Background document

"Burden and prevention of Viral Hepatitis in Arctic region."

Viral Hepatitis Prevention Board Meeting
Copenhagen, Denmark, 22-23 March 2012.

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Content

This pre-meeting document contains general information on the Arctic Region and a list of selected abstracts/ references from a Pubmed MEDLINE search on different search terms. The references are ranged by publication year (most recent first) and for each year in alphabetical order of the first author's name.

1. Arctic general background

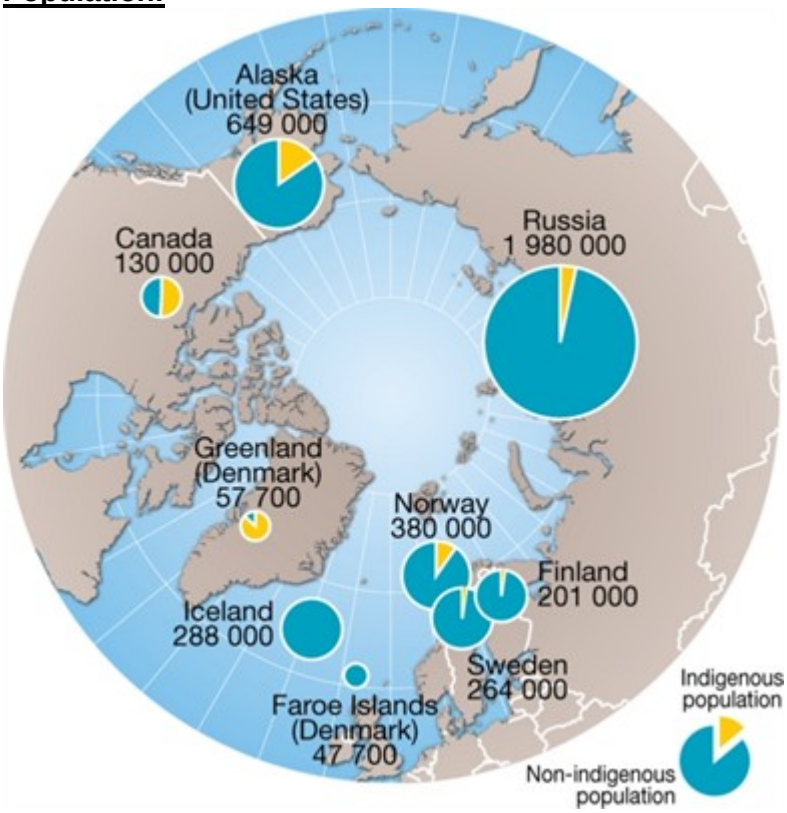
(Source World factbook https://www.cia.gov/library/publications/the-world-factbook/graphics/ref_maps/pdf/arctic.pdf)

(Wikipedia)

The Arctic is a polar region located at the northern-most part of the Earth. The Arctic consists of the Arctic Ocean and parts of Canada, Russia, Greenland, the United States, Norway, Sweden, Finland, and Iceland. The Arctic region consists of a vast, ice-covered ocean, surrounded by treeless permafrost. The area can be defined as north of the Arctic Circle (66° 33'N), the approximate limit of the midnight sun and the polar night. Alternatively, it can be defined as the region where the average temperature for the warmest month (July) is below 10 °C (50 °F); the northernmost tree line roughly follows the isotherm at the boundary of this region.

Socially and politically, the Arctic region includes the northern territories of the eight Arctic states, although by natural science definitions much of this territory is considered subarctic. The Arctic region is a unique area among Earth's ecosystems. The cultures in the region and the Arctic indigenous peoples have adapted to its cold and extreme conditions.

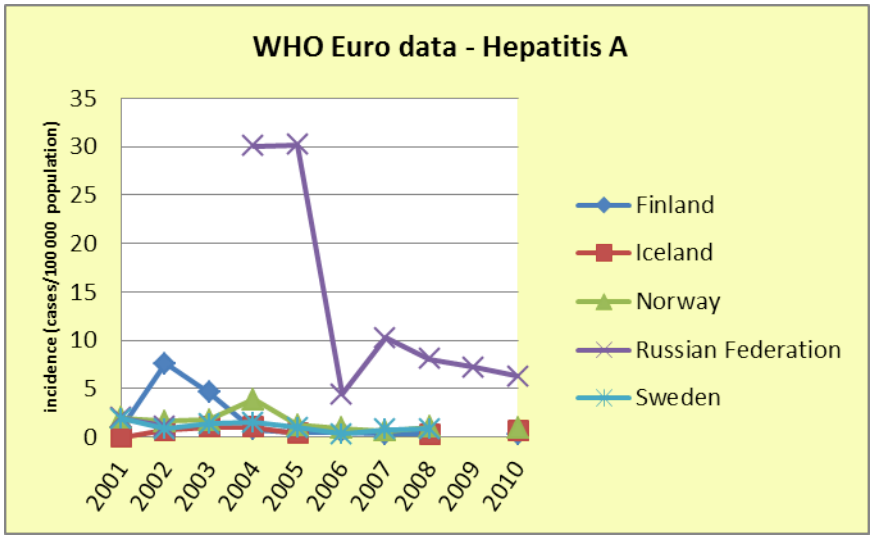
Population:

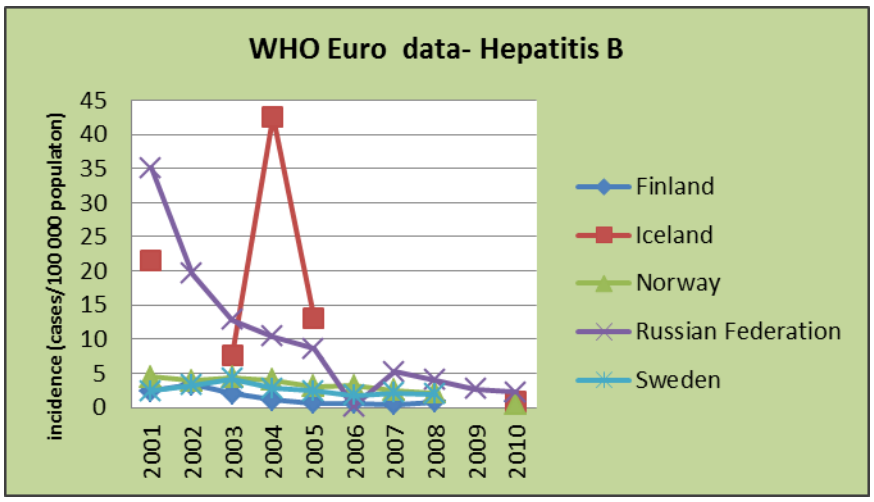


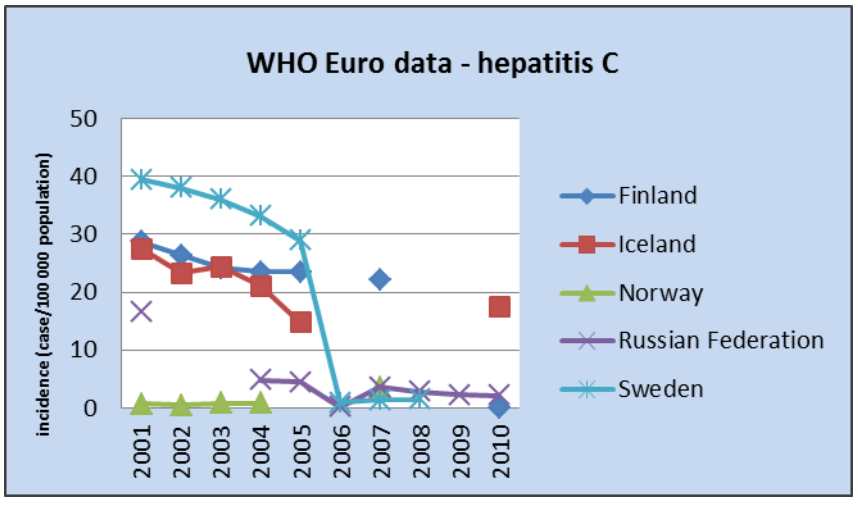
Source: Arctic Pollution Issues: A State of the Arctic Environment Report. Stefansson Arctic Institute, 2004. Arctic Human Development Report.

Hepatitis epidemiological data

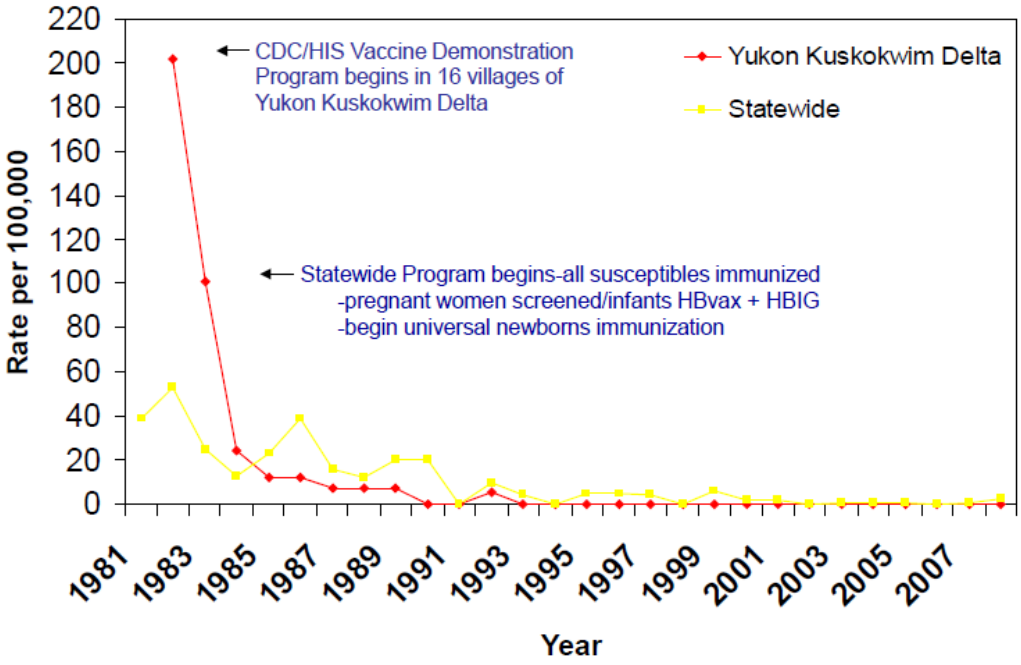
(Source: WHO Cisid database – No specific Arctic data but data on country level not on regional level – used case definition not specified)



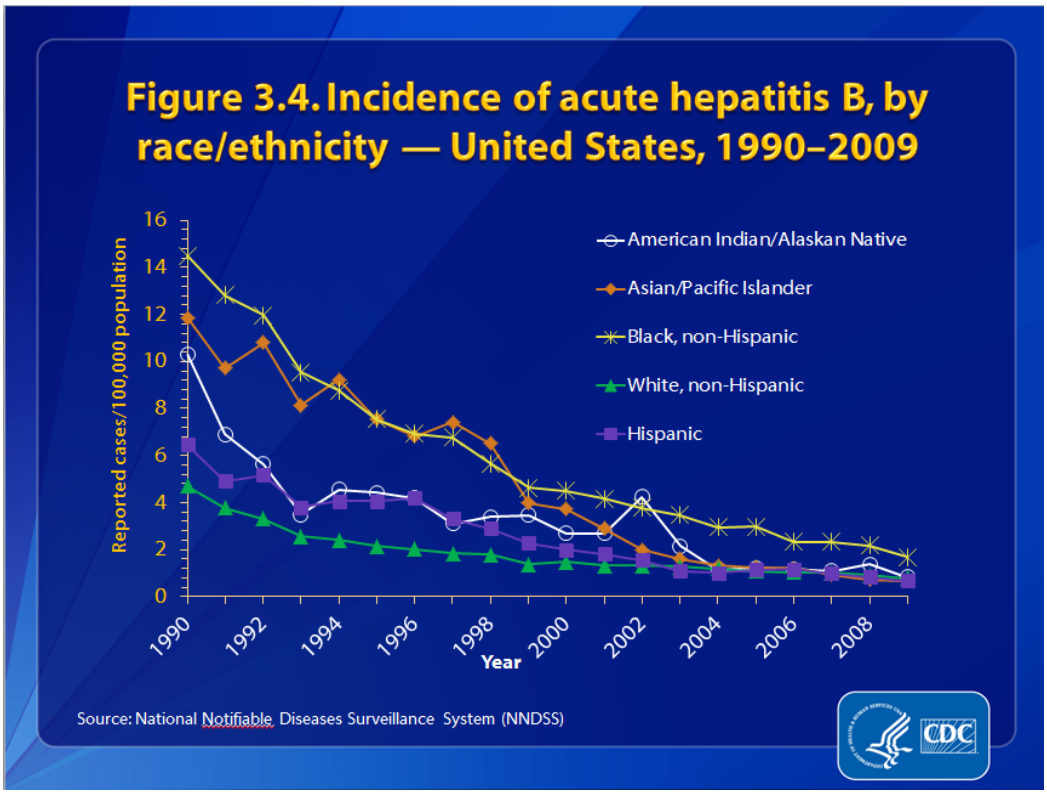




Alasaka: Incidence symptomatic Hepatitis B in Alaska Native peoples 1981-2008



(Source: presentation Brian McMahon, VHPB Milan meeting nov 2011)



2. Hepatitis in Arctic Region

Pubmed MEDLINE search on on *(hepatitis OR HAV OR HBV OR HCV OR HDV OR HEV) AND (epidemiology OR prevention OR vaccin OR vaccination OR control OR surveillance OR prevalence OR diagnostics) AND (arctic OR Alaska* OR alaska Native* OR Athapaskan* OR Athabaskan* OR Athabascan* OR haida OR Tlingit* OR tsimshian OR tuchone OR Inuit* OR Eskimo* OR inupiat OR yupik OR Aleut* OR* **munami t** *OR sami OR* **sawmi** *OR* **yap ik** *OR* **cupik** *OR lapland OR canadian north OR arctic regions OR arctic canada OR circumpolar OR northwest territories OR nunavut OR northern british columbia OR northern alberta OR northern saskatchewan OR northern manitoba OR northern quebec OR yukon OR norway OR sweden OR greenland OR faroe islands OR Iceland* OR Siberia* OR* **yakuta** *OR sakhalin OR russian far east OR kamchatka OR northwest territories OR nordic OR arctic regions OR chukotka OR svalbard OR rovaniemi OR oulu OR norwegian arctic OR sweden arctic OR danish arctic institute OR arctic finland OR finland arctic OR* **greenland c***) NOT autoimmune*)} in all fields and published **from 2007** on**,** was performed. After a manual search only the references and the abstracts really related to viral hepatitis and Arctic region were selected and classified by region. The references are ranged by publication year (most recent first) and for each year in alphabetical order of the first author's name.

General Arctic (2)

Tulisov, A., B. J. McMahon, A. Koch, G. Minuk, V. Chulanov, M. G. Bruce, J. Uhanova, M. Borresen, J. Williams, C. Osiowy, et al. "**Viral hepatitis in the Arctic. A review from a Circumpolar Workshop on Viral hepatitis, ICCH13**." Alaska Med **2007** 49(2 Suppl): 193-203.

This article is a review of the viral hepatitis workshop, held during the 13th International Congress of the Circumpolar Health consists of a review of data on viral hepatitis in the Arctic territories of four countries: Canada, Greenland, Russia and United States (Alaska). The main purpose of the workshop was to exchange knowledge on viral hepatitis in the Arctic and identify further needs for collaborative hepatitis research, which is planned to be implemented through the established Viral Hepatitis Working Group in the Arctic. The review is based on the available published research results, surveillance data and professional opinions of the authors. The information is presented by Arctic country. Viral hepatitis constitutes an important problem among Aboriginal peoples of the Arctic; the incidence of most types of viral hepatitis is higher among indigenous populations than in the general public. However, due to differences in the available information from each of the four Arctic countries, it is difficult to compare differences in types of disease in them. The main areas for future research are: HBV genotypes distribution, relations between different types of HBV, HCV and disease outcomes, HBV mutation rate and specific substitutions in the HBV genome over time in the Arctic, and occurrence of active liver disease in HBsAg carriers living in the Arctic, as well as further research in viral hepatitis A, C, D and E.

Sakamoto, T., Y. Tanaka, J. Simonetti, C. Osiowy, M. L. Borresen, A. Koch, F. Kurbanov, M. Sugiyama, G. Y. Minuk, B. J. McMahon, et al. "**Classification of hepatitis B virus genotype B into 2 major types based on characterization of a novel subgenotype in Arctic indigenous populations**." J Infect Dis **2007** 196(10): 1487-1492.

Hepatitis B virus genotype B (HBV/B) has been classified into 5 subgenotypes. Except for Bj/B1 in Japan, the subgenotypes (Ba/B2-B5) have undergone recombination with HBV/C in the core promoter/precore/core genomic region. Phylogenetic analyses of complete sequences show that the Arctic strains belong to a novel subgenotype (HBV/B6) without the recombination, analogous to what is seen with Bj/B1. Comparison of 50 HBV/B6 carriers from the Arctic versus 50 Bj and 50 Ba age- and sex-matched carriers from Asia revealed that

clinical characteristics of HBV/B6 carriers were similar to those of Bj/B1 carriers in Japan. The results suggest that HBV/B may be classified into nonrecombinant (Bj/B1 and B6) and recombinant (Ba/B2-B5) types.

Alaska (21)

McMahon, B. J., L. R. Bulkow, R. J. Singleton, J. Williams, M. Snowball, C. Homan and A. J. Parkinson. "**Elimination of hepatocellular carcinoma and acute hepatitis B in children 25 years after a hepatitis B newborn and catch-up immunization program**." Hepatology **2011** 54(3): 801-807.

Alaska Native people experience the highest rates of acute and chronic hepatitis B virus (HBV) infection and hepatocellular carcinoma (HCC) in the United States. We examined the effect of a universal newborn immunization with hepatitis B vaccine and mass population screening immunization program initiated in 1984 on rates of HBV and HCC in children 25 years later. During this time, the population of Alaska Native people grew from an estimated 75,000 to 130,000 persons. A surveillance system to detect acute HBV infection in Alaska Native facilities was established in 1981. Cases of HCC in children under 20 years of age were identified using a National Cancer Institute (NCI)-funded Cancer Registry established in 1969 coupled with an active surveillance program of screening persons with chronic HBV semiannually for alpha-fetoprotein since 1982. The incidence of acute symptomatic HBV infection in persons <20 years of age fell from cases 19/100,000 in 1981-1982 to 0/100,000 in 1993-1994. No cases of acute HBV have occurred in children since 1992. The incidence of HCC in persons <20 years decreased from 3/100,000 in 1984-1988 to zero in 1995-1999 and no cases have occurred since 1999. The number of identified hepatitis B surface antigen-positive children <20 years in the Alaska Native population declined from 657 in 1987 to two in 2008. Conclusion: Universal newborn vaccination coupled with mass screening and immunization of susceptible Alaska Natives has eliminated HCC and acute symptomatic HBV infection among Alaska Native children and this approach is the best way to prevent HBV-related disease in children.

Cheek, J. E., T. W. Hennessy, J. T. Redd, N. Cobb and R. T. Bryan. "**Epidemic assistance from the Centers for Disease Control and Prevention involving American Indians and Alaska Natives, 1946-2005**." Am J Epidemiol **2011** 174(11 Suppl): S89-96.

The authors describe 169 Centers for Disease Control and Prevention epidemic-assistance investigations involving American Indians and Alaska Natives that occurred during 1946-2005. The unique relation between the US federal government and American Indian and Alaska Native tribes is described in the context of transfer in the 1950s of responsibility for Indian health to the US Public Health Service, which at the time included the Communicable Disease Center, the Centers for Disease Control and Prevention's precursor. The vast majority of epidemic-assistance investigations were for infectious disease outbreaks (86%), with a relatively limited number, since 1980 only, involving environmental exposures and chronic disease. Although outbreaks investigated were often widespread geographically, the majority were limited in scope, typically involving fewer than 100 patients. Epidemic-assistance investigations for hepatitis A, gastrointestinal and foodborne infectious diseases, vaccine-preventable diseases, zoonotic and vectorborne diseases, acute respiratory tract infections, environmental exposures, and chronic diseases are described chronologically in more detail.

Byrd, K. K., J. T. Redd, R. C. Holman, D. L. Haberling and J. E. Cheek. "**Changing trends in viral hepatitis-associated hospitalizations in the American Indian/Alaska Native population, 1995-2007**." Public Health Rep **2011** 126(6): 816-825.

OBJECTIVE: We described the changing epidemiology of viral hepatitis among the American Indian/Alaska Native (AI/AN) population that uses Indian Health Service (IHS) health care. METHODS: We used hospital discharge data from the IHS National Patient Information Reporting System to determine rates of hepatitis A-, B-, and C-associated hospitalization among AI/ANs using IHS health care from 1995-2007 and summary periods 1995-1997 and 2005-2007. RESULTS: Hepatitis A-

associated hospitalization rates among AI/AN people decreased from 4.9 per 100,000 population during 1995-1997 to 0.8 per 100,000 population during 2005-2007 (risk ratio [RR] = 0.2, 95% confidence interval [CI] 0.1, 0.2). While there was no significant change in the overall hepatitis B-associated hospitalization rate between time periods, the average annual rate in people aged 45-64 years increased by 109% (RR=2.1, 95% CI 1.4, 3.2). Between the two time periods, the hepatitis C-associated hospitalization rate rose from 13.0 to 55.0 per 100,000 population (RR=4.2, 95% CI 3.8, 4.7), an increase of 323%. The hepatitis C-associated hospitalization rate was highest among people aged 45-64 years, males, and those in the Alaska region. CONCLUSIONS: Hepatitis A has decreased to near-eradication levels among the AI/AN population using IHS health care. Hepatitis C-associated hospitalizations increased significantly; however, there was no significant change in hepatitis B-associated hospitalizations. Emphasis should be placed on continued universal childhood and adolescent hepatitis B vaccination and improved vaccination of high-risk adults. Prevention and education efforts should focus on decreasing hepatitis C risk behaviors and identifying people with hepatitis C infection so they may be referred for treatment.

Villa, E. and G. Fattovich. "**No inflammation? No cancer! Clear HBV early and live happily**." J Hepatol **2010** 52(5): 768-770.

COMMENTARY ON: Clearance of Hepatitis B Surface Antigen and Risk of Hepatocellular Carcinoma in a cohort Chronically Infected with Hepatitis B Virus. Simonetti J, Bulkow L, McMahon BJ, Homan C, Snowball M, Negus S, Williams J, Livingston SE. Hepatology. 2009 Nov 30. [Epub ahead of print]. Copyright 2009. Reprinted with permission of John Wiley and Sons, Inc. Abstract: Some individuals who are chronically infected with hepatitis B virus (HBV) eventually lose hepatitis B surface antigen (HBsAg). Hepatocellular carcinoma (HCC) has been demonstrated to occur in a few patients after loss of HBsAg. Neither factors associated with loss of HBsAg nor the incidence of HCC thereafter have been clearly elucidated. We performed a prospective population-based cohort study in 1271 Alaska native persons with chronic HBV infection followed for an average of 19.6 years to determine factors associated with loss of HBsAg and risk of developing HCC thereafter. HBsAg loss occurred in 158 persons for a rate of HBsAg clearance of 0.7%/year. Older age, but not sex, was associated with clearance of HBsAg, and loss of HBsAg was not associated with any particular HBV genotypes (A-D, and F) found in this population. Participants were followed for an average of 108.9 months after HBsAg loss. Six patients, two with cirrhosis and four without, developed HCC a mean of 7.3 years after HBsAg clearance (range, 2.0-15.5 years). The incidence of HCC after clearance of HBsAg was 36.8 per 100,000 per year (95% CI 13.5-80.0) which was significantly lower than the rate in those who remained HBsAg-positive (195.7 cases per 100,000 person-years of follow-up [95% CI 141.1-264.5; P<0.001). After loss of HBsAg, HBV DNA was detected in the sera of 28 (18%) of those who cleared a median of 3.6 years after clearance. Conclusion: HCC can occur in persons with chronic hepatitis B who have lost HBsAg, even in the absence of cirrhosis. These persons should still be followed with periodic liver ultrasound to detect HCC early.

Singleton, R. J., S. Hess, L. R. Bulkow, L. Castrodale, G. Provo and B. J. McMahon. "**Impact of a statewide childhood vaccine program in controlling hepatitis A virus infections in Alaska**." Vaccine **2010** 28(38): 6298-6304.

Historically, Alaska experienced cyclic hepatitis A virus (HAV) epidemics, and the HAV rate among Alaska Native people was significantly higher than among other racial/ethnic groups. We evaluated the impact of universal childhood vaccination, initiated in 1996, on HAV epidemiology in Alaska by analyzing HAV cases reported to the State of Alaska. HAV incidence in all age groups declined 98.6% from 60.0/100,000 in 1972-1995 to 0.9/100,000 in 2002-2007. The largest decrease (99.9%) was in Alaska Native people, whose incidence (0.3) in 2002-2007 was lower than the overall U.S. 2007 rate (1.0). Among age groups, the decrease (99.8%) among children aged 0-14 years was the largest. Routine childhood vaccination has nearly eliminated HAV infection in Alaska.

Simonetti, J., L. Bulkow, B. J. McMahon, C. Homan, M. Snowball, S. Negus, J. Williams and S. E. Livingston. "**Clearance of hepatitis B surface antigen and risk of hepatocellular carcinoma in a cohort chronically infected with hepatitis B virus**." Hepatology **2010** 51(5): 1531-1537.

Some individuals who are chronically infected with hepatitis B virus (HBV) eventually lose hepatitis B surface antigen (HBsAg). Hepatocellular carcinoma (HCC) has been demonstrated to occur in a few patients after loss of HBsAg. Neither factors associated with loss of HBsAg nor the incidence of HCC thereafter have been clearly elucidated. We performed a prospective population-based cohort study in 1,271 Alaska Native persons with chronic HBV infection followed for an average of 19.6 years to determine factors associated with loss of HBsAg and risk of developing HCC thereafter. HBsAg loss occurred in 158 persons for a rate of HBsAg clearance of 0.7%/year. Older age, but not sex, was associated with clearance of HBsAg, and loss of HBsAg was not associated with any particular HBV genotypes (A, B, C, D, and F) found in this population. Participants were followed for an average of 108.9 months after HBsAg loss. Six patients, two with cirrhosis and four without, developed HCC a mean of 7.3 years after HBsAg clearance (range, 2.0-15.5 years). The incidence of HCC after clearance of HBsAg was 36.8 per 100,000 per year (95% CI 13.5-80.0) which was significantly lower than the rate in those who remained HBsAg-positive (195.7 cases per 100,000 person-years of follow-up [95% CI 141.1-264.5; P < 0.001]). After loss of HBsAg, HBV DNA was detected in the sera of 28 (18%) of those who cleared a median of 3.6 years after clearance. CONCLUSION: HCC can occur in persons with chronic hepatitis B who have lost HBsAg, even in the absence of cirrhosis. These persons should still be followed with periodic liver ultrasound to detect HCC early.

McMahon, B. J., D. Bruden, M. G. Bruce, S. Livingston, C. Christensen, C. Homan, T. W. Hennessy, J. Williams, D. Sullivan, H. R. Rosen, et al. "**Adverse outcomes in Alaska natives who recovered from or have chronic hepatitis C infection**." Gastroenterology **2010** 138(3): 922-931 e921.

BACKGROUND & AIMS: The factors associated with adverse outcome from hepatitis C virus (HCV) infection are incompletely understood. To determine the incidence and risk factors associated with the development of end-stage liver disease (ESLD) and liver-related death (LRD), we conducted a retrospective/prospective population-based study in a cohort of Alaska Native persons chronically infected with HCV from 1994 to 2005. METHODS: We followed 960 persons prospectively for an average of 7.2 years and retrospectively for 12.1 years with data from medical records and serum samples. We compared data from subjects that were chronically infected with those who recovered from HCV infection, stratified by alcohol use. Survival models were used to examine factors associated with ESLD and LRD in chronically infected patients. RESULTS: During prospective follow-up, 80 (8.8%) and 47 (5.2%) patients developed ESLD and LRD, respectively. In examining incidence per 100 person-years, no difference was found among heavy alcohol users in the incidence of LRD (2.28 versus 3.50; P = .34) or ESLD (3.21 versus 5.69; P = .13) in persons with chronic HCV compared with those recovered from HCV infection. In subjects that consumed <50 g alcohol/d, the incidences of LRD were 0.77 and 0.09 (P = .01) and of ESLD were 1.58 versus 0.36 (P = .002), respectively, in subjects with chronic infection versus those that recovered. Multivariate analysis showed that older age, heavy alcohol use, and HCV genotype 3 were associated with ESLD. CONCLUSIONS: A history of heavy alcohol use is associated with the highest incidence of LRD and ESLD, regardless of whether patients are chronically infected or recover from HCV infection.

Livingston, S. E., H. Deubner, D. L. Bruden, B. J. McMahon, C. E. Homan, L. J. Townshend-Bulson, M. G. Bruce, T. W. Hennessy, J. L. Williams and D. R. Gretch. "**Factors associated with the progression of fibrosis on liver biopsy in Alaska Native and American Indian persons with chronic hepatitis C**." Can J Gastroenterol **2010** 24(7): 445-451.

BACKGROUND: Various factors influence the development and rate of fibrosis progression in chronic hepatitis C virus (HCV) infection. OBJECTIVES: To examine factors associated with fibrosis in a longterm outcomes study of Alaska

Native/American Indian persons who underwent liver biopsy, and to examine the rate of fibrosis progression in persons with subsequent biopsies. METHODS: A cross-sectional analysis of the demographic, inflammatory and viral characteristics of persons undergoing liver biopsy compared individuals with early (Ishak fibrosis score of lower than 3) with those with advanced (Ishak score of 3 or greater) fibrosis. Persons who underwent two or more biopsies were analyzed for factors associated with fibrosis progression. RESULTS: Of 253 HCV RNA-positive persons who underwent at least one liver biopsy, 76 (30%) had advanced fibrosis. On multivariate analysis, a Knodell histological activity index score of 10 to 14 and an alpha-fetoprotein level of 8 ng/mL or higher were found to be independent predictors of advanced liver fibrosis (P<0.0001 for each). When surrogate markers of liver inflammation (alanine aminotransferase, aspartate aminotransferase/alanine aminotransferase ratio and alpha-fetoprotein) were removed from the model, type 2 diabetes mellitus (P=0.001), steatosis (P=0.03) and duration of HCV infection by 10-year intervals (P=0.02) were associated with advanced fibrosis. Among 52 persons who underwent two or more biopsies a mean of 6.2 years apart, the mean Ishak fibrosis score increased between biopsies (P=0.002), with progression associated with older age at initial biopsy and HCV risk factors. CONCLUSIONS: The presence of type 2 diabetes mellitus, steatosis and duration of HCV infection were independent predictors of advanced fibrosis in the present cohort, with significant fibrosis progression demonstrated in persons who underwent serial biopsies.

Singleton, R., S. Holve, A. Groom, B. J. McMahon, M. Santosham, G. Brenneman and K. L. O'Brien. "**Impact of immunizations on the disease burden of American Indian and Alaska native children**." Arch Pediatr Adolesc Med **2009** 163(5): 446-453.

American Indian and Alaska Native (AI/AN) people have suffered disproportionately from infectious diseases compared with the general US population. As recently as 25 years ago, rates of hepatitis A and B virus, Haemophilus influenzae type b, and Streptococcus pneumoniae infections were as much as 10 times higher among AI/AN children compared with the general US child population. In the past quarter century, routine use of childhood immunizations for hepatitis A and B viruses has eliminated disease disparities for these pathogens in AI/AN children, and significant decreases have been demonstrated for H influenzae type b, S pneumoniae, and pertussis. Nevertheless, certain infectious diseases continue to occur at higher rates in AI/AN children. The reason for continued disparities is most likely related to adverse living conditions such as household crowding, lack of indoor plumbing, poverty, and poor indoor air quality. Although tremendous strides have been made in eliminating disparities in infectious disease among AI/AN children, further gains will require addressing disparities in adverse living conditions.

McMahon, B. J., C. M. Dentinger, D. Bruden, C. Zanis, H. Peters, D. Hurlburt, L. Bulkow, A. E. Fiore, B. P. Bell and T. W. Hennessy. "**Antibody levels and protection after hepatitis B vaccine: results of a 22-year follow-up study and response to a booster dose**." J Infect Dis **2009** 200(9): 1390-1396.

BACKGROUND: The duration of protection in children and adults (including health care workers) resulting from the hepatitis B vaccine primary series is unknown. METHODS: To determine the protection afforded by hepatitis B vaccine, Alaska Native persons who had received plasma-derived hepatitis B vaccine when they were >6 months of age were tested for antibody to hepatitis B surface antigen (anti-HBs) 22 years later. Those with levels <10 mIU/mL received 1 dose of recombinant hepatitis B vaccine and were evaluated on the basis of anti-HBs measurements at 10-14 days, 30-60 days, and 1 year. RESULTS: Of 493 participants, 60% (298) had an anti-HBs level >or=10 mIU/mL. A booster dose was administered to 164 persons, and 77% responded with an anti-HBs level >or=10 mIU/mL at 10-14 days, reaching 81% by 60 days. Response to a booster dose was positively correlated with younger age, peak anti-HBs response after primary vaccination, and the presence of detectable anti-HBs before boosting. Considering persons with an anti-HBs level >or=10 mIU/mL at 22 years and those who responded to the booster dose, protection was demonstrated in 87% of the participants. No new acute or chronic hepatitis B virus infections were identified. CONCLUSIONS: The protection afforded by primary

immunization with plasma-derived hepatitis B vaccine during childhood and adulthood lasts at least 22 years. Booster doses are not needed.

Fischer, G. E., S. P. Bialek, C. E. Homan, S. E. Livingston and B. J. McMahon. "**Chronic liver disease among Alaska-Native people, 2003-2004**." Am J Gastroenterol **2009** 104(2): 363-370.

OBJECTIVES: A higher proportion of deaths among American-Indian/Alaska-Native (AI/AN) people has been attributed to chronic liver disease (CLD) compared with other racial/ethnic groups in the United States. The objectives of this study were to determine CLD prevalence and to define its etiologies and complications among AN and AI people, who received health care from an urban hospital center. METHODS: We conducted a retrospective, cross-sectional study of AN and AI people > or =18 years old who had at least one patient encounter at the Alaska Native Medical Center during January 2003-December 2004. RESULTS: A total of 1,886 (7.2%) of 26,166 AI/AN people met criteria for having CLD. The most commonly identified etiologies were alcohol-related liver disease (42%), nonalcoholic fatty liver disease (31%), chronic hepatitis C virus infection (26%), and chronic hepatitis B virus infection (8%). Compared with women, men had a higher overall prevalence of CLD (81.9 vs. 64.7 per 1,000), but were less likely to die from a CLD-related cause (1.5 vs. 2.7 per 1,000). These differences in the CLD deaths were mostly attributed to alcohol-related liver disease. CONCLUSIONS: This is the first known population-based study to examine the burden and etiology of CLD among AN people. Causes of CLD were similar among AI/AN people as those reported among other racial/ethnic groups in the United States. Identifying specific etiologies of CLD among populations can help target appropriate prevention and treatment strategies as they are specific to the causes of CLD.

Groom, A. V., M. L. Washington, P. J. Smith and R. T. Bryan. "**Underimmunization of American Indian and Alaska Native children**." Pediatrics **2008** 121(5): 938-944.

OBJECTIVE: The goal was to determine whether disparities in childhood immunization coverage exist between American Indian/Alaska Native children and non-Hispanic white children. METHODS: We compared immunization coverage with the 4 diphtheria-tetanus-pertussis, 3 poliovirus, 1 measles-mumps-rubella, 3 Haemophilus influenza type b, and 3 hepatitis B(4:3:1:3:3) series and its individual vaccine components (> or = 4 doses of diphtheria, tetanus, and pertussis vaccine; > or = 3 doses of oral or inactivated polio vaccine; > or = 1 dose of measles, mumps, and rubella vaccine; > or = 3 doses of Haemophilus influenzae type b vaccine; and > or = 3 doses of hepatitis B vaccine) between American Indian/Alaska Native children and non-Hispanic white children from 2000 to 2005, using data from the National Immunization Survey. RESULTS: Although immunization coverage increased for both populations from 2001 to 2004, American Indian/Alaska Native children had significantly lower immunization coverage, compared with non-Hispanic white children, over that time period. In 2005, coverage continued to increase for American Indian/Alaska Native children but decreased for non-Hispanic white children, and no statistically significant disparity in 4:3:1:3:3 coverage was evident in that year. CONCLUSIONS: Disparities in immunization coverage for American Indian/Alaska Native children have been present, but unrecognized, since 2001. The absence of a disparity in coverage in 2005 is encouraging but is tempered by the fact that coverage for non-Hispanic white children decreased in that year.

Bruce, M. G., D. Bruden, B. J. McMahon, C. Christensen, C. Homan, D. Sullivan, H. Deubner, J. Williams, S. E. Livingston and D. Gretch. "**Clinical significance of elevated alpha-fetoprotein in Alaskan Native patients with chronic hepatitis C**." J Viral Hepat **2008** 15(3): 179-187.

The clinical significance of elevated serum alpha-fetoprotein (AFP) in patients with chronic hepatitis C virus (HCV) infection is not well defined. We analysed data from a population-based cohort of patients with HCV infection to assess the prevalence of elevated serum AFP, to determine its association with clinical and virologic parameters and with clinical outcomes. We defined a slightly elevated serum AFP

level as 8 to <15 and a high-AFP level as > or =15 microg/L. Among 541 HCV-RNA-positive persons, 61 (11%) had a slightly elevated or high AFP at the time of consent. AFP > or =8 microg/L was associated with the older age, aspartate aminotransferase/alanine aminotransferase ratio >1, and higher alkaline phosphatase levels, but not with heavy alcohol use, IV drug use, genotype, viral load or duration of HCV infection. Among 192 persons with an AFP at liver biopsy, 17% had an AFP > or =8 microg/L. The sensitivity/specificity of an AFP level > or =8 in detecting Ishak 3-6 fibrosis was 39%/95%. Among 372 persons with a minimum of four AFP measurements over 6 years, 5% had persistently elevated AFP >8 microg/L, 19% had both elevated and normal AFP measurements, and 76% had persistently normal AFP. Elevated AFP at consent was associated with hepatocellular carcinoma (HCC) and end-stage liver disease. Over 6 years of follow-up, persistently elevated AFP was associated with the development of HCC; no person with AFP persistently <8 microg/mL developed HCC. Serial AFP measurements appear to be useful in identifying persons with advanced fibrosis and help to determine who needs periodic screening with liver ultrasound to detect HCC.

Hammitt, L. L., L. Bulkow, T. W. Hennessy, C. Zanis, M. Snowball, J. L. Williams, B. P. Bell and B. J. McMahon. "**Persistence of antibody to hepatitis A virus 10 years after vaccination among children and adults**." J Infect Dis **2008** 198(12): 1776-1782.

BACKGROUND: Hepatitis A vaccination is effective in preventing disease. However, the duration of protection after vaccination is unknown. METHODS: We enrolled persons who responded to a 3-dose primary series of hepatitis A vaccine. For adults, the first dose was 720 ELISA units (EU) of hepatitis A vaccine, readministered at 1 and 12 months after the first vaccination (hereafter, "0-1-12 months"); for children aged 3-6 years, the first dose was 360 EU, readministered according to 1 of 3 vaccination schedules: 1 and 2 months after the first vaccination ("0-1-2 months"), 1 and 6 months after the first vaccination ("0-1-6 months"), or 1 and 12 months after vaccination ("0-1-12 months"). Specimens collected 1 month and 1-10 years after vaccination were tested for antibody to hepatitis A virus (anti-HAV) by ELISA. Long-term antibody persistence was estimated by using the observed rate of decline in geometric mean concentration (GMC). RESULTS: A total of 144 children and 128 adults were enrolled. Children vaccinated at 0-1-2 months had a significantly lower GMC of antibody than children vaccinated at 0-1-12 months, but this difference was statistically significant only through 4 years of follow-up. All 67 children tested at 10 years and 25 (96%) of 26 adults tested at 8-9 years had detectable anti-HAV. The estimated duration of antibody persistence was 21-27 years, depending on the vaccination schedule. CONCLUSIONS: Anti-HAV persists in adults and children for more than 10 years after the primary vaccination series. Additional studies are needed to evaluate the duration of antibody persistence beyond 10 years and to assess the long-term immunogenicity of the currently recommended 2-dose schedule.

Samandari, T., A. E. Fiore, S. Negus, J. L. Williams, W. Kuhnert, B. J. McMahon and B. P. Bell. "**Differences in response to a hepatitis B vaccine booster dose among Alaskan children and adolescents vaccinated during infancy**." Pediatrics **2007** 120(2): e373-381.

BACKGROUND: The duration of protection provided by hepatitis B vaccination is unknown, but the presence of immune memory can be evaluated indirectly by measuring the immune response to a booster dose of vaccine. METHODS: Participants included 74 adolescents (aged 11.7-14.9 years) who had received a plasma-derived 3-dose primary vaccine series and 138 adolescents (aged 10.0-14.7 years) and 166 children (aged 5.0-7.0 years) who received a recombinant 3-dose primary vaccine series. All were born to hepatitis B surface antigen-negative mothers and had received the first dose of hepatitis B vaccine within 7 days of birth. The proportion of participants with serologic evidence of protective immunity (antibody to hepatitis B surface antigen > or = 10 mIU/mL) at baseline (prebooster), the proportion who developed an anamnestic response (increase to > or = 10 mIU/mL or at or more than fourfold increase in antibody to hepatitis B surface antigen to > 10 mIU/mL), and the geometric mean concentration by 1, 2, and 4 weeks after a 5-microg recombinant vaccine booster dose were determined. RESULTS: No participant had evidence of

chronic hepatitis B virus infection. Overall, 99% of the group of children who received recombinant hepatitis B vaccine, 83% of the group of adolescents who received recombinant hepatitis B vaccine, and 69% of the group of adolescents who received the plasma-derived vaccine had an anamnestic response to a booster dose; among responders, the geometric mean concentration at 2 weeks postbooster was 3360 and 128 mIU/mL among adolescents who received plasma-derived vaccine with antibodies to hepatitis B surface antigen > or = 10 and < 10 mIU/mL at baseline, respectively, compared with 1283 and 369 mIU/mL among adolescents who received recombinant hepatitis B vaccine and 5091 and 696 mIU/mL for children who received recombinant hepatitis B vaccine. The anamnestic response rate at 2 weeks postbooster among participants with antibodies to hepatitis B surface antigen < 10 mIU/mL at baseline was inversely associated with age; 97% of 5-year-olds responded compared with 60% of 14-year-olds. CONCLUSIONS: Although most participants responded to a booster dose of hepatitis B vaccine, the significance of the increased proportion of nonresponses among older adolescents might indicate waning immune memory.

Mala, T. A. "**The Alaska-Siberia Medical Program: 24 years in retrospect**." Alaska Med **2007** 49(2 Suppl): 22-24.

OBJECTIVES: The purpose of this paper is to give the reader some idea of life in Siberia and Alaska during the creation of our first medical exchanges during the most difficult of political times. STUDY DESIGN: Various projects were designed using National Institutes of Health (NIH) criteria for our medical exchange. METHODS: As we took these first steps between the Siberian Branch of the Academy of Medical Sciences of the USSR and the Institute for Circumpolar Health Studies at the University of Alaska Anchorage, USA, the general areas of our first studies were: 1) Circadian Rhythm and Work-Related Injuries in the North; 2) Alcohol and its Abuse with Treatment Methodologies; 3) Public Health Administration and Design in the Far East and Alaska; 4) Cystic Echinococcosis in the Arctic and Sub-Arctic; 5) Viral Hepatitis in the Arctic; 6) Cardiology; 7) Nutrition; and 7) Diabetes Prevention. RESULTS: A film made by the University of Alaska which was shown on PBS' "Breaking the Ice: The Alaska-Siberia Medical Research Program"; various papers and books published on both sides; and a major contribution made to world peace through the medical workers on both sides of the Bering Sea. CONCLUSION: This major effort for peace showed the world how the peoples of Siberia and Alaska could come together and work for world peace through joint collaborations. Native people were reunited after years of separation, new avenues were created in anthropology, biology and medicine and, subsequently, the border was again opened between our peoples.

Livingston, S. E., J. P. Simonetti, B. J. McMahon, L. R. Bulkow, K. J. Hurlburt, C. E. Homan, M. M. Snowball, H. H. Cagle, J. L. Williams and V. P. Chulanov. "**Hepatitis B virus genotypes in Alaska Native people with hepatocellular carcinoma: preponderance of genotype F**." J Infect Dis **2007** 195(1): 5-11.

BACKGROUND: The development of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B virus (HBV) infection has been associated with specific HBV genotypes and the presence of specific mutations. METHODS: From a cohort of Alaska Native people with chronic HBV infection, we genotyped 47 patients with HCC and 1129 patients without HCC, and we tested patients with HCC and control patients for mutations in the basal core promoter and precore regions. RESULTS: Genotype F was found in 68% of patients with HCC, versus 18% of those without HCC (P<.001). For patients with genotype F, the median age at diagnosis of HCC was lower than that for patients with other genotypes (22.5 vs. 60 years, respectively; P=.002). Overall, there were no significant differences in the number of basal core promoter and precore region mutations between patients with HCC and control patients. CONCLUSIONS: We found a significant association between genotype F and the development of HCC among Alaska Native people with chronic HBV infection but no significant association between HCC and basal core promoter or precore mutations in genotype F.

Livingston, S. E., J. P. Simonetti, L. R. Bulkow, C. E. Homan, M. M. Snowball, H. H. Cagle, S. E. Negus and B. J. McMahon. "**Clearance of hepatitis B e antigen in patients with chronic hepatitis B and genotypes A, B, C, D, and F**." Gastroenterology **2007** 133(5): 1452-1457.

BACKGROUND & AIMS: Persistence of hepatitis B e antigen (HBeAg) in chronic hepatitis B has been associated with increased risk for development of cirrhosis and hepatocellular carcinoma. Five hepatitis B virus genotypes were identified in Alaska Native persons; we analyzed clearance of HBeAg by age and genotype. METHODS: In this prospective cohort study, 1158 Alaska Native persons throughout Alaska were tested serially for HBeAg for a median of 20.5 years and were genotyped. Initial and final HBeAg-positive specimens, time to clearance, age at clearance, and subsequent HBeAg results were analyzed for persons initially HBeAg-positive. Subsequent HBeAg results were analyzed for persons initially negative. RESULTS: Genotypes A, B, C, D, and F were identified. Genotype C persons initially HBeAg-positive were more likely than those with other genotypes to be positive on initial and final specimens ($P < .001$ for each) and time to HBeAg clearance was longer ($P < .001$). Age at which 50% of persons cleared HBeAg was <20 years for those infected with genotypes A, B, D, and F and 47.8 years in genotype C ($P < .001$). After losing HBeAg, those with genotypes C and F were more likely to revert to the HBeAg-positive state ($P < .001$). CONCLUSIONS: Genotype may have a strong effect on mode of transmission and outcome. Genotype C may have been responsible for most perinatal transmission, given that seroconversion from HBeAg occurs decades later than in other genotypes.

Hurlburt, K. J., B. J. McMahon, J. P. Simonetti, S. E. Livingston, L. R. Bulkow, M. M. Snowball, V. P. Chulanov, O. P. Nainan and J. L. Williams. "**Hepatitis B-associated vasculitis in Alaska Natives: viral genotype, clinical and serologic outcome**." Liver Int **2007** 27(5): 627-632.

BACKGROUND: The highest incidence of hepatitis B virus (HBV)-associated vasculitis in the world has been reported in Alaska Natives. We examined the incidence of HBV-associated vasculitis before and after mass HBV vaccine immunization and the association between HBV genotype and vasculitis in a population-based cohort study in Alaska natives chronically infected with HBV. METHODS: Genotyping was performed in vasculitis cases and 644 hepatitis B-positive controls without vasculitis using polymerase chain reaction and sequencing of the S gene. Occurrence of HBV vasculitis from 1974 to 2004 was calculated. HBV vasculitis patients and controls were also tested for basal core promoter and precore mutations. RESULTS: Fifteen cases of HBV-associated vasculitis were identified: 13 (86%) had genotype D and one each genotype A and F. Genotype D was more commonly found in patients with vasculitis than controls [odd ratio (OR)=5.9, confidence interval (95% CI) 1.2, 21.8; $P<0.015$). CONCLUSIONS: HBV-associated vasculitis was associated with genotype D.

Hammitt, L. L., T. W. Hennessy, A. E. Fiore, C. Zanis, K. B. Hummel, E. Dunaway, L. Bulkow and B. J. McMahon. "**Hepatitis B immunity in children vaccinated with recombinant hepatitis B vaccine beginning at birth: a follow-up study at 15 years**." Vaccine **2007** 25(39-40): 6958-6964.

BACKGROUND: The duration of protection after hepatitis B vaccination of infants is unknown. We determined antibody to hepatitis B surface antigen (anti-HBs) and response to a booster dose 15 years after vaccination among Alaskan children born to hepatitis B surface antigen-negative mothers. These children had protective anti-HBs concentrations when tested after receiving a three-dose series of 2.5 microg recombinant hepatitis B vaccine starting at birth. METHODS: Participants received 5 microg of recombinant hepatitis B vaccine. Sera were collected at baseline, 10-14 days and 1 month after vaccination, and tested for antibody to hepatitis B core antigen (anti-HBc) and anti-HBs. An anamnestic response was defined as an anti-HBs increase within 15 days, from either undetectable to >/=10 mIU/mL, or, if the baseline concentration was detectable, a 4-fold increase. RESULTS: None of 37 participants (mean age 14.6 years) were anti-HBc positive. An anamnestic response (GMC=254 mIU/mL, range 16-2767 mIU/mL) was observed in 18 (51%) of 35

participants who had sera collected within 15 days after the booster. CONCLUSIONS: In this small study, half of children who had received hepatitis B vaccine starting at birth did not have evidence of immune memory as measured by development of anamnestic responses to booster vaccination. Additional studies are needed to assess whether this indicates susceptibility to infection and whether persons vaccinated starting at birth may benefit from a hepatitis B vaccine booster to maintain long-term protection.

Cagle, H. H., J. Jacob, C. E. Homan, J. L. Williams, C. J. Christensen and B. J. McMahon. "**Results of a general hepatitis C lookback program for persons who received blood transfusions in a neonatal intensive care unit between January 1975 and July 1992**." Arch Pediatr Adolesc Med **2007** 161(2): 125-130.

OBJECTIVE: To notify persons who received a blood transfusion in a neonatal intensive care unit between January 1975 and July 1992 of their risk for hepatitis C infection and to encourage them to seek hepatitis C antibody testing. DESIGN: Neonatal intensive care unit, blood bank, and public access records were queried to identify current mailing addresses and persons deceased. All persons were notified by letter. SETTING: Anchorage, Alaska. PARTICIPANTS: Persons who received health care in an integrated health care system, the Alaska Native Medical Center, or in the private sector. Main Exposure Transfusion in the neonatal period. MAIN OUTCOME MEASURES: Prevalence of test results positive for the hepatitis C virus antibody and RNA and awareness of having received a blood transfusion in a neonatal intensive care unit. RESULTS: Alaska Native Medical Center (n = 401) and private sector (n = 1396) persons were targeted for notification. Letters were mailed to 277 Alaska Native Medical Center (69%) and 374 private sector (27%) persons, with 151 (55%) and 65 (17%) screened for hepatitis C, respectively. Among those screened (n = 216), 7 (3%) were hepatitis C antibody positive, with 6 (<3%) also hepatitis C virus-RNA positive. Among 147 persons who responded, 75 (51%) were unaware they had received a transfusion. CONCLUSIONS: Compared with the private sector, a higher proportion of persons were identified and tested from the integrated health care system and more than half of respondents were unaware of their transfusion history. It would be prudent to screen neonatal intensive care unit patients who received transfusions before July 1992 for hepatitis C virus infection.

Canada (14)

Wong, W. W., G. Woo, E. Jenny Heathcote and M. Krahn. "**Cost effectiveness of screening immigrants for hepatitis B**." Liver Int **2011** 31(8): 1179-1190.

BACKGROUND: The prevalence of chronic hepatitis B (CHB) infection among the immigrants of North America ranges from 2 to 15%, among whom 40% develop advanced liver disease. Screening for hepatitis B surface antigen is not recommended for immigrants. AIMS: The objective of this study is to estimate the health and economic effects of screening strategies for CHB among immigrants. METHODS: We used the Markov model to examine the cost-effectiveness of three screening strategies: (i) 'No screening'; (ii) 'Screen and Treat' and (iii) 'Screen, Treat and Vaccinate' for 20-65 years old individuals who were born abroad but are currently living in Canada. Model data were obtained from the published literature. We measured predicted hepatitis B virus (HBV)-related deaths, costs (2008 Canadian Dollars), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratio (ICER). RESULTS: Our results show that screening all immigrants will prevent 59 HBV-related deaths per 10, 000 persons screened over the lifetime of the cohort. Screening was associated with an increase in quality-adjusted life expectancy (0.024 QALYs) and cost ($1665) per person with an ICER of $69, 209/QALY gained compared with 'No screening'. The 'Screen, Treat and Vaccinate' costs an additional $81, generates an additional 0.000022 QALYs per person, with an ICER of $3, 648,123/QALY compared with the 'Screen and Treat'. Sensitivity analyses suggested that the 'Screen and Treat' is likely to be moderately cost-effective. CONCLUSION: We show that a selective hepatitis B screening programme targeted at all immigrants in Canada is likely to be moderately cost-effective. Identification of silent CHB

infection with the offer of treatment when appropriate can extend the lives of immigrants at reasonable cost.

Osiowy, C., B. Larke and E. Giles. "**Distinct geographical and demographic distribution of hepatitis B virus genotypes in the Canadian Arctic as revealed through an extensive molecular epidemiological survey**." J Viral Hepat **2011** 18(4): e11-19.

Very little is known of hepatitis B virus (HBV) in Canadian Arctic indigenous populations, where HBV was considered endemic prior to the introduction of HBV vaccine. This study expands upon an HBV seroepidemiological survey conducted between 1983 and 1985 throughout the Canadian Arctic, to characterize HBV in this population. Archived hepatitis B surface antigen (HBsAg)-positive sera (n = 401) were processed for HBV DNA, followed by sequencing and phylogenetic analysis of the HBsAg- and HBcAg-coding regions. Sixty-nine per cent of samples (277/401) were DNA positive, with most having low viral load (median 3.4 log 10 IU/mL). The predominant HBV genotype observed was genotype B (HBV/B, 75%), followed by HBV/D (24%) and HBV/A (1%). All HBV/B strains clustered within subgenotype B6, a newly recognized HBV genotype among western circumpolar Inuit and Alaska Native people. HBV/D strains included both D3 (88%) and D4 (12%) subgenotypes, while all HBV/A strains were subgenotype A2. An association of HBV genotype B with Inuit living in the eastern Arctic and an association of genotype D with First Nation (Dene) living in the western Arctic was observed. This study establishes the high prevalence of HBV/B6 and HBV/D genotypes in Arctic populations and reveals their marked distribution within the Canadian Arctic based on geographical and demographic attributes.

Miller, C. L., M. E. Pearce, A. Moniruzzaman, V. Thomas, W. Christian, M. T. Schechter and P. M. Spittal. "**The Cedar Project: risk factors for transition to injection drug use among young, urban Aboriginal people**." CMAJ **2011** 183(10): 1147-1154.

BACKGROUND: Studies suggest that Aboriginal people in Canada are over-represented among people using injection drugs. The factors associated with transitioning to the use of injection drugs among young Aboriginal people in Canada are not well understood. METHODS: The Cedar Project is a prospective cohort study (2003-2007) involving young Aboriginal people in Vancouver and Prince George, British Columbia, who use illicit drugs. Participants' venous blood samples were tested for antibodies to HIV and the hepatitis C virus, and drug use was confirmed using saliva screens. The primary outcomes were use of injection drugs at baseline and tranisition to injection drug use in the six months before each follow-up interview. RESULTS: Of 605 participants, 335 (55.4%) reported using injection drugs at baseline. Young people who used injection drugs tended to be older than those who did not, female and in a relationship. Participants who injected drugs were also more likely than those who did not to have been denied shelter because of their drug use, to have been incarcerated, to have a mental illness and to have been involved in sex work. Transition to injection drug use occurred among 39 (14.4%) participants, yielding a crude incidence rate of 19.8% and an incidence density of 11.5 participants per 100 person-years. In unadjusted analysis, transition to injection drug use was associated with being female (odds ratio [OR] 1.98, 95% confidence interval (CI) 1.06-3.72), involved in sex work (OR 3.35, 95% CI 1.75-6.40), having a history of sexually transmitted infection (OR 2.01, 95% CI 1.07-3.78) and using drugs with sex-work clients (OR 2.51, 95% CI 1.19-5.32). In adjusted analysis, transition to injection drug use remained associated with involvement in sex work (adjusted OR 3.94, 95% CI 1.45-10.71). INTERPRETATION: The initiation rate for injection drug use of 11.5 participants per 100 person-years among participants in the Cedar Project is distressing. Young Aboriginal women in our study were twice as likely to inject drugs as men, and participants who injected drugs at baseline were more than twice as likely as those who did not to be involved in sex work.

Blasig, A., E. C. Wagner, D. Pi, M. Bigham, V. P. Remple, K. J. Craib, P. Doyle, S. Dobson, E. M. Yoshida, D. Patrick, et al. "**Hepatitis C infection among pregnant women in British Columbia: reported prevalence and critical appraisal of current prenatal screening methods**." Can J Public Health **2011** 102(2): 98-102.

BACKGROUND: Despite the fact that hepatitis C virus (HCV) is a relatively common infection in Canada, particularly in British Columbia (BC), there is a paucity of information on actual HCV prevalence in pregnant women. At present, pregnant women are only screened if they fit risk criteria, which may result in under-identification of HCV in this population. The purpose of this study was to determine the overall prevalence rate, age and geographic distribution of reported HCV infection among pregnant women in BC, and compare results to a previously conducted anonymous seroprevalence survey. METHODS: Reported HCV prevalence was determined through a confidential database linkage of all prenatal screening results at the Canadian Blood Services (CBS) with all HCV test results at the Provincial Laboratory, from May 2000 to Oct 2002. Data were stratified by age group and geographic location, and subsequently compared to an anonymous prenatal seroprevalence survey conducted in 1994. RESULTS: The overall HCV prevalence rate was 50.3/10,000 (95% CI 46.3-54.6), or 0.5% of the cohort. Prevalence was highest in the northern BC region (66.2/10,000, 95% CI 51.4-85.3) and lowest in the populous suburban region southwest of Vancouver (38.0/10,000, 95% CI 32.3-44.8). Of note, the rate of reported HCV among pregnant women was significantly lower than the anonymous seroprevalence rate: 50.3/10,000 vs. 91.3/10,000 ($p < 0.0001$). CONCLUSION: Rates of reported HCV among pregnant women were approximately 50% lower than the rates determined by the anonymous seroprevalence survey. Further research is needed to determine the relative merits of the current selective screening policy versus universal prenatal HCV screening in pregnancy.

O'Leary, C., Z. Hong, F. Zhang, M. Dawood, G. Smart, K. Kaita and J. Wu. "**A mathematical model to study the effect of hepatitis B virus vaccine and antivirus treatment among the Canadian Inuit population**." Eur J Clin Microbiol Infect Dis **2010** 29(1): 63-72.

The prevalence of hepatitis B among the Canadian Inuit population is 4%. This study will use a mathematical model to compare the roles of vaccination and therapy to predict future prevalence and incidence among the Canadian Inuit population for the next 50 years. We applied a mathematical model developed by Medley et al. (Nat Med 7(5):619-624, 2001), combined with data on hepatitis B incidence, prevalence, and vaccination coverage, to predict trends of hepatitis B virus (HBV) among the Inuit population over the next 50 years. The current estimated prevalence of HBV is 6.04% and the incidence is 3.4/100,000 persons among Canadian Inuit. If HBV vaccination coverage levels of 47.2% remain unchanged, the prevalence of HBV will decrease to 1.91% and the incidence will decrease to 0.81/100,000 persons by 2058. If vaccination coverage levels are increased to 57.2%, the prevalence and incidence of HBV will decrease to 1.74% and 0.63/100,000 persons, respectively. If we increase both immunization and therapy by 10%, this will produce the greatest reduction in prevalence and incidence, to 1.56% and 0.54/100,000 persons, respectively. The combination of immunization and treatment programs seems to have the best result in decreasing the prevalence and incidence of HBV among the Inuit population.

Krajden, M., A. Yu, H. Braybrook, A. S. Lai, A. Mak, R. Chow, D. Cook, R. Tellier, M. Petric, R. D. Gascoyne, et al. "**GBV-C/hepatitis G virus infection and non-Hodgkin lymphoma: a case control study**." Int J Cancer **2010** 126(12): 2885-2892.

We investigated whether there was an association between GBV-C viremia and the development of non-Hodgkin lymphoma (NHL) in 553 NHL cases and 438 controls from British Columbia, Canada. Cases were aged 20-79, diagnosed between March 2000 and February 2004, and resident in Greater Vancouver or Victoria. Cases and controls were tested for GBV-C RNA by RT-PCR and positive samples were genotyped. Overall, GBV-C RNA was detected in 4.5% of NHL cases vs. 1.8% of controls [adjusted odds ratio (OR) = 2.72, 95% confidence interval (CI) = 1.22-6.69]. The association between GBV-C RNA detection and NHL remained even after individuals with a history of prior transfusion, injection drug use and hepatitis C virus sero-positivity were excluded. GBV-C viremia showed the strongest association with diffuse large B cell lymphoma (adjusted OR = 5.18, 95% CI = 2.06-13.71).

Genotyping was performed on 29/33 GBV-C RNA positive individuals; genotypes 2a (n = 22); 2b (n = 5) and 3 (n = 2) were identified, consistent with the distribution of genotypes found in North America. This is the largest case-control study to date associating GBV-C viremia and NHL risk. As GBV-C is known to be transmitted through blood products this may have important implications for blood safety.

Kazatchkine, C. "**Historic trauma contributes to high rates of hepatitis C among Aboriginal youth: study**." HIV AIDS Policy Law Rev **2010** 14(3): 22-23.

A recent study conducted of Aboriginal youth in British Columbia suggests that trauma associated with the residential schools system increases the risk of hepatitis C virus (HCV) infection among those who inject drugs. The study also warns of a larger epidemic of HCV in the northern area of the province.

Panessa, C., W. D. Hill, E. Giles, A. Yu, S. Harvard, G. Butt, A. Andonov, M. Krajden and C. Osiowy. "**Genotype D amongst injection drug users with acute hepatitis B virus infection in British Columbia**." J Viral Hepat **2009** 16(1): 64-73.

The eight genotypes of hepatitis B virus (HBV) exhibit distinct geographical distributions. This study identified HBV genotypes and transmission modes associated with acute infection in British Columbia (BC), Canada, from 2001 to 2005. Seventy cases of acute HBV in BC were identified from laboratory reports using a standardized case definition. Interviews for risk factors and hepatitis history were conducted for each case. HBV genotypes were determined by BLAST comparison analysis of the surface (S) or preS gene sequence. To illustrate the distribution of genotypes identified amongst acute cases in BC, an annotated map was produced showing the global occurrence of HBV genotypes. The majority of acute HBV cases occurred in Caucasian, Canadian-born males, with 30% of cases reporting injection drug use (IDU) and 21% reporting incarceration. The most common genotype observed was genotype D (62.9%), followed by genotypes A (18.6%), C (11.4%), B (4.3%), and E (1.4%). A significant association was observed between Genotype D and IDU (P = 0.0025) and previous incarceration (P = 0.0067). Phylogenetic analysis of the S gene sequence demonstrated identical or high genetic relatedness amongst genotype D viral strains (86% sub-genotype D3), thus verifying transmission clustering amongst BC injection drug users. The association between acute HBV genotype and reported transmission modes has not been previously described in North America. Tracking of genotypes can help identify disease transmission patterns and target at-risk populations for preventive immunization.

Mehrabadi, A., K. Paterson, M. Pearce, S. Patel, K. J. Craib, A. Moniruzzaman, M. T. Schechter and P. M. Spittal. "**Gender differences in HIV and hepatitis C related vulnerabilities among aboriginal young people who use street drugs in two Canadian cities**." Women Health **2008** 48(3): 235-260.

OBJECTIVES: Vulnerability to HIV and Hepatitis C virus (HCV) infection for indigenous populations worldwide must be contextualized in experiences of current and past trauma. Aboriginal women entrenched in poverty face further gender-specific harms which place them at increased risk for HIV infection. METHODS: This study was cross-sectional and based on a community-based sample of Aboriginal young people (Metis, Aboriginal, First Nations, Inuit, and non-status Indians) between the ages of 14 and 30 years who used injection or non-injection non-cannabis illegal drugs (street drugs) in the previous month. Between October 2003 and July 2005, 543 participants living in either Vancouver or Prince George, Canada, were recruited by word of mouth, posters, and street outreach. Young people in the study completed a questionnaire administered by Aboriginal interviewers. Female participants (n = 262) were compared to male participants (n = 281) with respect to sociodemographics, trauma, sexual risk variables, and drug use patterns. Trained nurses drew blood samples for HIV and HCV antibodies and provided pre- and post-test counseling. RESULTS: Proportions positive for HIV and HCV were significantly higher among young women. HIV was 13.1% [9.5, 17.7] in women compared to 4.3% [2.5, 7.4] in men, and HCV was 43.6% [37.6, 49.8] in women as compared to 25.4% [20.5, 30.9] in men. When the analysis was restricted to young people who reported injection drug use, the proportions positive for HIV and HCV remained significantly

higher among young women. Experiences of forced sex were reported by 70% of young women compared to 29% of young men, $p < 0.001$, while the median age of first forced sex was 6-years-old for both men and women. DISCUSSION: The results of the final model indicated that HIV had been associated with residing in Vancouver, having injected for longer, and sexual abuse, but not being female. However, this gendered analysis demonstrated that a greater proportion of young women were experiencing sexual abuse, and sexual abuse was associated with HIV positive status. Harm reduction and drug treatment programs are urgently required that target women at a young age and address complex traumatic experiences associated with childhood sexual abuse.

Mehrabadi, A., K. J. Craib, K. Patterson, W. Adam, A. Moniruzzaman, B. Ward-Burkitt, M. T. Schechter and P. M. Spittal. "**The Cedar Project: a comparison of HIV-related vulnerabilities amongst young Aboriginal women surviving drug use and sex work in two Canadian cities**." Int J Drug Policy **2008** 19(2): 159-168.

BACKGROUND: In Canada, Aboriginal women and youth continue to be overrepresented amongst new cases of HIV, and are considered at increased risk for sex and drug-related harm. Young women involved in sex work are particularly vulnerable. The purpose of this study is to determine HIV-related vulnerabilities associated with sex work amongst young Aboriginal women in two Canadian cities. METHODS: This study is based on a community-based cohort of Aboriginal young people (status and non-status First Nations, Inuit and Metis) between the ages of 14 and 30 who used injection or non-injection illegal drugs (street drugs) in the previous month. Participants lived in Vancouver, Canada, or Prince George, a remote, northern Canadian city. Between October 2003 and July 2005, 543 participants were recruited by word of mouth, posters, and street outreach. A baseline questionnaire was administered by Aboriginal interviewers, and trained nurses drew blood samples for HIV and HCV antibodies and provided pre- and post-test counselling. This study included 262 young women who participated at baseline. Analyses were conducted to compare socio-demographics, drug use patterns, injection practices, sexual experiences, and HIV and HCV prevalence between young women who reported being involved in sex work in the last 6 months (n=154) versus young women who did not (n=108). Logistic regression was used to identify factors independently associated with recent sex work involvement. RESULTS: Both sexual violence and drug using patterns were found to be markedly different for women having recently been involved in sex work. Multivariate analysis revealed daily injection of cocaine (AOR=4.4; 95% CI: 1.9, 10.1 and smoking crack (AOR=2.9; 95% CI: 1.6, 5.2) in the previous 6 months, and lifetime sexual abuse (AOR=2.5; 95% CI: 1.4, 4.4) to be independently associated with sex work. INTERPRETATION: Harm reduction and treatment programs that address historical and lifetime trauma amongst Aboriginal people and prioritize emotional and physical safety for young Aboriginal women involved in sex work are required.

Zahariadis, G., S. S. Plitt, S. O'Brien, Q. L. Yi, W. Fan and J. K. Preiksaitis. "**Prevalence and estimated incidence of blood-borne viral pathogen infection in organ and tissue donors from northern Alberta**." Am J Transplant **2007** 7(1): 226-234.

To determine the potential safety benefit of introducing nucleic acid testing (NAT) in tissue and organ donors, the risk of virus transmission was examined in a Canadian population. Anonymous data on Northern Alberta tissue and organ donors from 1998 to 2004 were used to determine the seroprevalence and estimate the seroincidence and residual risk of HIV, HBV, HCV and HTLV infection. Of the 3372 donors identified, 71.1% were surgical bone, 13.2% were living organ and 15.6% were deceased organ/tissue donors. Seroprevalence was: HIV 0.00%, HBV 0.09%, HCV 0.48% and HTLV 0.03%. Incidence (/100,000 p-yrs) and residual risks (/100,000 donors) could only be estimated for HBV (24.2 and 3.9) and HCV (11.2 and 2.2). Risk estimates were higher for deceased donors than surgical bone donors. HCV had the highest prevalence and HBV had the highest estimated incidence. HIV and HTLV risks were extremely low precluding accurate quantification. In this region of low overall viral prevalence, HCV NAT would be most effective in deceased organ donors. In surgical bone donors the cost of implementing NAT is high without

significant added safety benefit.

Whitlock, M., S. Lord, J. A. Buxton, P. Doyle and M. Bigham. "**Evaluating the impact of public health notification of suspected transfusion-transmissible hepatitis C virus infection and effectiveness of lookback and traceback investigations by Canadian Blood Services in British Columbia, Canada, August 2002 through February 2005**." Transfusion **2007** 47(8): 1534-1539.

BACKGROUND: Suspected transfusion-transmissible infections (TTIs) have been reported to public health (PH) in British Columbia (BC) since August 2002. The impact of PH notification of suspected transfusion-transmissible hepatitis C virus (TT-HCV) infection over the first 2.5 years and the effectiveness of HCV lookback (LB) and traceback (TB) investigations conducted by Canadian Blood Services (CBS) in BC were evaluated. STUDY DESIGN AND METHODS: Suspected TT-HCV cases reported to CBS in BC between August 28, 2002, and February 28, 2005, were analyzed. The incremental yield of plausible TTIs from PH-reported suspected TTIs was calculated. The effectiveness of LB and TB investigations was assessed with respect to the impact of improved anti-HCV donor screening, the number of newly recognized HCV infections, and the timeliness of initiating investigations. RESULTS: Nine of 553 (1.6%) investigations were initiated after PH reporting, yielding an additional 2 of 237 (i.e., 0.8%) plausible TTIs. Ninety-two percent of investigations with transfused units involved transfusions before implementing second-generation anti-HCV enzyme immunoassay (EIA) donor screening. Almost one-third of HCV-infected persons in linked investigations (i.e., LB triggered by a TB and vice versa) were newly identified. Recently tested, PH-reported cases incurred a mean delay exceeding 6 months until initiating a LB or TB investigation. CONCLUSION: PH reporting of TTIs and investigating transfusions after second-generation anti-HCV EIA donor screening identified few plausible TT-HCV infections. Many HCV-infected recipients or lapsed donors first became aware of their infection status as a result of CBS investigations. The current process of reporting suspected TTIs incurs significant time delay.

Spittal, P. M., K. J. Craib, M. Teegee, C. Baylis, W. M. Christian, A. K. Moniruzzaman and M. T. Schechter. "**The Cedar project: prevalence and correlates of HIV infection among young Aboriginal people who use drugs in two Canadian cities**." Int J Circumpolar Health **2007** 66(3): 226-240.

INTRODUCTION: During the past decade, the number of Aboriginal people diagnosed with HIV in Canada has grown more than any other ethnicity. Whereas the majority of infections are related to injection drug use, factors that explain elevated risk and transmission of HIV among Aboriginal young people who use illicit drugs are not well understood. STUDY DESIGN: Observational study. METHODS: The Cedar Project is an observational study of Aboriginal youth living in Vancouver and Prince George, BC. Eligibility criteria include age (14-30 years) and self-reported use of non-injection or injection drugs at least once in the month before enrolment. Between October 2003 and April 2005, 512 participants were recruited and completed a questionnaire administered by an Aboriginal interviewer. Multivariable logistic regression analysis was used to model the independent association of demographic and behavioural variables of individuals with HIV infection. RESULTS: Of the participants, 235 resided in Prince George and 277 in Vancouver. Among the 276 participants that used injection drugs, HIV prevalence was significantly higher in Vancouver (17% vs. 7%) but HCV prevalence was higher in Prince George (62% vs. 57%). In Vancouver, 40% of injectors reported daily heroine use compared with 12% in Prince George. In contrast, Prince George participants were more likely to report daily injection of cocaine compared with those in Vancouver (37% vs. 21%). A higher percentage of Prince George participants reported having difficulty accessing clean syringes (22% vs. 8%). History of non-consensual sex, residing in Vancouver and duration of injection drug use were independent factors associated with increased risk of HIV infection. CONCLUSIONS: HIV and HCV prevalence are elevated in young Aboriginal drug users residing in Vancouver and Prince George. Heterogeneity exists in these locations with respect to drug of choice and access to clean syringes.

Prevention and treatment programs are urgently required in this population.

Minuk, G. Y., A. Sun, D. F. Sun, J. Uhanova, L. E. Nicolle, B. Larke and A. Giulivi. "**Serological evidence of hepatitis E virus infection in an indigenous North American population**." Can J Gastroenterol **2007** 21(7): 439-442.

BACKGROUND: Hepatitis E virus (HEV) infections are thought to be uncommon in North America. Recently, HEV transmission has been reported following the consumption of deer meat. Because deer are closely related to caribou and caribou meat is a staple of the Canadian Inuit and the American Eskimo diet, the present study explored the seroprevalence of HEV infection in an isolated Canadian Inuit community. METHODS: Stored sera were thawed and tested for immunoglobulin (Ig) G and IgM anti-HEV by ELISA, and tested for HEV-RNA by reverse transcriptase polymerase chain reaction. RESULTS: The study consisted of 393 sera (representing approximately 50% of the community's inhabitants). Eleven samples (3%) were IgG anti-HEV-positive. Their mean age was 29+/-8 years and three were male. Two of 11 (18%) were also IgM anti-HEV-positive. All IgG anti-HEV-positive individuals were HEV-RNA-negative. Liver biochemistry was normal in all. Seven of 11 (64%) were also positive for anti-hepatitis A virus, five (46%) were hepatitis B virus seropositive and none (0%) were positive for anti-hepatitis C virus. There were no associations between infections with HEV and other hepatropic viruses. Serological testing was negative for HEV infection in 25 caribou from an adjacent region. CONCLUSION: The results of the present study showed that serological evidence of HEV infection was present in 3% of the observed Canadian Inuit population; the presence of IgM anti-HEV suggested recent infection and HEV did not appear to coinfect with other common hepatotropic viruses. The source of HEV infection in the population remains unclear. These findings are interesting but preliminary. Additional data are required to determine whether HEV infections are responsible for otherwise unexplained acute hepatitis in the Canadian Inuit population and visitors returning from northern North American communities.

Greenland (5)

Rex, K. F., H. B. Krarup, P. Laurberg and S. Andersen. "**Population-based comparative epidemiological survey of hepatitis B, D, and C among Inuit migrated to Denmark and in high endemic Greenland**." Scand J Gastroenterol **2012**.

Abstract Objective. Infection with hepatitis B virus (HBV) is endemic among Arctic populations where it may have a benign course. However, the relation of HBV to migration to low endemic areas is unknown, as it is for hepatitis D and C, and details on the influence of delta virus at a population level are lacking. Material and methods. Population-based investigation of Greenlanders living in Denmark (n = 136) and in Greenland (n = 441). We tested for HBsAg, anti-HBs, anti-HBc, HBeAg, anti-HBe, HBV-DNA, HBV genotypes, anti-HDV, HDV-RNA, anti-HCV, HCV-Elisa test, HCV-RNA, aspartate aminotransferase, gamma-glutamyl transferase, bilirubin, and albumin, and performed a physical examination. Results. Participation rate was 52/95% in Denmark/Greenland. Half of participants in Denmark had lived more than half of their lives in Denmark, and 54.5% had been exposed to HBV. This was similar to 53% among Greenlanders living in West Greenland (p = 0.76). HBsAg was positive in 4.4% of Greenlanders in Denmark (n = 6), who all were anti-HBe positive and had low viral load. Serological signs of HBV infection associated with having both parents born in Greenland (p = 0.007) and with IV drug use (p = 0.03). We found serological signs of HDV exposure among participants in Denmark/Greenland in 0.7/1.1% (n = 1/5) and HCV exposure in 1.5/0.0% (n = 2/0). Liver biochemistry was elevated in Greenlanders exposed to HDV. Conclusions. Hepatitis B, D, and C occurrences among Greenlanders in Denmark mirrored that of Greenland. Importantly, previously undetected exposure to delta virus associated with elevated liver biochemistry, and the introduction of delta virus is a liability to Greenlanders and to Greenland.

Borresen, M. L., A. Koch, R. J. Biggar, K. Ladefoged, M. Melbye, J. Wohlfahrt and T. G.

Krause. "**Effectiveness of the Targeted Hepatitis B Vaccination Program in Greenland**." Am J Public Health **2011**.

Objectives. To evaluate the effectiveness of the hepatitis B virus (HBV) vaccination program in Greenland, which targets children born to mothers who are positive for HBV surface antigen (HBsAg), we determined vaccination coverage, levels of postvaccination antibodies, and frequency of breakthrough infections in at-risk children. Methods. We conducted a population-based retrospective cohort study with data from nationwide registries. We identified all children born to HBsAg positive mothers from 1992 to 2007 and collected data on their HBV vaccination status. In 2008 to 2010, we tested the children for HBV core antibody, HBsAg, and anti-HBsAg antibody (HBsAb). Results. Of 4050 pregnant women, 3.2% were HBsAg positive. Of 207 children born to these women, 20% received no vaccinations, and only 58% received at least 3 vaccinations. At follow-up, HBsAb levels in vaccinated children were much lower than expected, and 8 (6%) of 140 at-risk children had breakthrough infections, with 4 chronically infected (persistently HBsAg positive). Conclusions. The prevention program targeting children at risk for HBV in Greenland is ineffective. HBV vaccination should be included in the universal childhood vaccination program, and postvaccination HBsAb levels should be monitored. (Am J Public Health. Published online ahead of print September 22, 2011: e1-e8. doi:10.2105/AJPH.2011.300239).

Borresen, M. L., A. Koch, R. J. Biggar, M. Andersson, J. Wohlfahrt, K. Ladefoged and M. Melbye. "**Hepatocellular carcinoma and other liver disease among Greenlanders chronically infected with hepatitis B virus: a population-based study**." J Natl Cancer Inst **2011** 103(22): 1676-1685.

BACKGROUND: In Greenland, the prevalence of hepatitis B surface antigen carriers, reflecting chronic hepatitis B virus (HBV) infection, is 5%-10%. However, the incidence of cirrhosis and hepatocellular carcinoma in this population has been reported to be low. We investigated this discrepancy in a large population-based cohort study. METHODS: In total, 8879 Greenlanders (16% of the population) were recruited for population-based surveys performed from May 5 to July 7, 1987, and from November 1 to November 21, 1998, with follow-up until March 31, 2010. HBV status was based on serological testing, supplemented by data from all available HBV registries in Greenland to determine changes in HBV status over time. Information on morbidity and mortality was obtained from the Patient Discharge Registry, the Cancer Registry, and the Central Registration System. Sex, age, ethnicity, and period-adjusted incidence rate ratios (IRRs) were estimated using Poisson regression. World standardized rates were derived from these and World Health Organization data. RESULTS: The 650 chronically HBV-infected persons had higher rates of hepatocellular carcinoma (adjusted IRR = 8.70; 95% CI = 2.06 to 36.7), liver disease (adjusted IRR = 5.73, 95% CI = 3.52 to 9.34), and all-cause mortality (adjusted IRR = 1.47; 95% CI = 1.21 to 1.79) than the 5160 HBV-negative persons. However, the world standardized incidence rates of hepatocellular carcinoma (38.5 cancers per 100 000 person-years) and cirrhosis (24 cases per 100 000 person-years) among chronically HBV-infected persons were low compared with results from population-based studies from countries with low, intermediate, and high rates of endemic HBV infection. CONCLUSION: The relatively low incidence of hepatocellular carcinoma and other HBV-related morbidity among chronic HBV-infected persons in Greenland suggest a more benign course of HBV among the Greenlandic Inuit than in populations in other parts of the world.

Borresen, M. L., O. R. Olsen, K. Ladefoged, B. J. McMahon, T. Hjuler, I. Panum, J. Simonetti, C. Jones, H. Krarup and A. Koch. "**Hepatitis D outbreak among children in a hepatitis B hyper-endemic settlement in Greenland**." J Viral Hepat **2010** 17(3): 162-170.

Hepatitis B virus (HBV) infection is endemic in Greenland with 5-10% of the population being HBsAg-positive (chronic carriers). Surprisingly, despite of the high prevalence of HBV infection, acute and chronic hepatitis B, liver cirrhosis and primary hepatocellular carcinoma appear much less frequently than expected. The reasons for the low frequencies are unknown, but as a consequence implementation of a childhood HBV vaccination programme, though debated for years, has never been instituted. We describe an outbreak of hepatitis D (HDV) infection among children in a

hepatitis B hyper-endemic settlement of 133 inhabitants on the west coast of Greenland. In 2006 a total of 27% of the inhabitants were HBsAg-positive (chronic carriers) and 83% were HBcAb-positive (previously exposed). Forty-six percent of the HBsAg-positive persons were below 20 years of age. On follow-up 1 year later a total of 68% of the HBsAg-positive persons were HDV-IgG positive. Five children, who were HBsAg-positive in 2006, had HDV-seroconverted from 2006 to 2007, indicating a HDV-super-infection. Most of the HDV-IgG positive children had markedly elevated liver enzymes. In the multivariate analysis, among the HBV and HDV markers, presence of HDV-IgG was most strongly associated with elevation of liver enzymes. In conclusion, the HBV-HDV super-infection and presumed HDV outbreak in this settlement challenges the notion that HBV infection may not be as harmless in Greenland as previously anticipated. The findings strongly suggest that HBV vaccination should be included in the child-immunization program in Greenland.

Krarup, H. B., S. Andersen, P. H. Madsen, H. Okkels, B. H. Hvingel and P. Laurberg. "**Benign course of long-standing hepatitis B virus infection among Greenland Inuit?**" Scand J Gastroenterol **2008** 43(3): 334-343.

OBJECTIVE: Chronic hepatitis B virus (HBV) infection can present in different ways, from inactive carrier to liver failure or cancer. The role of the virus subtype is controversial. The purpose of this study was to characterize HBV infection in detail and its impact on general health, body-build and liver biochemistry. MATERIAL AND METHODS: The study comprised a population-based cohort of Inuit exposed to HBV 3-7 decades ago in the capital in West Greenland, a coastal town and four settlements in rural East Greenland. Participants included 95% of the invited Inuit: 229 men, 205 women, aged 50-69 years. RESULTS: Only 25% of the participants had never had HBV infection. HBsAg was positive in 86 participants (20.0%), more being found positive in rural East Greenland than in the city in West Greenland (28.9% versus 2.7%; $p < 0.001$). HBV-DNA was positive in 61 of those with median HBV-DNA 40,000 copies/ml. HBV genotype could be determined in 52: 47 participants had genotype B, 4 genotype D, and 1 had both B and D. At sequencing, genotype B resembled subtype Bj, but with more than 5% diversity in the C-gene it could be a new subtype B. Pre-core mutation was found in 55 of 56 participants investigated. None of the participants had signs of liver disease, and HBV infection did not influence body-build or liver biochemistry. CONCLUSIONS: More than 75% of participants had a marker of present or previous HBV infection but the infection seemed dormant. The majority harbored a special variant of genotype B that might be a new subtype giving a relatively benign disease. The role of detailed subtyping of HBV for prognostic evaluation should be investigated in more detail.

Iceland (3)

Gunnarsdottir, S. A., R. Olsson, S. Olafsson, N. Cariglia, J. Westin, B. Thjodleifsson and E. Bjornsson. "**Liver cirrhosis in Iceland and Sweden: incidence, aetiology and outcomes**." Scand J Gastroenterol **2009** 44(8): 984-993.

OBJECTIVE: The objectives of this study were to investigate the incidence, aetiology and mortality of liver cirrhosis in Iceland and in Gothenburg in Sweden. Further objectives were prognosis in relation to different aetiologies and to evaluate the relationship between alcohol consumption in these countries and the incidence of alcoholic cirrhosis in recent decades. The incidence and mortality of liver cirrhosis in Iceland has been reported to be the lowest in the Western world. There are very few data on aetiology, incidence and prognosis among cirrhotics in Sweden. MATERIAL AND METHODS: All patients diagnosed with liver cirrhosis in Gothenburg (600,000 inhabitants) and Iceland (300,000 inhabitants) during the period 1994-2003 were included. RESULTS: A total of 918 patients in Gothenburg and 98 in Iceland were identified. The annual incidence in Gothenburg was 15.3+/-2.4/100,000 compared to 3.3+/-1.2/100,000 in Iceland ($p<0.0001$). In Gothenburg, 69% were male and in Iceland 52% ($p<0.001$). In Gothenburg, 50% of the patients had alcoholic cirrhosis compared to 29% in Iceland ($p<0.0001$). In Gothenburg, the patients had a higher Child-Pugh score (9.0) (SD 2.5) compared to Iceland (7.3) (SD 2.7) ($p<0.0001$).

There was no difference in survival between patients with alcoholic liver disease and those with other aetiologies. CONCLUSIONS: The incidence of liver cirrhosis is low in Iceland, i.e. 24% of the incidence in Gothenburg, due to the lower incidence of alcoholic and hepatitis C cirrhosis in Iceland. No increasing trends in the incidence of cirrhosis in these two countries were observed during the study period.

Thjodleifsson, B. "**[Cirrhosis hepatis, viral hepatitis C and alcohol consumption in Iceland]**." Laeknabladid **2008** 94(1): 7.

Palsson, P. S., J. G. Jonasson and S. Olafsson. "**[Hepatitis C: a clinical-histopathological study]**." Laeknabladid **2008** 94(1): 13-17.

OBJECTIVE: Hepatitis C is a common cause of chronic hepatitis and cirrhosis in Western countries. In recent years a large group of individuals have been diagnosed with the disease in Iceland. The aim of this study was to investigate histological parameters of patients with hepatitis C and to correlate histological findings with clinical findings. MATERIALS AND METHODS: In this retrospective study, all patients diagnosed with hepatitis C in Iceland that had a liver biopsy in the years 1991-2001 were included. Data on age, route of infection, duration of infection and co-infection was obtained from medical records. Liver biopsy specimens were evaluated and inflammatory activity graded and the degree of fibrosis staged. RESULTS: In all 97 patients (58 males, 39 females) were included in the study. The mean age was 35.6 years (range 11-64). Risk factors were intravenous drug abuse in 70 (72.6%), blood transfusion in 12 (12.4%) and eight had no known risk factors. Estimated duration of infection was 8.85 years (range 1-31). Average inflammatory grade was 2.84 (range 0-8) and average fibrosis stage was 0.95 (range 0-6). The majority (72.6%) of patients had minimal or no inflammation and 85.5% had minimal or no fibrosis. Only four patients had cirrhosis. Significant correlation was observed between the age at infection and the degree of fibrosis. No correlation was detected between the duration of infection or route of infection and histopathological parameters. CONCLUSION: Patients with hepatitis C that underwent a liver biopsy in 1991-2000 had mild histopathological changes in the liver. This is most likely due to short duration of infection and young age of the patients in this study.

Nordic countries (general) (4)

Mereckiene, J., S. Cotter, P. Lopalco, F. D'Ancona, D. Levy-Bruhl, C. Giambi, K. Johansen, L. Dematte, S. Salmaso, P. Stefanoff, et al. "**Hepatitis B immunisation programmes in European Union, Norway and Iceland: where we were in 2009?**" Vaccine **2010** 28(28): 4470-4477.

In January 2009 25 European Union (EU) Member States (MSs), Norway and Iceland, participated in a survey seeking information on national hepatitis B vaccination programmes. Details of vaccination policy, schedule, population groups targeted for vaccination, programme funding, vaccine coverage and methods of monitoring of vaccine coverage were obtained. Twenty (74%) countries reported that they have a universal hepatitis B vaccination programme, in addition to immunisation of at risk groups; seven (26%) countries recommend HBV for high risk groups only (with some inter-country variation on groups considered at high risk). Among countries without universal hepatitis B vaccination programmes, the major factor for non-introduction is low disease endemicity.

Pukkala, E., J. I. Martinsen, E. Lynge, H. K. Gunnarsdottir, P. Sparen, L. Tryggvadottir, E. Weiderpass and K. Kjaerheim. "**Occupation and cancer - follow-up of 15 million people in five Nordic countries**." Acta Oncol **2009** 48(5): 646-790.

We present up to 45 years of cancer incidence data by occupational category for the Nordic populations. The study covers the 15 million people aged 30-64 years in the 1960, 1970, 1980/1981 and/or 1990 censuses in Denmark, Finland, Iceland, Norway and Sweden, and the 2.8 million incident cancer cases diagnosed in these people in a follow-up until about 2005. The study was undertaken as a cohort study with linkage

of individual records based on the personal identity codes used in all the Nordic countries. In the censuses, information on occupation for each person was provided through free text in self-administered questionnaires. The data were centrally coded and computerised in the statistical offices. For the present study, the original occupational codes were reclassified into 53 occupational categories and one group of economically inactive persons. All Nordic countries have a nation-wide registration of incident cancer cases during the entire study period. For the present study the incident cancer cases were classified into 49 primary diagnostic categories. Some categories have been further divided according to sub-site or morphological type. The observed number of cancer cases in each group of persons defined by country, sex, age, period and occupation was compared with the expected number calculated from the stratum specific person years and the incidence rates for the national population. The result was presented as a standardised incidence ratio, SIR, defined as the observed number of cases divided by the expected number. For all cancers combined (excluding non-melanoma skin cancer), the study showed a wide variation among men from an SIR of 0.79 (95% confidence interval 0.66-0.95) in domestic assistants to 1.48 (1.43-1.54) in waiters. The occupations with the highest SIRs also included workers producing beverage and tobacco, seamen and chimney sweeps. Among women, the SIRs varied from 0.58 (0.37-0.87) in seafarers to 1.27 (1.19-1.35) in tobacco workers. Low SIRs were found for farmers, gardeners and teachers. Our study was able to repeat most of the confirmed associations between occupations and cancers. It is known that almost all mesotheliomas are associated with asbestos exposure. Accordingly, plumbers, seamen and mechanics were the occupations with the highest risk in the present study. Mesothelioma was the cancer type showing the largest relative differences between the occupations. Outdoor workers such as fishermen, gardeners and farmers had the highest risk of lip cancer, while the lowest risk was found among indoor workers such as physicians and artistic workers. Studies of nasal cancer have shown increased risks associated with exposure to wood dust, both for those in furniture making and for those exposed exclusively to soft wood like the majority of Nordic woodworkers. We observed an SIR of 1.84 (1.66-2.04) in male and 1.88 (0.90-3.46) in female woodworkers. For nasal adenocarcinoma, the SIR in males was as high as 5.50 (4.60-6.56). Male waiters and tobacco workers had the highest risk of lung cancer, probably attributable to active and passive smoking. Miners and quarry workers also had a high risk, which might be related to their exposure to silica dust and radon daughters. Among women, tobacco workers and engine operators had a more than fourfold risk as compared with the lung cancer risk among farmers, gardeners and teachers. The occupational risk patterns were quite similar in all main histological subtypes of lung cancer. Bladder cancer is considered as one of the cancer types most likely to be related to occupational carcinogens. Waiters had the highest risk of bladder cancer in men and tobacco workers in women, and the low-risk categories were the same ones as for lung cancer. All this can be accounted for by smoking. The second-highest SIRs were among chimney sweeps and hairdressers. Chimney sweeps are exposed to carcinogens such as polycyclic aromatic hydrocarbons from the chimney soot, and hairdressers' work environment is also rich in chemical agents. Exposure to the known hepatocarcinogens, the Hepatitis B virus and aflatoxin, is rare in the Nordic countries, and a large proportion of primary liver cancers can therefore be attributed to alcohol consumption. The highest risks of liver cancer were seen in occupational categories with easy access to alcohol at the work place or with cultural traditions of high alcohol consumption, such as waiters, cooks, beverage workers, journalists and seamen. The risk of colon cancer has been related to sedentary work. The findings in the present study did not strongly indicate any protective role of physical activity. Colon cancer was one of the cancer types showing the smallest relative variation in incidence between occupational categories. The occupational variation in the risk of female breast cancer (the most common cancer type in the present series, 373 361 cases) was larger, and there was a tendency of physically demanding occupations to show SIRs below unity. Women in occupations which require a high level of education have, on average, a higher age at first child-birth and elevated breast cancer incidence. Women in occupational categories with the highest average number of children had markedly lower incidence. In male breast cancer (2 336

cases), which is not affected by the dominating reproductive factors, there was a suggestion of an increase in risk in occupations characterised by shift work. Night-shift work was recently classified as probably carcinogenic, with human evidence based on breast cancer research. The most common cancer among men in the present cohort was prostate cancer (339 973 cases). Despite the huge number of cases, we were unable to demonstrate any occupation-related risks. The observed small occupational variation could be easily explained by varying PSA test frequency. The Nordic countries are known for equity and free and equal access to health care for all citizens. The present study shows that the risk of cancer, even under these circumstances, is highly dependent on the person's position in the society. Direct occupational hazards seem to explain only a small percentage of the observed variation - but still a large number of cases - while indirect factors such as life style changes related to longer education and decreasing physical activity become more important. This publication is the first one from the extensive Nordic Occupational Cancer (NOCCA) project. Subsequent studies will focus on associations between specific work-related factors and cancer diseases with the aim to identify exposure-response patterns. In addition to the cancer data demonstrated in the present publication, the NOCCA project produced Nordic Job Exposure Matrix (described in separate articles in this issue of Acta Oncologica) that transforms information about occupational title histories to quantitative estimates of specific exposures. The third essential component is methodological development related to analysis and interpretation of results based on averaged information of exposures and co-factors in the occupational categories.

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

Infection with hepatitis B causes between 500,000 and 1.2 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.

Stene-Johansen, K., G. Tjon, E. Schreier, V. Bremer, S. Bruisten, S. L. Ngui, M. King, R. M. Pinto, L. Aragones, A. Mazick, et al. "**Molecular epidemiological studies show that hepatitis A virus is endemic among active homosexual men in Europe**." J Med Virol **2007** 79(4): 356-365.

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.

Finland (1)

Rapola, S. "**National immunization program in Finland**." Int J Circumpolar Health **2007** 66(5): 382-389.

In the national immunization program, all Finnish children are vaccinated against 9 infectious diseases: diphtheria, tetanus, pertussis, polio, severe infections due to Haemophilus influenzae type b, measles, mumps, rubella and influenza. In addition, vaccination against tuberculosis, hepatitis A- and B-, influenza or tick-borne encephalitis are given to those at risk of contracting the diseases. More than 95% of children are vaccinated according the optimal schedule. Vaccine preventable diseases are rare in Finland. In Finland, all vaccines are imported. The decisions regarding the vaccination program are made by the Ministry of Social Affairs and Health. The National Public Health Institute is responsible for the control of the communicable diseases and the implementation of the vaccination program in practice. Evaluation of the implementation of new vaccines in the vaccination program is ongoing.

Norway (11)

Rimseliene, G., O. Nilsen, H. Klovstad, H. Blystad and P. Aavitsland. "**Epidemiology of acute and chronic hepatitis B virus infection in Norway, 1992-2009**." BMC Infect Dis **2011** 11: 153.

BACKGROUND: Norway is classified as a low prevalence country for hepatitis B virus infection. Vaccination is only recommended for risk groups (intravenous drug users (IDUs), Men who have Sex with Men (MSM), immigrants and contacts of known carriers). We describe the epidemiology of reported cases of hepatitis B in Norway, during the years 1992-2009 in order to assess the validity of current risk groups and recommend preventive measures. METHODS: We used case based data from the national surveillance system on acute and chronic hepatitis B. The Norwegian Statistics Bureau provided population and migration data and the Norwegian Institute for Alcohol and Drug Research the estimated number of active IDUs between 2002-2007. Incidence rates (IR) and incidence rate ratios (IRR) for acute hepatitis B and notification rates (NR) and notification rate ratios (NRR) for chronic hepatitis B with 95% confidence intervals were calculated. RESULTS: The annual IR of acute hepatitis B ranged from 0.7/100,000 (1992) to 10.6/100,000 (1999). Transmission occurred mainly among IDUs (64%) or through sexual contact (24%). The risk of acquiring acute hepatitis B was highest in people aged 20-29 (IRR = 6.6 [3.3-13.3]), and in males (IRR = 2.4 [1.7-3.3]). We observed two peaks of newly reported chronic hepatitis B cases in 2003 and 2009 (NR = 17.6/100,000 and 17.4/100,000, respectively). Chronic hepatitis B was more likely to be diagnosed among immigrants than among Norwegians (NRR = 93 [71.9-120.6]), and among those 20-29 compared to those 50-59 (NRR = 5.2 [3.5-7.9]). CONCLUSIONS: IDUs remain the largest risk group for acute hepatitis B. The observed peaks of chronic hepatitis B are related to increased immigration from high endemic countries and screening and vaccination of these groups is important to prevent further spread of infection. Universal screening of pregnant women should be introduced. A universal vaccination strategy should be considered, given the high cost of reaching the target populations. We recommend evaluating the surveillance system for hepatitis B as well as the effectiveness of screening and vaccinating immigrant populations.

Kristiansen, M. G., M. L. Lochen, T. J. Gutteberg, L. Mortensen, B. O. Eriksen and J. Florholmen. "**Total and cause-specific mortality rates in a prospective study of community-acquired hepatitis C virus infection in northern Norway**." J Viral Hepat **2011**

18(4): 237-244.

Knowledge of the natural course and especially the total and cause-specific mortality of community-acquired chronic HCV infection is limited. The aims of our study were to determine the total and cause-specific mortality in patients infected with chronic hepatitis C in a community-based setting in northern Norway. This prospective cohort study included 1010 HCV-positive patients diagnosed with recombinant immunoblot assay between 1 January 1990 and 1 January 2000, with a median observation time from diagnosis to follow-up of 7 years. Data were collected from medical records in the period between 1 January 2004 and 30 June 2006. Time and cause of death were ascertained from the Norwegian Causes of Death Register. Age-adjusted death rates and standardised mortality ratios (SMRs) were compared with those of the general Norwegian population. In total, 122 deaths were recorded. The Kaplan-Meier estimate of survival was 88% at 14 years. The SMR in the cohort relative to the general population was 6.66. Most of the excess deaths in both genders were because of liver-related causes, those associated with a drug-using lifestyle and suicide. The statistically significant increase in SMRs ranged from 4.2 for death by cancer in women to 64.6 for liver disease in women. There was no statistically significant increase in SMRs from cardiovascular disease in either gender or from cancer in men. In conclusion, our study shows that the death rate in patients infected with hepatitis C is 6.66 times higher than in the general Norwegian population.

Dalgard, O. "**[New guidelines for investigation and treatment of hepatitis C]**." Tidsskr Nor Laegeforen **2011** 131(1): 15.

Olsen, K., P. E. Dahl, E. J. Paulssen, A. Husebekk, A. Widell and R. Busund. "**Increased risk of transmission of hepatitis C in open heart surgery compared with vascular and pulmonary surgery**." Ann Thorac Surg **2010** 90(5): 1425-1431.

BACKGROUND: We report a case of patient-to-surgeon transmission of hepatitis C virus (HCV), and the subsequent transmission of HCV to surgical patients. METHODS: In 2007, a cardiac surgeon tested positive for hepatitis C. A complete look-back investigation was initiated that involved screening of all patients on the surgeon's operating lists between September 2004 and April 2007. Genotyping and phylogenetic analyses were performed where HCV RNA was detected. RESULTS: Of the 499 patients invited to HCV testing, 431 responded, 13 of whom were found anti-HCV positive. One patient, who had surgery in August 2005, was found most likely to be the source of transmission to the surgeon. Of the 270 patients who had surgery after this incident, 10 became infected, giving an estimated rate of transmission of 3.7%. The HCV polymerase chain reaction positive samples were found to be the same genotype 1a strain by phylogenetic analyses. All the 10 subsequently infected patients had undergone open heart surgery, whereas none of the 103 noncardiac patients became infected, giving an estimated risk of transmission during open heart surgery of 6.0% (95% confidence interval [3.3% to 10.7%]). CONCLUSIONS: The transmission rate from an HCV positive surgeon to patients in a cardiothoracic setting was higher than previously reported and significantly higher during open heart surgery compared with vascular and pulmonary surgery. These results indicate the need for unequivocal routines for testing and handling of HCV positive health care workers and patients.

Kristiansen, M. G., T. J. Gutteberg, L. Mortensen, L. K. Berg, R. Goll and J. Florholmen. "**Clinical outcomes in a prospective study of community-acquired hepatitis C virus infection in Northern Norway**." Scand J Gastroenterol **2010** 45(6): 746-751.

OBJECTIVE: Knowledge on the natural course of the morbidity of unselected community-acquired hepatitis C virus (HCV) infection is limited. The aim of our study was to characterize the clinical outcomes of both hepatic and extrahepatic morbidity in patients infected with HCV in a community-based setting in Northern Norway. MATERIAL AND METHODS: This prospective cohort study included 1010 HCV-positive patients diagnosed by recombinant immunoblot assay (RIBA), between 1 January 1990 and 1 January 2000. Questionnaires were sent to those physicians in Northern Norway who had requested the RIBA tests during the relevant period. Data

were collected from medical records in the period between 1 January 2004 and 30 June 2006. Access to confidential information was obtained from the Norwegian Directorate of Health. RESULTS: Median age at follow-up was 39 and 41 years in females and males, respectively. In patients with positive HCV RNA status following results were found: Alanine aminotransferase was elevated in 27.4%, decompensated liver disease in 2.9% and hepatocellular carcinoma in 0.4%. Median observation period from estimated acquisition of the disease to follow-up in these patients was 26 years. Depression was reported in 10.7% of chronic infected subjects. Renal failure caused by membranoproliferative glomerulonephritis occurred in 0.2%. CONCLUSIONS: In an unselected HCV-RNA positive population severe liver disease developed in a sub-group of patients. These observations suggest that chronic HCV disease in relatively young subjects may cause a substantial burden on the health system in the future.

Kristiansen, M. G., M. L. Lochen, T. J. Gutteberg, E. Falk, L. Mortensen, J. Florholmen and B. O. Eriksen. "**Hepatitis C virus infection was not found in patients with sporadic porphyria cutanea tarda, membranoproliferative glomerulonephritis or membranous glomerulonephritis in Northern Norway**." Scand J Gastroenterol **2009** 44(7): 894-896.

Kristiansen, M. G., B. O. Eriksen, J. M. Maltau, B. Holdo, T. J. Gutteberg, L. Mortensen, M. L. Lochen and J. Florholmen. "**Prevalences of viremic hepatitis C and viremic hepatitis B in pregnant women in Northern Norway**." Hepatogastroenterology **2009** 56(93): 1141-1145.

BACKGROUND/AIMS: No data exist for current infections of hepatitis C and hepatitis B virus in pregnant women in Northern Norway. The aim of this study was to determine the prevalences of viremic hepatitis C and hepatitis B of pregnant women in Northern Norway. A cross-sectional, multi-center study with participation of all hospitals and delivery rooms in this region was performed. METHODOLOGY: All pregnant women who consecutively underwent ultrasound screening in 17th - 19th weeks of pregnancy during the period between October 2003 and October 2004 were invited to participate in the study. On the day of ultrasonography venous blood samples were collected for analysis of serum for antibody to hepatitis C virus, hepatitis C virus ribonucleicacid, recombinant immunoblot assay, hepatitis B surface antigen, antibody to hepatitis B surface antigen and antibody to hepatitis B core antigen. RESULTS: Out of 4087 eligible pregnant women 1668 (41%) were included in the study. The prevalences of viremic hepatitis C (hepatitis C virus ribonucleicacid positive) and viremic hepatitis B (hepatitis B surface antigen positive) were 0.2% (95% CI 0.0 - 0.5) and 0.1% (95% CI 0.0 - 0.3) respectively. CONCLUSIONS: The prevalences of viremic hepatitis C and hepatitis B in pregnancy in Northern Norway were low.

Vik, I. S., K. Skaug, O. Dalgard, T. W. Steen and G. Hoddevik. "**[Hepatitis C--a health problem also in Norway]**." Tidsskr Nor Laegeforen **2008** 128(5): 563-566.

BACKGROUND: Hepatitis C is a large global health problem; approximately 20 - 30 000 are infected in Norway. Hepatitis C-infection is often chronic and can progress into chronic liver disease, liver cirrhosis and hepatocellular carcinoma. The most important transmission route is through percutaneous exposure to infected blood. The aim of this article is to describe the clinical course, microbiological diagnostic approaches, therapy, prophylaxis and public health aspects of Hepatitis C infection. MATERIAL AND METHODS: The paper is based on results from annual health examinations (conducted since 2001) of persons who abuse drugs intravenously in Oslo, from diagnostic work in a national reference laboratory for Hepatitis C and studies of literature (retrieved from Pubmed). RESULTS AND INTERPRETATION: The prevalence of Hepatitis C varies by country and subgroup of patients. In Norway the prevalence is 0.13 % among new blood donors, 0.7 % among pregnant women, 0.55 % in the general adult population and approximately 70 % among persons who abuse drugs intravenously. Treatment with pegylated interferon and ribavirin induces sustained virological response in 80 % of patients with genotypes 2 and 3 and in 30 - 40 % of those with genotype 1.

Ritland, S. "**[Hepatitis C--a health problem also in Norway]**." Tidsskr Nor Laegeforen **2008** 128(10): 1191; author reply 1191.

Melum, E., S. Friman, K. Bjoro, A. Rasmussen, H. Isoniemi, H. Gjertsen, L. Backman, A. Oksanen, M. Olausson, F. F. Duraj, et al. "**Hepatitis C impairs survival following liver transplantation irrespective of concomitant hepatocellular carcinoma**." J Hepatol **2007** 47(6): 777-783.

BACKGROUND/AIMS: Liver transplantation (LTX) is the only curative treatment for end-stage liver disease caused by hepatitis C (HCV). Hepatocellular carcinoma (HCC) is common in patients with HCV cirrhosis. METHODS: Two hundred and eighty-two HCV patients listed for LTX in the Nordic countries in a 17-year period were included. For comparison a group of patients with non-viral chronic liver disease (n=1552) was used. RESULTS: Two hundred and fifty-three (90%) patients received a first liver allograft. HCC was found in 38% of the explanted livers. Survival at 1, 3 and 5years was 82%, 69% and 61% vs. 85%, 80% and 76% for the comparison group (p<0.0001), this survival difference was also evident when excluding patients with HCC (p=0.007). HCV patients with HCC had 1, 3 and 5year survival of 73%, 52% and 46% compared with 88%, 80% and 71% for the HCV patients without HCC (p=0.0005). In an intention-to-treat analysis (from time of acceptance to the waiting list) HCV was also associated with an impaired survival. CONCLUSIONS: HCV cirrhosis, which is now also an important indication for LTX in the Nordic countries, and significantly impairs survival following LTX. Concomitant HCC and donor age are the two most important factors contributing to an impaired survival.

Krook, A. L., D. Stokka, B. Heger and E. Nygaard. "**Hepatitis C treatment of opioid dependants receiving maintenance treatment: results of a Norwegian pilot study**." Eur Addict Res **2007** 13(4): 216-221.

BACKGROUND: Many physicians are still skeptic to treat opioid dependants, with or without maintenance treatment, for hepatitis C (HCV) because of concerns about psychiatric comorbidity, stability and adherence. In Norway, there are about 3,500 patients participating in the restrictive medication-assisted rehabilitation (LAR) programs in which all patients are given methadone or buprenorphine maintenance therapy. This study was undertaken to determine whether HCV combination therapy with pegylated interferon alpha-2a plus ribavirin is feasible, efficient and safe in this patient group. METHOD: Seventeen patients with HCV genotype 3a were treated for 24 weeks. To optimize compliance, the treatment was given from a department of infectious diseases in cooperation with an LAR center. All injections were given in the LAR center and the patients were given psychosocial support. RESULTS: The compliance was 100%. All responded to the therapy and 16 (94%) were sustained responders. DISCUSSION/CONCLUSION: This study indicates that compliance and treatment outcome of opioid dependants on methadone or buprenorphine maintenance after 24 weeks of HCV treatment corresponds to that for non-dependants if extra support is given. The treatment should be undertaken in collaboration with specialists in addiction medicine, hepatology and infectious diseases.

Sweden (24)

Reepalu, A., M. A. Blome, J. Bjork, A. Widell and P. Bjorkman. "**The risk of cancer among persons with a history of injecting drug use in Sweden - a cohort study based on participants in a needle exchange program**." Acta Oncol **2012** 51(1): 51-56.

BACKGROUND: Injecting drug use (IDU) may lead to exposure to a range of carcinogenic agents. We investigated the risk and distribution of cancers among individuals with a history of IDU in Sweden. MATERIAL AND METHODS: The cancer incidence in a cohort of longitudinally followed participants in a needle exchange program (NEP), recruited between 1987 and 2007, was compared to that in the Swedish general population, matching for age group and gender. Baseline demographic and drug use data were collected and longitudinal testing of serological

markers for HIV, hepatitis B and C virus was performed during NEP participation. Standardized incidence ratios (SIR) for types of cancer found in the study cohort were calculated, using data from the Swedish National Cancer Registry for reference. RESULTS: The mean follow-up time for the 3255 participants was 11.8 years, constituting 38 419 person years at risk. The mean age at end of follow-up was 42.7 years, and 75% of participants were men. Seventy-eight cases of cancer were observed (SIR 1.1 [95% CI = 0.9-1.4]). The SIR was significantly increased for five cancer types among men; primary liver, laryngeal, lung, oropharyngeal and non-melanoma skin cancer (respective SIR 12.8 [95% CI = 4.2-30.0], 9.2 [95% CI = 1.9-26.8], 3.2 [95% CI = 1.5-6.1], 7.3 [95% CI = 1.5-21.2], and 3.5 [95% CI = 1.1-8.2]), and for cancers of endocrine organs among women (5.3 [95% CI = 1.7-12.4]). CONCLUSION: Although the standardized overall cancer incidence in this relatively young IDU cohort was similar to that in the general population, the risk of specific types of cancer was significantly increased, suggesting that IDU confers elevated risks for certain malignancies. These findings prompt further studies to investigate causative factors and suggest the need for surveillance among persons with a history of IDU.

Ydreborg, M., A. Soderstrom, A. Hakanson, A. Alsio, B. Arnholm, P. Malmstrom, K. Hellstrand, J. Westin and M. Lagging. "**Look-back screening for the identification of transfusion-induced hepatitis C virus infection in Sweden**." Scand J Infect Dis **2011** 43(6-7): 522-527.

BACKGROUND: Following the discovery of the hepatitis C virus (HCV) in 1989, screening of all blood donors for antibodies became mandatory in Sweden as of 1 January 1992. METHODS: Serum samples were collected from patients who had received a blood transfusion in the period prior to 1992 in western Sweden. The prevalence of HCV infection was assessed by antibody screening. RESULTS: Of 13,573 screening serologies, 124 patients (0.9%) had antibodies against HCV; 113 (0.8%) had detectable HCV RNA indicating an ongoing infection. Ninety-one (73%) were female, of whom 32 had been transfused in conjunction with childbirth. A review of the 32 liver biopsy reports available showed that 2 patients had cirrhosis and an additional 9 patients had periportal or septal fibrosis. CONCLUSION: A considerable portion of screened patients had an ongoing HCV infection and were eligible for antiviral treatment. Look-back screening for HCV among recipients of blood transfusions prior to 1992 is meaningful and should include women transfused in childbirth.

Widen, F., L. Sundqvist, A. Matyi-Toth, G. Metreveli, S. Belak, G. Hallgren and H. Norder. "**Molecular epidemiology of hepatitis E virus in humans, pigs and wild boars in Sweden**." Epidemiol Infect **2011** 139(3): 361-371.

Hepatitis E infections in humans are usually acquired in endemic countries in Asia or Africa. In Sweden 17 cases infected in Europe, between 1993 and 2009, were identified. All had clinical hepatitis E with unknown source of infection. Hepatitis E virus (HEV) was identified in faecal samples from 63 piglets in 12 pig farms in Sweden. HEV was also identified in blood from 13 out of 159 investigated Swedish wild boars from nine counties. Partial HEV genomes from humans, pigs and wild boars were sequenced and compared by phylogeny. The results showed close relatedness between HEV strains from piglets from the same farm and from wild boars from the same county. HEV strains from humans showed relatedness with strains from pigs and wild boars from the same county. This study showed that HEV strains form geographical clusters in the phylogenetic tree. The methods used in this study may thus be used for tracing the origin of an infecting strain. Furthermore, this study indicated that there are endemic sources of human HEV infections in Sweden.

Schmeink, C. E., R. L. Bekkers, A. Josefsson, J. H. Richardus, K. Berndtsson Blom, M. P. David, K. Dobbelaere and D. Descamps. "**Co-administration of human papillomavirus-16/18 AS04-adjuvanted vaccine with hepatitis B vaccine: randomized study in healthy girls**." Vaccine **2011** 29(49): 9276-9283.

BACKGROUND: To evaluate co-administration of GlaxoSmithKline Biologicals' human papillomavirus-16/18 AS04-adjuvanted vaccine (HPV) and hepatitis B vaccine

(HepB). METHODS: This was a randomized, controlled, open, multicenter study. Healthy girls, aged 9-15 years, were randomized to receive HPV (n=247), HepB (n=247) or HPV co-administered with HepB (HPV+HepB; n=247) at Months 0, 1 and 6. Antibodies against hepatitis B surface antigen (HBs), HPV-16 and HPV-18 were measured, and reactogenicity and safety monitored. Co-primary objectives were to demonstrate non-inferiority of hepatitis B and HPV-16/18 immune responses at Month 7 for co-administered vaccines, compared with vaccines administered alone, in the according-to-protocol cohort. RESULTS: The pre-defined criteria for non-inferiority were met for all co-primary immunogenicity endpoints at Month 7. Anti-HBs seroprotection rates >/=10mIU/mL were achieved by 97.9% and 100% of girls, respectively, following co-administration or HepB alone. Anti-HBs geometric mean titers (GMTs) (95% confidence interval) were 1280.9 (973.3-1685.7) and 3107.7 (2473.1-3905.1) milli-international units/mL, respectively. Anti-HPV-16 and -18 seroconversion rates were achieved by >/=99% of girls following co-administration or HPV alone. Anti-HPV-16 GMTs were 19819.8 (16856.9-23303.6) and 21712.6 (19460.2-24225.6) ELISA units (ELU)/mL, respectively. Anti-HPV-18 GMTs were 8835.1 (7636.3-10222.1) and 8838.6 (7948.5-9828.4) ELU/mL, respectively. Co-administration was generally well tolerated. CONCLUSIONS: The study results support the co-administration of HPV-16/18 AS04-adjuvanted vaccine with hepatitis B vaccine in adolescent girls aged 9-15 years. CLINICAL TRIALS REGISTRATION: ClinicalTrials.gov registration number NCT00652938.

Herbinger, K. H., H. D. Nothdurft and R. Prymula. "**Online survey: knowledge about risks, prevention and consequences of infections with HBV among travellers from four European countries**." Curr Med Res Opin **2011** 27(3): 489-496.

OBJECTIVE: To evaluate knowledge about risks, prevention and consequences of infection with hepatitis B virus (HBV) among travellers from four low HBV risk, European countries. METHODS: Individuals from an internet panel and based in the Czech Republic, the Netherlands, Spain and Sweden were invited to take part in an online survey. A total of 4203 respondents met the inclusion criteria and completed the survey. RESULTS: The majority (62.3%) of respondents did not know the main travel destinations with moderate or high prevalence for HBV. Also, 20.1% were somewhat or very unaware of the ways in which HBV can be caught and travellers aged 18-35 years were significantly more likely ($p < 0.01$) to have participated in at least one risky activity abroad. Three-quarters (74.9%) thought they were somewhat or very aware of the health implications of contracting HBV, but only 11.8% of participants selected more than three out of the six correct answers relating to conditions caused by HBV. Only 39.3% of those who knew their vaccination status had received vaccination against HBV within the previous 5 years, although some patients may have been vaccinated prior to this period. CONCLUSIONS: As country-specific variables were not analysed in this study, the results do not allow interpretation by country. A high proportion of the respondents were at an elevated risk of HBV infection while visiting moderate or high prevalence countries. They were unlikely to be immunised or take appropriate precautions; participation in risk activities abroad was high, and knowledge of HBV was limited. These findings indicate there is a need for healthcare professionals and the travel industry to educate travellers on the risks of HBV infections while abroad and the importance of preventing infection through vaccination.

Duberg, A. S., H. Pettersson, S. Aleman, A. Blaxhult, L. Daviethsdottir, R. Hultcrantz, E. Back, K. Ekdahl and S. M. Montgomery. "**The burden of hepatitis C in Sweden: a national study of inpatient care**." J Viral Hepat **2011** 18(2): 106-118.

The spread of hepatitis C virus (HCV) in Sweden in the 1970s indicated that serious liver complications (SLC) would increase in the 2000s. The aim of this study was to analyse the burden of HCV-associated inpatient care in Sweden, to demonstrate the changes over time and to compare the findings with a noninfected population. The HCV-cohort (n: 43,000) was identified from the national surveillance database 1990-2006, and then linked to national registers to produce an age-, sex-, and region-matched noninfected comparison population (n: 215,000) and to obtain information

on demographics, cancers, inpatient care and prescriptions. Cox regression was used to estimate the likelihood (hazard ratios) for admission to hospital in the HCV compared with the noninfected cohort. The hazard ratios were 4.03 (95% CI: 3.98-4.08) for all care, 77.52 (71.02-84.60) for liver-related care and 40.74 (30.58-54.27) for liver cancer care. The admission rate in the HCV-cohort compared with the noninfected cohort, the rate ratio (age- and sex-adjusted) for all inpatient care was 5.91 (95% CI: 5.87-5.94), and the rate ratio for liver-related care was 70.05 (66.06-74.28). In the HCV-cohort, 45% of all episodes were for psychiatric, mostly drug-related, care. Inpatient care for SLC increased in the 2000s. To conclude, drug-related care was common in the HCV-infected cohort, the demand for liver-related care was very high, and SLC increased notably in the 2000s, indicating that the burden of inpatient care from serious liver disease in HCV-infected individuals in Sweden is an increasing problem.

Davidson, T., B. Ekermo, H. Gaines, B. Lesko and B. Akerlind. "**The cost-effectiveness of introducing nucleic acid testing to test for hepatitis B, hepatitis C, and human immunodeficiency virus among blood donors in Sweden**." Transfusion **2011** 51(2): 421-429.

BACKGROUND: The purpose of this study was to estimate the cost-effectiveness of using individual-donor nucleic acid testing (ID-NAT) in addition to serologic tests compared with the sole use of serologic tests for the identification of hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) among blood donors in Sweden. STUDY DESIGN AND METHODS: The two strategies analyzed were serologic tests and ID-NAT plus serologic tests. A health-economic model was used to estimate the lifetime costs and effects. The effects were measured as infections avoided and quality-adjusted life-years (QALYs) gained. A societal perspective was used. RESULTS: The largest number of viral transmissions occurred with serologic testing only. However, the risks for viral transmissions were very low with both strategies. The total cost was mainly influenced by the cost of the test carried out. The cost of using ID-NAT plus serologic tests compared to serologic tests alone was estimated at Swedish Krona (SEK) 101 million (USD 12.7 million) per avoided viral transmission. The cost per QALY gained was SEK 22 million (USD 2.7 million). CONCLUSION: Using ID-NAT for testing against HBV, HCV, and HIV among blood donors leads to cost-effectiveness ratios that are far beyond what is usually considered cost-effective. The main reason for this is that with current methods, the risks for virus transmission are very low in Sweden.

Blome, M. A., P. Bjorkman, L. Flamholc, H. Jacobsson, V. Molnegren and A. Widell. "**Minimal transmission of HIV despite persistently high transmission of hepatitis C virus in a Swedish needle exchange program**." J Viral Hepat **2011** 18(12): 831-839.

The aim of this study was to examine the prevalence and incidence of HIV and hepatitis B and C (HBV and HCV) among injecting drug users in a Swedish needle exchange programme (NEP) and to identify risk factors for blood-borne transmission. A series of serum samples from NEP participants enrolled from 1997 to 2005 were tested for markers of HIV, HBV and HCV (including retrospective testing for HCV RNA in the last anti-HCV-negative sample from each anti-HCV seroconverter). Prevalence and incidence were correlated with self-reported baseline characteristics. Among 831 participants available for follow-up, one was HIV positive at baseline and two seroconverted to anti-HIV during the follow-up of 2433 HIV-negative person-years [incidence 0.08 per 100 person-years at risk (pyr); compared to 0.0 in a previous assessment of the same NEP covering 1990-1993]. The corresponding values for HBV were 3.4/100 pyr (1990-1993: 11.7) and for HCV 38.3/100 pyr (1990-1993: 27.3). HCV seroconversions occurred mostly during the first year after NEP enrolment. Of the 332 cases testing anti-HCV negative at enrolment, 37 were positive for HCV RNA in the same baseline sample (adjusted HCV incidence 31.5/100 pyr). HCV seroconversion during follow-up was significantly associated with mixed injection use of amphetamine and heroin, and a history of incarceration at baseline. In this NEP setting, HIV prevalence and incidence remained low and HBV incidence declined because of vaccination, but transmission of HCV was persistently high. HCV RNA testing in anti-HCV-negative NEP participants led to more accurate identification

of timepoints for transmission.

Davidsdottir, L., A. S. Duberg, A. Torner, S. Aleman, E. Back, K. Ekdahl, A. Blaxhult, A. Ekbom and R. Hultcrantz. "**Hepatocellular carcinoma in individuals with HBV infection or HBV-HCV co-infection in a low endemic country**." Scand J Gastroenterol **2010** 45(7-8): 944-952.

OBJECTIVE: The aim of this nationwide cohort study was to assess the risk for hepatocellular carcinoma (HCC) in patients with chronic hepatitis B virus (HBV) infection or HBV and hepatitis C virus (HCV) co-infection in Sweden, a low endemic country. MATERIAL AND METHODS: A total of 12,080 patients with HBV and 3238 patients with HBV-HCV co-infection were notified to the Swedish institute for Infectious Disease Control between 1990 and 2004. After excluding 1850 patients with acute HBV and 584 patients infected in adult life, we analyzed the cohort of 9646 subjects with chronic HBV infection. In the co-infection cohort, 1697 patients were analyzed after excluding 1541 cases with acute HBV. The Swedish national cancer registry was used for follow-up. The HCC incidence rate in the cohorts was compared with the HCC incidence rate in the general population and the standardized incidence ratio (SIR) was calculated for different strata according to estimated infection period. RESULTS: HCC was found in 45 patients in the HBV cohort. In the stratum of 40-49 years of infection we found a SIR of 47 and in stratum 50-59 years the SIR was 54. In the co-infected cohort 10 HCCs were found. The SIR in the stratum 20-29 years of infection was 34 and the SIR in the stratum 30 years and over was 91. CONCLUSIONS: This national cohort study of HBV infected and HBV-HCV co-infected subjects in a low endemic country confirms a highly increased risk of liver cancer compared to the general population.

Norder, H., L. Sundqvist, L. Magnusson, S. Ostergaard Breum, M. Lofdahl, L. E. Larsen, C. K. Hjulsager, L. Magnius, B. E. Bottiger and F. Widen. "**Endemic hepatitis E in two Nordic countries**." Euro Surveill **2009** 14(19).

Antibodies against hepatitis E virus (anti-HEV) were found in 248 Swedish and Danish patients between 1993 and 2007. Most patients were symptomatic and tested for anti-HEV due to travel abroad. Among patients with known country of infection, most were infected in Asia, mainly on the Indian subcontinent. However, 29 patients were infected in Europe, nine of these had HEV IgM and/or HEV RNA in serum. In sera from 65 of 141 tested patients HEV RNA could be detected, and 63 strains could be typed by limited sequencing within ORF2. HEV RNA was found in sera from 71% of the patients with HEV IgM and IgG and in 18% of the patients with only detectable HEV IgG. It was also found up to three weeks after the onset of disease in 67% of the patients with known date of onset. Patients infected in Europe were infected by genotype 3, and were older than those infected by genotype 1 (mean age 55.3 vs 30 years, $p<0.001$). Since it is known that genotype 3 can infect domestic pigs, HEV strains from 18 piglets in 17 herds in Sweden and Denmark were sequenced. Phylogenetic analyses of the genotype 3 strains showed geographical clades and high similarity between strains from patients and pigs from the same area. There are thus autochthonous hepatitis E cases in Scandinavia, and there are probably many undiagnosed ones. Patients with hepatitis of unknown etiology should therefore be investigated for anti-HEV even if they have not been outside Europe, since infections acquired from pigs or other animals should be taken into consideration.

Lidman, C., L. Norden, M. Kaberg, K. Kall, J. Franck, S. Aleman and M. Birk. "**Hepatitis C infection among injection drug users in Stockholm Sweden: prevalence and gender**." Scand J Infect Dis **2009** 41(9): 679-684.

Hepatitis C virus (HCV) infection is widespread among injection drug users. Young women seem to be at higher risk of acquiring HCV. To optimize future intervention and prevention measures, we studied the epidemiology of human immunodeficiency virus (HIV), hepatitis B (HBV), and HCV infection among men and women. Inclusion criteria for this cross-sectional multicentre study were: history of ever injecting drugs, age > 18 y, and no previous HIV diagnosis. In 310 participants, plasma/serum samples were analysed for HBV, HIV and HCV (anti-HCV, HCV-RNA, and HCV genotype). HCV antibodies were noted in 268 (86.5%) participants, of whom 207

(77.0%) also had detectable HCV-RNA. Genotypes 1 and 3 dominated, at 35.9% and 33.0%, respectively. Women acquired HCV (but not HBV) to a significantly higher degree (RR 2.97, 95% confidence interval 1.11-7.93) during the first y of injecting drugs. They also recovered spontaneously from HCV infection more frequently (RR 2.49, 95% CI 1.28-4.53). The HCV prevalence of about 50% within 2 y after initiation of injection drug use underlines the need for early intervention efforts. Possible causes for higher HCV prevalence and the implications of favourable spontaneous recovery rates among women should be considered when designing intervention and prevention measures.

Lagging, M., R. Wejstal, I. Uhnoo, B. Gerden, B. Fischler, S. Friman, F. Josephson, O. Karlstrom, P. Sangfelt, R. Schvarz, et al. "**Treatment of hepatitis C virus infection: updated Swedish Consensus recommendations**." Scand J Infect Dis **2009** 41(6-7): 389-402.

In a recent expert meeting, Swedish recommendations for the treatment of HCV infection were upgraded. The panel recommends vaccination against both hepatitis A and B in patients with HCV. Therapy for symptomatic acute HCV infection should be initiated if spontaneous resolution has not occurred within 12 weeks, whereas asymptomatic acute HCV should be treated upon detection. Patients with genotype 2/3 infection should generally be treated for 24 weeks. In patients with a very rapid viral response (vRVR), i.e. HCV RNA below 1000 IU/ml on d 7, treatment can be shortened to 12-16 weeks, provided that no dose reduction has been made. For genotype 1 patients with rapid viral response (RVR), 24 weeks treatment is recommended. For patients with a complete early viral response (cEVR), 48 weeks treatment is recommended, whereas 72 weeks treatment should be considered for patients with partial early viral response (pEVR). For patients with difficult-to-treat disease and with pronounced anaemia, erythropoietin can be used to maintain the ribavirin dose. In HCV-HIV coinfected patients, combination therapy for HCV should, if possible, be initiated before anti-retroviral therapy (ART) is indicated. For liver transplant patients pre-emptive therapy is not recommended; hence, treatment should be deferred until histological recurrence.

Kilpi, T. M., S. A. Silfverdal, L. Nilsson, R. Syrjanen, C. Belloni, M. Desole, C. Triban, J. Storsaeter, M. Soila and J. M. Jacquet. "**Immunogenicity and reactogenicity of two diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio virus-Haemophilus influenzae type b vaccines administered at 3, 5 and 11-12 months of age**." Hum Vaccin **2009** 5(1): 18-25.

The use of combination vaccines in the routine childhood program reduces distress to the recipients and is likely to improve uptake rates and timeliness of vaccination but requires careful evaluation and surveillance. The aim of this study was to evaluate the immunogenicity and reactogenicity of two commercial diphtheria-tetanus- acellular pertussis-hepatitis b-inactivated polio virus-Haemophilus influenzae type b (DTaP-HBV-IPV/Hib) combination vaccines when administered to infants at 3, 5 and 11-12 months of age. A total of 494 infants were randomized to receive three doses of either Infanrix hexa (GlaxoSmithKline Biologicals; N = 246) or Hexavac (Sanofi Pasteur MSD; N = 248) in 10 centers in Italy, Finland and Sweden. After the third dose, antibodies to diphtheria, tetanus, polio and Hib were at the protective level in nearly all infants in both groups whereas the proportion of subjects who had achieved the protective concentration of >or=10 mIU/ml to hepatitis B surface antigen was 99.1% (95% CI 96.7-99.9) in the Infanrix hexa group as compared to 94.4% (95% CI 90.4.97.1) in the Hexavac group. Antibody titers to all three polio antigens were highest in Italy and lowest in Finland. Clinically relevant general reactions (such as fever of >39.5 degrees C) were mostly reported in less than 5% of the vaccinees. Three doses of DTaP-HBV-IPV/Hib combination vaccines produced sufficient immune responses in nearly all vaccinees.

Hagen, K. "**[Risk of infections among orienteers]**." Tidsskr Nor Laegeforen **2009** 129(13): 1326-1328.

BACKGROUND: Research on orienteers is useful for assessing the risk of infections associated with physical activity in the forest. In this paper four types of infections are

reviewed, and the efficacy of preventive initiatives is discussed. MATERIAL AND METHODS: The paper is based on literature retrieved from a non-systemic search in PubMed. RESULTS: Hepatitis B infection was more prevalent among orienteers before they were obliged to use protective clothing. In the 1980s, there was an increase of sudden unexpected death among young Swedish orienteers. Bartonella infection was later suggested as an underlying cause. No unexpected deaths have occurred among young orienteers after 1992 when specific advice was given regarding training and competitions. Orienteers do not seem to be affected by lyme borreliosis or tick-borne encephalitis (TBE) more often than others, but only two old studies have been performed. INTERPRETATION: Orienteers may be at risk of acquiring infection from lyme borreliosis and TBE in Norway in the future, as the incidence of these contagions is increasing. Norwegian medical personnel should consider TBE vaccination of orienteers and others who wander in areas with a high prevalence of infected ticks.

Falconer, K., J. K. Sandberg, O. Reichard and A. Alaeus. "**HCV/HIV co-infection at a large HIV outpatient clinic in Sweden: feasibility and results of hepatitis C treatment**." Scand J Infect Dis **2009** 41(11-12): 881-885.

We investigated the prevalence of hepatitis C virus (HCV) co-infection in HIV-infected patients at a large Swedish outpatient clinic. We also evaluated the feasibility of treating this patient group with pegylated-interferon alpha-2a and ribavirin (RBV) and found that only a small fraction of the HCV/HIV co-infected patients met the criteria for HCV treatment when following international guidelines. Thus, 11 patients were treated, and HCV kinetics were measured during early treatment. The overall treatment response rate was surprisingly high (73%) and correlated to early virological response.

Bjornsson, E., H. Verbaan, A. Oksanen, A. Fryden, J. Johansson, S. Friberg, O. Dalgard and E. Kalaitzakis. "**Health-related quality of life in patients with different stages of liver disease induced by hepatitis C**." Scand J Gastroenterol **2009** 44(7): 878-887.

OBJECTIVE: Patients with hepatitis C have been shown to have impaired health-related quality of life (HRQoL). The aim of this study was to determine HRQoL in patients in different stages of hepatitis C virus (HCV) and to compare HRQoL in HCV cirrhosis with non-HCV-induced cirrhosis. MATERIAL AND METHODS: Out of 489 consecutive patients who fulfilled the inclusion criteria, 472 (96%) agreed to participate in the study: 158 patients with mild/moderate fibrosis with chronic hepatitis C (CHC group), 76 patients with HCV compensated cirrhosis (CC), 53 patients with HCV decompensated (DC) cirrhosis, 52 non-cirrhotic patients with sustained viral response (SVR), and a control group consisting of 32 patients with non-HCV CC and 101 with non-HCV DC who completed the Short Form-36 (SF-36) and EQ-5D questionnaire. RESULTS: The CHC group had significantly lower SF-36 scores than healthy controls, with the exception of scores for the dimensions physical function and bodily pain. HCV patients with DC had lower scores in all SF-36 dimensions in comparison with those of the CHC group, as well as in physical and mental component summaries ($p<0.001$). In comparison with the CHC group, the HCV CC group had lower scores on the SF-36 general health dimension ($p<0.05$) and lower SF-36 physical component summary (PCS) scores ($p<0.05$). No major differences were seen in patients with HCV- and non-HCV-induced cirrhosis. CONCLUSIONS: Impairment in HRQoL in patients with HCV was associated with the severity of liver disease, patients with decompensated cirrhosis exhibiting the highest impairment in HRQoL. The etiology of liver disease does not seem to be important in determining HRQoL in cirrhosis.

Verbaan, H., V. Molnegren, I. Pentmo, L. Rubin and A. Widell. "**Prospective study of nosocomial transmission of hepatitis C in a Swedish gastroenterology unit**." Infect Control Hosp Epidemiol **2008** 29(1): 83-85.

A prospective study of incident hepatitis C in 515 gastroenterology patients was conducted by follow-up sampling at 3-6 months after admission to the gastroenterology unit to test for antibodies to hepatitis C virus and for hepatitis C virus RNA. Universal precautions were implemented, and the use of multidose vials had

been banned in this unit. Despite 5,964 exposure-days for several risk factors associated with nosocomial hepatitis C virus transmission, no incident case of hepatitis C occurred.

Strauss, R., A. Torner, A. S. Duberg, R. Hultcrantz and K. Ekdahl. "**Hepatocellular carcinoma and other primary liver cancers in hepatitis C patients in Sweden - a low endemic country**." J Viral Hepat **2008** 15(7): 531-537.

The aim of this study was to assess the risk of hepatocellular carcinoma (HCC) and other primary liver cancers (PLC) in the nationwide cohort of hepatitis C virus (HCV) infected patients in Sweden. The basis was the total HCV-cohort notified in 1990-2004, after excluding 3238 people also reported with hepatitis B, the study cohort consisted of 36 126 people contributing an observation time of 246 105 person-years. The most common route of transmission was intravenous drug use (57%). The national Cancer Registry was used for follow-up, and 354 developed PLC (mainly HCC), of whom 234 were eligible for statistical analysis. The PLC incidence in the HCV cohort was compared with the incidence in the general population, and a standardized incidence ratio (SIR) was calculated for six different strata according to estimated duration of infection. The highest relative risk, SIR: 46 (95% CI: 36-56) was found in the stratum 25-30 years with HCV infection and SIR: 40 (95% CI: 31-51) in the stratum 30-35 years with infection. In the entire community-based HCV cohort in Sweden we found a highly increased risk of liver cancer compared to the general population. The highest relative risk was among people who had been infected for more than 25 years.

Sjoberg, K., A. Widell and H. Verbaan. "**Prevalence of hepatitis C in Swedish diabetics is low and comparable to that in health care workers**." Eur J Gastroenterol Hepatol **2008** 20(2): 135-138.

OBJECTIVES: An association between hepatitis C virus (HCV) infection and diabetes has been reported, in particular from countries with a high prevalence of HCV. To assess if this association could be found in a region with low prevalence of HCV (0.33%), we determined the prevalence of anti-HCV in a large cohort of patients with diabetes. METHODS: The prevalence of anti-HCV was determined with an enzyme-linked immunosorbent assay in 874 patients with diabetes representing 72.5% of a total research cohort of 1205 patients who were invited to participate. The results were confirmed with immunoblot. Samples from confirmed patients were tested for HCV RNA and genotyped. RESULTS: In 499 patients with type 1 diabetes and 375 patients with type 2 diabetes six patients were anti-HCV positive (four with type 1 diabetes and two with type 2 diabetes corresponding to a prevalence of 0.80 and 0.53%, respectively, in accordance with the prevalence among health care workers in Sweden; 0.68%). Liver biopsies in three of the patients showed only mild inflammation without fibrosis and in two of the other three the albumin and/or PT-INR level was normal contradicting any substantial impairment of the liver function. CONCLUSIONS: The low anti-HCV prevalence that we found contradicts an etiologic role of HCV in the development of diabetes in Sweden. The risk of being infected with HCV when attending the health care system seems to be rather small in a low-prevalence area.

Lindh, M., I. Uhnoo, J. Blackberg, A. S. Duberg, S. Friman, B. Fischler, O. Karlstrom, G. Norkrans, O. Reichard, P. Sangfeldt, et al. "**Treatment of chronic hepatitis B infection: an update of Swedish recommendations**." Scand J Infect Dis **2008** 40(6-7): 436-450.

The main goal for treatment of chronic hepatitis B is to prevent complications such as liver cirrhosis or hepatocellular carcinoma. Knowledge from population studies of the long-term risk of chronic HBV infection, as well as the recent introduction of pegylated interferon and additional nucleoside analogues has changed the therapeutic situation. Recently, a Swedish expert panel convened to update the national recommendations for treatment. The panel recommends treatment for patients with active HBV infection causing protracted liver inflammation or significant liver fibrosis, verified by liver histology. In general, pegylated interferon alpha-2a is recommended as first-line treatment, in particular for HBeAg-positive patients with HBV genotypes A or B. Among nucleoside analogues, entecavir is the first choice and adefovir or tenofovir

can be used as alternatives. Lamivudine monotherapy is not recommended due to the high risk of resistance development. Combinations of nucleoside analogues such as tenofovir and lamivudine or emtricitabine are alternatives for patients with non-response or infection with resistant variants, or as first choice for patients with advanced liver disease. Nucleoside analogue treatment should be monitored to detect primary non-response and virological breakthrough. Special recommendations are given for HBV/HIV coinfected patients, immunosuppressed patients, children, and for treatment before and after liver transplantation. The present guideline is translated from Swedish, where it is published on the MPA and RAV websites (www.mpa.se and www.rav.nu.se) including 7 separate papers based on thorough literature search. The complete reference list can be received from the Medical Products Agency upon request.

Duberg, A. S., A. Torner, L. Davidsdottir, S. Aleman, A. Blaxhult, A. Svensson, R. Hultcrantz, E. Back and K. Ekdahl. "**Cause of death in individuals with chronic HBV and/or HCV infection, a nationwide community-based register study**." J Viral Hepat **2008** 15(7): 538-550.

Studies on chronic viral hepatitis and mortality have often been made on selected populations or in high-endemic countries. The aim of this study was to investigate the causes of death and the mortality rates in the nationwide cohorts of people chronically infected with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) in Sweden, a low-endemic country. All notifications on chronic HBV infection and HCV infection 1990-2003 were linked to the Cause of Death Register. A total of 9517 people with chronic HBV infection, 34 235 people with HCV infection and 1601 with chronic HBV-HCV co-infection were included, and the mean observation times were 6.4, 6.3 and 7.9 years, respectively. The mortality in the cohorts was compared with age- and gender-specific mortality in the general population and standardized mortality ratios (SMR) were calculated. All-cause mortality was significantly increased, SMR 2.3 (HBV), 5.8 (HCV) and 8.5 (HBV-HCV), with a great excess liver-related mortality in all cohorts, SMR 21.7, 35.5 and 46.2, respectively. In HCV and HBV-HCV infected there was an increased mortality due to drug-related psychiatric diagnoses (SMR: 20.7 and 27.6) and external causes (SMR: 12.4 and 11.4), predominantly at younger age. To conclude, this study demonstrated an increased all-cause mortality, with a great excess mortality from liver disease, in all cohorts. In people with HCV infection the highest excess mortality in younger ages was from drug-related and external reasons.

Duberg, A., R. Janzon, E. Back, K. Ekdahl and A. Blaxhult. "**The epidemiology of hepatitis C virus infection in Sweden**." Euro Surveill **2008** 13(21).

In Sweden, infection with hepatitis C virus (HCV) has been a notifiable disease since 1990, when diagnostic methods became available. Blood donor screening indicated that about 0.5% of the Swedish population (9 millions) had been HCV infected. Here we present the Swedish hepatitis C epidemic based on data from all the HCV notifications 1990-2006. During this time about 42,000 individuals (70% men) were diagnosed and reported as HCV infected. The majority (80%) were born in 1950 or later, with a high percentage (60%) born in the 1950s and 1960s. Younger people, 15-24 years old at notification, were reported on the same level each year. The main reported routes of HCV transmission were intravenous drug use in 65%, blood transfusions/products in 6%, and sexual in 2%, though unknown or not stated in 26%. Approximately 6,000 of all notified individuals have died during the study period. To conclude, the Swedish HCV epidemic is highly related to the increase of intravenous drug use in the late 1960s and 1970s, with a high proportion of people now chronically infected for more than 25 years, resulting in an increase of severe liver complications in form of cirrhosis and hepatocellular carcinoma. Furthermore the unchanged number of notifications of newly infected younger people indicates an ongoing HCV epidemic.

Cardell, K., B. Akerlind, M. Sallberg and A. Fryden. "**Excellent response rate to a double dose of the combined hepatitis A and B vaccine in previous nonresponders to hepatitis B vaccine**." J Infect Dis **2008** 198(3): 299-304.

BACKGROUND: Hepatitis B vaccine has been shown to be highly efficient in preventing hepatitis B. However, 5%-10% of individuals fail to develop protective levels (>or=10 mIU/mL) of antibodies to hepatitis B surface antigen (anti-HBs) and are considered to be nonresponders. METHODS: A total of 48 nonresponders and 20 subjects naive to the HBV vaccine received a double dose of combined hepatitis A and B vaccine (Twinrix) at 0, 1, and 6 months. The levels of anti-HBs and antibodies to hepatitis A virus (anti-HAV) were determined before vaccination and 1 month after each dose. RESULTS: Among 44 nonresponders, protective anti-HBs levels were found in 26 (59%) after the first dose and in 42 (95%) after the third dose. Among the control subjects, the corresponding figures were 10% and 100%, respectively. All subjects seroconverted to anti-HAV. The titers of both anti-HBs and anti-HAV were lower in the previously nonresponsive subjects (P< .01). CONCLUSION: Revaccination of nonresponders to the standard hepatitis B vaccine regimen with a double dose of the combined hepatitis A and B vaccine was highly effective. This is most likely explained by the increased dose, a positive bystander effect conferred by the hepatitis A vaccine, or both.

Dannetun, E., A. Tegnell and J. Giesecke. "**Parents' attitudes towards hepatitis B vaccination for their children. A survey comparing paper and web questionnaires, Sweden 2005**." BMC Public Health **2007** 7: 86.

BACKGROUND: The World Health Organisation, WHO, recommends that most countries should vaccinate all children against hepatitis B. Sweden has chosen not to do so, but the issue is reassessed regularly. The objective of this survey was to assess knowledge and attitudes towards hepatitis B vaccine for children among parents living in Sweden, and to compare distribution of responses and response rate between parents answering a postal questionnaire and those responding via the Internet. METHODS: A population-based cross-sectional survey, where the sampling frame consisted of all parents to a child born 2002 living in Sweden. Two independent samples of 1001 parents in each sample were drawn. All parents were contacted by postal mail. The parents in the first sample were invited to participate by answering a paper questionnaire. The parents in the second sample were given an individual user name along with a password, and asked to log on to the Internet to answer an identical electronic questionnaire. RESULTS: A total of 1229 questionnaires were analysed. The overall response rate for paper questionnaires was 55%, and 15% for the web version. Knowledge of the disease hepatitis B was overall high (90%). A higher degree of knowledge was seen among parents with education beyond high school (p = 0.001). This group of parents also had a higher tendency to reply via the Internet (p = 0.001). The willingness to accept hepatitis B vaccine for their child was correlated to the acceptance of the present childhood vaccination programme (p = 0.001). CONCLUSION: The results reveal a high level of knowledge of the disease and a positive attitude to having their children vaccinated. This study also displays that the conventional postal method of surveying still delivers a higher response rate than a web-based survey.

Russia (2)

Paltsev, A. I. "**Clinical-epidemiological features, diagnostics, treatment of chronic viral hepatitises, combined with opisthorchosis in inhabitants of Siberia and the Northern regions of Russia**." Alaska Med **2007** 49(2 Suppl): 153-160.

The clinical laboratory investigations of patients with chronic viral hepatitises combined with chronic opisthorchosis are presented. Among the examined, 60 patients lived in Western Siberia and 50 patients in the North. More severe course of combined diseases was marked in the Northerners. Prevalence of such syndromes as diskynetic, cholestasis, hepatomegalies, and disorders of microbiocenosis of gastrointestinal tract has proved this fact. Features of treatment of combined diseases have been shown, stage therapy has been developed.

Petrovic, B., Z. Velickovic and B. Tiodorovic. "**Ongoing outbreak of hepatitis A in Nis, Serbia: a preliminary report**." Euro Surveill **2007** 12(12): E071220 071224.

2. Hepatitis Bibliography of the Speakers

List of publications achieved via speakers form when this form was not available a Pubmed MEDLINE search was performed on Name of the speaker in [Author]-field and 'Hepatitis' in [all fields]. If more than 10 references only the most recent articles are shown.
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