63 patients), and low grade (36 patients). Immunophenotype distribution was type B (86 patients) and type T (13 patients). Seven of the 99 NHL patients (7%) were infected with HCV (both using serology and PCR), five of them with immunophenotype B and two with immunophenotype T. The prevalence of HCV infection according to NHL phenotype was 5.8% in B-cell NHL and 15.4% in T-cell NHL. The HCV genotype was 1b in six cases, and 3a in one. In voluntary blood donors (mean age 45 years), HCV infection was detected in 517/55 587 (0.93%). Therefore, HCV infection was more frequent in NHL patients than in controls (odds ratio = 8.1; 95% CI = 3.7-17.6). The odds ratio for the association of HCV and B-cell NHL was 6.2 (95% CI = 2.5-15.3), and for T-cell NHL 16.4 (95% CI = 3.7-72.8). The prevalence of HCV infection in patients with NHL (both B- and T-type) is higher than that observed in controls, suggesting a role of HCV in lymphoma aetiopathogenesis.

González R, Echevarría JM, Avellón A, Barea L, Castro E. Acute hepatitis B virus window-period blood donations detected by individual-donation nucleic acid testing: a report on the first two cases found and interdicted in Spain. *Transfusion* 2006; 46:1138-1142.

Spanish Red Cross Blood Transfusion Center, Madrid, Spain.

Mathematical models predict that, in Spain, a significant number of blood units will be obtained during the window period of the hepatitis B virus (HBV) infection. Routine nucleic acid testing (NAT) on individual blood units may provide experimental data to evaluate such a theoretical risk. Between February and July 2005, a total of 34,631 individual units were screened for HBV DNA by a multiplex transcription-mediated amplification (TMA) test. Units that repeatedly reacted in the test, but did not react for HBV surface antigen (HBsAg), were submitted to additional testing by both molecular and conventional assays, and the donors were recalled for follow-up studies and the collection of clinical and epidemiologic data. Confirmatory testing and follow-up studies identified 2 blood units donated during the HBV infection window period (1/17,316 units studied). Sequencing of amplification products obtained by nested polymerase chain reaction (n-PCR) revealed two HBV strains from genotypes D/ayw3 and F/adw4q-, but did not identify HBsAg mutants. The HBV DNA concentration in the index donations was estimated to be below the n-PCR detection level (180 IU/ml), in both cases. One donor developed acute hepatitis 2 months after donating blood, but the other remained asymptomatic and displayed normal alanine aminotransferase levels at follow-up. The HBV infection window period is a real issue in the setting of Spanish blood transfusions. NAT of individual units by TMA would make a significant contribution to improving the safety of the blood supply in Spain. Additional studies involving a larger number of units and longer periods of time are required, however, to ascertain the true incidence of the problem in this country.

González-García JJ, Mahillo B, Hernandez S, Pacheco R, Diz S, García P, Esteban H, Arribas JR, Quereda C, Rubio R, Díez J, Moreno S, Vázquez-Rodríguez JJ, on behalf of the GESIDA 29/02 and FIPSE 12185/01 Multicenter Study. Prevalences of hepatitis virus coinfection and indications for chronic hepatitis C virus treatment and liver transplantation in Spanish HIV-infected patients. *Enferm Infecc Microbiol Clin* 2005; 23:340-348. [Article in Spanish]

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The aims of this study were to estimate the prevalence of HIV and hepatitis virus coinfection in the Spanish population and to determine the percentage of patients who are candidates for chronic hepatitis C virus (HCV) treatment and liver transplantation within this population. A cross-sectional study was performed in 2002 in two Spanish populations of HIV-infected patients: 1,260 patients from 39 centers throughout Spain (P1) and 1,560 patients from three tertiary teaching hospitals in Madrid (P2). The following hepatitis A virus (HAV), hepatitis B virus (HBV) and HCV serological prevalence were found in the P1 and P2 groups, respectively: HAV-IgG antibodies: 74% and 78%; HBsAg1: 4.9% and 4.8%; HBsAg-, anti-HBc1, anti-HBs1: 39% and 39%; HBsAg-, anti-HBc1, anti-HBs-: 25% and 31%; HBsAg-, anti-HBc-, anti-HBs1: 7% and 8%; HBsAg-, anti-HBc-, anti-HBs-: 22% and 16%. Anti-HCV1: 61% and 65%, respectively. Of the patients with positive HCV serology, 88.8% and 84.6% of each group were positive for HCV-RNA by polymerase chain reaction. Multiple coinfections with hepatitis viruses were found in 3.2% and 2.8%, respectively; of these, 70% and 78% had coinfection with HBV, HCV and HDV. Liver cirrhosis was found in 5.8% and 9.6% of the patients coinfecting with HIV and HCV, respectively. Liver transplant was indicated in approximately one out of every six coinfecting patients with liver cirrhosis. The 43 and 37% of the HCV coinfecting patients were good candidates for anti-HCV treatment, but only 14% and 15% of patients had initiated it. A high percentage of HIV-infected patients in Spain were coinfecting with hepatitis viruses, especially HCV. The

number of possible candidates for liver transplantation is rising and could increase in the next few years. In the future, greater efforts to treat HIV-and hepatitis virus-coinfected patients will be required.

González Cerrajero M, Pazos García A, de los Santos Gil I, Sanz Sanz J. Prevalence of hepatitis C virus among HIV-infected patients in Area 2 of Madrid. *An Med Interna* 2006; 23:111-114. [Article in Spanish]

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The evolution of HIV infection, a rapid and fatal illness not long time ago, has become a chronic disease due to the implementation of new antiretroviral treatment. Therefore it is essential to focus on the management of concurrent illnesses such as chronic hepatitis C infection, specially as they share common routes of transmission. A cross-sectional survey was done to determine the prevalence of HIV and HCV coinfection, measuring different HIV and HCV variables among 651 HIV infected patients of a health area in Madrid. 500 patients (76.8%) were male and 151 female (23%). HCV serology was performed in all the patients and resulted positive in 45.7% (298) most of them drug users (84.8%). The CD4 cell count was lower in patients HIV-HCV coinfecting compared to those HCV negative ($p < 0.001$). This study shows a high prevalence of HIV-HCV coinfection, mainly due to parenteral transmission. We emphasise the low percentage of coinfecting patients treated with interferon and ribavirine which probably will increase in the future.

González-Praetorius A, Rodriguez-Avial C, Fernandez C, Teresa Pérez-Pomata Mf M, Gimeno C, Bisquert J. The prevalence of hepatitis A in the Guadalajara province. Is Spain a country with low endemia?. *Enferm Infecc Microbiol Clin* 2001; 19:428-431. [Article in Spanish]

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Spain, together with the other southern European countries, was considered to be an area with a moderate degree of endemia. This fact has consequences for tourists that visit these areas and for vaccination strategies. A prevalence study was proposed in order to get to know the situation of this infection in the Guadalajara province. 284 specimens of serum were taken from patients who were classified according to their age, sex and place of residence (with more or less than 10.000 inhabitants). In these specimens the presence of hepatitis A antibodies were studied, using a Microparticule Enzyme Immunoassay (MEIA) (Abbott). An increase in the prevalence was observed in older people, there is a low prevalence population ($\leq 5\%$) in people aged between 0-29 years and a high prevalence population ($>80\%$) in adults aged between 30 and 74 years. No differences were observed related to sex. In the stratified analysis according to age, differences were observed between the groups from rural and urban origins. The low prevalence of hepatitis A was found among the younger population, as seen in other studies carried out on a national level, and this together with a decrease in the frequency, means that Spain is included among the countries with low endemia. This fact has consequences for tourists who visit our country and for vaccination strategies, due to the increase in the number of adults who are susceptible to the infection.

González Praetorius A, Rodriguez-Avial C, Fernandez C, Pérez Pomata MT, Gimeno C, Bisquert J. Incidence and risk factors for hepatitis A in the province of Guadalajara (Spain). *Gastroenterol Hepatol* 2002; 25:230-234. [Article in Spanish]

Seccion de Microbiologia, Hospital General de Guadalajara, Spain.

The decrease in the prevalence of hepatitis A in Spain may modify the characteristics of this infection because of the rise in the susceptible adult population. The aim of this study was to determine the incidence of this disease, as well as the epidemiological characteristics and the complications of patients diagnosed in the province of Guadalajara between 1991 and 1999. The inclusion criterion was the presence of specific IgM together with an increase in alanine aminotransferase concentrations and/or symptoms compatible with acute hepatitis. The mean incidence was 7.13 cases/105 inhabitants. Considerable differences were found between years due to the presence of an outbreak. Most cases occurred in children and young adults. The most frequent risk factor found overall was contact with an infected individual but the distribution of risk factors differed between children and adults. The decrease in the prevalence of hepatitis A in Spain entails an increase in the susceptible adult population. Consequently, hepatitis A may cease to be a typically pediatric disease and may become one that also affects young adults in whom it may have different characteristics. This consideration should be borne in mind when designing a vaccination strategy.

Gutierrez M, Tajada P, Alvarez A, De Julian R, Baquero M, Soriano V, Holguin A. Prevalence of HIV-1 non-B subtypes, syphilis, HTLV, and hepatitis B and C viruses among immigrant sex workers in Madrid, Spain. *J Med Virol* 2004; 74:521-527.

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Sexually transmitted disease (STD) remains a major public health challenge in developed countries, exacerbated by the advent of the HIV epidemic. The objectives of this study were to assess the prevalence of serological markers of syphilis, HIV-1/2, HTLV-I/II, HBV, and HCV infections among immigrant sex workers in Madrid, Spain and to characterise the HIV-1 variants in seropositive individuals. Sera from 762 immigrant commercial sex workers (75.3% from sub-Saharan Africa, 18.2% from South America, and 6.4% from Eastern Europe) were collected between 1998 and 2003 in Madrid and examined. Antibody detection was performed by screening assays (RPR, ELISAs) and confirmed by FTA-Abs, LIAs and Western-blot tests. HIV-1 subtyping was carried out by phylogenetic analyses of the protease and envelope genes. Antibodies to HIV-1 were found in 5.2%, while 3.5% tested positive for HBsAg, 3% for syphilis antibodies, 0.8% for HCV antibodies, and 0.2% for HTLV-I antibodies. None were reactive for HIV-2 or HTLV-II antibodies. HIV-1 seroprevalence among Africans and Ecuadorians was 4.5 and 10.9%, respectively. All HIV-1 seropositive Ecuadorians were transsexual men, and 28.6% had active syphilis infection. Up to 80% of HIV-1 positive specimens were characterised as non-B subtypes, with subtypes G, A, and G/A recombinants being the most frequent among African individuals. In contrast, South Americans with HIV-1 infection carried exclusively subtype B variants. A relatively high proportion of immigrant sex workers in Madrid were infected with HIV-1 and syphilis, whereas infections with hepatitis viruses or HTLV were uncommon.

Gutierrez-Zufiaurre N, Sánchez-Hernandez J, Muñoz S, Marin R, Delgado N, Saenz C, Muñoz-Bellido JL, García-Rodríguez JA. Seroprevalence of antibodies against *Treponema pallidum*, *Toxoplasma gondii*, rubella virus, hepatitis B and C virus, and HIV in pregnant women. *Enferm Infecc Microbiol Clin* 2004; 22:512-516. [Article in Spanish]

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The prevalence of antibodies against *Treponema pallidum*, *Toxoplasma gondii*, rubella virus, hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) was investigated in pregnant women. With the use of several serological methods in samples from women who had their first obstetric visit in 2001, we studied the prevalence of serum antibodies against *T. pallidum*, *T. gondii*, rubella virus, HBV and HCV in 2,929 pregnant women, and anti-HIV antibodies in the 1,349 women agreeing to this test. Antibodies against *T. pallidum* were not

detected in any case. HBsAg was found in 11 patients (0.4%), six of whom (54.5%) were not aware of their condition. The presence of anti-rubella antibodies was almost universal (99.95%). In the total population, 18.8% of patients had anti-*T. gondii* antibodies; only one had a serological profile suggesting acute toxoplasmosis. Among the 1,349 women studied, anti-HIV antibodies were detected in two intravenous drug abusers who were aware of their condition. Anti-HCV antibodies were found in 0.4% of the series, and 36.4% of the HCV-positive patients had no knowledge of their condition. Active infection by *T. pallidum* in pregnant women in Spain is currently exceptional. The level of immunization against rubella virus is excellent. Seropositivity to *T. gondii* is lower than rates reported in earlier studies. The prevalence of HBsAg and anti-HCV antibodies is around 0.4%, and seropositive status is often discovered in routine serological studies performed during pregnancy. HIV seropositivity is low, and the pregnant women included in this study were aware of their condition.

Hernandez-Aguado I, Ramos-Rincon JM, Avinio MJ, González-Aracil J, Pérez-Hoyos S, de la Hera MG, on behalf of the Valencian Epidemiology and Prevention of HIV disease Study Group. Measures to reduce HIV infection have not been successful to reduce the prevalence of HCV in intravenous drug users. *Eur J Epidemiol* 2001; 17:539-544.

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The objective of the study was to determine whether measures taken to prevent human immunodeficiency virus (HIV) infection also lead to a reduction in the prevalence of hepatitis C virus (HCV) infection among intravenous drug users (IDU). Antibodies to HCV, HIV and hepatitis B virus (HBV) were determined in IDU who voluntarily attended AIDS prevention and information centres for the first time between 1990 and 1996. Of the 5473 IDU studied, determination of HCV was done in 3238 cases. The prevalence of antibodies to HCV was 85%. During the first period studied (1990-1992), the prevalence of antibodies to HCV was 84.5%, during the second (1993-1994) 84.1% and during the third (1995-1996) 87%; in the case of HBV the prevalence during the three periods was 74.5, 67.6 and 66.8% respectively, and for HIV it was 41.9, 38.8 and 36.6% respectively (RR: 0.72; 95% confidence interval (CI): 0.65-0.81). Among drug users addicted for less than 2 years, the trend of the prevalence of antibodies to HCV and HBV remained constant, while the prevalence of HIV infection decreased (RR: 0.61; 95% CI: 0.42-0.89). Measures to prevent transmission of HIV in drug users do not lead to a reduction in the prevalence of HCV infection. Further study is necessary to obtain a better understanding of how HCV is transmitted among drug users in order to apply measures which are effective in preventing HCV infection.

Huerga H, López-Velez R. Infectious diseases in sub-Saharan African immigrant children in Madrid, Spain. *Pediatr Infect Dis J* 2002; 21:830-834.

Tropical Medicine Unit, Department of Infectious Diseases, Hospital Ramon y Cajal, Madrid, Spain.

Immigration flow from developing countries to European countries is growing continually, but data about imported infectious diseases in immigrant children are few. We designed a descriptive and retrospective study of 125 sub-Saharan African children < 14 years of age attending a tropical medicine referral unit in Madrid, Spain, between 1989 and 2001. Of the 125 children 79% had 1 or more symptoms. The remaining 21% (26 cases) were asymptomatic and were screened for infectious diseases. Of them 57.7% (15 cases) had 1 or more infectious diseases. Significant association (< 0.05) was found between fever and malaria, between cutaneous pruritus and filariasis and between eosinophilia and filariasis and intestinal helminthiasis. Seventy-nine percent had infectious pathology and 33.3% were infected by 3 or more agents. Fifty-six (44.8%) cases of

malaria were diagnosed: 7 (12.5%) were asymptomatic; 43 (76.8%) were caused by and 5 (8.9%) were mixed malarial infections. Intestinal parasitic infection was diagnosed in 44 (49.4%) of the 89 cases investigated. No significant difference existed between gastrointestinal symptoms and the presence of intestinal parasites (> 0.05). Thirty-nine (21.9%) cases of filariasis were diagnosed. Hepatitis B serology was performed in 75 children: 24 (32%) were cured hepatitis B (antibody-positive only); 5 (6.6%) were hepatitis B surface antigen-positive; and 1 of 59 cases (1.7%) was hepatitis C-positive. The prevalence of latent tuberculosis infection was 12.9% (7 of 54 purified protein derivative skin tests performed). The high infection rates of some diseases in immigrant children point to the need for screening sub-Saharan African children.

Jadoul M, Poignet JL, Geddes C, Locatelli F, Medin C, Krajewska M, Barril G, Scheuermann E, Sonkodi S, Goubau P, on behalf of the HCV Collaborative Group. The changing epidemiology of hepatitis C virus (HCV) infection in haemodialysis: European multicentre study. *Nephrol Dial Transplant* 2004; 19:904-909.

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The high prevalence of anti-hepatitis C virus (HCV) antibodies in HD patients has been known since the early 1990s but its evolution over the last decade is poorly documented. All chronic HD patients from 15 Belgian units were tested at (re)start of HD and every 18 months for anti-HCV antibodies (ELISA 2 in May 1991 and November 1992, then ELISA 3 until May 2000). All chronic HD patients from HD units from eight other European countries, whose prevalence of anti-HCV (+) patients had been studied in 1991-1994 (and published except in one country), were tested for anti-HCV antibodies in 1999. Anti-HCV (+) prevalence decreased ($P < 0.001$) from 13.5 (1991) to 6.8% (2000) in the Belgian cohort ($n = 1710$). Prevalence also decreased ($P < 0.05$) in the participating units from France (42-30%), Sweden (16-9%) and Italy (28-16%), tended to decrease in the participating units from UK (7-3%, $P = 0.058$) and Hungary (26-15%, $P = 0.057$) but did not change (NS) in the participating units from Germany (7 to 6%), Spain (5 to 12%) and Poland (42 to 44%). In the Belgian cohort, the prevalence of anti-HCV(+) at (re)start of HD did not change significantly over 1991-2000. The prevalence of anti-HCV(+) in HD has decreased markedly over the last decade in the participating units from most European countries. This decrease should reduce further the risk of nosocomial and occupational HCV infection in HD and ultimately contribute to improved long-term prognosis of HD patients and kidney graft recipients.

Jardi R, Butí M, Cotrina M, Rodriguez F, Allende H, Esteban R, Guardia J. Determination of hepatitis delta virus RNA by polymerase chain reaction in acute and chronic delta infection. *Hepatology* 1995; 21:25-29.

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The objective of this study was to evaluate the usefulness of hepatitis delta virus (HDV) RNA detection by polymerase chain reaction (PCR) in acute and chronic D hepatitis and to correlate with HDV-RNA detection by dot blot and hepatic delta antigen. Serum samples from 33 patients with acute hepatitis B surface antigen (HBsAg)-positive hepatitis (15 with hepatitis B and D coinfection, 8 with HDV superinfection, and 10 with acute hepatitis B), 85 patients with chronic HBsAg-positive hepatitis (73 with chronic D hepatitis and 12 with chronic B hepatitis), and consecutive serum samples from nine patients with chronic D hepatitis treated with interferon alfa-2b were studied. HDV-RNA was detected by PCR in 93% of the patients with hepatitis B and D coinfection, in 100% of the patients with hepatitis D superinfection, and in 1 of the 10 patients with acute hepatitis B who subsequently seroconverted to total antibody to hepatitis delta antigen (HDAg), whereas HDV-RNA was found by dot blot technique in 60% of the hepatitis B and D coinfection cases, in 62.5% of the patients with hepatitis D superinfection, and in none of the acute

hepatitis B cases. In chronic D hepatitis, HDV-RNA tested positive by PCR assay in 97% of patients with intrahepatic HDAg, in one patient with undetectable hepatic HDAg, and in none of the patients with chronic hepatitis B. In the treated patients, HDV-RNA was observed to become negative by PCR only in the three patients who had a persistent response to interferon.

Jardi R, Rodriguez F, Butí M, Costa X, Cotrina M, Galimany R, Esteban R, Guardia J. Role of hepatitis B, C, and D viruses in dual and triple infection: influence of viral genotypes and hepatitis B precore and basal core promoter mutations on viral replicative interference. *Hepatology* 2001; 34:404-410.

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The interactions among hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis delta virus (HDV) were studied by measuring HBV-DNA and HCV-RNA levels and by determining the influence of viral genotypes and mutations in HBV basal core promoter (BCP) and precore regions. We included 65 consecutive patients, 25 HBV/HCV, 18 HBV/HDV, and 22 HBV/HCV/HDV. Controls consisted of 55 patients with chronic HBV and 55 with chronic HCV infection. HBV-DNA and HCV-RNA levels were lower in coinfections than in single infections ($P < 0.05$). HBV/HCV coinfection was associated with lower HBV viremia (8.2×10^4 copies/ml) and lower HCV-RNA levels (7×10^5 IU/ml), than the corresponding control group ($P < 0.05$), with more marked decrease in HBV replication ($P < 0.05$). Moreover, in HBV/HCV coinfection and in triple coinfection we observed an inverse relationship between HBV-DNA and HCV-RNA levels ($P < 0.05$). HBV/HDV coinfection was associated with lower HBV viremia (2.5×10^4 copies/ml) than that found in HBV infection ($P < 0.05$). Patients with triple coinfection showed lower HBV-DNA and HCV-RNA levels than control groups ($P < 0.05$). Prevalence of precore mutations was lower in HCV coinfections ($P < 0.05$). No significant association was observed between HCV-RNA levels and HBV precore mutations, BCP mutations or HBV genotypes, or between HBV-DNA levels and HCV genotypes ($P < 0.05$). In conclusion, HCV exhibited stronger inhibitory action in the reciprocal inhibition seen in HBV/HCV coinfection. HDV was the dominant virus in HBV/HDV coinfection and in triple coinfection, and had a greater unfavorable influence on HCV than on HBV replication. The reciprocal inhibition of viral replication seemed to be little influenced by the inherent genomic factors studied.

Jimenez Fabrega X, Carballo Almeida A, Batalla Martínez C, Comin Bertran E, Cuenca Oliva AM, Ezpeleta García A, López Gonzalo E, Parellada Esquiús N. The prevalence of infection by the hepatitis B, C and human immunodeficiency viruses in drug users. *Aten Primaria* 1999; 24:368-371. [Article in Spanish]

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The aim was to estimate the prevalence of the hepatitis B (HBV) infection, hepatitis C (HCV) and human immunodeficiency virus (HIV) and its coexistence in intravenous drug users, in order to start afterwards a vaccination and sanitary training programmes. Intravenous drug users attended in a health centre and in the drugs addition deshabitation centre of reference located in a marginal urban quarter. Patients were detected from the health centre. During one year (June 1995-1996) facts were collected. The age, sex, consumption, type, administration mechanism and also the described serologies were analysed. It has been carried out descriptive statistics and applied the chi-square [correction of square-ji] test. A study of 355 patients, 295 (83.1%) males and 60 (16.9%) females was carried out. The average age was 28.6 years (SD = 6.5). All serologies in 113 (31.8%) were available. The positive serologies for HIV, 64.6% for HBV and 64.4% had 71.1% for HCV. The three of them coexisted in a 35.4% between HIV, 39.1% of them were VHB and 88% VHC. 49.1% were VHB and VHC. The infection from any of the three virus was related with

intravenous administration mechanism, but not with sex or drug type. The infection caused from the virus above mentioned is frequent in drug users. A not negligible percentage of patients could benefit from the hepatitis B vaccine administration (67.6%) or other preventive measures.

Junquera S, Mateos M, Lasa E, Chacon J, Baquero F. Seroepidemiologic study of hepatitis A in the community of Madrid during the year 2002. *Enferm Infecc Microbiol Clin* 2004; 22:448-451. [Article in Spanish]

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The aim of this study was to investigate the prevalence and risk factors associated with hepatitis A virus (HAV) infection in a representative population sample to determine who can benefit from vaccination strategies and to investigate the age limit at which previous HAV antibody screening is not required. From April to September 2002, we studied a total of 557 patients, 90 children and 467 blood donors, aged 1-65 years. Information on demographic variables (age, gender, place of residence and education level) was recorded. Patients with history of hepatitis or other liver diseases were excluded. Anti-HAV antibodies (IgG) were determined with an automated enzyme immunoassay (AxSYM, Abbott Diagnostics). The chi-square and Mantel-Hänszel tests were used for the statistical analysis. The overall prevalence of HAV infection was 41.5%. There was a significant increase in prevalence with age (chi-square TL:205, $P < 0.0001$), with rates from the youngest to oldest groups of 5.5%, 23.5%, 28.1%, 64.2% and 93.2%, respectively. Apart from age, the only other risk factor independently associated with prevalence was the level of education, with higher prevalence at the lower education levels (OR 5 2.7; chi-square = 32.11, $P < 0.0001$). The prevalence of anti-HAV antibodies has decreased in recent years in the community of Madrid. Among the population less than 35 years of age, 75% of individuals are susceptible to the infection and could benefit from universal vaccination without previous screening for anti-HAV antibodies.

Laguno M, Sánchez-Tapias JM, Murillas J, Fornis X, Blanco JL, Martínez E, Larrousse, Leon A, Lonca M, Milinkovic A, Miro JM, García F, Gatell JM, Mallolas J. Advances in the diagnosis and treatment of hepatitis C virus infection in patients with and without HIV infection. *Enferm Infecc Microbiol Clin* 2005; 23:32-40. [Article in Spanish]

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The chronic infection by the hepatitis C virus represents a serious sanitary problem affecting 1-3% of the world-wide population. It is transmitted by sexual route, vertical route and mainly after blood exposure by percutanea route. While HIV shares similar routes of transmission, the co-infection HCV-HIV is very frequent and the chronic hepatopathy and complications associated with its clinical course are an important cause of morbi-mortality in this population. The gold standard of the treatment for the HCV, has been the interferon and later the combination therapy of interferon plus ribavirine. Currently, the combination of ribavirine and a new pegilated formulation of the interferon has become the standard in the treatment reaching rates of sustained viral response around 40-80%.

Leon P, López JA, Amela C, Elola C, Echevarría JM, on behalf of the Spanish Group for the Study of Blood Donors with Risk of HCV Transmission. Prevalence of types of hepatitis C virus in Spanish blood donors: results of a state-based multicenter study. *Enferm Infecc Microbiol Clin* 1999; 17:448-534. [Article in Spanish]

Servicio de Microbiología Diagnostica, Centro Nacional de Epidemiología, Madrid.

The prevalences established up to the present in Spain for the different types of hepatitis C virus are based on data obtained in populations in which the nature of the population itself may have biased the data in favor of certain types of the virus. The study of seropositive blood donors identified through screening of blood donations may provide prevalences closer to the truth among the general population. Typing of genomes in samples from 441 donors was performed using the blood bank generated during the multicenter study performed by the Spanish Study Group of Blood Donors with Risk of Transmission of the Hepatitis C Virus. The antibodies present were typed in the seropositive samples in the above donors and in 337 more in whom a viral genome was not detected. In total, the infection was typed in 685 donors. On analysis of the results corresponding to 386 donors, whose number and distribution by autonomous communities were previously fixed to represent all of Spain, type 1 was largely the more prevalent (85.5%) followed by types 3 (4.4%), 2 (4.1%), 4 (3.4%) and 5 (0.5%) and by a group of apparent mixed infections which altogether represented 2.1% of the total. Among the donors in whom the genomes were typed, infectious due to the 1b subtype (78% of the 441 samples genotypes) clearly predominated. The participation of the different types of type 1 was significantly greater in those lacking antibodies detectable versus epitopes codified in the NS4 region of the viral genome. This study avoids some bias in sampling which may have affected previous studies and provides data which should more closely approach the real prevalence in the general Spanish population. Thus, it should provide a better base of comparison for any study on the distribution of the types of the hepatitis C virus in selected populations or others performed during the investigation of outbreaks of hepatitis C virus infection.

Leon P, Pozo F, Echevarría JM. Detection of hepatitis B virus variants resistant to lamivudine and famciclovir among randomly selected chronic carriers from Spain. *Enferm Infecc Microbiol Clin* 2004; 22:133-137.

Diagnostic Microbiology Department, National Center for Microbiology. Instituto de Salud Carlos III, Majadahonda, Madrid, Spain.

Treatment for chronic hepatitis B with lamivudine is often hampered by the emergence of point mutations in the YMDD motif of the HBV DNA polymerase gene that confer drug resistance. This usually occurs after several months of therapy, but early detection of lamivudine-resistant mutants has been reported among patients in South Korea. Data from Japan and France suggest that naturally occurring, lamivudine-resistant hepatitis B virus (HBV) variants can be found among chronic carriers who have never received lamivudine treatment. Famciclovir can be used as an alternative when lamivudine-resistant variants emerge, though the substitute treatment may also give rise to the emergence and selection of drug-resistant variants. The presence of mutations related with lamivudine and famciclovir resistance was studied in serum samples from 79 randomly selected Spanish HBV carriers, using a line probe assay (LiPA) on HBV genome fragments amplified by polymerase chain reaction. Data concerning antiviral therapy prior to sampling were available for these patients. Mutations related with resistance to either drug were detected in ten patients. Three of them (3.8% of the 79 carriers studied) had no record of prior lamivudine or famciclovir treatment at the time of sampling. Wild-type strains together with either the rtM204I (M552I) or rtV207I (V555I) point mutation were found in two of these cases, and the rtV207I mutation alone was detected in the third. These findings seem to indicate that lamivudine and famciclovir-resistant variants circulate among Spanish HBV carriers. Since it is expected that antiviral therapy will be ineffective when drug-resistant variants are present before the beginning of treatment, it could be beneficial to test for these variants as an additional routine procedure when designing antiviral therapy on an individual basis.

Llach-Berne M, Panella H, Domínguez A, Cayla JA, Godoy P, Alvarez J, Sala R, Camps N, on behalf of the Grupo de Estudio de Hepatitis A. Descriptive study of hepatitis outbreaks occurring in Catalonia (1999-2003). *Enferm Infecc Microbiol Clin.* 2006; 24:431-436. [Article in Spanish]

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The currently low endemic level of hepatitis A in Spain favors manifestation of the disease as outbreaks among specific risk groups. The aim of this study is to analyse the hepatitis A outbreaks investigated in Catalonia (Spain) during the period of 1999 to 2003. The criteria for including an outbreak were defined and outbreaks were classified according to the type of transmission. The variables analysed were space, time, socio-demographic parameters, setting, risk factors, and preventive measures adopted. The incidence rate and rate ratio were calculated according to age and sex. Among 74 outbreaks, 73 fulfilled the inclusion criteria. Most outbreaks involved person-to-person transmission (83.8%) and the rest had a common source of infection (14.9%). In total, 334 cases were included (cumulative incidence 1999-2003: 5.27 per 100,000 inhabitants), with an average age of 24.5 years. The settings yielding the most cases were family (143), community (97) and schools/preschools (87). The number of cases per outbreak ranged from 2 to 11, except one outbreak that occurred in 83 young homosexual men with high-risk sexual practices. The main factors related to the case index or to coprimary cases included belonging to age groups with low immunity (children and young adults) and travelling to or from endemic areas. Hepatitis A outbreaks in Catalonia are still frequent. They mainly occur in the family environment, by person-to-person transmission and in the most vulnerable groups (preschool or school employees, travelers, and men who perform high-risk sexual practices with other men).

Lopalco PL, Salleras L, Barbuti S, Germinario C, Bruguera M, Butí M, Domínguez A. Hepatitis A and B in children and adolescents--what can we learn from Puglia (Italy) and Catalonia (Spain)? *Vaccine* 2000; 19:470-474.

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Viral hepatitis remains a major contributor to the global disease burden. Mass immunisation strategies against hepatitis B have been adopted by more than 90 developing and industrialised countries. Countries with low hepatitis A endemicity are experiencing cyclical outbreaks and an epidemiological shift, with larger numbers of individuals at risk of infection at an older age, resulting in increased morbidity. The high cost of outbreaks in these countries has made immunisation strategies cost-effective. The development of a vaccine against hepatitis A and a combined vaccine against hepatitis A and hepatitis B offers potentially exciting opportunities for a preventative approach in areas of both low and high endemicity. Existing mass immunisation programmes against hepatitis B will facilitate the adoption of joint strategies illustrated by the examples of Puglia (Italy) and Catalonia (Spain)

López-Aldeguer J, González-García J, Suarez-Lozano I, Estrada Pérez V, Pedreira Andrade JD, Segura Porta F. Treatment of HIV infection in patients with comorbidity. *Enferm Infecc Microbiol Clin* 2002; 20(Suppl 2):10-18. [Article in Spanish]

Unidad de Enfermedades Infecciosas, Hospital Universitario La Fe, Valencia.

HIV-positive patients often have concurrent diseases that may condition antiretroviral treatment. Changes may be due to interactions between medicines, specific toxicity of the antiretroviral treatment or malfunction of the diseased organ affecting the metabolism of the antiretrovirals. In cases of opportunist illness, tuberculosis or lymphoma / neoplasia of solid organ, certain points

must be remembered. Only in case of severe immuno-depression will anti-tuberculosis and anti-retroviral treatment be initiated simultaneously. If the CD4 figure is over 350, antiretroviral treatment must be postponed till after tuberculosis. In case of lymphoma or solid tumour, once the side-effects of chemotherapy after the first cycles are known, antiretroviral treatment will be started. The use of opiates counter-indicates the start of treatment because of lack of adherence, but can be given if the patient is taking methadone. Coinfection with the hepatitis B or C virus will affect antiretroviral medication, depending on the degree of liver-cell failure and on how the hepatitis is treated. Some change in the antiretroviral treatment may improve the metabolic disturbances or the appearance of the body. However, hyperlactacidaemia requires modification or withdrawal of the nucleoside analogues. In case of renal failure only the drugs eliminated through this pathway need their dose adjusted so as to avoid the toxicity related to greater exposure to the drugs or their metabolites. Before a serious intercurrent picture, withdrawal of antiretroviral treatment for a limited period of times does not worsen the prognosis.

López-Caleya JF, Martín V, Martín L, Pérez-Simon R, Carro JA, Alcoba M. Prevalence of coinfection by human immunodeficiency virus and hepatitis C virus in the Leon Health Area: 1992-2000]. *Enferm Infecc Microbiol Clin* 2006; 24:365-369. [Article in Spanish]

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The aim was to ascertain the prevalence of HIV and hepatitis C (HCV) coinfection in the Health Area of Leon in the period of 1992 to 2000. The study included patients with HIV infection, residing for at least two years in the area, and attended at the Department of Internal Medicine of Leon Hospital. Sociodemographic information and risk behavior were recorded. Data from the Municipal Census of 1 May 1996 were used to calculate prevalence. Statistical analyses were carried out with the chi-square test or analysis of variance, according to the cases. The prevalence of HCV infection among HIV-positive patients was 56.8%. Coinfected men were younger than women and coinfection was higher in the parenteral transmission than in the sexual transmission groups. Prevalence was estimated at 53.2 cases per 100,000 inhabitants of the Area (82.7 for men and 25.7 for women). The groups showing the highest prevalence were men aged 25-34 and 35-44 years. The epidemiology of the coinfection was mainly attributable to injected drug use. There was a decrease in the number of coinfection cases diagnosed during the study period. The prevalence of HIV/HCV coinfection in the Leon Health Area was lower than the rate estimated for Spain as a whole owing to a lower incidence of HIV infection and intravenous drug use. Nevertheless, HIV/HCV coinfection is a major public health problem, and resources should be allocated for its prevention and treatment.

Lumbreras B, Jarrin I, del Amo J, Pérez-Hoyos S, Muga R, García-de la Hera M, Ferreros I, Sanvisens A, Hurtado I, Hernandez-Aguado I. Impact of hepatitis C infection on long-term mortality of injecting drug users from 1990 to 2002: differences before and after HAART. *AIDS* 2006; 20:111-116.

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We aimed at assessing the impact of HIV and hepatitis C virus (HCV) infection on long-term mortality in injecting drug users (IDU). Design: community-based prospective cohort study. Mortality data from follow-up in clinical sites and the Mortality Registry by December 2002 were collected for 3247 IDU who attended three centres for voluntary counselling and testing for HIV/AIDS, HCV and hepatitis B virus (HBV) in 1990-1996. Mortality rates by Poisson regression were adjusting for age, sex, duration of drug use, education, HBV and calendar period (1990-1997 and 1998-2002). Overall, 11.2% were HIV/HCV negative, 43.7% positive only for HCV and 45.1% positive for both. During 26 772 person-years of follow-up, 585 deaths were detected (2.19/100 person-years). Before 1997, HIV/HCV-positive subjects had a five-fold increase in risk

of death [relative risk (RR), 5.4; 95% confidence interval (CI), 2.5-11.4] compared with those negative for both; after 1997, a three-fold increase was observed (RR, 2.7; 95% CI, 1.7-4.2). Being HCV positive/HIV negative was not associated with an increase in the risk of death either before (RR, 1.3; 95% CI, 0.6-2.9) or after (RR, 1.2; 95% CI, 0.8-1.9) 1997 compared with HCV/HIV negative. While increases in mortality were seen in those HCV/HIV negative (RR, 1.6; 95% CI, 0.7-3.7) and those only positive for HCV (RR, 1.5; 95% CI, 1.0-2.1), a 20% reduction among coinfecting IDUs was observed after 1997 (interaction $P = 0.033$). HCV/HIV coinfection has had a large impact on mortality in IDU. After 1997, mortality increased in HIV negative/HCV positive subjects and decreased in HIV positive/HCV positive.

Mallolas J, Sánchez-Tapias JM, Moreno S, Gatell JM, Tellez MJ, Rubio R, Ledesma E, Domingo P, Barreiro P, Pedreira J, Romero M, González-Lahoz J, Lissen E. Consensus conference on chronic viral hepatitis and HIV infection: updated Spanish recommendations. *J Viral Hepat* 2004; 11(1):2-17.

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Chronic hepatitis B and C represent a leading cause of morbidity and mortality among human immunodeficiency virus (HIV)-infected patients worldwide. New treatment options against both hepatitis B (HBV) and C (HCV) viruses have prompted us to update previous recommendations for the management of coinfecting individuals. Fifteen topics (nine related to HCV, five to HBV and one to both viruses) were selected for this purpose. A panel of Spanish experts in the field was invited to review these areas and propose specific recommendations, which were scored according to the Infectious Disease Society of America (IDSA) grading system. These guidelines represent a comprehensive and updated overview on the management of hepatitis B and C in HIV-infected patients.

Martínez-Bauer E, Crespo J, Romero-Gomez M, Moreno-Otero R, Sola R, Tesei N, Pons F, Fornis X, Sánchez-Tapias JM. Development and validation of two models for early prediction of response to therapy in genotype 1 chronic hepatitis C. *Hepatology* 2006; 43:72-80.

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Early prediction of response to therapy in genotype 1 chronic hepatitis C is difficult. Two predictive models, a pretreatment scoring model (PreT-SM) and a fourth week of therapy scoring model (4w-SM) were constructed in a cohort of 104 patients from a single center (estimation cohort) and validated in a cohort of 141 patients from four independent centers (validation cohort). Individual scores were calculated using variables independently associated with sustained virological response (SVR). Baseline viral load, aspartate aminotransferase/alanine aminotransferase ratio, serum cholesterol, and a numerical score for noninvasive estimation of liver fibrosis were included in the PreT-SM; HCV RNA clearance and PreT-SM scores were included in the 4w-SM. Receiver operating characteristic analysis revealed the area under the curve in the estimation cohort and in the validation cohort to be, respectively, 0.856 and 0.847 for the PreT-SM and 0.908 and 0.907 for the 4w-SM. Low scores were associated with SVR, high scores with non-SVR. The best cutoff scores from the PreT-SM (7 and 9.70) identified, respectively, 36% of patients with SVR and 41% of those with non-SVR from the validation cohort, with high accuracy ($> \text{or} = 90\%$ positive predictive value [PPV] and specificity). Similarly, cutoff scores of 3.20 and 5.60 from the 4w-SM identified, respectively, 71% of patients with SVR and 53% of those with non-SVR from the same cohort with high accuracy (PPV and specificity $> 92\%$). In conclusion, these models predicted response to therapy before or after 4 weeks of treatment in approximately 60% of genotype 1 patients and may be valuable for the management of this condition.

Martínez-Campillo F, Teran M, Alvarez M, Rigo MV, Roda J, Salinas M, García JM. Prevalence of anti-HAV antibodies and efficacy of pre-vaccine detection at institutions for mentally retarded of the city of Alicante. *Aten Primaria* 2000; 25:552-555. [Article in Spanish]

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The aim of this study was to investigate the prevalence and efficacy of the anti-HAV antibodies detection in institutions for mentally retarded people in the city of Alicante. Design: prevalence study. Setting: two institutions for mentally retarded people in the city of Alicante. Participants: One hundred and seven residents and seventy seven in care of them. We have investigated the anti-HAV antibodies prevalence by enzyme immunoanalysis of microparticle test. The efficacy of the anti-HAV antibodies detection before the vaccination has been studied by calculating the threshold of prevalence with the following formula: unit cost of detection + (1 - X) x unit cost vaccination anti-HAV negative subjects = unit cost vaccination. The global prevalence of anti-HAV antibodies was 56.5% (95% CI, 49-63.7). The prevalence of the residents was 55.1% (95% CI, 45.2-64.7) and 58.4% in care of them (95% CI, 46.6-69.5). Among the sociodemographic variables evaluated only the age was associated with the prevalence of anti-HAV antibodies ($p < 0.001$). The unit cost of prevaccination detection of anti-HAV antibodies was calculated as 998 pesetas and the unit cost of the vaccination as 3595, obtaining a prevalence anti-HAV threshold of 27.8%. The prevalence of anti-HAV antibodies in this collective studied is similar to the prevalence of anti-HAV antibodies of the Spaniard population. The direct vaccination without a previous marker study is recommended to people under the age of 31 in this population group.

Moreno R, Berenguer M. Liver transplantation in patients with chronic viral hepatitis. *Rev Gastroenterol Mex.* 2005; 70:180-191. [Article in Spanish]

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Liver transplantation (LT) for end-stage liver disease secondary to hepatitis viruses has evolved rapidly during the last two decades. Currently, due to significant improvements in immunosuppressive therapy and surgical techniques, excellent survival rates and quality of life can be achieved. Among several circumstances that may pose a threat to long-term survival, the greatest is likely the recurrence of the original liver disease. Recurrence of viral infection and hepatitis is a common problem for patients undergoing LT for hepatitis B or hepatitis C. In the early 1980s, results of LT for chronic hepatitis B virus (HBV) infection were hampered by recurrent infection and subsequent allograft failure. However, following the introduction of passive immunoprophylaxis with hepatitis B immunoglobulin (HBIG) and treatment with potent oral nucleoside analogs, there has been a resurgence in the interest for this indication. HCV-related end-stage liver disease virus accounts for approximately 50% of LT in the United States and Europe. Despite the decrease in the number of new HCV infections, the prevalence of advanced HCV-related liver disease is steadily increasing. In light of the near universal recurrence of posttransplantation HCV infection and our limited ability to treat recurrent disease, transplantation is in danger of being overrun by viral hepatitis, unless effective strategies can be used to treat disease. This review summarises available data and highlights appropriate strategies to improve outcomes.

Moreno Planas JM, Fernandez Ruiz M, Portero Azorin F, Boullosa Grana E, Rubio González E, Martín García S, Martínez Arrieta F, Jimenez Garrido M, Sánchez Turrion, Cuervas-Mons Martínez V. Prevalence of hepatitis C virus genotypes in a Spanish liver transplant unit. *Transplant Proc* 2005; 37:1486-1487.

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Among the at least six major identified genotypes of HCV, genotype 1b, the one associated with a poorer prognosis, is the most prevalent in Spain. We aimed to compare the distribution of hepatitis C virus genotypes in our liver transplant unit with that of the other HCV patients at our institution (n = 413) in order to assess whether genotype 1b is more prevalent among patients with more severe liver disease. One hundred eight patients of mean age 56 years included 81 (75%) OLT recipients and 27 (25%) with HCV cirrhosis. Determination of HCV genotypes was made with the Inno-LiPA HCV III. The overall distribution of genotypes was: 1b, 93 patients (86.1%); 1a; eight patients (7.4%); 3, four patients (3.7%); 4; two patients (1.9%), and 2; one patient (0.9%). The distribution was similar among patients with cirrhosis and OLT. Genotype 1b patients were older. Eleven (78.6%) of 14 patients with hepatocellular carcinoma had genotype 1b. In the control group the distribution was: 1b, 287 patients (69.5%); 1a, 54 patients (12.1%); 3, 41 patients (9.9%); 4, 20 patients (4.8%), and genotype 2, 11 patients (2.7%). This differences in the distribution of genotypes between our population and the control group was statistically significant ($P < .001$). Genotype 1b, the most prevalent genotype in our liver transplant unit, included older patients in whom hepatocellular carcinoma was common, perhaps due to their higher prevalence of cirrhosis.

Muga R, Sanvisens A, Bolao F, Toi J, Santesmases J, Pujol R, Tural C, Langohr K, Rey-Joly C, Muñoz A. Significant reductions of HIV prevalence but not of hepatitis C virus infections in injection drug users from metropolitan Barcelona: 1987-2001. *Drug Alcohol Depend* 2006; 82(Suppl 1):S29-S33.

Department of Internal Medicine, Hospital Universitari Germans Trias i Pujol Badalona, Spain.

The objective was to characterise trends from 1987 to 2001 in the prevalence of HIV and HCV infections among 2219 injection drug users (IDUs) starting treatment for substance abuse in two large hospitals in metropolitan Barcelona. The study population comprised IDUs with HIV tests completed from 1987 to 2001 and admitted for detoxification. Testing for HCV started in 1991 (n = 1132). Characterisation of temporal trends was carried out using logistic regression methods. Stratification was used to describe possible heterogeneities of the temporal trends. The overall prevalence of HIV, HCV, and HBV (HBsAg+) was 55%, 88%, and 7%, respectively. Adjusted by duration of IDU, sex, and age at initiation, the prevalence of HIV infection declined significantly ($p < 0.001$) from 1989 to 2004. The substantially higher prevalence of HCV showed a decline ($p = 0.065$) of lesser magnitude. The decline of HIV infection was consistently observed among those with duration of IDU of less than 10 years. In turn, the decline of HCV was restricted to those with short duration of IDU (< 4 years) because the prevalence of HCV infection was close to 100% for durations longer than 4 years in all calendar periods. Preventive interventions and treatment for substance abuse might have contributed to the waning of the HIV epidemic in Spain. However, the extremely high levels of HCV infection and the underlying prevalence of HIV might lead to a large health burden of liver disease.

Muniain-Mujika I, Calvo M, Lucena F, Gironés R. Comparative analysis of viral pathogens and potential indicators in shellfish. *Int J Food Microbiol* 2003; 83:75-85.

Department of Microbiology, Biology School, University of Barcelona, Diagonal Ave., 645 08028 Barcelona, Spain.

Shellfish can be responsible of outbreaks of infectious diseases and current health measures do not guarantee the absence of viral pathogens in this product. Here we examine the presence of pathogenic viruses and potential indicators in shellfish in a comparative analysis. Sixty shellfish samples collected in three areas with different levels of faecal contamination were analysed for *Escherichia coli*, total coliforms, *Clostridium perfringens*, somatic coliphages, F-specific phages

of RNA (F-RNA), bacteriophages infecting *Bacteroides fragilis* RYC2056, human adenovirus, enterovirus and hepatitis A virus (HAV). Viruses were eluted in a glycine buffer at pH 10. The overall percentage of viral pathogens detected was 47% for human adenoviruses, 19% for enteroviruses and 24% for HAV. Since all the samples positive for enterovirus and HAV were also positives for human adenovirus, the latter may be considered useful as a molecular index of viral contamination in shellfish. No significant differences in the bioaccumulation of bacteria and bacteriophages for oysters or mussels were observed. It was found that the probability of detection of any of the pathogenic virus decreases as the temperature of shellfish growing waters increases. However, the probability of detecting viruses increases when phages of *B. fragilis* are found. Although more data are needed in order to fulfil the need of viral indicators for controlling the presence of human viruses in shellfish, the obtained results indicate that phages infecting *B. fragilis* RYC2056 could be a suitable group of bacteriophages to be used as an indicator of the presence of viruses in shellfish.

Muñoz-Gomez R, García-Monzon C, García-Buey L, Lo Iacono O, Borque MJ, García-Sánchez A, Pajares JM, Moreno-Otero R. Hepatitis C virus infection in Spanish volunteer blood donors: HCV RNA analysis and liver disease. *Eur J Gastroenterol Hepatol* 1996; 8:273-277.

Liver Unit, Hospital de la Princesa, Universidad Autonoma, Madrid, Spain.

The objective was to evaluate in a large group of volunteer blood donors the prevalence of antibodies to hepatitis C virus (anti-HCV) and the relation of transaminase (ALT) levels and viraemia to liver damage. Design: a prospective study. Setting: Transfusion Centre of the Autonomous Community of Madrid and the Liver Unit of the Princesa University Hospital. From a population of 55,587 volunteer blood donors, 160 seropositive cases were further evaluated for virological and histological assessment. Anti-HCV was tested by ELISA-2 and RIBA-2 assays. HCV RNA was analysed by nested PCR. Liver biopsies were obtained in 35 volunteer blood donors with abnormal ALT levels. The prevalence of anti-HCV detected by ELISA-2 was 0.93%. Serum ALT was abnormal in 61 of the 160 volunteers (38.1%). Of these, RIBA-2 was positive in 96.7% and HCV RNA was detectable in 96.1%. Serum ALT was normal in the remaining 99, 70.7% being RIBA-2 negative and 98.3% HCV RNA negative. The majority of biopsies (85.6%) showed chronic hepatitis. This study demonstrates that in blood donors screening for anti-HCV, a positive ELISA-2 test, when associated with abnormal ALT levels, is effective in recognising subjects with active infection detected by HCV RNA and liver disease. Concerning ELISA-2 positive volunteer blood donors with normal ALT, long-term studies are warranted to elucidate whether they are really infected by HCV.

Navas E, Salleras L, Gisbert R, Domínguez A, Bruguera M, Rodriguez G, Gali N, Prat A. Efficiency of the incorporation of the hepatitis A vaccine as a combined A+B vaccine to the hepatitis B vaccination programme of preadolescents in schools. *Vaccine* 2005; 23:2185-2189.

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In 1998, the Department of Health of Catalonia (Spain) began universal vaccination of preadolescents against hepatitis A by replacing the simple hepatitis B vaccine with a combined hepatitis A+B vaccine. Economic analyses were made of the two alternative strategies: to continue with the simple hepatitis B vaccination or to replace the simple vaccine with a combined hepatitis A+B vaccine. The analysis was made from the societal perspective and the time horizon considered was 25 years. In the base case, (estimated annual hepatitis A incidence of 15 per 100,000 and incremental price of the hepatitis A+B vaccine over the simple hepatitis B vaccine of 1.98) the net present value of the programme was positive (+533,708) and the benefit-cost ratio

was 2.58. If the estimated disease incidence were reduced by half, the programme would still be efficient.

Nogales MC, Serrano MC, Suarez E, Corpas R, Perez L, Claro R, Jarana R, Romero-Gomez M, Martin-Mazuelos E. Determination of hepatitis B virus genotype and detection of lamivudine-resistance mutations. *Gastroenterol Hepatol* 2004; 27:515-520. [Article in Spanish]

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The objectives were to determine hepatitis B virus (HBV) genotypes in southern Seville (Spain) and investigate the development of lamivudine-resistance mutations by using a hybridisation technique with specific probes and by comparing the results with those of the direct sequencing technique. To evaluate the temporal relationship between variations in the level of HBV-DNA and detection of mutant variants. To analyse the influence of several genotypes on the pattern of mutations developed and on values of viral load and alanine aminotransferase (ALT) after their development. In 37 patients with chronic HBV infection, HBV genotype was determined using the LiPA technique. In 10 of these patients undergoing lamivudine treatment for a mean of 19.2 months, the development of lamivudine-resistant mutations was investigated. In these 10 patients, the LiPA technique was compared with direct sequencing. During lamivudine treatment, we determined HBV-DNA by polymerase chain reaction (PCR) and ALT every 3-6 months. The most frequent genotypes were D (45.9%) and A (18.9%); 2 patients were genotype B while 18.9% had mixed genotypes. Sequencing showed identical results except in one mixed genotype. Mutations were found in 60% of the cases. The results of sequencing were in agreement, except in the detection of mixed populations composed of mutants and wild-type (WT). Patients with genotype A showed the pattern M204I+WT in the first 12 months and those with genotype D showed the pattern L180M+M204V with or without WT at 18 months. In 5/6 cases, an increase of > 1 log₁₀ in HBV-DNA was observed 3-8 months before the mutation was detected by LiPA. In patients with genotype B, levels of HBV-DNA and ALT after the development of mutations was lower than basal levels and was also lower than those in patients with genotypes A and D. The LiPA technique for determination of HBV genotype and detection of lamivudine-resistance mutations shows excellent correlation with the most complex sequencing technique. Genotype D predominates in southern Seville. During lamivudine treatment, an increase in the level of HBV-DNA detected by PCR predicts the development of mutations before these are demonstrated by LiPA.

Norder H, Courouce AM, Coursaget P, Echevarría JM, Lee SD, Mushahwar IK, Robertson BH, Locarnini S, Magnus LO. Genetic diversity of hepatitis B virus strains derived worldwide: genotypes, subgenotypes, and HBsAg subtypes. *Intervirology* 2004; 47:289-309.

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Sequences of 234 complete genomes and 631 hepatitis B surface antigen genes were used to assess the worldwide diversity of hepatitis B virus (HBV). Apart from the described two subgenotypes each for A and F, also B, C, and D divided into four subgenotypes each in the analysis of complete genomes supported by significant bootstrap values. The subgenotypes of B and C differed in their geographical distribution, with B1 dominating in Japan, B2 in China and Vietnam, B3 confined to Indonesia, and B4 confined to Vietnam, all strains specifying subtype ayw1. Subgenotype C1 was common in Japan, Korea, and China; C2 in China, South-East Asia, and Bangladesh, and C3 in the Oceania comprising strains specifying adrq-, and C4 specifying ayw3 is encountered in Aborigines from Australia. This pattern of defined geographical distribution was less evident for D1-D4, where the subgenotypes were widely spread in Europe, Africa, and Asia, possibly due to their divergence having occurred a longer time ago than for genotypes B and C, with D4 being the first

split and still the dominating subgenotype of D in the Oceania. The genetic diversity of HBV and the geographical distribution of its subgenotypes provide a tool to reconstruct the evolutionary history of HBV and may help to complement genetic data in the understanding of the evolution and past migrations of man.

Ortega Molina P, Astasio Arbiza P, Albaladejo Vicente R, Gomez Rabago ML, de Juanes Pardo JR, Domínguez Rojas V. Vaccine storage cold chain at primary care centers in one area of Madrid: keeping the chain intact and degree of knowledge. *Rev Esp Salud Publica* 2002;76:333-346. [Article in Spanish]

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Vaccines are heat-labile medications, and to guarantee their immunogenicity and safeguarding effectiveness as part of immunisation programmes, it is absolutely essential that the "Cold Chain" go unbroken. Fundamental thereto is the personnel responsible for the vaccines, who must know the stability-related characteristics of each preparation so as to prevent handling errors. The purpose of this study was that of ascertaining how the cold chain is kept intact in primary care systems in one healthcare area of the Autonomous Community of Madrid, as well as determining the degree of information possessed by those responsible for vaccines as far as their heat-stability is concerned. A cross-sectional study has been made at 46 primary care vaccination points. The data was gathered by means of a personal interview by one single researcher. The participation rate was 93.5% (43/46). In all cases, there was a maximum and minimum thermometer and monthly temperature record. An unsuitable temperature was found in three cases (6.97%). The percentage of professionals who were aware of the effect freezing has on vaccines varied greatly: 53.5%, 51.2%, 44.2% and 53.5% for diphtheria-tetanus-pertussis (DTP), hepatitis B (HBV), oral polio (OPV) and measles-mumps-rubella (MMR) respectively. And only 32% were familiar with the shake test. The professionals were found to be properly trained regarding the effect which high temperatures have on vaccines, but it is necessary for their training with regard to the instability of adsorbed preparations when frozen must be further strengthened.

Oviedo M, Muñoz MP, Domínguez A, Carmona G. Estimated Incidence of Hepatitis A Virus Infection in Catalonia. *Ann Epidemiol* 2006. [Epub ahead of print]

From the Epidemiological Surveillance Unit, Generalitat of Catalonia (M.O., A.D., G.C.); Department of Statistics and Operations Research, Polytechnic University of Catalonia (M.O., M.P.M.); and Department of Public Health, University of Barcelona, Spain (A.D.).

Hepatitis A normally is underreported by statutory disease reporting systems. The objective of this study is to estimate the incidence of hepatitis A virus (HAV) infection from prevalence surveys of infection carried out in representative samples of the population in 1989, 1996, and 2002 and the reported disease incidence during 1991 to 2003 in Catalonia. The real incidence of the infection was estimated from the reported incidence adjusted by the prevalence of susceptible individuals and the probability of presenting clinical manifestations. The bootstrap resampling technique was used to calculate 95% confidence intervals (CIs) of reported, clinical, and all infection cases. The infection rate estimated by the bootstrap method was 31.1/100,000 person-years (bootstrap studentised 95% CI, 19.4-56.0), and the rate of clinical hepatitis was 20.0/100,000 person-years (95% CI, 11.8-39.9), rates that were 6.3 and 4.1 times greater than the reported rate during the same period, respectively. In children younger than 5 years, the estimated infection rate was 13.8 times greater than the reported rate. Combined use of reported cases and results of seroprevalence surveys suggest that underreporting of HAV infection is substantial in Catalonia, especially in children younger than 5 years.

Oviedo-Joekes E, March Cerda JC, Ramos Montserrat MJ, Ballesta Gomez R, Prieto Rodriguez MA. Perceived health and use of health care services in inmates of an Andalusian prison, 1999. *Rev Esp Salud Publica* 2005; 79:35-46. [Article in Spanish]

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The study of the health condition of the populations under confinement in penitentiaries is based on the evidence of a more deteriorated health than the general population and a greater degree of social exclusion, which is associated with worse general health. This study is aimed at ascertaining how the inmates of an Andalusian penitentiary perceive their health condition and the use made thereby of the healthcare services, as well as the factors associated with those variables. We designed a descriptive, cross-sectional study. The data was collected with a questionnaire. The sample size was 450 inmates, 90.4% of whom were males. Seventy-two percent of those taking part in the study considered their health to be good or very good, 32.7% stating having seen the doctor once a month or more often. A total 43.1% of the participants stated having chronic illnesses, mainly HIV (19.1%) and hepatitis C (18.2%); 40.9% stating that they take medication. Worse health was perceived among the older inmates, those who have to serve longer than a five-year sentence, those who are repeat offenders and those not having pending trials. Those perceiving their health to have deteriorated over the past year have chronic illnesses and take medication. The regression model for the use of healthcare services shows that they are used to a greater extent by those who are serving a longer than a 5-year sentence, those who have been in prison for less than a year and those who take medication. The results show the importance of increasing the monitoring of possible addictive disorders upon entering prison and of the trend and treatment of chronic diseases.

Pallas JR, Farinas-Alvarez C, Prieto D, Delgado-Rodriguez M. Coinfections by HIV, hepatitis B and hepatitis C in imprisoned injecting drug users. *Eur J Epidemiol* 1999; 15:699-704.

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In order to know the prevalence and risk factors for coinfections by human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) among injecting drug users (IDUs), a cross-sectional study was carried out in two prisons of the province of Cantabria, northern Spain. Three hundred and sixty-two IDU inmates were recruited. All inmates were interviewed and their blood tested for HIV, HBV and HCV. Crude and multiple risk factor adjusted for (by polychotomous logistic regression) odds ratios were calculated. Prevalence of HBV-HCV coinfection (42.5%) was higher than HIV-HBV-HCV coinfection (37.3%), whereas mono-infections were very uncommon (overall: 13%). Long-term injectors and reincarceration were the foremost risk factors for both coinfections, showing a trend between the degree of association and the number of viruses infecting a patient. No significant relationship between coinfection status and sexual practices was observed. The results related to coinfections are consistent with previous studies of prevalence and risk factors for HIV, HBV and HCV, in indicating that the high rates of coinfections among IDU inmates emphasise the need to harm-reduction policy across prisons in Spain.

Pallas J, Farinas-Alvarez C, Prieto D, Llorca J, Delgado-Rodriguez M. Risk factors for mono-infections and coinfections with HIV, hepatitis B and hepatitis C viruses in northern Spanish prisoners. *Epidemiol Infect* 1999; 123:95-102.

Provincial Prison, Santander, Spain.

A cross-sectional study was conducted in prisons of Cantabria (northern Spain) from June 1992 to December 1994. Inmates were asked to participate in a survey on prevalence and risk factors for monoinfections and coinfections with HIV, HBV and HCV. Crude and multiple odds ratios of risk factors were calculated (by polychotomous logistic regression). Prevalence of coinfections was higher than that of monoinfections. IDU risk factors were the main independent variables associated with monoinfections and coinfections with these agents. The strength of association increased with the degree of coinfection for IDU risk factors and penal status, e.g. duration of injecting drug use for more than 5 years yielded an adjusted OR ranging from 1.3 (95% CI: 0.4-5.1) for HBV monoinfection to 180 (95% CI: 61.0-540.0) for HIV-HBV-HCV coinfection. In comparison, sexual behaviours were less important than IDU risk factors.

Peña MJ, Molina L, Hortal L, Gallego R, Rodriguez JL, Pérez MC, Palop L, Fiuza MD, Lafarga B. Epidemiologic study of infection by hepatitis C virus in a hemodialysis unit. *Enferm Infecc Microbiol Clin* 2000; 18:496-499. [Article in Spanish]

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The aim was to analyze the prevalence of infection, the frequency of HCV genotypes and the epidemiology characteristics among the patients in hemodialysis treatment in one 25 years old hospital haemodialysis center and one 15 years old secondary unit by a transversal cross-section study in 1998. 171 haemodialysed-patients were studied. Patients sera were analyzed by the presence of HCV antibodies anti-VHC by a enzymeimmunoassay (Abbott Científica) and the presence of antibodies was confirmed by a line immunoassay (Inno-LIA HCV AbIII) and by the presence of VHC-RNA by reverse transcriptase PCR (Cobas Amplicor HCV). Genotypes were determinate by reverse hybridisation (Inno-LIA HCV III). Fifty (29.2%) of the patients were HCV antibody positive. Forty-five (26.3%) were HCV-RNA positive, all of them with antibodies positive. The distribution of genotypes was: 1b, 34 (75.5%); 4f, 4 (8.9%); 1a, 3 (6.7%); 1, 3 (6.7%) and 1 case could not be typed (2.2%). In 14 patients (28.0%), seroconversions were documented. Twenty-one patients (42.0%) were diagnosed when the routine tests were available and 15 patients (30.0%) were diagnosed pre-dialysis. The multivariate analysis showed that the risk of HCV infection was greater for patients who had been more 8 years on dialysis (OR: 6.22; 95% CI: 1.24-31.07). Data presented indicate that the prevalence of HCV infections in our hemodialysis units and the number of seroconversions were high and the HCV subtype 1b was more frequent; because of this, the screening by both serological and molecular methods is necessary, at least twice a year, to identify all the infected patients. Besides, we think that is necessary to increase the control of the completion of the Universal Precautions.

Pérez-Gracia MT, Garcia-Valdivia MS, Galan F, Rodriguez-Iglesias MA. Detection of hepatitis E virus in patients sera in southern Spain. *Acta Virol* 2004; 48:197-200.

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The aim of the present study was to detect acute Hepatitis E virus (HEV) infection in patients with abnormal alanine transaminase (ALT) in which other viral hepatitis infections had been excluded in southern Spain, an area adjacent to regions where this disease is endemic. Of 336 sera tested 30 (8.92%) were positive for IgM antibodies against HEV (anti-HEV IgM) and 7 (2.08%) were negative in a repeated assay. Immunoblot analysis (IBA) was applied to the 37 positive sera in the first assay; its results were positivity for 26 (7.73%), ambiguous for 5 and negative for 6 sera. Amplification of ORF1 and ORF2 of HEV by means of nested RT-PCR was carried out with the 37 sera that were either positive or ambiguous by ELISA; a positive result was obtained only with one serum for the ORF2 protein. IgM antibodies against the HEV ORF2 protein could be a useful marker in the diagnosis of acute infection and a substitute for the determination of viral RNA in

serum; this is of both diagnostic and epidemiological importance as it would allow the patients transmitting the infection to be recognised by means of a simple determination of antibodies. The sequence of the ORF2 fragment of HEV occurring in samples taken from both humans and animals amplified in this study has considerable homology with the sequences of HEV strains/isolates of European origin. These results demonstrate that an autochthonous HEV circulates in Spain.

Pérez-Gracia MT, Rodríguez-Iglesias M. Hepatitis E virus: current status. *Med Clin (Barc)* 2003; 121:787-792. [Article in Spanish]

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In areas with tropical or subtropical climate and poor sanitary conditions, hepatitis E is the major cause of enterically transmitted non-A, non-B hepatitis, and is responsible for both water-borne outbreaks and sporadic cases of acute hepatitis. The causative agent is the hepatitis E virus (HEV), a non-enveloped, single-stranded, positive-sense RNA molecule of an approximately 7.2 kb length. Recently, HEV strains have been isolated in swine in industrialised countries. In addition, cases of acute hepatitis due to novel HEV variants have been reported in humans without recognised risk factors for hepatitis E in Europe, Japan and the US. Some of the novel strains were found to be closely related to swine HEV isolates from the same area, suggesting that hepatitis E is a zoonotic disease. Thus hepatitis E is becoming a concern in countries where HEV is not, traditionally, believed to be endemic. This review summarises the current knowledge of the biology, structure and transmission of the virus as well as the diagnosis of the infection. We also analyse the present status in areas with a low incidence of acute hepatitis E and the role of animals as potential vectors of the virus.

Pina S, Buti M, Cotrina M, Piella J, Gironés R. HEV identified in serum from humans with acute hepatitis and in sewage of animal origin in Spain. *J Hepatol* 2000; 33:826-833.

Department of Microbiology, University of Barcelona, Spain.

Hepatitis E virus (HEV) is an enterically transmitted pathogen that appears sporadically in non-endemic countries. We studied HEV as a causal agent of acute hepatitis cases in the Spanish population, and the role of pigs as an animal reservoir. The presence of HEV-RNA was analysed by nested polymerase chain reaction in 37 serum samples from patients with acute viral hepatitis, 48 porcine serum samples, 6 pig faecal samples and 12 slaughter-house sewage samples. Presence of antibodies was also tested in porcine sera. HEV-RNA was found in 3 human serum samples from patients presenting IgG anti-HEV antibodies. Nucleotide sequence analysis identified 2 strains with 93.4% identity, phylogenetically most closely related to the Greece1 isolate, and more closely related to North American and other European strains than to those from endemic regions. HEV-RNA was also detected in slaughterhouse sewage mainly from pigs, presenting 92-94% nucleotide similarity compared to the strains detected in the human sera. Twenty-five per cent of the pigs tested presented IgG anti-HEV antibodies. These data suggest that the HEV could be more widespread than previously thought, and present new evidence of the close relationship between HEV strains detected in pigs and those from acute hepatitis patients.

Pina S, Butí M, Jordi R, Clemente-Casares P, Jofre J, Gironés R. Genetic analysis of hepatitis A virus strains recovered from the environment and from patients with acute hepatitis. *J Gen Virol* 2001; 82:2955-2963.

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The molecular epidemiology of hepatitis A virus (HAV) was studied by analysing HAV strains recovered from environmental water samples over a 7 year period and strains recovered from patients with acute hepatitis over a 5 year period. A total of 54 samples of raw domestic sewage and 66 samples of river water were collected. HAV particles were concentrated and detected by nested RT-PCR. HAV infection in patients with acute hepatitis was serologically diagnosed in 26 of 74 serum samples, which were also analysed by nested RT-PCR. HAV RNA was detected in 57.4% of sewage samples, 39.2% of Llobregat river water samples, 20% of Ter river water samples and 61.6% of serum samples. The HAV genomes detected were characterised further by directly sequencing a region of the 5' non-translated region, the VP1/2A junction region and, in some samples, the 2B region. Results showed a 95% prevalence of genotype I, with nearly 50% being either subgenotype IA or subgenotype IB. Various strains were found simultaneously in both environmental and clinical samples. These strains were closely related to those described in distant geographical areas. Genotype IIIA was also found in 5% of sewage samples and in 12.5% of serum samples. Strains belonging to a common endemic genotype were not identified. The abundance of HAV in the environment produces a situation of sanitary risk, especially considering the low prevalence of antibodies in the young population.

Plans-Rubio P. Critical prevalence of antibodies minimizing vaccination costs for hepatitis A, hepatitis B, varicella, measles and tetanus in adults and adolescents in Catalonia, Spain. *Vaccine* 2004; 22:4002-4013.

Department of Health, General Direction of Public Health, Travessera de les Corts 131-159, 08028 Barcelona, Spain.

The prevalence of seropositive individuals that makes costs of vaccinating all individuals equal to that for screening and vaccination of susceptible individuals is defined as the critical prevalence of antibodies (p^*). Screening and vaccination is more efficient when the prevalence of seropositive individuals (p) in the population is higher than p^* . In this study, the formula to obtain p^* was derived from the cost-effectiveness equations, showing that it depends on screening and vaccination costs, programme compliance, screening test performance, vaccine efficacy and disease costs. The formula was used to determine the least costly vaccination strategy for hepatitis A and B, varicella, measles and tetanus in adults and adolescents in Catalonia. The least costly vaccination strategy was vaccination without screening (since p was lower than p^*) for hepatitis B, measles and tetanus in adults and adolescents (5-14 years) and for hepatitis A in individuals aged 5-24 years, and screening and vaccination (since p was higher than p^*) for varicella in adults and adolescents and for hepatitis A in adults aged > 24 years. Vaccination strategies based on the critical prevalence of antibodies could maximise the immunity level in the community from available resources.

Puig-Basagoiti F, Forns X, Furcic I, Ampurdanes S, Gimenez-Barcons M, Franco S, Sánchez-Tapias JM, Saiz JC. Dynamics of hepatitis C virus NS5A quasispecies during interferon and ribavirin therapy in responder and non-responder patients with genotype 1b chronic hepatitis C. *J Gen Virol* 2005; 86:1067-1075.

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The quasispecies nature of hepatitis C virus (HCV) may have important implications concerning resistance to antiviral agents. To determine whether HCV NS5A quasispecies composition and dynamics are related to responsiveness to combined interferon (IFN) and ribavirin therapy, extensive sequence analyses of cloned RT-PCR amplification products of HCV-1b NS5A quasispecies of sequential isolates from 15 treated (nine sustained responders and six non-responders) and three untreated patients were performed. Accumulation of mutations in NS5A during therapy was relatively frequent in the V3 domain, but unusual elsewhere. Amino acid changes were the result of the imposition of minor variants that were already present before treatment and always occurred within the first week of therapy. Before treatment, the complexity and diversity of quasispecies were lower in isolates from responders than in those from non-responders, particularly in the V3 domain, where differences in nucleotide entropy (0.35 vs 0.64, $P = 0.003$), genetic distance (0.0145 vs 0.0302, $P = 0.05$) and non-synonymous substitutions (0.0102 vs 0.0203, $P = 0.036$) were statistically significant. These differences became more apparent during treatment, because complexity and diversity remained stable or tended to increase in non-responders, whereas they tended to decrease in responders. These observations suggest that the composition and dynamics of HCV NS5A quasispecies, particularly in the V3 domain, may play a role in the response to combined IFN/ribavirin therapy.

Ramos B, Nuñez M, Toro C, Sheldon J, García-Samaniego J, Rios P, Soriano V. Changes in the distribution of hepatitis C virus (HCV) genotypes over time in Spain according to HIV serostatus: Implications for HCV therapy in HCV/HIV-coinfected patients. *J Infect* 2006 Mar 25; [Epub ahead of print]

Department of Infectious Diseases, Hospital Carlos III, Calle Sinesio Delgado 10, 28029 Madrid, Spain.

Changes in the prevalence of distinct hepatitis C virus (HCV) genotypes and subtypes over time have not been explored in detail. A retrospective analysis was carried out in all specimens from subjects with chronic hepatitis C sent for testing to a reference laboratory in Spain since 1998-2004. A total of 1226 distinct subjects were analyzed. The most frequent HCV genotype was 1 (64.1%), followed by 3 (20.9%) and 4 (11.7%). The most frequent HCV subtype was 1b (32.4%). A total of 797 patients (65%) were HIV-positive. Although genotype 1 was the most frequent, it represented 74.6% of HIV-negative and 58.5% of HIV-positive patients ($p < 0.01$). While HCV subtype 1a was the most frequent among HIV-positive subjects (32.1%), 1b was the most common in HIV-negative patients (53.8%). There was a significant increase in the prevalence of genotype 4 and conversely a decline in genotype 3 among HIV-positive patients over time. Genotype 1 is the most frequent HCV variant circulating in Spain. Genotypes 3 and 4 are significantly more prevalent in HIV/HCV-coinfected than in HCV-monoinfected patients. However, HCV-3 has declined and HCV-4 is increasing in the former group. These findings are relevant given their different susceptibility to interferon-based therapies.

Ribes J, Cleries R, Borrás J, Galceran J, Bosch FX. Time trends in incidence and mortality for chronic liver disease and liver cancer in the interval 1980-1997 in Catalonia, Spain. *Eur J Gastroenterol Hepatol* 2004; 16:865-872.

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It has been reported that the incidence of liver cancer and intrahepatic bile duct tumours might be increasing in some developed countries. The purpose of this study was to examine time trends of incidence and mortality rates of liver cirrhosis and liver cancer for the period 1980-1997 in Catalonia, Spain. Data were obtained from the Catalan Mortality Registry and the Tarragona Cancer Registry. Joinpoint analysis was used to detect time-related changes in incidence and mortality of liver diseases. The cohort effect on mortality and incidence rates was explored by an age-period-cohort model. Mortality from liver cirrhosis decreased during the study period for both sexes and all age groups, with the exception of men aged between 25 and 35 years. No changes in incidence or mortality rates were observed for liver cancer. Mortality rates for intrahepatic bile duct tumours increased in men and women, while incidence rates remained stable. This study identified in Catalonia an increase in mortality due to liver cirrhosis among 25-35-year-old men. Mortality rates for intrahepatic bile duct tumours increased for all age groups and both sexes. The former could be related to hepatitis C or B viruses and human immunodeficiency virus co-infection, while the latter remains unexplained.

Ribes J, Cleries R, Rubio A, Hernandez JM, Mazzara R, Madoz P, Casanovas T, Casanova A, Gallen M, Rodriguez C, Moreno V, Bosch FX. Cofactors associated with liver disease mortality in an HBsAg-positive Mediterranean cohort: 20 years of follow-up. *Int J Cancer* 2006; 119:687-694.

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The risk of developing liver cancer in hepatitis B virus (HBV) carriers differs across geographical areas, suggesting that exposure to other risk factors may contribute to HBV-linked cancer risk. Our study estimates the mortality due to liver disease and the role of other risk factors in a Spanish HBV cohort. 2,352 hepatitis B surface antigen (HBsAg)-positive and 15,504 HBsAg-negative subjects were identified among blood donors during 1972-1985 and were followed until December 2000 through the Mortality Registry. Clinical examination and an epidemiological questionnaire were performed on 1,000 HBsAg-positive survivors during 1994-1996. In subjects deceased from liver disease, medical records were revised and relatives were interviewed. A nested case-control analysis was conducted comparing both groups. In HBsAg-positive men, an excess mortality from liver cancer [standardised mortality ratio (SMR): 14.1; 7.7-23.6], cirrhosis (SMR: 10.5; 7.0-15.1), haematological neoplasms (SMR: 3.2; 1.2-6.9) and AIDS was detected (SMR: 5.5; 2.2-11.4). In women, an excess was found for cirrhosis (SMR: 7.2; 1.4-21.1). Progression factors to liver disease were alcohol intake [odds ratio (OR): 6.3; 3.1-12.8], diabetes (OR: 3.6; 1.3-9.6), HBV replication (OR: 50.0; 14.9-167.3) and hepatitis C virus (HCV) infection (OR: 27.4; 7.1-107.7). In conclusion, in Spain after 20 years of follow-up, chronic HBV exposure appears as a major risk factor for liver cancer among men and for cirrhosis in both sexes. The risk of death from liver disease among HBV carriers with the presence of HBV replication, HCV, alcohol consumption and diabetes was significantly increased and suggests synergism among these exposures and HBV. Mortality from haematological neoplasms was detected and could be associated to HIV coinfection. These results support screening and adequate follow-up among HBsAg-positive subjects at high risk to develop liver disease, particularly when these risk cofactors are present.

Riestra S, Fernandez E, Leiva P, García S, Ocio G, Rodrigo L. Prevalence of hepatitis C virus infection in the general population of northern Spain. *Eur J Gastroenterol Hepatol* 2001; 13:477-481.

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The goal was to estimate the prevalence of hepatitis C in a population of northern Spain and describe (i) the risk factors associated with infection and (ii) the distribution of genotypes. Design:

randomised cross-sectional study. A random sample of 1,170 people participated in the study. Sociodemographic data were obtained. Antibodies against hepatitis C virus (anti-HCV) and hepatitis C virus (HCV) genotypes were determined. Nineteen of 1,170 (1.6%) subjects were anti-HCV positive (95% CI 1.0-2.6%). In 12 cases (63%), viraemia was present, and the predominant genotype was 1b (80%). Anti-HCV positive subjects were older than anti-HCV negative subjects (55.8 +/- 15.3 v. 44.8 +/- 20.9; P = 0.02). Two peaks of maximum frequency were found (in the fourth decade and in those over 60 years). Parenteral drug addiction predominates among those of the fourth decade, while transfusion and surgery predominate in people over 60 years. Three (16%) subjects knew they were carriers of HCV. Only three variables remained significant in the multivariate model (illegal drug use, P < 0.0001; previous hepatitis, P < 0.0001; and age, P < 0.02). Our study emphasises the need to develop health policies that can cope with the foreseeable increases in the problems associated with HCV infection in the near future.

Roca B, Suarez I, González J, Garrido M, de la Fuente B, Teira R, Geijo P, Cosin J, Pérez-Cortés S, Galindo MJ, Lozano F, Domingo P, Viciano P, Ribera E, Vergara A, Sánchez T. Hepatitis C virus and human immunodeficiency virus coinfection in Spain. *J Infect* 2003; 47:117-124.

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In a cross-sectional study, based on a cohort composed of HIV-infected patients of fifteen tertiary level institutions of Spain, the main data of the entire cohort are described, characteristics of patients with or without hepatitis C coinfection are compared, and the possible association of hepatitis C virus coinfection with socioeconomic, HIV-related, and hepatitis B-related variables is assessed. A total of 4,709 patients are studied. Median of age is 37 years, 78.3% are male. HIV risk behaviours are: parenteral drug use in 63.8% of patients, heterosexual in 22.3%, and homosexual in 10.8%. Serology of hepatitis C is positive in 69.2% of participants. The following variables are associated with increased prevalence of hepatitis C coinfection, both in univariate and in multivariate analysis: HIV risk behaviour, positive anti-HBs, longer time elapsed since HIV infection diagnosis, younger age, lower social status, lower CD4 cell count increase between nadir and last available result, and lower educational level (all P < 0.001). Patients with heterosexual behaviour are more frequently coinfecting than patients with homosexual behaviour (P < 0.001). This study highlights that, in Spain, more than two thirds of patients with HIV infection are coinfecting with hepatitis C virus.

Rodríguez C, Castilla J, del Romero J, Lillo A, Puig ME, García S. Prevalence of hepatitis B virus infection and needs of vaccination in high risk populations. *Med Clin (Barc)* 2003; 121:697-699. [Article in Spanish]

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We aimed to evaluate the serological status of hepatitis B virus (HBV) and the vaccination's needs among high risk populations. Patients and method: cross-sectional study of subjects first attending a HIV diagnosis clinic in Madrid during 2000-2002. Patients who had not been vaccinated for HBV were classified according to the serological markers as active infection (HBsAg+), past infection (anti-HBc+ and HBsAg) or susceptible (anti-HBc). A total of 7,827 patients were analysed: 5.2% injecting drug users, 21% homosexual men, 38% female sex workers, and 34% subjects with other heterosexual risks. 50% were from countries other than Spain. HIV prevalence was 4.1%. 10.4% had completed or initiated the vaccination. The prevalence of HBsAg was 1.2% and it was associated with age over 30 years and an origin country in Africa or eastern Europe. 76% were susceptible to HBV and this status was independently associated with male sex, age lower than 30 years, heterosexual risk, Spaniard or Latin American origin, and HIV seronegative.

Vaccination should be intensified in health care settings commonly attended by these population groups.

Rodríguez JC, García J, Moya I, Ayelo A, Vázquez N, Sillero C, Royo G. Genetic variability of hepatitis C virus in the health area of Elche (Spain). Correlation between core antigen and viral load. *Gastroenterol Hepatol* 2003; 26:407-410. [Article in Spanish]

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We investigated the prevalence of the various genotypes of hepatitis C virus (HCV) in 281 patients evaluated between March, 2000 and March, 2002 in the health area of Elche. Of these patients, 55 were coinfecting with human immunodeficiency virus (HIV). The genotype was related to viral load and the co-existence of HIV infection. Likewise, the relationship between these parameters and the presence of the HCV core antigen was established. The results indicate that genotype 1b was the most prevalent (38.4%) followed by genotype 3a (23.1%). Patients coinfecting with HIV presented fewer infections due to group 1 genotypes ($p < 0.05$). Patients with HIV presented a greater viral load in all the genotypes, with genotype 3 presenting a high viral load. Detection of the HCV core antigen showed a close correlation with viral load determinations. Although not yet sufficiently assessed, determination of the HCV core antigen constitutes a simple technique that could eventually contribute to improving the management of patients with chronic HCV hepatitis.

Rodríguez-Frias F, Jardí R, Butí M, Schaper M, Hermosilla E, Valdes A, Allende H, Martell M, Esteban R, Guardia J. Hepatitis B virus genotypes and G1896A precore mutation in 486 Spanish patients with acute and chronic HBV infection. *J Viral Hepat* 2006; 13:343-350.

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This study aims to determine the prevalence of hepatitis B virus (HBV) genotypes (A-F) and their association with the G1896A precore mutation in 486 patients positive for HBV surface antigen. Genotypes were determined by RFLP and precore mutation by real-time PCR. Genotypes D (48.1%) and A (39.5%) were the most common, followed by F (4.1%) and B, C and E (<1%). The A to D ratio (A:D) was 1.4 in HBeAg+ chronic hepatitis B (CHB), 0.6 in HBeAg- CHB and 1.4 in HBeAg- inactive carriers. Distribution of these genotypes was different between HBeAg+ CHB and HBeAg- CHB ($P = 0.02$), and between HBeAg- CHB and HBeAg- inactive carriers ($P = 0.009$). Genotype A was the most prevalent in HBeAg+ CHB with elevated alanine aminotransferase (ALT) (68.6%) and genotype D in HBeAg+ CHB with fluctuating ALT (60.7%). There was a difference in genotype prevalence between chronic and acute infection ($P = 0.03$). The precore mutant correlated with high levels of HBV-DNA in genotype d HBeAg- CHB. Genotype D is not as highly prevalent in Spanish patients as would be expected in a Mediterranean area. The unequal prevalence of genotypes between acute and chronic infection suggests that genotype A is associated with a higher tendency to cause chronic infection.

Rodríguez-Mendez ML, González-Quintela A, Aguilera A, Carballo E, Barrio E. Association of HCV and HBV markers in Spanish HIV-seropositive patients in relation to risk practices. *Hepatogastroenterology* 2003; 50:2093-2097.

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HBV, HCV, and HIV have some transmission routes in common. Viral liver disease is a leading cause of mortality in HIV-infected patients. The study was aimed at evaluating the prevalence of HBV and HCV markers in subjects with different risk practices for HIV infection. A total of 699

subjects were studied. Of these subjects, 517 were intravenous drug users (373 HIV-positive and 144 HIV-negative), 127 had heterosexual risk practice (66 HIV-positive and 61 HIV-negative), 31 had homosexual risk practice (all HIV-positive), 15 had post-transfusional HIV infection, and nine had HIV infection of unknown source. Patients with anti-HBc antibody were considered HBV-positive, and cases with anti-HCV antibodies were considered HCV-positive. Among patients with HIV infection, most intravenous drug users (79%) had markers of both HBV and HCV, compared with 20%, 11%, and 10% of cases infected by transfusional, heterosexual, and homosexual route, respectively ($p < 0.001$). Absence of both HBV and HCV markers was observed in most HIV-positive heterosexuals (62%) compared with 40% of post-transfusional cases, 32% of homosexuals and 4% of intravenous drug users (p : NS, $p = 0.009$, and $p < 0.001$, respectively). Isolated HBV-positivity was the most frequent pattern in HIV-infected homosexuals (58%), compared with 27% of post-transfusional, 21% of heterosexuals and 11% of intravenous drug users (p : NS, $p < 0.001$ and $p < 0.001$, respectively). HIV-negative intravenous drug users had a lower prevalence of HBV/HCV association than HIV-positive cases ($p < 0.001$). Isolated HCV-positivity was more frequent in HIV-negative than in HIV-positive intravenous drug users (27% vs. 6%, $p < 0.001$). In heterosexuals, isolated HBV-positivity was more prevalent in HIV-positive than in HIV-negative cases (21% vs. 7%, $p = 0.04$). HBV and HCV seroprevalence in HIV infected patients vary depending on the risk practice. This suggests a variable transmissibility depending on the route considered. Within the same risk practice, differences in HCV and HBV seroprevalence between HIV-positive and HIV-negative cases suggest that some factors associated with HIV infection may influence the rate of infection by HCV and HBV.

Rodriguez-Vidigal FF, Baz MJ, Fernandez FJ, Najarro F. Hepatitis C virus infection in a first level rural hospital: descriptive study in the decade 1991-1999. *Enferm Infecc Microbiol Clin* 2003; 21:142-146.

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The aim was to assess epidemiology, clinical manifestations and prognostic factors in subjects diagnosed with hepatitis C virus (HCV) infection in a first level rural hospital. This retrospective study includes 142 patients diagnosed with HCV infection at the Hospital de Llerena, from August 1991 to December 1999. Epidemiological and clinical parameters were collected at a mean of 2.7 years after diagnosis and prognostic factors were analysed. HCV infection predominated in males (69%) and the mean age of patients was 48.3 \pm 19.3 years. Mechanisms of transmission included unknown (46.5%), intravenous drug use (39.4%), and transfusions (14.1%). Human immunodeficiency virus coinfection was present in 23% of patients and hepatitis B virus (HBV) coinfection in 5.6%. At the time of diagnosis, 111 patients (78.2%) were asymptomatic; 26 (18.3%) presented with complications of portal hypertension and 5 (3.5%) with extrahepatic symptoms. Ultrasonographic signs of portal hypertension were observed in 32.4% of cases. Hepatocarcinoma was detected in 17 patients (12.0%) and extrahepatic neoplasms in 14 (9.9%). Twenty-eight patients died (19.7%). Independent risk factors for mortality included HBV coinfection (OR 26.9; 95% CI 2.19-331.47), ultrasonographic signs of portal hypertension (OR 11.0; 95% CI 3.38-32.61) and diagnosis of hepatocarcinoma (OR 182.7; 95% CI 14.85-2248.21). Between 1990 and 1999 in our hospital HCV infection was frequently diagnosed in advanced stages and was associated with high mortality, particularly when ultrasonographic signs of portal hypertension or HBV coinfection were present.

Rodriguez-Vidigal FF, Baz MJ, Romero J, del Puerto M. Epidemiology of hepatocellular carcinoma in a rural area. Role of hepatotropic viruses on survival. *An Med Interna* 2005; 22:162-166. [Article in Spanish]

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Chronic hepatitis C and B are the main causes of hepatocellular carcinoma (HCC) worldwide. It is not clear whether chronic hepatitis C or B virus (HCV or HBV) infection is a prognostic factor for HCC. This study aimed to assess epidemiology of HCC in a rural area and to determine if chronic HCV or HBV infection had any impact on survival after the diagnosis of HCC. Fifty-one consecutive patients were retrospectively studied. All of them were diagnosed of HCC between January 1994 and December 2002 in a First Level Hospital. The following variables were analysed: age, sex, HCV and HBV infection, chronic alcohol abuse (daily intake upper 80 g), clinical presentation, Child stage, number of liver nodules, therapeutic options and survival. The mean age at diagnosis of HCC was 68,5 years old (age range 45-90) and 45 patients (88,6%) were male. Heavy alcohol intake (66%) and chronic HCV infection (42,8%) were the most prevalent etiologic factors. Chronic HBV was found in 11,9%. Chronic HCV or HBV infection was present in 48,9%. Twenty-five percent were asymptomatic and 66% were in Child stage A. The rate single lesion / multilobular HCC was 52/48. Only 6% of all patients could be treated with a curative intention. The mean survival was 10,9 +/- 9,1 months, and there were no differences in age, sex, Child stage and number of nodules. There was a significantly higher survival in patients with chronic HCV or HBV infection (16,7 +/- 13,1 months versus 4,75 +/- 5,3 months in seronegative patients; p = 0.02). On multivariate analysis, only chronic HCV or HBV infection was associated with survival longer than 10 months (OR 22,3; CI 95% 1,8-277,9). In our area, heavy alcohol abuse and HCV infection were the most prevalent etiologic factors of HCC. Chronic HCV or HBV infection was associated with longer survival in patients with HCC.

Romalde JL, Torrado I, Ribao C, Barja JL. Global market: shellfish imports as a source of reemerging food-borne hepatitis A virus infections in Spain. *Int Microbiol* 2001; 4:223-226.

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A total of 16 mollusk imports from South America to Spain, including clam and scallop species, were analyzed for hepatitis A virus (HAV), due to the great concern about this type of food after an important hepatitis A outbreak in eastern Spain in September 1999. In addition, clams from the stock that had caused the outbreak were also tested. Of the 17 stocks, four were positive for the presence of HAV RNA as demonstrated by RT-PCR and Southern hybridisation. Contradictory analyses confirmed the results of the primary tests in all cases. The findings obtained in this work strongly support the role of mollusk imports from endemic areas of HAV as an important vehicle of hepatitis A, and demonstrate the imperative need for sanitary control measures to prevent future outbreaks of this disease.

Rubio Caballero M, Rubio Rivas C, Nogues Biau A, Manonelles Fernandez A. Epidemiology of chronic hepatitis C virus in patients infected by human immunodeficiency virus. Study of 767 patients. *Med Clin (Barc)* 2005;125:56-58. [Article in Spanish]

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To study the epidemiological aspects of hepatitis C virus (HCV) infection in patients co-infected by human immunodeficiency virus (HIV). This study was carried out in 767 HIV infected patients who were followed-up at the HIV/AIDS Unit of the Internal Medicine Department of the Arnau de Vilanova University Hospital of Lleida (Spain). In addition to clinical records and information about the probable contagion route, gender and starting year of intravenous drug use, patients were analyzed for the presence of hepatitis C antibodies, viral load and HCV genotype, alanine

aminotransferase concentration, CD4+ lymphocytes and viral load of HIV. The stage of HIV infection was also recorded. 546 patients (71.18%) had antibodies to HCV, and 499 of them (91.39%) were intravenous drugs users. Of the HCV+ patients, 61 (11.17%) seemed to have cleared the virus spontaneously. Commonest HCV genotype was 1 (52.57%), followed by 3 (25.56%) and 4 (18.76%). In patients with genotype 1, subtype 1a was the more frequent (65.49%) The variation of the genotypes according to the year of contagion showed a progressive increase of genotype-1 and a progressive decrease of genotype 3. The distribution of patients in the different clinics stages of HIV infection was homogeneous. In our health care area, most HIV+ patients, especially the intravenous drug users are co-infected with HCV. Commonest genotype was 1 and commonest subtypes was 1a.

Rubio M, Rubio C, Nogues A, Manonelles A. Hepatitis C virus genotypes. Study of 302 patients coinfecting by the human immunodeficiency virus. *Med Clin (Barc)* 2001; 116:650-655. [Article in Spanish]

Medicina Interna. Hospital Universitario Arnau de Vilanova, Lleida.

The objective was to study the distribution of different HCV genotypes in HIV-infected patients. This study was carried out in 302 HIV/HCV-coinfecting patients who were followed-up at the HIV/AIDS Unit of the Arnau de Vilanova University Hospital of Lleida (Spain). HCV genotypes were determined by Inno-Lipa HCV II technique (Innogenetics, Belgium). 143 patients (51.43%) had a genotype-1, followed by genotype-3 (81 patients; 29.13%), genotype-4 (53 patients; 19.06%), and genotype-2 (one patient; 0.35%). It was not possible to know the genotype in 24 patients (NT). In our health care area, HCV genotype-1 was the commonest among HIV/HCV-coinfecting patients. However, a given HIV-infected patient with HCV antibodies has practically the same probability of having a genotype-1 as a genotype non-1.

Ruiz-Sánchez A, Soriano V. HIV and HCV coinfection. *Enferm Infecc Microbiol Clin* 2006; 24:335-345. [Article in Spanish]

Servicio de Enfermedades Infecciosas, Hospital Carlos III, Madrid, España.

Chronic hepatitis due to hepatitis C virus (HCV) infection is now one of the leading causes of morbidity and mortality among HIV-infected individuals. Coinfecting patients present an accelerated course toward cirrhosis and an enhanced risk of liver toxicity associated with the use of antiretroviral agents. Treatment of chronic hepatitis C in HIV1 patients is less efficacious than in HCV-monoinfecting individuals and requires particular expertise.

Saiz de la Hoya P, Bedia M, Murcia J, Cebria J, Sánchez-Paya J, Portilla J. Predictive markers of HIV and HCV infection and co-infection among inmates in a Spanish prison. *Enferm Infecc Microbiol Clin* 2005; 23:53-57. [Article in Spanish]

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The objective was to study the prevalence and factors associated with HIV and HCV infection among inmates of a Spanish prison. A cross-sectional study was carried out in July 2001. We determined HCV (ELISA and RIBA-3) and HIV (ELISA and Western-blot) serology in the prison population. Study variables included age, sex, nationality and previous intravenous drug use (IDU). In IDU inmates we analyzed the age when intravenous drug use was initiated, years of consumption, age at first admission in prison and syringe sharing with other inmates. The subpopulations of Arab and Romani (gypsy) inmates were studied differentially. A total of 800

inmates (mean age 34.2 6 6.2 years) were evaluated; 74.3% were Spanish and 33.6% IDU. HCV serology was obtained in 730 inmates and HIV serology in 773 with the following seroprevalence results: HCV 38.2%, HIV 19.1% and HCV-HIV co-infection 18.8%. The variables associated with HCV or HIV infection in the univariate analysis were Spanish nationality, previous IDU and coinfection by the other virus. In the multivariate analysis, only coinfection and, particularly, previous IDU (HCV infection: adjusted ORp 104.8 [95% CI: 49.4-222.2]) (HIV infection adjusted ORp 45.1 [95% CI: 14.0-144.9]) maintained an association with the two infections. The prevalence of HIV and HCV infection and coinfection is high in Spanish prisons. Infection by either of these viruses and previous IDU were independently associated with both infections. The percentage of non-Spanish inmates with these infections is low.

Salleras L, Bruguera M, Butí M, Domínguez A. Prospects for vaccination against hepatitis A and B in Catalonia (Spain). *Vaccine* 2000; 18(Suppl 1):S80-S82.

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Catalonia is in an area of intermediate endemicity for hepatitis A virus (HAV) infection. An Expert Committee has recently proposed the implementation of universal hepatitis A vaccination for 12-year-olds, based on the fact that no risk factors can be identified for hepatitis A in 50% of cases, and also that selective vaccination targeted at high-risk groups has a limited potential to reduce the incidence of hepatitis A. The well-established programme of hepatitis B vaccination of pre-adolescents in Catalonian schools has high levels of vaccination coverage. This will provide a means to introduce hepatitis A vaccination in a cost-effective way in schools, by replacing the single vaccine with the combined hepatitis A and B vaccine. High-risk groups will also continue to be targeted. A pilot programme has commenced in the 1998/1999 school year and will be evaluated after 3 years. If it is successful, it will be extended indefinitely.

Salleras L, Domínguez A, Bruguera M, Cardenosa N, Batalla J, Carmona G, Navas E, Taberner JL. Dramatic decline in acute hepatitis B infection and disease incidence rates among adolescents and young people after 12 years of a mass hepatitis B vaccination programme of pre-adolescents in the schools of Catalonia (Spain). *Vaccine* 2005; 23:2181-2184.

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The aim of the study was to describe the impact of hepatitis B vaccination and disease incidence in adolescents and young people 12 years after the launching of a mass hepatitis B vaccination of pre-adolescents in schools. Vaccination coverage was assessed using administrative and serological data. Infection trends were evaluated by means of seroepidemiological surveys. High levels of vaccination coverage and vaccine-induced immunity were achieved. The resulting low proportions of susceptible adolescents and young people have undoubtedly contributed to the substantial reduction in the prevalence of hepatitis B infection in the 15-24 years age group (0.9 per 100 in 2001 versus 9.3 per 100 in 1986) and in the reported incidence of hepatitis B cases (80% reduction). Over the last 3 years, the declining trend seems to have been halted, although 35% of cases reported during this period corresponded to immigrants.

Sánchez G, Pinto RM, Vanaclocha H, Bosch A. Molecular characterization of hepatitis A virus isolates from a transcontinental shellfish-borne outbreak. *J Clin Microbiol* 2002; 40:4148-4155.

Department of Microbiology, University of Barcelona, Barcelona. Department of Epidemiology, Generalitat Valenciana, Valencia, Spain.

One hundred eighty-four serologically confirmed cases of hepatitis A were reported in eastern Spain in 1999. A matched case-control study implicated imported coquina clams complying with European Union shellfish standards as the source of infection; this implication was confirmed by the detection by reverse transcription-PCR of hepatitis A virus (HAV) RNA in shellfish samples. In spite of the recognized low variability of HAV, genetic characterisation of the complete capsid region of virus isolates from patient serum samples revealed the existence of both synonymous and nonsynonymous variants. Two antigenic variants were detected, one in a discontinuous epitope defined by monoclonal antibody K3-4C8 and a second in a linear VP1 epitope of the virus. In spite of these antigenic variants, all isolates were assigned to genotype IB, providing further evidence that the outbreak originated from a common source, although multiple strains were likely to be involved.

Sánchez-Tapias JM, Diago M, Escartin P, Enriquez J, Romero-Gomez M, Barcena R, Crespo J, Andrade R, Martínez-Bauer E, Pérez R, Testillano M, Planas R, Sola R, García-Bengoechea M, García-Samaniego J, Muñoz-Sánchez M, Moreno-Otero R, on behalf of the TeraViC-4 Study Group. Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. *Gastroenterology* 2006; 131:451-460.

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Patients with chronic hepatitis C who do not respond rapidly to therapy have a low chance of developing a sustained virologic response (SVR) when treated for 48 weeks. This study investigated whether treatment for 72 weeks increases the rate of SVR in patients with detectable hepatitis C virus (HCV)-RNA levels at week 4 of treatment. A total of 510 treatment-naïve patients were treated with peginterferon-alfa2a (180 µg/wk) plus ribavirin (800 mg/day). Patients with detectable HCV-RNA levels at week 4 (n = 326) were randomized to complete 48 (group A, n = 165) or 72 weeks (group B, n = 161) of treatment. Patients with undetectable HCV-RNA levels at week 4 (n = 184) were allocated into group C (n = 148) or group D (n = 36), according to HCV genotype and baseline viraemia, and treated for 24 or 48 weeks, respectively. All patients were followed-up for 24 weeks after the end of treatment. The end-of-treatment response rate (61%) was similar in groups A and B, but the SVR rate was higher in group B (45% vs 32% in A; P = 0.01). In genotype 1-infected patients randomised to group A (n = 149) or B (n = 142), SVR rates were 28% and 44%, respectively (P = 0.003). The incidence of adverse events was similar in all groups. Treatment discontinuation was more frequent in group B (36%) than in group A (18%) (P = 0.0004). SVR rates in groups C and D were 79% and 64%, respectively. Extension of treatment with peginterferon-alfa2a plus ribavirin from 48 to 72 weeks significantly increases the rate of SVR in patients with detectable viraemia at week 4 of treatment.

Santana OE, Rivero LE, Liminana JM, Hernandez LA, Santana M, Martin AM. Seroepidemiological study of hepatitis A in Gran Canaria (Spain). *Enferm Infecc Microbiol Clin* 2000; 18:170-173. [Article in Spanish]

Servicio de Microbiología, Hospital Universitario Insular de Gran Canaria, Universidad de Las Palmas de Gran Canaria.

The aim of this study was to assess the seroprevalence and the risk factors of hepatitis A virus (HAV) infection in the population from Gran Canaria (Spain) and to determine at which age pre-vaccination testing would be useful. A transversal observational study of the presence of HAV antibodies (IgG) on serum samples obtained from a population ranging from 8 months to 63 years old was performed between January 1995 and December 1996. IgG anti-HAV were detected by a

commercial immunoenzyme assay. The study included 547 persons resident in Gran Canaria. Epidemiological data (age, sex, number of family members, educational level, urban/rural residence and previous history of hepatitis) were gathered through a personal interview. Confusing variables were excluded by mean a multiple logistic regression analysis. Global prevalence of anti-HAV (IgG) was 36.0% (CI 95% 32.0-40.0). The prevalence of anti-HAV increased significantly with age from 2.3% in children under 4 years until 98.9% in older than 40 years (OR 3956.0; CI 95% 241.7-64,753.5). Only three independent data (age, sex and educational level) were significantly associated with HAV seroprevalence. A previous history of hepatitis A was present only in 4.8% of HAV-positive subjects. The low prevalence of anti-HAV (IgG) in persons under 25 years old suggest that in the adolescent population the implementation of universal vaccination programmes is recommended even without previous serologic screening. Otherwise, the results suggest that HAV prevaccination screening in our geographical were must be limited to subjects older than 25 years.

Sanz E, Moreira VF, Merono E, de la Serna C, Mir N, Mateos ML. Acute hepatitis E in Spain. *Gastroenterol Hepatol* 1999; 22:180-182. [Article in Spanish]

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Hepatitis E virus (HEV) is the worldwide leading cause of non-A non-B enterically transmitted hepatitis, and affects most commonly the population in developing countries. Cases outside this area, are nearly always imported, although apparent local acquisition has been occasionally reported. We assisted three patients with acute HEV hepatitis, confirmed by the presence of serum anti-HEV IgM. One of them did not report travelling outside of Spain in the previous years. HEV has to be included in the differential diagnosis of acute non-A non-B non-C hepatitis, even in cases in which an exposure in endemic areas cannot be recalled.

Sola R, Cruz De Castro E, Hombrados M, Planas R, Coll S, Jardi R, Sunyer J, Covas I, Marrugat J. Prevalence of hepatitis B and hepatitis C viruses in different counties of Catalonia, Spain: cross-sectional study. *Med Clin (Barc)* 2002; 119:90-95. [Article in Spanish]

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There are few data available in our community regarding the prevalence of hepatitis B (HBV) and hepatitis C (HCV) virus infection in the general population. The aim of this study was to determine the prevalence and serologic characteristics of HBV and HCV in Catalonia. For this purpose, HBsAg and anti-HCV were assessed in serum aliquots obtained from a sample of 2194 individuals, who were chosen at random out from different Catalanian counties. In those cases in which any of the markers were positive, the following analyses were performed afterwards: serum transaminases, HBV-DNA detection by PCR (in HBsAg positives) and HCV-RNA detection by PCR and genotypes (in antiHCV positives). All subjects yielding positive results were interviewed in order to determine possible risk factors. HBV prevalence was 1.69% (95% CI, 1.62-1.76) and that of HCV was 2.64% (95% CI, 2.53-2.75). HCV prevalence increased with age (1.7% in younger than 50 years and 3.6% in older than 50 years, $p < 0.01$), but not that of HBV. Only a small proportion (12.1%) of HBV carriers had detectable HBV-DNA levels. On the contrary, quite an important proportion of HCV carriers (68.6%) had detectable HCV-RNA levels. Predominant HCV genotype was 1 (79.3%). Transaminases levels were within normal limits in many HBV and HCV carriers (70.9 and 60%, respectively). Prevalence of HBV and HCV in Catalonia was 1.69% and 2.64%, respectively. Most HCV carriers had positive serum HCV-RNA, whereas serum HBV-DNA was negative in most HBV carriers.

Soriano V, Martin-Carbonero L, Maida I, García-Samaniego J, Nuñez M. New paradigms in the management of HIV and hepatitis C virus coinfection. *Curr Opin Infect Dis* 2005; 18:550-560.

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Chronic hepatitis C virus infection is currently one of the leading causes of morbidity and mortality in HIV-infected individuals, mainly in haemophiliacs and intravenous drug users. The bidirectional interferences between hepatitis C virus and HIV have clinical consequences and complicate the management of coinfecting individuals. There is an increased rate of liver complications among coinfecting patients due to the decrease in opportunistic infections resulting from the use of potent antiretroviral therapy and accelerated progression to liver cirrhosis in the HIV setting. Conversely, the risk of hepatotoxicity of antiretrovirals is higher in the presence of chronic hepatitis C. While the standard therapy for hepatitis C in HIV is the combination of pegylated interferon plus ribavirin, overall treatment responses are lower in HIV-coinfecting than in hepatitis C virus-monoinfecting patients. Moreover, interactions between ribavirin and HIV drugs (i.e. didanosine, zidovudine) are associated with higher risks of side effects. Given the accelerated progression to end-stage liver disease in coinfecting patients, treatment of hepatitis C should be a priority. While hepatitis C therapy should not be denied in the absence of contraindication, it should be re-assessed at week 12 and therapy continued only in patients showing more than 2 log drops in viraemia, to avoid side effects. Most recent data suggest that adequate selection of candidates, expert management of side effects, and prescription of appropriate ribavirin doses (in genotypes 1-4) and extending treatment (in genotypes 2-3) all might allow response rates in coinfecting patients to approach those seen in hepatitis C virus-monoinfecting individuals.

Soriano V, Miro JM, García-Samaniego J, Torre-Cisneros J, Nuñez M, del Romero J, Martin-Carbonero L, Castilla J, Iribarren JA, Quereda C, Santin M, González J, Arribas JR, Santos I, Hernandez-Quero J, Ortega E, Asensi V, del Pozo MA, Berenguer J, Tural C, Clotet B, Leal M, Echevarría JM, Avellón A, Magnius LO. Molecular epidemiology of hepatitis B virus in Spain: identification of viral genotypes and prediction of antigenic subtypes by limited sequencing. *J Med Virol* 2005; 76:176-184.

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The hepatitis B virus (HBV) genotypes were studied by a line probe assay (LiPA) and by direct sequencing of a 339 nucleotide fragment from the S region of the viral genome in samples from 269 carriers living in Spain, either native to Spain (231) or immigrants from Africa, Asia, and Eastern Europe (38). The sequences were also used to predict the HBV surface antigen (HBsAg) subtype on the basis of the amino acids specified at selected positions of the HBsAg molecule. Agreement between the two genotyping methods was found in most cases (98.1%) and a HBV genotype could be assigned to all samples. The viral groups D/ayw2 (30.1%), D/ayw3 (28.6%), and A/adw2 (21.2%) were prevalent, with an additional participation of the groups D/ayw4 (4.8%), F/adw4q- (1.9%), A/ayw1 (1.9%), and D/adw3 (0.7%), all of them present among the autochthonous carriers. Strains from genotypes B and C were found exclusively among Chinese immigrants. Genotype E strains were found in immigrants from Central Africa and in one patient native of Spain. Point mutations leading to amino acid changes of residues involved in the expression of the HBsAg subtype determinants were found in 12 samples (4.5%). Some mutations would predict the putative novel genotype-subtype associations A/adw4q+, A/ayr, D/ayr, and E/ayw1, while others would suggest the loss of subtype-specific determinants. The finding of HBV strains characteristic for Africa among the autochthonous carriers confirms the emergence of African HBV strains in Spain.

Soriano R, Tiberio G, Martínez Artola V, Casares N, Berrade F. Hepatitis A seroprevalence in Navarra. *Rev Clin Esp* 2004; 204:145-150. [Article in Spanish]

Ciencias de la Salud, Universidad Publica de Navarra, Pamplona.

The aim was to determine the hepatitis A seroprevalence in Navarra. Because of the improvement in the hygienic-sanitary conditions, we hope to find a decline of the total prevalence. Population and random sample of Navarra, obtained by stratified sampling with proportional allocation of sex, age, and area of health care: 1,440 individuals over 15 years of age. Detection of total antibodies by enzyme immunoassay of microparticles. Global seroprevalence: 79.24%. By age: 9.09% (16-19 years), 35.32% (20-29 years), 77.78% (30-39 years), 97.31% (40-49 years), 98.58% (50-59 years), 97.51% (60-69 years), 99.33% (70-79 years) and 100% (>79 years). By gender: 78.76% in men and 79.7% in women. Rural area 82.04% and urban area 75.77%. Areas of health care: Tafalla, 89.06%; Estella, 87.91%; Tudela, 82.88%; northern, 77.22%; Pamplona, 75.05%, and eastern, 70.97%. The global prevalence is 79.24% and increasing progressively with the age. Greater seroprevalence in rural areas and in people in contact with livestock. Characteristics of the persons with seroprevalence for HAV in Navarra: inhabitant of the average area, of rural area, with average age and in contact with livestock.

Suarez González A, Solis Sánchez G, Otero Guerra L, Viejo De La Guerra G, Alvarez Navascues C, García López R. Prevalence of immunity to hepatitis viruses in pregnant women from the health area of Gijon (Spain). *Gastroenterol Hepatol* 2004; 27:347-352. [Article in Spanish]

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The objective of the study is to determine the prevalence of hepatitis B or C chronic infection, and hepatitis A or E immunity among pregnant women from Gijon, as well as their clinical and epidemiological antecedents. HBsAg and anti-HCV were determined in 2287 pregnant women consecutively attended in the Cabuenes Hospital, Gijon. Ninety nine of them, non-European or Gipsy, were also tested for anti-HAV IgG and anti-HEV IgG as were a sample of 325 and 365 respectively of the remaining 2188. Several clinical and epidemiological parameters were checked in all of them. Hepatitis B virus: 10.8% (246/2287) were previously vaccinated. Among the 2043 non vaccinated, 0.8% (17 cases) were HBsAg+. None of them had HBV replication and in 59% (10/17) the HBV infection was unknown. Hepatitis C virus: 1.44% (33/2287) women were anti-VHC+, 1.26% (29/2287) anti-VHC and PCR+. In 28% of them (8/29) no parenteral risk factor was identified. Again, the infection was unknown in 58% (17/29) previously unknown. Hepatitis A virus: excluding non-European and Gipsy women, with a rate of immunity against HAV in younger than 29 years-old of 57% (12/21) and 89% (16/18), respectively, the anti-HAV IgG was positive in 17% (22/128) of the women younger than 29 years-old, 28% (60/214) between 29 and 36 years-old, and in 56% (13/23) of those older than 36 years-old. Hepatitis E virus: anti-HEC IgG was found in 2% (2/99) non European or Gipsy pregnant women and in 0.6% of the rest (2/325). Conclusions: a). Vaccination rate against hepatitis B virus is still low among pregnant women in Gijon; b). most of HBsAg+ or anti-VHC+ ignore it and many of them have not an evident risk factor; c). susceptibility to hepatitis A infection is high, with progress towards adult age, and d). remember the possibility of infection by hepatitis E virus.

Tanaka Y, Kurbanov F, Mano S, Orito E, Vargas V, Esteban JI, Yuen MF, Lai CL, Kramvis A, Kew MC, Smuts HE, Netesov SV, Alter HJ, Mizokami M. Molecular tracing of the global hepatitis C virus epidemic predicts regional patterns of hepatocellular carcinoma mortality. *Gastroenterology* 2006; 130:703-714.

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Molecular evolutionary analysis based on coalescent theory can provide important insights into epidemiologic processes worldwide. This approach was combined with analyses of the hepatitis C virus (HCV) epidemiologic-historical background and HCV-related hepatocellular carcinoma (HCC) in different countries. The HCV gene sequences of 131 genotype 1b (HCV-1b) strains from Japan, 38 HCV-1a strains from the United States, 33 HCV-1b strains from Spain, 27 HCV-3a strains from the former Soviet Union (FSU), 47 HCV-4a strains from Egypt, 25 HCV-5a strains from South Africa, and 24 HCV-6a strains from Hong Kong isolated in this study and previous studies were analysed. The coalescent analysis indicated that a transition from constant size to rapid exponential growth (spread time) occurred in Japan in the 1920s (HCV-1b), but not until the 1940s for the same genotype in Spain and other European countries. The spread time of HCV-1a in the United States was estimated to be in the 1960s; HCV-3a in the FSU, HCV-5a in South Africa, and HCV-6a in Hong Kong in the 1960s, mid-1950s, and late 1970s, respectively. Three different linear progression curves were determined by analysis of the relationship between HCV seroprevalence and HCC mortality in different geographic regions; a steep ascent indicated the greatest progression to HCC in Japan, a near horizontal line indicated the least progression in the United States and the FSU, and an intermediate slope was observed in Europe. These findings strongly suggest that the initial spread time of HCV is associated with the progression dynamics of HCC in each area, irrespective of genotype.

Tarrago D, López-Velez R, Turrientes C, Baquero F, Mateos ML. Prevalence of hepatitis E antibodies in immigrants from developing countries. *Eur J Clin Microbiol Infect Dis* 2000; 19:309-311.

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The aim of the present study was to investigate the prevalence of anti-hepatitis E virus (HEV) antibodies among indigenous Spanish blood donors and immigrants from developing countries in order to determine whether immigrants pose a significant risk for the transmission of HEV to the healthy Spanish population. The seroprevalence of HEV was determined in a cohort of 90 asymptomatic immigrants (mostly from countries in sub-Saharan Africa) who had recently arrived in Madrid, Spain, and in 863 blood donors, who represented the healthy Spanish population. The results showed that the prevalence of HEV antibodies was 1.9 times higher in the immigrants than in the blood donors (5.5% in immigrants, 95% CI 1.8-12.4; 2.9% in blood donors, 95% CI 1.9-4.2). Combined with the estimated population figures of 300,000 undocumented immigrants versus 39,000,000 Spaniards, these results indicate that sub-Saharan immigrants cannot currently be considered a major risk source for the transmission of HEV in Spain.

Tassies D, Magallon M, Quintana M, Fernandez-Urgelles RP, Rodriguez-Pinto C, Tusell J, Altisent C, Reverter JC, Mazzara R, Ordinas A, Monteagudo J. Hepatitis G virus infection markers (RNA and anti-E2 antibodies) in a multicenter cohort of hemophiliacs. *Haematologica* 1999; 84:930-936.

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The objectives were to investigate the prevalence and evolution of hepatitis G virus (HGV) infection in hemophiliacs and to correlate evolution of HGV infection markers with immunologic parameters in those patients co-infected with HIV. HGV RNA and anti-E2 antibodies were studied in 124 patients. Serial samples were drawn every 4 months from 1992 to 1996. Lymphocyte subsets including T-helper lymphocytes, T-suppressor lymphocytes, T-cytotoxic lymphocytes,

activated T-lymphocytes and natural killer cells were analysed. Prevalences were 22.6% for HGV RNA and 18.5% for anti-E2. Four patients had both HGV RNA and anti E2, so the overall prevalence of HGV infection in haemophiliacs was 37.9% (11.5% in 200 controls, $p < 0.0001$). After a median follow-up of 36.6 months 20 patients remained HGV RNA positive, whereas HGV RNA had cleared in 8, with an actuarial probability of clearance at 36 months of 34.6%. Only 2 patients developed anti-E2 antibodies. Four patients cleared anti-E2, with an actuarial probability at 36 months of 24.8%. In patients with HIV infection, both lower CD4+ lymphocyte count ($p=0.01$) or higher CD8+ lymphocyte count ($p = 0.03$) showed predictive value for probability of clearing HGV-RNA. CD4+/CD8+ ratio ($p = 0.002$) was the only variable included in the best model for HGV-RNA disappearance. A more accurate estimation of the prevalence of HGV infection can be achieved with the determination of both HGV RNA and anti-E2. Anti-E2 response can be undetectable or transitory after disappearance of HGV-RNA, giving therefore rise to the possibility of underestimating HGV prevalence with currently diagnostic methods. In HIV-positive patients, cellular immune function seems to be involved in the resolution of HGV infection, following the significant correlation found between clearance of HGV-RNA and CD4+/CD8+ lymphocyte populations.

Tomas JF, Pinilla I, García-Buey ML, García A, Figuera A, Gomez-García de Soria GG, Moreno R, Fernandez-Ranada JM. Long-term liver dysfunction after allogeneic bone marrow transplantation: clinical features and course in 61 patients. *Bone Marrow Transplant* 2000; 26:649-655.

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This retrospective study has aimed at determining the prevalence, aetiology and clinical evolution of chronic liver disease (CLD) after allogeneic bone marrow transplantation (BMT). A total of 106 patients who had been transplanted in a single institution and who had survived for at least 2 years after BMT were studied. The prevalence of CLD was 57.5% (61/106). In 47.3% of cases more than one aetiopathogenic agent coexisted. The causes of CLD were iron overload (52.4%), chronic hepatitis C (47.5%), chronic graft-versus-host disease (C-GVHD) (37.7%), hepatitis B (6.5%), non-alcoholic steatohepatitis (NASH) (4.9%), autoimmune hepatitis (AIH) (4.9%) and unknown two (3.3%). Twenty-three patients with iron overload underwent venesections which were well tolerated. An improvement in liver function tests (LFTs) was observed in 21 (91%) patients. All six patients with siderosis as the only cause of CLD normalised LFT as well as three patients with HCV infection. Clinical evolution was satisfactory for patients with GVHD, AIH, NASH and hepatitis B. At the last visit 23 patients continued with abnormal LFTs, and 19 of them were infected by the HCV. A sustained biochemical and virologic response was achieved in only one case out of six patients with CHC who received interferon. We have found that CLD is a common complication in long-term BMT survivors. The aetiology is often multifactorial, iron overload, CHC and C-GVHD being the main causes. The CLD followed a rather 'benign' and slow course in our patients as none of them developed symptoms or signs of liver failure and we did not observe an increase in morbidity or mortality in these patients, but a longer follow-up is necessary in HCV infected patients based on the natural history of this infection in other populations.

Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, González-García J, Lazzarin A, Carosi G, Sasadeusz J, Katlama C, Montaner J, Sette H Jr, Pässe S, De Pamphilis J, Duff F, Schrenk UM, Dieterich DT, on behalf of the APRICOT Study Group. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004; 51:438-40.

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Hepatitis C virus (HCV) infection is highly prevalent and is associated with substantial morbidity and mortality among persons infected with the human immunodeficiency virus (HIV). We compared the efficacy and safety of pegylated interferon alfa-2a (peginterferon alfa-2a) plus either ribavirin or placebo with those of interferon alfa-2a plus ribavirin for the treatment of chronic HCV infection in patients who were also infected with HIV. A total of 868 persons who were infected with both HIV and HCV and who had not previously been treated with interferon or ribavirin were randomly assigned to receive one of three regimens: peginterferon alfa-2a (180 µg per week) plus ribavirin (800 mg per day), peginterferon alfa-2a plus placebo, or interferon alfa-2a (3 million IU three times a week) plus ribavirin. Patients were treated for 48 weeks and followed for an additional 24 weeks. The primary end point was a sustained virologic response (defined as a serum HCV RNA level below 50 IU per milliliter at the end of follow-up, at week 72). The overall rate of sustained virologic response was significantly higher among the recipients of peginterferon alfa-2a plus ribavirin than among those assigned to interferon alfa-2a plus ribavirin (40 percent vs. 12 percent, $P < 0.001$), or peginterferon alfa-2a plus placebo (40 percent vs. 20 percent, $P < 0.001$). Among patients infected with HCV genotype 1, the rates of sustained virologic response were 29 percent with peginterferon alfa-2a plus ribavirin, 14 percent with peginterferon alfa-2a plus placebo, and 7 percent with interferon alfa-2a plus ribavirin. The corresponding rates among patients infected with HCV genotype 2 or 3 were 62 percent, 36 percent, and 20 percent. Neutropaenia and thrombocytopaenia were more common among patients treated with regimens that contained peginterferon alfa-2a, and anaemia was more common among patients treated with regimens containing ribavirin. Among patients infected with both HIV and HCV, the combination of peginterferon alfa-2a plus ribavirin was significantly more effective than either interferon alfa-2a plus ribavirin or peginterferon alfa-2a monotherapy.

Touceda S, Pereira M, Agulla A. Prevalence of hepatitis C virus genotypes in the area of El Ferrol (La Coruna, Spain). *Enferm Infecc Microbiol Clin* 2002; 20:200-204. [Article in Spanish]

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The aim was to determine the prevalence of hepatitis C virus (HCV) genotypes in the area of El Ferrol, as well as their distribution according to risk factors. A total of 479 patients with hepatitis C were studied, including 254 with no known risk factors, 161 intravenous drug abusers (IVDA) and 64 with a history of blood transfusions. The presence of HCV RNA was studied by RT-PCR, and a reverse hybridisation method (INNO-LiPA) was used for genotyping. Genotype distribution was as follows: 1b, 269 (56.2%); 1a, 79 (16.5%); 3a, 59 (12.3%); 4c/4d, 35 (7.3%); 1, 19 (4.0%); 2a/2c, 3 (0.6%); 4, 3 (0.6%); 2b, 2 (0.4%). In 10 patients (2.1%) genotype could not be determined. In patients with no known risk factor, the predominant genotype was 1b, detected in 191 of the 254 patients in this group (75.2%). Distribution of genotypes was more varied in the IVDA group, with the most frequent being 1a in 49 (30.4%) and 3a in 43 (26.7%). In the 64 patients who had received transfusions, 1b was predominant, detected in 54 of 64 patients (84.4%). The predominant HCV genotype in our area is 1b. Differences in genotype distribution were observed in the population groups studied, according to their underlying risk factors.

Touzet S, Krämer L, Colin C, Pradat P, Lanoir D, Bailly F, Coppola RC, Sauleda S, Thursz MR, Tillmann H, Alberti A, Braconier JH, Esteban JI, Hadziyannis SJ, Manns P, Saracco G, Thomas HC, Trépo C, on behalf of the HENCORE Group (Hepatitis C European Network for Co-operative Research). Epidemiology of hepatitis C virus infection in seven European Union countries: a critical analysis of the literature. *Eur J Gastroenterol Hepatol* 2000; 12:667-678.

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Hepatitis C is now recognised as the most common infection causing chronic liver disease in the European population. Our aim was to assess the prevalence of the antibody to hepatitis C virus (HCV), and the incidence of HCV seroconversion in the general population and the main risk groups, namely intravenous drug users, haemodialysis and transfused patients, in seven countries of the European Union, by carrying out a critical analysis of the literature. Data sources used were the Medline database and a manual search using the key words: hepatitis C, prevalence, incidence, transmission, risk factors and epidemiology. Articles published between January 1990 and March 1997 were reviewed. Articles were reviewed according to a critical analysis method regarding title, type of article, study design, period and population, tests, results and their consistency with data. The tests performed were mainly second- or third-generation serological tests. The average prevalence rate in blood donors was 1%, with a north-south gradient ranging from 0.04% to 2%. Prevalence varied from 20% to 30% in haemodialysis patients. The incidence in transfused patients was less than 1% after 1991. The prevalence in intravenous drug users was about 80%. Multicentre studies conducted in larger samples are needed to obtain more accurate and reliable results, in particular. However, the epidemiological studies available allowed us to assess the magnitude of HCV infection in Europe.

Trapero Marugan M, Perez Gisbert J, Pajares García JM, Moreno Otero R. Spanish scientific publications on hepatitis C virus. A Medline study (1980-2002). *Gastroenterol Hepatol* 2004; 27:397-402. [Article in Spanish]

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The aim was to analyze the scientific publications on hepatitis C virus infection from Spanish hospitals between 1980 and 2002. Articles published from January 1980 to December 2002 and contained in the Medline database were selected using the following key words: "Hepatitis C" [MeSH] AND ((Spain [AD] OR Espana [AD] OR Spanien [AD] OR Espagne [AD] OR Espanha [AD]) OR (Spanish [LA]) OR Spain)). Geographical and institutional distribution, national or international publication, subject matter of the article, and date of publication were recorded. Bibliometric indicators of output and impact were estimated. A total of 1.051 articles were studied, of which 346 were excluded. The number of articles published increased from 0 in 1980 to 121 in 1998 and decreased to 36 in 2002. More articles were published in international journals than in Spanish journals (59.2% versus 40.8%). The main topic was epidemiology (28.6%) in the first decade and treatment (20.2%) in the second. Original articles were the most common type of article (80.5%). The centers with the greatest output were Hospital Clinic in Barcelona (11.6%), Vall d'Hebron Hospital (8.9%) in Barcelona and Fundacion Jimenez Diaz in Madrid (8.9%). The mean impact factor increased linearly from 0 in 1980 to 3 in 2002. The number and impact factor of scientific publications on hepatitis C virus by Spanish authors has grown significantly during the last 2 decades.

Vall Mayans M, Arellano E, Armengol P, Escriba JM, Loureiro E, Saladie P, Sanz B, Saravanya M, Vall M, Villena MJ. HIV infection and other sexually-transmitted infections among immigrants in Barcelona. *Enferm Infecc Microbiol Clin* 2002; 20:154-156. [Article in Spanish]

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Immigration is a recent phenomenon in Spain. Certain subgroups of the immigrant population may be vulnerable to acquiring sexually transmitted infections (STI). Design: a descriptive study of the seroprevalence of certain STI (HIV, hepatitis B and syphilis) and the general characteristics of persons tested for HIV infection in a specialised clinic in Barcelona during the year 2000.

Seroprevalence of HIV was similar in immigrants and native residents (1.8% vs. 1.7% respectively). However, the seroprevalences of hepatitis B virus (anti-HBc) (19.5% vs. 8.3%) and syphilis (RPR 1 TPHA) (3.2% vs. 1.1%), as well as other STI and the practice of prostitution, were higher in immigrants. Several STI, including hepatitis B and syphilis, were found more frequently in immigrants than in the native population, whereas HIV seroprevalence was similar in the two groups.

Vargas V, Comas P, Castells L, Quer J, Esteban JI, Allende E, Esteban R, Guardia J, Margarit C. Incidence and outcome of hepatitis C virus infection after liver transplantation. *Transpl Int* 1994; 7(Suppl 1):S216-S220.

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The objective of this study was to determine the incidence and outcome of hepatitis C virus (HCV) infection after liver transplantation (OLT). Fifty-two transplanted patients were studied. Serum samples were examined for antibodies to HCV (anti-HCV) and HCV-RNA by PCR, before and after OLT. Patients were distributed into two groups: group 1 consisted of 24 patients (pretransplant anti-HCV positive) and group 2 consisted of 28 patients (pretransplant anti-HCV negative). One year after OLT, HCV-infected patients were evaluated by liver biopsy. HCV-RNA was detected in 28 of the 52 (53.9%) patients after OLT. Twenty-two patients in group 1 (96%) were reinfected. In group 2, acquired HCV infection was detected in six (21.4%) patients. At 6 and 12 months, one and five of six patients had seroconverted, respectively. Liver biopsy in 23 HCV-infected patients showed chronic hepatitis in 18 (78%) cases (2, chronic persistent hepatitis; 3, chronic lobular hepatitis and 13, chronic active hepatitis). Fourteen of the 23 (60.8%) patients were asymptomatic. Most symptomatic patients had chronic hepatitis with cholestasis. Overall, 18 of 20 cases of chronic hepatitis diagnosed in OLT recipients were HCV related. Mortality beyond 6 months after OLT was slightly higher in the HCV-infected group ($P = 0.055$). In conclusion, HCV reinfection is almost universal. Acquired HCV infection post-OLT is frequent. HCV-infected patients frequently develop chronic hepatitis. Most chronic hepatitis after transplantation are HCV related.

Zampieron A, Jayasekera H, Elseviers M, Lindley E, De Vos JY, Visser R, Harrington M. European study on epidemiology and management of hepatitis C virus (HCV) infection in the haemodialysis population. Part 3: prevalence and incidence. *EDTNA ERCA J* 2006; 32:42-44.

Padua University Hospital, Italy.

An analysis of the literature showed a high prevalence of HCV in the European dialysis population in the nineties. The prevalence was similar in most countries in northern Europe, but infection was more common in France, Italy, Spain, Portugal and Greece (1) and in Eastern European countries (2). The reported prevalence of anti-HCV-positive patients in the EDTA registry was 21% in 1992 and 18% in 1993 (3) ranging from 1% in Finland to 42% in Egypt (4). The incidence of HCV, in new patients starting renal replacement therapy, ranged from 3% to 7% (5,6) and reported seroconversion rates during dialysis treatment varied between 1% (7) and 16% (8) per year.

Part II Additional bibliographical sources and websites

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