

# **Prevention and control of viral hepatitis in France: lessons learnt and the way forward**

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# Part I Prevention and control of viral hepatitis in France: lessons learnt and the way forward – bibliography (in alphabetical order) –

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**Andrieu J, Barny S, Colardelle P, Maisonneuve P, Giraud V, Robin E, Bréart G, Coste T.** Prevalence and risk factors of hepatitis C virus infection in a hospitalized population in a gastroenterology unit. Role of endoscopic biopsies. *Gastroenterol Clin Biol* 1995; 19:340-345. [Article in French]

Service de Gastroentérologie, Hôpital André Mignot, Le Chesnay.

In order to study the prevalence and risk factors of HCV infection in a population hospitalized in a Gastroenterology Unit, 3,767 patients were tested for serum anti-HCV, and 2,607 filled out a questionnaire about risk factors. With the RIBA 2 test, the overall prevalence was 5.9%. Because of the age distribution, two populations were studied. In patients younger than 45, intravenous drug use was the only independent risk factor linked to serum anti-HCV positivity (Odds ratio: 151, CI 95%: 66.9-340). In patients older than 45, the independent risk factors were chronic liver disease (Odds ratio: 8.5, CI 95%: 4.4-16.8), per-endoscopic biopsies (Odds ratio: 2.7, CI 95%: 1.4-5.4), and blood transfusions (Odds ratio: 1.8, CI 95%: 0.9-3.5). Two variables were dominant for the entire population: IV drug use and chronic liver disease. In patients without these factors, only one risk factor was linked to serum anti-HCV positivity: perendoscopic biopsies (Odds ratio: 5.2, CI 95%: 1.6-16.5). These results suggest that HCV may be transmitted by perendoscopic biopsies.

**Aron E.** Hepatitis B vaccination. Advocating for a protection principle. *Bull Acad Natl Med* 2002; 186:361-366. [Article in French]

Hepatitis B is a worldwide disease. More than 350 million persons are chronic carriers and around one-quarter of these chronic carriers will develop cirrhosis or liver cancer within 30 years. Since 1981, more than a billion doses of hepatitis B vaccine have been used worldwide and it is considered one of the safest vaccines ever produced. The suggestion of a link between hepatitis B vaccine and demyelinating diseases has arisen because of case reports, although inevitably some people will develop symptoms of demyelination by chance after receiving hepatitis B vaccine. Scientific data could never demonstrate a causal association between hepatitis B vaccine and central nervous system diseases, including MS. However, the hypothesis of a potential causal relationship between vaccination and multiple sclerosis (MS) and other demyelinating diseases was brought to public debate by the French Health Authority after the publication of these cases. Since 1998, in France, several court decisions held pharmaceutical companies responsible for the development of multiple sclerosis in patients who were given hepatitis B vaccine on two grounds: the chronological coincidence between vaccination and the development of the plaintiffs' MS, and the fact that a causal link between the two cannot be excluded, although the Appeals Court did declare that "it is indisputable that there is no definite scientific evidence of a relation between vaccination and the onset of the disease". On 1st October 1998, the French Minister of Health decided to stop hepatitis B vaccination in schools. Stopping immunization on the basis of unfounded worries has led to decreased vaccine coverage levels among children. Two recent studies published in the *N Engl J Med* in February 2001 confirm the lack of evidence of an association between hepatitis B vaccination and multiple sclerosis. The Academie nationale de Medecine should be consulted about this major public health issue.

**Arrada A, Zak Dit Zbar O, Vasseur V.** Prevalence of HBV and HCV infections and incidence of HCV infection after 3, 6 and 12 months detention in La Santé prison, Paris. *Ann Med Interne (Paris)* 2001; 152(Suppl 7):6-8. [Article in French]

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The concentration of a marginal population (35% drug addicts) in prisons necessitates systematic and rigorous screening for hepatitis B and hepatitis C in subjects at risk. In June 1998, a screening program was initiated to determine the prevalence of HBV and HCV infections in prisoners and to determine the incidence after 3, 6 and 12 months detention. The screening program was proposed to 900 prisoners in a Paris prison (Maison d'arrêt de Paris-La Santé) from June 3 to November 10, 1998. The program included hepatitis B and hepatitis C serology at incarceration. For prisoners who were seronegative for HCV at incarceration, a new HCV serology was proposed after 3, 6 and 12 months detention. It was postulated that HCV contamination could occur during incarceration (syringe sharing, tattooing). After one year of incarceration, no seroconversions for HCV were observed among the prisoners participating in this study. These findings should be interpreted with caution due to the particular detention conditions at the prison involved, raising important methodology interrogations concerning this type of survey.

**Association Nationale des Gastroentérologues des Hôpitaux Généraux.** Who dies with hepatitis C virus in France? *Gastroenterol Clin Biol* 2001; 25:347-352. [Article in French]

To describe the characteristics of anti-HCV positive patients who have died in France. Prospective study of deceased or transplanted anti-HCV positive patients between January 1994 and February 1996, followed in Gastroenterology and Liver Units in 18 French General Hospitals. Retrospective study of patients with cirrhosis unrelated to HCV infection who died during the same period in 8 of these hospitals. Ninety-seven anti-HCV positive patients, 53 males and 44 females, deceased during the study period (except one transplanted patient), at a mean age of 67 (median: 71), from liver disease in 79% of cases (all had cirrhosis, and 49 hepatocellular carcinoma). The supposed sources of infection were: blood transfusion (44%), intravenous drug use (10%), unknown (46%). All 27 patients (22 men) with a daily alcohol intake of 80 g or more had cirrhosis, and died an average of 10 years earlier. The anti-HCV negative patients with alcoholic cirrhosis who died were three times as numerous, and had similar characteristics to anti-HCV positive alcoholic patients. HCV-infected patients who die of liver disease lose 5 to 10 years of life expectancy, and 10 years more if they drink 80 g or more of alcohol daily.

**Balinska MA.** What is vaccine advocacy? Proposal for a definition and action. *Vaccine* 2004; 22:1335-1342.

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Successful immunization programmes have reduced the burden of a number of infectious diseases on a global scale. Yet, as the fear of sequelae of vaccine-preventable diseases diminishes in the public, the focus of interest has shifted towards true and alleged "side effects". Maintaining confidence in the necessity, tolerability and safety of immunizations is of paramount importance today. This requires, amongst other prerequisites, precise definitions of "adverse events following immunization". In Europe, a collaborative effort named EUSAFEVAC in concert with the globally active "Brighton Collaboration" has been initiated. Volunteers from academic institutions, vaccine licensing authorities, public health institutes, governmental organizations, safety units within the

vaccine manufacturing industry as well as practising physicians are working together to achieve this goal.

**Becheur H, Harzic M, Colardelle P, Deny P, Coste T, Dubeaux B, Chochon M, Roussin-Bretagne S, Doll J, Andrieu J.** Hepatitis C virus contamination of endoscopes and biopsy forceps. *Gastroenterol Clin Biol* 2000; 24:906-910. [Article in French]

Service d'Hépatogastroentérologie, Centre Hospitalier de Versailles, Le Chesnay.

Procedures such as digestive endoscopy may explain some unclear contaminations by HCV. The aims of this study were to detect HCV genome on endoscopes and biopsy-forceps used in patients with known chronic HCV infection and to determine its presence in their gastric juice and saliva. A gastroscopy with antral biopsies was performed in 48 patients with non-treated replicative chronic hepatitis C. Samples were obtained after pushing 10 mL of sterile water through the biopsy-suction channel and after immersing the brush used to clean this channel. The biopsy-forceps were also immersed and their tips brushed in 10 mL of sterile water. This sampling technique was repeated three times: immediately after the endoscopic procedure (T0), after washing with a detergent (T1) and after immersion for 20 minutes in a 2% glutaraldehyde solution (T2). The HCV genome was detected by polymerase chain reaction (PCR, Amplicor - Roche Diagnostics Systems). For the last 15 patients, samples of gastric juice and saliva were obtained before antral biopsies and used to detect HCV genome. HCV genome was detected in the biopsy-suction channel in 13 cases (27%) at T0 and in one case (2%) at T1. It was undetectable after completion of the disinfection procedure (T2). Three biopsy-forceps (6%) were PCR positive immediately after the endoscopy but none at T1 and T2. HCV genome was found in the gastric juice in three cases. In all of them, it was also found at T0 in the biopsy-suction channel but not on the biopsy-forceps. When saliva contained HCV genome (4 cases), it was present in the biopsy-suction channel in only one case. In this case, the gastric juice was also PCR positive. HCV genome is detected in 27% of cases in the biopsy-suction channel after an endoscopic procedure performed on patients with chronic HCV infection. The biopsy-forceps are PCR positive in 6% of cases. The infected gastric juice may play a role in the contamination of the endoscopes. The complete disinfection procedure seems effective to eliminate HCV.

**Benhamiche AM, Faivre C, Minello A, Clinard F, Mitry E, Hillon P, Faivre J.** Time trends and age-period-cohort effects on the incidence of primary liver cancer in a well-defined French population: 1976-1995. *J Hepatol* 1998; 29:802-806.

Registre Bourguignon des Cancers Digestifs, INSERM CRI95 05, Faculté de Médecine, Dijon, France.

There is growing interest worldwide in primary liver cancer. The aim of this study was to describe the incidence of this cancer over a 20-year period in a well-defined French population. Time trends by 4-year period were studied by sex, age group, place of residence, histological type and associated cirrhosis. Trends were also analysed using the age-period-cohort model. Primary liver cancer incidence in men increased from 7.5/100000 for the period 1976-79 to 10.2/100000 for the period 1992-95. The mean annual variation was +2.2%, ( $p < 0.05$ ). The increase in incidence was seen mainly in the 55-64 and 65-74 age groups and concerned hepatocellular carcinomas. In men, the increase in incidence rates with time was observed mainly in rural areas, whereas incidence rates in urban areas remained stable. The rise in incidence was due mostly to an increase in primary liver cancer with cirrhosis, in relation to a progressive increase in post-hepatitic cirrhosis and a recent increase in alcoholic cirrhosis. The estimated cumulative risk for the life span 30-74 years increased from 0.8% for the 1904-1908 cohort to 2.1% for the 1934-1938 cohort. There was no significant trend in female rates. In France, incidence rates for primary liver cancer are increasing in men, whilst they are remaining stable in women. Our data confirm the primary

importance of alcohol in the aetiology of this cancer. Further studies are necessary to unravel the respective roles of alcohol and hepatitis C virus in the increasing incidence of primary liver cancer.

**Boutron MC, Faivre J, Milan C, Bedenne L, Hillon P, Klepping C.** Primary liver cancer in Côte d'Or (France). *Int J Epidemiol* 1988; 17:21-26.

Registre des Tumeurs Digestives (INSERM SCN17), Faculté de Médecine, Dijon, France.

The registry of digestive tract tumours established for the department of Côte d'Or (France) was used to study the incidence and some of the characteristics of primary liver cancer (PLC) in this area. The annual age-standardized incidence rate was 7.6/100,000 for males, and 1.8/100,000 for females. As compared to other areas the Côte d'Or is in the intermediate incidence areas. The risk of PLC was higher in urban than in rural areas in men ( $p$  less than 0.01). There was no significant variation in PLC incidence over the eight years of the study. Alfafoetoprotein levels over 200 ng/ml were observed in only 48.9% of the cases. Alfafoetoprotein measurement has to be complemented by other investigations in screening of high-risk patients. Liver cirrhosis was present in 70.9% of the cases in which the information was available. The male:female ratio in the non-cirrhotic group was 1.5:1, very different to the 8.8:1 in the cirrhotic group. Cirrhosis was associated with excessive alcohol consumption in 92% of cases. The prevalence of serological markers of hepatitis B virus infection was investigated in 91 patients. Hepatitis Bs-antigen was found in 8.8% and evidence of past or present infection in 28.2%. In view of the prevalence of chronic alcoholism in patients with cirrhosis it is suggested that alcohol leads to an increased risk of cirrhosis followed by an increased incidence of PLC. Further studies are needed to elucidate the eventual role of HBV infection and other suspected environmental factors in the aetiology of PLC.

**Bralet MP, Régimbeau JM, Pineau P, Dubois S, Loas G, Degos F, Valla D, Belghiti J, Degott C, Terris B.** Hepatocellular carcinoma occurring in nonfibrotic liver: epidemiologic and histopathologic analysis of 80 French cases. *Hepatology* 2000; 32:200-204.

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Hepatocellular carcinoma (HCC) occurring in nonfibrotic liver represents a rare, ill-defined subgroup of HCC without cirrhosis in which mechanisms of hepatocarcinogenesis remain unclear. The aim of our study was to assess epidemiological factors and detailed histopathologic changes in the nontumoral liver of patients developing such tumors. Of 330 HCCs resected in our institution between 1985 and 1998, we retrospectively analyzed 80 cases (53 men, 27 women; mean age, 51 +/- 16 years) in which the nontumoral liver showed no ( $n = 28$ ) or minimal ( $n = 52$ ) portal fibrosis without any septal fibrosis. In the group with no portal fibrosis there was no male predominance, and patients were significantly younger (44 +/- 19 years vs. 54 +/- 14 years) than those with minimal portal fibrosis. Sixty-seven tumors were typical HCCs, 8 were of fibrolamellar type, and 5 were hepatocholangiocarcinomas. Mean tumor size was 10 +/- 5 cm. Risk factors for HCC development were found in 30 patients: hepatitis B ( $n = 17$ ) or C ( $n = 2$ ) virus infections, alcohol consumption ( $n = 11$ ), and hemochromatosis ( $n = 1$ ). In the nontumoral liver, periportal and lobular necrosis, mild portal inflammation, steatosis, and iron overload were present in 15%, 57%, 52%, and 54% of cases, respectively. Liver cell changes were noted in 6%. This study emphasizes the need for strict criteria to classify HCC without cirrhosis. HCC in nonfibrotic liver is a distinct subgroup in which nontumoral liver shows nonspecific minimal changes without regeneration or premalignant lesion. Etiologic factors are often unidentified, although presence of HBV infection in 21% suggests a direct oncogenic role of this virus.

**Buisson Y, Meyran M.** Prevention of hepatitis A and hepatitis B by vaccination. *Ann Gastroenterol Hepatol (Paris)* 1995; 31:306-308. [Article in French]

Laboratoire de Biologie Clinique, Hôpital d'Instruction des Armées Val-de-Grâce, Paris.

In spite of low endemic levels in France, hepatitis A and hepatitis B remain major concerns for public health. Seroprevalence of antibodies against hepatitis A (anti-HAV), declining below 15% in the 20 years-aged subjects, highlights an increasing susceptibility to hepatitis A. Later in the life, HAV infections become more serious and expansive. Control measures against hepatitis B have nearly stopped HBV spread linked to blood transfusions and mothers to infants transmission. Now, common risk factors are first sexual exposure, then injecting drug use, especially among young people. Vaccination is recognized as the most effective process for prevention. Recombinant hepatitis B vaccines have taken the place of plasma-derived vaccines. Although non responder individuals and escape mutants of HBV may hamper vaccinal coverage, hepatitis vaccines are highly immunogenic in immunocompetent people, allowing simplified schedules and reduced HBsAg dosages for children. Inactivated HAV vaccines now licensed prove to be highly immunogenic after only one injection. Hepatitis B vaccination targeted on high risk groups remains imperative but inadequate for reducing hepatitis B occurrence. A universal hepatitis B vaccination program in childhood and early adolescence would nearly stop the spread of HBV in the populations before ten years. Likewise, hepatitis A vaccination of travelers to endemic areas, all individuals exposed to contaminations from fecal sources, and food handlers, could reduce the spread of HAV in the community but would not completely prevent outbreaks of hepatitis A. Advantages of universal immunization of babies are not proved yet. Implementation of preventive strategies first needs a comprehensive surveillance of viral hepatitis in France.

**Cacoub P, Geffray L, Rosenthal E, Perronne C, Veyssier P, Raguin G, on behalf of the Joint Study Group on Hepatitis C Virus of the French National Society of Internal Medicine and the French Society of Infectious Diseases (GERMVIC Study Group).** Mortality among human immunodeficiency virus-infected patients with cirrhosis or hepatocellular carcinoma due to hepatitis C virus in French Departments of Internal Medicine / Infectious Diseases, in 1995 and 1997. *Clin Infect Dis* 2001; 32:1207-1214.

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Several studies have suggested that the progression of hepatitis C virus (HCV) infection is more severe in patients infected by the human immunodeficiency virus (HIV). Two national retrospective multicenter cohort surveys were performed in France that included 17,487 HIV-infected patients during 1995 and 26,497 during 1997. The following data was evaluated: total number of deaths; number of deaths linked to AIDS, cirrhosis, or hepatocellular carcinoma (HCC); and number of deaths related to other (non-HCV-linked) causes. In 1995, the causes of death were as follows: AIDS, 1307 (7.47%); cirrhosis or HCC, 21 (0.12%); and other (non-HCV--linked) causes, 99 (0.56%). In 1997, the causes of deaths were as follows: AIDS, 459 (1.73%); cirrhosis or HCC 36 (0.13%); and other (non-HCV--linked) causes, 48 (0.18%). Comparative results between the 1995 and 1997 surveys showed a dramatic decrease in AIDS-related mortality rates (7.47% vs. 1.73%;  $P < .001$ ) but not in HCV-related mortality rates (0.06% vs. 0.07%;  $P = 0.79$ ). In France, despite the high prevalence of HCV infection in HIV-positive patients, the mortality rate in 1995 and 1997 caused by HCV-related cirrhosis or HCC was low.

**Cadilhac P, Roudot-Thoraval F.** Seroprevalence of hepatitis A virus infection among sewage workers in the Parisian area, France. *Eur J Epidemiol* 1996; 12:237-240.

Service de Médecine Professionnelle et Préventive, Conseil Général du Val-de-Marne, Créteil, France.

Sewers are an ideal environment to be occupationally exposed to viral hepatitis A (HAV) infection, because of high frequency and ability of the virus to remain viable for prolonged periods in sewage. However, data on the occupational risk of HAV infection among sewage workers is not well documented. In a cross sectional study comparing sewage workers (n = 155) to those not occupationally exposed to it (n = 70), we found a non significant increase in HAV seropositivity among sewage workers of 12.9% (p = 0.07). The prevalence of HAV antibody was significantly associated with duration of occupational exposure to sewage (p < 0.015), stay in HAV endemic areas (p < 0.03), age (p < 0.001), and number of siblings (p < 0.03). A stepwise logistic regression analysis gave an adjusted odds ratio for HAV seropositivity 2.15 fold greater in sewage workers compared to those not occupationally exposed to it. So, although there was no significant difference in the prevalence of HAV antibody between sewage workers and others, exposure to sewage was an independent risk factor for HAV seropositivity, and this raises the question of whether it is necessary to vaccinate sewage workers against viral hepatitis A.

**Cadranel JF, Di Martino V, Cesbron H, Cazier A, Demontis R, Coutarel P, Bachmeyer C, Cordier F, Lukumbo S, Fievet P, Mougeot-Martin M, Van Batten C, Devergie B, Dumouchel P.** Epidemiological characteristics of hepatitis C in a primary referral hospital. Impact Of systematic screening on therapeutic management and natural history. *Gastroenterol Clin Biol* 2000; 24:161-167. [Article in French]

Unité d'Hépatologie, Service de Médecine Générale et Digestive, Centre Hospitalier Laennec, BP 72, 60109 Creil.

To study the epidemiological characteristics of patients with chronic hepatitis C virus followed in a primary referral hospital and the clinical influence of "systematic screening" defined as the screening of patients without symptoms and with known risk factors of hepatitis C (past transfusion, past or present intravenous drug use, haemodialysis) on the natural history and treatment of chronic hepatitis C virus. The files of 311 consecutive patients who screened positive for anti-hepatitis C virus and were seen at the primary referral hospital, Creil, from January 1992 to February 1996, were analyzed. Patients who underwent "systematic screening" were younger with a shorter duration of infection. They were more often intravenous drug addicts and had lower alanine aminotransferase activity and Knodell scores than patients who underwent screening during "a diagnostic procedure", because of symptoms and/or abnormal liver biochemistry. Increased age at contamination and alcohol consumption of more than 40 g per day was associated with an increased risk of cirrhosis while patients who underwent "systematic screening" had a lower risk of cirrhosis and higher survival rate. Interferon therapy was attempted less often in anti-hepatitis C virus positive patients from "systematic screening" programs. Anti-hepatitis C virus positive patients from "systematic screening" programs had a benign disease and were rarely treated with interferon compared to anti-hepatitis C virus positive patients diagnosed during a "diagnostic procedure".

**Cadranel JF, Caron C, Collot G, Van Batten C, Dumouchel P.** Hepatitis B: epidemiology, natural history, biology, treatment monitoring. *Pathol Biol (Paris)* 1999; 47:917-927. [Article in French]

Unité d'Hépatologie, Centre Hospitalier Laennec, Creil.

Hepatitis B virus (HBV) infection is a worldwide public health problem. In France, 150,000 individuals are infected with the HBV. Although many are asymptomatic carriers, about 30% have chronic hepatitis, a condition associated with a risk of cirrhosis and hepatocellular carcinoma. Antiviral treatments, most notably interferon alpha, probably modify the natural history of hepatitis B, decreasing the risk of hepatocellular carcinoma and increasing survival. Nucleoside analogs, particularly lamivudine, have also demonstrated potent antiviral activity, which should

however be weighed against the increasing risk over time of mutation development in the YMDD region of the DNA polymerase reverse transcriptase. Antiviral therapy monitoring should include clinical safety evaluations and periodic laboratory tests including blood cell counts, transaminase activities, and serum DNA levels. The improving results provided by antiviral drugs should not deflect attention away from the importance of large-scale hepatitis B immunization of neonates, which has been shown to decrease the incidence of hepatocellular carcinoma in areas with high levels of hepatitis B endemicity.

**Chemin I, Zoulim F, Merle P, Arkhis A, Chevallier M, Kay A, Cova L, Chevallier P, Mandrand B, Trépo C.** High incidence of hepatitis B infections among chronic hepatitis cases of unknown aetiology. *J Hepatol* 2001; 34:447-454.

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In approximately 5% of chronic liver disease cases, no aetiology can be identified. We selected sera from 50 patients with chronic hepatitis of unknown aetiology who were enrolled in this follow-up study whose aim is to gain insight into the possible role of viruses and to define potential clinical outcomes. Patients' sera were screened with highly sensitive polymerase chain reaction assays for hepatitis B (HBV), C, D, and G viruses and TT virus. Sera were also retested for antibodies against the core antigen of HBV. Surprisingly, HBV DNA was detected in both serum and liver in 15/50 (30%) patients. Immunostaining for HBV antigens on biopsies from patients positive for HBV DNA showed HBcAg and/or HBsAg expression at low levels in 9/15 samples. Eleven of the fifteen patients were anti-HBc positive. With one exception, all patients carried HBV genomes at low levels (10(4) copies/ml or less). Histological signs of chronic liver disease were observed in all patients. Unrecognised HBV infections may account for a high proportion of chronic hepatitis cases of unknown aetiology. Improved HBV detection tests, which appear mandatory for the diagnosis and management of non-A non-E hepatitis as well as for improved safety of transfusions and transplantations are needed.

**Chiron JP, Coursaget P, Yvonnet B.** Philippe Maupas : hepatitis B vaccine discoverer. *Rev Hist Pharm (Paris)* 1998; 46:279-292. [Article in French]

Laboratoire de Microbiologie-Immunologie, Faculté des Sciences Pharmaceutiques, Tours.

Philippe Maupas Day 8th February 1981, an official ceremony with all the Profession, the Tours Faculty of Pharmacy was called Philippe Maupas, Hepatitis B vaccine discoverer - Galien Prize 1981. This communication presents the man, the scientist and the teacher. Born on 30th June 1939 in Toulon (south of France), married and the father of two children, Ph. Maupas was a man of action and an humanist. Full of enthusiasm, always available, passionate about his work, he never hesitated to brave the odds if he felt it would be of use to the community. With a pluridisciplinary training - Veterinary Doctor (1965), Pharmacist (1970), Science Doctor (1970) and Physician Doctor (1976) - he was Professor of Microbiology and Dean of the Faculty of Pharmacy of Tours. His scientific career fully illustrates his thirst for knowledge and his unflinching struggle against infectious diseases. Ph. Maupas approached his research work in a relaxed, imaginative frame of mind. Always passionate about his work and fired by spirit of Louis Pasteur, he was moved by a preoccupation of efficacy and a will of prevention in Public Health. He carried out research into both animal and human infectious diseases as well as anthroozoonosis. Ph. Maupas's most remarkable discoveries concerned the hepatitis B virus: he produced the first vaccine against hepatitis B and applied it to the prevention in man of this disease (1976); he confirmed the aetiological link between the hepatitis B and primary liver cancer.

**Claudon-Charpentier A, Hoibian M, Glasser P, Lalanne H, Pasquali JL.** Drug-addicted prisoners: seroprevalence of human immunodeficiency virus and hepatitis B and C virus soon after the marketing of buprenorphine. *Rev Med Interne* 2000; 21:505-509. [Article in French]

Service Pharmacie, Hôpital de Hautepierre, Hôpitaux Universitaires de Strasbourg, France.

Considering the importance to public health and the frequency with which drug addicts are imprisoned, we studied the prevalence of human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), as well as drug addiction of patients admitted to the Elsau prison in Strasbourg (France). The prospective study included all entering inmates from 1 September to 31 October 1997 (270 persons) to whom HIV, HBV and HCV blood tests were offered as well as a questionnaire on their drug addiction. Thirty-six percent of the entering inmates were drug addicts, of whom 1% were HIV positive, 11.2% HBV positive and 30% HCV positive, compared to, respectively, 0.6, 9.9 and 6.4% for non-drug addicts. Ninety-five of the 98 patients used several drugs, including buprenorphine for 53 patients. At the beginning of this study, buprenorphine had been available in France for 9 months. The results are to be taken seriously regarding the misuse of this product in this selected population (intravenous use, multiple drug use, dealing).

**Colin C, Vergnon P, Jullien AM, Excoffier S, Matillon Y, Trépo C.** Cost-effectiveness of screening blood donors for hepatitis C and non-A, non-B, non-C hepatitis. The EATHIS Eco Research Group. European Acute Transfusion Hepatitis Interferon Study. *Eur J Clin Microbiol Infect Dis* 1997; 16:220-227.

Département d'Information Médicale des Hospices Civils de Lyon, Hôtel-Dieu, France.

The current approach to screening for hepatitis C and non-A, non-B, non-C hepatitis in French blood transfusion centers involves a combination of a transaminase assay and tests for antibodies to hepatitis B core antigen (anti-HBc) and antibodies to hepatitis C virus (anti-HCV). A decision-analysis model was used to assess the cost-effectiveness ratio of this approach compared to the former approach, which included only transaminase and anti-HBc screening. Cost data were collected by a questionnaire sent to 26 centers throughout France. The average costs of diagnostic kits, equipment, staff, and administration were calculated. Estimates of prevalence and sensitivity values came from the medical literature. The cost-effectiveness ratio was expressed in French francs per infected donor detected. A sensitivity analysis of the variables in the model was performed to estimate the validity of the cost-effectiveness ratio. For 100,000 donations the incremental cost of the current approach reached FrF 2,566,111 (about US \$500,000), with a marginal effectiveness of 180 donations detected. The sensitivity analysis showed the effect of prevalence on the incremental cost-effectiveness ratio. Transfusion centers may change their screening approach in areas of high or low prevalence of hepatitis C in France.

**Confavreux C, Suissa S, Saddier P, Bourdes V, Vukusic S, on behalf of the Vaccines in Multiple Sclerosis Study Group.** Vaccinations and the risk of relapse in multiple sclerosis. *N Engl J Med* 2001; 344:319-326.

European Database for Multiple Sclerosis Coordinating Center and the Service de Neurologie A, Hôpital Neurologique, Lyons, France.

There has been some concern that vaccination may precipitate the onset of multiple sclerosis or lead to relapses. Since the recent hepatitis B vaccination program in France, there have been new reports of an increased risk of active multiple sclerosis after vaccination. We conducted a case-crossover study to assess whether vaccinations increase the risk of relapse in multiple sclerosis. The subjects were patients included in the European Database for Multiple Sclerosis who had a

relapse between 1993 and 1997. The index relapse was the first relapse confirmed by a visit to a neurologist and preceded by a relapse-free period of at least 12 months. Information on vaccinations was obtained in a standardized telephone interview and confirmed by means of medical records. Exposure to vaccination in the two-month risk period immediately preceding the relapse was compared with that in the four previous two-month control periods for the calculation of relative risks, which were estimated with the use of conditional logistic regression. Of 643 patients with relapses of multiple sclerosis, 15 percent reported having been vaccinated during the preceding 12 months. The reports of 94 percent of these vaccinations were confirmed. Of all the patients, 2.3 percent had been vaccinated during the preceding two-month risk period as compared with 2.8 to 4.0 percent who were vaccinated during one or more of the four control periods. The relative risk of relapse associated with exposure to any vaccination during the previous two months was 0.71 (95 percent confidence interval, 0.40 to 1.26). There was no increase in the specific risk of relapse associated with tetanus, hepatitis B, or influenza vaccination (range of relative risks, 0.22 to 1.08). Analyses based on risk periods of one and three months yielded similar results. Vaccination does not appear to increase the short-term risk of relapse in multiple sclerosis.

**Costa-Mattioli M, Cristina J, Romero H, Perez-Bercof R, Casane D, Colina R, Garcia L, Vega I, Glikman G, Romanowsky V, Castello A, Nicand E, Gassin M, Billaudel S, Ferre V.** Molecular evolution of hepatitis A virus: a new classification based on the complete VP1 protein. *J Virol* 2002; 76:9516-9525.

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Hepatitis A virus (HAV) is a positive-stranded RNA virus in the genus Hepatovirus in the family Picornaviridae. So far, analysis of the genetic variability of HAV has been based on two discrete regions, the VP1/2A junction and the VP1 N terminus. In this report, we determined the nucleotide and deduced amino acid sequences of the complete VP1 gene of 81 strains from France, Kosovo, Mexico, Argentina, Chile, and Uruguay and compared them with the sequences of seven strains of HAV isolated elsewhere. Overall strain variation in the complete VP1 gene was found to be as high as 23.7% at the nucleotide level and 10.5% at the amino acid level. Different phylogenetic methods revealed that HAV sequences form five distinct and well-supported genetic lineages. Within these lineages, HAV sequences clustered by geographical origin only for European strains. The analysis of the complete VP1 gene allowed insight into the mode of evolution of HAV and revealed the emergence of a novel variant with a 15-amino-acid deletion located on the VP1 region where neutralization escape mutations were found. This could be the first antigenic variant of HAV so far identified.

**Costa-Mattioli M, Monpoeho S, Nicand E, Aleman MH, Billaudel S, Ferre V.** Quantification and duration of viraemia during hepatitis A infection as determined by real-time RT-PCR. *J Viral Hepat* 2002; 9:101-106.

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Human transmission studies and molecular techniques have provided evidence that transient viraemia occurs during infection with hepatitis A virus (HAV). However, the duration of its presence and levels during the phases of clinical disease and convalescence has not yet been well studied in human patients. Real-time RT-PCR techniques are increasingly used to quantify RNA viruses for diagnosis and/or research purposes. We have optimized a one-step RT-PCR that contains a dual-labelled fluorogenic probe to quantify the 5' noncoding region (5' NCR) of HAV. This method has a dynamic range (5-5 x 10<sup>6</sup> copies). The coefficient of regression of the standard curve was, on average 0.978. Intra-assay CVs% varied from 6.1% to 0.98%, and

interassay CVs% from 6.46% to 2.1%. In the currently reported study 41 HAV IgM positive serum samples and 200 serum samples from healthy blood donors were tested by the quantitative RT-PCR method. The mean values on the first day of diagnosis found was  $6.38 \times 10^5$  copies/mL. In a longitudinal study, viraemia persisted for an average of 60 days after clinical onset. These results show that viraemia in HAV infection lasts for many weeks.

**Courouce AM, Pillonel J, Saura C.** Screening for markers of infections transmitted by transfusions in the blood collected in France from 1996 to 1998. *Transfus Clin Biol* 2000; 7:153-170. [Article in French]

Institut National de la Transfusion Sanguine, Paris, France.

From 1996 to 1998, a decrease in positive donation rates has been observed for HIV, HCV and HBs Ag in first-time donors, while these rates remained stable for HTLV. In repeat donors, the same decrease was observed for HCV and HBs Ag while the rates remained stable for HIV. No HTLV-positive donations from repeat donors were noted in 1998. About half of the HIV-positive repeat donors were regular donors (less than two years between the two donations), as well as 88% of HBV-infected repeat donors. Inversely, only 20% of HCV-positive repeat donors were regular donors. Anti-HBc antibodies have been found in 20% of HIV-infected donors, in 22% of HCV-infected donors, and were associated with HBs Ag in 99% of the cases. Elevated ALT was observed in 47% of donors with anti-HCV and in 10% of donors with HBs Ag. The major risk factors are at-risk sexual behavior for HIV and use of intravenous drugs and nosocomial infections for HCV. Being a native of an endemic country has been found to be the major risk for HBV. The major HTLV risk factor was directly or indirectly linked to the Caribbean area.

**Coursaget P, Yvonnet B, Sarr M, Vincelot P, Tortey E, Mboup S, Chiron JP, Diop-Mar I.** Clinical trial of hepatitis B vaccine in a simplified immunization programme. *Bull World Health Organ* 1986; 64:867-871.

A study was conducted in the rural areas of Senegal to assess the immunogenic effect of 2 doses of hepatitis B vaccine with a 6-month interval followed by a booster dose after another month and to compare them with those obtained using 2 doses of a vaccine with a 2-month interval or 3 doses at 1-month intervals. The study population of infants received 3 injections of hepatitis B vaccine at 6-month intervals (T0, T6, and T12, respectively), with the 3rd dose as a booster. Other vaccines also were administered to subsets of children: BCG and diphtheria/tetanus/pertussis-polio (DTP-polio) at T0 and DTP-polio at T6 and T12. 664 infants received the 1st dose of hepatitis B vaccine, 409 the 2nd dose, and 177 the 3rd dose. Blood samples were taken at the time of each injection and in the case of 89 infants also 2 months after the last (booster) dose. Only 26.7% of the infants completed the entire series of injections. Only results from infants who were seronegative at T0 are presented, i.e., 281 infants at T6, 116 at T12, and 65 at T14. At T0 the mean age of the seronegative infants was 10.2 months and that of the seropositive infants with anti-HB antibodies was 7.4 months. The mean age of infants who were only anti-HBc-positive was 4.8 months and that of infants who were already HBsAg-positive at T0 was 14.3 months. The results were compared with those reported for 2 other groups of Senegalese infants: 72 seronegative infants who were immunized using a protocol of 2 doses of hepatitis B vaccine with a 2-month interval; and 111 seronegative infants immunized using 3 doses at 1-month intervals. Both groups also received a booster 12 months after the 1st dose. The anti-HBs response was determined 6 months after the T0 dose of hepatitis B vaccine for the 281 infants who were seronegative. 185 of these children (65.8%) exhibited anti-HB antibodies, but the geometric mean titre (GMT) was only 6.1 mIU/ml. The anti-HBs response of the 116 infants who received the 2nd dose of vaccine was determined when the 3rd (booster) injection was given (T12): 104 were positive for anti-HBs (89.7%), and the anti-HBs GMT was 83.7 mIU/ml. Assay of blood samples from 65 infants 2 months after the booster dose indicated that 62 (95.4%) had anti-HBs antibodies, the anti-HBs

GMT reaching 348 mIU/ml. The study results establish that infants administered two 5-mcg doses of hepatitis B vaccine with a 6-month interval exhibit a seroconversion rate and antibody levels comparable to those produced using a protocol comprising 2 doses with a 2-month interval or 3 doses at 1-month intervals.

**Degos F, Christidis C, Ganne-Carrie N, Farmachidi JP, Degott C, Guettier C, Trinchet JC, Beaugrand M, Chevret S.** Hepatitis C virus related cirrhosis: time to occurrence of hepatocellular carcinoma and death. *Gut* 2000; 47:131-136.

Service d'Hépatogastro-Enterologie, Hôpital Beaujon, Clichy, France.

In patients with hepatitis C virus (HCV) infection and cirrhosis, long term outcome and the incidence of hepatocellular carcinoma (HCC) are still debated. From January 1987 to January 1997, 416 patients (240 male, median age 57 years) with uncomplicated Child-Pugh A HCV related cirrhosis were followed in two Paris area centres from diagnosis of cirrhosis until death or reference date (1 June 1998). The analysis used a three state disability model generalising the Cox model. Of the 416 patients, 60 developed HCC with a five year rate of 13.4% (95% confidence interval (CI) 9.0-17.8%) and 83 died (including 34 with HCC), with a five year death rate of 15.3% (95% CI 12.6-18.0%). By multivariable analysis, time to HCC relied on age (hazard ratio (HR) 1.05 per year;  $p = 0.0005$ ), male sex (HR 2.13;  $p = 0.01$ ), oesophageal varices (HR 2.36;  $p = 0.008$ ), decreased platelet count (HR 0.99;  $p = 0.03$ ), and bilirubin level (HR 1.01;  $p = 0.003$ ), while death after HCC was mainly related to tobacco consumption (HR 1.04;  $p = 0.0006$ ). In contrast, death free of HCC was dependent on age (HR 1.04;  $p = 0.01$ ), oesophageal varices (HR 2.75;  $p = 0.001$ ), low platelet count (HR 0.99;  $p = 0.006$ ), and albumin level (HR 0.90;  $p = 0.0001$ ). The incidence of HCC and mortality should be higher in these patients than previously stated, and prognostic factors of HCC and death are closely related age and symptoms of portal hypertension.

**Delarocque-Astagneau E, Baffoy N, Thiers V, Simon N, de Valk H, Laperche S, Courouge AM, Astagneau P, Buisson C, Desenclos JC.** Outbreak of hepatitis C virus infection in a hemodialysis unit: potential transmission by the hemodialysis machine? *Infect Control Hosp Epidemiol* 2002; 23:328-334.

Institut de Veille Sanitaire, Paris, France.

To identify the routes of transmission during an outbreak of infection with hepatitis C virus (HCV) genotype 2a/2c in a hemodialysis unit. A matched case-control study was conducted to identify risk factors for HCV seroconversion. Direct observation and staff interviews were conducted to assess infection control practices. Molecular methods were used in a comparison of HCV infecting isolates from the case-patients and from patients infected with the 2a/2c genotype before admission to the unit. A hemodialysis unit treating an average of 90 patients. A case-patient was defined as a patient receiving hemodialysis with a seroconversion for HCV genotype 2a/2c between January 1994 and July 1997 who had received dialysis in the unit during the 3 months before the onset of disease. For each case-patient, 3 control-patients were randomly selected among all susceptible patients treated in the unit during the presumed contamination period of the case-patient. HCV seroconversion was associated with the number of hemodialysis sessions undergone on a machine shared with (odds ratio [OR] per additional session, 1.3; 95% confidence interval [CI95], 0.9 to 1.8) or in the same room as (OR per additional session, 1.1; CI95, 1.0 to 1.2) a patient who was anti-HCV (genotype 2a/2c) positive. We observed several breaches in infection control procedures. Wetting of transducer protectors in the external pressure tubing sets with patient blood reflux was observed, leading to a potential contamination by blood of the pressure-sensing port of the machine, which is not accessible to routine disinfection. The molecular analysis of HCV infecting isolates identified among the case-patients revealed two

groups of identical isolates similar to those of two patients infected before admission to the unit. The results suggest patient-to-patient transmission of HCV by breaches in infection control practices and possible contamination of the machine. No additional cases have occurred since the reinforcement of infection control procedures and the use of a second transducer protector.

**Denis F.** Hepatitis B vaccination in France: vaccination coverage in 2002. *Bull Acad Natl Med* 2004; 188:115-123. [Article in French]

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In parts of Europe where the relevant data are available, the vaccinal coverage rate of children against hepatitis B virus ranges from 27.5 to 99.0% and that of adolescents from 52 to 98%. In France, an exhaustive population survey conducted in 2002 revealed an overall vaccine coverage rate of over 21.7% and very low three-dose coverage rates among infants (19.8%), children (23.3%), and adolescents (46.2%) which are inadequate to protect future generations from HBV infection and its consequences. Unless major efforts are made to vaccinate these populations and high-risk groups, complete elimination of HBV transmission might take another 20 years to achieve.

**Denis F, Delpeyroux C, Debrock C, Rogez S, Alain S.** Seroprevalence of hepatitis A in hospitalized patients in Limoges University Hospital. *Gastroenterol Clin Biol* 2003; 27:727-731. [Article in French]

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Age-specific prevalence of hepatitis A virus (HAV) antibodies (IgG and IgM anti HAV). For eight years between 1994 and 2002, 15 329 hospitalized patients were tested. The prevalence of anti HAV according to age group was as follows: 20 to 29: 28.5%; 30 to 39: 47.4%; 40 to 49: 64.8%; 50 to 59: 82.1%; more than 90% after 60 years old and 97% in patients older than 80. This was not a cross sectional seroepidemiological investigation because serum samples were selected by prescription especially among children. Recent HAV infections as shown by IgM positivity (136 patients) was observed among all age groups, particularly before ten years old (28.7%), but was still significant after sixty (19.8%). The age-specific seroprevalence of HAV antibodies compared with previous French prevalence data revealed a good correlation with results obtained in West-Central region and in national investigations in general populations but more elevated than observed in French recruits.

**Denis F, Goudeau A, Aufrère A.** Vaccination against hepatitis B in France in 1996. *Bull Soc Pathol Exot* 1998; 91:37-40. [Article in French]

Service de Bactériologie-Virologie-Hygiène, CHU Dupuytren, Limoges.

A national campaign aimed at promoting immunization against hepatitis B was launched in 1994. Two years later, a survey was designed to estimate the situation of the hepatitis B vaccination in France. Around ninety per cent of physicians were hepatitis B vaccinated. The rate of vaccinated population among public hospitals personnel were more than 90% and lower in private hospitals (79%). A quarter of the general population was vaccinated and the higher rate (69%) was observed in the 13-20 years young people. Progressively the contribution of the physicians to the vaccination was increasing (89% in 1996). After a selective vaccination of risk groups and the instauration of the prevention of mother/infant transmission, the French programme was extended

to cover adolescents and children. The success of the hepatitis B vaccination campaign was obtained by the promotion message toward population and physicians.

**Desenclos JC.** Epidemiology of hepatitis C. *Rev Prat* 2000; 50:1066-1070. [Article in French]

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The hepatitis C virus (HCV) has spread in a silent way by blood transfusion, then was massively introduced in the intravenous drug user community and is now recognized as a potential nosocomial viral infection. In France the prevalence of HCV seropositivity is around 1.1% with 500,000 to 650,000 persons affected, among whom 80% are chronic carriers of the virus. The proportion of HCV seropositive patients who knew their HCV serostatus increased from approximately 20% in 1994 to around 50% in 1998. The prevalence of HCV infection varies by region (1.7% in Provence-Alpes-Cote d'Azur), increases with age, particularly after 50 years among women. The residual risk associated with transfusion is currently 2.7 per million blood donations, transmission among drug users remains high despite harm reduction measures and nosocomial transmission has been increasingly documented. In 1997, 1,800 deaths associated with hepatitis C occurred in France.

**Desenclos JC, Bourdiol-Razes M, Rolin B, Garandeau P, Ducos J, Bréchet C, Thiers V.** Hepatitis C in a ward for cystic fibrosis and diabetic patients: possible transmission by spring-loaded finger-stick devices for self-monitoring of capillary blood glucose. *Infect Control Hosp Epidemiol* 2001; 22:701-707.

Institut de Veille Sanitaire, Saint-Maurice, France.

To identify the routes of transmission in a nosocomial outbreak of hepatitis C virus (HCV) infection. Epidemiological investigation, including screening for HCV of hospitalized patients, and a retrospective cohort study, review of hygiene and medical practices, and molecular comparison of HCV isolates. A specialized care unit for cystic fibrosis (CF) and diabetic patients at an acute-care facility in the south of France. Of the 57 CF patients (age in 1995: 2-28 years), 38 (66.7%) were tested and 22 (57.9%) were anti-HCV positive. Eight (50%) of 16 patients with anti-HCV antibody tested by polymerase chain reaction were viremic. No patients had received blood products or had any history of intravenous drug use. All 18 (100%) patients with CF who had ever undergone self-monitoring of capillary blood glucose in the unit were anti-HCV positive, compared to 4 (20%) of 20 who had not (relative risk, 5.0; 95% confidence interval, 2.1-12.0). Seventy (39.5%) of the patients with diabetes were screened for anti-HCV; 12 (18.8%) tested positive, with 3 (25%) positive for HCV-RNA. Patients with diabetes had routine capillary blood glucose monitoring while hospitalized and shared with CF patients the same spring-triggered devices for capillary blood glucose monitoring. The disposable platform of the devices was not changed between patient use. All HCV isolates belonged to the type 1, subtype b, and phylogenetic analysis showed a close homology by sequencing of NS5b and E2/HVR regions. As reported earlier for the hepatitis B virus, shared spring-triggered devices for capillary blood glucose monitoring by finger puncture may transmit HCV. Strict application of Standard Precautions procedures is warranted in any healthcare setting.

**Deuffic S, Buffat L, Poynard T, Valleron AJ.** Modeling the hepatitis C virus epidemic in France. *Hepatology* 1999; 29:1596-1601.

Unité de Recherche 'Epidémiologie et Sciences de l'Information' (INSERM U444), Faculté de Médecine Saint-Antoine, Paris, France.

A backcalculation approach allows a reconstruction of the history of hepatitis C virus (HCV) infection in France and predictions of mortality from hepatocellular carcinoma (HCC) related to the virus. The model uses information from the literature about the natural history of the disease, epidemiological data about infected subjects in three French cohorts, and mortality data from national statistics. It seeks to determine the annual transition probabilities from chronic hepatitis to cirrhosis and the HCV incidence per year in the past. These unknowns are found by fitting the observed deaths from HCC that are attributable to HCV. Optimal values for these unknowns then allow to project the number of HCC deaths attributable to HCV for each year through 2025 (for patients infected before 1996). The model traces the HCV epidemic in France back to around the 1940s. It predicts that HCC mortality related to HCV will continue to increase through 2020 in the absence of treatment, with a 150% increase in the yearly incidence among men and 200% among women. The model also confirms that progression to cirrhosis depends strongly on sex and age. At any age, the annual probability of progression is 10 times greater for men than for women. Moreover, for men aged between 61 and 70 years, this probability is 300 times greater than that for men aged between 21 and 40 years.

**Deuffic-Burban S, Poynard T, Valleron AJ.** Quantification of fibrosis progression in patients with chronic hepatitis C using a Markov model. *J Viral Hepat* 2002; 9:114-122.

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The knowledge of fibrosis progression in chronic hepatitis C and the impact of new treatments on progression is limited by the number of available liver biopsies per patient. Moreover, liver biopsies identify a patient's stage of fibrosis at a given point in time, but cannot quantify the time spent in that stage nor the date of transition to that stage. This paper assesses the potential of Markov modelling to overcome these difficulties. The data from interferon-treated (n = 185) and untreated patients (n = 102) are analysed to illustrate the power of this technique. The model accurately reproduced the distributions of patients in the different fibrosis stages at two subsequent biopsies. A quantification of the role of cofactors in the progression of the disease, and the impact of interferon treatment are given. In subjects who are 40 years old and have been infected for 10 years, the model predicted that 274 of 1000 untreated patients, but only 42 of 1000 treated patients, would progress from F0 or F1 to F3 or F4 fibrosis over the next 5 years. The model also confirms that as age and duration of infection increase, the risk of fibrosis progression increases, while the impact of treatment with interferon decreases. Hence Markov modelling is an accurate tool in the analysis of fibrosis progression in chronic hepatitis C. It will be valuable for the quantification of the effect of new treatments on fibrosis progression in hepatitis C.

**Deuffic S, Poynard T, Valleron AJ.** Correlation between hepatitis C virus prevalence and hepatocellular carcinoma mortality in Europe. *J Viral Hepat* 1999; 6:411-413.

Unité de Recherche Epidémiologie et Sciences de l'Information (INSERM U444), Faculté de Médecine Saint-Antoine, Paris, France.

In Europe, as worldwide, hepatocellular carcinoma (HCC) death rates are highly variable. Recent studies have reported that hepatitis C virus (HCV) infection may be responsible for the increased mortality from HCC in the UK and in France. We investigate here the potential relationship between HCC mortality and HCV prevalence in Europe. Population and mortality data of HCC were obtained for 22 European countries from the World Health Organization (WHO) databank. Age-standardized death rates were computed. The HCV prevalence among blood donors and the WHO estimate of HCV prevalence were used as two indicators of prevalence in the general population, when data were available. Spearman rank analysis was conducted between HCC mortality and HCV prevalence. For men, age-standardized death rates per 100 000 varied from

0.61 (Greece) to 12.19 (Hungary). HCC mortality among men was positively correlated with HCV prevalence among blood donors and with the WHO estimate: rank correlation coefficients were, respectively, 0.76 ( $P = 0.02$ ) and 0.72 ( $P = 0.03$ ). This study showed that the reported differences of HCC mortality in Europe correlate with HCV prevalence.

**Deuffic-Burban S, Wong JB, Valleron AJ, Costagliola D, Delfraissy JF, Poynard T.** Comparing the public health burden of chronic hepatitis C and HIV infection in France. *J Hepatol* 2004; 40:319-326.

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In France, the prevalence of hepatitis C virus (HCV) exceeds that of HIV, but in the absence of treatment, HIV infection progresses more rapidly than HCV. More HIV-infected patients, however, have received treatment. Using reported public health data in France and natural history models, we applied the back-calculation method to project future mortality from HCV and HIV incorporating current therapies. The HCV model was based on literature data for the natural history of HCV and reports of hepatocellular carcinoma mortality. The HIV model used estimates from the French Hospital Database on HIV and reported AIDS cases and deaths. Peak annual mortality from HIV at 5000 occurred in 1994 and was 1000 in 1998, but HCV mortality likely increased through the 1990s and reached 3000 in 1998. Considering only HCV infections occurring until 1998 and currently available therapy, our model suggested that annual HCV-related mortality would continue to rise and would reach 4500 deaths in 2022. In contrast, AIDS-related deaths began to decrease in 1997. The public health burden of HCV is likely on the rise, while the burden of HIV, given the fairly widespread use of effective medications, may be on the decline. These results may help health policymakers in planning their responses to these epidemics.

**Di Martino V, Rufat P, Boyer N, Renard P, Degos F, Martinot-Peignoux M, Matheron S, Le Moing V, Vachon F, Degott C, Valla D, Marcellin P.** The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. *Hepatology* 2001; 34:1193-1199.

Service d'Hépatologie, INSERM U481 et Centre de Recherche Claude Bernard sur les Hépatites Virales, Hôpital Beaujon, Clichy, France.

In this study we analyzed the influence of human immunodeficiency virus (HIV) infection on the course of chronic hepatitis C through multivariate analysis including age, alcohol consumption, immune status, and hepatitis C virus (HCV)-related virologic factors. Eighty HIV-positive and 80 HIV-negative injection drug users included between 1980 and 1995 were matched according to age, gender, and duration of HCV infection and followed-up during 52 months. The progression to cirrhosis was the primary outcome measure. The impact of HIV on HCV-RNA load, histologic activity index, response to interferon therapy, and liver-related death was also considered. In HIV-positive patients, chronic hepatitis C was characterized by higher serum HCV-RNA levels ( $P = 0.012$ ), higher total Knodell score ( $P = 0.011$ ), and poorer sustained response to interferon therapy ( $P = 0.009$ ). High serum HCV-RNA level was associated with low CD4-lymphocyte count ( $P = 0.001$ ). Necroinflammatory score was higher in HIV-positive patients ( $P = 0.023$ ) independently of the CD4-lymphocyte count, whereas increased fibrosis was related to decreased CD4-lymphocyte count ( $P = 0.011$ ). The progression to cirrhosis was accelerated in HIV-positive patients with low CD4 cell count (RR = 4.06,  $P = 0.024$ ) and in interferon-untreated patients (RR = 4.76,  $P = 0.001$ ), independently of age at HCV infection ( $P = 0.001$ ). Cirrhosis caused death in 5 HIV-positive patients. The risk of death related to cirrhosis was increased in heavy drinkers (RR = 10.8,  $P = 0.001$ ) and in HIV-positive patients with CD4 cell count less than 200/mm<sup>3</sup> (RR = 11.9,  $P =$

0.007). In this retrospective cohort study, HIV coinfection worsened the outcome of chronic hepatitis C, increasing both serum HCV-RNA level and liver damage and decreasing sustained response to interferon therapy. Age and alcohol were cofactors associated with cirrhosis and mortality. Interferon therapy had a protective effect against HCV-related cirrhosis no matter what the patient's HIV status was.

**Dubois F, Desenclos JC, Mariotte N, Goudeau A, on behalf of the Collaborative Study Group.** Hepatitis C in a French population-based survey, 1994: seroprevalence, frequency of viremia, genotype distribution, and risk factors. *Hepatology* 1997; 25:1490-1496.

Institut Régional pour la Santé, La Riche, France.

The aims of this study were the following: 1) to estimate the prevalence of hepatitis C virus (HCV) antibody (anti-HCV) in a population-based survey of French residents not selected for risk factors; 2) to investigate the association between anti-HCV seropositivity, viremia, the infecting HCV genotype, and the alanine transaminase (ALT) level; and 3) to identify risk factors for HCV infection by a nested case control study within this survey sample. The anti-HCV seroprevalence survey was performed in 6,283 volunteers (20- to 59-years-old) randomly selected from 45,377 consecutive individuals undergoing routine medical checkup in social security medical centers covering 4 of the 22 "regions" of France. Seventy-two volunteers were anti-HCV positive, a crude prevalence of 1.15%. Fifty percent of these positive volunteers also had an abnormal ALT level and 81% were HCV-RNA positive by polymerase chain reaction (PCR). The prevalence weighted for age, sex, and place of residence was 1.05% (95% CI: 0.75-1.34). The weighted prevalence was lower among men > 40-years-old (0.5%; 95% CI: 0.1-1.0) and was close to 1% in all other age and sex groups. Prevalence was inversely correlated with socioprofessional status with the highest rate being found among those with no paid employment (2.2%; 95% CI: 1.3-3.0). The HCV prevalence (1.7%; 95% CI: 1.0-2.3) was highest in southeastern France. Seventy-eight percent of positive intravenous (I.V.) drug abusers were infected with HCV genotypes 1a or 3, whereas 80% of the transfusion-associated cases were infected by HCV genotypes 1b or 2a. Only three variables were significantly associated with HCV seropositivity in multivariate analysis: I.V. drug abuse (21 cases, 14 men all < 40-years-old), previous transfusion (22 cases, 18 women), and not having paid employment. Although routes of transmission other than I.V. drug abuse and transfusion may not be formally excluded they were not found to be statistically significant. Hepatitis C appears to be a major public health concern in France. A more active screening policy may be required because only 17 of 72 cases (24%) were aware of their HCV seropositivity before enrollment in the study.

**Elghouzzi MH, Bouchardeau F, Pillonel J, Boiret E, Tirtaine C, Barlet V, Moncharmont P, Maisonneuve P, du Puy-Montbrun MC, Lyon-Caen D, Courouge AM.** Hepatitis C virus: routes of infection and genotypes in a cohort of anti-HCV-positive French blood donors. *Vox Sang* 2000; 79:138-144.

Etablissement de Transfusion Sanguine de l'Ouest Francilien, Rungis, France.

We evaluated and analysed risk factors of HCV-infected blood donors according to HCV genotypes in order to improve the transfusion policy and safety of blood supply. HCV-RNA was analysed in sera from 518 anti-HCV-positive blood donors, who were invited to medical consultation and interview as to risk factors by means of an extensive questionnaire. HCV genotyping was done on all samples positive for HCV-RNA. Of the 518 sera, 399 (77%) were HCV-RNA positive, and 394 of 399 HCV genotypes were identified. Major genotypes were 1b (34.3%), 3a (24%), 1a (19.5%) and 2 (11.4%). Of the donors, 289 (55.8%) were interviewed regarding their risk behaviour: 27% were former intravenous drug users (IVDUs), 26% had been transfused, 8% had a history of invasive diagnostic procedures, and 13% a history of surgery. Among the 224 interviewed donors, genotypes 1a and 3a were mainly associated with IVDU (51

and 45% respectively) and genotype 1b, with transfusion and nosocomial infections (40 and 25%, respectively). In this population of anti-HCV-positive blood donors, nosocomial infection may be a route of HCV spread, but the main risk factor remains IVDU, particularly in young men. The transfusion policy will improve if predonation interviews of such young men are done with a specific and sensitive questionnaire.

**Emmanuelli J.** Harm reduction policy related to drug use: the needles exchange programs. *Med Sci (Paris)* 2004; 20:599-603. [Article in French]

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In several developed countries, needles exchange programs (NEPs) are a key preventive tool in harm reduction policy related to drug use. Many studies about NEP show it reduces HIV infections related to syringes sharing when part of others preventive actions. NEPs seem to have no impact on HCV transmission. Furthermore, young drug users, who are at high risk for HIV and HCV infections, are not attending NEPs very often. Trying to maintain high accessibility to sterile syringes, efforts must be stressed on hard-to-reach populations such as young injection drug users (IDU), focusing on their social network. Emphasis must also be put on prevention of unsafe sexual intercourse, often related to syringe sharing, which must be more prevented. Finally, design of assessment studies should be improved.

**Eveillard M, Daroukh A, Desjardins P, Legrand S, Odzo-Gakala M, Bourlioux P.** Seroprevalence of hepatitis B and C viruses in a psychiatric institution. *Pathol Biol (Paris)* 1999; 47:543-548. [Article in French]

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Many patients admitted to psychiatric institutions have a history of risk factors for contamination with the hepatitis B and C viruses (HBV and HCV). Immunization policies for psychiatric institution patients are not widely know. A study conducted in a 600-bed psychiatric institution in Paris, France, to evaluate the proportion of potentially contaminating patients at admission, as well as immunization use in HBV-negative patients. Serologic markers for the HBV and HCV were looked for prospectively in all patients admitted over a two-month period. Immunization use was evaluated in the patients who had a first serologic test in 1995 or 1996 and follow-up tests until the end of 1997. The prospective part of the study demonstrated preadmission exposure to the HBV in 23.0 +/- 6.0% of patients. This proportion was larger in men (26.0%) than in women (14.8%), although the difference was not statistically significant ( $P = 0.10$ ). Four patients (2.0%) tested positive for the HbS Ag. Among the HBV-negative patients, 13.0% received the vaccine; all had protective antibody levels. These patients were younger and more likely to be first-time admissions (18.4% vs 3.6%,  $P < 0.01$ ). HCV seroprevalence was 6.0%. Serologic tests for the HBV were requested for 327 patients between January 1995 and december 1996. Among the patients who were seronegative at admission and received follow-up at the study hospital, only 13.8% were immunized at this hospital. Of the HCV-positive subjects, 63.3% were also HBV-positive. None of the HCV-positive HBV-negative subjects received immunization subsequently. Six to eight per cent of patients admitted to the study hospital are potentially contaminating for the HBV or HCV. The level of hepatitis B vaccine use is too low, particularly in high-risk patients. These data indicate a need for policies aimed at effectively preventing HBV and HCV transmission (information, education, immunization campaigns), both during the psychiatric institution stay and after discharge.

**Fouchard-Hubert I, Tréchet JF, Geagea E, Payan C, Rabjeau J, Cales P, on behalf of the Hepatitis Network of Maine-et-Loire.** The Hepatitis Network in Maine-et-Loire city hospitals: six year follow-up of patients and physicians. *Gastroenterol Clin Biol* 2000; 24:82-88. [Article in French]

Service d'Hépatogastroentérologie, Centre Hospitalier Universitaire, Angers.

To evaluate 6 years of a city-hospital hepatitis network. The network was set up in 3 steps: 1988: intrahospital network, 1991: city-hospital network, 1997: compliance with government regulations. The whole activity from 1991 to 1997 was evaluated and special attention was paid to patient files and participating physicians. From June 1991 to December 1997 (6.5 years), 759 patient files were registered which corresponds to 531 patients (male 57%) with a mean age of 44 +/- 16 years (+/- standard deviation). Four hundred and twenty one patients (79%) had hepatitis C, 95 (18%) hepatitis B and 15 (3%) co-infection; 83% of patients had had a liver biopsy confirming cirrhosis in 21.5%. The annual number of files registered increased continuously. This was more a result of recruiting known patients than new patients, after the network had been in place for several years, mainly with hepatitis B virus (known patients in 1997: hepatitis B virus: 53% vs 33% for hepatitis C virus,  $P < 0.05$ ). Treatment protocols (73%) were more frequent for hepatitis C virus patients than for hepatitis B (73% vs 59%,  $P < 0.01$ ). Therapeutic trial proposals (37%) increased from 21% in 1991 to 59% in 1997,  $P < 0.01$ . Participation in monthly meetings by academic hepato-gastroenterologists increased slightly while that of regional hospital hepato-gastroenterologists increased markedly and that of private hepato-gastroenterologists remained stable. The annual proportion of files submitted by academic hepato-gastroenterologists decreased in parallel to the increase in submission of patient files by other hepato-gastroenterologists. During 6 years of activity, the network grew with an increase in the annual number of patient files, growing participation in therapeutic trials as well as in monthly meetings by practitioners.

**Fagnani F, Le Fur C, Durand I, Gibergy M.** Economic evaluation of a combined DTPa, hepatitis B, polio, Hib vaccine. Potential impact of the introduction of Infanrix-Hexa in the French childhood immunisation schedule. *Eur J Health Econ* 2004; 5:143-149.

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A new hexavalent combination vaccine, Infanrix-HEXA, including a recombinant hepatitis B vaccine in addition to the vaccines for diphtheria, tetanus, pertussis, poliomyelitis, and Haemophilus influenzae type B, has recently become available in France. The objectives of this study were to: (1) estimate the break-even price of Infanrix-Hexa for the National Sickness Fund; (2) evaluate its potential impact on vaccine coverage for hepatitis B and the corresponding budget impact. The public price of Infanrix-HEXA associated with a break-even point would be 53.77 euro. Our analyses suggested that other estimates based on a societal perspective including opportunity and indirect costs remained close to this value. The annual additional reimbursed cost of protecting an infant against the risk of hepatitis B would be 28.20 euro per child, or about 21 million euro for an annual cohort of 760,000 births (total cost, 35 million euro). The number of infants protected against hepatitis B could increase from 230,000 in the current situation to about 600,000.

**Ganne-Carrie N, Chevret S, Barbare JC, Chaffaud C, Grando V, Vogt AM, Beaugrand M, Trinchet JC, on behalf of the Association Française pour l'Etude du Foie; Association Nationale des Gastroentérologues des Hôpitaux Généraux.** Practical screening and early treatment of hepatocellular carcinoma. Results of a French survey. *Gastroenterol Clin Biol* 2002; 26:570-577. [Article in French]

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To describe French practices for screening hepatocellular carcinoma. A standardized questionnaire was mailed to all French hospital hepato-gastroenterologists in June 1999. 411 out of 623 practitioners responded (66%). 394 (96%) routinely screen hepatocellular carcinoma, mainly with ultrasound (98%) and mainly at 6-month intervals (77%). Screening was performed in cirrhosis (100%) or extensive fibrosis (54%), independent of the etiology (21%) or the Child-Pugh score of the chronic liver disease (41%), but based on age and treatment feasibility. If of a small hypoechogenic nodule was detected in a young patient with compensated HCV-cirrhosis, 59% of practitioners performed a histological examination. In case of non biopsy-proven hepatocellular carcinoma, a second biopsy (49%), treatment (either percutaneous alcohol injection, resection or transplantation) (24%) or an ultrasonographic follow-up (23%) was proposed. In case of biopsy-proven hepatocellular carcinoma, resection (49%), transplantation (30%) or percutaneous alcohol injection (16%) was proposed. Almost all French specialists routinely screen cirrhotic patients for hepatocellular carcinoma, but use somewhat different modalities. In case of small HCC without contraindications to curative treatment, surgical resection is performed in half the patients.

**Gervais A, Boyer N, Marcellin P.** Tolerability of treatments for viral hepatitis. *Drug Saf* 2001; 24:375-384.

Service d'Hépatologie and INSERM U-481, Hôpital Beaujon, Clichy, France.

Interferon-alpha is the most widely used antiviral drug in chronic hepatitis B and C. Tolerability is usually good and serious adverse effects are rare. Most of the adverse effects are mild or transient and do not necessitate drug withdrawal. More than 90% of patients who are given interferon-alpha achieve 6 months to 1 year of treatment without serious adverse effects. The serious adverse effects usually occur in predisposed patients with pre-existing organ dysfunction. Nevertheless, careful selection of patients for therapy and observation during therapy are recommended. Nucleoside analogues are promising drugs in the treatment of chronic hepatitis B through inhibition of viral DNA polymerase. Lamivudine has been licensed for use in this indication. Its tolerability is excellent even when used for periods of 1 year or more. The main concern is the relatively high incidence of viral resistance resulting in breakthrough during or relapse after therapy. In the treatment of chronic hepatitis C, ribavirin, in combination with interferon-alpha is currently the reference therapy. The main adverse effect is haemolytic anaemia, which necessitates careful monitoring and adjustment of dosage in many cases. Recently, large trials showed the better efficacy of pegylated interferons as compared with standard interferon. The combination of pegylated interferon with ribavirin is under evaluation.

**Goegebeur G, Benhamiche AM, Minello A, Rassiat E, Clinard F, Milan C, Faivre J, Hillon P, on behalf of the Research Group of the REBOHC.** The characteristics of patients with hepatitis C virus antibodies followed in specialized university hospital units are different from those of patients in the general population. *Gastroenterol Clin Biol* 2000; 24:1042-1046. [Article in French]

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To compare the characteristics of patients with anti-hepatitis C virus antibodies followed in a University Hospital Department of Hepatogastroenterology with those in patients who received medical care elsewhere. Since 1994, a specialized viral hepatitis register has recorded since 1994 all new cases of anti-hepatitis C virus antibodies diagnosed in inhabitants of the French department of Côte-d'Or (493931). The factors correlated with the type of medical care in patients followed in

the University Department were studied by logistical regression. One hundred of the 498 new patients with anti-hepatitis C virus antibodies diagnosed in the Côte-d'Or between 1994 and 1996 were followed in a University Hospital Department. Multivariate analysis showed that age (< 60), contamination due to transfusion, elevated ALT levels and no excessive alcohol consumption were factors significantly correlated with follow-up at the University Department. Liver biopsy was more often performed (66%) and a treatment was more often prescribed (34%) in patients followed in a University Department of Hepatogastroenterology patients than in other patients (20.4%;  $P < 0.0001$  et 7.5%;  $P < 0.0001$  respectively). This study shows that patients with anti-hepatitis C virus antibodies who are followed by a specialised University Department are a selected group; these patients are more likely to be treated than others. This study emphasizes that the greatest care must be taken when extending the extension of results of hospital series to a non-selected population.

**Goudeau A, Dubois F.** Diagnosis and biological surveillance of hepatitis C virus infections. *Rev Prat* 2000; 50:1071-1077. [Article in French]

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HCV-specific laboratory assays are broadly used to establish the diagnosis, to survey viral replication and to monitor anti-viral treatments. Third-generation ELISA's have an excellent sensitivity well adapted to the early diagnosis. Positive or dubious screening tests must be controlled on a second blood sample. We recommend the use of an immunoblot assay for this control. Regular survey of the immunoblot profile may facilitate the identification of recent infections and help distinguish between active or resolutive infections. PCR assays which detect HCV ARN in serum are very usefull to decide and monitor anti-viral treatments. Their cut-off is usually in the range of 100 genomes/mL. Quantitative assays to measure viral load may also rely on PCR technology or be based on the so-called "branched DNA" technology slightly less sensitive. Genotyping or serotyping of HCV is crucial to adapt specific treatment protocols to the less responsive genotypes 1a et 1b. Cloning and sequencing of HCV isolates is necessary to explore nosocomial clusters of infections or intra-familial cases.

**Goudeau A, Dubois F.** Incidence and prevalence of hepatitis B in France. *Vaccine* 1995; 13(Suppl 1):S22-S25.

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Reporting of hepatitis B is not compulsory in France, but it is estimated that 8500-9000 acute cases and 100,000 hepatitis B infections occur every year. Seroprevalence studies have been carried out in selected populations. Every blood donation is screened for HBsAg, alanine aminotransferase elevation and anti-HBc antibody. Prevalence of HBsAg has declined from 13.9 positive donations in 1986 per 10,000 to 5.3 in 1991. In pregnant women, overall seroprevalence is estimated at 0.8-1%, which represents more than 5000 children born each year to carrier mothers. Screening of HBsAg for all women when six months pregnant is now compulsory. Heterosexual patients at STD clinics were shown to have a very high risk of being infected with hepatitis B virus, with a chronic carrier rate of 4-5%. In hospital employees before the introduction of vaccination, the overall incidence of hepatitis B was 100-300 acute cases per 100,000 employees per year. Risk varied according to exposure to blood; the highest incidence was found in nurses in dialysis wards. Vaccination against hepatitis B is now compulsory for all hospital and laboratory workers and medical and paramedical students. In preventive medicine consultants, routine medical check-up showed an overall HBV prevalence of 2.2% and a carrier rate of 0.3% in men

and 0.1% in women. Immunization of all newborns and adolescents has recently been adopted in France, vaccination at school of adolescents aged 10-11 years being the main target.

**Gout O.** Vaccinations and multiple sclerosis. *Neurol Sci* 2001; 22:151-154.

Federation of Neurology, Hôpital de la Salpêtrière, Paris, France.

Two problems must be considered in regard to the relationship between vaccinations and MS: Do vaccinations favour the first attack of MS? Do they increase the short- or long-term risk in patients with known disease? Answers to these questions are difficult due to the paucity of reported cases, our ignorance of the precise frequency of neurological adverse events in vaccines based on prospective studies, and finally by the lack of a well established pathophysiology. In most instances, the role of the vaccine is based on a temporal link between the injection and the onset of neurological disease, and more rarely to a positive reintroduction. Acute disseminated encephalomyelitis (ADEM), a monophasic and multifocal illness of the white and grey matter, has been observed following various viral or bacterial infections as well as vaccine injections for diseases such as pertussis, tetanus and yellow fever. The similarities between ADEM and experimental allergic encephalitis (EAE) are suggestive of an immunological process. In addition to the dramatic presentation of ADEM, more limited white matter involvement, such as optic neuritis or myelitis, has been reported following vaccine injections, and has occasionally been counted as the first attack of MS. In France, 25 million inhabitants, almost half of the population, were vaccinated against hepatitis B (HB) between 1991 and 1999. Several hundred cases of an acute central demyelinating event following HB vaccination were reported to the pharmacovigilance unit, leading to a modification of vaccination policy in the schools and the initiation of several studies designed to examine the possible relationship between the vaccine and the central demyelinating events. The results of these studies failed to establish the causality of the HB vaccine. Nevertheless, molecular mimicry between HB antigen(s) and one or more myelin proteins, or a non-specific activation of autoreactive lymphocytes, could constitute possible pathogenetic mechanisms for these adverse neurological events.

**Guérin N.** Assessing immunization coverage: how and why? *Vaccine* 1998; 16(Suppl):S81-S83.

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Assessment of immunization coverage is an important part of evaluating an immunization programme and it is a useful aid in programme management and decision making. Coverage assessment should be carried out at the national and district levels. Routine methods currently used in EU countries vary and are not always accurate, and should be validated regularly by specific surveys.

**Guérin N, Antona D.** Expanded program of vaccination. Results and prospects. *Ann Med Interne (Paris)* 1998; 149:372-378. [Article in French]

Centre International de l'Enfance et de la Famille, Bois de Boulogne, Paris.

The expanded program on immunization, jointly launched by WHO and UNICEF in 1974 aimed in the beginning at immunizing 80% of the children of the world against measles, tetanus, pertussis, poliomyelitis, diphtheria and tuberculosis. After reaching the objectives in 1990, countries have been urged towards eradication of poliomyelitis, elimination of neonatal tetanus, and measles control. Immunization against hepatitis B and yellow fever were also proposed according to local epidemiology. Tremendous results have been already delivered: the American continent has eliminated poliomyelitis since August 1991, it has reduced dramatically the

incidence of measles. All the countries, including those from Africa, are organizing campaigns aiming at polio eradication. Active surveillance systems have been implemented. But financial and operational constraints persist, linked to vaccines prices, their heat sensitivity, injection techniques, and to the sterilisation and waste disposal. Major efforts are still needed.

**Hanslik T, Wechsler B, Vaillant JN, Audrain L, Prinseau J, Baglin A, Flahault A.** A survey of physicians' vaccine risk perception and immunization practices for subjects with immunological diseases. *Vaccine* 2000; 19:908-915.

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Various publications have caused concern by implying that immunization may be linked to new cases or flare-ups of immunological diseases (IDs). In view of the resulting uncertainty, we studied physicians' vaccine risk perception and immunization practices for adults with IDs. A questionnaire was mailed to three groups of physicians in France: internal medicine specialists, general practitioners, and travel clinic physicians. Thirteen vaccines currently used for adults in France were studied. Risk perception was rated on a 10 cm visual analog scale (VAS). The distribution of the answers was compared between and within groups of physicians. Potential associations between risk perception and reported practices were investigated by multivariate analysis. In the three groups of physicians (n = 762), the tetanus and Salk poliomyelitis vaccines had the lowest risk perception. The yellow fever, BCG and Sabin poliomyelitis vaccines were the least well perceived. The distribution of risk perception for these three live vaccines and the hepatitis B vaccine was uniform according to VAS grading. For the other vaccines studied, the distribution was skewed to the low-risk perception side of the VAS. Risk perception was greater for physicians who stated: (1) that certain IDs carried a high risk of adverse events following immunization; (2) that they sought the advice of the referent physician before immunization; (3) warned their patients of the risk of an ID flare-up after vaccination; (4) sought information about recent immunization in patients with a flare-up; and (5) had experience of the side effects of immunization in adults with ID. Risk perception was lower for physicians who said they updated immunizations, and for the internists. The worse the vaccine risk perception by physicians, the more uniform the distribution of perception, thus reflecting the disagreement of the scientific community about the risk of using such vaccines for adults with an ID. Risk perception and immunization practices were related in adults with ID. Understanding of decisions concerning immunization may help to improve immunization updating and prevent risk amplification when evidence is lacking.

**Imbs JL, Decker N, Welsch M.** Pharmacovigilance of hepatitis B vaccines. *Bull Acad Natl Med* 2003; 187:1489-1498. [Article in French]

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Since the hepatitis B vaccine are on the market in France, until the end of 2002, 1211 observations of demyelinating disease of the central nervous system (1109 cases of which 895 multiple sclerosis) or peripheral (102 cases of which 49 Guillain Barre Syndrome), have been reported to the french network of pharmacovigilance and to the AFSSAPS. It is not possible to singularize these observations, neither from a clinical nor an epidemiological point of view. No risk factor has been detected. Only the chronology could suggest a causal relationship, the vaccine preceding the pathology in all the cases notified.

**Izopet J, Pasquier C, Sandres K, Puel J, Rostaing L.** Molecular evidence for nosocomial transmission of hepatitis C virus in a French hemodialysis unit. *J Med Virol* 1999; 58:139-144.

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A systematic virological follow-up of hemodialysis patients identified 11 cases of de novo hepatitis C virus (HCV) infection in the same unit that were not due to blood transfusion. There were three groups of infection, each occurring within a period of 3 months: four infections with genotype 1b, two infections with genotype 1b, and five infections, four with genotype 1a and one with genotype 5a. The possibility of patient-to-patient transmission was addressed by sequencing the first hypervariable region of the HCV genome in sera taken shortly after infection. Phylogenetic analysis indicated clustering of most of the cases of de novo infections. Sequence homologies identified potential contaminators among already infected patients. All patients who were infected with closely related HCV isolates were found to have been treated in the same area and during the same shift or on the previous one. These infections could have been due to occasional breaches of the usual hygiene measures. Strict adherence to hygiene standards and routines, continuously supervised, remains the key rule in the management of dialysis patients. Nevertheless, the isolation of patients with HCV could reduce the risk of infection because occasional lapses of preventive hygiene measures or unpredictable accidents can always take place in a hemodialysis unit. This policy needs to be evaluated by large-scale prospective studies.

**Josset V, Torre JP, Tavalacci MP, Van Rossem-Magnani V, Anselme K, Merle V, Godart J, Libert A, Ladner J, Czernichow P.** Efficiency of hepatitis C virus screening strategies in general practice. *Gastroenterol Clin Biol* 2004; 28:351-357.

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Hepatitis C viral infection (HCV) is a frequent and severe disease; screening strategies to-date remain insufficient. To assess the efficiency of HCV screening of high-risk groups among patients consulting general practitioners. A cost-effectiveness analysis was performed involving general medicine screening practices recorded during a survey of 127 practitioners (10,041 patients) conducted in 1997. A reference strategy, defined as HCV screening for illicit drug users and transfused patients, and five extended strategies, where the screening population was broadened to include other risk groups as well, were considered. Average cost and marginal cost-effectiveness ratios were determined for each extended strategy and compared with those observed for the reference strategy. The sensitivity of HCV screening to funding modalities, HCV seroprevalence and proportion of HCV high-risk groups among patients attending general practitioners was studied. The reference strategy was the most cost-effective method irrespective of the funding modality considered. Fixed practitioner payment was the least efficient funding modality. The average cost of one positive test was sensitive to variations of HCV seroprevalence in the high-risk group as well as the proportion of high-risk patients among the general practitioners' patients. Extension of hepatitis C screening to risk groups other than transfused patients and illicit drug users implies a substantial increase in healthcare costs as well as social consensus for such expenditures.

**Joussemet M, Depaquit J, Nicand E, Mac Nab C, Meynard JB, Teyssou R, Fabre G, Buisson Y.** Fall in the seroprevalence of hepatitis A in French youth. *Gastroenterol Clin Biol* 1999; 23:447-450. [Article in French]

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An anti-hepatitis A virus seroprevalence survey was performed in 1997 in 1052 French army

recruits (mean age: 21.2 years). To describe epidemiological trends, the current pattern was compared to previous results obtained by similar methods in 1985, 1990 and 1993. In 1997, overall anti-hepatitis A virus seroprevalence was 11.5%. The greatest risk factor of hepatitis A infection was related to travel in intermediate or highly endemic areas for hepatitis A virus: 46% of overseas residents (odds ratio = 10.3), 28% of recruits who had travelled in developing countries (odds ratio = 3.7) and 7.65% of French living in industrialised countries are anti-hepatitis A virus antibody positive. Moreover, seroprevalence was higher in subjects with a history of ictericia (adjusted odds ratio = 3.5) and families with at least 3 children (adjusted odds ratio = 3). No association was found with drinking water, socioeconomic status such as baccalaureat degree, or parents profession. The seroepidemiological shift of hepatitis A, as assessed in three previous studies, shows a marked decrease of 20% in 12 years from 30.4% in 1985, to 21.3% in 1990, to 16.3% in 1993, and to 11.5% in 1997. The decrease in the prevalence of anti-hepatitis A virus was more marked in young adults who had never travelled in endemic countries (decrease of 20%) than those who had visited or lived in developing countries (decrease of 10%). Although France is not highly endemic for hepatitis A thanks to improved hygiene and housing conditions over the past 20 years, a pattern of intermediate endemicity was seen in French overseas areas in which the risk of outbreaks of hepatitis A was higher. The decrease in anti-hepatitis A virus seroprevalence in French youth can be used to draft a public health policy for hepatitis A control.

**Jullien AM.** Transfusion and hepatitis C. *Pathol Biol (Paris)* 1995; 43:725-734. [Article in French]

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Hepatitis C has been a major transfusion risk until the beginning of the 90s, since it accounted for more than 90% of non-A, non-B hepatitis, 5% to 10% of infected surgical recipients and up to 50% of multitransfused patients, altogether 100,000 to 400,000 blood components recipients in France. The decline in incidence was based principally on sequential introduction of donor testing, starting with surrogate markers in 1988 (transaminase ALT and antibody anti-core HBc), followed since 1990 by specific assays (anti-hepatitis C virus antibodies) and on blood donor selection. Two risk factors have been identified in donors, intravenous drug use and previous transfusion. The risk of transmission was estimated, after screening by first generation tests at 1 per 1670 units transfused. After second generation testing, the risk ranged from 1 in 2000 to 1 in 6000 units transfused, corresponding to a reduction of more than 90%. The estimation of the residual risk (mean: 1/100,000 donations in USA), principally due to incidence in regular donor required mathematical calculation. The new "hemovigilance" system in France with mandatory notification of all posttransfusion incidents and infections will contribute to evaluate and to prevent residual cases. However, further studies are necessary to precise other risk factors in donors, as well as the role of nosocomial infections in recent cases, and possibly the role of additional agents such as GB viruses in post-transfusion hepatitis.

**Jullien-Depradeux AM, Bloch J, Le Quellec-Nathan M, Abenhaim A.** National campaign against hepatitis C in France (1999-2002). *Acta Gastroenterol Belg* 2002; 65:112-114.

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Since 1988, several measures have been applied in France to control HCV infection. HCV seroprevalence in the adult population is estimated at 1.1% (500,000 to 650,000 persons) and the number of chronically infected at 400,000 to 500,000 persons. In 1994, most of them might not be aware of their infection. Blood products administration and injecting-drug use are identified as the main transmission routes. The national hepatitis C plan (1999-2002) was based on scientific data and developed after a consensus conference and several expert consultations. It involves six programs and quantified objectives: prevention of new infections, enforcement of screening

access; improvement of care management; implementation of a surveillance system, clinical research and evaluation. Specific financial supports were attributed for the implementation of the plan. The 2001 progress report confirmed a major increase in national and regional actions. In 2000, considering the high proportion of persons still unaware of their infection (at least one third) and the increase of treatment efficacy, the target population of the screening strategy was considerably extended after scientific analysis. A national consciousness-raising campaign directed at general practitioners was launched in June 2000. In 2001, a media campaign directed to the general population was developed, in newspapers and on radio stations. Since the end of 1999, a national toll free phone number provides information to the public. In order to improve access to screening, a new regulation added HCV testing to the missions of anonymous and free HIV testing centres, as well as of family planning centres. The hepatitis C prevention strategy is still included in a national public health program and improved in view of its renewal.

**Jusot JF, Aubert C, des Floris MF, Rotily M, Lancon F, Colin C, Jullien AM, Fournel JJ, Laubriat L, Fabre G, Botte C, Montcharmont P.** Declared hepatitis C screening strategies in blood recipients in French hospitals. *Transfus Clin Biol* 2002; 9:130-136.

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In spite of official recommendations and measures in France, screening strategies of hepatitis C performed in the field of transfusion are not clearly known. The aim of this study is to describe the screening strategies before and after the current year of the transfusion in blood recipients in several French medical departments and hospitals. A qualitative study using the key informant technique was carried out. A sample of 179 departments and 64 hospitals in charge of patients transfused with low or high-volumes of homologous blood products was constituted. The key informants were asked about the number of homologous blood products, the number of recipients transfused in the hospital, the volume of transfusion performed, the existence of a single defined screening strategy, the time of prescription of the biological tests (before or after transfusion), the tests performed on cryopreserved blood samples, and the indications of the transfusion. The main screening strategy was HCV serology (second or third generation of enzyme immunoassays) with transaminase assessments before and after transfusion in 14% of the declared screening strategies. Screening tests were more frequently prescribed after transfusion, in at least 64% of the declared screening strategies according to the volume of transfusion. HCV serology was the common test prescribed in 61 and 50% of the screening strategies for low and high-volume transfusion respectively. The screening strategies showed a large heterogeneity combining HCV serology, transaminase assessment, before or after transfusion. A great heterogeneity of screening strategies was found. The most frequent was HCV serology with transaminase assessment before and after transfusion. Recommendations on screening strategies are needed in order to limit practice heterogeneity. This study will help building a cost-efficacy model in order to guide public health decision making.

**Kuo YH, Fabiani JN, Mohamed AS, Couetil JP, Lévy M, Gutmann L, Carpentier AF, Belec L.** Decreasing occupational risk related to blood-borne viruses in cardiovascular surgery in Paris, France. *Ann Thorac Surg* 1999; 68:2267-2272.

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Surgeons face the risk of patient-to-physician transmission of blood-borne viruses. This risk is related to the seroprevalence of the viruses in the patient population. The seroprevalence of the human immunodeficiency virus, hepatitis B virus, and hepatitis C virus were determined in cardiovascular patients at Hopital Broussais in Paris, France, over a 5-year period (1994 to 1998). Hepatitis C virus is the most prevalent virus in the patient population, whereas human immunodeficiency virus is the least frequent. The seroprevalence of hepatitis C virus and human

immunodeficiency virus has decreased over time, whereas hepatitis B virus has remained constant. We apply the seroprevalence data to a mathematical model to estimate the occupational risk of seroconversion faced by surgeons over the length of their career. Our results show that the principal risk faced by the surgeon arises from hepatitis B virus and hepatitis C virus. The decreasing seroprevalence of the hepatitis C virus has resulted in a decrease in the occupational risk. The probability of becoming infected with a blood-borne virus over the career of the surgeon is notable. The greatest occupational risk to the surgeon is from the hepatitis viruses and not HIV.

**Laperche S, Guillon C, Smilovici W, Courouge AM.** Blood donors infected with the hepatitis B virus but persistently lacking antibodies to the hepatitis B core antigen. *Vox Sang* 2001; 80:90-94.

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Antibodies to the core of hepatitis B virus (anti-HBc) are considered to be the best serologically reliable markers of hepatitis B virus (HBV) infection. Through a national epidemiological survey, two young and first-time blood donors, originating from HBV-endemic areas, were identified as HBV carriers with an absence of anti-HBc reactivity. We followed up these two subjects in order to investigate the evolution of their HBV serological profiles. Nucleotide sequencing was performed of the entire pre-C/C region of the strains infecting these donors. The same serological profile of active viral replication with an apparent persistent lack of anti-HBc and normal alanine aminotransferase (ALT) levels was found for both subjects throughout a follow-up of 19 months and 4 months, respectively. Neither donor was immunocompromised. Nucleotide sequence analysis of the pre-C/C region did not show mutations or deletions in encoded proteins. The hypothesis of an in utero HBV infection responsible for an immune tolerance to HBV seems to be the most probable explanation for this particular immunological situation. Such occurrences in the blood donor population are probably rare as less than 0.1% of hepatitis B surface antigen (HBsAg)-positive donors exhibit such a profile, in our experience. Moreover, this phenomenon does not impose a risk of HBV transmission by blood donation, as the exclusion of HBV-infected blood donation is based on HBsAg detection. However, such a risk might be encountered with the hepatitis C virus (HCV) for which at present only antibodies to HCV are screened.

**Lefrère JJ, Cantaloube JF, Defer C, Mercier B, Loiseau P, Vignon D, Pawlotsky JM, Biagini P, Lerable J, Rouger P, Roudot-Thoraval F, Ferec C.** Screening for HBV, HCV and HIV genomes in blood donations: shortcomings of pooling revealed by a multicentre study simulating real-time testing. *J Virol Methods* 1999; 80:33-44.

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This study was undertaken in order to determine whether screening of viremic blood donations by testing of pooled donor samples could constitute a technically feasible transfusional safety measure. A pilot study of real-time simulation, on a day-to-day basis, of screening of three viral genomes (hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV)) was conducted by five French Blood Centers on plasma samples collected from blood donors and studied within undiluted samples and within sample pools of various sizes. This study was carried out within time conditions compatible with the release of platelets. For the detection of HCV and HIV genomes, the five laboratories achieved a sensitivity that decreased with the size of the sample pool. Four were successful in detecting all undiluted samples. In the 1/10 diluted samples, four failed to detect one HIV or HCV sample. In the 1/100 diluted samples, all laboratories failed to detect one or more HIV or HCV samples. For HBV genome, no participating laboratories detected all of the samples of the panel, even undiluted samples, and the sample pooling considerably affected sensitivity. The improvement and standardization of assays needs to

be attained, and training of laboratories appears to be a step crucial for routine screening of viral genomes in blood donations.

**Lefrère JJ, Girot R, Lefrère F, Guillaume N, Lerable J, Le Marrec N, Bouchardeau F, Laperche S.** Complete or partial seroreversion in immunocompetent individuals after self-limited HCV infection: consequences for transfusion. *Transfusion* 2004; 44:343-348.

Laboratory of Hematology, Hospital of Amiens, Paris, France.

The disappearance of anti-HCV antibodies over time, after a self-limited infection, also referenced seroreversion, has been observed. The frequency of this phenomenon remains controversial, especially in immunocompetent subjects. However, it has important implications in the context of transfusion inquiries, in particular in case of a blood donor suspected to have transmitted HCV through a past blood donation. Our findings are presented of a longitudinal study, including 16 patients from a cohort of 78 immunocompetent, multitransfused individuals who were positive for anti-HCV (EIA and confirmatory assay [RIBA]) and followed over a long period of time without having received any antiviral therapy. The aim was to establish whether a past and self-resolved HCV infection could evolve toward a negative serology. The 16 patients were classified in three groups: 1) 12 patients who remained anti-HCV positive with no evolution in their RIBA pattern after a mean follow-up of 7.6 years; 2) one patient who presented a complete seroreversion 6 years after enrollment; and 3) three patients with a partial seroreversion over a mean follow-up of 16 years. HCV infection is not always characterized by a persistent antibody response, even in immunocompetent individuals. This should be taken into consideration when transfusion inquiries are conducted.

**Lefrère JJ, Loiseau P, Martinot-Peignoux M, Mariotti M, Ravera N, Thauvin M, Marcellin P, Janot C.** Infection by hepatitis C virus through contaminated intravenous immune globulin: results of a prospective national inquiry in France. *Transfusion* 1996; 36:394-397.

Institut National de Transfusion Sanguine, Hôpital Saint-Louis, Paris, France.

A recent hepatitis C virus (HCV) outbreak has been suspected of being caused by an infusion of intravenous immune globulin. Three laboratories were mandated by the French regulatory agency to prospectively screen on a national scale those persons having received suspected batches: 233 exposed patients were recalled and tested for HCV antibody and for HCV RNA. Nineteen patients (8.1%) were found positive for HCV RNA; 7 of these 19 were positive for the HCV antibody. The link between HCV infection and intravenous immune globulin was reinforced by the overrepresentation of the 2b genotype (58%), which contrasts with the low prevalence of this genotype in France (1%).

**Lefrère JJ, Roudot-Thoraval F, Lunel F, Alain S, Chaix ML, Dussaix E, Gassin M, Izopet J, Pawlotsky JM, Payan C, Stoll-Keller F, Thibault V, Trabaud MA, Bettinger D, Bogard M, Branger M, Buffet-Janvresse C, Charrois A, Defer C, Laffont C, Lerable J, Levayer T, Martinot-Peignoux M, Mercier B, Rosenberg AR.** Expertise of French laboratories in detection, genotyping, and quantification of hepatitis C virus RNA in serum. *J Clin Microbiol* 2004; 42:2027-2030.

Centre Hospitalo-Universitaire d'Amiens, France.

Before initiating new large-scale therapeutic trials for hepatitis C virus (HCV)-infected patients, the French Health Authorities for HCV research decided to organize an evaluation of the expertise of laboratories that could be engaged to undertake molecular biology assays in such trials; 21

experienced laboratories participated in this national evaluation of laboratory expertise, which was performed in two successive rounds. The first round evaluated the laboratories for their abilities to detect HCV RNA in serum, determine genotypes, and quantify HCV RNA loads. The results observed by qualitative assays for HCV RNA detection were 100% sensitivity and 100% specificity for all laboratories. The genotyping results were 100% concordant for 9 laboratories and greater than 90% for 10 laboratories. By contrast, large coefficients of variation were observed for quantitative determination of HCV RNA loads, leading to a second round with standardized quantitative assays only. The dispersion of the results was larger by the AMPLICOR HCV Monitor assay than by the branched-DNA assay (mean coefficients of variation, 57.4 and 16.9%, respectively). In the majority of cases, discrepancies between the results of the two tests were found for samples with high viral loads. These results indicate the usefulness of validating, by controlling for expertise, both the reliabilities of laboratories involved in multicenter work and the standardized assays chosen for use in the evaluation of the biological impacts of new therapies.

**Lévy R, Tardy JC, Bourlet T, Cordonier H, Mion F, Lornage J, Guérin JF.** Transmission risk of hepatitis C virus in assisted reproductive techniques. *Hum Reprod* 2000; 15:810-816.

Laboratoire de Biologie de la Reproduction and Laboratoire de Virologie, Hôpital Nord, 42055 Saint Etienne, France.

Medical assistance for procreation in a couple where one or both parents has hepatitis C viral infection (HCV) raises the issue of the transmission of the infection to the baby and/or of possible contamination of both the technicians and the gametes or embryos from virus-free parents in the laboratory. It becomes essential to assess transmission risk in assisted reproductive techniques in order to define clearly the management of couples according to their viral status. To define the HCV transmissibility risk in assisted reproduction related to the presence of virus in semen from infected infertile men, HCV RNA detection was performed in sera, and semen and sperm fractions obtained after Percoll gradient centrifugation. HCV RNA was detected in 5% (2/39) of the semen samples tested: in the raw semen, in the seminal fluid and in the cell pellet but never after Percoll selection. According to these results, we suggest a strategy for HCV-infected infertile men who need assistance for procreation.

**Lévy-Bruhl D, Desenclos JC, Rebière I, Drucker J.** Central demyelinating disorders and hepatitis B vaccination: a risk-benefit approach for pre-adolescent vaccination in France. *Vaccine* 2002; 20:2065-2071.

Département des Maladies Infectieuses, Institut de Veille Sanitaire, 12 rue du Val d'Osne, 94415 Saint-Maurice Cedex, France. d.levybruhl@invs.sante.fr

The objective of the study was to provide immunization policy decision makers with a risk-benefit analysis for pre-adolescents vaccination, for various scenarios regarding the existence and the strength of an association between hepatitis B vaccination and the occurrence of first episode of central demyelinating (FECD) disease. The risks were assessed as the attributable risks of FECD for various time intervals between vaccination and onset of FECD and the benefits as the number of acute fulminant hepatitis B and cirrhosis prevented in a vaccinated annual cohort. Even in the worst-case considered, the number of complications prevented by the vaccination outweighs quantitatively the potential risks. Even if both sides of the balance are of different medical and sociological nature, this result is in favor of reinforcing the pre-adolescent vaccination strategy in France.

**Lucidarme D, Bruandet A, Ilf D, Harbonnier J, Jacob C, Decoster A, Delamare C, Cyran C, Van Hoenacker AF, Fremaux D, Josse P, Emmanuelli J, Le Strat Y, Desenclos JC, Filoche**

**B.** Incidence and risk factors of HCV and HIV infections in a cohort of intravenous drug users in the North and East of France. *Epidemiol Infect* 2004; 132:699-708.

Service de Pathologie Digestive, Centre Hospitalier Saint Philibert, rue du Grand But - BP, Lomme Cedex, France.

In order to evaluate the incidence and risk factors of infection by hepatitis C virus (HCV) among injecting drug users (IDUs), we conducted a prospective cohort study of HCV- and human immunodeficiency virus (HIV)-negative IDUs in the North and East of France. A total of 231 HCV and HIV IDUs who had injected drugs at least once in their lifetime were followed up every 3 months over a 12-month period. Serum anti-HCV and anti-HIV were tested at inclusion in the study and at the end of the follow-up. Data on injecting practices were collected at inclusion and at each visit. Of the 231 participants included, 165 (71.4%) underwent a final HCV and HIV serum test. The incidence was nil for HIV infection and 9/100 person-years (95% CI 4.6-13.4) for HCV infection. In a multivariable analysis, we found that syringe and cotton sharing were the only independent predictive factors of HCV seroconversion.

**Lucidarme D, Decoster A, Delamare C, Schmitt C, Kozlowski D, Harbonnier J, Jacob C, Cyran C, Forzy G, Defer C, Illef D, Emmanuelli J, Filoche B.** An inter-laboratory study of anti-HCV antibody detection in saliva samples. *Gastroenterol Clin Biol* 2003; 27:159-162. [Article in French]

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The purpose of this study was to evaluate the efficacy of anti-hepatitis C virus (HCV) antibody detection in the saliva samples of 108 drug users in an inter-laboratory study. Between January and June 2001, 108 subjects in Lille, Metz and Lens received a test to detect anti-HCV antibodies in their saliva. Two consecutive saliva samples were taken in each subject (Salivette system, Sarstedt). An HCV serology (AxSYM HCV 3.0, Abbott) was also performed and serum HCV RNA detection by Amplicor HCV 2.0 (Roche) was performed when HCV serology was positive. Sixty three patients had a negative HCV serology, 45 had a positive HCV serology, and 31 of these had positive HCV RNA as well. Tests for the detection of the anti HCV antibody in saliva samples were performed as a blind study in both the Lille and the Thionville laboratories. The sensitivity of saliva anti-HCV antibody tests was respectively 71% (32/45) and 78% (35/45) in Lille and Thionville. In the event of positive HCV viremia, the sensitivity was respectively 90% (28/31) and 93% (29/31). The specificity was respectively 97% (61/63) and 98.5% (62/63). Results from the two laboratories agreed for 101 saliva tests while discrepancies were found in 7 (Kappa Concordance Coefficient: 0.85). This study confirms, in a large, unselected population sample, that anti-HCV antibody detection tests in saliva allow the detection of 90% of viremic HCV-antibody-positive patients with excellent specificity. The simplicity and reproductibility of this technique makes it a precious tool for epidemiological studies.

**Lucidarme D, Dumas F, Arpurt JP, Pariente EA, Naudin G, Forzy G, Defer C, Maniez M, Couzigou P, Filoche B.** Rapid progress of cirrhosis in hepatitis C: the role of age at the time of viral contamination. *Presse Med* 1998; 27:608-611. [Article in French]

Service de Pathologie Digestive, CH Saint-Philibert, Lomme.

The aim of this study was to assess predictive factors for the progression to liver cirrhosis in hepatitis C. One hundred thirty six patients (79 men; 57 women; mean age 39 years) with transfusion or intravenous drug use-associated hepatitis C virus (HCV) infection were studied. Sex, cause of infection, duration of contamination, and genotype were studied as predictive factors

of progression to liver cirrhosis. One hundred twenty three patients presented with chronic hepatitis without cirrhosis and 13 had cirrhosis. At the time of liver biopsy, rates of cirrhosis were: 0% before 40 years, 10% between 40 and 60 years, and 47% after 60 years. ( $p < 0.05$ ). Rates of cirrhosis according to the age at the time of contamination were as follows: 3% before 30 years; 16% between 30 and 50 years; 46% after 50 years even though duration of the disease was comparable in the three groups. In multivariate analysis, two independent factors were associated with liver cirrhosis: age at contamination and duration of infection. Duration of infection and especially age at contamination seem better correlated with the probability of cirrhosis than the route of transmission or the genotype 1b. The results of this study suggest that progression to cirrhosis is slower in cases of contamination before 30 years of age than later on. Age at the time of contamination is an important predictive factor of progression to cirrhosis.

**Lucidarme D, Foutrein P, Creusy C, Forzy G, Foutrein-Comes MC, Muysen A, Bailly D, Parquet PJ, Filoche B.** Prevalence of hepatitis C, B and D markers and histopathological aspects in a group of intravenous drug addicts. *Gastroenterol Clin Biol* 1994; 18:964-968. [Article in French]

Service de Pathologie Digestive, CH Saint-Philibert, Lomme.

The aim of this study was to assess the prevalence of infection by HCV, HBV, HDV and HIV and their biological and histopathological patterns in 104 intravenous drug users. Seventy-five patients (72%) had anti-HCV antibodies. Transmission was rapid because 33% of those who had been drug users for 6 months or less had anti-HCV antibodies. The contamination rate was very high because 90% of those who had been drug users for 2 years or less had anti-HCV antibodies. Thirty-four (33%) had an HBV marker, and 6 were HBs Ag carriers. None of the patients had anti-HDV antibodies. Only one patient had anti-HIV antibodies. Twenty-five anti-HCV antibody positive drug users underwent liver biopsy. Seven (28%) had normal ALAT levels and 18 (72%) had permanently or intermittently elevated ALAT levels. The mean histological activity on the Knodell index was 4.1 (range: 1-8). This study indicates that contamination by HCV is almost inevitable after 2 years of intravenous drug use. The low prevalence of HBV, HDV, and HIV infection might be explained by a low endemic state of these viruses in our area.

**Lunel F, Cadranel JF, Rosenheim M, Dorent R, Di Martino V, Payan C, Fretz C, Ghossoub JJ, Bernard B, Dumont B, Perrin M, Gandjbachkh I, Huraux JM, Stuyver L, Opolon P.** Hepatitis virus infections in heart transplant recipients: epidemiology, natural history, characteristics, and impact on survival. *Gastroenterology* 2000; 119:1064-1074.

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We have observed a high prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection in heart transplant recipients (HTRs). The aim of this study was to assess the epidemiology, natural history, and clinical and biological characteristics of viral hepatitis in HTRs. From 1983 to 1992, 874 patients underwent heart transplantation at the Pitie-Salpetriere Hospital, Paris, France, 459 of whom qualified for analysis. A total of 140 patients had posttransplantation hepatitis B, C, or non-A-E. Sixty-nine patients developed HBV infection, 49 HCV infection, 11 HBV-HCV coinfection, and 11 non-A-E hepatitis. HBV was transmitted nosocomially from patient to patient, most likely during endomyocardial biopsies. HCV was mainly transmitted through blood transfusions or the transplanted organ. Clinical and biological findings after 2 years of follow-up showed that 3 patients with an HBV genotype A precore mutant had severe or subfulminant hepatitis and that patients with HBV and HCV infection always progressed to chronicity. In general, patients had mild alanine aminotransferase level increases, a high level of viral replication, and few severe histologic lesions, except for patients infected by precore HBV mutants. Patients coinfecting by HBV and HCV tended to have more severe liver lesions. The

survival rate 5 years after transplantation in patients with viral hepatitis (HBV, 81%; HCV, 89%; HBV and HCV coinfection, 100%; non-A-E hepatitis, 73%) was similar to that in patients without liver test abnormalities (76%). The actuarial survival curve was also similar in patients with or without liver test abnormalities. In our experience, histologic liver lesions do not progress rapidly in patients with post-heart transplant infection caused by HBV or HCV. HBV or HCV infection seems to have little impact on the 5-year survival rate of HTRs.

**Mallet E, Fabre P, Pines E, Salomon H, Staub T, Schodel F, Mendelman P, Hessel L, Chrissomalis G, Vidor E, Hoffenbach A, on behalf of the Hexavalent Vaccine Trial Study Group.** Immunogenicity and safety of a new liquid hexavalent combined vaccine compared with separate administration of reference licensed vaccines in infants. *Pediatr Infect Dis J* 2000; 19:1119-1127.

The immunogenicity and safety of a new liquid hexavalent vaccine (diphtheria-tetanus-acellular pertussis-inactivated polio vaccine-hepatitis B-polyribosyl ribitol phosphate conjugated to tetanus protein; Hexavac; Aventis Pasteur MSD, Lyon, France) are compared with those of reference vaccines [diphtheria-tetanus-acellular pertussis-inactivated polio vaccine reconstituting lyophilized purified Haemophilus influenzae polysaccharide conjugated to tetanus protein vaccine (Pentavac; Aventis Pasteur MSD) and hepatitis B vaccine (H-B-Vax II; Aventis Pasteur MSD)] injected separately at the same visit in a prospective multicenter, comparative, open label trial. Infants were randomized to receive Hexavac (n = 423) or Pentavac and H-B-Vax II (n = 425) as a primary immunization series at 2, 4 and 6 months of age. Seroprotection and seroconversion rates against all antigens at 1 month after the primary series were compared between the two vaccine groups with 95% confidence intervals (CI<sub>0.95</sub>) and were considered clinically equivalent (not inferior) when the upper limit of the 95% confidence interval on the difference (reference, hexavalent) was below predefined differences. Hexavac met and surpassed the pre-defined criteria for clinical equivalence to Pentavac and H-B-Vax II given concomitantly. It elicited similar seroprotection and seroconversion rates against all antigens. Seroprotection and seroconversion rates obtained 1 month after the third dose of Hexavac were >90% for all antigens. The postimmunization antibody geometric mean titers (GMT) for hepatitis B and purified Haemophilus influenzae polysaccharide were about 2-fold higher in infants who received the reference vaccines than in infants who had received Hexavac. GMTs for poliovirus antibodies tended to be enhanced in infants vaccinated with Hexavac. GMTs for all other antigens were very similar among both groups. Hexavac was generally well-tolerated. At least one local reaction was reported in 20.3% of Hexavac injections compared with 15.8% at the Pentavac injections site and 3.8% at the H-B-Vax II injections site. These reactions were generally mild and transient. At least one systemic adverse event was reported in 45.7% of Hexavac injections compared with 42.2% of Pentavac and H-B-Vax II injections (mild fever, irritability and drowsiness were most frequently reported). The frequency of adverse events was not significantly different between groups. No vaccine-related serious adverse event occurred during the study. This liquid hexavalent vaccine was generally well-tolerated and provided immune responses adequate to be protective against six infectious diseases with a single injection, given at 2, 4 and 6 months of age.

**Mansuy JM, Peron JM, Abravanel F, Poirson H, Dubois M, Miedouge M, Vischi F, Alric L, Vinel JP, Izopet J.** Hepatitis E in the south west of France in individuals who have never visited an endemic area. *J Med Virol* 2004; 74:419-424.

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A total of 431 consecutive patients from the Midi Pyrenees area with acute hepatitis with unknown etiology in 2001-2002 were tested for the presence of immunoglobulin G-class (IgG) anti-hepatitis E virus (HEV) antibodies. Forty-six (10.7%) had anti-HEV IgG, and the results were questionable

for a further 17 (3.9%). Real time PCR based on TaqMan detection was used to identify HEV genome fragments in the serum of patients with positive or questionable anti-HEV serology. HEV RNA was found in 25.4% of cases. All amplification products were sequenced and analyzed. Phylogenetic analysis revealed that all the strains were genotype 3. In conclusion, virological and epidemiological data indicate that genotype 3 viruses are circulating in the south west part of France (Midi-Pyrenees) in patients with acute hepatitis and who have not visited recently areas in which HEV is endemic.

**Marcellin P.** Post-hepatitis B, B-D and C cirrhosis. *Rev Prat* 1991; 41:1149-1155. [Article in French]

Service d'Hépatologie et INSERM U24, Hôpital Beaujon, Clichy.

Three viruses are responsible for posthepatitic cirrhosis: hepatitis B virus, hepatitis D (also called delta) virus and hepatitis C virus formerly known as non-A, non-B virus. Delta virus is a defective organism which can replicate only when coinfection with hepatitis B virus is present. These three viruses cause chronic active hepatitis which, after a period of 5 to 30 years, gives rise to posthepatitic cirrhosis. Chronic infections with these viruses account for more than 90 p. 100 of chronic active hepatitis in France and constitute a major cause of cirrhosis. Beside complications (hepatocellular insufficiency, portal hypertension, hepatocellular carcinoma) which are common to all types of cirrhosis irrespective of their origin, the course of posthepatitic cirrhosis is characterized by possible episodes of reactivation of chronic hepatitis and by a very high risk of hepatocellular carcinoma. Two kinds of treatment are now available: antiviral therapy (basically with interferon alpha) and liver transplantation. Antiviral therapy must, of course, be given before the stage of cirrhosis has been reached. Liver transplantation in these patients raises special problems due to recurrence of viral infection in the graft. Vaccination against hepatitis B virus, which also prevents the B-delta coinfection, must be systematic in populations at risk.

**Martinot-Peignoux M, Roudot-Thoraval F, Mendel I, Coste J, Izopet J, Duverlie G, Payan C, Pawlotsky JM, Defer C, Bogard M, Gerolami V, Halfon P, Buisson Y, Fouqueray B, Loiseau P, Lamoril J, Lefrere JJ, Marcellin P, on behalf of the GEMHEP.** Hepatitis C virus genotypes in France: relationship with epidemiology, pathogenicity and response to interferon therapy. *J Viral Hepat* 1999; 6:435-443.

Unité de Recherche INSERM U481 and Centre de Recherche Claude Bernard sur les Hépatites Virales, Hôpital Beaujon, Clichy.

The aim of this study was to investigate the following in a large population of French patients with chronic hepatitis C: the geographical distribution of hepatitis C virus (HCV) genotypes; the relationship between HCV genotypes and epidemiological characteristics; severity of the disease; and response to interferon (IFN) therapy. Data from 14 tertiary referral centres, corresponding to 1872 patients with chronic hepatitis C, were prospectively collected from 1989 to 1997. HCV genotyping was performed using the line probe assay (LiPA). HCV genotypes 1b, 3, 1a, 2, 4 and a mixed infection were found in 41%, 22%, 16%, 11%, 4% and 4% of our population, respectively. HCV genotype distribution was homogeneous, except for genotype 2 that was found more frequently in the southwest than in the other regions (21% vs 9.2%) ( $P = 0.001$ ). HCV distribution was associated with gender, age, and source and duration of infection. In multivariate analysis, these correlations were related to the source of infection, which was the only independent factor significantly associated with genotype ( $P = 0.001$ ). Genotype 1b was significantly more common in patients with cirrhosis, but in multivariate analysis cirrhosis was independently related to older age at exposure and longer duration of infection ( $P = 0.001$ ). A sustained response to IFN therapy was observed in 11% of patients infected with genotypes 1a or 1b vs 32% of those infected with genotypes 2 or 3 ( $P = 0.001$ ). This study shows that HCV genotype is mainly related to the source

infection, but not to the intrinsic pathogenicity of HCV, and is a strong predictor of sustained response to therapy.

**Massari V, Maison P, Desenclos JC, Flahault A.** Six years of sentinel surveillance of hepatitis B in general practice in France. *Eur J Epidemiol* 1998; 14:765-767.

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Despite the availability of a safe and efficacious vaccine, new cases of infection by hepatitis B virus (HBV) still occur at a substantial rate. This increases the current prevalence of chronic HBV carriers (10% of newly infected subjects) and in the long run, will raise the incidence of chronic liver disease. The surveillance of viral hepatitis commenced in December 1990 by the French sentinel network for electronic surveillance of communicable diseases. Between 1991 and 1996, a decrease in the annual incidence was observed although it was not significant ( $p = 0.06$ ). The mean number of cases for this period was 12 per 100,000 inhabitants. The sex ratio (M/F) was 1.6 ( $p < 0.01$ ) and the median age, 32 years. Heterosexual transmission was suspected in 25% of cases, homo-bisexual transmission in 10%, use of injected drugs in 19%, percutaneous exposure in 9%, and blood transfusion or hemodialysis in 6%. Although the incidence of HBV infection is decreasing, the prevalence of chronic infection will continue to rise. However, the universal hepatitis B immunisation strategy proposed by WHO will dramatically limit the expansion of the population of chronically infected subjects if high coverage is achieved rapidly.

**Maugat S, Astagneau P, Thibault V, Desruennes E, Baffoy N, Desenclos JC, Brucker G.** Nosocomial risk factors of hepatitis C infection. A multicenter study in a hospital-based population. *Rev Epidemiol Santé Publique* 2003; 51:301-308. [Article in French]

Centre de Coordination de la Lutte contre l'Infection Nosocomiale pour l'Inter-région Nord, Paris, Institut Biomedical des Cordeliers, 15-21, rue de l'Ecole-de-Médecine, 75006 Paris.

Drug abuse and blood transfusion are well known risk factors for hepatitis C virus (HCV) infection. However, the route of transmission remains undetermined for 30% of HCV infections. The potential for nosocomial transmission of HCV in health care settings has been suggested but remains poorly estimated. The aim of the study was to assess the prevalence and to identify risk factors for hepatitis C virus (HCV) infection in hospitalized patients frequently exposed to invasive procedures. A multi-center sero-prevalence study was conducted in hospitalized patients who underwent invasive procedures in interventional radiology wards in 6 University hospitals in Paris between 1998 and 1999. Each patient presenting in the ward was consecutively interviewed by a medical investigator. Data were collected on a standardized questionnaire including items on socio-demographic characteristics, past exposure to intravenous drug use, blood transfusions, underlying diseases and type and number of previous invasive procedures. Before procedure, HCV antibody testing (ELISA) was performed in all patients after informed consent. In all HCV-positive patients, HCV viremia was detected using polymerase chain reaction. Overall, 91 of 944 (9.7%) patients were HCV-positive, of whom 90% had positive viremia and 10 were identified HCV positive by the screening. HCV prevalence decreased with age and ranged from 4.5% to 22% according to center. Logistic regression analysis showed that intravenous drug use, history of blood transfusions and endoscopy were found as independent risk factors for HCV infection (odds ratio [CI95%]: 77.3 [23.3-256.3], 4.7 [2.7-8.2] et 1.20 [1.01-1.44]). No other risk factor for nosocomial or iatrogenic transmission was identified. The results suggest that, except for blood transfusions, other healthcare-related procedures may partly explain HCV transmission. This emphasizes the need to reinforce compliance with standard precautions of hygiene.

**Maugat S, Carbonne A, Astagneau P.** Significant reduction of nosocomial infectious: stratified analysis of prevalence national studies performed in 1996 and 2001 in the French inter-region North. *Pathol Biol (Paris)* 2003; 51:483-489. [Article in French]

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In France, repeated prevalence studies of nosocomial infections (NI) are part of governmental plan against NI built in 1995 by the Ministry of Health. To evaluate strand of NI prevalence, we performed a comparative analysis of two successive national point-prevalence surveys occurring in 1996 and 2001 for the Northern France. Comparison concerned the hospitals, which participated in the two studies of 1996 and 2001 in Northern France. The studies were designed as a point-prevalence survey on voluntary basis. For each patient, risk factors and presence of active NI at the day of the study were recorded on standardised form. Criteria of NI used were these of "100 recommendations" of CTIN and of CCLIN North guideline. Prevalence rate (PR) and frequency of risk factors were compared. The risk factors significantly linked to NI by logistic regression were used to build a score of five risk levels of NI (PREVARISK) allowing an adjusted comparison of the 2 years. Total of 161 hospitals participated at the two studies, including respectively 61 422 and 58 749 patients. Between 1996 and 2001, crude PR of infected patients and of NI decreased respectively from 7.8% to 7.3% and 9.0% to 8.0% ( $P < 10^{-4}$ ), so then relative decreases were of 6.4% and 11.1%. In contrast, the frequency of risk factors, except surgery in the past 30 days, significantly increased. Risk factors included in PREVARISK were: age > 65 years, immunosuppression, surgery in the past 30 days, urinary tract and central catheter. In patients with a low risk level (PREVARISK = 0), the relative decrease of infected patients and NI PR were of 17% and 19%. The decrease was not significant for patients with high risk level (PREVARISK  $\geq$  3). Our analyses show a decrease of PR adjusted on risk factors, especially in patients with a low risk level. These result suggest an efficacy of program against NI in studied hospitals especially for patients for whom NI would be potentially avoidable.

**Maupas P, Goudeau A, Coursaget P, Drucker J, Bagros P.** Immunisation against hepatitis B in man. *Lancet* 1976; 1:1367-1370.

An inactivated vaccine against hepatitis B was prepared from blood-donor HBs antigen purified on immunoabsorbents. Its safety and efficacy were tested in chimpanzees. Vaccination was then applied in an attempt to protect patients and staff in a haemodialysis unit. The efficacy of the vaccine in man was assessed by observing humoral and cellular immune reactions and by comparing changes in HBs antigenaemia in vaccinated and non-vaccinated subjects. The results indicate that this vaccine protects against hepatitis B in the circumstances in which it was administered.

**Meffre C, Larsen C, Périn A, Bouraoui L, Delarocque-Astagneau E.** Surveillance of screening for hepatitis C through the laboratory network RENA-VHC, France, 2000-2001. *Euro Surveill* 2003; 8:101-107.

Institut de Veille Sanitaire, Saint-Maurice, France.

Over the period 2000-2001, 189 private or hospital laboratories scattered throughout France participated to the laboratory network RENA-VHC. A total of 759 591 serologies (screening tests and validation of screening tests) were performed, revealing an increase of 10% between 2000 and 2001. The rate of the amount of tests to validate screening found positive over the overall amount of tests performed was 1.2% in 2000 and 1.0% in 2001. This suggests that screening covered more people with little risk of acquiring HCV infection. The per-sons confirmed HCV positive were predominantly men (sex ratio 1.5) of which 31% were 30 to 39 years of age.

**Merle V, Gorla O, Gourier-Frery C, Benguigui C, Michel P, Huet P, Czernichow P, Colin R.** Risk factors of contamination by hepatitis C virus. Case-control study in the general population. *Gastroenterol Clin Biol* 1999; 23:439-446.

Réseau Hépatite C de Haute-Normandie.

In 30% of patients with hepatitis C virus, the source of infection is unknown. To identify the risk factors of infection by hepatitis C virus in a case-control study. Cases had positive hepatitis C virus serology, and were living in Fecamp (Normandy, France). Controls (2 for each case) were age and sex-matched subjects with negative hepatitis C virus serology, living in Fecamp. Demographic, medical, professional, and environmental data were collected. Statistical analysis included chi 2 or Fisher's exact test and multiple logistic regression. The risk factors of hepatitis C virus by univariate analysis were: history of transfusion, high number of sexual partners, hepatitis C virus infection in a relative, history of digestive or genitourinary surgery, an invasive medical procedure, digestive endoscopy, biopsy, lumbar or pleural puncture, medical care after an accident, injections, multiple deliveries or abortion. Risk factors of hepatitis C virus infection by multivariate analysis: hepatitis C virus infection in a relative (Odds ratio: 4.58), history of transfusion (Odds ratio: 2.32), of a surgical procedure (Odds ratio: 2.50), of medical care after an accident (Odds ratio: 1.51), of injections (Odds ratio: 2.24). Our results suggest the possible nosocomial transmission of hepatitis C virus. Intrafamilial transmission is also possible.

**Merle P, Trépo C.** Vaccination against hepatitis B. *Arch Pediatr* 1998; 5:326-332. [Article in French]

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Although relatively uncommon among French children, hepatitis B virus infection is a major problem of public health which deserves coordinated strategies of prevention and immunization, in order to eliminate chronic carriers among groups at risk. The participation of pediatricians to these strategies is essential, knowing that transmission of hepatitis B virus from asymptomatic carrier mothers to their newborns contributes to new generation of chronic carriers who will be exposed to cirrhosis and hepatocellular carcinoma. Four hepatitis B vaccine are presently available in France with equal good efficiency and tolerance. These vaccines allow a protection against hepatitis B in 90 to 95% of the vaccinated subjects. Active search for new vaccines, particularly DNA vaccines, is in progress to extend the protection to the 5-10% non or low responders. The current recommended strategy of immunization in France associates immunizations of infants, preadolescents and groups at risk. In addition newborns from carrier mothers must receive combined passive and active immunization at birth.

**Merle P, Trépo C, Zoulim F.** Current management strategies for hepatitis B in the elderly. *Drugs Aging* 2001; 18:725-735.

Laboratoire de Recherche sur les Virus des Hépatites et Pathologies Associées, Lyon, France.

Despite the availability of an efficient vaccine, chronic hepatitis B virus (HBV) infection remains a major public health problem worldwide. The World Health Organization estimates that there are still 350 million chronic carriers of the virus who are at risk of developing chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC). Antiviral therapy consists of the administration of either interferon-alpha (IFN alpha) or lamivudine. In the elderly, specific issues should be addressed. Because of the long duration of viral infection, screening for HCC is warranted in these patients, as new therapeutic options are being developed. Antiviral treatment for chronic hepatitis

B is indicated in patients with elevated transaminases, the presence of HBV replication, and inflammatory activity on liver histology analysis, providing the patient has no other serious health problem impacting on life expectancy. Since IFN alpha therapy may cause many general adverse effects, lamivudine may be the best current treatment option in this patient population. The pharmacokinetics of lamivudine in the elderly are slightly different from those in younger adults but this does not require dose adjustment, except in the presence of renal function impairment. However, the beneficial effects of lamivudine therapy must be weighed against the selection of drug-resistant mutants. New therapeutic strategies are now under evaluation and may be available in the future for the elderly population. Besides mass HBV vaccination programmes, people sharing a house with patients infected with HBV should be vaccinated to prevent viral transmission.

**Michault A, Faulques B, Sevadjan B, Troalen D, Marais A, Barau G.** Prevalence of hepatitis A, B, C virus markers in Réunion (south hospital and Saint Pierre prison). *Bull Soc Pathol Exot* 2000; 93:34-40. [Article in French]

Laboratoire de Bactériologie-Parasitologie-Virologie, Centre Hospitalier Sud Réunion, Saint Pierre.

We studied the prevalence of Hepatitis A, B, C in different groups in the population of the South of Reunion Island. The aims of this study were the following: to estimate the prevalence of Hepatitis C virus (HCV) (anti-HCV antibodies) and Hepatitis B virus (HBV) (anti-HBc, HBs Ag and anti-HBs) in a population of 1455 women, who delivered in the Centre hospitalier Sud Reunion (CHSR), to estimate the prevalence of these two viruses in a population selected for risk factors (100 prisoners), to estimate the prevalence of Hepatitis A in a group of 400 persons (aged 0 to 19) hospitalised in CHSR since 1st January 1998 (100 for each 5-year age bracket), to research risks factors in these populations and immunity. The overall prevalence of anti-HCV was 0.14% in pregnant women and risk factor associated was found in 28.9% of this population (2.9% history of transfusion, 0.21% drug users). In the group of prisoners seroprevalence was 2%, far below that of prisoners in France. Anti-HCV seroprevalence is weak in Reunion Island and very inferior to seroprevalence in the French population as in other Indian Ocean islands. This is due to the low risk of parenteral transmission. Anti-HBc was found in 90 serum samples from women (overall prevalence 6.35%) and of these 90 positive samples, 9 were positive for HBs Ag (overall prevalence 0.63%), 68 were positive for anti-HBs (4.81%) and 22 (1.54%) were anti-HBc isolated (without HBs Ag and anti-HBs). The overall prevalence of anti-HBs was 62.8%. In the population of 100 prisoners, 2 were HBs Ag positive, 10 anti-HBc positive (2 anti-HBc isolated, 2 associated with HBs Ag, 6 with anti-HBs). The prevalence of anti-HBs was 22%. The major risk factor observed in this population of prisoners was tattooing and/or piercing (46%). These results show that: Reunion island is an area of low endemicity for HBV virus. The measure of protective inoculation is well followed. i.v. drug abuse and previous transfusion are weak routes of transmission. In the group aged 0 to 19, overall prevalence of anti-HAV was 11.9% with the highest rate found among 15 to 19 year-olds (25%). Seroprevalence falls with socio-economic progress. At the present time, the endemic is intermediate in Reunion Island. Given immunity levels within the young population, there is a risk of outbreak. This risk is due to the conditions in Reunion Island, but also to people who travel to other Indian Ocean countries where endemicity is high. It is thus very important that a vaccination strategy be determined.

**Minello A, Boschi F, Harb M, Milan C, Faivre J, Hillon P.** Creation of a viral hepatitis B and C register in the Côte d'Or department. Methodology and initial results. *Gastroenterol Clin Biol* 1998; 22:766-771. [Article in French]

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The epidemiological status of viral B and C hepatitis remains unknown in the general French population. This is why a specialized registry was created in the French Côte-d'Or administrative area (493,931 inhabitants) on 1994 January 1st. The three sources of information were: a) biological and virological analysis laboratories, which report all new HBs Ag and HCV Ab cases, b) specialists in gastroenterology, hepatology, infectious diseases and internal medicine, c) pathologists. Additional information was obtained from the medical practitioner who prescribed the serology. Between January and December 1994, 241 new cases of HBs Ag and HCV Ab were reported: 168 cases of HCV Ab (96 males, 72 females) and 73 cases of HBs Ag (37 males, 36 females) including 10 mixed cases (HBs Ag and HCV Ab). The annual standardized rate of detection of patients with HCV Ab was 26.4 +/- 4.6/100,000 inhabitants. Contamination was a result of intravenous drug addiction in 54 cases (32%), blood transfusion in 39 cases (23%) and remained unknown in 56 cases (33%). A liver biopsy was performed in 42 patients, 17 were treated with interferon during the two years following diagnosis. The standardized detection rate of patients with HBs Ag was 12.9 +/- 2.6/100,000 inhabitants. Contamination resulted from sexual transmission in 17 cases (23%), was related to a lengthy stay in endemic countries in 10 cases (14%) or to intravenous drug addiction in 6 cases (8%), and remained unknown in 37 cases (51%). A liver biopsy was performed in 6 cases and 2 patients were treated. These preliminary French population based data show that the annual frequency of detection of HBs Ag and HCV Ab is high and that care of these patients must be improved.

**Moncharmont P, Bourgeot C, Papon S, Duraffourg M.** Antibodies against hepatitis B virus core antigen among blood donors. *Transfus Clin Biol* 2000; 7:63-69. [Article in French]

Etablissement de Transfusion Sanguine de Lyon, France.

The prevalence of antibodies to the hepatitis B virus (HBV) core antigen (anti-HBc) and the risk factors are evaluated in different blood donor groups. In 1998, on 12,456 first donations, 163 (1.31%) were positive with the two anti-HBc screening tests. Samples were from 69 women (42.3%) and 94 men (57.7%). Three subjects had no anti-HBs but were anti-HBc IgM negative. Forty (24.5%) donors were born in another country than France, and the majority (25 donors, 62.5%) were from North Africa. HBV vaccine had been previously given in 14 subjects (8.6%). Eight (4.9%) had hepatitis before the first donation. Trips in endemic areas (Africa and Asia) were taken by 26 subjects out of 76 donors with follow-up. Two (2.6%) had been previously transfused and six (7.9%) had contact with HBV-infected people. Among 78,033 repeat donations, 26 were positive with the two Anti-HBc screening tests (0.033%). Sixteen were negative after a second test and were probably false positive. Among the ten last donors, nine were Anti-HBs positive. One had anti-HBc IgM and had been recently infected by HBV. The prevalence of Anti-HBc in first-donation persons remains low. Trips in endemic areas and contact with an HBV-infected subject are the most frequent risk factors. Lastly, HBV seroconversion in repeat blood donors is a rare event. Anti-HBc screening in transfusion remains limited.

**Nalpas B, Delaroque-Astagneau E, Bihan CL, Drucker J, Desenclos JC.** Medical practices regarding hepatitis C virus infection in Europe. *J Viral Hepat* 1998; 5:131-141.

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Six hundred and ninety-three European Association for the Study of the Liver (EASL) members, belonging to one of the 15 European Union (EU) member-states, were surveyed, through a standardized 45-item questionnaire, on their medical practices regarding hepatitis C virus (HCV) infection. The response rate was 45%, roughly similar in all the countries concerned. Responders were classified into three groups according to their geographical origin: North, Centre and South. A consensus existed with regard to the necessity of HCV screening in well-defined situations, such as history of blood transfusion, haemodialysis, haemophilia or intravenous drug addiction (90% of

positive answers) while opinions substantially differed for vertical and nosocomial transmission of HCV. For the prevention of sexual and vertical transmission, opinions differed greatly: 22% were in favour of barrier methods for HCV-positive subjects while 34% were against; 49% allowed breast-feeding for babies born to HCV-positive mothers while 14% were against. Conversely, there was relative homogeneity in the issue of domestic prevention (70% in favour of precautions). Algorithms for prescription of virological tests were inhomogeneous (recombinant immunoblot assay was used by 60%; polymerase chain reaction was requested by 77% when alanine aminotransferase (ALT) was elevated vs 89% when normal): medical evaluation varied according to ALT values: liver biopsy and liver ultrasonography were carried out in 90 and 91% vs 40 and 70% for increased and normal ALT, respectively. Thirty per cent of respondents advised patients to stop alcohol consumption and 60% advised moderation. Two-thirds of the responders did not take into account histological severity and virological parameters before initiating antiviral therapy. Eighty per cent of the participants claimed that they administered interferon (IFN) for 12 months. For most of the items studied, there was a large variation, not only between the three groups, but also within each group. Ninety-two per cent of the responders claimed that they were well trained on HCV but they were rather critical of the quality of the information diffused (satisfaction rate: 45%). Altogether, our survey demonstrates that preventive and medical practices towards HCV are not homogeneous throughout the EU; this suggests the need for a European consensus conference in this regard.

**Nalpas B, Zylberberg H, Dubois F, Presles MA, Gillant JC, Lienard M, Delemotte B, Brechot C.** Prevalence of infection by hepatitis viruses in a rural area. Analysis according to risk factors and alcohol consumption. *Gastroenterol Clin Biol* 2000; 24:536-540. [Article in French]

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To evaluate the prevalence of serum markers of hepatitis A, B and C viruses in a rural area according to risk factors and alcohol consumption. Transversal study of unselected subjects living and working in a rural area. Each subject included was asked to fill out an anonymous self-administered questionnaire dealing with his own risk factors, sexual behaviour and alcohol consumption. A blood sample was collected for detection of HBsAg, anti-HBc, anti-HBs, anti-HAV and anti-HCV antibodies. Three hundred three subjects with a mean age of 48 years were included. Main risk factors for viral infection were: blood transfusion (9.4%), intravenous drug addiction (0.73%), acupuncture (17.5%), tattoos (5.8%), past hospitalizations (71.5%), homosexuality (1.1%), conjugal unfaithfulness (11%), sexual partners > 5 (21.3%). Most subjects with at risk sexual behaviour had sexual relations without protection. Anti-HAV prevalence was 87.2% (95% confidence interval 83.4-91.0%). None of the subjects was HBsAg positive and 6.0% (confidence interval 4.7-8.7%) had anti-HBV antibodies. HBV prevalence was correlated to homosexuality only. Two subjects (0.67%, confidence interval 0-1.6%) without any identified risk factor had anti-HCV antibodies. There was no correlation between serum viral marker positivity and an excess alcohol consumption (>80 g of ethanol/d) which was present in 46 subjects. However HBV prevalence was 28.6% in the seven subjects who had been treated for alcoholism; these 7 subjects had a highly at risk sexual behaviour. In a rural area, infection by HAV is very frequent. The prevalence of HBV and HCV did not greatly differ from that observed in the general and urban population. The frequent failure to use protection in subjects with at risk sexual behaviour reinforces the need of prevention programs in rural areas.

**Ouzan D, Cavailler P, Hofliger P, Mamino C, Joly H, Tran A.** Modalities of care in anti HCV positive patients identified in General Medicine in the Alpes-Maritimes district. *Gastroenterol Clin Biol* 2003; 27:376-380. [Article in French]

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Little is known about the management of HCV infected patients after screening in general medicine. On May 2000, 75 General Practitioners (GP) from South Eastern France were involved in an HCV screening campaign. Fifteen per cent of 6321 patients seen during this period presented at least one of the following risk factors: blood transfusion before 1991, drug abuse, imprisonment. Among the 238 HCV positive patients, 9 new cases were reported. To describe the management of these patients. One hundred and fifty-nine of these 238 cases were studied (100 males and 59 females). Mean age was 42 +/- 12 years. Mean delay between contamination and the discovery of HCV positive status was 8 +/- 6 years. Main routes of infection were: drug abuse (78%), transfusion before 1991 (15%), imprisonment (7%). The GP performed the entire follow up of cases in 34%. The following investigations were performed: ALT dosage in 98% (elevated: 59%, normal: 41%), qualitative HCV RNA detection in 77% (positive 78%, negative 22%), quantitative HCV RNA detection in 27%. A liver biopsy was performed in 62 patients (39%). Among the 159 patients 39 (19%) were treated with Interferon (with or without Ribavirin). Treatment and liver biopsy were not performed for the following reasons: patient refusal (26%), normal ALT values (26%), HIV co-infection (27%), elderly patients (3%), decompensated cirrhosis (5%), drug abuse or excessive alcohol intake (12%). The main reasons that adequate management in hepatitis C patients failed was fear of liver biopsy and/or Interferon therapy, and a population difficult that was difficult to treat (HIV coinfecting, drug abuse or chronic alcoholism), A better collaboration between general practitioners and specialists could help improve the management of these patients.

**Ouzan D, Hofliger P, Cavailler P, Mamino C, Tran A.** Screening and hepatitis C management survey in general medicine in the Alpes-Maritimes and east Var area. *Gastroenterol Clin Biol* 2003; 27:90-93.

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This study was performed to assess screening and management of hepatitis C by community-based practitioners in the Alpes Maritimes district in the South of France and to compare their practices with the recommendations issued by the consensus conferences in 1997 and 1999. This information was to be used to adapt continuing medical education to the needs of practitioners in the area. Two hundred and nineteen general practitioners who were members of eighteen continuing medical education associations accepted to complete a questionnaire containing eighteen closed questions. It was issued late 1999 during one of the monthly meetings and completed by all the participating physicians. Only 32% of general practitioners knew the conclusions of one of the two French and European consensus conferences concerning hepatitis C. General practitioner practices were in accordance with recommendations for targeted screening in case of transfusion before 1991 (88%), intra-venous drug use (94%) and increased ALT (91%); however intra nasal drug use (35%) and imprisonment (46%) were underestimated risk factors. Frequency of screening was correlated to duration of practice ( $P < 0.01$ ), size of practice ( $P < 0.02$ ) and follow-up of hepatitis C infected patients, regardless of treatment ( $P < 0.03$ ). Upon discovery of a positive HCV status, 80% of general practitioners prescribed initial investigations but these included costly and needless procedures such as hepatic imaging (56%), RNA quantification (39%) and viral genotype (6%). On the other hand, 79% general practitioners recommended a liver biopsy for patients with elevated transaminase levels. When transaminase levels were normal, only 13% requested qualitative detection of viral RNA. Generally, general practitioners were confused concerning the indications for qualitative or quantitative viral RNA investigations. Few general practitioners followed treated HCV-infected patients and renewed interferon therapy prescriptions. Condom use was advised by 56% of GPs for couples in which one of the partners had a positive HCV status. This study demonstrates the weak impact of consensus conferences on hepatitis C management for general practitioners in the Alpes Maritimes. It provides an opportunity to identify the need for specific training which will be developed within the Cote d'Azur Hepatitis C Network.

**Pawlotsky JM.** Hepatitis C virus genetic variability: pathogenic and clinical implications. *Clin Liver Dis* 2003; 7:45-66.

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HCV is variable because of the properties of the viral RdRp, high levels of replication, and large population sizes. The Darwinian evolution of HCV has been characterized by the emergence of the HCV genotypes, including six main types and a large number of subtypes. The study of HCV genotype epidemiology provides useful information on the worldwide HCV epidemics. The HCV genotype is an important predictor of the response to IFN-alpha-based antiviral therapy, and genotype determination is currently used to tailor treatment indications. In addition, HCV circulates and behaves in infected individuals as mixtures of closely related but distinct viral populations referred to as quasispecies. This particular nature of the virus influences its transmission, the pathogenesis of liver disease and extra-hepatic manifestations, and the outcome during and after antiviral therapy or after transplantation for HCV-related end-stage liver disease. Further studies are needed to understand better the implications of HCV quasispecies diversity in the pathophysiology of HCV infection.

**Pawlotsky JM.** Molecular diagnosis of viral hepatitis. *Gastroenterology* 2002; 122:1554-1568.

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Molecular biology-based assays are invaluable tools for the management of chronic viral hepatitis. They can be used to test blood donations, diagnose active infection, help to establish the prognosis, guide treatment decisions, and assess the virological response to therapy. This article reviews current molecular biology-based techniques and assays, and their practical use in the management of hepatitis B and C virus infection.

**Pawlotsky JM.** Mechanisms of antiviral treatment efficacy and failure in chronic hepatitis C. *Antiviral Res* 2003; 59:1-11.

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The treatment of chronic hepatitis C is currently based on a combination of pegylated interferon (IFN)-alpha and ribavirin. When successful, this treatment leads to sustained HCV clearance which, in virtually all cases, signifies viral eradication. However, approximately 20% of patients with hepatitis C virus (HCV) genotype 2 or 3 infection, and 50% of patients with genotype 1 infection, fail to eradicate the virus. The risk of treatment failure is related to multiple factors, including the treatment schedule, adherence of therapy, host factors, and the severity of HCV-associated disease. Viral factors can also lead to true "HCV resistance". The mechanisms underlying this resistance are unknown, but indirect evidence suggests that chronic infection is associated with phenomena that protect HCV from the antiviral action of IFN-alpha and hinder the clearance of infected cells. This article discusses current knowledge of the mechanisms of action of IFN-alpha and ribavirin, the virological characteristics of chronic hepatitis C treatment success and failure, and possible underlying mechanisms.

**Pawlotsky JM.** Pathophysiology of hepatitis C virus infection and related liver disease. *Trends Microbiol* 2004; 12:96-102.

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Hepatitis C virus (HCV) infects over 170 million people worldwide. Chronic infection occurs in 50-80% of cases and eventually leads to cirrhosis and hepatocellular carcinoma. The HCV lifecycle is only partly understood owing to the lack of a productive cell culture system. Several molecules have been implicated in the receptor complex at the surface of target cells, but the mode of HCV entry remains unknown. Persistent infection appears to be due to weak CD4+ and CD8+ T-cell responses during acute infection, which fail to control viral replication. When chronic infection is established, HCV does not appear to be cytopathic. Liver lesions appear to result from locally driven immune responses, which are mainly non-specific. Local inflammation triggers fibrogenesis, in which hepatic stellate cells play a major role. Cirrhosis is facilitated by external factors, such as chronic alcohol consumption and viral co-infections. Patients with cirrhosis are at high risk of developing hepatocellular carcinoma. The role of HCV proteins in hepatocarcinogenesis is unknown. Further progress in our understanding of HCV infection and pathogenesis awaits the advent of new model systems and technologies.

**Pawlotsky JM, Dahari H, Neumann AU, Hezode C, Germanidis G, Lonjon I, Castera L, Dhumeaux D.** Antiviral action of ribavirin in chronic hepatitis C. *Gastroenterology* 2004; 126:703-714.

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In the patients with chronic hepatitis C, the addition of ribavirin to interferon (IFN)-alpha significantly increases the virologic responses. Our aim was to assess the antiviral action of ribavirin on hepatitis C virus (HCV) as a function of ribavirin pharmacokinetics and to evaluate the influence of this antiviral effect on IFN-alpha efficacy. Forty-five patients with chronic hepatitis C (genotype 1b) received various schedules of IFN-alpha and/or ribavirin administration. Frequent blood sampling was performed for HCV RNA kinetics and ribavirin pharmacokinetics assessment. Ribavirin monotherapy induced a significant, moderate, early, and transient viral load decrease in approximately half of the patients. The occurrence of this effect was associated with longer ribavirin clearance half-lives and higher serum ribavirin concentrations. Ribavirin antiviral effect partly reduced the rebound preceding the second IFN-alpha injection in patients receiving standard IFN-alpha 3 times per week plus ribavirin. The magnitude of the rebound was inversely related to ribavirin concentrations. These patients subsequently experienced a slow, but significant, second slope of viral decrease and cleared HCV RNA. The addition of ribavirin to daily IFN-alpha monotherapy did not have any impact on the second phase of viral decline. Ribavirin exerts a significant, moderate, and transient antiviral effect in a significant proportion of patients with chronic hepatitis C. The antiviral effect of ribavirin correlates with ribavirin pharmacokinetics and is partly responsible for the improved efficacy of the combination of standard IFN-alpha and ribavirin compared with IFN-alpha monotherapy by increasing the incidence of the initial response.

**Pawlotsky JM, Tsakiris L, Roudot-Thoraval F, Pellet C, Stuyver L, Duval J, Dhumeaux D.** Relationship between hepatitis C virus genotypes and sources of infection in patients with chronic hepatitis C. *J Infect Dis* 1995; 171:1607-1610.

Department of Bacteriology and Virology, Hôpital Henri Mondor, Université Paris XII, Créteil, France.

This study examined the relationships between hepatitis C virus (HCV) genotypes and the routes of HCV transmission in 101 patients with chronic hepatitis C. Patients who received blood transfusions (43%) and those with chronic hepatitis C of unknown cause (37%) had similar mean ages, age distribution, and HCV genotype distribution (1a, 19% vs. 14%; 1b, 52% vs. 54%; 3a, 10% vs. 9%; other, 19% vs. 23%). Intravenous drug users (IVDUs) were significantly younger and had a different genotype distribution (1a, 33%; 1b, 0; 3a, 63%; other, 5%;  $P < 0.001$ ). Transmission of HCV 3a has been observed only over the past 20 years; other genotypes were transmitted up to 40 years ago. These results suggest that for 20 years there have been two independent ongoing hepatitis C epidemics. One affects persons who received blood transfusions or whose source of infection is unknown. These persons are older and are mainly infected by HCV 1b. The second type of infection occurs in IVDUs and infects younger persons, mainly with HCV 3a.

**Pillonel J, David D, Pinget R, Laperche S.** Prevalence of HBV, HCV, HIV and HTLV in autologous blood donors in France between 1993 and 2000. *Transfus Clin Biol* 2002; 9:289-296.

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The epidemiological surveillance of autologous blood donors has been carried out in France since 1993. The number of autologous donors increased regularly from 1993 to 1997 but has decreased during the last three years to become less than 50,000 in 2000. The sex-ratio was stable over time (0.85 male for 1 female). The population of autologous donors grew older between 1993 and 2000: the proportion of those aged under 50 years old decreased from 29% in 1993 to 18% in 2000 while the proportion of those over 69 increased from 22 to 34%. Between 1993 and 2000, HbsAg prevalence decreased by a factor of 2.5 and HCV prevalence by a factor of 5. For HIV, a slight decrease was observed and the prevalence of HTLV was stable over time. In 2000, HCV prevalence (0.23%) was two times higher than HBsAg prevalence (0.12%), fifteen times higher than HTLV prevalence in Continental France (0.015%) and one hundred times higher than HIV prevalence (0.002%). The prevalence was similar in men and women for HCV, about two times higher in men than in women for HBsAg and three times higher for HIV. On the contrary, HTLV prevalence was about two times higher in women than in men. HBsAg and HCV prevalence rates were also calculated by age group. The prevalence rates for HBsAg increased up to the 30-39 age group among women and the 40-49 age group among men; then the rates decreased but were higher in men than in women. For HCV, while the prevalence increased continuously with age among women, a peak was reached for men in the 30-39 age group followed by a decrease up to the 50-59 age group and the prevalence was stable afterwards. The very low level of the current risk of transmitting viral infections by homologous transfusion and technical changes in autologous transfusion seem to be the two main factors that contributed to the recent decline in the number of autologous donors. The decrease in HBsAg and anti-HCV prevalence between 1993 and 2000 is multifactorial, but the drop observed for HCV is probably linked to a decrease in HCV prevalence of the general population over the last ten years.

**Pillonel J, Laperche S, Saura C, Desenclos JC, Courouge AM, on behalf of the Transfusion-Transmissible Agents Working Group of the French Society of Blood Transfusion.** Trends in residual risk of transfusion-transmitted viral infections in France between 1992 and 2000. *Transfusion* 2002; 42:980-988.

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Monitoring trends in residual risks of transfusion-transmitted viral infections (HIV, HTLV, HBV, and HCV) is important to assess improvements in blood safety. In France, these trends were analyzed between 1992 and 2000. As risk is predominantly associated with the window period, residual risks were estimated by multiplying incidence rates by the durations of the window periods. Incidence rates were calculated from the data collected by the blood transfusion centers belonging to the Transfusion-Transmissible Agents Working Group, which currently collects more than 50 percent of the 2.5 million blood samples donated each year in France. Trend analysis showed a significant decrease in residual risks for HCV ( $p = 0.01$ ) and HBV ( $p < 0.001$ ). Although residual risks decreased for HIV and HTLV, the trends were not significant. In 1998 through 2000, residual risks were estimated to be 1 in 470,000 donations for HBV, 1 in 860,000 for HCV, 1 in 1,370,000 for HIV, nil for HTLV, and 1 in 250,000 for the four viruses combined. In France, the current risk of a blood recipient becoming infected with a retrovirus or a hepatitis virus is extremely low. The implementation of NAT in July 2001 is predicted to reduce the residual risk to 1 in 2,700,000 donations for HIV and 1 in 8,300,000 for HCV.

**Piroth L, Binquet C, Vergne M, Minello A, Livry C, Bour JB, Buisson M, Duong M, Grappin M, Portier H, Chavanet P.** The evolution of hepatitis B virus serological patterns and the clinical relevance of isolated antibodies to hepatitis B core antigen in HIV infected patients. *J Hepatol* 2002; 36:681-686.

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The evolution of hepatitis B virus (HBV) serological patterns and the clinical relevance of isolated anti-HBc pattern are not well established in HIV infected patients. A cohort of 240 patients was followed for 6.9 +/- 3.4 years, with iterative HBV serologic assays performed (mean interval of 2.2 years). Five patients without HBV markers at baseline subsequently developed positive anti-HBs (incidence 0.66/100 patient-year), as did two patients with chronic HBs antigenemia (incidence 1.66/100 patient-year). Only one patient with isolated anti-HBc pattern developed HBs chronic antigenemia. Persistent isolated anti-HBc pattern was observed in 37 patients (13 with detectable blood HBV DNA) and was strongly associated with positive hepatitis C virus (HCV) viremia (hazard ratio = 9.5, confidence interval 95%: 4.5-20.0,  $P < 0.0001$ ). Hepatic lesions were more severe in HCV infected patients with persistent isolated anti-HBc pattern than in those without (Knodell score 9.2 +/- 4.6 versus 6.7 +/- 5.0,  $P = 0.04$ ). In time updated analysis, this pattern was not associated with an increased risk of hepatotoxicity, by contrast with HCV infection or positive HBs antigenemia. In HIV infected patients, HBV serological status must be systematically and regularly assessed, and systematic HBV vaccination must be proposed in those without HBV marker. Isolated anti-HBc pattern must be considered in the management of hepatitis C, but not for antiretroviral therapy.

**Pol S.** Immunotherapy of chronic hepatitis B by anti HBV vaccine. *Biomed Pharmacother* 1995; 49:105-109.

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Vaccine therapy is now used in various infectious diseases. The hepatitis B virus (HBV) leads to chronic infection in around 5% of patients with a high risk of chronic active hepatitis which may result in cirrhosis and hepatocellular carcinoma. The partial efficacy of antiviral therapies (40% of sustained inhibition of HBV replication), their cost, the numerous side effects and the immune-mediated pathology of HBV infection explain the emergence of new immune therapies in treating HBV infection. Experimental and clinical arguments are in favor of vaccine therapy in HBV chronic infection. Thirty-two consecutive chronic HBsAg carriers with chronic hepatitis and detectable serum HBV DNA were given 3 standard injections of the GenHevac B vaccine at one

month intervals. Six months after the first injection, 12 patients (37.5%) had undetectable HBV DNA while 3 others showed significant decrease in HBV DNA titers. Eight of these 15 responders received a standard course of alpha-interferon (5 MU thrice weekly subcutaneously for 4 months) and all still had undetectable HBV replication. By contrast, among 13 (of the 17) non responders to vaccine who were given alpha-interferon, only 3 stopped HBV replication. In summary, serum HBV DNA disappeared in 18 of the 32 patients (53.1%) who were given vaccine therapy, with or without interferon. Vaccination was uneventful. Active immune therapy against HBV appears as efficient and less expensive than antiviral therapies in stopping HBV replication. Such a result should be confirmed by controlled randomized trials.

**Poynard T, Ratzu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J.** Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. *J Hepatol* 2001; 34:730-739.

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In hepatitis C there is controversy over the linearity of the rate of progression and the significance of gender, mode of infection and viral factors. 2313 untreated patients with a reliable estimated duration of infection and liver fibrosis were included. Fibrosis progression was calculated using the Kaplan-Meier method and the rate of fibrosis progression using the hazard function. Seven risk factors were assessed: age at biopsy, gender, alcohol consumption, mode of infection, activity grade, hepatitis C virus genotype and RNA level. The percentage of patients without cirrhosis was 91% after 20 years of infection (95% CI:90-92%) and 56% after 40 years (95% CI:48-64%). Three independent factors were associated ( $P < 0.001$ ) with a faster progression rate: age at infection, alcohol consumption of 50 g or more per day, and male gender. The mode of infection, histologic activity, genotype and viral load were not independently associated with fibrosis. Fibrosis progression was mainly dependent on age and the duration of infection and can be divided into four successive periods with very slow, slow, intermediate and rapid progression rates. In patients infected with hepatitis C, the majority of fibrosis progression occurred in those aged fifty years or older.

**Pradat P, Caillat-Vallet E, Sahajian F, Bailly F, Excler G, Sepetjan M, Trépo C, Fabry J, on behalf of the ADHEC members.** Prevalence of hepatitis C infection among general practice patients in the Lyon area, France. *Eur J Epidemiol* 2001; 17:47-51.

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To estimate the prevalence of hepatitis C virus (HCV) infection among patients in general practices. A screening campaign requested by the French Health Insurance Fund and involving 271 general practitioners (GPs) and 96% of the 95 medical laboratories was conducted in the Lyon area. Each GP participated for one week and offered an HCV screening to all patients aged 18-69 years during this period. Risk factors were estimated by a medical questionnaire (MQ) filled in by the physician. From May to October 1997, 11,805 subjects were recruited into the study. Among them, 101 were known HCV positive. The MQ was filled up in 86% of the 11,704 remaining patients. Only 59% of those (6876/11,704) went to a laboratory to be tested. Fifty-one were ELISA positive of whom 30 were confirmed by RIBA or PCR. If we add 101 patients that were known HCV positive and estimate the prevalence among patients who did not go to the laboratory, this study gives a total estimated prevalence of 1.3%. The prevalence of HCV infection among patients of GPs is about 1.3%, very close to the estimate in the French general population. The substantial number of patients known HCV positive is probably related to the participation of GPs sensitised to HCV issues and who already have screened most of their HCV patients.

**Raguin G, Rosenthal E, Cacoub P, Veyssier P, Piette JC, Micoud M, on behalf of the GERMIVIC (Joint Study Group on Hepatitis C virus of the French National Society of Internal Medicine and the French Society of Infectious Diseases).** Hepatitis C in France: a national survey in the Departments of Internal Medicine and Infectious Diseases. *Eur J Epidemiol* 1998; 14:545-548.

Service de Médecine Interne et Maladies Infectieuses, Hôpital de La Croix Saint Simon, Paris, France.

Infection with Hepatitis C virus is a significant public health problem that has important clinical and financial consequences. Understanding of the epidemiology of HCV is needed to help define future therapeutic and preventive strategies. So far, the importance and characteristics of the epidemics have been best appreciated in specialist units dealing with liver disease. The purpose of our study was to survey the number and characteristics of hepatitis C antibody positive patients in Departments of Internal Medicine and Infectious Diseases. We conducted a multicentre national prospective analysis of all positive HCV-antibody patients, either inpatient or outpatient, reported over a period of one month across France. Two thousand and two cases were identified. Epidemiological, clinical and therapeutic characteristics are described. Risk factors were identified in 86%. For 10% of the patients, hepatitis C seropositivity was discovered during the period of survey. At the time of first diagnosis, 47% of patients presented with no clinical or biological abnormality. Coinfection with HIV was frequent (59%). Only 20.3% of the patients had received or were receiving a treatment with interferon. Within the limits of the methodology used, this study shows that Hepatitis C infection is a substantial clinical problem in French Departments of Internal Medicine and Infectious Diseases. Our findings may help the public health authorities in better appreciating the impact of hepatitis C and making policy decisions.

**Ranger-Rogez S, Alain S, Denis F.** Hepatitis viruses: mother to child transmission. *Pathol Biol (Paris)* 2002; 50:568-575. [Article in French]

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The infection by the hepatitis viruses, when appearing during the pregnancy, could result in damages for the infant. However, risks differ according to the implicated virus. Hepatitis B virus infection, for which prevalence varies according to areas, is injurious when the mother is chronic HBsAg carrier. Risk consists of neonate's contamination during the labour, and if contaminated, the neonate becomes a chronic carrier himself in 80 to 90% of cases. When the mother is positive for viral DNA in her serum, transmission rate is estimated at 90%. In the opposite, if the mother is negative for viral DNA in the serum, transmission rate is about 10 to 30%. HBsAg screening is obligatory in France during the sixth month of pregnancy: in case of positivity, serovaccination of the neonate is systematically carried out. Protection rate is 100% if the mother had a low viral load (<150 pg/ml) at the end of pregnancy, and weaker (about 70%) if the mother had a higher level of viral DNA. Transmission risk of hepatitis C virus (HCV) is much lesser, since it is about 5% for a woman who is positive for viral RNA at the end of her pregnancy, and at least 10% if the woman is moreover positive for the HIV. Risk is more important if the woman had an important plasmatic viral load (> 10(5) copies/ml) and if the duration between membrane rupture and delivery is long. Vaginal delivery and breast-feeding are not advised. Neonates from mothers who replicate the HCV at the end of pregnancy are serologically evaluated until 12-15 months of age, in order to determine their possible contamination. Delta virus transmission from mother to infant is exceptional and could be avoided by the HBV serovaccination of the new-born. Intra-utero transmission of hepatitis A virus is very rare, but perinatal transmission could occur. Materno-fetal transmission of hepatitis E virus has been reported, but the virus is essentially dangerous for the mother, resulting in a mortality rate of 15 to 25% if the acute infection occurs during the third trimester of the pregnancy.

**Raoult D, Foucault C, Brouqui P.** Infections in the homeless. *Lancet Infect Dis* 2001; 1:77-84.

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Homeless people in developed countries have specific problems predisposing them to infectious diseases. Respiratory infections and outbreaks of tuberculosis and other aerosol transmitted infections have been reported. Homeless intravenous drug users are at an increased risk of contracting HIV, and hepatitis B and C infections. Skin problems are the main reason the homeless seek medical attention, and these commonly include scabies, pediculosis, tinea infections, and impetigo. Many foot disorders are more prevalent in the homeless including ulcers, cellulitis, erysipelas, and gas gangrene. The louse transmitted bacteria *Bartonella quintana* has recently been found to cause clinical conditions in the homeless such as urban trench fever, bacillary angiomatosis, endocarditis, and chronic afebrile bacteraemia. Treatment of homeless people is complicated by financial constraints, self-neglect, and lack of adherence. Patients with serious and contagious illnesses should be hospitalised. Physicians should be aware of these specific issues to enhance care.

**Rey JF, Halfon P, Feryn JM, Khiri H, Masseyeff MF, Ouzan D.** Risk of transmission of hepatitis C virus by digestive endoscopy. *Gastroenterol Clin Biol* 1995; 19:346-349.

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In 30 to 50% of cases, the route of transmission of virus C remains unknown. The aim of this study was to investigate the effectiveness of manual cleaning and disinfection procedures after endoscopic examinations in highly infected patients. In 39 patients with chronic hepatitis C and a high level of replication, a gastroscopy with biopsy was performed with a fully submersible endoscope. Cleaning and disinfection were carried out with the following protocol: cleaning with detergent solution (Sekulyse), rinsing, 3 to 5 min immersion into a glutaraldehyde disinfectant solution (Sekucid) and final rinsing. One hundred mL of sterile water was flushed through the biopsy channel immediately after removal of the endoscope (T1), after cleaning (T2), and after final disinfection (T3). These 100 mL were collected in aliquots for viral and bacterial screening. Virus C particles were searched for in the effluent of the biopsy channel using two methods of polymerase chain reaction. Virus C particles were found in 2 of 39 patients in T1 aliquots collected before washing. Routine cleaning with a detergent eliminated all viral particles, as tests were negative at T2 and T3. The usual bacteria (*Pseudomonas*, *Streptococcus*, *Neisseria*...) were detected at T1 and had disappeared after total disinfection at T3. Virus C hepatitis could be transmitted during endoscopic examination, but cleaning and disinfection procedures effectively eliminated all viral particles.

**Rezende G, Roque-Afonso AM, Samuel D, Gigou M, Nicand E, Ferre V, Dussaix E, Bismuth H, Feray C.** Viral and clinical factors associated with the fulminant course of hepatitis A infection. *Hepatology* 2003; 38:613-618.

Centre Hépato-Biliaire, Equipe Propre de l'Institut National de la Santé, Unité Propre de Recherche de l'Enseignement Supérieur No. 3541, Formation de Recherche Associée a l'Association Claude Bernard, Villejuif, France.

Fulminant hepatitis is a severe complication of hepatitis A virus infection. Its mechanism is

unknown. Liver transplantation can be necessary, but spontaneous recovery is frequent. There are no data on the level of viral replication according to the clinical form of hepatitis A. We reviewed the files of 50 patients with acute hepatitis A. Nineteen patients had fulminant hepatitis (defined by encephalopathy and factor V < 50%), and, from them, 10 patients underwent transplantation. Hepatitis A virus (HAV) RNA was quantified by real-time PCR on sera obtained at admission. The genotype was determined by phylogenetic analysis of HAV RNA. HAV RNA was detected in serum by RT-PCR in 39 out of 50 patients. Encephalopathy and low factor V level were significantly related to female gender, HAV PCR negativity (9/19 vs. 5/31, respectively;  $P = 0.03$ ), a low serum HAV RNA level (log, 3.6 +/- 0.6 vs. 4.4 +/- 0.9, respectively;  $P = 0.02$ ), genotypes other than IA, and acetaminophen intake. In multivariate analysis, low or undetectable HAV viral load and a high bilirubin level were independently associated with both low factor V levels and fulminant hepatitis and also with death or transplantation. In conclusion, HAV-related liver failure is due to an excessive host response associated with a marked reduction in viral load. Serum HAV RNA assay could be of help in the management of severe hepatitis A.

**Rosenthal E, Poirée M, Pradier C, Perronne C, Salmon-Ceron D, Geffray L, Myers RP, Morlat P, Pialoux G, Pol S, Cacoub P, on behalf of the GERMIVIC Joint Study Group.** Mortality due to hepatitis C-related liver disease in HIV-infected patients in France (Mortavic 2001 study). *AIDS* 2003; 17:1803-1809.

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To determine mortality due to end-stage liver disease (ESLD) in a nationwide cohort of HIV-infected patients 5 years after the introduction of highly active antiretroviral therapy (HAART) and to compare this with that observed before and during the early years of HAART. All departments of internal medicine and infectious diseases from the GERMIVIC Study Group prospectively recorded all deaths in HIV-infected patients during 2001. Sixty-five departments, following a total of 25 178 HIV-infected patients, participated in the study. Results were compared with those of previous surveys conducted using similar methodology in 1995 and 1997. Among 265 deaths observed during 2001, 129 (48.7%) were related to AIDS, 38 (14.3%) to ESLD, and 98 (36.7%) to other causes. Mortality due to ESLD represented 28% of non AIDS-related deaths; 36 of the 38 patients (95%) dying from ESLD had chronic hepatitis C virus (HCV) infection. In 2001, deaths due to ESLD (14.3%) were significantly more frequent than in 1995 (1.5%;  $P < 0.01$ ) and 1997 (6.6%;  $P < 0.01$ ). During this interval, the prevalence of hepatocellular carcinoma as a cause of death increased (1995, 4.7%; 1997, 11%; 2001, 25%;  $P < 0.05$ ), as did alcohol consumption ( $P < 0.01$ ). In the post-HAART era, ESLD due to HCV is a growing cause of mortality in HIV-infected patients. Increased longevity attributable to HAART, and a higher prevalence of alcohol consumption, are probably involved in this trend.

**Rotily M, Vernay-Vaisse C, Bourlière M, Galinier-Pujol A, Rousseau S, Obadia Y.** HBV and HIV screening, and hepatitis B immunization programme in the prison of Marseille, France. *Int J STD AIDS* 1997; 8:753-759.

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This study estimated the prevalence of hepatitis B virus (HBV) and human immunodeficiency virus (HIV) serological markers among inmates and evaluated inmates' compliance with an HBV immunization programme. During the mandatory consultation at the sexually transmitted disease (STD) clinic of the Marseille Prison (HIV counselling, and syphilis/HIV screening), physicians offered serological testing (anti-HBs, anti-HBc, HbsAg, anti-HIV) and Engerix B vaccination to each entrant. The number participating in the survey is 391/411 (89%); 75% were aged 18 to 35 years and 79% were men; 42% reported having had multiple sexual partners during the last 12 months. Report of an intravenous drug user (IDU) sexual partner was more frequent among

women than men (22% vs 8%). Injecting drug use over lifetime was reported by 23%; 27% declared having shared their injection equipment during the last 12 months. 124/267 (32%) had an HBV marker: anti-HBs + only (immunized): 2.3%; anti-HBs + and anti-HBc +: 21.7%; anti-HBc + only: 6.4%; HBsAg +: 1.3%. The HIV seroprevalence was 6% (21% among IDUs). This survey underlines the high HBV and HIV seroprevalence among prisoners and the high proportion of inmates at risk for these infections. There is an urgent need for immunization and education programmes in this population. It demonstrates an HBV immunization programme is feasible and accepted by inmates and staff members.

**Roudot-Thoraval F, Bastie A, Pawlotsky JM, Dhumeaux D, on behalf of the Study Group for the Prevalence and the Epidemiology of Hepatitis C Virus.** Epidemiological factors affecting the severity of hepatitis C virus-related liver disease: a French survey of 6,664 patients. *Hepatology* 1997; 26:485-490.

Département de Santé Publique, Hôpital Henri Mondor, Université Paris XII, Créteil, France.

Cirrhosis is a frequent and severe event in the course of chronic hepatitis C, but it is unclear why some patients develop cirrhosis after a given period whereas others do not. We studied a large cohort of patients with chronic hepatitis C to determine the role of the route of transmission of hepatitis C virus (HCV) in the onset of cirrhosis. Six thousand six hundred sixty-four patients were enrolled in a nationwide survey of chronic hepatitis C in France. We first randomly defined a representative sample of 30 hospitals with medical units managing patients with HCV infection. All patients with chronic hepatitis C were enrolled if hepatitis C was diagnosed or treated in these units in 1991, 1992, or 1993. A questionnaire was filled in from the patients' charts and covered demographic data, risk factors for HCV infection, clinical and histological data, hepatitis B virus (HBV) and human immunodeficiency virus status, and alcohol intake. Descriptive statistics were prepared, and factors potentially related to the onset of cirrhosis were identified by means of univariate analysis followed by stepwise logistic regression analysis. Among the patients enrolled, 21.4% had biopsy-proven cirrhosis. Prevalence of cirrhosis markedly varied according to the route of transmission of HCV. It was significantly more frequent in blood recipients (23.4%) than in drug users (7.0%). Although the occurrence of cirrhosis was dependent on disease duration, it remained more frequent in blood recipients than in drug users for a given duration. Apart from the route of transmission, excessive alcohol intake was also associated with a higher risk of cirrhosis (34.9% vs. 18.2%;  $P < 0.001$ ), and so was HBV infection (24.6% vs. 21.1%;  $P < 0.05$ ). These factors acted independently of the route of transmission. Hepatocellular carcinoma was observed in 3.6% of all patients and in 17.8% of cirrhotic patients, and its occurrence was strongly and mainly related to the presence of cirrhosis. In conclusion, cirrhosis occurred in about 20% of the HCV-infected patients in this study and was more frequent in blood recipients than in drug users, independently of disease duration. Expected changes in the epidemiology of HCV infection might modify the risk of developing cirrhosis and, thereafter, cancer.

**Roudot-Thoraval F, Monnet E, Mercet P, Bastie A, Dhumeaux D, Miguet JP.** Strategies of hepatitis C screening in general practice. Results of a two-center randomized trial. *Gastroenterol Clin Biol* 2000; 24:1037-1041. [Article in French]

Service de Santé Publique, Hôpital Henri-Mondor, Créteil.

To improve the detection of patients infected with hepatitis C virus. A study was undertaken in the general medicine setting in two hepatitis C networks. General practitioners volunteered and received training on hepatitis C, then were randomly assigned to one of two screening strategies: group 1: general practitioners prescribed hepatitis C virus testing if the risk factors for HCV hepatitis C virus infection were identified during questioning of patients, group 2: general practitioners were helped in their screening approach by posters and leaflets on the risk factors of

hepatitis C virus, available in the waiting room. A total of 184 general practitioners enrolled 90 from group 1 and 94 from group 2. During a 15-month-period, 617 serologies were prescribed, 323 by general practitioners in group 1 (in patients who were an average of 40 year-old) and 294 in group 2 (in patients who were an average of 44 year-old); 489 serologies (79.3%) were actually performed (261 and 228 respectively) and 25 (5.1%) tested positive (15 and 10 respectively). The number of prescribed, performed, and positive serologies did not differ from one group to the other. The motive for hepatitis C virus screening was similar in both groups and included a history of transfusion in 27% of cases, intravenous drug use in 6%, increased ALT or symptoms compatible with hepatitis in 13%, nosocomial exposure in 22%. Risk factors in the 25 patients who were hepatitis C virus positive were drug use (44%), history of transfusion before 1991 (16%), elevated ALT or symptoms (12%), others (28%). This study comparing screening strategies in general medicine, resulted in the diagnosis of hepatitis C virus infection in 5% of tested patients, regardless of the strategy. However, the fewer serologies prescribed by general practitioners (an average of 3 tests in a 15-month-period) suggests a low rate of identified risk factors in general practice, and emphasizes that other types of screening procedures should be implemented and evaluated.

**Sablon E, Shapiro F, Zoulim F.** Early detection of hepatitis B drug resistance: implications for patient management. *Expert Rev Mol Diagn* 2003; 3:535-547.

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Despite the availability of safe and effective prophylactic vaccines, hepatitis B viral disease has remained a tenacious scourge, ranking ninth globally among all causes of mortality (up to 1 million deaths annually). Approximately 6% of the global population - more than 350 million people - have failed to resolve viral infection and become chronic carriers, eventually placing between 15 and 25% of such individuals at risk for end-stage liver disease. Until recently, the immunomodulator interferon-alpha and especially the nucleoside analog lamivudine (Epivir) have been the treatments of choice for chronic hepatitis B viral infection. However, the inexorable development of drug resistance to lamivudine has been a major clinical impediment to the long-term use of such treatment. Herein, the current and future diagnostic methods for early detection of emerging drug resistance to the hepatitis B virus is reviewed. Given the recent approval of adefovir dipivoxil (Hepsera) and the possibility that other nucleoside and nucleotide analogs could soon become part of the hepatitis B virus therapeutic arsenal, the clinical ramifications for coordinated use of diagnostic tests together with new antihepatenaviral agents for optimal patient management is also discussed.

**Saliou P, Ajjan N, Guérin N.** Efficacy and tolerance of vaccinations in premature infants. *Arch Pediatr* 2002; 9:629-637. [Article in French]

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Immunization may prevent an enhanced risk of infectious diseases, providing that it is completed on time. A review of the literature summarizes several studies on effectiveness, safety and duration of protection in preterm infants. Immune maturation depends on chronological age rather than gestational age. Then immunization against diphtheria-tetanus-pertussis-poliomyelitis-*Haemophilus influenzae* b should be initiated at 2 months of age and completed prior than 6 months. The youngest preterm infants, still hospitalized at 8 weeks of age should be monitored following the first immunization as they may develop apnea episodes, probably linked with the pertussis component of the vaccine. In premature, BCG vaccination induces a delayed hypersensitivity to tuberculin less important than in full-term neonates, and should not be given right after birth in newborns less than 33 weeks of gestational age. Hepatitis B vaccination should be offered as soon

as two months of age and even at birth to children born from HBsAg carriers. Neither duration of immunity, nor safety are modified by prematurity.

**Soubeyrand B, Boissard F, Bruel M, Debois H, Delattre D, Gauthier A, Soum S, Thébault C.** Central nervous system demyelinating disease following hepatitis B vaccination with GenHevac B. Review of ten years of spontaneous notifications (1989-1998). *Presse Med* 2000; 29:775-780. [Article in French]

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To describe and analyze spontaneous reports of central nervous system (CNS) demyelinating disease including multiple sclerosis, following vaccination with GenHevac B vaccine, from 1989 to December 31, 1998. Descriptive analysis of adverse event reports in the vaccinated population, including the number of cases of CNS demyelinating disease, their frequencies, their dates of onset in relation to dates of report and their distribution according to age, sex and the number of injections. A Kaplan-Meier curve was used to analyze the time period between the last dose of vaccine and the onset of CNS demyelinating disease. Overall, 187 cases of CNS demyelinating disease were spontaneously reported, (0.54 reports per 100,000 doses of GenHevac B distributed). The average time period between the occurring date of onset of the disease and its subsequent report was 24 months. The average age of onset was 31.7 years old and 73% of cases were women. The time between the last dose of vaccine and the onset of disease was regularly distributed from 1 day to 5 years (median: 60 days). These results, together with available clinical, epidemiological data regarding multiple sclerosis, do not suggest a causal relationship between CNS demyelinating disease and vaccination with GenHevac B.

**Thermet A, Rollier C, Zoulim F, Trépo C, Cova L.** Progress in DNA vaccine for prophylaxis and therapy of hepatitis B. *Vaccine* 2003; 21:659-662.

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Increasing lines of evidence suggest that DNA vaccine is of interest to fight chronic hepatitis B virus (HBV) infection. We used the Pekin duck infected by duck HBV (DHBV), closely related to the human virus, which is an attractive model allowing study of protective and therapeutic effectiveness of DNA vaccines against hepatitis B. Immunisation with a plasmid encoding the DHBV large (L) envelope protein induced a strong, specific, highly neutralising and long-lasting anti-preS humoral response in uninfected ducks. Importantly, maternal antibodies elicited by such DNA immunisation were vertically transmitted and protected progeny against viral challenge. Therapeutic immunisation of chronic DHBV-carrier ducks with this plasmid DNA led to the dramatic and sustained decrease in viral replication and even to clearance of intrahepatic viral covalently close circular DNA (cccDNA) pool in some animals. Our recent combination therapy data showed even a more pronounced antiviral effect of DNA vaccine to DHBV envelope protein when associated with antiviral drug (lamivudine) treatment. Therefore, DNA-based vaccine appears as a promising new approach for prophylaxis and therapy of hepatitis B.

**Touzé E, Fourrier A, Rue-Fenouche C, Ronde-Oustau V, Jeantaud I, Bégaud B, Alperovitch A.** Hepatitis B vaccination and first central nervous system demyelinating event: a case-control study. *Neuroepidemiology* 2002; 21:180-186.

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To investigate the relationship between hepatitis B (HB) vaccination and a first central nervous system (CNS) demyelinating event in adults. In 1998, we conducted a multicentre, hospital-based

case-control study which enrolled 402 cases of first CNS demyelinating event occurring between 1994 and 1995 and 722 controls matched for centre, age, sex and date of admission. An independent expert committee validated the diagnoses of cases and controls. Data on vaccinations were obtained from a standardized phone interview. Forty percent of eligible cases and 50% of eligible controls could not be localized or were excluded because they did not satisfy inclusion or matching criteria. Conditional logistic regression performed on 236 and 355 matched controls showed that adjusted odds ratios for the first CNS demyelinating event within 2 months following an injection of HB vaccine were 1.8 [95% confidence interval (CI), 0.7-4.6] in the whole group and 1.4 (95% CI, 0.4-4.5) in the subgroup of cases (n = 152) and controls (n = 253) referring to vaccination certificates during the phone interview. Restricting the analyses to the cases with definite or probable multiple sclerosis, these odds ratios were 2.0 (95% CI, 0.8-5.4) and 1.6 (95% CI, 0.4-5.6), respectively. Odds ratios tend towards 1 for a longer interval between HB vaccine and demyelinating event. This study was sufficiently powerful to rule out a strong association between HB vaccine exposure and a subsequent demyelinating event. However, it could not provide a clear indication of a moderately increased risk of a CNS demyelinating event shortly after HB vaccination in adults.

**Touzé E, Gout O, Verdier-Taillefer MH, Lyon-Caen O, Alperovitch A.** The first episode of central nervous system demyelination and hepatitis B virus vaccination. *Rev Neurol (Paris)* 2000; 156:242-246. [Article in French]

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Central nervous system (CNS) demyelinating episodes have been described following numerous vaccines but there is no definite conclusion about a causal relationship. Recently, in France, in the context of an Expanded Program on Immunization, several cases of CNS demyelination have been observed following injection of recombinant hepatitis B (HB) vaccine, leading to great concern. We performed a hospital-based case-control study of 121 patients with a first episode of CNS demyelination occurring between July 1993 and December 1995 and 121 age and sex matched controls seen in the same period. Data on vaccinations history of cases and controls were collected by a postal questionnaire and confirmed by a phone interview. Adjusted odds ratio (OR) obtained from conditional logistic regression between a first episode of CNS demyelination and any vaccination were equal to 1.4 (95 p. 100 CI 0.5-4.3) for an exposure within the 60 previous days and 2.1 (95 p. 100 CI 0.7-6.0) for an exposure within the 61-180 previous days. Similar results were found for HB vaccine exposure within the 60 previous days (adjusted OR = 1.7, 95 p. 100 CI 0.5-6.3) or within the 61 to 180 previous days (adjusted OR = 1.5, 95 p. 100 CI 0.5-5.3). These findings did not permit to exclude confidently an association between HB vaccine and the occurrence of a first CNS demyelinating episode.

**Venard V, Corsaro D, Kajzer C, Bronowicki JP, Le Faou A.** Hepatitis B virus X gene variability in French-born patients with chronic hepatitis and hepatocellular carcinoma. *J Med Virol* 2000; 62:177-184.

Unité Mixte de Recherche 7565 UHP-CNRS - Laboratoire de Bactériologie-Virologie, Faculté de Médecine, Vandoeuvre les Nancy, France.

The polymorphism of the hepatitis B virus (HBV) X gene from patients born in Lorraine has been studied in serum samples from 22 HBV infected patients, 14 presenting with chronic hepatitis and 8 with hepatocellular carcinoma (HCC). Subtypes adw and ayw represented 21 of the 22 sequenced isolates. The sequence of the X gene of HBV strains from these patients differed from the ones of Far East origin by A to T(1678) and G to A(1759) changes for subtype ayw and C to T(1792) for adw. The expression of the preC region, as indicated by the detection of HBe antigen

(HBeAg), was not observed in 11 patients. In 6 patients (3 HCC and 3 non HCC), the absence of HBeAg could be related to a stop codon at position 28. For the 5 remaining patients, the precore stop mutation at codon 28 was not evidenced but 3 out these 5 patients had mutations at nt 1764 and nt 1766 in the promoter of the preC/C gene. These two mutations were also observed in 2 patients with HBeAg, indicating that they are not implicated in the suppression of expression of this gene. Independently of the serotype, two main differences were noted between aminoacid (aa) sequences of chronic hepatitis and HCC related strains: first, twice as many aa changes were found in HCC patients than in chronic hepatitis B carriers (mean of aa changes per patient 4.1 vs. 2.0) and second, we found apparition of polar aa in HCC patients. Most mutations already described in patients from the Far East with HCC have been found in strains of patients from Lorraine. The changes K130M and V131I, considered as "hot spot mutations," were found in strains of HCC patients carrying an ayw subtype of the HBV genome but not in the ones of chronically infected patients. In contrast, strains of the adw subtype had these two changes in the two groups of patients. However when considering the 22 sequenced genes, these hot spot mutations were associated with HCC ( $P = 0.034$ ).

**Vergnon P, Colin C, Jullien AM, Bory E, Excoffier S, Matillon Y, Trépo C.** Medical and economic evaluation of donated blood screening for hepatitis C and non-A, non-B, non-C hepatitis. *Rev Epidemiol Santé Publique* 1996; 44:66-79. [Article in French]

Département d'Information Médicale des Hospices Civils de Lyon, Hôtel Dieu, Lyon.

The aim of this study was to evaluate the cost of hepatitis C and non-A non-B non-C screening strategy in donated blood, currently used in French transfusion centres and to assess the effect in the blood transfusion centres according to the prevalence of the disease and the intrinsic values of tests. This screening strategy was based on alanine aminotransferase assay, and HBe and HCV antibodies detection. In 1993, a survey was conducted in 26 French transfusion centers to estimate the costs of the screening strategy currently used. Average expenditure on diagnostic sets, equipment, staff and administration charges for hepatitis C and non-A non-B non-C screening were calculated. From these results, we estimated the cost of the previous strategy which did not involve HCV antibody testing, so as to determine the incremental cost between the two strategies. We used clinical decision analysis and sensitivity analysis to estimate the incremental cost-effectiveness ratio with data gathered from the literature and examine the impact on blood transfusion centre. Implemented for 100,000 volunteer blood donations, the incremental cost of the new strategy was FF 2,566,111 (1992) and the marginal effectiveness was 180 additional infected donations detected. The sensitivity analysis showed the major influence of infection prevalence in donated blood on the incremental cost-effectiveness ratio: the lower the prevalence, the higher the cost-effectiveness ratio per contaminated blood product avoided.

**Vincelet C, Bourgin C, Quinet B, Tabone MD.** Estimation of vaccination rates in children of 10 months, 2 years and 4 years of age who underwent a health checkup at the Well Child Clinic in Paris during the year 1997. *Arch Pediatr* 1999; 6:1271-1278. [Article in French]

Centre de Bilans de Santé de l'Enfant de la CPAM de Paris, France.

In France, the vaccination program has changed through the last years. We report a study on immunization rates of children who underwent a complete health checkup at a Well Child Clinic in Paris. We studied three groups of children (children at the ages of 10 months, 2 years and 4 years) regarding types of daycare and medical care. Nine hundred children who underwent a health checkup between April and June 1997 were included in the study. Data were collected from immunization records and parents' interviews. In 10-month-old children, prevalence rates of immunization against diphtheria, tetanus, poliomyelitis and pertussis (DTP) and immunization against *Haemophilus influenzae type b* (Hib) disease were 98% and 96%, respectively. Only 1.7%

were immunized against measles. Forty-two percent of children had complete or ongoing immunization against hepatitis B. The vaccination coverage for BCG was 94%. In two-year-old children, boosting for DTPP vaccine had been performed by 90%, more than 90% were immunized against measles and 50% had received at least one shot to prevent hepatitis B. At the age of 4 years, 99% were immunized against DTPP, 78% were immunized against Hib disease, 98% against measles and 48% for hepatitis B. All children were immunized with BCG, and 98% were BCG-controlled (22% had tuberculin intradermal reaction). The highest immunization rates were observed in children who had preventive care in 'Maternal and Infantile Protection Centres.' Immunization rates were not influenced by the type of daycare, except for measles in two-year-old children managed by private pediatricians. We observed high immunization rates of children who underwent health checkups. Late immunization against measles and low immunization rates against hepatitis B reflect the difficulties encountered in mobilising physicians and families for these vaccinations.

**Yazdanpanah Y, Boëlle PY, Carrat F, Guiguet M, Abiteboul D, Valleron AJ.** Risk of hepatitis C virus transmission to surgeons and nurses from infected patients: model-based estimates in France. *J Hepatol* 1999; 30:765-769.

INSERM Unit 444, Institut Fédératif Saint-Antoine de Recherche sur la Santé, Paris, France.

The aim of this study was to estimate the annual number of cases of hepatitis C virus transmission from infected patients to uninfected surgeons or nurses due to percutaneous injury during invasive procedures. The risk of transmission was estimated using a model involving three probabilities: A, that a health care worker sustains at least one percutaneous injury during a procedure; B, that 1 to 10% of patients are seropositive for hepatitis C virus; and C, that infection by this virus is transmitted to the Health Care Worker after such exposure. Probability A was estimated from the results of 2 French multicentric prospective trials. Probability C was estimated from the results of 9 international prospective studies. A ten-fold decreased risk was assumed for surgeons who wear gloves and use solid-bore suture needles. During a single procedure, the estimated probability of hepatitis C virus transmission from an infected patient to an uninfected surgeon ranged from  $4.2 \times 10^{-5}\%$  to  $4.2 \times 10^{-4}\%$ , and from  $2.98 \times 10^{-6}\%$  to  $2.98 \times 10^{-5}\%$  to an uninfected nurse. For surgeons, the estimated annual cumulative risk of occupational infection ranged from 0.01% to 0.1% (1 in 10000 to 1 in 1000), and for nurses from 0.0054% to 0.054% (1 in 18700 to 1 in 1900). Between 2 and 21 surgeons out of a total 20000 are estimated to acquire occupationally-related hepatitis C virus infection, and between 16 and 167 nurses out of a total 300000. These estimates strongly justify introducing preventive measures to protect health-care workers from bloodborne infection.

## Part II Additional bibliographical sources

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## **Annex 1**

Calendrier vaccinal 2004  
Avis du Conseil Supérieur d'Hygiène Publique de France,  
19 mars 2004

[Vaccination calendar 2004]  
[Advice of the High Commission for Public Health in France,]  
[March 19, 2004]

*BEH* 2004; 28-29:121-125  
[http://www.sante.gouv.fr/htm/pointsur/vaccins/beh\\_2004.pdf](http://www.sante.gouv.fr/htm/pointsur/vaccins/beh_2004.pdf)

## Annex 2

Avis du Comité Technique des Vaccinations (CTV)  
et du Conseil Supérieur d'Hygiène Publique de France (CSHPF)  
Section Maladies Transmissibles  
concernant la vaccination contre l'hépatite virale B  
(séance du CTV du 14 septembre 2004)  
(séance du CSHPF du 26 septembre 2004)

[Advice of the CTV and the CSHPF]  
[Section Infectious Diseases]  
[regarding vaccination against hepatitis B]  
[(session of the CTV, September 14, 2004)]  
[(session of the CSHPF, September 26, 2004)]

[http://www.sante.gouv.fr/htm/dossiers/cshpf/a\\_mt\\_260904\\_vac\\_hepBHernan.pdf](http://www.sante.gouv.fr/htm/dossiers/cshpf/a_mt_260904_vac_hepBHernan.pdf)