

**'Prevention of Viral Hepatitis in The Netherlands:
Lessons learnt and the way forward'**

Viral Hepatitis Prevention Board Meeting
Rotterdam, The Netherlands, November 13-14, 2008

Alex Vorsters
VHPB Secretariat

This pre-meeting document is a list of selected abstracts from a Medline (ERL WebSPIRS Health Sciences) search on '{Netherlands or Dutch} and {hepatitis or HAV or HBV or HCV or HDV or HEV}' in title or content and a ISI Web of Knowledge search on '{Netherlands or Dutch} and {hepatitis or HAV or HBV or HCV or HDV or HEV}'. The references are ranged by publication year (most recent first) and for each year in reversed alphabetical order of the first author's name.

T. Marschall, M. Kretzschmar, M. J. Mangen, S. Schalm. High impact of migration on the prevalence of chronic hepatitis B in the Netherlands. *Eur J Gastroenterol Hepatol.* 2008; 20(12):1214-25.

OBJECTIVES: A representative serosurveillance study (1995) resulted in an estimate of 0.2% for the HBsAg prevalence in the Netherlands. Some risk groups, especially migrants, were not well represented in the study, which probably led to an underestimation of the true HBsAg prevalence. The aim of this study was to calculate an adjusted HBsAg prevalence estimate for the total Dutch population including these risk groups. **METHODS:** According to their country of origin first-generation migrants (FGM) were classified into groups with low, intermediate and high prevalence using data from the WHO and Statistics Netherlands. The number of chronic HBsAg carriers in different age and population groups was estimated based on studies about age-specific prevalence in different countries. The number of carriers in the indigenous population was estimated using the serosurveillance study. A combination of these estimates led to an estimate of the total prevalence rate in the Netherlands. **RESULTS:** Nearly 10% of the Dutch population are FGM. Of these, about 18% were born in low-endemic, 71% in middle-endemic and 11% in high-endemic countries. The overall prevalence of HBsAg in FGM is estimated to be at 3.77%. Combining these results with the results of the serosurveillance study the HBsAg prevalence in the Dutch population is estimated to be between 0.32 and 0.51%, and when including injecting drug users and mentally handicapped persons the prevalence rates are 0.36 and 0.55%, respectively. **CONCLUSION:** Our results show the high importance of targeting migrants and their close contacts adequately in screening programmes, vaccination and treatment for chronic hepatitis B.

H. L. Zaaijer, S. Bouter and H. J. Boot. Substitution rate of the hepatitis B virus surface gene. *Journal of Viral Hepatitis.* 2008; 15(4):239-245

Molecular epidemiology of hepatitis B virus (HBV) often relies on the comparison of HBV surface (S) gene sequences, although little is known about the substitution rate of the HBV S-gene. In this study, we compared HBV S-gene sequences in longitudinal sample pairs of 40 untreated, chronically HBV-infected patients, spanning 210 years of cumulative follow-up. The 40 patients included HBV e-antigen positive and negative persons; with HBV DNA levels ranging from 10(3) to 10(9) cps/mL and belonging to HBV genotypes A, B, C, D and E. In the 40 sample pairs, 70 nucleotide changes occurred in the HBV S-gene (0-8 per patient), resulting in an average substitution rate of 5.1×10^{-4} nucleotide changes/site/year (range: $0-1.3 \times 10^{-2}$). Surprisingly, the number of substitutions was strongly associated with the inverse level of viremia; and only weakly with the duration of follow-up: in 11 highly viremic patients (HBV DNA $\geq 10(8)$ cps/mL), only four substitutions occurred despite a cumulative observation period of 56 years (substitution rate: 1.1×10^{-4}), while in the 10 patients with viremia below 10(4) cps/mL, 29 substitutions occurred during 30 years of follow-up (substitution rate: 14.6×10^{-4}). We conclude that in chronic hepatitis B virus infection the rate of nucleotide substitution in the HBV S-gene is inversely related to the level of viremia and thus varies widely from person to person; hampering the phylogenetic analysis of possible chains of HBV infection.

P. T. L. van Wijk, M. Pelk-Jongen, C. Wijkmans, A. Voss, A. Timen and P. M. Schneeberger.

Variation in interpretation and counselling of blood exposure incidents by different medical practitioners. *American Journal of Infection Control.* 2008; 36(2):123-8

BACKGROUND: Blood exposure incidents pose a risk for transmission of bloodborne pathogens for both health care workers and public health. Despite several national and international guidelines, counsellors have often different opinions about the risks caused by these incidents. Little is known about the consequences of these variations in risk assessment on the effectiveness of the treatment and the costs for the health care system. **METHODS:** The aim of this study was to reveal differences among diverse groups of counsellors in assessing the same blood exposure incidents. Subjects included 4 different kinds

of counsellors: public health physicians from infectious disease departments and medical microbiologists, occupational health practitioners, and HIV/AIDS specialists from hospital settings. Surveys with cases of blood exposure incidents were sent to the counsellors in The Netherlands asking questions about their risk assessment and consequent treatment. Questions were categorized for hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV risks. RESULTS: Of the 449 surveys sent, 178 were returned, of which 158 were eligible for the study. In general, occupational health practitioners and medical microbiologists showed a more rigorous approach especially with regard to prophylactic treatment when counselling HBV risk situations, whereas public health physicians and HIV/AIDS specialists were more thorough in the handling of HCV risk accidents. In HIV counselling, HIV/AIDS specialists were far more rigorous in their treatment than the other groups. For 7 of the total of 12 cases, the risk assessment with regard to HBV, HCV, and HIV differed significantly. CONCLUSION: The assessment of blood exposures significantly differs depending on the medical background of the counsellor handling the incident, leading to remarkable inconsistencies in the response to prevent the transmission of bloodborne pathogens and/or to increased costs for unnecessary diagnostic tests and preventive measures. Although national guidelines for the counselling and treatment of blood exposure incidents are essential, the assessment of blood exposure incidents should be limited to as few as possible, well-trained professionals, operating in regional or national call centers, to ensure comparable assessment and corresponding application of preventive measures for all victims.

P. T. L. van Wijk, M. Pelk-Jongen, C. Wijkmans, A. Voss and P. M. Schneeberger. Three-year prospective study to improve the management of blood-exposure incidents. *Infection Control and Hospital Epidemiology*. 2008; 29(9):871-877

Objective. Throughout 2003-2005, all blood-exposure incidents registered by an expert counseling center in The Netherlands accessible by telephone 24 hours a day, 7 days a week, were analyzed to assess quality improvement in the center's management of such incidents. The expert center was established to handle blood-exposure incidents that occur both inside and outside of a hospital. Infection control practitioners carried out risk assessment, made the practical arrangements associated with managing incidents, and carried out treatment and follow-up, all in accordance with standardized procedures. Design. We analyzed the time it took for exposed individuals to report the incident, the time required to perform a human immunodeficiency virus (HIV) test for the source individual when needed, occurrence of injuries, hepatitis B (HBV) vaccination status of exposed individuals, and adherence to protocol at the expert center. Results. A mean of 465 incidents was registered during each year of the 3-year study period. Although 698 (50%) of 1,394 reported exposures took place in a hospital, 704 (50%) took place outside of a hospital, and 460 (33%) occurred at a time other than regular office hours. HIV tests for source individuals were performed increasingly quickly over the course of the 3-year study period because of earlier reporting and improvements in practical matters associated with performing and processing the tests. The percentage of healthcare workers employed outside a hospital who were vaccinated against HBV increased from 34% (52 of 152) to 70% (119 of 170) during the 3-year study period. Consequently, the administration of immunoglobulin and unnecessary laboratory testing were reduced. In assessing the quality of the expert center, flaws in the handling of incidents were identified in 148 (37%) of 396 incidents analyzed in 2003, compared with 38 (8%) of 461 incidents analyzed in 2005. Conclusions. The practical matters associated with management of blood-exposure incidents, such as timely reporting and administration of prophylaxis, should be optimized for incidents that occur at times other than regular office hours and outside of hospitals. The establishment of a 24-hour centralized counseling facility that was open 7 days a week to manage blood exposures resulted in significant improvements in incident management and better care.

H. van Vlierberghe. The hepatitis C virus burden: a Dutch point of view. *Netherlands Journal of Medicine*. 2008; 66(1):1-2

J. van Steenberg, M. Petrignani, A. Kroneman and M. Koopmans. [The molecular epidemiology of hepatitis A in The Netherlands; the usefulness of typing isolated viral strains].[comment]. *Nederlands Tijdschrift voor Geneeskunde*. 2008; 152(7):408

M. Toy, I. K. Veldhuijzen, M. C. Mostert, R. A. de Man and J. H. Richardus. Transmission routes of hepatitis B virus infection in chronic hepatitis B patients in The Netherlands. *Journal of Medical Virology*.

2008; 80(3):399-404

The Netherlands is a low endemic country for hepatitis B virus (HBV). Rotterdam, a city in The Netherlands harbors a large group of chronic hepatitis B (CHB) patients of which most are born abroad. The study included 464 consecutive CHB patients who were reported to the Municipal Public Health Service in Rotterdam from January 1, 2002 to September 15, 2005. The HBV genotypes, possible transmission routes of infection and travel history of CHB patients born in The Netherlands, were compared with those CHB patients living in The Netherlands but who were foreign-born, taking into account the ethnicity of the mother. Of the 464 patients with CHB infection, 14% were Dutch-born and 86% were foreign-born. The CHB patients in the Dutch-born group had genotypes A (35%), B (15%), C (11%), D (37%), and G (2%). In the foreign-born group, the distribution of genotypes was A (20%), B (15%), C (11%), D (40%), and E (15%). In the Dutch-born group, sexual transmission accounted for a larger proportion of infections ($P < 0.0001$) compared to the foreign-born group, whereas perinatal transmission is reported to be higher in the foreign-born group and in the Dutch-born group with a foreign mother. The genotypes of the chronic HBV strains determined corresponded well with the HBV genotypes expected from the countries of origin of the patients or their mothers. Genotypes A and D are predominant in CHB patients in The Netherlands.

C. Smit, C. van den Berg, R. Geskus, B. Berkhout, R. Coutinho and M. Prins. Risk of hepatitis-related mortality increased among hepatitis C virus/HIV-coinfected drug users compared with drug users infected only with hepatitis C virus - A 20-year prospective study. *Aids-Journal of Acquired Immune Deficiency Syndromes*. 2008; 47:221-225

Background: Progression of liver-related disease is accelerated in individuals coinfecting with HIV and hepatitis C virus (HCV). Because the life expectancy of HIV-infected drug users (DUs) improved after the widespread use of highly active antiretroviral therapy (HAART), HCV-related death is likely to become more important. To disentangle the effects of HCV and HIV, we compared the overall and cause-specific mortality between HCV/HIV-infected DUs and HCV-infected DUs and DUs without HCV or HIV, followed up between 1985 and 2006. Methods: A total of 1295 participants in the Amsterdam Cohort Study were included. Cause-specific hazard ratios (CHRs) were estimated for the eras before (< 1997) and since HAART (≥ 1997) within and among serologic groups. Results: The risk of dying decreased for most causes of death ≥ 1997 ; this decrease was not the same for the different serologic groups. Among HCV/HIV-coinfected DUs, the risk of hepatitis/liver-related death did not substantially change overtime (CHR = 0.87, 95% confidence interval [CI]: 0.21 to 3.58), whereas the risk of AIDS-related mortality decreased. Compared with DUs solely infected with HCV, HCV/HIV-coinfected DUs were at increased risk of dying from hepatitis/liver-related disease (CHR = 7.15, 95% CI: 1.98 to 25.8), other natural causes (CHR = 3.09, 95% CI: 1.41 to 6.79), and non-natural causes (CHR = 2.30, 95% CI: 1.07 to 4.95) in the HAART era. Conclusions: HCV/HIV-coinfected DUs remain at increased risk of dying from hepatitis/liver-related death in the HAART era compared with HCV-monoinfected DUs. This risk did not change in HCV/HIV-coinfected DUs after HAART was introduced, suggesting that in the HAART era, HIV continues to accelerate HCV disease progression. Efforts should be made to establish effective treatment for HCV infection in HCV/HIV-coinfected individuals.

S. Slavenburg, F. M. Verduyn-Lunel, J. T. Hermsen, W. J. G. Melchers, R. H. M. te Morsche and J. P. H. Drenth. Prevalence of hepatitis C in the general population in the Netherlands. *Netherlands Journal of Medicine*. 2008; 66(1):13-7

BACKGROUND: Chronic hepatitis C virus (HCV) is transmitted by blood-blood contact and this leads to high HCV prevalence in risk populations such as haemophilia patients and intravenous drug users. The prevalence in the general Dutch population is unknown, although it appears to be very low in screened blood donors (0.0169%). AIM: The objective of this study is to estimate the prevalence of HCV in a general population sample living in an urbanized region in the Netherlands. METHODS: We randomly selected 2200 EDTA blood samples that had been submitted for analysis of biochemical parameters to a regional servicing laboratory for general practitioners (SHO, Arnhem/Nijmegen, the Netherlands). HCV antibody testing was performed using a three-step approach. For initial screening, an enzyme immunoassay (Bioelisa HCV 4.0, Biokit, Spain) was used. Positive samples were subjected to a second, microparticle enzyme-linked immunoassay (AxSYM HCV version 3.0, Abbott laboratories, IL, USA). Genotypes were determined by Line Probe Assay. RESULTS: A total of four persons (two females, two males) (0.2%) tested positive for HCV antibodies. The average OD/cut-off ratio of the screening assay

was 2.9 (range 1.0 to 7.3) and serological findings were confirmed using a specific second immunoassay. HCV RNA (genotype 1b) was found in the sera of two persons. CONCLUSION: The HCV prevalence in our sample of the Dutch population was 0.2% which accords with earlier estimates from prevalence studies in the Netherlands.

C. Lindenburg, C. Weegink, J. Schinkel, P. Jansen, M. Beld, A. Urbanus, A. Krol, G. Casteelen, G. van Santen, C. van den Berg, R. Coutinho and M. Prins. Hepatitis C screening and treatment among drug users in Amsterdam: Promising interim-results of the Dutch-C project (drug users treatment for chronic hepatitis C). *Journal of Hepatology*. 2008; 48:S285-S285

G. Kazemier, H. J. Metselaar, R. A. de Man, T. C. K. Tran, T. H. N. Groenland and H. W. Tilanus. [Liver transplantation with a living donor: the first 3 cases in Rotterdam]. *Nederlands Tijdschrift voor Geneeskunde*. 2008; 152(14):817-21

Liver transplantation with a part of the liver from a healthy living donor can be life saving for selected patients with end-stage liver failure. The experiences with the first 3 adult patients in the Netherlands were as follows. The first patient was a 56-year-old man with primary sclerosing cholangitis, who received half of the liver from his 53-year-old sister. Postoperatively, the donor developed a urinary tract infection, which was treated with antibiotics. The recipient developed fever and paralytic ileus 6 days after transplantation. Relaparotomy revealed minimal bile leakage from the cut surface of the liver, which was corrected with a suture. Three years after donation, both donor and recipient were doing well. The second patient was a 63-year-old man with hepatic cirrhosis due to hepatitis B, recurrent bleeding from varices, and hepatocellular carcinoma. The carcinoma was treated percutaneously with radiofrequency ablation. He was given a liver transplant from his 28-year-old son. The donor later developed transient ileus and mild liver function disorders. The recipient developed a bacterial infection of the ascites, which was treated with antibiotics, and later *Candida*-oesophagitis and a herpes simplex infection, which were also treated successfully. More than 2 years after donation and transplantation, both donor and recipient were in good condition. The third patient was a 42-year-old man with a chronic hepatitis B virus infection and 2 hepatocellular carcinomas. The donor was his 34-year-old sister-in-law. The recipient developed prolonged jaundice due to stenosis at the site of the bile duct anastomosis, for which a stent was placed. He was discharged in good condition but died 11 months later of cerebral metastases. One year after the procedure, the donor was doing well. The Rotterdam liver transplantation programme with living donors demonstrates that excellent results can be accomplished with minimal risk for the donor.

M. Kretzschmar and A. de Wit. Universal hepatitis B vaccination. *Lancet Infectious Diseases*. 2008; 8(2):85-87

S. Jadhav, M. Datla, H. Kreeftenberg and J. Hendriks. The Developing Countries Vaccine Manufacturers' Network (DCVMN) is a critical constituency to ensure access to vaccines in developing countries. *Vaccine*. 2008; 26(13):1611-5

Six years after its establishment, the Developing Countries Vaccine Manufacturers' Network (DCVMN) has become the main representing body for emerging vaccine manufacturers from the developing world. The Network's main strategic priority (increase access to DPT-based combination vaccines containing vaccines against Hepatitis B (HepB) and *Haemophilus influenzae* type b (Hib)) has now come close to fulfillment due in part to the transfer of conjugation technology from The Netherlands Vaccine Institute (NVI) to various manufacturers of the Network. It is argued that at the international level more push mechanisms for product development involving DCVM are needed, including those promoting access to technology and transfer of technology, know how and technical skills from Organization for Economic Co-operation and Development (OECD) countries to developing countries. At the national level, governments of countries in which DCVMN manufacturers operate should provide more generous funding for all aspects of vaccines and immunization including incentives to manufacturers to develop and import new technologies. These two approaches will contribute to the long-term viability of domestic or regional vaccine manufacturing, which in itself is critical to ensure global equity of access to vaccines.

S. J. M. Hahne, I. K. Veldhuijzen, L. J. M. Smits, N. Nagelkerke and M. J. W. van de Laar. Hepatitis B virus transmission in The Netherlands: a population-based, hierarchical case-control study in a very low-incidence country. *Epidemiology & Infection*. 2008; 136(2):184-95

We report the first population-based case-control study on acute hepatitis B in a very low-incidence country. A case was a Netherlands resident, notified between May 1999 and July 2000 with symptoms and serology compatible with acute hepatitis B. Population controls were randomly selected, with oversampling from men and persons aged 20-39 years. Risk factors were studied using logistical regression, distinguishing confounders and mediators through hierarchical analysis. Participants were 120 cases and 3948 controls. The risk of acute hepatitis B was increased in men who have sex with men, with reporting to have had more than two partners in the past 6 months the only significant risk. In children, adult females and heterosexual males, having parents born in a hepatitis B endemic country was a significant risk. For adult females and heterosexual males, this was largely explained by having a foreign partner. For children this was partly explained by parenteral exposures abroad.

S. J. M. Hahne, M. Ramsay, and R Coutinho. Universal hepatitis B vaccination. *Lancet Infectious Diseases*. 2008; 8(2):87-88

M. J. de Vries, B. te Rijdt and C. M. J. van Nieuwkerk. Transmission of hepatitis C genotypes in the Netherlands amongst recently genotyped patients. *Netherlands Journal of Medicine*. 2008; 66(1):40-1

D. J. A. de Jong, M. J. de Vries, L. J. M. Boonman-de Winter and P. van Wijngaarden. Referral of hepatitis C virus seropositive patients in primary care in the Netherlands. *Netherlands Journal of Medicine*. 2008; 66(1):42-3

J. de Bruijne, E. H. C. J. Buster, H. C. Gelderblom, J. T. Brouwer, R. J. de Knegt, K. J. van Erpecum, S. W. Schalm, C. M. Bakker, H. L. Zaaijer, H. L. A. Janssen, H. W. Reesink and H. Netherlands Association of Gastroenterologists and. Treatment of chronic hepatitis C virus infection - Dutch national guidelines. *Netherlands Journal of Medicine*. 2008; 66(7):311-22

The development of this guideline was initiated and coordinated by the Netherlands Association of Gastroenterologists and Hepatologists (Nederlandse Vereniging van Maag-Darm-Leverartsen). The aim is the establishment of practical guidelines in the evaluation and antiviral treatment of patients with chronic hepatitis C virus (HCV) infection. This includes recommendations for the initial evaluation of patients, the choice and duration of antiviral therapy and the follow-up after antiviral therapy. Hepatitis C is a slowly progressive disease. The initial evaluation of chronically HCV-infected patients should include liver biochemistry testing, virological testing and abdominal ultrasound imaging. Liver biopsy is no longer a routine procedure. Antiviral treatment should be considered for all HCV-infected patients. Current antiviral treatment is a long-term process and is associated with substantial side effects. When deciding whether to start treatment or not, the chance of successful treatment (80% with hepatitis C genotype 2 and 3 and 50% with hepatitis C genotype 1 and 4), the fibrosis stage, the expected side effects and the compliance of the patient should be taken into consideration. In the absence of significant fibrosis and necroinflammation in liver biopsy, postponing treatment is an option. Current antiviral treatment is contraindicated in patients with Child-Pugh-class B or C cirrhosis. The possibility of a liver transplantation should be investigated in these patients. Significant comorbidity with a limited life expectancy is an absolute contraindication for antiviral treatment. Treatment of chronic hepatitis C consists of administration of peginterferon and ribavirin for 24 or 48 weeks. Patients with hepatitis C genotype 1 or 4 are treated for 48 weeks. Patients with hepatitis C genotype 2 or 3 are treated for 24 weeks. In patients with undetectable HCV RNA after four weeks (28 days) of treatment, a shorter treatment is equally effective (12 to 16 weeks for hepatitis C genotype 2 or 3; 24 weeks for hepatitis C genotype 1 or 4). Outpatient clinic visits are recommended at the start and after 2, 4, 8, and 12 weeks of treatment, and thereafter every four to six weeks until the end of treatment. It is recommended to stop treatment if the HCV RNA level has not decreased by at least 2 log₁₀ IU/ml (c/ml) after 12 weeks of treatment or when HCV RNA is still detectable after 24 weeks of treatment. The recommended frequency of outpatient clinic visits for patients who are not being treated is once every six months in patients with cirrhosis, otherwise every 12 months. It is expected that new anti-HCV-medication (STAT-C, specifically targeted antiviral therapy for HCV) will become available in the near future. Therefore treatment of chronic HCV infection will probably be more effective in the future.

E. H. C. J. Buster, K. J. van Erpecum, S. W. Schalm, H. L. Zaaijer, J. T. Brouwer, H. C. Gelderblom, R. J. de Knegt, C. Minke Bakker, H. W. Reesink, H. L. A. Janssen and H. Netherlands Association of Gastroenterologists and. Treatment of chronic hepatitis B virus infection - Dutch national guidelines. *Netherlands Journal of Medicine*. 2008; 66(7):292-306

The development of this guideline was initiated and coordinated by the Netherlands Association of Gastroenterologists and Hepatologists (Nederlandse Vereniging van Maag-Darm-Leverartsen). The aim is the establishment of national standards in the evaluation and antiviral treatment of patients with chronic hepatitis B virus (HBV) infection. This includes recommendations on the initial evaluation of patients, choice and duration of antiviral therapy, follow-up after antiviral therapy and monitoring of patients not currently requiring antiviral therapy. The initial evaluation of chronic HBV-infected patients should include testing of liver biochemistry, virus serology and abdominal imaging. In patients without cirrhosis, antiviral treatment is recommended for those with a serum HBV DNA of at least 1.0×10^5 c/ml ($\geq 2.0 \times 10^4$) IU/ml) in combination with: a) elevation of serum alanine aminotransferase (ALAT) level above twice the upper limit of normal during at least three months, and/or b) histological evidence of porto-portal septa or interface hepatitis on liver histology. In patients with cirrhosis, antiviral treatment is recommended if serum HBV DNA is 1.0×10^4 c/ml ($\geq 2.0 \times 10^3$) IU/ml) or higher, independent of ALAT levels or histological findings. If the patient has decompensated cirrhosis, antiviral treatment is recommended if serum HBV DNA is 1000 c/ml (≥ 200 IU/ml) or higher. Patients who do not have an indication for antiviral treatment should be monitored because there is a risk of (re)activation of disease activity. Monitoring every three to six months is recommended for HBeAg-positive and HBeAg-negative patients with high viraemia (HBV DNA $\geq 1.0 \times 10^5$ c/ml or $\geq 2.0 \times 10^4$ IU/ml) and normal ALAT levels. For patients with serum HBV DNA below 1.0×10^5 c/ml ($< 2.0 \times 10^4$ IU/ml) the recommended frequency of monitoring is every three to six months for HBeAg-positive patients and every six to 12 months for HBeAg-negative patients. Peginterferon (PEG-IF N) therapy should be considered as initial therapy in both HBeAg-positive and HBeAg-negative patients without contraindications for treatment with this drug because of the higher chance of achieving sustained response compared with nucleos(t)ide analogue therapy. In patients starting nucleos(t)ide analogue therapy, the use of lamivudine is not preferred if long-term antiviral treatment is expected due to the high risk of antiviral resistance against this drug. Of the currently licensed nucleos(t)ide analogues, entecavir has the lowest risk of antiviral resistance (compared with lamivudine, adefovir and telbivudine), while suppression of viral replication seems most profound with either entecavir or telbivudine. The recommended duration of treatment with PEG-IF N is one year for both HBeAg-positive and HBeAg-negative patients. In HBeAg-positive patients, nucleos(t)ide analogue therapy should at least be continued until HBeAg seroconversion and a decline in HBV DNA to below 400 c/ml (80 IU/ml) has been achieved and maintained for six months during therapy. Whether nucleos(t)ide analogue therapy can be safely discontinued in HBeAg-negative patients is unknown; usually prolonged or indefinite antiviral treatment is necessary. Patients receiving PEG-IF N should be monitored once a month, while three monthly monitoring suffices for those receiving nucleos(t)ide analogues. Genotypic analysis of the HBV polymerase is indicated if an increase in serum HBV DNA of at least 1 log(10) c/ml (IU/ml) compared with the nadir value is observed during nucleos(t)ide analogue therapy. Antiviral therapy should be changed as soon as possible in case of confirmed genotypic resistance. Adding a second antiviral agent seems beneficial over switching to another agent. With the availability of multiple new antiviral drugs for the treatment of chronic hepatitis B, effective treatment is now possible for more patients and for longer periods. However, the complexity of HBV therapy has also increased. Nowadays, virtually all chronic HBV-infected patients can be effectively managed.

D. Bresters, I. C. M. Van Gils, F. W. Dekker, A. C. Lankester, R. G. M. Bredius and J. J. Schweizer. Abnormal liver enzymes two years after haematopoietic stem cell transplantation in children: prevalence and risk factors. *Bone Marrow Transplantation*. 2008; 41(1):27-31

To establish the prevalence of elevated liver enzymes in children transplanted in a Dutch haematopoietic stem cell transplantation (HSCT) centre, we retrospectively assessed AST and ALT values at 2 years after HSCT. Age, sex, diagnosis, type of transplant, conditioning regimen and early post-transplant complications involving the liver (veno-occlusive disease, acute GVHD, viral reactivation) were analysed as risk factors. AST and ALT values were available at 2 years after HSCT in 216 of 290 patients (75%) alive at that time and were above normal in 53 (25%) and at least twice normal in 17 (8%) patients. Older age at HSCT and a diagnosis of benign haematological disease are risk factors for abnormal liver enzymes late after HSCT. In half of the patients with benign haematological disease, iron overload is the

most likely aetiological factor. Chronic hepatitis B or C is uncommon in our centre. In conclusion, the prevalence of abnormal liver enzymes late after HSCT in our centre is lower than reported in previous studies. Abnormal liver enzymes occur more often in children who are older at HSCT and transplanted for benign haematological disease. Long-term follow-up is crucial to establish if elevated liver enzymes precede clinical liver disease.

M. Bouwknecht, B. Engel, M. M. P. T. Herremans, M. A. Widdowson, H. C. Worm, M. P. G. Koopmans, K. Frankena, A. M. De Roda Husman, M. C. M. De Jong and W. H. M. Van Der Poel.

Bayesian estimation of hepatitis E virus seroprevalence for populations with different exposure levels to swine in The Netherlands. *Epidemiology & Infection*. 2008; 136(4):567-76
Hepatitis E virus (HEV) is ubiquitous in pigs worldwide and may be zoonotic. Previous HEV seroprevalence estimates for groups of people working with swine were higher than for control groups. However, discordance among results of anti-HEV assays means that true seroprevalence estimates, i.e. seroprevalence due to previous exposure to HEV, depends on choice of seroassay. We tested blood samples from three subpopulations (49 swine veterinarians, 153 non-swine veterinarians and 644 randomly selected individuals from the general population) with one IgM and two IgG ELISAs, and subsets with IgG and/or IgM Western blots. A Bayesian stochastic model was used to combine results of all assays. The model accounted for imperfection of each assay by estimating sensitivity and specificity, and accounted for dependence between serological assays. As expected, discordance among assay results occurred. Applying the model yielded seroprevalence estimates of approximately 11% for swine veterinarians, approximately 6% for non-swine veterinarians and approximately 2% for the general population. By combining the results of five serological assays in a Bayesian stochastic model we confirmed that exposure to swine or their environment was associated with elevated HEV seroprevalence.

M. Bouwknecht, K. Frankena, S. A. Rutjes, G. J. Wellenberg, A. Husman, W. H. M. van der Poel and M. C. M. de Jong. Estimation of hepatitis E virus transmission among pigs due to contact-exposure.

Veterinary Research. 2008; 39(5):
Locally acquired hepatitis E in humans from industrialized countries has been repeatedly suggested to originate from pigs. Pigs may serve as a reservoir of hepatitis E virus (HEV) for humans when a typical infected pig causes on average more than one newly infected pig, a property that is expressed by the basic reproduction ratio R_0 . In this study, R_0 for HEV transmission among pigs was estimated from chains of one-to-one transmission experiments in two blocks of five chains each. Per chain, susceptible first-generation contact pigs were contact-exposed to intravenously inoculated pigs, subsequently susceptible second-generation contact pigs were contact-exposed to infected first-generation contact pigs, and lastly, susceptible third-generation contact pigs were contact-exposed to infected second-generation contact pigs. Thus, in the second and third link of the chain, HEV-transmission due to contact with a contact-infected pig was observed. Transmission of HEV was monitored by reverse transcriptase polymerase chain reaction (RT-PCR) on individual faecal samples taken every two/three days. For susceptible pigs, the average period between exposure to an infectious pig and HEV excretion was six days (standard deviation: 4). The length of HEV-excretion (i.e. infectious period) was estimated at 49 days (95% confidence interval (CI): 17-141) for block 1 and 13 days (95% CI: 11-17) for block 2. The R_0 for contact-exposure was estimated to be 8.8 (95% CI: 4-19), showing the potential of HEV to cause epidemics in populations of pigs.

K. Borgen, T. Herremans, E. Duizer, H. Vennema, S. Rutjes, A. Bosman, A. M. de Roda Husman and M. Koopmans. Non-travel related Hepatitis E virus genotype 3 infections in the Netherlands; a case series 2004 - 2006. *BMC Infectious Diseases*. 2008; 8:61

BACKGROUND: Human hepatitis E virus (HEV) infections are considered an emerging disease in industrialized countries. In the Netherlands, Hepatitis E virus (HEV) infections have been associated with travel to high-endemic countries. Non-travel related HEV of genotype 3 has been diagnosed occasionally since 2000. A high homology of HEV from humans and pigs suggests zoonotic transmission but direct molecular and epidemiological links have yet to be established. We conducted a descriptive case series to generate hypotheses about possible risk factors for non-travel related HEV infections and to map the genetic diversity of HEV. METHODS: A case was defined as a person with HEV infection laboratory confirmed (positive HEV RT-PCR and/or HEV IgM) after 1 January 2004, without travel to a high-endemic

country three months prior to onset of illness. For virus identification 148 bp of ORF2 was sequenced and compared with HEV from humans and pigs. We interviewed cases face to face using a structured questionnaire and collected information on clinical and medical history, food preferences, animal and water contact. RESULTS: We interviewed 19 cases; 17 were male, median age 50 years (25-84 y), 12 lived in the North-East of the Netherlands and 11 had preexisting disease. Most common symptoms were dark urine (n = 16) and icterus (n = 15). Sixteen ate pork \geq once/week and six owned dogs. Two cases had received blood transfusions in the incubation period. Seventeen cases were viremic (genotype 3 HEV), two had identical HEV sequences but no identified relation. For one case, HEV with identical sequence was identified from serum and surface water nearby his home. CONCLUSION: The results show that the modes of transmission of genotype-3 HEV infections in the Netherlands remains to be resolved and that host susceptibility may play an important role in development of disease.

H. J. Boot, J. Cremer, F. D. Koedijk, W. M. van Ballegooijen and E. L. Op de Coul. Improved tracing of hepatitis B virus transmission chains by phylogenetic analysis based on C region sequences. *J Med Virol.* 2008; 80(2):233-41

An effective vaccine is available for the hepatitis B virus (HBV), which is a very contagious human pathogen. The prevalence of chronic HBV infection is very low in the Netherlands (<0.5%), and no universal vaccination is in place. Instead, a program of vaccination for targeted groups at high risk of HBV exposure has been implemented. Because transmission of HBV can occur by various routes, the effectiveness of this targeted vaccination strategy is difficult to assess. Molecular typing data for the surface protein encoding gene of HBV isolates, in combination with epidemiological data, provide some insight into the main transmission routes. Due to the low mutation rate of the HBV genome, many isolates have identical S region sequences, which hampers phylogenetic analysis and identification of transmission chains. The molecular epidemiological analysis of acute HBV isolates based on the surface and core protein encoding regions were compared. The nucleotide diversity found in the C region was statistically significant greater (1.5 times) than in the S region, and phylogenetic analysis based on the C region showed a higher resolution. C region analysis resulted in an almost 50% reduction of genotype A isolates with identical sequences. C region analysis also indicated that no long-chain transmission of genotype D strains is occurring in the Netherlands, as all genotype D isolates have unique C region sequences. Defining the goals of molecular typing of HBV isolates should precede the choice for phylogenetic analysis on the basis of either C or S region sequences.

P. W. M. Bergervoet, N. van Riessen, F. W. Sebens and W. C. van der Zwet. Application of the forensic luminol for blood in infection control. *Journal of Hospital Infection.* 2008; 68(4):329-333
Transmission of hepatitis C virus occurs frequently in haemodialysis units. A possible route of transmission is indirectly via the hospital environment although this has never been recorded. We investigated the haemodialysis unit in Deventer Hospital., Deventer, The Netherlands, with the forensic Luminol test. With this test, invisible traces of blood can be visualised based on the principle of biochemiluminescence. We demonstrated extensive contamination of the environment with traces of blood. The aim of this article is to introduce this method to infection control professionals, so it can be used to monitor cleaning and disinfection procedures, and alert healthcare workers to the possibility of contamination of the hospital. environment with blood. (c) 2008 The Hospital Infection Society. Published by Elsevier Ltd. All rights reserved.

J. Zuckerman, J. van Hattum, M. Cafferkey, I. Gjørup, T. Hoel, M. L. Rummukainen and O. Weiland. Should hepatitis B vaccination be introduced into childhood immunisation programmes in northern Europe? *Lancet Infectious Diseases.* 2007; 7(6):410-419

Infection with hepatitis B causes between 500 000 and 1 center dot 2 million deaths per year worldwide, and is the leading cause of liver cancer. Over 12 years ago, WHO recommended that universal childhood hepatitis B vaccination be implemented globally. Despite this, Denmark, Finland, Iceland, Ireland, the Netherlands Norway, Sweden, and the UK have yet to implement such a policy and instead currently adopt an "at-risk" strategy. Although all eight countries are classed as having low endemicity, factors such as increased travel and integration of immigrant communities are increasing the number of at-risk individuals in these countries. Considering the difficulty in identifying all at-risk individuals, and the lack of effectiveness of at-risk vaccination on reducing the overall incidence of hepatitis B, we recommend that

these countries reassess their hepatitis B prevention strategies. Universal vaccination against hepatitis B is the only way to eliminate the major public-health impact of this disease.

Q. Waldhober, M. L. A. Heijnen, E. A. Croes, B. J. F. Boon, C. Hoebe and S. Hahne. Evidence-based changes in hepatitis B risk group vaccination policy in the Netherlands. *European Journal of Public Health*. 2007; 17:212-212

I. K. Veldhuijzen, M. C. Mostert, H. G. M. Niesters, J. H. Richardus and R. A. de Man. Accuracy of a referral guideline for patients with chronic hepatitis B in primary care to select patients eligible for evaluation by a specialist. *Gut*. 2007; 56(7):1027-1028

R. van Houdt, G. J. B. Sonder, N. Dukers, L. Bovee, A. van den Hoek, R. A. Coutinho and S. M. Bruisten. Impact of a targeted hepatitis B vaccination program in Amsterdam, The Netherlands. *Vaccine*. 2007; 25(14):2698-2705

To evaluate hepatitis B virus (HBV) risk group vaccination in Amsterdam, which started in 1998, we examined 342 reported acute HBV-cases and sequenced 85 DNA isolates. The reported number of cases declined from 214 in 1992-1997 to 128 in 1998-2003, due to a decline in injecting drug users (IDU) and their heterosexual partners. Phylogenetic analyses showed that after 1998, the IDU cluster nearly disappeared, probably due to a decline in injecting. Acute HBV remained stable among men having sex with men; given their increased sexual risk behavior, vaccination has probably prevented an increase in their acute infections. Currently, 48-72% of the people who should be included in the program are still susceptible to HBV. (c) 2006 Elsevier Ltd. All rights reserved.

R. van Houdt, S. M. Bruisten, F. D. Koedijk, N. H. Dukers, E. L. Op de Coul, M. C. Mostert, H. G. Niesters, J. H. Richardus, R. A. de Man, G. J. van Doornum, J. A. van den Hoek, R. A. Coutinho, M. J. van de Laar and H. J. Boot. Molecular epidemiology of acute hepatitis B in the Netherlands in 2004: nationwide survey. *J Med Virol*. 2007; 79(7):895-901

To gain insight into hepatitis B virus (HBV) transmission in the Netherlands, epidemiological data and sera were collected from reported cases of acute HBV infections in the Netherlands in 2004. Cases were classified according to mode of transmission. A fragment of the S-gene of HBV (648 bp) was amplified, sequenced, and subjected to phylogenetic analysis. Of the 291 acute HBV cases reported in 2004, 158 (54%) were available for genotyping. Phylogenetic analysis identified 6 genotypes: A (64%), B (3%), C (3%), D (21%), E (5%) and F (5%). Of HBV infected men having sex with men, 86% were infected with genotype A, accounting for 43% of all patients infected with this genotype. There were only three reported cases of injecting drug use of which one was available for sequencing (genotype A). Unlike the genotype A cluster, sequences within the genotype B-E clusters were heterogenic. Within genotype F, several isolates had identical sequences, but patients could not be epidemiologically linked. Sexual transmission, particularly by men having sex with men was the most important transmission route for HBV. Injecting drug use plays a minor role. Genotype A is predominant in the Netherlands, especially among men having sex with men. In addition to imported strains, there seems to be a pool of related but non-identical strains circulating among chronic carriers in the migrant population, from which occasionally new patients are infected, primarily by heterosexual transmission.

S. M. van der Plas, B. E. Hansen, J. B. de Boer, T. Stijnen, J. Passchier, R. A. de Man and S. W. Schalm. Generic and disease-specific health related quality of life of liver patients with various aetiologies: A survey. *Quality of Life Research*. 2007; 16(3):375-388

Most studies on health related quality of life (HRQoL) of chronic liver patients were done in small clinical populations or restricted to one aetiology or disease stage. There is still a need for a study in a large liver patient population with various aetiologies and disease stages, approaching a population-based study. We evaluated the impact of liver disease aetiology on generic HRQoL, disease-specific HRQoL and fatigue and we compared HRQoL and fatigue between aetiological groups and healthy Dutch controls. Members of the Dutch liver patient association completed the Liver Disease Symptom Index, Short Form-36, and Multidimensional Fatigue Index-20. We compared the HRQoL between patients with viral hepatitis, autoimmune hepatitis, cholestatic diseases, hemochromatosis and other liver diseases by linear, ordinal and logistic regression, corrected for disease stage and other significant factors. Viral hepatitis patients showed a worse mental health than other aetiological groups. Hemochromatosis

patients demonstrated 17% more bodily pain than viral hepatitis patients and the strongest decrease in role emotional health with increasing age. Aetiological groups showed a worse generic HRQoL and more fatigue than controls. In conclusion, viral hepatitis and hemochromatosis patients have a more impaired HRQoL than patients of other liver disease aetiological groups.

C. Van den Berg, C. Smit, G. Van Brussel, R. Coutinho and M. Prins. Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users. *Addiction*. 2007; 102(9):1454-1462

Objatives To investigate the impact of harm-reduction programmes on HIV and hepatitis C virus (HCV) incidence among ever-injecting drug users (DU) from the Amsterdam Cohort Studies (ACS). **Methods** The association between use of harm reduction and seroconversion for human immunodeficiency virus (HIV) and/or hepatitis C virus (HCV) was evaluated using Poisson regression. A total of 714 DU were at risk for HIV and/or HCV during follow-up. Harm reduction was measured by combining its two most important components-methadone dose and needle exchange programme (NEP) use-and looking at five categories of participation, ranging from no participation (no methadone in the past 6 months, injecting drug use in the past 6 months and no use of NEP) to full participation (≥ 60 mg methadone/day and no current injecting or ≥ 60 mg methadone/day and current injecting but all needles exchanged). **Results** Methadone dose or NEP use alone were not associated significantly with HIV or HCV seroconversion. However, with combination of these variables and after correction for possibly confounding variables, we found that full participation in a harm reduction programme (HRP) was associated with a lower risk of HIV and HCV infection in ever-injecting drug users (DU), compared to no participation [incidence rate ratio 0.43 (95% CI 0.21-0.87) and 0.36 (95% CI 0.13-1.03), respectively]. **Conclusions** In conclusion, we found that full participation in HRP was associated with a lower incidence of HCV and HIV infection in ever-injecting DU, indicating that combined prevention measures-but not the use of NEP or methadone alone-might contribute to the reduction of the spread of these infections.

C. van den Berg, C. Smit, M. Bakker, R. B. Geskus, B. Berkhout, S. Jurriaans, R. A. Coutinho, K. C. Wolthers and M. Prins. Major decline of hepatitis C virus incidence rate over two decades in a cohort of drug users. *European Journal of Epidemiology*. 2007; 22(3):183-193

Injecting drug users (DU) are at high risk for hepatitis C virus (HCV) and HIV infections. To examine the prevalence and incidence of these infections over a 20-year period (1985-2005), the authors evaluated 1276 DU from the Amsterdam Cohort Studies who had been tested prospectively for HIV infection and retrospectively for HCV infection. To compare HCV and HIV incidences, a smooth trend was assumed for both curves over calendar time. Risk factors for HCV seroconversion were determined using Poisson regression. Among ever-injecting DU, the prevalence of HCV antibodies was 84.5% at study entry, and 30.9% were co-infected with HIV. Their yearly HCV incidence dropped from 27.5/100 person years (PY) in the 1980s to 2/100 PY in recent years. In multivariate analyses, ever-injecting DU who currently injected and borrowed needles were at increased risk of HCV seroconversion (incidence rate ratio 29.9, 95% CI 12.6, 70.9) compared to ever-injecting DU who did not currently inject. The risk of HCV seroconversion decreased over calendar time. The HCV incidence in ever-injecting DU was on average 4.4 times the HIV incidence, a pattern seen over the entire study period. The simultaneous decline of both HCV and HIV incidence probably results from reduced risk behavior at the population level.

T. J. W. van de Laar, A. K. van der Bij, M. Prins, S. M. Bruisten, K. Brinkman, T. A. Ruys, J. T. M. van der Meer, H. J. C. de Vries, J. W. Mulder, M. van Agtmael, S. Jurriaans, K. C. Wolthers and R. A. Coutinho. Increase in HCV incidence among men who have sex with men in Amsterdam most likely caused by sexual transmission. *Journal of Infectious Diseases*. 2007; 196(2):230-238

We retrospectively screened 1836 men who have sex with men (MSM) participating in the Amsterdam Cohort Studies (1984 - 2003) for hepatitis C virus (HCV) antibodies. HCV incidence was 0.18/100 person-years (PY) in human immunodeficiency virus (HIV) - positive MSM (8/4408 PY [95% confidence interval {CI}, 0.08 - 0.36]) but was 0/100 PY in MSM without HIV (0/7807 PY [95% CI, 0.00 - 0.05]). After 2000, HCV incidence among HIV- positive men increased 10-fold to 0.87/100 PY (5/572 PY [95% CI, 0.28 - 2.03]). Additional hospital cases (n=34) showed that MSM in Amsterdam who acquired HCV infection after 2000 reported high rates of ulcerative sexually transmitted infections (59%)

and rough sexual techniques (56%), denied injection drug use, and were infected mainly with the difficult-to- treat HCV genotypes 1 (56%) and 4 (36%). Phylogenetic analysis showed 3 monophyletic clusters of MSM- specific HCV strains. The emergence of an MSM- specific transmission network suggests that HIV- positive MSM with high- risk sexual behaviors are at risk for sexually acquired HCV. Targeted prevention and routine HCV screening among HIV- positive MSM is needed to deter the spread of HCV.

G. Tjon, M. Xiridou, R. Coutinho and S. Bruisten. Different transmission patterns of hepatitis A virus for two main risk groups as evidenced by molecular cluster analysis. *Journal of Medical Virology*. 2007; 79(5):488-494

Men who have sex with men and traveling children are the most important risk groups for transmission of hepatitis A virus (HAV) in Amsterdam, The Netherlands. Between these two risk groups, different HAV genotypes are found. In this study the patterns of introduction and transmission of HAV were investigated in the two groups. HAV sequences from Amsterdam patients were divided according to risk: (I) travelers and their contacts, (II) homosexual men and their contacts. The sequences in each risk group were then grouped into clusters based on the genetic distances between the sequences. Among travelers many sporadic cases were found, the clusters were small, and introduced frequently into the population, mostly in the second half of each calendar year, indicating a seasonal pattern of introduction and transmission after the summer holidays. Among men who have sex with men the clusters were bigger and remained present for a longer time; sporadic cases were few, and introduction of new strains occurred only occasionally but throughout the year. Our findings indicate that new HAV strains are frequently imported into Amsterdam by travelers, but they are limited in the extent and season of their spread. In contrast, HAV is only occasionally imported into the male homosexual and bisexual population, but remains endemic and spreads to a large number of individuals without a seasonal pattern.

J. W. C. Tervaert, P. van Paassen and J. Damoiseaux. Type II cryoglobulinemia is not associated with hepatitis C infection - The Dutch experience. *Autoimmunity, Pt C*. 2007; 1107(251-258)

Mixed cryoglobulinemia (MC) are cryoprecipitable immunocomplexes. In type II MC, a combination of polyclonal and monoclonal immunoglobulins is found, whereas in type III a combination of polyclonal immunoglobulins is detected. MC is usually associated with hepatitis C (HCV) infection as has been found in studies that have been performed in countries with a high prevalence of HCV. Because HCV has an extremely low prevalence in the Netherlands (<0.1% of the population), we wondered whether HCV is also associated with MC in our regional referral center. To answer this question, we tested consecutive patients with type II MC for HCV antibodies and for HCV-mRNA by polymerase chain reaction (PCR). Between January 2000 and June 2005, 22 patients tested positive for type II MC. Seven patients had essential MC, 2 patients had MC due to a lymphoproliferative disease, 10 patients had MC in the context of a systemic autoimmune disease, and 3 patients had MC without a clear diagnosis. HCV antibodies were not detected in any of the 22 patients. Also, all samples tested negative for HCV-mRNA. During follow-up none of these patients developed an HCV infection. In summary, the estimated occurrence of HCV in 60-90% of patients with MC is not found in our region where MC is only infrequently associated with HCV. In a substantial proportion of our patients a really "essential MC" is observed. A search for yet unknown etiological factors is clearly needed in these patients, who frequently have severe renal involvement warranting aggressive immunosuppressive therapy.

K. Stene Johansen, G. Tjon, E. Schreier, V. Bremer, S. Bruisten, S. L. Ngui, M. King, R. M. Pinto, L. Aragonés, A. Mazick, S. Corbet, L. Sundqvist, H. Blystad, H. Norder and K. Skaug. Molecular epidemiological studies show that hepatitis A virus is endemic among active homosexual men in Europe. *J Med Virol*. 2007; 79(4):356-65

Large outbreaks of hepatitis A have occurred in Denmark, Germany, the Netherlands, Norway, Spain, Sweden, and the United Kingdom during the period 1997-2005 affecting homosexual men. A collaborative study was undertaken between these countries to determine if the strains involved in these hepatitis A outbreaks were related genetically. The N-terminal region of VP1 and the VP1/P2A region of the strains were sequenced and compared. The majority of the strains found among homosexual men from the different European countries formed a closely related cluster, named MSM1, belonging to genotype IA. Different HAV strains circulated among other risk groups in these countries during the same period, indicating that specific strains were circulating among homosexual men exclusively. Similar strains found among homosexual men from 1997 to 2005 indicate that these HAV strains have been circulating

among homosexual men for a long time. The homosexual communities are probably too small within the individual countries to maintain HAV in their population over time, whereas the homosexual communities across Europe are probably sufficiently large to sustain continued circulation of homologous HAV strains for years resulting in an endemic situation among homosexual men. (c) 2007 Wiley-Liss, Inc.

S. A. Rutjes, W. J. Lodder, M. Bouwknegt and A. M. de Roda Husman. Increased hepatitis E virus prevalence on Dutch pig farms from 33 to 55% by using appropriate internal quality controls for RT-PCR. *Journal of Virological Methods*. 2007; 143(1):112-116

Pigs have been suggested to be a potential reservoir for locally acquired human hepatitis E virus (HEV) infections in the Netherlands. To study possible trends in HEV prevalence in the Dutch pig population, 97 pig farms have been screened for the presence of HEV in stools. The prevalence rate of HEV was estimated at 55% (53/97) in 2005, indicating a significant increase as compared to the prevalence rate of 22% (25/115) as was reported in 1999. The current data suggest that this increase is due to the inclusion of appropriate quality assurance controls such as internal amplification controls for RT-PCR. The abundant presence of pigs excreting HEV raises concerns on potential zoonotic transmission of the virus, either by exposure through the environment or by consumption of contaminated pork products. Moreover, one of the detected strains belonged to a European cluster which was not detected in the Netherlands before, suggesting that HEV strains spread through European countries. These data demonstrate the need to include appropriate controls in diagnostic assays, especially in complex matrices such as feces which are known to contain PCR inhibitory substances. (C) 2007 Elsevier B.V. All rights reserved.

W. Melenhorst, Y. L. L. Gu, W. J. M. Jaspers and A. H. Verhage. Locally acquired hepatitis E in the Netherlands: Associated with the consumption of raw pig meat? *Scandinavian Journal of Infectious Diseases*. 2007; 39(5):454-456

We here present 2 patients who developed hepatitis E, without having been abroad or in contact with anyone who did, indicating locally acquired hepatitis E. We point out that the consumption of raw pig meat could be of relevance in HEV-associated hepatitis in the Netherlands.

T. Marschall, M. Kretzschmar and S. Schalm. High impact of migration on the prevalence of chronic hepatitis B in the Netherlands. *European Journal of Public Health*. 2007; 17:64-64

A. Kok, F. R. Zuure, C. J. Weegink, R. A. Coutinho and M. Prins. Hepatitis C in Nederland: schaarse gegevens over actuele prevalentie en de noodzaak van epidemiologisch onderzoek en innovatieve opsporingsmethoden. [Hepatitis C in the Netherlands: sparse data on the current prevalence and the necessity for epidemiological studies and innovative methods for detecting infected individuals]. *Ned Tijdschr Geneeskd*. 2007; 151(43):2367-71

Hepatitis C is a blood-borne virus infection with an estimated 180 million infected individuals worldwide. Hepatitis C virus (HCV) infection may lead to liver failure and cancer of the liver. In 2004, in view of the improved treatment options, the Dutch Health Council again recommended that the groups at risk of HCV infection should be tracked down and informed, and that epidemiological studies should be conducted. Currently, there are few data on the prevalence of HCV infection in the Netherlands. HCV risk groups are (former) injecting drug users, haemodialysis patients and haemophiliacs, people treated with blood or blood products before 1992, people who have undergone certain invasive or medical procedures with insufficiently sterilised instruments, household contacts and partners of HCV-infected individuals and children born to HCV-infected mothers. Insight into the epidemiology of HCV infection in the Netherlands is necessary so that reliable estimates of the magnitude of hepatitis C as a public health problem can be made. Several projects for the detection of HCV infected individuals and epidemiological studies have started in 2007.

F. D. Koedijk, E. L. op de Coul, H. J. Boot and M. J. van de Laar. Surveillance van hepatitis B in Nederland, 2002-2005: acute infectie vooral via seksueel contact, chronische via verticale transmissie door moeders uit endemische gebieden. [Hepatitis B surveillance in the Netherlands, 2002-2005: acute infection is mainly via sexual contact while chronic infection is via vertical transmission through mothers from endemic regions]. *Ned Tijdschr Geneeskd*. 2007; 151(43):2389-94

OBJECTIVE: To study the trends in the prevalence of hepatitis B infections in the Netherlands on the basis of reported cases. DESIGN: Retrospective, descriptive. METHOD: Analysis of data collected from

the obligatory notification of hepatitis B to the Dutch Public Health Services in the Netherlands in the period 2002-2005. RESULTS: In the period from January 2002 to December 2005, 7352 hepatitis B virus (HBV) infections were reported, of which 1168 (16%) were acute and 5849 (80%) were chronic infections. Of the acute HBV infections, 34% were transmitted by homo- or bisexual contact and 25% by heterosexual contact. The number of reports of acute HBV infection due to heterosexual transmission increased significantly and originated relatively more often in Dutch patients. The number of reports of chronic HBV infection in men increased significantly; in women there was a decrease over time. Of the chronic HBV infections, 40% were transmitted from mother to child; this was reported especially often by patients from HBV endemic areas. CONCLUSION: Sexual contact was the most important risk factor for the transmission of acute HBV infections, whereas vertical transmission was the greatest risk factor by far for chronic HBV infection. Transmission via heterosexual contact had become increasingly important in the transmission of acute HBV; transmission by homo- or bisexual contact remained constant. Immigration continued to play an important role in the epidemiology of HBV in the Netherlands; the majority of the chronic carriers had been born and infected in an HBV endemic area.

M. Herremans, H. Vennema, J. Bakker, B. van der Veer, E. Duizer, C. A. Benne, K. Waar, B. Hendrixks, P. Schneeberger, G. Blaauw, M. Kooiman and M. P. Koopmans. Swine-like hepatitis E viruses are a cause of unexplained hepatitis in the Netherlands. *J Viral Hepat.* 2007; 14(2):140-6

Hepatitis E virus (HEV) infections in developed countries are recognized as an imported disease related to travel to endemic regions. However, increasing evidence suggests that HEV infection may also occur in the developed countries and that swine may act as a possible reservoir. To investigate the indigenous transmission of HEV in the Netherlands, sera from 50 blood donors and 1027 sera from patients with acute hepatitis were screened with an ELISA for HEV-specific IgG and IgM. Because the Netherlands is considered a nonendemic region, all positive ELISA results were confirmed by immunoblot to exclude false-positive results. Evidence of recent HEV infection was detected in 0% of the blood donors and 4.4% of the cases, based on combined positive IgM and IgG responses. The serodiagnosis was confirmed by a positive polymerase chain reaction (PCR) in 24 patients with hepatitis (2.3% overall, 51% of confirmed IgM+/IgG+ cases). IgG antibodies alone were detected in 4.2% of patients. We found related sequences to virus strains detected in Dutch pigs (genotype 3, 91-97% homology) in 89% of PCR-confirmed HEV patients. The detection of unique swine-like HEV sequences in 16 indigenous hepatitis patients without a recent travel history suggests that HEV is endemic in the Netherlands. We recommend including HEV tests in unexplained acute hepatitis patients, despite their travel history.

M. Herremans, E. Duizer, E. Jusic and M. P. G. Koopmans. Detection of hepatitis E virus-specific immunoglobulin A in patients infected with hepatitis E virus genotype 1 or 3. *Clinical and Vaccine Immunology.* 2007; 14(3):276-280

Currently, diagnosis of acute hepatitis E virus (HEV) in patients is primarily based on anti-HEV immunoglobulin M (IgM) detection. However, several investigations suggest the use of HEV-specific IgA for diagnosing acute HEV infections. We evaluated two commercially available assays, an IgA enzyme-linked immunosorbent assay (ELISA) (Diacheck) and an adapted immunoblot protocol (Mikrogen) for IgA detection and compared the performance in genotype 1- and 3-infected patients. The specificity of the IgA assays was high, with no positive reactions in a control group of 18 acute hepatitis patients who were negative for HEV. The sensitivity calculated in nine PCR-positive type 1-infected patients was 100% in both assays but was clearly lower in genotype 3-infected patients (n = 14), with sensitivities of only 67% and 57% for the ELISA and immunoblot assay, respectively. The lower IgA responses detected in genotype 3-infected patients could be caused by the use of only the genotype 1 and 2 antigens in the serological assays. Interestingly in two patients with possible infection through blood transfusion no response or intermediate IgA responses were detected, and this might confirm the parenteral route of transmission. In both the type 1- and type 3-infected patients both the IgA and IgM responses disappeared simultaneously. We conclude that IgA detection is of limited value for the serodiagnosis of acute HEV cases, particularly with genotype 3.

M. Herremans, J. Bakker, E. Duizer, H. Vennema and M. P. G. Koopmans. Use of serological assays for diagnosis of hepatitis E virus genotype 1 and 3 infections in a setting of low endemicity. *Clinical and Vaccine Immunology.* 2007; 14(5):562-568

Because of the occurrence of genotype 3 hepatitis E virus (HEV) in regions of low endemicity, it is

important to validate the currently used serological assays for diagnosing infections with viruses belonging to this lineage, since these assays only use antigens derived from genotype 1 and 2 viruses. We evaluated the Genelabs enzyme-linked immunosorbent assay (ELISA) and the RecomBlot from Mikrogen for the detection of HEV-specific immunoglobulin M (IgM) and IgG under conditions of low endemicity. We compared test results of 16 patients with locally acquired genotype 3 HEV, 8 genotype 1 patients, 167 healthy controls from the general population, and 101 cases with hepatitis due to other viral causes. The measured specificities of the ELISA (98%) and the RecomBlot (97%) were comparable to those given by the manufacturer for IgM but were significantly lower for IgG (93% by ELISA and 66% by immunoblotting, versus reported values of 98% for ELISA and 95% for blotting). Antibody levels detected following infections with genotype 3 were lower than those following genotype 1 infections except for those measured in the IgM ELISA. Reactivity to the four antigens used in the immunoblot assay were analyzed and showed differences in the IgM immunoblot reactions between genotype 1 patients and genotype 3 patients. The ORF3 antigen was the most specific antigen. The specificity could be improved by a combined testing regimen with confirmation by immunoblotting of all positive ELISA results and by raising the cutoff of the IgG immunoblot assay without loss of sensitivity. We conclude that a combination of ELISA and immunoblotting is needed for acceptable specificity and sensitivity of HEV assays under conditions of low endemicity.

R. A. de Man. Hepatitis B en C: gezien de behandel mogelijkheden voorrang geven aan het bereiken van risicogroepen. [Hepatitis B and C: in view of the treatment options, priority should be given to reaching the groups at risk]. *Ned Tijdschr Geneesk.* 2007; 151(43):2365-6

There are now effective treatments for both hepatitis B and C. For hepatitis B, a highly effective vaccine is available that is in common use in the Netherlands for the prevention of infection in the children of HBsAg-positive mothers. In the Dutch policy regarding viral hepatitis, a key role is given to contact with the groups at risk. The problem with this is that an individual must first acknowledge, on the basis of the information that is available and known to him or her, that he or she is at risk before becoming eligible for the next step, such as vaccination or a screening study. Immigration, sexual transmission and trips to endemic areas are important factors in the dissemination of hepatitis B in the Netherlands. For a vaccination policy that is based on the approach to groups at risk, the challenge is to achieve at least 80% coverage of the relevant groups, such as travellers and homosexual men. The situation is comparable for hepatitis C: a hepatitis that progresses slowly in the course of 20-30 years but is still asymptomatic at the beginning can be completely cured, provided that drug treatment is started on time. The challenge here is again to reach the highly varied groups at risk. Specifically for hepatitis C, a major campaign, supported by the Dutch Health Council, was started in 2007.

S. M. Bruisten, G. M. Tjon, J. A. van den Hoek, C. J. Wijkmans, H. M. Gotz and R. A. Coutinho.

Moleculaire epidemiologie van hepatitis A in Nederland; het nut van het typeren van geïsoleerde virusstammen. [The molecular epidemiology of hepatitis A in The Netherlands; the usefulness of typing isolated viral strains]. *Ned Tijdschr Geneesk.* 2007; 151(50):2779-86

OBJECTIVE: To investigate the epidemiological links between several outbreaks of hepatitis A in The Netherlands (2001-2004). DESIGN: Descriptive. METHOD: Blood samples taken in connection with reports of hepatitis A to municipal health centres from 2001-2004, were typed by determining the nucleotide sequence of the VP3-VP1 and the VP1-P2A regions of the genome of the hepatitis A virus (HAV). Genetic distances were represented graphically by means of a phylogenetic tree. RESULTS: The study into the spread of various subtypes of HAV showed a clear link between the HAV-(sub)genotype and risk of transmission: in men that have sex with men only genotype 1A occurred, in travellers to African countries genotype 1B was predominantly seen. CONCLUSION: A database containing various viral strains from people with hepatitis A in The Netherlands could, if kept up to date, be used as an aid in confirming the classical way of tracing sources as well as for the evaluation of preventative measures.

M. Bouwknegt, F. Lodder Verschoor, W. H. van der Poel, S. A. Rutjes and A. M. de Roda Husman. Hepatitis E virus RNA in commercial porcine livers in The Netherlands. *J Food Prot.* 2007; 70(12):2889-95

Human hepatitis E virus (HEV) infections by genotype 3 strains in industrialized countries are hypothesized to be caused by pigs. To examine this hypothesis, the potential health risks of transmission

routes should be examined. Possible foodborne transmission was studied by quantifying the presence and infectivity of HEV in commercial porcine livers in The Netherlands. A comparison of four tissue disruption and seven RNA extraction methods revealed that mechanical disruption followed by silica-based RNA extraction gave the highest RNA yields and was therefore employed on commercial porcine livers. Four (6.5%) of 62 porcine livers were HEV RNA positive by reverse transcriptase PCR and Southern blot hybridization. Each positive liver was estimated to contain approximately 65 PCR-detectable units per g. Sequences were obtained for three of four positive livers and classified as HEV genotype 3. Ninety-three percent similarity to Dutch human HEV sequences and 97% similarity to Dutch swine HEV sequences were observed. To determine whether positive livers contained infectious HEV particles, extracts from livers with known HEV RNA sequences were inoculated intravenously in pigs. Two control pigs were included: one was inoculated with a high dose known to result in infection (10(4) PCR-detectable units of HEV RNA), and the other was inoculated with a lower concentration of virus that equaled the concentration of PCR-detectable units in commercial livers (approximately 20 PCR-detectable units). Infection was observed in the high-dose control, but not in other pigs, suggesting a dose-dependent response in pigs. Hence, the implications of HEV RNA in commercial porcine livers in The Netherlands are unknown. However, HEV RNA is present in commercial porcine livers, and sufficient heating of porcine livers before consumption as precautionary measure is recommended.

B. A. Borkent-Raven, M. P. Janssen, A. De Wit, F. D. Koedijk, B. A. Van Hout and C. L. Van der Poel. Costs and effects of HBV-NAT screening in the Netherlands. *Transfusion*. 2007; 47:266A-266A

G. G. G. Baaten, G. J. B. Sonder, N. Dukers, R. A. Coutinho and J. A. R. Van den Hoek. Population-based study on the seroprevalence of hepatitis A, B, and C virus infection in Amsterdam, 2004. *Journal of Medical Virology*. 2007; 79:1802-1810

In order to enhance screening and preventive strategies, this study investigated the seroprevalence of hepatitis A, B, and C in the general adult urban population and in subgroups. In 2004, sera from 1,364 adult residents of Amsterdam were tested for viral markers. Sociodemographic characteristics were collected using a standardized questionnaire. For hepatitis A, 57.0% was immune. Of first-generation immigrants from Turkey and Morocco, 100% was immune. Of all Western persons and second-generation non-Western immigrants, approximately half was still susceptible. For hepatitis B, 9.9% had antibodies to hepatitis B core antigen (anti-HBc) and 0.4% had hepatitis B surface antigen. Anti-HBc sero-prevalences were highest among first-generation immigrants from Surinam, Morocco, and Turkey, and correlated with age at the time of immigration, and among men with a sexual preference for men. Seroprevalence among second-generation immigrants was comparable to Western persons. The seroprevalence of hepatitis C virus antibodies was 0.6%. In conclusion, a country with overall low endemicity for viral hepatitis can show higher endemicity in urban regions, indicating the need for differentiated regional studies and prevention strategies. More prevention efforts in cities like Amsterdam are warranted, particularly for hepatitis A and B among second-generation immigrants, for hepatitis B among men with a sexual preference for men, and for hepatitis C. Active case finding strategies are needed for both hepatitis B and C.

M. J. Vries, B. T. Rijdt and C. M. J. Van Nieuwkerk. Genotype distribution amongst hepatitis C patients in the Netherlands. *Netherlands Journal of Medicine*. 2006; 64(4):109-113

Background: The prevalence of the genotypes of the hepatitis C virus (HCV) differs according to geographical location. In the United States and in European countries, the majority of patients are infected with genotype 1, 2 or 3. There is a lack of data on the distribution of HCV genotypes in the Netherlands. Methods: The current survey determined the distribution of HCV genotypes amongst recently genotyped patients seen by physicians treating hepatitis C in the Netherlands. Results: Almost half of the 351 patients (49.3%) were infected with genotype 1. Genotype 3 was the second most dominant genotype with a prevalence of 29.3%. Genotypes 2 and 4 were found in 9.7 and 10.5% of the patients, respectively. For 61.5% of the patients (n=216), the subtype was available. For genotype 1 the prevalence of subtype 1a and 1b was very similar, while for genotype 3 a large majority of patients were infected with subtype 3a. Conclusion: This survey gives the first estimation of the distribution of HCV genotypes amongst unselected HCV patients in the Netherlands.

D. Vos, H. M. Gotz and J. H. Richardus. Needlestick injury and accidental exposure to blood: The need

for improving the hepatitis B vaccination grade among health care workers outside the hospital. *American Journal of Infection Control*. 2006; 34(9):610-612

To describe the characteristics of needlestick injuries occurring to health care workers outside the hospital, a new case report form was implemented and analyzed after 12 months. A total of 144 incidents were reported. Of the needlestick injuries in nursing assistants, 84% involved an insulin needle or pen. Thirty-five percent of all health care workers and 47% of the nursing assistants were not vaccinated against hepatitis B. Hepatitis B vaccination grade in health care workers outside the hospital should be improved, in particular among nursing assistants.

P. T. L. van Wijk, M. Pelk-Jongen, C. Wijkmans, A. Voss and P. M. Schneeberger. Quality control for handling of accidental blood exposures. *Journal of Hospital Infection*. 2006; 63(3):268-274

A regional counselling service was established to handle all accidental blood exposures using a standardized protocol. Levels of risk were assessed using an algorithm. Accidents that posed a risk for the transmission of hepatitis B (HBV), hepatitis C (HCV) and human immunodeficiency virus (HIV) were classified as 'high risk', whereas accidents that posed a risk for HBV alone were classified as 'low risk'. Medical interventions were implemented according to the level of risk. During a one-year period, all accidents were registered and analysed for adherence to the standard protocol. In 2003, the centre handled 454 incidents. Of these, 36 (7.9%) incidents were assessed as no risk, 329 (72.5%) were assessed as low risk, and 67 (14.8%) were assessed as high risk. Due to incomplete registration, 22 (4.8%) incidents could not be analysed further. In total, 36% of the incidents with risk for HBV transmission and 40% of the incidents with risk for HCV and HIV transmission were not handled according to the proposed protocol. Breaches consisted of over-reaction (25/396) as well as insufficient response (123/396). Potentially inadequate treatment occurred for HIV postexposure prophylaxis in 12 of 63 incidents. Incomplete follow-up for HCV occurred in 11 of 63 incidents, and lack of HBV immunoglobulin administration occurred in five of 396 incidents, including three high-risk incidents. In 21 of 396 low-risk exposures, the breaches in protocol resulted from late reporting. It remains difficult to achieve an acceptable level of standardized care when using standard operational procedures. Documentation and evaluation of flaws are essential to improve the system.

P. T. L. van Wijk, M. Pelk-Jongen, E. de Boer, A. Voss, C. Wijkmans and P. M. Schneeberger.

Differences between hospital- and community-acquired blood exposure incidents revealed by a regional expert counseling center. *Infection*. 2006; 34(1):17-21

Objective: One year (2003) regional analysis of all blood exposure incidents from hospitals as well as from the community. Design: Establishment of an easily accessible regional expert counseling center, operating 24 h a day, for all accidental blood exposures. Tasks of the center were to register incoming calls, to inform and counsel the victim, to assess the risk of the incident, and to provide a plan of further actions, including prophylactic measures. Setting: A Dutch region (Northeast Brabant) with 500,000 inhabitants and two major hospitals (1,786 beds). Results: A total of 454 incidents (1.2 per day) were recorded. Only half of the incidents occurred in the hospital setting (n = 234), whereas the others (n = 220) took place in the community setting. Nearly all (95%, n = 432) incidents occurred during work, and most of them (84%, n = 385) were related to health care activities. In the hospital setting injuries occurred with physicians (13%), nursing staff (45%), operating room (OR) staff (13%), ancillary (18%), others (10%). In the community setting, incidents took place among healthcare workers (48%), detention and police officers (10%), civilians (10%), general practitioners/dentists and their staff (8%), cleaning staff (4%) and work-related incidents not fitting into any of the above categories (7%). More low risk incidents took place outside the hospital (87% vs. 68% in hospital), while high-risk incidents predominantly occurred within the hospital setting (23% vs. 6%). The hepatitis-B immunization rate was significantly lower in victims from the community than in those working in hospitals (38% vs. 96%). Reports from incidents in the community setting were delayed. Conclusions: Incidents that expose individuals to blood-borne pathogens occur equally frequent in the hospital and non-hospital (community) setting. Therefore, a regional expert counseling center, accessible around-the-clock, for all types of blood-exposure incidents is needed. Blood-exposure prevention programs should aim at a reduction of high-risk incidents within hospitals, and at increasing the awareness for vaccination and early reporting within the community setting.

H. Van Soest, G. J. Boland and K. J. Van Erpecum. Hepatitis C: changing genotype distribution with

important implications for patient management. *Netherlands Journal of Medicine*. 2006; 64(4):96-99
In the Netherlands an estimated 0.1 to 0.4% of the population are chronic hepatitis C (HCV) carriers (15,000 to 60,000 persons). HCV is characterised by genetic heterogeneity and six different genotypes have been identified. The distribution of HCV genotypes is relevant for the clinician, since there are important genotype-specific differences in response to interferon-alpha based treatment regimens. Between 1993 and 2005 a shift was observed in the Netherlands from a dominant prevalence of genotype I to a situation in which genotype non-I is becoming more important.

R. Van Houdt, G. J. Sonder, N. Dukers, L. Bovee, J. A. R. Van den Hoek, R. A. Coutinho and S. M. Bruisten. Evaluation of the hepatitis B vaccination program targeted towards high-risk groups in Amsterdam, the Netherlands. *Journal of Clinical Virology*. 2006; 36:S198-S198

E. M. van der Snoek, J. B. F. de Wit, H. M. Gotz, P. G. H. Mulder, M. H. A. Neumann and W. I. van der Meijden. Incidence of sexually transmitted diseases and HIV infection in men who have sex with men related to knowledge, perceived susceptibility, and perceived severity of sexually transmitted diseases and HIV infection: Dutch MSM-cohort study. *Sexually Transmitted Diseases*. 2006; 33(3):193-198
Background: This longitudinal study was conducted to investigate whether knowledge, perceived susceptibility, and perceived severity of HIV infection and sexually transmitted diseases (STDs) are associated with the incidence of STDs and new HIV infections among men who have sex with men (MSM). Methods: A 3-year cohort study was conducted among 190 HIV-negative MSM. Data were collected on the incidence of STDs and new HIV infections, as well as on knowledge and perceived susceptibility to and perceived severity of HIV infection and STDs. Knowledge and perceptions were assessed in self-administered questionnaires. Results: In the course of the 3-year study, six MSM (3.2%) HIV-seroconverted and 78 (41.1%) participants were diagnosed with at least one STD. MSM seemed to be better informed about HIV infection compared with STDs, and HIV infection was perceived as more severe than other STDs. In multivariable analyses, low perceived severity of HIV infection significantly ($P = 0.025$) predicted increased likelihood of infection with STDs or HIV, and the practice of anal intercourse was (marginally) associated with an increased risk of acquiring STDs or HIV ($P = 0.052$). Conclusions: A high perceived severity of HIV infection seems to induce sexual behavior that protects against STDs and HIV infection. More research is needed to establish the specific behaviors by which perceived severity of STDs/HIV influences the incidence of STDs and HIV.

A. K. van der Bij, R. A. Coutinho and C. L. van der Poel. Surveillance of risk profiles among new and repeat blood donors with transfusion-transmissible infections from 1995 through 2003 in the Netherlands. *Transfusion*. 2006; 46(10):1729-1736

To evaluate the effectiveness of blood donor selection, this study reports risk profiles of donors with transfusion-transmissible infections as obtained by ongoing surveillance, 1995 through 2003, in the Netherlands. A surveillance program was installed to monitor risk profiles among new and repeat donors infected with human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV), or human T-lymphotropic virus (HTLV), or positive for the presence of syphilis antibodies. At posttest counseling, a physician interviewed donors to clarify possible sources of infection. A total of 167 repeat donors and 404 new donors were interviewed: 33 with HIV, 123 with HCV, 279 with HBV, 21 with HTLV, and 112 with syphilis antibodies. Most HBV, HCV, and HTLV infections were among new donors (80, 85, and 67%), whereas most HIV infections were among repeat donors (79%). Nearly 25 percent of the donors did not report factors at screening that would have deferred them from donating blood. At posttest interviews, new donors with HCV often reported injecting drug use (19%). Repeat donors with HIV often reported male-to-male sex (8/26, 31%). A significant level of deferrable behavioral risks was found among donors with confirmed transfusion-transmissible infections that persist despite current donor selection. Reporting such behavior at initial donor selection would have eliminated a substantial part of the infections found. This study argues against relaxing the existing donor deferral of persons practicing male-to-male sex, given their significant proportion of HIV infections among repeat donors. Systematic surveillance of risk factors among infected blood donors provides ongoing information about the effectivity of donor selection and is recommended to evaluate and optimize blood policies.

T. J. van de Laar, M. H. Koppelman, A. K. van der Bij, H. L. Zaaier, H. T. Cuijpers, C. L. van der Poel, R. A. Coutinho and S. M. Bruisten. Diversity and origin of hepatitis C virus infection among unpaid

blood donors in the Netherlands. *Transfusion*. 2006; 46(10):1719-28

BACKGROUND: To improve transfusion policy and to increase understanding of the spread of hepatitis C virus (HCV) in the general population, HCV infections among voluntary Dutch blood donors were examined with molecular epidemiologic techniques. **STUDY DESIGN AND METHODS:** During 6 years, 1997 through 2002, confirmed anti-HCV-positive donors were interviewed on HCV-associated risk behavior with a standardized questionnaire. Additionally, HCV isolates were genotyped, partially sequenced, and compared to sequences obtained from Dutch injecting drug users (IDUs). **RESULTS:** HCV prevalence and incidence rates among Dutch donors were extremely low; the residual risk of transmitting HCV was calculated to be 1 in 30 million donations. Former IDUs (21%), transfusion recipients (30%), and immigrants (>12%) were identified as major HCV risk groups. Cryptogenic transmission caused 18 percent of infections among new donors and all infections among repeat donors. Compared to IDUs, genotype distribution among donors was highly diverse; major subtypes were 3a (27%), 1a (24%), 1b (24%), 2a/b (10%), and 4 (9%). Half of the donors were infected with IDU-related subtypes 1a and 3a, whereas subtype 1b mainly spread via blood transfusion and various other nosocomial modes of transmission in the past. HCV infections acquired in endemic countries could be clearly identified based on genotype. **CONCLUSION:** Different modes of transmission are linked to infections with certain HCV subtypes, suggesting separate HCV epidemics, but spillover between different risk groups underlines the value of molecular epidemiologic techniques to gain insight into the origin and dynamics of HCV infections on a population level.

G. J. B. Sonder, L. Bovee, T. D. Baayen, R. A. Coutinho and J. A. R. van den Hoek. Effectiveness of a hepatitis A vaccination program for migrant children in Amsterdam, The Netherlands (1992-2004). *Vaccine*. 2006; 24(23):4962-4968

Objective: To evaluate the impact and effectiveness of risk-group vaccination against hepatitis A targeted at migrant children living in a country with low endemicity of hepatitis A. **Methods:** Retrospective population based data analysis. Routinely collected data on hepatitis A incidence in migrant children and other risk groups in Amsterdam from 1 January 1992 to 2004 were analyzed and related to exposure, immunity and vaccination coverage in migrant children. **Results:** The overall hepatitis A incidence in Amsterdam declined after a pediatric vaccine was introduced in 1997. This decline was seen in migrant children traveling to hepatitis A-endemic countries, contacts with hepatitis A patients, primary school students, injecting drug users, and persons with unknown source of infection, but not in men who have sex with men (MSM) or in travelers to endemic countries other than migrant children. **Conclusion:** The hepatitis A vaccination campaigns are effective: they reduce both import and secondary HAV cases. The campaigns could be more efficient and cost-effective if the hepatitis B vaccinations currently given to these groups were replaced by a combined hepatitis A and B vaccine. This would increase the hepatitis A vaccination coverage considerably and further reduce the hepatitis A incidence. (c) 2006 Elsevier Ltd. All rights reserved.

S. Rutjes, T. Schreuder, H. Reesink, P. L. Jansen, W. Lodder, F. Lodder-Verschoor, H. van den Berg, M. Bouwknecht, E. Duizer and A. M. D. Husman. HEV genotype 3 reservoirs in the Netherlands. *Hepatology*. 2006; 44(4):674A-675A

K. Lindenburg, C. Weegink, J. Schinkel, P. Jansen, M. Beld, A. Krol, G. Casteelen, G. van Santen, R. Coutinho and M. Prins. Hepatitis C screening and treatment among drug users in Amsterdam: Interim results of the inclusion procedure in the Dutch C project. *Hepatology*. 2006; 44(4):329A-329A

C. E. A. Lindenburg, A. Krol, C. Smit, M. C. A. Buster, R. A. Coutinho and M. Prins. Decline in HIV incidence and injecting, but not in sexual risk behaviour, seen in drug users in Amsterdam: a 19-year prospective cohort study. *Aids*. 2006; 20(13):1771-1775

Objective: To study temporal changes in HIV incidence, HIV transmission routes, and both injecting and sexual risk behaviour in the open Amsterdam Cohort Study (ACS) among drug users. Initiated in 1985, the ACS enables us to study changes in trends since HAART became widespread in 1996. **Methods:** Person-time techniques were used to study the trend in HIV incidence among HIV-negative drug users. HIV transmission routes were determined using detailed standardised questionnaires. Trends in injecting and sexual risk behaviours were evaluated with a logistic regression model adjusted for correlations between visits of the same individual. **Results:** The 1315 HIV-negative individuals, of whom 93

seroconverted for HIV, yielded 6970 HIV-negative person-years of follow-up. The HIV incidence was seven per 100 person-years in 1986 and varied between 0 and 0.5 per 100 person-years after 1999. The odds ratio was 15.6 (95% confidence interval, 2.6-94.6) for HIV transmission through unprotected heterosexual contact versus injecting after 1996 compared with the period before. Reports of both injecting and borrowing needles significantly declined over the period 1985-2004. Reports of sexual risk behaviour and sexually transmitted infections at follow-up visits decreased before 1996, but not after 1996. Conclusion: The HIV incidence among drug users in the ACS has declined since 1985. Accompanied by a reduction in injecting drug use and needle sharing, this decline occurred despite continued sexual risk behaviour. At present, new HIV seroconversions are related mainly to unprotected heterosexual contacts. Therefore, HIV prevention programmes for drug users should pay specific attention to the importance of safe sex practices. (c) 2006 Lippincott Williams & Wilkins.

R. P. M. Koene, H. Gotz, J. A. R. Van den Hoek, M. L. A. Heijnen, J. A. Steenbergen and L. Kroes. Prevalence of isolated anti-hepatitis B core in risk groups participating in the hepatitis B vaccination campaign in The Netherlands. *European Journal of Public Health*. 2006; 16:30-30

F. D. H. Koedijk, R. Van Houdt, S. M. Bruisten, E. L. M. Op de Coul, N. Dukers, M. Mostert, H. G. M. Niesters, M. J. W. Van de Laar and H. J. Boot. Molecular epidemiology of hepatitis B in the Netherlands; A low endemic country with a selective vaccination program. *European Journal of Epidemiology*. 2006; 21:121-121

C. Y. Eger, E. J. Giltay and J. H. W. Maasen. No carriers of hepatitis C among operating room personnel in a university hospital setting in The Netherlands. *Journal of Hospital Infection*. 2006; 62(1):114-115

G. A. de Wit, M. Kretzschmar, M. J. J. Mangen and M. J. W. van de Laar. Is a catch-up hepatitis B vaccination campaign in Dutch high-risk adults cost-effective? *European Journal of Public Health*. 2006; 16:52-52

M. J. de Vries, B. te Rijdt and C. M. van Nieuwkerk. Genotype distribution amongst hepatitis C patients in The Netherlands. *Neth J Med*. 2006; 64(4):109-13

BACKGROUND: The prevalence of the genotypes of the hepatitis C virus (HCV) differs according to geographical location. In the United States and in European countries, the majority of patients are infected with genotype 1, 2 or 3. There is a lack of data on the distribution of HCV genotypes in The Netherlands. METHODS: The current survey determined the distribution of HCV genotypes amongst recently genotyped patients seen by physicians treating hepatitis C in The Netherlands. RESULTS: Almost half of the 351 patients (49.3%) were infected with genotype 1. Genotype 3 was the second most dominant genotype with a prevalence of 29.3%. Genotypes 2 and 4 were found in 9.7 and 10.5% of the patients, respectively. For 61.5% of the patients (n=216), the subtype was available. For genotype 1 the prevalence of subtype 1a and 1b was very similar, while for genotype 3 a large majority of patients were infected with subtype 3a. CONCLUSION: This survey gives the first estimation of the distribution of HCV genotypes amongst unselected HCV patients in The Netherlands.

K. Waar, M. Herremans, H. Vennema, M. P. G. Koopmans and C. A. Benne. Hepatitis E is a cause of unexplained hepatitis in The Netherlands. *Journal of Clinical Virology*. 2005; 33(2):145-149

Background: Hepatitis E virus (HEV) is the major etiologic agent of enterically transmitted viral hepatitis in much of the developing world. Evidence provided in recent years shows that HEV is also prevalent in very low numbers in non-endemic countries. Recently, a cluster of three patients with acute hepatitis E but no history of travel to endemic countries was discovered in the geographical area provided with service by the Public Health Laboratory Groningen and Drenthe, The Netherlands. Objective: This led to the question whether hepatitis E is a cause of unexplained hepatitis in this district. Study design: The prevalence of anti-HEV IgG and IgM among 209 patients with clinical signs of hepatitis, negative test for hepatitis A-C, no history of foreign travel and no other cause of hepatocellular damage was compared with a matched control group of 209 individuals. Results: We found a significant difference in seroprevalence between the two groups for IgG anti-HEV as determined with the Abbot HEV ETA (6.2% versus 0.5%); however this difference could not be confirmed with the Genelabs Diagnostics HEV IgG

ELISA (6.7% versus 3.8%). For confirmed cases of IgM anti-HEV we also detected a significant difference between the two groups (3.3% versus 0.5%). Remarkably, the combination of IgG and IgM anti-HEV was only found among hepatitis patients. Conclusion: This study provides evidence of locally acquired hepatitis E in The Netherlands. Therefore, in cases of unexplained acute hepatitis, the diagnosis of hepatitis E should be considered even in the absence of foreign travel. (C) 2004 Elsevier B.V. All rights reserved.

R. Verrando, G. Robaey, C. Mathei and F. Buntinx. Methadone and buprenorphine maintenance therapies for patients with hepatitis C virus infected after intravenous drug use. *Acta Gastro-Enterologica Belgica*. 2005; 68(1):81-85

Heroin addiction is a chronic relapsing disease that is difficult to cure, but stabilisation and harm reduction can importantly increase the life time expectancy and the quality of life of the patient, his immediate vicinity and society in general. Currently, no proven effective pharmacological interventions are available for cocaine addiction, and treatment has to rely on existing cognitive behaviour therapies combined with contingency management strategies. Substitution therapy, however, is effective in caring for heroin addicts. Methadone is a synthetic opioid that counteracts withdrawal symptoms of heroin. Buprenorphine is a derivative of the morphine alkaloid, thebaine, and is a partial opioid agonist at the μ opioid receptor in the nervous system. A substitution treatment program effectively reduces and often eliminates heroin injection behaviour, rendering patients more socially stabilised. Reduction in the number of viral co-infections can be observed. Methadone undergoes oxidative biotransformation in the liver, but is also stored in the liver and released into the blood in unchanged form. The usual dose can be continued in patients with stable chronic liver disease, including advanced cirrhosis. In acute liver disease or acute decompensation of chronic liver disease, close clinical observation for signs of narcotic overdose or withdrawal is necessary. A modest alteration in methadone dose may be appropriate for some patients. Buprenorphine can cause liver dysfunction after sublingual and even more after intravenous administration. It is advised to follow the liver function during buprenorphine treatment and to warn the clients for intravenous use of buprenorphine. Neither methadone nor buprenorphine do influence the effect of interferon and ribavirin during the treatment of chronic hepatitis C patients. It may be necessary to increase the dosage of methadone during interferon treatment.

I. K. Veldhuijzen, L. J. Smits and M. J. van de Laar. The importance of imported infections in maintaining hepatitis B in The Netherlands. *Epidemiol Infect*. 2005; 133(1):113-9

In The Netherlands, in May 1999 an enhanced surveillance of hepatitis B was begun to collect detailed information of patients with acute hepatitis B virus (HBV) infection. The objective was to gain insight in transmission routes and source of infection of new HBV cases. Through public health services, patients were interviewed on risk factors. It appeared that the majority (59%) acquired the infection through sexual contact; 52% of these by homosexual and 48% by heterosexual contact. In 60% of the heterosexual cases, the source of infection was a partner originating from a hepatitis B-endemic region. Sexual transmission is the most common route of transmission of acute hepatitis B in The Netherlands and introduction of infections from abroad plays a key role in the current epidemiology of HBV. As well as prevention programmes targeted at sexual high-risk groups, prevention efforts should focus more on the heterosexual transmission from HBV carriers.

R. van Houdt, S. M. Bruisten, N. Dukers, L. Bovee, J. A. R. van den Hoek and R. A. Coutinho. Changes in transmission patterns of hepatitis B over the last decade in Amsterdam. *Journal of Hepatology*. 2005; 42:152-152

A. K. Van der Bij, N. Kloosterboer, M. Prins, B. Boeser-Nunnink, R. B. Geskus, J. M. A. Lange, R. A. Coutinho and H. Schuitemaker. GB virus C coinfection and HIV-1 disease progression: The Amsterdam Cohort Study. *Journal of Infectious Diseases*. 2005; 191(5):678-685

Background. The effect that GB virus C (GBV-C) coinfection has on human immunodeficiency virus type 1 (HIV-1) disease progression is controversial and therefore was studied in 326 homosexual men from the prospective Amsterdam Cohort Studies who had an accurately estimated date of HIV-1 seroconversion and were followed up for a median period of 8 years. Methods. A first plasma sample, obtained shortly after HIV-1 seroconversion, and a last plasma sample, obtained before 1996, were tested for GBV-C RNA and envelope protein-2 antibodies. The effect that GBV-C has on HIV-1 disease

progression was studied by use of time-dependent Cox proportional-hazards models with adjustment for baseline variables and time-updated HIV-1 RNA and CD4(+) cell count. Results. Men who lost GBV-C RNA between collection of the first sample and collection of the last sample had a nearly 3-fold-higher risk of HIV-1 disease progression than did men who had never had GBV-C RNA. This effect became much smaller after adjustment for time-updated CD4(+) cell count. Conclusion. Rather than a positive effect of GBV-C RNA presence, a negative effect of GBV-C RNA loss on HIV-1 disease progression was found, which disappeared after adjustment for time-updated CD4(+) cell count. We therefore hypothesize that GBV-C RNA persistence depends on the presence of a sufficient number of CD4(+) cells- and that the CD4(+) cell decrease associated with HIV-1 disease progression is a cause, not a consequence, of GBV-C RNA loss.

T. J. W. van de Laar, M. W. Langendam, S. M. Bruisten, E. A. E. Welp, I. Verhaest, E. J. C. van Ameijden, R. A. Coutinho and M. Prins. Changes in risk behavior and dynamics of hepatitis C virus infections among young drug users in Amsterdam, the Netherlands. *Journal of Medical Virology*. 2005; 77(4):509-518

To elucidate the character and magnitude of the hepatitis C virus (HCV) epidemic among drug users in Amsterdam, 197 young drug users from the period 2000 to 2004 were compared with 215 counterparts from 1985 to 1989. Although injection risk behavior and HCV seroprevalence decreased sharply over time, HCV seroprevalence remains high (44%) among young drug users who have ever injected. Phylogenetic analysis shows that current HCV infections originate from diversification of strains already circulating in the past, but also from the recent introduction of new subtypes. HCV subtypes 1a and 3a remain the most prevalent among drug users in Amsterdam, but other subtypes such as 4d and 2b have entered the population. In conclusion, both the unpopularity of injecting drug use and the success of prevention campaigns are likely to be responsible for the decline in the seroprevalence of HCV and increased median time to seroconversion. Treatment of those infected chronically, in combination with the continuation of prevention programs, might decrease future HCV transmission.

G. M. Tjon, C. J. Wijkmans, R. A. Coutinho, A. G. Koek, J. A. van den Hoek, A. C. Leenders, P. M. Schneeberger and S. M. Bruisten. Molecular epidemiology of hepatitis A in Noord-Brabant, The Netherlands. *J Clin Virol*. 2005; 32(2):128-36

BACKGROUND: Previous studies on the molecular epidemiology of hepatitis A virus (HAV) in Amsterdam, The Netherlands, show that subgenotype 1A is mainly seen among homosexual men practising anonymous oral-anal sex in saunas and darkrooms, while subgenotype 1B is usually detected among children originating from Morocco, and subgenotype 3A is mostly found among travellers to Pakistan. OBJECTIVE: We studied the genotype distribution in a more rural area of The Netherlands, Noord-Brabant, and compared it with Amsterdam. STUDY DESIGN: We collected blood and feces samples from 34 HAV IgM(+) individuals who were reported from August 2001-March 2003 at the Municipal Health Service (MHS) Heart for Brabant (Brabant). We also collected feces samples from nine household contacts of whom the HAV IgM status was not known. HAV RNA was isolated and subsequently amplified by reverse transcriptase polymerase chain reaction (RT-PCR) at the VP1-P2a and the VP3-VP1 region, sequenced and analysed. RESULTS AND CONCLUSIONS: In most cases, relations between risk groups and HAV subgenotypes in Noord-Brabant were similar to those in Amsterdam. Next to genotypes 1 and 3 we also detected a genotype 2/7 strain in a Noord-Brabant case. Also, in contrast to the Amsterdam study, sporadic transmission occurred among various risk groups. Children involved in a school-related outbreak were infected with strains identical to one that was previously isolated from a man who has sex with men (MSM). Also, Dutch patients having no epidemiological link with Turkish or Moroccan children harboured strains imported from high-endemic countries. Furthermore, we report a special case in which HAV may be causally involved in meningitis. The results of this study show that the molecular epidemiology of HAV in The Netherlands can be more complicated than previously anticipated and that HAV phylogenetic studies can provide important information for the design of appropriate public health measures.

G. M. Tjon, H. Gotz, A. G. Koek, O. de Zwart, P. L. Mertens, R. A. Coutinho and S. M. Bruisten. An outbreak of hepatitis A among homeless drug users in Rotterdam, The Netherlands. *J Med Virol*. 2005; 77(3):360-6

From the end of January to mid-June 2004 (weeks 5-24) a hepatitis A virus (HAV) outbreak occurred

among a homeless and drug user community in Rotterdam, The Netherlands. To prevent further spread of the virus within this group and to the general population, the Municipal Health Service of Rotterdam organized a mass vaccination campaign during which 83% (1,515/1,800) of the homeless people were vaccinated. As part of a national HAV typing study, blood and/or fecal samples of 30 Rotterdam HAV IgM+ patients who fell ill during the period of 1 September 2003-1 December 2004 were tested. The tests included RT-PCR and sequencing at the VP3-VP1 and VP1-P2a regions of the HAV genome. It was found that 12 homeless people, one family member of a homeless person and two people without a known risk were infected with a unique subtype 3a strain. Four of the homeless patients became ill after vaccination and were probably infected at the time. This study shows that Dutch homeless people and drug users involved in HAV outbreaks should be offered HAV vaccine actively to prevent further spread of the infection. Furthermore, it was shown by molecular techniques that the unique subtype 3a strain was not found before the Rotterdam outbreak or afterwards, indicating that the mass vaccination campaign was successful.

G. J. B. Sonder, R. M. Regez, K. Brinkman, J. M. Prins, J. W. Mulder, J. Spaargaren, R. A. Coutinho and A. van den Hoek. Prophylaxis and follow-up after possible exposure to HIV, hepatitis B virus, and hepatitis C virus outside hospital: evaluation of policy 2000-3. *British Medical Journal*. 2005; 330(7495):825-829

Problem Prophylactic treatment and follow-up after exposure to HIV, hepatitis B, and hepatitis C outside hospital needs to be improved. Background and setting Until January 2000, people in Amsterdam could report exposure outside hospital to either a hospital or the municipal health service. If they reported to the municipal health service, they were then referred to hospitals for HIV prophylaxis, whereas the municipal health service handled treatment and follow-up related to hepatitis B and hepatitis C and traced sources. For cases reported to a hospital, hospital staff often did not trace HIV sources or follow up patients for hepatitis B and hepatitis C. Key measures for improvement Providing adequate treatment for HIV, hepatitis B and hepatitis C after exposure for all reported exposures outside hospital. Strategies for change On 1 January 2000, a new protocol was introduced in which three Amsterdam hospitals and the municipal health service collaborated in the treatment and follow-up of exposures outside hospital. Both municipal health service and hospitals can decide whether HIV prophylaxis is necessary and prescribe accordingly. All people exposed in the community who report to hospitals are subsequently referred to the municipal health service for further treatment and follow-up. Effects of change The protocol is effective in that most people comply with treatment and follow-up. When indicated, HIV prophylaxis is started soon after exposure. In nearly two thirds of cases the municipal health service traced and tested tire source. Lessons learnt Provision of treatment and follow-up in one place enables treatment, tracing and testing sources, and follow-up, including counselling and registration of all reported exposures in Amsterdam, which allows for swift identification of emerging epidemiological trends. Since May 2004 all Amsterdam hospitals have participated in the protocol.

G. J. B. Sonder, L. Bovee, R. A. Coutinho, D. Baayen, J. Spaargaren and A. van den Hoek. Occupational exposure to bloodborne viruses in the Amsterdam police force, 2000-2003. *American Journal of Preventive Medicine*. 2005; 28(2):169-174

Objectives: To assess and evaluate the rate and outcome of occupational exposure to hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) in the Amsterdam police force. Methods: Retrospectively, all accidents with risk for viral transmission reported to the Municipal Health Service between January 1, 2000 and December 31, 2003 were described and analyzed in 2004. Results: Over a 4-year period, 112 exposures with a viral transmission risk were reported (the estimated exposure rate was 68/10,000/year). Of these exposures, 89 (79%) sources were tested, finding 4% HBV-positive, 4% HIV-positive, and 18% HCV-positive. Immunoglobulin for HBV infection was given 44 times; HIV post-exposure prophylaxis was prescribed 16 times and 13 of 16 discontinued the course within a few days because the transmission source tested HIV-negative. No seroconversions were seen in persons exposed. Conclusions: The rate of exposure is low. The majority of the sources could be traced and tested. However, a comprehensive and effective protocol is essential in minimizing the risk of occupational HBV, HCV, and HIV infection in police officers, even if HBV vaccination is provided. (C) 2005 American journal of Preventive Medicine.

G. Robaey and F. Buntinx. Treatment of hepatitis C viral infections in substance abusers. *Acta Gastro-*

Enterologica Belgica. 2005; 68(1):55-67

Aims : To examine the evidence for excluding chronic hepatitis C (CHC) patients with substance abuse from treatment with interferon (IFN) and ribavirin. **Methods :** We reviewed clinical trials focussing on the treatment of chronic hepatitis C of patients with substance abuse between 2001 and 2004. Ten clinical trials concerning antiviral treatment in substance abusers were described of which six were controlled ones. There were no randomised trials. There was one controlled multi-centre trial. One trial used pegylated IFN. **Results :** In the total group of substance abusers the sustained viral response (SVR) and the adherence was not different from control groups. In former drug users, active drug users and patients taking substitution therapy for opioid dependence the sustained viral response and adherence was not different from control populations. However, non-substituted active drug users seemed more likely to be lost to follow-up. Discontinuation of treatment occurred most frequently during the first 8 weeks of therapy. Neurobehavioural changes leading to depression started in the first 8 weeks of treatment. Although follow-up periods after SVR were short, the currently described re-infection rate occurring in active intravenous drug users remains low. **Conclusions :** There is no evidence to withhold antiviral treatment against HCV in active substance abusers. It seems important to advise to start substitution therapy in non-substituted active drug users, increase substitution therapy dose in substituted patients and treat depression as early as possible. More prospective controlled trials on HCV treatment in active and difficult-to-reach substance users are needed.

D. Posthouwer, I. Plug, J. G. van der Bom, K. Fischer, F. R. Rosendaal and E. P. Mauser-Bunschoten. Hepatitis C infection among Dutch haemophilia patients: a nationwide cross-sectional study of prevalence and antiviral treatment. *Haemophilia*. 2005; 11(3):270-275

Hepatitis C is a major co-morbidity among patients with haemophilia who received inadequately or non-virus-inactivated clotting factor concentrates before 1992. The objectives of this study were to investigate the prevalence of hepatitis C and the use of antiviral therapies during the last decade among patients with haemophilia in the Netherlands. We performed a cross-sectional study and a questionnaire was sent to all 1519 patients known with haemophilia in the Netherlands between 2001 and 2002. The study population for the present study consisted of 771 patients who had received clotting factor products before 1992 of whom 638 reported their hepatitis C status. In total, 441 of the 638 (68%) patients ever had a positive test for hepatitis C virus (HCV); 344 patients (54%) had a current infection, and 97 (15%) had cleared the virus. Among 344 patients currently HCV infected, 111 (32%) had received treatment for hepatitis C, while 34% (33/97) of patients with an infection in the past had been treated for hepatitis C. In 2002 the prevalence of hepatitis C among patients with haemophilia who received clotting factor products before 1992 was 54%. The majority of patients with a current HCV infection had not been treated with antiviral therapy.

D. Posthouwer, I. Plug, J. G. van der Bom, K. Fischer, F. R. Rosendaal and E. P. Mauser-Bunschoten. Hepatitis C and health-related quality of life among patients with hemophilia.

Haematologica. 2005; 90(6):846-50

Hepatitis C has a negative effect on health-related quality of life (HRQoL). It is not clear whether hepatitis C affects HRQoL of patients with hemophilia. The objective of this study was to assess the effect of hepatitis C virus (HCV) infection on HRQoL in patients with hemophilia. A cross-sectional study was performed among all registered hemophilia patients in the Netherlands. HRQoL was determined by using the self-administered SF-36 questionnaire. Patients were eligible for the study if they completed the SF-36, had been treated with clotting factor products before 1992, and had reported their hepatitis C status. Data on the severity of hemophilia were obtained from the hemophilia treatment centers. The validity of the self-reported data on hepatitis C status was verified in a random sample of 92 (15%) patients; 92% reported their hepatitis C status correctly. Fifty-five percent (333/602) of the study population had a current HCV infection. All eight domains of the SF-36 were lower in patients with a current HCV infection than they were in patients who had never been infected with HCV. After adjustment for age, severity of hemophilia, human immunodeficiency virus (HIV) status, employment status, and joint limitations, hepatitis C infection was associated with a decrease of HRQoL on the domains of general health (difference 6.9 [95% confidence interval (C.I.) 2.7 to 11.2]) and vitality (3.8 [95% C.I. 0.1 to 7.7]). Hemophilia patients infected with HCV scored lower on the HRQoL domains of general health and vitality than hemophilia patients who had never been infected with HCV.

M. Mostert, R. de Man, G. van Doornum, B. Niesters, H. Gotz and J. H. Richardus. Additional value of genetic fingerprinting in source and contact tracing of hepatitis B virus infection in the community. *Hepatology*. 2005; 42(4):350A-350A

W. F. Leemans, H. L. Zaaijer and R. A. de Man. Lack of implementation of hepatitis B treatment guidelines: Why effective antiviral treatment does not reach the patient. *Hepatology*. 2005; 42(4):584A-585A

F. W. G. Leebeek, E. P. Mauser-Bunschoten, J. van der Meer, J. A. Willemse, S. Dutch Haemophilia Treaters and S. Netherlands Haemophilia. Hepatitis C in haemophilia patients in the Netherlands. *Lancet*. 2005; 366(9487):715-715

G. Laffan. Dutch government urged to inform public of blood mistakes. *Lancet*. 2005; 365(9478):2165-2165

The Dutch Health Ministry is facing growing pressure to contact people that may have contacted hepatitis C through blood transfusions during the 1980s. The Health Ministry avoided searching for potentially infected people due to the costs and relatively small gains. However, pressure for action is now mounting.

E. Hak, Y. Schonbeck, H. De Melker, G. A. Van Essen and E. A. M. Sanders. Negative attitude of highly educated parents and health care workers towards future vaccinations in the Dutch childhood vaccination program. *Vaccine*. 2005; 23(24):3103-3107

Background: It is unknown whether further expansion of the Dutch childhood vaccination program with other vaccines will be accepted and whom should be targeted in educational strategies. Aim: To determine attitudes of parents towards possible future vaccinations for their children and the behavioural determinants associated with a negative attitude. Design: Questionnaire study. Methods: Parents of children aged between 3 months and 5 years of day-care centres were asked to fill out a questionnaire. Determinants of a negative attitude to comply with possible future vaccinations against example diseases such as pneumonia or influenza, hepatitis B, TBC, smallpox and SARS were assessed using polytomous logistic regression analysis. Results: Of the 283 respondents, 123 (43%) reported a positive attitude towards all vaccinations, 129 (46%) reported to have a positive attitude to have their child vaccinated against some diseases and 31 (11%) had no intention to comply with any new vaccination. Determinants of a fully negative attitude were a high education of the parent (odds ratio [OR] 3.3, 95% confidence interval [95% CI]: 1.3-8.6), being a health care worker (OR 4.2, 95% CI: 1.4-12.6), absence of religion (OR 2.6, 95% CI: 1.0-6.7), perception of vaccine ineffectiveness (OR 6.9, 95% CI: 2.5-18.9) and the perception that vaccinations cause asthma or allergies (OR 82.4, 95% CI: 8.9-766.8). Conclusion: Modifiable determinants for a negative attitude to comply with new vaccinations are mainly based on lack of specific knowledge. These barriers to vaccinations might be overcome by improving health education in the vaccination program, especially when targeted at educated parents and health care workers. (c) 2005 Elsevier Ltd. All rights reserved.

H. M. Gotz, G. van Doornum, H. G. M. Niesters, J. G. den Hollander, H. B. Thio and O. de Zwart. A cluster of acute hepatitis C virus infection among men who have sex with men - result from contact tracing and public health implications. *Aids*. 2005; 19(9):969-974

Objective: An acute hepatitis C virus (HCV) infection in an HIV-positive man who had sex with men (MSM) was notified. In the period of his seroconversion he was also diagnosed with a rectal lymphogranuloma venereum (LGV) infection, and was part of a cluster of 15 LGV cases in 2003. Our aim was to investigate HCV transmission and to search for potential spread among sexual contacts and known LGV patients. Methods: Our case series included the index, two recent contacts, and 14 LGV cases. They were interviewed about parenteral exposure for HCV, history of sexually transmitted diseases (STDs), sexual behaviour and drug use. Laboratory investigations included anti-HCV antibodies, HCV-polymerase chain reaction, and HCV genotyping. Results: Seven out of 17 MSM recently seroconverted for HCV (41%). Three genotypes were found. Parenteral risk factors were excluded. Six out of seven had LGV proctitis coinciding with HCV seroconversion, six (86%) were HIV infected. Unprotected anal contact was practised by both HCV uninfected and infected cases. Unprotected active and passive fisting was reported by all seven HCV infected men, compared with two of nine uninfected

men ($P = 0.003$). Non-intravenous drug use during sexual activities was common among all MSM. Numerous, often anonymous, sexual contacts in various European countries were reported. Conclusions: A cluster of acute HCV infection is reported among mostly HIV-positive MSM, with multiple partners throughout Europe. Sexual techniques potentially leading to mucosal damage (fisting), concomitant STDs such as LGV and drug use seem facilitating factors for spread. Extensive case finding and partner tracing is advocated as well as targeted prevention messages. (c) 2005 Lippincott Williams & Wilkins.

J. B. F. de Wit, R. Vet, M. Schutten and J. van Steenbergen. Social-cognitive determinants of vaccination behavior against hepatitis B: an assessment among men who have sex with men. *Preventive Medicine*. 2005; 40(6):795-802

Background. Many individuals who are at risk for infection with the hepatitis B virus (HBV), including men who have sex with men (MSM), are not vaccinated. This study assessed social-cognitive determinants of obtaining vaccination against HBV Methods. A targeted survey was conducted among 432 MSM by means of a written questionnaire that contained assessments of social-cognitive determinants of vaccination behavior derived from the Health Belief Model (HBM) and the Theory of Planned Behavior. Vaccination behavior was anonymously linked to questionnaire data for which informed consent was obtained. Results. Of the 290 men eligible for vaccination, 248 (86%) had obtained vaccination. Multivariate logistic regression analysis showed that these men were younger, more often were in a steady relationship, and had fewer sex partners. In addition, significant effects were also found for central factors proposed by the Health Belief Model. Notably, men who obtained vaccination against HBV perceived more personal threat from HBV None of the Theory of Planned Behavior variables were related to obtaining vaccination. Conclusions. Findings suggest that health education interventions that address perceived susceptibility and severity are likely to contribute to increased uptake of HBV vaccination among MSM. Influencing perceived susceptibility in particular is important, more so than increasing perceived severity by scare tactics. © 2004 Elsevier Inc. All rights reserved.

T. J. W. de Laar, M. Koppelman, H. L. Zaaijer, A. K. Van der Bij, H. T. Cuijpers, C. L. Van der Poel, R. A. Coutinho and S. M. Bruisten. Diversity and origin of hepatitis C virus (HCV) among voluntary Dutch blood donors. *Journal of Hepatology*. 2005; 42:168-169

J. E. Arends, C. A. Boucher and A. I. Hoepelman. Hepatitis C virus and human immunodeficiency virus coinfection: where do we stand? *Neth J Med*. 2005; 63(5):156-63

Both human immunodeficiency virus (HIV) and hepatitis C (HCV) are globally infecting millions of people. Since these viruses are both transmitted through blood-blood contact the rate of coinfection is as high as 30% and among i.v. drug users in the Western world 70%. In The Netherlands, 8% of HCV-infected patients are coinfecting with HIV. After the successful introduction of antiretroviral therapy (HAART) the survival of patients with HIV has increased considerably. Coinfection leads to accelerated progression of liver cirrhosis and liver failure but conflicting evidence exists about the effect of HCV on the natural course of HIV. Four randomised controlled trials have shown that treatment with pegylated interferon plus ribavirin leads to an overall sustained viral response (SVR) rate between 27 and 44%. Divided by genotype the SVR is between 14 and 38% in genotype 1 (and 4) while between 53 and 73% for genotype 2 and 3. These percentages are calculated based on an intention-to-treat analysis. Although lower than in HCV-monoinfected patients this is much higher than achieved with conventional interferon. However, coinfecting patients with genotypes 2 and 3 also need to be treated for 48 weeks in contrast to monoinfected patients. As the number and severity of side effects is low, coinfecting patients now have a substantially better option for treatment.

J. E. van Steenbergen, G. Tjon, A. van den Hoek, A. Koek, R. A. Coutinho and S. M. Bruisten. Two years' prospective collection of molecular and epidemiological data shows limited spread of hepatitis A virus outside risk groups in Amsterdam, 2000-2002. *Journal of Infectious Diseases*. 2004; 189(3):471-482 We performed a viral sequencing study on samples representing all reported primary cases of acute hepatitis A virus (HAV) infection reported for 2 years in Amsterdam. Two regions of HAV RNA were amplified, sequenced, and used for phylogenetic analysis. Of 156 cases, strains of 104 isolates (66.6%) clustered into 3 genotypes: 1A, 1B, and 3. Two separate transmission circles occurred, without mutual interrelation. In genotype 1A, 4 clusters occurred in men having sex with men (MSM), and the fifth cluster was related to a virus from Morocco. In genotype 1B, 6 small clusters were directly related to the

Moroccan virus. In genotype 3, strains were related to a virus from Pakistan. Our analysis indicates that, to stop transmission of HAV in Amsterdam, the entire MSM population and travelers to countries where HAV is endemic, especially children, should be vaccinated. Prevention strategies need not include the vaccination of all children living in Amsterdam.

J. E. van Steenbergen, D. Baayen, P. G. H. Peerbooms, R. A. Coutinho and A. van den Hoek. Much gained by integrating contact tracing and vaccination in the hepatitis B antenatal screening program in Amsterdam, 1992-1999. *Journal of Hepatology*. 2004; 40(6):979-985

Background/Aims: Hepatitis B control in Europe concentrates on antenatal screening to reduce vertical transmission. To reduce horizontal transmission and the pool of infectious individuals, the Municipal Health Service of Amsterdam integrated tracing and immunising of contacts in the antenatal screening program. Methods: An eight year (1992-1999) descriptive study of this public health program, where contacts are tested for serological markers of previous infection, and vaccination is offered to susceptible contacts. Chronically infected contacts are counselled and referred for treatment if justified. Results: For 738 newly identified women testing positive for the hepatitis B surface antigen, 1219 contacts were reported; 1100 (90.4%) contacts participated, 476 (43%) had serological markers of previous infection, of whom 119 (25%) were infectious. Of 603 eligible contacts, 568 (94%) completed the vaccination series. Country of origin was an independent predictor of contact participation and compliance with completion of the vaccination series. Postvaccination titres for antibodies against the surface antigen were below 10 IU/L in 4.5% of contacts under 30, in 12.2% of those over 30. Conclusions: Tracing and immunising susceptible contacts of women screened as HBsAg-positive, should be an integral component of any country's HBV control program. (C) 2004 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

G. J. B. Sonder, J. E. van Steenbergen, L. Bovee, P. G. H. Peerbooms, R. A. Coutinho and A. van den Hoek. Hepatitis A virus immunity and seroconversion among contacts of acute hepatitis A patients in Amsterdam, 1996-2000: An evaluation of current prevention policy. *American Journal of Public Health*. 2004; 94(9):1620-1626

Objectives. We evaluated the hepatitis A virus (HAV) control policy (hygienic precautions and passive immunization with immune globulin) for "household contacts" (defined as all people who lived in the same house and who shared the same toilet with the patient, people who took care of an HAV-infected child, and sexual partners of the patient) of acute hepatitis A patients between 1996 and 2000. Methods. We examined the characteristics and the serological outcomes of household contacts. All susceptible contacts were invited for retesting 6 weeks after they received immune globulin. Results. Of 1242 contacts of 569 HAV patients, more than 50% (n=672) were found to be HAV immune. Among the remaining contacts, 161 (28.2%) had a concurrent infection, and 86 of these individuals were symptomatic. The remaining 409 susceptible contacts received immune globulin, with 186 (45%) returning for retesting 6 weeks later (64 [34%] were infected, but only 12 had symptoms). Conclusions. Immune globulin does not protect all household contacts from HAV infection; however, it attenuates symptoms and effectively reduces further HAV transmission.

M. C. Smit, M. H. Haverkamp, A. J. Weersink, C. A. Boucher and I. M. Hoepelman. Patienten met een coinfectie van HIV en hepatitis-B-virus (HBV): gunstig effect van lamivudine, als onderdeel van antiretrovirale combinatiebehandeling, op HBV mogelijk afhankelijk van het CD4-celaantal. [Patients co-infected with HIV and hepatitis-B virus (HBV): the favourable effect of lamivudine, as part of combined antiretroviral therapy, on HBV may be dependent upon the number of CD4-cells]. *Ned Tijdschr Geneeskd*. 2004; 148(47):2330-4

OBJECTIVE: To determine the effect of lamivudine on HBV co-infection in HIV-infected patients. DESIGN: Retrospective METHOD: The HBsAg status and the use of lamivudine were determined retrospectively in a cohort of 800 HIV-infected patients under treatment at the Infectious Diseases outpatient clinic of the University Medical Centre in Utrecht, The Netherlands. In the group of HBsAg-positive patients using lamivudine 150 mg twice daily as part of highly active antiretroviral therapy (HAART), the HBV-DNA was measured quantitatively in the remaining plasma. In addition, the HBsAg, HBeAg, activity of alanineaminotransferase (ALAT) and CD4-count were obtained from the patient records. RESULTS: The study identified 29 (3.6%) HIV-infected patients to be HBsAg-positive. Plasma samples of 14 of these 29 patients were positive for HBV-DNA before the start of the therapy. Ten of

these 14 patients had CD4 counts of at least 200×10^6 cells/l, while four patients had less than 200×10^6 cells/l. In contrast to the group with less than 200×10^6 cells/l, a significant decrease in HBV-DNA load was seen after six months of therapy in the patients with at least 200×10^6 CD4-cells/l (t-test for repeated measurements; $p = 0.001$). The difference between the two groups in the effect of lamivudine was statistically significant ($p = 0.021$). At final evaluation after a mean follow-up of 32 and 13 months, respectively, HBV-DNA could no longer be detected in 7 patients; ALAT normalised in 9 patients (64%).
CONCLUSION: In this retrospective study, lamivudine was effective in the therapy of HIV-infected patients with a HBV co-infection. The decrease in the amount of circulating HBV was associated with the number of CD4 cells.

T. A. Ruys, J. G. den Hollander, M. G. Beld, M. E. van der Ende and J. T. van der Meer. Seksuele overdracht van hepatitis C bij homoseksuele mannen. [Sexual transmission of hepatitis C in homosexual men]. *Ned Tijdschr Geneeskd.* 2004; 148(47):2309-12

An acute hepatitis C infection was diagnosed in three HIV-positive gay men, aged 43, 48 and 30 years, respectively. In all three, unprotected sexual intercourse and fisting was a universal risk factor for the infection. They all denied having used drugs intravenously, which is the most common risk factor. The third man had a documented proctitis (lymphogranuloma venereum) at the time when the HCV transmission must have taken place. No serious complications occurred during the acute HCV infection. Because the infection did not resolve spontaneously after a few months, all three men were treated with pegylated interferon and ribavirin. Recently, the number of cases of acute HCV infection has been seen to increase in The Netherlands. This may be due primarily to an increase in unprotected sexual intercourse and fisting. This hypothesis is supported by a documented increased prevalence of sexually transmissible diseases among gay men in The Netherlands. As acute infections may turn into chronic infections, treatment of an acute infection should be considered in order to prevent the chronic disease.

J. H. Richardus, D. Vos, I. K. Veldhuijzen and J. Groen. Seroprevalence of hepatitis A virus antibodies in Turkish and Moroccan children in Rotterdam. *Journal of Medical Virology.* 2004; 72(2):197-202

Seasonal fluctuations in hepatitis A have been observed in the Netherlands related to Turkish and Moroccan children after visiting their home countries. This study determined the prevalence and associated factors of hepatitis A virus (HAV) antibodies in Turkish and Moroccan children in Rotterdam. A random sample was taken of children in Rotterdam, aged 5-16 years, of Turkish and Moroccan origin, together with a random sample of native Dutch children aged 5-7 and 14-16 years. Blood was collected by finger prick on filter paper. IgG and IgM anti-HAV was detected by an enzyme-linked immunoassay (EIA). The 319 Turkish, 329 Moroccan, and 248 native Dutch children participated in the study. In Turkish children, IgG anti-HAV increased from 2.2% to 22.2% over the age groups. In Moroccan children, IgG anti-HAV increased from 10.2% to 57.7%. In native Dutch children, 0.8% had IgG anti-HAV in the youngest and 3.1% in the oldest age group. The percentage IgG-positive also having IgM anti-HAV was 21% in Turkish, and 41% in Moroccan children. No IgG-positive native Dutch children had IgM anti-HAV. The prevalence of IgG anti-HAV was associated with increased age, being Moroccan, longer stay in the country of origin before migrating to the Netherlands, and known contact to HAV. The majority of Turkish and Moroccan children aged 4-16 years in Rotterdam are not protected against HAV, but do have a high risk of becoming infected while visiting their native country. Active vaccination against HAV of these children is indicated, with as primary aim their own protection. Prevention of HAV-transmission in the general community should be seen as a secondary benefit. In addition, possible Dutch contacts of nonvaccinated Turkish and Moroccan children, such as day care workers and teachers, should also be vaccinated against HAV. (C) 2004 Wiley-Liss, Inc.

H. W. Reesink, M. Koppelman, M. Sjerps and H. T. Cuijpers. Evaluation of a multiplex assay for HCV/HIV-1/HBV NAT screening in the Netherlands. *Transfusion.* 2004; 44(9):88A-88A

M. J. Postma, J. M. Bos, P. Beutels, H. Schilthuis and J. A. van den Hoek. Pharmaco-economic evaluation of targeted hepatitis A vaccination for children of ethnic minorities in Amsterdam (The Netherlands). *Vaccine.* 2004; 22(15-16):1862-7

OBJECTIVE: Estimate cost-effectiveness of vaccination against hepatitis A virus (HAV) for children of ethnic minorities in Amsterdam. **BACKGROUND:** Pharmaco-economic analysis is relevant for motivating reimbursement of vaccination costs in the framework of a programmatic approach to vaccination of ethnic

minorities. DESIGN: Pharmaco-economic modeling. METHOD: In cost-effectiveness analysis, costs, benefits and health gains were estimated for a large-scale HAV-vaccination for children of Turkish and Moroccan origin. Analysis was performed from the societal perspective, as recommended in the Dutch guidelines for pharmaco-economic research. This implies that indirect costs of production losses are included in the analysis. Cost-effectiveness was expressed in net costs per adult HAV-infection averted in incremental and aggregate analysis. Incremental analysis compares targeted vaccination with the current limited-scale HAV-vaccination that exists, whereas aggregate analysis compares targeted vaccination with the sheer absence of vaccination. RESULTS: Net aggregate costs of targeted HAV-vaccination for Turkish and Moroccan children in Amsterdam amounts to 61.000. Cost-effectiveness was estimated, in aggregate and incremental analysis, at 13.500 and 11.100 respectively per adult HAV-infection averted. Uni- and multivariate sensitivity analyses show that major impact on cost-effectiveness may be expected from reductions in the vaccine price through economies of scale. Probabilistic sensitivity analysis indicates possible large fluctuations in cost-effectiveness from 1 year to another, related to varying incidence of disease. CONCLUSION: HAV-vaccination for children from ethnic minorities in Amsterdam is not cost saving, but may have a favourable cost-effectiveness. Such a vaccination program fits into the recent Dutch policy of specific vaccinations directed at groups of ethnic minorities, such as for hepatitis B.

M. C. Mostert, J. H. Richardus and R. A. de Man. Referral of chronic hepatitis B patients from primary to specialist care: making a simple guideline work. *Journal of Hepatology*. 2004; 41(6):1026-1030
Background/Aims: To evaluate a guideline selecting patients at the primary care level for referral to a specialist, to identify bottlenecks and subsequently implement and evaluate improvements. Methods: Retrospective patient files analysis and a prospective cohort study. The study was conducted in Municipal Public Health Service (PHS), University Medical Center. Patients diagnosed with chronic hepatitis B virus (HBV) infection were referred to the PHS. Improvement of bottlenecks were identified in the referral chain, based on the guideline. Number of patients receiving correct advice, number of patients reaching the hospital for specialist care, time between notification of the PHS and final arrival in the hospital. Results: The guideline for the referral of chronic HBV patients appeared to be appropriate, although one-third of the selected patients was not seen by the specialist. After the intervention more HBV patients (76 versus 61 %) received correct advice from the PHS, and the number of HBV patients seen by the specialist increased by 18%. Conclusions: The referral guideline works, yet we could improve the efficiency of the guideline increasing the proportion of eligible patients reaching specialist care. In countries where mandatory reporting of HBV infections exists this guideline can be adapted to local health systems. (C) 2004 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

M. Koppelman and H. L. Zaaijer. Diversity and origin of hepatitis B virus in Dutch blood donors. *Journal of Medical Virology*. 2004; 73(1):29-32
Two considerations led us to study the genetic diversity and origin of hepatitis B virus (HBV) in Dutch blood donors. Firstly, an HBV-infected Dutch blood donor was found negative by four assays used commonly for detection of HBV surface antigen (HBsAg). How variable is HBsAg among HBV infected blood donors? Secondly, the WHO recommends universal vaccination against HBV, but north-west European countries limit vaccination to groups at risk of HBV. This policy may reduce hepatitis B among low-risk, unvaccinated persons if HBV strains that infect low-risk persons stem from local at-risk groups. Studying the nucleotide sequence of the S-gene of HBV from 63 Dutch blood donors, considerable variation was found. The majority of the donor strains (52/63, 83%) appears closely related to local HBV isolates as present in intravenous drug users, immigrants, and homosexual men. The remaining 11 (17%) HBV strains belong to various non-Western genotypes. This implies that an indigenous Dutch HBV strain (heterosexually transmitted, not associated with intravenous drug abuse, or immigrants) does not exist, and it supports the policy in low endemic countries to limit vaccination to at-risk groups. On the other hand, it must be realised that, after 20 years of vaccination of at-risk groups, HBV still circulates in the at-risk groups and Dutch blood donors acquire the HBV strains involved. (C) 2004 Wiley-Liss, Inc.

F. G. Cobelens, H. J. van Schothorst, P. M. Wertheim Van Dillen, R. J. Ligthelm, I. S. Paul Steenstra and P. P. van Thiel. Epidemiology of hepatitis B infection among expatriates in Nigeria. *Clin Infect Dis*. 2004; 38(3):370-6
Adult expatriates in countries where hepatitis B virus (HBV) is highly endemic have an increased risk of HBV infection, but little is known about risks to their children or about patterns of spread. The

epidemiology of HBV infection was studied among 124 unvaccinated Dutch missionaries and family members who lived in a rural area of Nigeria. Antibodies to hepatitis B core antigen were found in 5 (9.8%) of 51 adults (incidence rate, 1.7 per 1000 person-months at risk [PMAR]) and 9 (12.3%) of 73 children (incidence rate, 2.8 per 1000 PMAR). Vertical transmission of HBV was a likely source of infection in 1 child and was a possible source of infection in 2 others. The prevalence of HBV infection showed strong family clustering ($P < .0001$), was associated with a history of temporary adoption of Nigerian children ($P = .004$), and increased with both the number of adoptive children ($P = .009$) and the total time that these children had stayed in the family ($P = .036$). Horizontal transmission from adoptive Nigerian children probably played an important role in the spread of HBV infection in this expatriate community.

M. A. Widdowson, W. J. Jaspers, W. H. van der Poel, F. Verschoor, A. M. de Roda Husman, H. L. Winter, H. L. Zaaijer and M. Koopmans. Cluster of cases of acute hepatitis associated with hepatitis E virus infection acquired in the Netherlands. *Clin Infect Dis.* 2003; 36(1):29-33

Increasing evidence suggests that hepatitis E virus (HEV) infection may occur in developed countries and that swine may act as a reservoir. We report a cluster of 2 confirmed cases and 1 presumptive case of hepatitis associated with HEV. The typed strain from 1 case was related to HEV strains found in North America and Europe, and it was also related to a cluster of swine HEV strains found in The Netherlands. Our findings indicate that locally acquired HEV infections in industrialized countries may be overlooked. Routine testing for HEV infection in patients with acute hepatitis in The Netherlands should be considered before a diagnosis of autoimmune hepatitis is reached and steroid therapy is initiated.

S. Chaves, M. A. Widdowson and A. Bosman. Surveillance of HCV infection in the Netherlands. *Euro Surveill.* 2003; 8(5):108-13

Two surveillance systems exist in the Netherlands to monitor hepatitis C (HCV) infections. Aggregated weekly laboratory data have been available since 1990. In 1999, HCV infection became a notifiable disease. Data showed the number of reported cases has remained stable. Male cases predominated (66%), mainly between age 15 to 54. Injecting drug use was the main route of transmission (64%). Despite its added value, the notifiable system should include more clinical data to better scrutinize future changes in transmission patterns.

E. Buster, A. A. van der Eijk and S. W. Schalm. Doctor to patient transmission of hepatitis B virus: implications of HBV DNA levels and potential new solutions. *Antiviral Research.* 2003; 60(2):79-85
Hepatitis B virus (HBV)-infected health care workers (HCWs) can infect patients undergoing exposure prone procedures. Until now reviews have focused on the problem of the HBeAg-positive HCWs. After transmission of HBV by HBeAg-negative surgeons, the focus of Public Health Policy in the UK and the Netherlands has changed from HBeAg status to serum HBV DNA level. Viral load and the volume of blood transmitted determine the transmission risk of HBV. We have estimated the number of infectious particles transmitted by needlesticks, in comparison with those attributed in maternal-fetal transfusion. The blood volume transmitted by needlestick is roughly 1-30% of that of delivery. As vertical transmission with maternal HBV DNA levels below $10(7)$ g Eq/ml is rarely documented, HBV transmission by needlesticks is, according to our assumptions, unlikely to occur with HBV DNA levels below $10(7)$ g Eq./ml. Sera of transmitting HCWs contained HBV DNA levels between $5.0 \times 10(9)$ and $6.35 \times 10(4)$ g Eq./ml. Interpretation of these levels is hampered as the sera were taken at least 3 months after transmission. To prevent both loss of expertise and nosocomial infection, highly viremic HCWs can be offered antiviral therapy. Lamivudine and alpha-interferon can now be complemented with adefovir, tenofovir and entecavir to provide effective new therapies for chronic HBV-infected HCWs. (C) 2003 Elsevier B.V. All rights reserved.

L. M. Wolters, H. G. Niesters, B. E. Hansen, M. E. van der Ende, F. P. Kroon, C. Richter, K. Brinkman, P. L. Meenhorst and R. A. de Man. Development of hepatitis B virus resistance for lamivudine in chronic hepatitis B patients co-infected with the human immunodeficiency virus in a Dutch cohort. *J Clin Virol.* 2002; 24(3):173-81

INTRODUCTION: With the introduction of HAART, the HIV-1 has turned from a lethal into a chronic infection in the majority of patients. In homosexual populations, 20% of HIV-1 infected patients suffer from a chronic HBV infection, which may eventually lead to complications of the liver disease because of

prolonged survival. Lamivudine is effective in reducing both HIV-1 and HBV viral replication. However, resistance for lamivudine may complicate the course of the HBV disease in HIV-1-infected patients. We, therefore, conducted a retrospective study in HIV-1-HBV co-infected patients on lamivudine therapy. PATIENTS AND METHODS: All HIV-1-HBV co-infected patients who were treated with lamivudine for over 6 months in five major referral clinics in The Netherlands with HBV DNA above 2.0×10^5 geq ml(-1) at baseline, were evaluated. Retrospectively, the course of HBV DNA in available serum samples was established. If HBV DNA was detectable with the sensitive PCR-assay, YMDD-analyses of the polymerase gene of the hepatitis B virus was executed with the INNO-LiPA-DR-strip. RESULTS: Forty-six patients were evaluated. The median level of HBV DNA at start of lamivudine therapy was 1.31×10^9 geq ml(-1) (range 3.5×10^5 - 2.0×10^{10} , n=43). Of three patients no baseline sample was available, but since HBV DNA was still above 2.0×10^5 geq ml(-1) at week 3, 7 and 11, these patients were included. Median duration of lamivudine therapy was 97 weeks (range 27-263). The percentage of detected mutations was 25 and 52% at 1 and 2 years, respectively. Twenty-two patients ultimately developed a mutation. Both baseline Body Mass Index (BMI) and the decrease in CD4 cell count as a time dependent factor were significantly related to the emergence of mutations. In 10 out of 12 evaluated patients, HBV DNA levels returned to baseline level or even above baseline level after the development of mutant virus. One patient (5%) developed a flare of serum transaminases (ALT>10 x ULN) 24 weeks after first detection of variant virus. CONCLUSION: There is a linear time-dependent appearance of HBV mutations for lamivudine in our population. In a minority of patients (5%), development of a mutation was followed by a significant elevation of serum transaminases. A decline in CD4 cell count, which may indicate less response to HAART, induces a faster emergence of mutations and close surveillance of HBV co-infected patients on therapy may be indicated due to the prolonged survival of HIV-1 patients.

J. E. van Steenberg and H.-r. Working Grp Vaccination. Results of an enhanced-outreach programme of hepatitis B vaccination in the Netherlands (1998-2000) among men who have sex with men, hard drug users, sex workers and heterosexual persons with multiple partners. *Journal of Hepatology*. 2002; 37(4):507-513

Background/Aims: The Dutch Ministry of Health funded a pilot vaccination project targeting groups at high risk for sex- and drug-related hepatitis B transmission. Methods: In seven Municipal Health Service (MHS) areas, three-part hepatitis B vaccination was offered free to men who have sex with men (MSM), drug users (DUs), and heterosexuals with multiple partners, including sex workers (SWs). Four intervention areas recruited participants through care-givers and opinion leaders and offered vaccination at non-MHS sites. Three control areas only used flyers to offer vaccination at MHS during regular hours. Results: Over 18 months, 13 808 persons enrolled for the first vaccination, representing 63% of the targeted population in the intervention areas and 23% in control areas. In intervention areas, only 19% of DUs enrolled, versus 4% in control areas. In both areas, enrollment of the targeted heterosexual population (64%) was satisfactory. MSM were most compliant in having the full series. Of vaccination sources, general practitioners (GPs) attained highest compliance (71%, odds ratio 1.82). Conclusions: Dutch MHS facilities can reach high-risk individuals, but DUs require additional outreach. Vaccine coverage was disappointing, but our experience will be deployed nationwide and successful strategies might be employed elsewhere in countries of low endemicity. (C) 2002 European Association for the Study of the Liver. Published by Elsevier Science B.V. All rights reserved.

J. E. van Steenberg, H. G. M. Niesters, E. L. M. Op de Coul, G. J. J. van Doornum, A. Osterhaus, A. Leentvaar-Kuijpers, R. A. Coutinho and J. A. R. van den Hoek. Molecular epidemiology of hepatitis B virus in Amsterdam 1992-1997. *Journal of Medical Virology*. 2002; 66(2):159-165

To gain insight into the spread of hepatitis B among various risk groups in Amsterdam a 6-year (1992-1997) retrospective DNA sequencing study was carried out on isolates from stored sera from reported primary cases of acute hepatitis B infection. Cases were classified according to risk behavior, as determined in interviews. Of the available serum, a selected region of hepatitis B-virus-DNA was amplified and sequenced. The nucleotide alignments were subjected to phylogenetic tree analysis. When nucleotide alignments were subjected to phylogenetic analysis, the strains of 54 isolates, 26% of the 204 reported primary cases, clustered in five genotypes: A, C, D, E, and F. In genotype A, a cluster related to men having sex with men was identified. In genotype D, two subclusters could be identified: one was related to injecting drug use and another was related to the Moroccan population in Amsterdam. The remaining strains showed a high genetic variability within three different genotypes: F, E, and C. Of the 14

identical isolates in the "homosexual men cluster," one was isolated from a female heterosexual. Of the 14 identical strains in the "drug users strain," six were from non-drug using heterosexual active individuals. In the cluster of twelve isolates related to hepatitis B-endemic areas, probable modes of transmission were varied. Sequence analysis provides important insight into the spread of hepatitis B among various highrisk groups. The analysis indicates that the prevention strategy in The Netherlands fails to stop transmission of hepatitis B from persistently infected individuals originating from hepatitis B endemic countries. *J. Med. Virol* 66:159-165, 2002. (C) 2002 Wiley-Liss, Inc.

J. van Hattum. Health strategy on HCV in the Netherlands. *Acta Gastro-Enterologica Belgica*. 2002; 65(2):115-117

The current basis for the health care policy on hepatitis C in The Netherlands is an advisory report of the national Health Council, published in 1997. The Council confirmed that: Chronic hepatitis C (HC) is to be considered as a serious disease; the hepatitis C virus (HCV) can be detected easily and accurately; transmission of HCV occurs mainly via blood; the prevalence of HC is low in The Netherlands and comparable to or somewhat lower than other countries in Northern Europe; treatment is possible and worthwhile; patients have the right to be provided spontaneously with relevant information; the general population lacks adequate knowledge about the essentials of HCV infection, preventing them from taking adequate measures for their own health. The Council recommended that: general tracing and testing of all people who received blood products in the past would be inefficient; hospitals should keep precise records of the origin and use of blood products; as practically all active drug users in The Netherlands are involved in medical care in connection with their addiction, they will be tested for HCV and qualify for treatment of HC; information should be provided to the general population; medical doctors are stimulated to participate in training courses on HC; medical and non-medical professionals involved in increased risk of HCV transmission must be informed on hygiene. Epidemiological research of HCV infection in the various population groups of The Netherlands is stimulated. Currently, an active approach to the health care policy on hepatitis C is supported by the Ministry of Health, Welfare and Sport, including awareness programs in risk groups and training courses for professionals. Such programs are typically aiming at supporting and stimulating the own initiatives in the society, based on responsibilities of professional and patient's organisations and individuals at risk. Treatment of HC, given in accordance with the current consensus, including long term combination therapy with interferon and ribavirin, is available and refundable for all Dutch citizens. A special program for HC screening and treatment of drug addicts is being started up, using the special infrastructure for drug user control programs in The Netherlands.

I. J. Spijkerman, L. J. van Doorn, M. H. Janssen, C. J. Wijkmans, M. A. Bilkert Mooiman, R. A. Coutinho and G. Weers Pothoff. Transmission of hepatitis B virus from a surgeon to his patients during high-risk and low-risk surgical procedures during 4 years. *Infect Control Hosp Epidemiol*. 2002; 23(6):306-12

OBJECTIVE: We investigated cases of acute hepatitis B in The Netherlands that were linked to the same general surgeon who was infected with hepatitis B virus (HBV). **DESIGN:** A retrospective cohort study was conducted of 1,564 patients operated on by the surgeon. Patients were tested for serologic HBV markers. A case-control study was performed to identify risk factors. **RESULTS:** The surgeon tested positive for hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) with a high viral load. He was a known nonresponder after HBV vaccination and had apparently been infected for more than 10 years. Forty-nine patients (3.1%) were positive for HBV markers. Transmission of HBV from the surgeon was confirmed in 8 patients, probable in 2, and possible in 18. In the remaining 21 patients, the surgeon was not implicated. Two patients had a chronic HBV infection. One case of secondary transmission from a patient to his wife was identified. HBV DNA sequences from the surgeon were completely identical to sequences from 7 of the 28 patients and from the case of secondary transmission. The duration of the operation and the occurrence of complications during or after surgery were identified as independent risk factors. Although the risk of HBV infection during high-risk procedures was 7 times higher than that during low-risk procedures, at least 8 (28.6%) of the 28 patients were infected during low-risk procedures. **CONCLUSIONS:** Transmission of HBV from surgeons to patients at a low rate can remain unnoticed for a long period of time. Prevention requires a more stringent strategy for vaccination and testing of surgeons and optimization of infectious disease surveillance. Policies allowing HBV-infected surgeons to perform presumably low-risk procedures should be reconsidered.

H. W. Reesink, H. T. Cuypers, E. Adema, M. H. Molijn, R. Scheepers, G. A. Peeters and J. Ijlst. Minipool screening for HCV-RNA and HIV-RNA in the Netherlands. *Transfusion*. 2002; 42(9):80S-81S

M. Kretzschmar, G. A. de Wit, L. J. Smits and M. J. van de Laar. Vaccination against hepatitis B in low endemic countries. *Epidemiol Infect*. 2002; 128(2):229-44

A mathematical model that takes transmission by sexual contact and vertical transmission into account was employed to describe the transmission dynamics of hepatitis B virus (HBV) and vaccination against it. The model is an extension of a model by Williams et al. (*Epidemiol Infect* 1996; 116; 71-89) in that it takes immigration of hepatitis B carriers from countries with higher prevalence into account. Model parameters were estimated from data from The Netherlands where available. The main results were that, given the estimates for the parameters describing sexual behaviour in The Netherlands, the basic reproduction number R_0 is smaller than 1 in the heterosexual population. As a consequence, the immigration of carriers into the population largely determines the prevalence of HBV carriage and therefore limits the possible success of universal vaccination. Taking into account the prevalence of hepatitis B carriage among immigrants and an age-dependent probability of becoming a carrier after infection, we estimate that a fraction of between 5 and 10% of carrier states could be prevented by universal vaccination.

J. M. Jongerius, M. Sjerps, H. T. M. Cuijpers, H. A. J. van Drimmelen, C. L. van der Poel, H. W. Reesink, M. H. J. Molijn, G. A. H. Peeters, T. P. W. Peeters and P. N. Lelie. Validation of the NucliSens Extractor combined with the AmpliScreen HIV version 1.5 and HCV version 2.0 test for application in NAT minipool screening. *Transfusion*. 2002; 42(6):792-797

BACKGROUND: Routine HCV NAT minipool screening (48 donations) of all blood donations was implemented in July 1999 and was combined with HIV NAT in November 2000. This report describes the validation of the NAT methods and the results of quality control testing. STUDY DESIGN AND METHODS: Nucleic acid was extracted from 2-mL plasma samples by using an automated silica-based extraction method (NucliSens Extractor, Organon Teknika). Eluates were tested with RTPCR (AmpliScreen HIV-1 version 1.5 and AmpliScreen HCV version 2.0 test, Roche Diagnostic Systems). HIV-1 and HCV RNA reference panels and run controls (PeliCheck and PeliSpy, respectively, Sanquin-CLB) and human plasma minipools were used for NAT validation. RESULTS: The 95-percent detection limit (and 95% CI) for HIV-1 RNA genotype B, HIV-1 RNA genotype E, and HCV RNA genotype 1 was 32 (19-76), 30 (17-72), and 21 (13-44) genome equivalents (geq) per mL, respectively. During initial validation, 2332 samples for HIV-1 RNA and 2644 samples for HCV RNA were analyzed, with 13 (0.56%) and 12 (0.45%) invalid test results, respectively. Thereafter, over 19,600 samples (minipools and run controls) were analyzed during the first 11 months of routine screening. Invalid test results for HIV-1 RNA and HCV RNA were found in 1.1 and 1.07 percent of the samples tested, respectively. HIV-1 RNA minipool testing resulted in 27 (0.16%) initial false-positive results and 3 (0.02%) confirmed positive results. HCV RNA minipool testing resulted in four (0.02%) initial false-positive results and five (0.02%) confirmed positive results. CONCLUSION: Routine HIV and HCV NAT minipool screening using the NucliSens Extractor, AmpliScreen HIV-1 version 1.5, and AmpliScreen HCV version 2.0 meets the sensitivity criteria set by the regulatory bodies and provides sufficient specificity and robustness for timely release of blood donations.

R. Hoksbergen, C. van Dijkum and F. Stoutjesdijk. Experiences of Dutch families who parent an adopted Romanian child. *Journal of Developmental and Behavioral Pediatrics*. 2002; 23(6):403-409
The pilot phase of a longitudinal study of 83 children (response 86%) adopted from Romania is reported; the present status of the children is compared with the past status on the basis of parental recollection. At placement, the average age of the children was 2.9 years; at the time of the interview of the adoptive parents, the average age of the children was 6.8 years. At placement, 67% of the adoptive parents needed professional help, and 10% of the children were infected with Hepatitis B. Only 13% did not show any important psychosocial problems. The number of psychosocial problems reported by the parents at placement predicts 69% of the lag of development observed 4 years later; the age of arrival adds up to 72%. Most problems still exist 4 years after placement; however, no disruptions of the adoption have taken place yet.

M. G. Beld, K. Dijkman, J. Weel, S. Rebers, C. Sol, R. Boom and J. Werth. Detection of HCV RNA in

patients with renal failure: Clinical utility of the versant TMA assay for detection of HCV RNA in EDTA-plasma from patients on dialysis and peritoneal dialysis above the Roche Amplicor HCV test 2.0. *Hepatology*. 2002; 36(4):353A-353A

L. M. M. Wolters, H. G. M. Niesters, K. Brinkman, F. P. Kroon, C. Richter, P. Meenhorst and R. A. de Man. Development of hepatitis B virus resistance for lamivudine in a Dutch cohort of HIV-HBV co-infected patients. *Journal of Hepatology*. 2001; 34:155-155

J. E. van Steenberg, A. Leentvaar-Kuijpers, D. Baayen, H. T. M. Dukers, G. J. J. van Doornum, J. A. R. van den Hoek and R. A. Coutinho. Evaluation of the hepatitis B antenatal screening and neonatal immunization program in Amsterdam, 1993-1998. *Vaccine*. 2001; 20(1-2):7-11

In the enhanced antenatal hepatitis B screening and neonatal immunization program in Amsterdam, 691 hepatitis B surface antigen (HBsAg) positive expectant mothers were reported in the period 1993-1998. The coverage of the screening was calculated at 97%. HBsAg-prevalence was high in women from Ghana and South-East Asia, and lowest in Dutch women. Hepatitis B immune globulin (HB g) was administered within 24h to 95.9% of the neonates; 99.7% completed the vaccination series. About 6 weeks after the third vaccination the titer antiHBs was greater than or equal to 100IU/l in 85% of children; in 12% the titers were 10-100IU/l; 3% had titers < 10IU/l, of whom 3/521 initially had HBsAg. Low birth weight (OR 3.77), being a boy (OR 1.64) and country of origin were predictors of low postvaccination titers. Coordinated by 0.5 full time equivalent (fte) additional staff, the program was relatively cheap and successful. (C) 2001 Elsevier Science Ltd. All rights reserved.

W. H. van der Poel, F. Verschoor, R. van der Heide, M. I. Herrera, A. Vivo, M. Kooreman and A. M. de Roda Husman. Hepatitis E virus sequences in swine related to sequences in humans, The Netherlands. *Emerg Infect Dis*. 2001; 7(6):970-6

Hepatitis E virus (HEV), a major cause of viral hepatitis in much of the developing world, has recently been detected in swine in North America and Asia, raising concern about potential for zoonotic transmission. To investigate if HEV is commonly present in swine in the Netherlands, pooled stool samples from 115 swine farms and nine individual pigs with diarrhea were assayed by reverse transcription-polymerase chain reaction (RT-PCR) amplification. HEV RNA was detected by RT-PCR and hybridization in 25 (22%) of the pooled specimens, but in none of the individual samples. RT-PCR amplification products of open reading frames 1 and 2 were sequenced, and the results were compared with published sequences of HEV genotypes from humans and swine. HEV strains from swine in the Netherlands were clustered in at least two groups, together with European and American isolates from swine and humans. Our data show that HEV in swine in the Netherlands are genetically closely related to HEV isolates from humans. Although zoonotic transmission has not been proven, these findings suggest that swine may be reservoir hosts of HEV.

P. Van Damme. Hepatitis B: vaccination programmes in Europe - an update. *Vaccine*. 2001; 19(17-19):2375-2379

In the eight years since the Global Advisory Group of the Expanded Program on Immunisation set 1997 as the target for integrating hepatitis B (HB) vaccination into national immunisation programs world-wide, more than 116 countries have included HE vaccine as part of their routine infant or adolescent immunisation programs. Meanwhile, many countries have performed economic evaluation studies, while others have initiated sero-epidemiological studies to generate input data for burden of disease calculation. These studies have indicated that epidemiological and economic arguments cannot be used to delay the implementation of universal hepatitis B vaccination. Some countries have improved their surveillance system and included viral hepatitis in the surveillance programs. Other have put hepatitis B vaccination on the political agenda. By the year 2000, following countries of the WHO European Region (51 countries) have implemented a universal hepatitis B immunisation programme: Andorra, Albania, Austria, Belarus, Belgium, Bulgaria, Estonia, France, Germany, Greece, Italy, Israel, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, Moldova, Monaco, Poland, Portugal, parts of the Russian Federation, Romania, Slovakia, Slovenia, San Marino, Spain, Switzerland, Turkey and Uzbekistan. The Netherlands and some other European countries are seriously studying the issues or are making budgetary provisions for introduction of HB vaccine into their vaccination programme. Most of the European countries, which now use the vaccine routinely, have started with adolescent or infant

immunisation. Belgium (1999). France (1994) and Italy (1991) have begun with both adolescent and infant HE immunisation. France continues since 1st October 1998 with the infant immunisation programme only. The rewards of effective implementation of the programmes in these countries are becoming apparent: and their success offers an exemplary model for other countries. The deadline was 1997. Globally, work still remains to be done to support and implement interventions that will bring us closer to the WHO goal and to control, eliminate and eradicate hepatitis B in the coming generations at large. If all the 145 million infants born in 1991 had been vaccinated in this way, the number of chronic carriers would have been reduced by 7.5 million, and 1.8 million deaths prevented. (C) 2001 Elsevier Science Ltd. All rights reserved.

C. Hoebe, F. Smit, C. Vermeulen, J. Schippers and A. Van der Ven. HIV-positive drug users in South Limburg: number and characteristics; a capture-recapture analysis. *Nederlands Tijdschrift Voor Geneeskunde*. 2001; 145(23):1118-1122

Objective. To estimate the number of HIV positive drug abusers (HDs) in South Limburg, the Netherlands, and to ascertain the characteristics of this group, so that special HIV healthcare can be planned. **Design.** Capture-recapture analysis. **Method.** Capture-recapture analysis was carried out and abuser characteristics were determined using three incomplete, partially overlapping registers of HDs from the regional AIDS hospital, the Regional Institute for Addiction and the Municipal Health Service Centres in South Limburg. **Results.** From the So HDs included, the Municipal Health Service Centres observed 59 HDs, the Institute for Addiction 45 and the hospital 44. The capture-recapture analysis gave an estimate of 110 HDs (95% CI: 91-164) in South Limburg. Assuming 1100 drug users in South Limburg of which 76% had injected on one or more occasions, the HIV prevalence among injecting drug users was estimated at 13% (110/836). From the observed HDs 80% were male, with a mean age of 38 years (SD: 7) and a mean age at the onset of drug use of 18 years (SD: 5) All HDs currently injected or had previously injected. The first injected drugs were used at a mean age of 21 years (SD: 6). All HDs used heroine, 84% also used cocaine, 54% were homeless, 91% unemployed and 80% had a history of imprisonment. Further, 71% of the female HDs were prostitutes, 37% of the: male ones visited prostitutes, 81% had contracted hepatitis B (of which 20% were a carrier) and all HDs were infected with hepatitis C. An estimate based on prevalence data gave 143/836 (17%) and that based on capture-recapture analysis with two registrations was 102/836 (12%). **Conclusion.** The number of HDs was estimated to be 110, The population had a marginalized existence and there was a risk of HIV spreading.

H. T. Cuijpers, M. H. Molijn, H. J. Bos, A. P. Peeters, C. L. van der Poel and P. N. Lelie. Validation of the NucliSens Extractor in combination with the hepatitis C virus Cobas Amplicor 2.0 assay in four laboratories in the Netherlands utilizing nucleic acid amplification technology for blood screening. *Vox Sang*. 2001; 81(1):12-20

BACKGROUND AND OBJECTIVES: Since July 1 1999, four laboratories in the Netherlands have been routinely screening plasma minipools for the release of labile blood components utilizing hepatitis C virus nucleic acid amplification technology (HCV NAT). This report describes the performance evaluation of the HCV NAT method and the quality control results obtained during 6 months of routine screening.

MATERIALS AND METHODS: Plasma minipools of 48 donations were prepared on a Tecan Genesis robot. HCV RNA was isolated from 2 ml of plasma by using the NucliSens Extractor and amplified and detected with the Cobas HCV Amplicor 2.0 test system. For validation of the test system the laboratories used viral quality control (VQC) reagents of CLB. **RESULTS:** Initial robustness experiments demonstrated consistent detection of PeliSpy HCV RNA samples of 140 genome equivalents/ml (geq/ml) in each station of the installed Nuclisens Extractors. Further 'stress' tests with a highly viraemic sample of approximately 5×10^6 geq/ml did not contaminate negative samples processed on all Extractor stations in subsequent runs. In the validation period prior to July 1999, 1021 pools were tested with the following performance characteristics: 0.1%, initially false reactive; 0.89%, failure of internal control detection; 0.97%, no eluate generated by the Extractor; and 100% reactivity of the PeliSpy 140 geq/ml control in 176 Extractor runs and a 98% reactivity rate of the PeliSpy 38 geq/ml control in 102 test runs. By testing the PeliCheck HCV RNA genotype 1 dilution panels 49 times, an overall 95% detection limit of 30 geq/ml (approximately 8 IU/ml) and a 50% detection limit of 5 geq/ml was found by the four laboratories. In the first 6 months of routine screening, the minimum requirement for invalid results (2%) was exceeded with some batches of silica and NucliSens Extractor cartridges. From November 1999 to February 2000, the manufacturer (Organon Teknika) improved the protocol for silica absorption of the Nuclisens Extractor -- the cartridge

design as well as the software of the Extractor. During the next 6 months of observation in 2000, the percentages of false initial reactivities and invalids were 0.05% and 1.4%, respectively, in 8962 pools tested. Of these invalid results, 0.74% and 0.66% were caused by Extractor failure and negative internal control signals, respectively. The PeliSpy HCV RNA 'stop or go' run control of 140 geq/ml was 100% reactive, but invalid in 16/1375 (1.2%) of cases. The PeliSpy run control of 38 geq/ml for monitoring sensitivity of reagent batches was reactive in 95% of 123 samples tested. CONCLUSIONS: Each of the four HCV NAT laboratories in the Netherlands have achieved similar detection limits that are well below the sensitivity requirements of the regulatory bodies. After improvement of the NucliSens Extractor procedure, the robustness of the test system has proved to be acceptable for routine screening and timely release of all labile blood components.

S. M. Bruisten, J. E. van Steenberg, A. S. Pijl, H. G. Niesters, G. J. van Doornum and R. A. Coutinho. Molecular epidemiology of hepatitis A virus in Amsterdam, the Netherlands. *J Med Virol.* 2001; 63(2):88-95

The transmission of sporadic community-acquired hepatitis A virus (HAV) among different risk groups in Amsterdam was verified by applying molecular techniques on fecal samples. These were collected in 1997/1998 from 33 persons with HAV infection that was confirmed serologically. From 8 of these persons serial stool samples were collected. Nested RT-PCR targeting the VP3-VP1 and VP1-P2a regions followed by sequence analysis established the duration of fecal HAV RNA excretion in stool and the epidemiological molecular relationships between patients. The samples of 31 patients were RT-PCR positive, of which 24 were positive for both regions. Fecal HAV shedding was found to occur for at least 33 days after onset of disease, which was the longest time span tested. Sequencing showed that the hepatitis A virus subgenotype circulating among persons from Moroccan descent (type IB) was different from the subgenotype circulating among Dutch homosexual men (type IA). If the latter is endemic in the Netherlands, its presence is of importance to the national vaccination strategy. Copyright 2001 Wiley-Liss, Inc.

F. Termorshuizen, J. W. Dorigo-Zetsma, H. E. de Melker, S. van den Hof and M. A. E. Conyn-van Spaendonck. The prevalence of antibodies to hepatitis A virus and its determinants in The Netherlands: a population-based survey. *Epidemiology and Infection.* 2000; 124(3):459-466

The prevalence of antibodies to hepatitis A virus was assessed in a Dutch nationwide sample (n = 7367). A questionnaire was used to study the association with various sociodemographic characteristics. Overall, 33.8 % (95 % CI 31.6-36 %) of the population had hepatitis A antibodies. The seroprevalence was less than 10 % in people under 35; it increased from 25 % at 35 years to 85 % at 79 years. For those 15-49 years of age, Turks (90.9 %) and Moroccans (95.8 %) had greater seroprevalence than autochthonous Dutch (20.2 %) and other Western people (25 %). Low or middle socio-economic status, as indicated by the highest educational level achieved, was associated with greater seroprevalence, independently of age and reported immunization (OR 2.11 and 1.45; 95% CI 1.67-2.67 and 1.11-1.89, respectively). These data suggest autochthonous Dutch and other Westerners born after World War II were exposed to hepatitis A during childhood less frequently than older birth cohorts. Thus, more susceptibility is likely in the coming decades. Since this means a greater risk of outbreaks in future years, and since morbidity and mortality are more frequent in older persons, studying the cost effectiveness of selective and general vaccination might be worthwhile.

P. M. Schneeberger, I. Keur, A. M. van Loon, D. Mortier, K. O. de Coul, A. V. van Haperen, R. Sanna, T. G. van Der Heijden, H. van Den Hoven, H. W. van Hamersvelt, W. Quint and L. J. van Doorn. The prevalence and incidence of hepatitis C virus infections among dialysis patients in the Netherlands: a nationwide prospective study. *J Infect Dis.* 2000; 182(5):1291-9

A nationwide prospective survey on hepatitis C virus (HCV) infections among dialysis patients in The Netherlands was performed. Patients were recruited from 34 dialysis centers and were tested for antibodies and HCV RNA in 1995 and 1997. Seronegative serum samples were analyzed by reverse-transcriptase polymerase chain reaction in pools. HCV-RNA-positive serum samples were genotyped and were partly sequenced. In the first and second rounds, 67 (2.9%) of 2281 and 76 (3.4%) of 2286 patients were HCV positive, respectively. Of 960 patients with paired serum samples, 35 were HCV positive in both rounds, and 9 HCV-positive cases were newly identified in the second round. The incidence of HCV infection was 0.5 per 100 dialysis years. Phylogenetic analysis revealed clustered sequences that

indicated nosocomial transmission. Sixty percent of HCV infections, however, can be attributed to 4 interdependent risk factors (i.e., hemodialysis before 1992, kidney transplantation before 1994, and birth or dialysis in a foreign country). In conclusion, the prevalence of HCV infections in The Netherlands does not decline, and transmission within dialysis units continues. Adequate screening of HCV infections and strict enforcement of universal infection control practices are required.

H. W. Reesink, H. T. Cuypers and P. N. Lelie. Implementation of HCV-NAT testing in The Netherlands. *Dev Biol (Basel)*. 2000; 102:105-7

E. J. C. Van Ameijden, M. W. Langendam, J. Notenboom and R. A. Coutinho. Continuing injecting risk behaviour: results from the Amsterdam Cohort Study of drug users. *Addiction*. 1999; 94(7):1051-1061

Aims. To give a detailed description of injection-related risk behaviours, and to estimate the relative importance of these behaviours with regard to HIV transmission. **Design.** The present study was part of the Amsterdam Cohort Study of drug users. **Setting.** In Amsterdam, a city with extensive preventive measures, large HIV-risk reductions have taken place, but no further decreases have occurred since 1991. **Participants and measurements.** A detailed questionnaire on injecting risk behaviour was completed by a cross-section of participants in 1992/93 (n = 168). Among 48 HIV-seroconverters, a questionnaire was completed concerning possible HIV-transmission route. **Findings.** Of 96 HIV-negative participants, 23% deliberately borrowed a used syringe, 18% reported possible "accidental" borrowing, 9% front/backloading, 4% simultaneous injection, and 32% possible sharing of ancillary equipment. Of deliberate borrowers, 64% borrowed from a person with unknown or positive HIV serostatus, and 81% did not appropriately clean the equipment; 79% borrowed in the absence of serious withdrawal symptoms. Risk factors differed for deliberate and 'accidental' borrowing. Among the HIV seroconverters, the most likely transmission route was borrowing in 29% of cases, front/backloading in 8%, borrowing or front/backloading in 21%, unprotected sexual contact in 23% (mainly with regular partner) and either injecting or sexual risk in 13%. Women were much more likely to report sexual transmission ($p = 0.016$). Borrowing was admitted by 43% before, and 64% after awareness of HIV-seroconversion. **Conclusions.** As the injecting risk is high, usually deliberate, and often in the absence of withdrawal symptoms, further prevention seems difficult. Although deliberate borrowing is the main risk for HIV seroconversion, unprotected sexual contacts and front- and backloading may be more important than previously thought in Amsterdam. Under-reporting of borrowing is probably substantial, but does not alter the above conclusions.

T. Sheldon. Dutch consider obligatory testing of surgeons for hepatitis B. *British Medical Journal*. 1999; 319(7219):1219-1219

P. M. Schneeberger, C. J. Doorenbos, W. van der Vliet, P. Bergervoet, W. Quint and L. J. van Doorn. Nosocomiale transmissie van het hepatitis-C-virus in een Nederlands dialysecentrum. [Nosocomial transmission of hepatitis C virus in a Dutch dialysis center]. *Ned Tijdschr Geneesk*. 1999; 143(15):801-6

OBJECTIVE: To describe the transmission of hepatitis C virus (HCV) in a dialysis centre in the Netherlands, to analyse risk factors and to redefine additional preventive measures. **DESIGN:** Descriptive. **METHODS:** The data of patients attending the dialysis centre of the Deventer Hospital, the Netherlands, who had participated in a national prospective survey on the epidemiology of HCV among Dutch dialysis patients, were examined. In addition, patients who developed signs of hepatic failure in the ensuing year were included in this study. To diagnose an HCV-infection serology as well as polymerase chain reaction were used. Genotyping and sequence analysis were used to assess phylogenetic relations. Infection control practices were audited. **RESULTS:** In the dialysis centre a cluster of four almost identical HCV isolates genotype 2a was found. Within a period of one year another cluster of four HCV-infected dialysis patients was detected in the same centre. These four isolates were almost identical to a fifth isolate, genotype 2b, found in the earlier study from another patient dialysing in the same unit. It was observed that possibly contaminating procedures were not strictly separated. Some of the shared medical equipment was not sterilised but only cleaned. Also blood-contaminated gloves might have played a role in the transmission of HCV. **CONCLUSION:** Nosocomial transmission plays an important role in the epidemiology of HCV in dialysis patients. Shared medical equipment and blood-contaminated gloves may constitute a potential route of transmission. There is a need for stringent implementation and

regular auditing of infection control measures.

R. Reintjes, A. Bosman and O. de Zwart. Beleid bij screening van reizigers uit Rotterdam op antistoffen tegen hepatitis A voorafgaand aan eventuele immunisatie: gunstige kosten-batenverhouding. [Screening policy for travellers from Rotterdam for hepatitis A antibodies prior to eventual immunization: favourable cost-benefit ratio]. *Ned Tijdschr Geneesk.* 1999; 143(35):1777-80

OBJECTIVE: To evaluate costs and benefits of the screening and immunisation policy for hepatitis A virus (HAV) infection among travellers from Rotterdam. **DESIGN:** Descriptive and cost-benefit analysis. **METHOD:** From the data of the Municipal Health Service Rotterdam (GGD), the Netherlands, the details were collected on individuals travelling frequently to HAV endemic countries, who were born before 1950, or had lived for more than 10 years in an HAV endemic country or had ever suffered jaundice. Persons to whom these criteria applied were screened for HAV antibodies at the GGD before immunisation for HAV in the period January 1st 1996-June 30th 1998. Screening and vaccination policies were compared with a cost analysis. **RESULTS:** Antibodies against HAV were found in 79% of 1466 screened people. The lowest prevalence of antibodies was found among Dutch nationals (67%). A significantly higher prevalence was found amongst individuals from Turkey/Morocco (96%) and from the Cape-Verde Islands (97%). In the cost analysis the break even point, the prevalence level of HAV antibodies in the population at which screening cost as much as blind prophylaxis, lay for passive immunisation between 69% and 93%. For active immunisation this point lay around 17%. **CONCLUSION:** The selection criteria for prevaccination screening are effective in identifying individuals with a high probability of being immune against HAV infections. The current screening policy for antibodies against HAV is cost effective.

B. A. Koblin, B. H. B. van Benthem, S. P. Buchbinder, L. Ren, E. Vittinghoff, C. E. Stevens, R. A. Coutinho and G. J. P. van Griensven. Long-term survival after infection with human immunodeficiency virus type 1 (HIV-1) among homosexual men in hepatitis B vaccine trial cohorts in Amsterdam, New York City, and San Francisco, 1978-1995. *American Journal of Epidemiology.* 1999; 150(10):1026-1030
Information on long-term survival after infection with human immunodeficiency virus type 1 (HIV-1) is limited. In hepatitis B vaccine trials in Amsterdam, New York City, and San Francisco 262 gay men were followed up to 18 years (1978-1995). The median survival time from seroconversion was 12.1 years (95% confidence interval: 11.4, 12.9). The annual risk of dying increased at a constant rate until 8 years after seroconversion and then leveled off, suggesting a group that is relatively resistant to progression; These data provide a picture of the natural history of HIV-1 infection, especially in the era prior to widespread use of highly effective treatments.

J. Jongerius, G. Boland, C. van der Poel, M. Rasch, E. Italiaander, J. van der Reijden, P. Friedman, J. Cockerill, E. van Leeuwen and J. van Hattum. GB virus type C viremia and envelope antibodies among population subsets in The Netherlands. *Vox Sang.* 1999; 76(2):81-4
BACKGROUND AND OBJECTIVES: Two new flaviviruses, hepatitis G virus and GB virus type C (GBV-C), are possible causative agents for non-A-E hepatitis. In this study we established the prevalence of GBV-C markers in various population subsets in The Netherlands by assays for GBV-C antibodies and GBV-C nucleic acid. **MATERIALS AND METHODS:** We tested specimens from groups of patients with hepatitis of various causes, intravenous drug users (IVDUs), and blood donors for GBV-C RNA (LCx(R) GBV-C assay, Abbott Laboratories), and for antibodies to the GBV-C envelope E2 protein (GBV-C anti-E2) with an enzyme immunoassay (Abbott Laboratories). Patients and donors were represented in one group only. **RESULTS:** GBV-C RNA and GBV-C anti-E2 prevalence were, respectively, 2/34 (6%) and 3/34 (9%) among patients with non-A-E hepatitis, 2/10 (20%) and 0/10 (0%) among hepatitis B virus patients, 10/40 (25%) and 19/40 (48%) among hepatitis C virus (HCV) patients, 1/8 (13%) and 0/8 (0%) among patients with autoimmune hepatitis (AIH), 24/102 (24%) and 72/102 (71%) among IVDUs, 1/34 (3%) and 2/34 (6%) among blood donors with indeterminate anti-HCV recombinant immunoblot assay reactivity, and 3/250 (1.2%) and 8/250 (3.2%) among first-time blood donors. The profile of simultaneous GBV-C RNA positivity plus GBV-C anti-E2 positivity was found in 2/40 (5%) HCV patients, 4/102 (4%) IVDUs, and 1/250 (0.4%) first time blood donors. **CONCLUSION:** GBV-C infection appears not to be a major cause of non-A-E hepatitis and AIH, but is associated with parenteral risk. The prevalence of GBV-C viremia in first time blood donors is higher than that of HCV (1.2 vs. 0.04%), but GBV-C viremia in IVDUs is lower than HCV (24 vs. 59%). Most IVDUs have probably previously been exposed to GBV-C given the very high prevalence of GBV-C anti-E2 (71%). Most persons with GBV-C markers are GBV-C

RNA-negative and anti-E2-confirmed positive, suggesting that GBV-C infection is transient.

W. Goettsch, R. de Graaf, J. W. Dorigo Zetsma, G. van Zessen and H. Houweling. Broader vaccination of expatriates against HBV infection: do we reach those at highest risk? *Int J Epidemiol.* 1999; 28(6):1161-6

BACKGROUND: The effects of the implementation of a new Dutch hepatitis B virus (HBV) vaccination strategy (1991) for expatriates on HBV vaccination status and HBV infection prevalence were evaluated in a group of 864 expatriates returning from HBV-endemic areas. **METHODS:** During a routine medical examination at the participating medical centres Dutch expatriates were asked to complete a questionnaire and to donate a serum sample for HBV testing. Blood was tested for antibodies against the hepatitis B core (anti-HBc) and surface antigens (anti-HBs). The serological data were related to information gathered on aspects of residence, sexual risk behaviour and occupational risks. **RESULTS:** A significantly higher percentage of expatriates (37%) were vaccinated compared to a previous study in 1987-1989 (14%). However, the percentage of expatriates with HBV infection markers (5%) had not decreased significantly. Moreover, the risk for HBV infection, as determined with a questionnaire, was still affected by well-known risk factors such as homosexual contacts (odds ratio [OR] = 6.6, 95% CI: 1.7-26), more than five casual local partners (OR = 3.6, 95% CI: 1.2-11) and more than five occupational accidents in the last 3 years (OR = 20, 95% CI: 2-187). Detailed analysis of the vaccination status indicated that especially young female expatriates with low risk behaviour (65%) were protected, while older male expatriates with high risk behaviour were less protected (20%). **CONCLUSION:** We conclude that the new vaccination strategy has resulted in a higher percentage of expatriates protected. However, only a small proportion was reached of those at highest risk for HBV infection.

P. M. Schneeberger, N. Toonen, I. Keur and H. W. van Hamersvelt. Infection control of hepatitis C in Dutch dialysis centres. *Nephrology Dialysis Transplantation.* 1998; 13(12):3037-3040

Background. In dialysis patients, blood transfusions and long-term dialysis are well-known risk factors for transmission of hepatitis C virus (HCV). Transmission of HCV by transfusions has become extremely rare since the introduction of antibody screening. However, nosocomial transmission of HCV within dialysis units still occurs. We performed a survey of current infection control measures against HCV in Dutch dialysis centres that had participated in a national HCV prevalence study. **Methods.** All twenty-seven Dutch dialysis centres where HCV-positive patients had been identified (HCV prevalence 1-8%), participated. With the use of a questionnaire we evaluated screening procedures for resident patients and guest patients, routine hygienic measures in HCV-positive and -negative patients, and cleaning procedures of dialysis equipment. **Results.** All centres except one screened new patients for HCV antibodies, but the frequency of periodic follow-up screening varied. Most centres requested HCV antibody screening of guest patients in advance, but in daily practice 55% of the centres dialysed guest patients even when HCV antibody status was not available. The majority of centres had not implemented special precautions for patients with unknown HCV antibody status. In most centres the use of protective glasses, masks and aprons depended on the HCV antibody status of the patients. Surprisingly, 85% of the centres allowed their nurses to operate dialysis machines with gloves possibly blood contaminated. All centres sterilized their machines at the end of the day, but only 77% sterilized their machines between all dialysis sessions. Traces of blood were removed with alcohol in 63% of the centres. **Conclusion.** Dutch dialysis centres have not yet implemented an optimal policy for prevention of HCV. Especially, operating dialysis machines with gloves might be a potential source for nosocomial transmission of HCV, not yet covered by the issued guidelines. Because dialysis patients probably have a prolonged serological window phase after a recent HCV infection, it does not suffice to implement a preventive strategy against nosocomial transmission based on the results of HCV antibody screening. Universal, rigorous implementation of adequate infection control measures irrespective of HCV antibody status should be the cornerstone for prevention of nosocomial pathogens.

P. M. Schneeberger, I. Keur, W. van der Vliet, K. van Hoek, H. Boswijk, A. M. van Loon, W. C. van Dijk, R. H. Kauffmann, W. Quint and L. J. van Doorn. Hepatitis C virus infections in dialysis centers in The Netherlands: a national survey by serological and molecular methods. *Journal of Clinical Microbiology.* 1998; 36(6):1711-1715

A national survey of hepatitis C virus (HCV) infections among dialysis patients in The Netherlands was performed. The study involved 2,653 patients (2,108 hemodialysis patients and 545 chronic ambulatory

peritoneal dialysis [CAPD] patients) from 39 of the 49 dialysis centers in the country. Patient sera were analyzed by both serological and molecular methods. Screening by a third-generation enzyme immunoassay (EIA) yielded 79 reactive sera. The presence of anti-HCV antibodies was confirmed in 70 patients by a line immunoassay, All seropositive samples were tested by reverse transcriptase PCR, and 57 samples were found to contain HCV RNA. Of the nine EIA-positive and line immunoassay-negative or indeterminate samples, four were HCV RNA positive. All seronegative samples were screened for the presence of HCV RNA in pools of five sera. Of 2,576 antibody-negative samples, 6 contained HCV RNA. All antibody-positive and RNA-positive samples were also tested by a second serological assay. The prevalence of HCV infections among Dutch dialysis patients as determined by serology or the presence of HCV RNA was 3% (80 of 2,653), i.e., 3.5% (73 of 2,108) in patients treated on hemodialysis and 1.3% (7 of 545) in patients on CAPD. Of these 80 HCV-infected dialysis patients, 67 (84%) were HCV RNA positive. Serological screening alone would have diagnosed only 70 infected patients. Therefore, antibody screening combined with detection of HCV RNA should be considered as the "gold standard" for diagnosing HCV infection in dialysis patients. The prevalence of HCV-infected patients in Dutch dialysis centers ranged from 0 to 8%, suggesting the existence of local risk factors for acquiring HCV infection. Genotyping analysis by reverse hybridization line probe assay revealed the presence of genotypes 1a (23%), 1b (46%), 2 (3%), 2a (13%), 2b (1%), 3a (7%), and 4a (4%). In four (6%) samples multiple genotypes were detected. The genotype distribution of HCV isolates among Dutch dialysis patients was similar to the distribution among nondialysis patients from the Benelux, except for subtype 1a, which was significantly more prevalent among dialysis patients. In only one center, a high prevalence of an uncommon genotype was suggestive of infection from a common source.

A. Osterhaus, M. C. Vos, A. Balk, R. A. de Man, J. W. Mouton, P. H. Rothbarth, S. W. Schalm, A. M. Tomaello, H. G. M. Niesters and H. A. Verbrugh. Transmission of hepatitis B virus among heart transplant recipients during endomyocardial biopsy procedures. *Journal of Heart and Lung Transplantation*. 1998; 17(2):158-166

Background: The unexpected conversion to HBsAg seropositivity of three cardiac allograft recipients prompted us to conduct a multidisciplinary study to identify the source, transmission mode, and extent of the hepatitis B virus (HBV) infection among the 256 cardiac allograft recipients of our hospital. Methods: All recipients were retrospectively screened for serum markers of HBV infection. A selected genomic region defining subtypes of the viruses involved was amplified and sequenced. An epidemiologic case-control study for possible risk factors was conducted to identify the mode of transmission. Results: Eighteen additional HBV-infected patients were identified, none of whom had shown symptoms of HBV infection. The involvement of one virus (subtype ayw 3) was shown in 20 of the 21 HBV-infected patients. This virus is found in less than 10% of HBV-infected individuals in The Netherlands. The demonstration of a common source of infection, combined with results of the epidemiologic study, identified posttransplantation endomyocardial biopsy procedures as the most likely mode of transmission. However, we also found evidence of secondary virus transmission by cardiac catheterization procedures to nonallograft recipients. Conclusions: The immunosuppressive therapy practiced in these patients to prevent allograft rejection may have not only facilitated virus transmission by causing high levels of viremia but also left the spreading of HBV undetected by causing a subclinical course of the infection. These findings stress the necessity of strict hygienic precautions during intravascular diagnostic procedures and indicate that vaccination against and routine monitoring for certain bloodborne infections in cardiac allograft recipients should be considered.

A. C. M. Kroes, E. F. H. van Bommel, J. Kluytmans and W. Weimar. Hepatitis B and hemodialysis: The impact of universal precautions in preventing the transmission of bloodborne viruses. *Infection Control and Hospital Epidemiology*. 1998; 19(7):508-510

A detailed description is presented of the hemodialysis treatment for 6 weeks of a patient strongly positive for hepatitis B virus ([HBV], hepatitis B surface antigen, hepatitis B e antigen, HBV DNA), which was performed without any special precautions. All 59 patients potentially exposed to the HBV-positive patient, of whom 29 appeared fully unprotected by antibody, were followed for at least 9 months but remained negative. This illustrates the feasibility of following Universal Precautions instead of using exceptional procedures for one single agent.

A. H. Buma, P. Beutels, P. van Damme, G. Tormans, E. van Doorslaer and A. Leentvaar-Kuijpers.

An economic evaluation of hepatitis A vaccination in Dutch military personnel. *Military Medicine*. 1998; 163:564-567

We analyzed the cost-effectiveness of hepatitis A vaccination regimens using a mathematical simulation model. Passive immunization and two active vaccination strategies [with and without prior screening] were compared with "doing nothing." Hepatitis A antibodies were determined in 2,325 Dutch marines; other input data were retrieved from published and unpublished sources. The prevalence of hepatitis A antibody was 14%. Screening before vaccination was identified as appropriate at a prevalence > 20%. Passive immunization was the cheapest prevention for a single 6-month deployment per 10 years. The inactivated vaccine containing 1,440 enzyme-linked immunosorbent assay units without prior screening was identified as the best option for more frequent deployments. It was cost-saving with two or more missions per 10 years. A 5.3% hepatitis A attack rate validated the investment for this policy. Overall, immunization with inactivated hepatitis A vaccine without prior screening proved to be the optimum strategy for troops at regular risk.

M. Beld, M. Penning, M. Van Putten, A. Van Den Hoek, V. Lukashov, M. McMorrow and J. Goudsmit. Hepatitis C virus serotype-specific core and NS4 antibodies in injecting drug users participating in the Amsterdam cohort studies. *Journal of Clinical Microbiology*. 1998; 36(10):3002-3006

In the present study, the RIBA HCV serotyping SIA was evaluated with a cohort of injecting drug users. Serotyping may be a rapid and cost-effective method of determining genotypes in cohort studies. In this study, hepatitis C virus (HCV) antibody-positive sera from a cohort of 331 chronically infected injecting drug users, of which 167 were coinfecting with human immunodeficiency virus (HIV), were serotyped by the RIBA HCV Serotyping SIA. Among the 331 specimens, serotype-specific antibodies were detected in 250 (sensitivity, 75.5%), in which serotype 1 was predominant (57.2%), followed by serotype 3 (26.8%). Among the 331 specimens, 164 were HIV negative, and serotype-specific antibodies were detected in 151 (sensitivity, 92.1%), in which serotype 1 was predominant (59.6%), followed by serotype 3 (33.8%). For a subset of 58 samples taken from 19 chronically infected HCV seroconverters with a mean follow-up of 5 years, serotypes were compared with genotypes, which were determined by a line probe assay (HCV LiPa) and by direct sequencing of the products obtained by nested PCR of the 5' untranslated region. Among the 58 samples with known genotypes, serotype-specific antibodies were detected in 38 (total sensitivity, 65.5%), with a specificity of 78.9%. Thirty of these serotypeable samples revealed a serotype that corresponded to the genotype in the 58 samples (total positive predictive value, 51.7%). Of the 58 samples, 23 were coinfecting with HIV and when these were excluded, the total sensitivity increased to 76.5%, with a total specificity of 80.8% and a total positive predictive value of 61.8%. The serotyping assay showed a high total sensitivity (96.3%) for samples positive by HCV RIBA, version 3.0, with four bands. We conclude that the sensitivity of the RIBA HCV serotyping SU is limited by the immunocompetence of the HCV-infected host. In general, samples from HIV-negative individuals containing genotype 1a had higher sensitivity, specificity, and concordance in the serotyping assay compared with genotyping, whereas samples containing genotype 3a were found to be more cross-reactive and untypeable. Therefore, the prevalence of genotypes other than genotype 1 could be underestimated if they are determined by serotyping, and improvements in specificity are recommended.

Y. van Duynhoven, M. J. W. van de Laar, W. A. Schop, P. H. Rothbarth, W. I. van der Meijden, A. M. van Loon and M. J. W. Sprenger. Prevalence and risk factors for hepatitis B virus infections among visitors to an STD clinic. *Genitourinary Medicine*. 1997; 73(6):488-492

Objective: To determine the prevalence and risk factors for hepatitis B virus (HBV) infections among individuals attending an STD clinic in a low endemic region. Study design: A total of 1228 women and 1648 men attending the STD clinic at the University Hospital Rotterdam, Netherlands, were examined for HBV infection by determination of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B core antigen (anti-HBc). Demographic characteristics, information on sexual behaviour, and intravenous drug use were recorded. Results: The seroprevalence of HBsAg was 1.4% in women and 2.1% in men (0% in homosexual men). The seroprevalence of anti-HBc was 13% in women and 20% in men (36% in homosexual men). Native country, intravenous drug use, a history of STD, and the number of partners in the past half year (inversely) were independent risk factors for HBsAg positivity in women and heterosexual men. For anti-HBc independent associations were observed for native country, age, intravenous drug use, commercial sex, number of lifetime partners, homosexual contacts, orogenital contact (inverse), and a history of STD. Conclusion: The HBV prevalence in the STD clinic attendants

was high, exceeding the national estimate, and indicates that the STD clinic population may be considered a high risk group. Our data confirmed an increased risk for HBV infections among established risk groups. Therefore, these risk groups should be routinely screened to identify HBV cases for counselling and contact tracing.

M. H. J. Molijn, J. M. vanderLinden, L. K. Ko, J. Gorgels, W. Hop and D. J. vanRhenen. Risk factors and anti-HBc reactivity among first time blood donors. *Vox Sanguinis*. 1997; 72(4):207-210
Background and objectives: The usefulness of testing for antibody to hepatitis B core antigen (anti-HBc) as a surrogate marker for non-A, non-B hepatitis can no longer be clearly established in the face of anti-hepatitis C virus testing. Application of anti-HBc testing in blood donors for detection of hepatitis B in addition to hepatitis B surface antigen testing (HbsAg) is a matter of debate. Materials and methods: We examined the serology and risk analysis data in a group of first-time blood donors. In 1.48% of 16,081 donors, anti-HBc reactivity was found. We invited a study group of 112 donors for extensive interviewing about the risk of blood transmissible diseases, and for serological testing. A control group of 240 first-time donors was studied as well. Results: In the study group, the age was older ($p < 0.001$), a history of liver disease was more frequent ($p < 0.001$), and the donor ($p < 0.001$) or the donor's partner ($p < 0.05$) had either stayed longer in an HBV-endemic area or had been born in one. Combining these with the serological results, we found that strong anti-HBc reactivity was related to hepatitis B risk factors in HBsAg-negative donors. Conclusion: Anti-HBc testing in HbsAg-negative first-time donors makes it possible to identify hepatitis B risk factors with a prevalence of 0.02%. Our findings also stress the importance of including the history of the donor's partner(s) in the risk analysis before blood donation.

I. Keur, P. M. Schneeberger, Y. van der Graaf, J. Vos, W. C. van Dijk and L. J. van Doorn. Risk factors for HCV infection in two haemodialysis units in The Netherlands. *Neth J Med*. 1997; 50(3):97-101
BACKGROUND: In order to assess risk factors for HCV infection during haemodialysis, all patients receiving haemodialysis for more than 6 months in two separate units in the Netherlands were studied retrospectively. METHODS: Antibodies to HCV, HCV-RNA and HCV genotypes were determined. Risk factors were identified by analysis of an extensive collection of clinical data. RESULTS: In unit A, 8 out of 75 (11%) patients and in unit B 4 out of 122 (3%) patients had antibodies to HCV. Eleven out of the 12 anti-HCV-positive patients had detectable HCV-RNA. Genotyping showed the presence of 4 different genotypes in unit A (1, 1a, 2b, and 3a). Three patients in unit B were infected with the same genotype (1b), where one of these patients was also infected with genotype 1a. One patient in unit B did not have detectable HCV-RNA. The risk of acquiring a HCV infection in unit A was associated with the number of blood transfusions. However, in unit B this risk was associated with the duration of dialysis. Other factors such as the number of surgical procedures were not associated with HCV infection. CONCLUSIONS: Blood transfusions and the dialysis process itself are important and independent risk factors for HCV transmission in dialysis patients. Surgical events do not appear to be important risk factors. However, relative risks may vary considerably between different dialysis centres.

R. del Canho, P. M. Grosheide, J. A. Mazel, R. A. Heijtkink, W. C. Hop, L. J. Gerards, G. C. de Gast, W. P. Fetter, J. Zwijneberg and S. W. Schalm. Ten-year neonatal hepatitis B vaccination program, The Netherlands, 1982-1992: protective efficacy and long-term immunogenicity. *Vaccine*. 1997; 15(15):1624-30
From 1982 to 1989, 705 infants born to HBsAg-positive mothers entered the Dutch neonatal hepatitis B vaccination program and received passive-active hepatitis B immunization in three randomized controlled trials testing variations in time of starting active vaccination, dose and type of vaccine, and number of hepatitis B immunoglobulin (HBIG) injections. A meta-analysis of individual patient data of the three randomized trials was performed to determine which independent host and vaccination related factors influence protective efficacy and long-term immunogenicity, and to assess whether hepatitis B vaccination concomitant with standard DKTP vaccination provides optimal protection. Statistical methodology included multivariate logistic regression analysis. Eight infants (1.1%), all born to HBsAg-positive mothers, became HBsAg carriers within the first year of life. The protective efficacy rate (PER) of passive-active immunization at 12 months follow-up was 92% for the total group of children from 114 HBsAg-positive mothers with no significant differences between children starting active immunization at birth or at 3 months of age, between infants starting at 3 months of age receiving one or two doses of HBIG or between those receiving plasma derived or recombinant vaccine. The only factor that affected the PER

significantly was the level of maternal HBV DNA; PER was 100% if maternal HBV DNA was < 150 pg ml⁻¹ and 68% for HBV DNA levels > 150 pg ml⁻¹. After 5 years of follow-up, the group that started active immunization at birth had significantly more infants with loss of seroprotection (anti-HBs levels < 10 IU l⁻¹, 15%) than the corresponding group starting at 3 months of age (anti-HBs < 10 IU l⁻¹, 2%). One of 35 children with loss of seroprotection at 2 years became a HBsAg carrier in the fifth year of follow-up. This meta-analysis shows that the protective efficacy of passive-active hepatitis B vaccination is mainly influenced by maternal HBV DNA levels, and independent of the time of starting active vaccination at birth or at 3 months of age; long-term immunity was enhanced by starting active vaccination concomitant with DKTP vaccination. These findings allow incorporation of hepatitis B vaccine into the standard infant immunization programs for countries with a passive-active immunization strategy for the control of hepatitis B. Additional measures are needed to protect neonates of highly viremic women.

X. Q. Chen, M. Bulbul, G. C. de Gast, A. M. van Loon, D. R. Nalin and J. van Hattum. Immunogenicity of two versus three injections of inactivated hepatitis A vaccine in adults. *J Hepatol.* 1997; 26(2):260-4
AIM: To investigate the immunogenicity of two versus three injections of inactivated strain CR326F-derived hepatitis A vaccine in healthy adults. METHODS: Healthy adult volunteers (n = 105) at Utrecht University Hospital, The Netherlands, were randomly assigned to receive intramuscular injections (deltoid muscle) of 25 Units (U) at 0 and 6 months (group A, n = 53), or at 0, 2 and 6 months (group B, n = 52). Blood was drawn before and at various time points after vaccination for determination of serum antibody to hepatitis A (anti-HAV). RESULTS: One month after the first injection, the seroconversion rates (> or = 10 mIU/ml, international units) were 88% for group A and 90% for group B. Only 2/ 103 (one in each group) showed IgM anti-HAV. One month after the second injection, seroconversion rates were 100% in both groups. At months 3, 6 and 7, anti-HAV geometric mean titers were significantly different because of the different vaccination schedules, but they were similar at months 1, 2 and 12. The anti-HAV geometric mean titer increase after the second injection was higher when the interval between the two doses was of longer duration. Anti-HAV titers of females were significantly higher than those of males and vaccinees < or = 30 years had higher titers than those > 30 years. CONCLUSIONS: Two 25 U doses of the vaccine investigated given at 0 and 6 months, induce adequate anti-HAV titers in all adult healthy vaccinees and are as immunogenic as three doses given at 0, 2 and 6 months.

Y. Reisman, C. H. Gips, S. M. Lavelle and J. H. Wilson. Clinical presentation of (subclinical) jaundice--the Euricterus project in The Netherlands. United Dutch Hospitals and Euricterus Project Management Group. *Hepatogastroenterology.* 1996; 43(11):1190-5
BACKGROUND: From a primary clinical database, we wanted to obtain insight in disease distribution and clinical presentation of adult jaundiced patients in a Western country. MATERIALS AND METHODS: As part of the Euricterus project, 24 Dutch general and academic hospitals in a period of 2 years gathered prospectively 702 patients on a standard proforma. Patient aged 16 years or more (median 61) and with a serum bilirubin of 20 mmol/l or more (median 83) were included. The final diagnosis was established within 3 months. RESULTS: Pancreatic or biliary carcinoma (20%), gallstone disease (13%) and alcoholic liver cirrhosis (10%) were the 3 most frequent diagnoses. Imaging (79%), clinical course (63%) and chemistry/serology (57%) were the most used ascertaining methods. Pancreatic or biliary carcinoma and gallstone disease were more common and age higher in general hospitals (p = 0.0001), and 'immunological' liver disease, non-alcoholic cirrhosis and hepatocellular carcinoma (HCC) more common in academic hospitals (p = 0.001). Patients aged 90 years or older (13%) had pancreatic or biliary carcinoma, liver metastases or heart failure and patients with age less than 20 (0.9%) had acute viral hepatitis, nonalcoholic active liver disease or HCC. Risk factors were more apparent (p < 0.02) in those aged less than 61 years. Feeling unwell (78%), dark urine (67%) and anorexia (57%) were the 3 most frequent symptoms; the 3 most frequent signs were liver enlarged (39%), looking ill (29%) and appearing wasted (23%). CONCLUSIONS: Through Euricterus, fresh clinical knowledge has emerged of symptomatology, age stratification and hospital preponderance of (sub)clinical jaundice in this country. This is important both for teaching and in preparing clinical studies.

L. J. van Doorn, G. E. Kleter, L. Stuyver, G. Maertens, J. T. Brouwer, S. W. Schalm, R. A. Heijtkink and W. G. Quint. Sequence analysis of hepatitis C virus genotypes 1 to 5 reveals multiple novel subtypes in the Benelux countries. *J Gen Virol.* 1995; 76(Pt 7):1871-6
Hepatitis C virus (HCV) isolates from a cohort of 315 patients from the Benelux countries (Belgium, The

Netherlands, Luxembourg) were genotyped by means of reverse hybridization Inno-LiPA (line probe assay). Genotypes 1a, 1b, 2a, 2b, 3a, 4a and 5a were detected. From the cohort, isolates representing all types and those showing an aberrant LiPA pattern were further analysed by sequencing parts of the 5' UTR, core (nt 1 to 326; aa residues 1 to 108) and core/E1 (nt 477 to 924; aa residues 159 to 308) regions. Molecular evolutionary analysis of the core and core/E1 regions allowed discrimination between known and additional subtypes, especially within types 2 and 4. The core region is not suitable for classification of new subtypes because of the relatively high level of conservation. The core/E1 region displays a higher level of sequence variation and allows much more distinct discrimination between subtypes. Genotypes 2 and 4 are particularly heterogeneous, with at least 7 and 10 subtypes, respectively. In contrast to previous reports from Europe, HCV isolates from the cohort constituted a highly heterogeneous population of virus variants, especially within genotypes 2 and 4.

M. Triemstra, F. R. Rosendaal, C. Smit, H. M. Vanderploeg and E. Briet. Mortality in Patients with Hemophilia - Changes in a Dutch Population from 1986 to 1992 and 1973 to 1986. *Annals of Internal Medicine*. 1995; 123(11):823-&

Objective: To determine causes of death and mortality rates in patients with hemophilia over a period of 20 years, to assess changes in mortality, and to distinguish between hemophilia-related death and recent death induced by viral infections. Design: Cohort study of 919 patients followed from January 1986 to June 1992. Results were compared with outcomes of previous follow-up from 1973 to 1986. Setting: Consecutive national questionnaire surveys on hemophilia, using patient registries of the Netherlands Hemophilia Society and Dutch hemophilia centers. Patients: 919 males with hemophilia A or B who participated in a national questionnaire survey on hemophilia in 1985. Median duration of follow-up was 6.4 years, which yielded 5753 person-years of follow-up. The mean age at study entry was 30 years (range, 1 to 85 years). Measurements: Standardized mortality ratios, causes of death, median life expectancy, age-adjusted relative risks associated with the type or severity of hemophilia, presence of inhibitors, prophylaxis, and human immunodeficiency virus infection. Results: 45 patients (5%) died between January 1986 and June 1992; 22.6 patients had been expected to die. Thus, the overall standardized mortality ratio was 2.0. The overall median life expectancy was 66 years for the cohort studied from 1973 to 1986 and 68 years for the cohort studied from 1986 to 1992. When deaths related to viral infection were excluded, the life expectancy almost equaled that of the general male population. Between 1986 and 1992, 1 patient died of ischemic heart disease compared with the 5.2 who were expected to die of this disease. Infection with HIV was the strongest independent predictor of death (relative risk, 27.5 [95% CI, 5.7 to 132.8]). After adjustment for HIV infection, no other hemophilia-related risk factors were associated with the risk for death. Conclusions: The acquired immunodeficiency syndrome and hepatitis strongly influence mortality in patients with hemophilia. In the absence of viral infections, the life expectancy of patients with hemophilia would almost equal that of the general male population.

E. P. Mauser Bunschoten, H. L. Zaaier, A. A. van Drimmelen, H. M. van den Berg, G. Rosendaal and P. N. Lelie. Risk of hepatitis A in Dutch hemophilia patients. *Thromb Haemost*. 1995; 74(2):616-8

Recently, clotting factor preparations transmitted hepatitis A virus (HAV) to hemophilia patients. To study the risk of HAV infection in Dutch hemophilia patients, serum samples of 341 patients with hemophilia were tested for HAV antibodies (anti-HAV). 197/341 patients (group 1) were treated with clotting factor concentrates produced from large plasma pools, 144/341 patients (group 2) were treated with small pool cryoprecipitate. The test results were compared to those of healthy blood donors (n = 19,746) of the same age. In addition stored serum samples (1983-1994) from hemophilia patients were tested for HAV antibodies. No increased risk of HAV infection was found in Dutch hemophilia patients. The anti-HAV prevalence in group 1 was 20%, in group 2 13% and in blood donors 41%. A significantly (p < 0.002) lower percentage of HAV antibodies was found in hemophilia patients born in the 1950s using cryoprecipitate (11%) as compared to blood donors of the same age (40%), probably caused by passive administration of anti-HAV through clotting product. Passive immunization in the past was significantly (p < 0.02) more often found in group 2 (41.7%) than in group 1 (28%). In the period 1983 till 1988 five seroconversions were seen in group 1 (2%) and one in group 2 (0.7%). Anti-HAV seroconversions were not observed after 1988. In a risk analysis we estimated that 2 plasma pools of 10,000 Dutch blood donors per year may contain HAV. The absence of HAV among Dutch hemophilia patients suggests that this contamination is successfully inactivated.

E. P. Mauser Bunschoten, D. Bresters, A. A. van Drimmelen, G. Roosendaal, H. T. Cuyper, H. W. Reesink, C. L. van der Poel, H. M. van den Berg and P. N. Lelie. Hepatitis C infection and viremia in Dutch hemophilia patients. *J Med Virol.* 1995; 45(3):241-6

Serum samples from 316 patients visiting the Dutch National Hemophilia Center were collected from 1979 to 1993 and stored at -30 degrees C. Patients were placed into three different groups: 1) patients ever treated with large pool non-hepatitis C virus (HCV)-safe concentrate (n = 179); 2) patients treated with cryoprecipitate (n = 125); and 3) patients treated exclusively with HCV-safe concentrate (n = 12). In order to examine the prevalence of HCV infection in the different treatment groups serum samples were tested retrospectively for anti-HCV antibody using second generation enzyme-linked immunosorbent assay (ELISA) and recombinant immunoblot assay (RIBA-2). Significant differences in the prevalence of HCV infection were found between these 3 groups (group 1: 99%, group 2: 66%, group 3: 0%). The safety of currently administered clotting products is demonstrated in 57 patients who remained without HCV markers between 1989 and 1993. To examine the natural course of HCV infection fresh-frozen plasma samples were obtained recently from a subgroup of 277 hemophilia patients for HCV-RNA detection by a well-validated cDNA-PCR assay. In contrast to other reports, no evidence was found for seronegative HCV carriers. None of 52 patients without anti-HCV had detectable HCV-RNA. Of 225 patients with anti-HCV, 182 (81%) were HCV-RNA positive. None of 39 anti-HCV positive patients with a negative HCV-RNA reaction had serum alanine aminotransferase (ALT) levels above 50 U/l, whereas 44% of HCV-RNA positive patients had persistently elevated ATL levels above 50 U/l. (ABSTRACT TRUNCATED AT 250 WORDS)

A. Leentvaarkuijpers, J. L. Kool, P. J. Veugelers, R. A. Coutinho and G. J. P. Vangriensven. An Outbreak of Hepatitis-a among Homosexual Men in Amsterdam, 1991-1993. *International Journal of Epidemiology.* 1995; 24(1):218-222

Background. When in August 1992 it became evident that an outbreak of hepatitis A virus infections (HAV) was taking place in the male homosexual community in Amsterdam a case-control study was conducted to validate the assumption that the outbreak was associated with sexual practices involving oro-anal and digital-anal contact and frequent visits to gay saunas and darkrooms. Methods. In all, 37 cases reported to the Amsterdam Municipal Health Service (AMHS) in the period December 1991 to March 1993 and 68 anti-HAV negative controls completed an anonymous questionnaire concerning the practice of different sexual techniques and the number of visits to gay saunas and darkrooms in the 2 months preceding the onset of illness or date of interview. Controls were recruited from healthy homosexual men participating in a prospective study on HIV/AIDS conducted by the AMHS. Results. In univariate analysis a statistically significant association was found between visits to gay saunas and darkrooms, the number of visits to these locations (OR = 8.2) and HAV infection. In the logistic regression analysis the association for visits to saunas and darkrooms remained significant (OR = 10) whereas high-risk sexual techniques could not be included in the model. Conclusions. These results indicate that to prevent future outbreaks of HAV in male homosexuals in Amsterdam there is a need to stress in the 'safe sex' campaigns, directed at the prevention of HIV infection or in additional campaigns, the prevention of other sexually transmitted disease including HAV infection with emphasis on routes associated with certain sexual techniques and on visits to gay saunas and darkrooms.

P. M. Grosheide, J. W. Wladimiroff, R. A. Heijtkink, J. A. Mazel, G. Christiaens, A. S. M. Nuijten, S. W. Schalm, A. Duerloovollaard, J. Zwijnenberg, T. Vanderlaar, J. R. J. Banffer, M. Bakkerbendik, M. J. Borrian, H. Ribbertsmeenk, G. G. Degast, L. J. Gerards, H. Vandijk, W. P. F. Fetter and W. Baerts. Proposal for Routine Antenatal Screening at 14 Weeks for Hepatitis-B Surface-Antigen. *British Medical Journal.* 1995; 311(7014):1197-1199

Objective-To develop a low cost, high compliance screening programme for identification of carriers of hepatitis B surface antigen in the obstetric population of the Netherlands. Design-A seven year open, descriptive study of screening for hepatitis B surface antigen as part of routine prenatal laboratory testing at 14 weeks of gestation. Compliance with programme evaluated by checking delivery records (hospitals) or registration of births in the 30 participating municipalities (rural area). Setting-Three large city hospitals (two tertiary referral centres) and one rural area with a large number of home deliveries. Subjects-99 706 pregnant women applying for prenatal care for the first time. Main outcome measures-Proportion of pregnant women routinely screened; prevalence of hepatitis B surface antigen in large cities and rural

area. Results-Uptake of screening reached 97% in the hospitals after inclusion of 10% screened at delivery; the estimated uptake in the rural area was >95%. Prevalence of hepatitis B surface antigen was 1.6% in the large cities and 0.3% in the rural area. For screening at delivery the prevalence was 2.5 times higher (4%, $P < 0.01$) than for screening at week 14 of gestation. Conclusion-Incorporation of universal testing for hepatitis B surface antigen into routine prenatal laboratory testing is practical; high compliance is achieved when screening is supplemented with rapid screening at delivery for those who escaped routine prenatal care.

P. M. Grosheide, J. M. Klokmanhouweling, M. A. E. Conynvanspaendonck, H. P. Verbrugge, R. Latuperisa, J. A. Mazel, A. A. Lems, T. D. Ypma, L. J. Gerards, G. J. Aarts, D. J. A. Bolscher, G. J. J. Duffels, A. Koppenaar, B. Engel, J. G. Vandervoorn, E. H. Koster and J. B. Vandersteur. Program for Preventing Perinatal Hepatitis-B Infection through Screening of Pregnant-Women and Immunization of Infants of Infected Mothers in the Netherlands, 1989-92. *British Medical Journal*. 1995; 311(7014):1200-1202

Objectives-To launch a programme for the prevention of perinatal infection with hepatitis B in the Netherlands. Design-Routine antenatal screening and intervention programme. Setting-Community antenatal programme, the Netherlands. Subjects-Infants of mothers who were carriers of hepatitis B detected by routine screening. Interventions-Infants of infected mothers received hepatitis B immunoglobulin at birth and four doses of hepatitis B vaccine in conjunction with routine immunisation at 3, 4, 5, and 11 months of age. Main outcome measures-Results of screening and immunisation from 1989-92. Results-The coverage of screening increased from 46% in 1989 to 84% in 1992. Hepatitis B surface antigen was detected in 2145 women (0.44%). The coverage of postnatal immunoprophylaxis in 1645 neonates born to mothers who were carriers of hepatitis B was 85% (1398); in 3% (42) there was a delay in administration of immunoglobulin of over 24 hours. In 1991, 96% (537), 95% (532), 94% (525), and 87% (489) of the infants received the first, second, third, and fourth dose of vaccine, respectively. There was considerable variation in the timing of vaccination; 17% (258) of the infants received their first dose more than two weeks late. Of the 59% (583) of infants who received the fourth dose more than two weeks beyond target age, 14% (141) also received their first dose too late. Conclusions-A prevention programme for perinatal hepatitis B in an area of low prevalence, when incorporated into existing health care, is feasible and achieves satisfactory coverage rates. Intensive follow up is needed to improve adherence to the immunisation schedule.

R. A. deMan, R. P. Sprey, H. G. M. Niesters, R. A. Heijtink, P. E. Zondervan, W. Hop and S. W. Schalm. Survival and complications in a cohort of patients with anti-Delta positive liver disease presenting in a tertiary referral clinic. *Journal of Hepatology*. 1995; 23(6):662-667
Background/Aims: Our aim was to evaluate the clinical outcome and survival of patients with anti-Delta positive liver disease in The Netherlands. Methods: We evaluated those patients visiting our hospital between 1978 and 1993 with respect to clinical, virological and histological parameters. During the follow-up period the occurrence of complications of the liver disease and survival was determined. Thirty patients with a median age of 34 years (range 21-52) were included. Results: During an average follow up of 4.8 years, nine patients died. The overall 5-year survival as estimated by Kaplan-Meier analysis was 71%, which was comparable to hepatitis B cirrhosis patients. However, in the group without active hepatitis B replication (HBeAg-negative) a clear trend towards a worse survival was identified in Delta cirrhosis patients. Complications and deaths occurred exclusively in the patient group with cirrhotic liver disease. The complications (ascites, elevated bilirubin $>33 \mu\text{mol/l}$), variceal bleeding and spontaneous bacterial peritonitis) occurred in 52% of the patients with a follow up of more than 6 months ($n=27$). Fifty-seven percent of those patients died. In our population anti-Delta positive liver disease affects predominantly young patients and is related to advanced liver disease. Conclusions: In view of the high death rate, liver transplantation should be considered when signs or symptoms of decompensated liver disease occur.

G. J. J. Vandoornum, H. J. A. Vanhaastrecht, C. Hooykaas, J. A. R. Vandenhoeck, M. M. D. Vanderlinden and R. A. Coutinho. Hepatitis-B Virus-Infection in a Group of Heterosexuals with Multiple Partners in Amsterdam, the Netherlands - Implications for Vaccination. *Journal of Medical Virology*. 1994; 43(1):20-27

The aim of the study was to assess prevalence and incidence of hepatitis B virus (HBV) infection among

heterosexual men and women with multiple partners attending a sexually transmitted disease (STD) clinic and to establish risk factors of HBV infection in order to consider immunisation for those subjects. A prospective study of heterosexual men and women selected on having multiple partners and presenting to an STD clinic as new patients was carried out from October 1987 through December 1989. Follow-up continued until December 1990 at the STD clinic of the Municipal Health Service of Amsterdam. Five hundred ninety-eight men and women entered the study. More than 70% of both women and men had had commercial sexual partners in the last 5 years. Three hundred eighty-one participants were born in HBV low endemic countries, 205 came from HBV intermediate endemicity regions. The prevalence of HBV markers in both men and women from low endemic regions was 10%, and for men and women from middle endemic regions 42% and 19%, respectively. Logistic regression analysis showed that number of years involved in commercial sex was an independent risk factor in male participants from HBV low endemic regions (odds ratio [OR] 1.10 per year) and for women sexual contact with men at high risk of HBV infection (OR 2.59). In people from middle endemic regions more men than women had HBV markers, HBV-positive men were older than HBV-negatives (OR 1.05 per year), and for HBV-positive women the number of years involved in commercial sex was an independent predictor (OR 1.23 per year). No new cases of HBV infection were found in both groups (upper 95% limit of confidence 7.1 per 1,000 and 35.8 per 1,000 for the participants from low and middle endemic countries, respectively). The duration of follow-up was 419.9 person-years at risk for the group from low endemic regions and 83.7 person-years for the people from middle endemic regions. The participants must be considered to have been at continuous high risk of heterosexual transmission. The incidence of HBV was so low that we decided for the moment not to offer hepatitis B vaccination to all heterosexual men and women attending our STD clinic. (C) 1994 Wiley-Liss, Inc.

G. E. M. Kleter, L. J. Vandoorn, J. T. Brouwer, S. W. Schalm, R. A. Heijtkink and W. G. V. Quint. Sequence-Analysis of the 5' Untranslated Region in Isolates of at Least 4 Genotypes of Hepatitis-C Virus in the Netherlands. *Journal of Clinical Microbiology*. 1994; 32(2):306-310
The RNAs of hepatitis C virus (HCV) isolates from 62 patients with chronic HCV infection were analyzed by direct sequencing of the 5' untranslated region. Two important sequence motifs were recognized: one between positions -170 and -155 and the other between positions -132 and -117. These motifs are partly complementary. All three previously published genotypes were observed; 34 (55%) isolates were classified as type 1 (including prototype [from the United States] and HCV-BK [from Japan] sequences), 11 (18%) were classified as type 2 (including HC-J6 and HC-J8), and 12 (19%) were classified as type 3 (including EB1); one patient was infected with genotypes 1 and 2. Four (6%) isolates showed aberrant sequences and were therefore provisionally classified as genotype 4. These results indicate the significance of sequence variation among the 5' untranslated regions of different HCV genotypes and indicate that this region could possibly be used for consistent genotyping of HCV isolates.

R. Delcanho, P. M. Grosheide, M. Voogdschotanus, W. M. Huisman, R. A. Heijtkink and S. W. Schalm. Immunogenicity of 2 Different Dosages (10-Mu-G and 5-Mu-G) of Recombinant-DNA Hepatitis-B Vaccine in Healthy Neonates. *Vaccine*. 1994; 12(14):1323-1326
The immunogenicity of a half (5 mu g) and a full (10 mu g) dosage of recombinant DNA yeast-derived hepatitis B vaccine (HB-Vax-DNA) in healthy neonates was assessed in order to compare two candidate dosages of vaccine. After randomization 174 newborns of HBsAg-negative mothers entered the study. Neonates received four doses of either 10 or 5 mu g hepatitis B vaccine, according to the DTP-polio immunization schedule at months 3, 4, 5 and 11. No serious adverse reactions were observed; 15.5% of vaccinated newborns suffered mild transient local symptoms. The vaccine was highly immunogenic irrespective of dosage of vaccine; all infants developed anti-HBs levels greater than or equal to 10 IU l(-1), 99% greater than or equal to 100 IU l(-1). A dosage of 10 mu g hepatitis B vaccine produced higher antibody levels than 5 mu g hepatitis B vaccine after primary vaccination (first three doses) but not after booster vaccination (fourth dose) (p = 0.06 and 0.75, respectively). Either vaccine dosage can be recommended for incorporation in the Expanded Programme on Immunization in the Netherlands.

E. A. Beckers, P. M. Thijssen, T. Nijdam and D. J. Van Rhenen. Evaluation of anti-HCV ELISA seropositivity in voluntary blood donors: a proposal for donor counseling strategies. *Infusionsther Transfusionsmed*. 1994; 21(3):143-9
OBJECTIVE: To evaluate the anti-HCV (hepatitic C virus) reactivity for the development of an individual

donor counseling strategy which would prevent unnecessary donor deferment without compromising the safety of blood products. DESIGN: All donors, who were repeatedly reactive in the Ortho HCV ELISA as well as the Abbott HCV EIA screening tests were selected for follow-up testing. At follow-up three screening tests (Ortho, Abbott, and UBI HCV EIA) and two confirmation tests (Riba 4 and PCR HCV RNA) were performed. During the counseling interview risk factors and medical history were recorded. SETTING: Blood bank Zuid-Limburg, Maastricht, the Netherlands; estimated donor population 17,500. PARTICIPANTS: A total of 54 donors could be completely evaluated. RESULTS: The participants could be divided into five different categories, requiring specific donor information and different blood bank policies. The donors in categories 1 and 2 (n = 11) had false-positive reactions and were kept active. Category 3 and 4 donors (n = 28) showed indeterminate results and were permanently or temporarily excluded. Finally, in category 5 donors (n = 15) a HCV infection could be diagnosed on the basis of either Riba-positive or PCR-positive results. CONCLUSIONS: An anti-HCV screening policy should include a careful evaluation and confirmation of antibody reactivity. A strategy is suggested which allows an individual donor counseling, prevents unnecessary donor deferment, and avoids unnecessary fear of seropositivity.

H. L. Zaaijer, M. Kok, P. N. Lelie, R. J. Timmerman, K. Chau and H. J. H. Vanderpal. Hepatitis-E in the Netherlands - Imported and Endemic. *Lancet*. 1993; 341(8848):826-826

E. J. C. Vanameijden, J. A. R. Vandenhoeck, G. H. C. Mientjes and R. A. Coutinho. A Longitudinal-Study on the Incidence and Transmission Patterns of Hiv, Hbv and Hcv Infection among Drug-Users in Amsterdam. *European Journal of Epidemiology*. 1993; 9(3):255-262

In the present study data on the incidence of HBV and HCV were used to indicate the prevalence of and trends in risk behavior, assuming that drug users (DUs) who become infected with HBV or HCV are also at risk for infection with HIV. In addition, we determined to that extent the transmission patterns of HIV, HBV and HCV differed. DUs were selected from a cohort study in Amsterdam, had at least one follow-up visit between December 1985 and September 1989 and reported never to have had homosexual contacts. Among 305 DUs, of whom 70% injected recently, the prevalence of HIV, HBV and HCV were 31%, 68% and 65% respectively. These prevalences were strongly interrelated and the same risk factors were found. The cumulative incidence of either HIV or HBV or HCV was 30% among prevalent HIV-negatives. Despite a previously reported reduction in risk behavior, only the HIV incidence tended to decrease initially, and after 1986 the incidences of HIV, HBV and HCV remained disturbingly high and stable (mean: 4, 9 and 10 per 100 person-years, respectively). As at present HBV appears to be transmitted more heterosexually than HIV in our study group and the HIV-epidemic may follow the HBV-epidemic in its transmission patterns, preventive activities targeted at both injecting and sexual behavior should be expanded.

P. M. Schneeberger, J. Vos and W. C. Vandijk. Prevalence of Antibodies to Hepatitis-C Virus in a Dutch Group of Hemodialysis-Patients Related to Risk-Factors. *Journal of Hospital Infection*. 1993; 25(4):265-270

A. Leentvaar Kuijpers, S. Wiersma, G. J. van Doornum and R. A. Coutinho. Evaluatie van het hepatitis B-preventieprogramma bij pasgeborenen. II. Amsterdam, 1989-1991. [Evaluation of the hepatitis B prevention program in newborn infants. II. Amsterdam, 1989-1991]. *Ned Tijdschr Geneeskd*. 1993; 137(50):2594-8

OBJECTIVE. To evaluate the efficiency of the hepatitis B surface antigen (HBsAg) screening programme in pregnant women and the hepatitis B prevention programme in neonates of HBsAg-positive mothers from October 1989 to December 1991. DESIGN. Retrospective. SETTING. Amsterdam Public Health Service, the Netherlands. METHOD. Analysis of the data routinely collected from pregnant women and neonates of these women and calculation of the protective efficiency of this immunisation programme. RESULTS. In 1990, 79% and in 1991, 91% of all pregnant women were screened for HBsAg. The overall prevalence was 1.2% in 1990 as in 1991. Of the HBsAg-positive women 96% originated from countries where hepatitis B virus (HBV) is known to be endemic. At the age of ten months all infants had received passive and active immunisation. The anti-HBs titre was 10-50 IU/l in 8 (7%) infants, > 50 IU/l in 94 (88%), 3 were HBsAg-negative with no information on the anti-HBs titre and in 2 HBsAg was present. The protective efficiency of the immunisation schedule was 94% in children born of e-antigen-positive and

93% in children born of e-antigen-negative mothers. **CONCLUSION.** Active surveillance and intense follow-up are essential in achieving high coverage rates in screening of pregnant women and in immunising neonates of HBsAg-positive mothers.

H. L. Zaaijer, M. Kok and P. N. Lelie. Seroprevalentie van hepatitis E in Nederland. [Seroprevalence of hepatitis E in The Netherlands]. *Ned Tijdschr Geneeskd.* 1992; 136(44):2173-5

At serological testing of 269 blood samples from patients sent in for hepatitis diagnostics and of 275 randomly selected samples from blood donors from all over the Netherlands, eight and five samples, respectively, were found to contain a positive antibody titre against hepatitis E virus (HEV). Follow-up samples could be obtained from three patients: in one patient the anti-HEV IgG titre remained unchanged over a period of 6 months, in one other the titre fell below the limit of detection and in the third, the titre increased in a period of 2 weeks. This patient had developed jaundice after a stay in Bangladesh. It is possible that in some patients, hepatitis E is mistaken for hepatitis A.

P. Schneeberger, J. Vos, W. Vandijk and J. Vanhattum. Prevalence of Antibodies to Hepatitis-C Virus (Hcv) in a Dutch Group of Hemodialysis-Patients, Related to Risk-Factors. *Hepatology.* 1992; 16(4):A220-A220

G. J. J. Vandoornum, C. Hooykaas, M. T. Cuyper, M. M. D. Vanderlinden and R. A. Coutinho.

Prevalence of Hepatitis-C Virus-Infections among Heterosexuals with Multiple Partners. *Journal of Medical Virology.* 1991; 35(1):22-27

A study among heterosexual men and women with multiple sexual partners was carried out to assess the seroprevalence of antibody against hepatitis C virus (HCV). The 468 participants were recruited among visitors to the Clinic for Sexually Transmitted Diseases in Amsterdam. Sera were tested by an enzyme-linked immunosorbent assay (ELISA; Ortho), a recombinant-based immunoblot assay (RIBA; Chiron), and the polymerase chain reaction (PCR). A total of 468 persons were tested, and seven (1.5%) were found ELISA positive. Another 25 (5%) were ELISA indeterminate. Six of the seven ELISA-positive cases were RIBA positive. Further serum samples from five HCV ELISA-positive persons were tested by PCR, and four were found to be positive. The HCV ELISA-positive/RIBA-indeterminate reaction was PCR negative. None of the 17 RIBA-tested sera of the ELISA-indeterminate group yielded a positive result. There was a good correlation between an ELISA optical density/cut-off ratio greater than 2 and a positive RIBA result. The risk factor for HCV appeared to be the type of sexual partner, i.e., belonging to a "high-risk" group for human immunodeficiency virus infection and origin from hepatitis B-endemic countries. It is concluded that HCV may be transmitted through heterosexual contact but probably with low efficiency.

C. L. Van der Poel, H. W. Reesink, E. P. Mauser Bunschoten, R. H. Kaufmann, A. Leentvaar Kuypers, R. A. Chamuleau, W. Schaasberg, E. Bakker, P. J. Exel Oehlers, I. Theobalds and et al. Prevalence of anti-HCV antibodies confirmed by recombinant immunoblot in different population subsets in The Netherlands. *Vox Sang.* 1991; 61(1):30-6

The prevalence of antibodies to hepatitis C virus (anti-HCV) was studied in various population subsets in the Netherlands with anti-HCV C100 enzyme linked immunosorbent assay (ELISA), and confirmed with recombinant immunoblot assay (RIBA). Anti-HCV C100 ELISA positivity and RIBA positivity were found in 39 (0.7%) and 5 (0.1%) of 5,434 blood donors from Amsterdam; 25 (5%) and 2 (0.4%) of 481 blood donors from Surinam (South America); 19 (9%) and 2 (1%) of 213 multitransfused patients; 28 (4%) and 15 (2%) of 633 hemodialysis patients; 179 (80%) and 150 (67%) of 225 hemophilia A and B patients; 8 (80%) and 4 (40%) of 10 intravenous drug abusers; 18 (15%) and 2 (2%) of 119 anti-HIV-positive homosexual men; 2 (2%) and none of 106 anti-HIV-negative homosexual men; 6 (32%) and 3 (16%) of 19 patients with acute hepatitis non-A, non-B (NANBH); 13 (65%) and 8 (40%) of 20 patients with chronic NANBH and/or cryptogenic cirrhosis; and 4 (40%) and 1 (10%) of 10 patients with idiopathic autoimmune chronic hepatitis. Among blood donors, a positive correlation between a history of jaundice after the age of 18 years and the presence of RIBA-confirmed anti-HCV antibodies was found. Among both blood donors and hemodialysis patients, a positive correlation of RIBA-confirmed anti-HCV positivity with elevated alanine aminotransferase levels, but not with the presence of anti-hepatitis B core antibodies was found.(ABSTRACT TRUNCATED AT 250 WORDS)

C. van der Poel, H. Cuypers, H. Reesink, Q. L. Choo, G. Kuo, J. Han, S. Quan, A. Polito, J. Verstraten, J. van de Wouw and et al. Risk factors in hepatitis C virus-infected blood donors. *Transfusion*. 1991; 31(8):777-9

Risk factors of parenteral and nonparenteral exposure to hepatitis C virus (HCV) infection were studied in 125 blood donors in The Netherlands who were positive for anti-HCV on enzyme-linked immunosorbent assay (ELISA). Risk factors were related to confirmatory test results of four-antigen recombinant immunoblot assay (4-RIBA) and polymerase chain reaction (PCR) of the HCV 5' untranslated region. Twelve (10%) of the 125 anti-HCV C100 ELISA-positive blood donors were 4-RIBA positive. Eleven (92%) of 12 4-RIBA-positive blood donors were PCR positive, and all 113 remaining 4-RIBA-negative or -indeterminate donors were PCR negative. Eleven (92%) of 12 4-RIBA-positive blood donors had a risk factor of parenteral exposure, as compared to 17 (15%) of 113 4-RIBA-negative or -indeterminate donors. The prevalence of confirmed HCV infection among Amsterdam blood donors is calculated at 0.04 percent; parenteral exposure appears to be the major risk factor for HCV infection.

E. C. Buning. Effects of Amsterdam Needle and Syringe Exchange. *International Journal of the Addictions*. 1991; 26(12):1303-1311

The needle and syringe exchange in Amsterdam was initiated in 1984 by the Junky Union. To date, ample data are available to support the role of the needle exchange in facilitating drug injectors to use drugs in a safer way: no increase in drug use could be validated, participants of the exchange schemes were less involved in needle sharing, the supply of large quantities of needles to drug users did not lead to an increase in needle stick accidents by the general public, and, finally, the HIV prevalence among drug injectors has remained stable since 1986, while the incidence of acute hepatitis B has gone down.

J. A. R. Vandenhoek, H. J. A. Vanhaastrecht, J. Goudsmit, F. Dewolf and R. A. Coutinho. Prevalence, Incidence, and Risk-Factors of Hepatitis-C Virus-Infection among Drug-Users in Amsterdam. *Journal of Infectious Diseases*. 1990; 162(4):823-826

C. L. van der Poel, H. W. Reesink, P. N. Lelie, A. Leentvaar Kuypers, Q. L. Choo, G. Kuo and M. Houghton. Anti-hepatitis C antibodies and non-A, non-B post-transfusion hepatitis in The Netherlands. *Lancet*. 1989; 2(8658):297-8

In a prospective study carried out in the Netherlands (1984-86) to establish the incidence of post-transfusion hepatitis non-A, non-B (PTH-NANB) in patients undergoing open heart surgery, 393 patients received 5315 blood product transfusions. PTH-NANB developed in 9 patients (index cases); stored serum samples from these patients and from 9 control patients, matched for age, sex, and number of blood product transfusions, as well as serum samples of all implicated blood products, were selected retrospectively. Sera were tested under code with a radioimmunoassay for the detection of antibodies to hepatitis C virus (anti-HCV). PTH-NANB patients received 151 blood product transfusions and control patients 140. 4 of 9 PTH-NANB patients (3/5 chronic, 1/4 acute resolved hepatitis) and 0/9 controls seroconverted. 7 of the transfusions given to PTH-NANB patients but none of those given to control patients were anti-HCV positive. In 7 of 9 serum sets from PTH-NANB index cases plus implicated donors, either a donor or the recipient was anti-HCV positive. Among the donors implicated in transmission of PTH-NANB there was a strong correlation between raised alanine aminotransferase levels and the presence of anti-HCV antibodies.

S. W. Schalm, J. A. Mazel, G. C. Degast, R. A. Heijtkink, M. J. Botman, J. R. J. Banffer, L. J. Cerards, J. Zwijnenberg, W. P. F. Fetter, A. S. M. Nuijten, Y. W. Wladimiroff and G. Christiaens. Prevention of Hepatitis-B Infection in Newborns through Mass-Screening and Delayed Vaccination of All Infants of Mothers with Hepatitis-B Surface-Antigen. *Pediatrics*. 1989; 83(6):1041-1047

H. W. Reesink, A. Leentvaarkuypers, C. L. Vanderpoel, P. N. Lelie, R. N. I. Pietersz, D. K. F. Mulderfolkerts, T. Pieters, A. Vandenende, W. Schaasberg and R. A. Coutinho. Non-a Non-B Posttransfusion Hepatitis in Open-Heart-Surgery Patients in the Netherlands - a Prospective Trial. *Journal of Medical Virology*. 1987; 21(4):A44-A44

R. A. Heijtkink, S. W. Schalm, J. Kruining, M. J. M. Tyrrellheijgen, P. Bakker, J. Boot, P. I. M. Schmitz and N. Masurel. Hepatitis-B Vaccination in Health-Care Workers - Assessment of Simple Guidelines.

Netherlands Journal of Medicine. 1987; 30(3):117-127

D. de Hoop, W. J. Anker, R. van Strik, N. Masurel and E. Stolz. Hepatitis B antigen and antibody in the blood of prostitutes visiting an outpatient venereology department in Rotterdam. *Br J Vener Dis*. 1984; 60(5):319-22

We took blood samples from 128 prostitutes visiting the outpatient venereology department of the University Hospital, Rotterdam-Dijkzigt to test for the presence of hepatitis B surface antigen (HBsAg) and antibody to hepatitis B surface antigen (anti-HBs). The prevalence of anti-HBs was found to be significantly higher in the group of prostitutes than in "normal populations", and we concluded that more of the former had been in contact with the hepatitis B virus (HBV). We recommend that the advice on vaccination of the hepatitis B committee of the Health Council of The Netherlands should be followed by screening prostitutes for the presence of HBsAg and anti-HBs in the blood, and vaccinating those who have no anti-HBs.

E. E. Reerinkbrongers, P. N. Lelie, H. W. Reesink, P. J. Dees, H. G. J. Brummelhuis and W. G. Vanaken. Immunogenicity and Safety of Heat-Inactivated Hepatitis-B Vaccine (C1b) in Low-Risk Human Volunteers and in Patients Treated with Chronic-Hemodialysis in the Netherlands. *Developments in Biological Standardization*. 1983; 54(197-203

R. A. Coutinho, P. N. Lelie, P. Albrechtvanlent, L. Stoutjesdijk, J. Huisman, H. Kuipers, L. J. T. Schut, E. E. Reerinkbrongers, H. W. Reesink and W. G. Vanaken. Efficacy Trial of Heat-Inactivated Hepatitis-B Vaccine (C1b) in Male-Homosexuals in the Netherlands. *Developments in Biological Standardization*. 1983; 54(287-292

R. A. Coutinho, P. Albrechtvanlent, N. Lelie, N. Nagelkerke, H. Kuipers and T. Rijdsdijk. Prevalence and Incidence of Hepatitis-a among Male-Homosexuals. *British Medical Journal*. 1983; 287(6407):1743-1745

R. A. Heijntink, J. Vanhattum, S. W. Schalm and N. Masurel. Co-Occurrence of Hbsag and Anti-Hbs - 2 Consecutive Infections or a Sign of Advanced Chronic Liver-Disease. *Journal of Medical Virology*. 1982; 10(2):83-90

J. H. M. Berden, A. J. Hoitsma, W. Buijs, P. Reekers, S. H. Skotnicki, F. M. J. Debruyne and R. A. P. Koene. Results of Kidney Transplantations in Nijmegen (1968-1981). *Netherlands Journal of Medicine*. 1982; 25(3):73-78

J. R. J. Banffer. Markers of Hepatitis-B in a Group of Vietnamese Boat-Refugees in the Netherlands. *Tropical and Geographical Medicine*. 1982; 34(3):251-255

J. N. Katchaki, T. H. Siem, R. Brouwer, A. M. Vanloon and J. T. M. Vanderlogt. Post-Transfusion Non-a, Non-B Hepatitis in the Netherlands. *British Medical Journal*. 1981; 282(6258):107-108

A. Bleeker, R. A. Coutinho, J. Bakkerkok, D. Tio and G. A. J. Dekoning. Prevalence of Syphilis and Hepatitis-B among Homosexual Men in 2 Saunas in Amsterdam. *British Journal of Venereal Diseases*. 1981; 57(3):196-199

H. W. Reesink, I. C. E. Wesdorp, R. Grijm, P. Hengeveld, A. C. Jobsis, C. Aay and E. E. Reerinkbrongers. Follow-up of Blood-Donors Positive for Hepatitis-B Surface-Antigen. *Vox Sanguinis*. 1980; 38(3):138-146

H. W. Reesink, L. J. T. Lafeberschut, C. Aaij and E. E. Reerinkbrongers. Comparison of 6 3rd-Generation Tests for the Detection of Hbsag. *Vox Sanguinis*. 1980; 39(2):61-72

R. A. Coutinho, W. Duermeyer and J. Vanderveen. Epidemiology of Hepatitis a in Amsterdam, October 1978 December 1979. *Journal of Virological Methods*. 1980; 2(1-2):47-55

A. J. M. Vogten, I. H. Siegenbeekvanheukelom and L. Kater. Frequency and Clinical Significance of Hepatitis-a Antibodies in the Netherlands. *Netherlands Journal of Medicine*. 1979; 22(1):10-12