

**“Burden and prevention of Viral
Hepatitis in Israel: Lessons learnt
and the way forward.”**

Viral Hepatitis Prevention Board Meeting
Jerusalem, Israel, 14-15 March 2013.

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Content

This pre-meeting document contains general information on the Israel 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.

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Pubmed MEDLINE search 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 \(Israel\) NOT autoimmune since 2003*](#)(221)

In EndNote a manual selection was performed and only the relevant references and the abstracts related to viral hepatitis and Israel were selected and classified by the different meeting sessions.

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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 . If more than 10 references were retrieved, only the most recent articles are shown.

1. Israel general background

(Source World factbook <https://www.cia.gov/library/publications/the-world-factbook/geos/is.html>) and Wikipedia <http://en.wikipedia.org/wiki/Israel>



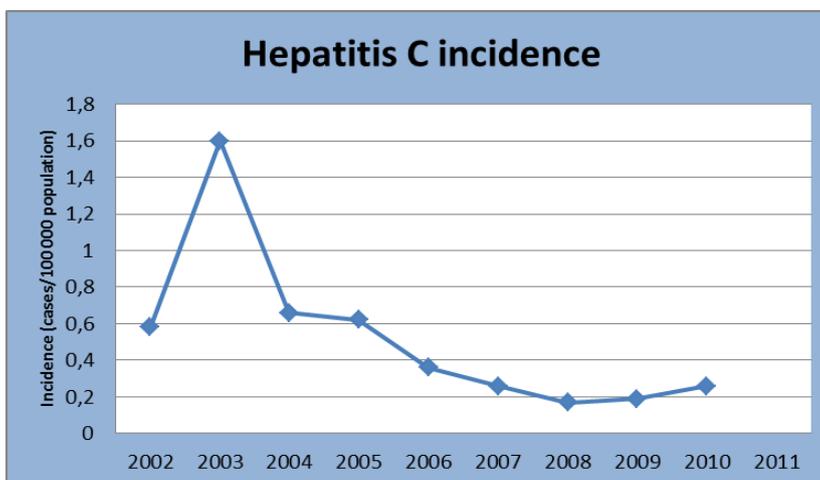
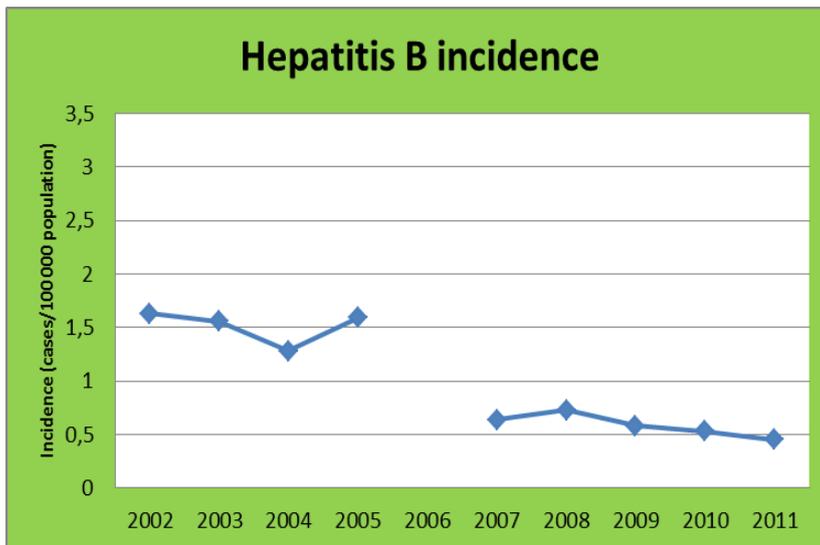
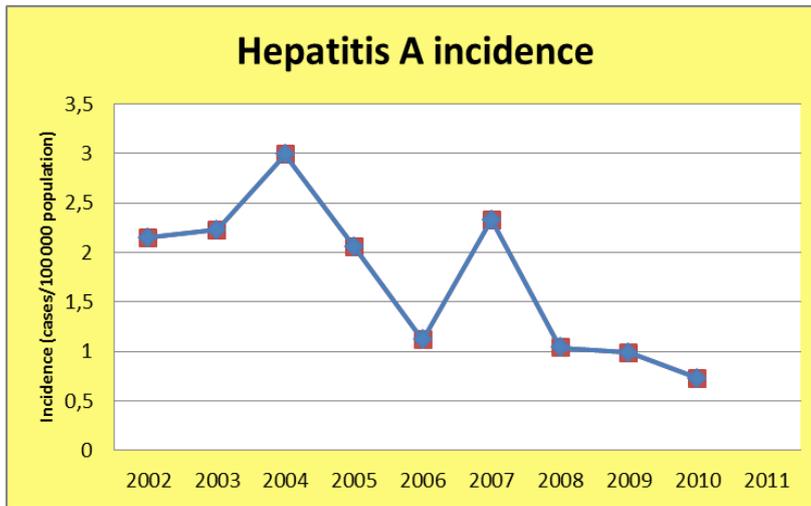
Demographics

In 2013, Israel's population was an estimated 7,980,900 people, of whom 6,014,400 are Jews.[3] Arab citizens of Israel comprise 20.6% of the country's total population. Over the last decade, large numbers of migrant workers from Romania, Thailand, China, Africa and South America have settled in Israel. Exact figures are unknown, as many of them are living in the country illegally, but estimates run in the region of 203,000. As of June 2012, approximately 60,000 African migrants have entered Israel.

Population growth : 1.541%
Birth rate: 18,97 births/1.000 population
Death rate: 5,5 deaths/1.000 population
Net migration rate: 1.94 migrant(s)/1.000 population
Sex ratio in total population: 1.01 male(s)/female
Health expenditures: 9,5% GDP (2009)
Physicians density: 3,633/ 1.000 population

Hepatitis epidemiological data

(Source: WHO Cisd database)



2. Hepatitis in Israel

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 \(Israel\) NOT autoimmune since 2003](#) } in all fields, was performed. After a manual search only the references and the abstracts really related to viral hepatitis and Israel were selected and classified by session of the meeting. The references are ranged by publication year (most recent first) and for each year in alphabetical order of the first author's name.

SESSION 2 HEALTH CARE AND THE HEALTH CARE SYSTEM IN THE COUNTRY (3)

Kagan, I., K. L. Ovadia and T. Kaneti. **"Perceived knowledge of blood-borne pathogens and avoidance of contact with infected patients."** *J Nurs Scholarsh* 2009 41(1): 13-19.

PURPOSE: To examine the relationship between nurses' knowledge of blood-borne pathogens (BBPs), their professional behavior regarding handwashing, compliance with standard precautions (SPs), and avoidance of therapeutic contact with BBP-infected patients. **DESIGN:** This cross-sectional design study took place in a regional medical center in Central Israel during 2003. **METHODS:** Of the 180 participants, 159 (88.3%) were women with an average educational level of 16.40 years (SD=2.66). The mean age of the sample was 39.41 (SD=10.1). Data were collected using a structured questionnaire including sociodemographic information, level of knowledge concerning three BBPs (human immunodeficiency virus [HIV], hepatitis B virus [HBV], and hepatitis C virus [HCV]), level of compliance with SPs, understanding of SP principles, and avoidance of therapeutic contact with BBP-infected patients. **FINDINGS:** Levels of HIV-related knowledge were significantly higher than were those of HBV- and HCV-related knowledge. Only 96 participants (54.5%) stated that all patients should be treated as BBP-carriers. The understanding of the basic principle of SPs did not influence the relationship between perceived knowledge and self-reported compliance with SPs; 77.3% of the sample reported that they avoid therapeutic contact with BBP-infected patients. The level of perceived knowledge did not contribute to the nurses' avoidance of care of BBP carriers. **CONCLUSIONS:** Perceived knowledge of BBPs has a weak effect on compliance with SPs and willingness to care for BBP-infected patients. **RECOMMENDATIONS:** Nurses must identify their preconceptions when caring for BBP-carriers. Further research on this issue is needed to attempt to understand the forces acting on our nursing staff, in order to ensure appropriate care of BBP-infected patients. **CLINICAL RELEVANCE:** Our study indicated some reluctance among nurses to care for patients with blood-borne pathogens. This appears to be the result of value systems and not a lack of knowledge, indicating a need to integrate a psychoeducational approach to education of nurses.

Kagan, I., K. L. Ovadia and T. Kaneti. **"Physicians' and nurses' views on infected**

health care workers." Nurs Ethics 2008 15(5): 573-585.

This study investigated 204 doctors' and nurses' perceived knowledge of bloodborne pathogens and their attitudes towards bloodborne pathogen-infected health care workers. A structured questionnaire examined: (1) their perceived knowledge of bloodborne pathogens; (2) their attitudes towards bloodborne pathogen-infected personnel; and (3) their opinions on limitation of employment of bloodborne pathogen-infected personnel and restrictions on performing clinical procedures. The levels of HIV-related knowledge were significantly higher than for hepatitis C and B viruses. Although the participants demonstrated more positive attitudes towards hepatitis C- and B-infected health care workers, 64% recommended restricting infected personnel from performing invasive procedures. Attitudes were negatively correlated with opinions on restricting infected personnel from health care work or limiting their involvement in clinical activities. This study highlights the need to formulate a policy to cope with the professional and moral dilemmas related to infected health care workers employed in hospitals, especially for those involved in invasive procedures.

Al-Khatib, I. A., M. Ishtayeh, H. Barghouty and B. Akkawi. "**Dentists' perceptions of occupational hazards and preventive measures in East Jerusalem.**" East Mediterr Health J 2006 12(1-2): 153-160.

Dentists, like other health professionals, are exposed to various occupational health problems, with specific ones of their own. A randomly distributed sample of 40 (42.2%) dentists working in East Jerusalem was interviewed. A questionnaire was used to detect their perception of occupational hazards. Most respondents were aware of biological hazards: 38% specifically mentioned hepatitis B virus and 13% human immunodeficiency virus. Perceived sources of stress included factors that coincided with international data, such as relationships with patients, physical strain and economic pressure, but also some specific to the Palestinian culture such as relationships with other dentists and Israeli occupation tax policy when dealing with the Arab dentists in East Jerusalem. Chemical dependency was not mentioned as a potential hazard.

SESSION 3 EPIDEMIOLOGY OF VIRAL HEPATITIS IN ISRAEL
SESSION 4 EPIDEMIOLOGY OF HEPATITIS VIRUSES IN SPECIAL RISK GROUPS (30)

Siman-Tov, D. D., R. Zemel, R. Tur Kaspas and J. M. Gershoni. "**The use of epitope arrays in immunodiagnosis of infectious disease: hepatitis C virus, a case study.**" Anal Biochem 2013 432(2): 63-70.

Serodiagnosis of infectious disease is often based on the detection of pathogen-specific antibodies in a patient's blood. For this, mixtures of pathogen-related antigens are used as bait to capture corresponding antibodies in solid phase immunoassays such as enzyme immunoassay (EIA). Western blots provide improved diagnostic power as compared with EIA due to the fact that the mixture of markers in the EIA well is resolved and tested as individual antigens on the Western blot. Hence, confirmation of EIA results is accomplished using the antigen arrays of Western blots. Here we

took this approach one step further and tested the attributes of using epitope arrays in a diagnostic platform coined "combinatorial diagnostics." As a case in point, we tested a panel of phage-displayed epitope-based markers in the serodiagnosis of hepatitis C virus (HCV). The repertoire of HCV antigens was deconvoluted into panels of distinct linear and conformational epitopes and tested individually by quantitative EIA. Combinatorial diagnostics proved to be effective for the discrimination between positive and negative sera as well as serotyping of HCV.

Maor, Y., G. Morali, D. Bashari, G. Penaranda, J. M. Schapiro, U. Martinowitz and P. Halfon. "**Genetic polymorphism of IL28B in hepatitis C-infected haemophilia patients in Israel.**" *Haemophilia* 2013 19(1): 150-156.

Single-nucleotide polymorphisms (SNPs) near the IL28B gene were identified as major predictors of treatment response (sustained virologic response--SVR) and spontaneous clearance of HCV. Haemophilia patients have the highest prevalence of HCV, and are a unique target for genetic studies. The Israeli population is ethnically heterogeneous; therefore, genetic variability is anticipated. To determine the IL28B haplotypes in HCV-infected haemophilia patients and association with SVR and spontaneous viral clearance. IL28B polymorphism at SNPs rs12979860 and rs8099917 was determined in sera obtained from 130 HCV-infected haemophilia patients. The frequency of the various haplotypes was analysed according to treatment response, spontaneous HCV clearance, viral load and degree of fibrosis. The CC haplotype at SNP rs12979860 was found in 31% of patients, whereas the TT genotype at SNP rs8099917 was detected in 57% of cases. SVR was achieved in 70% of patients carrying the CC haplotype ($P = 0.0196$ vs. CT/TT), and 50% of the TT genotype at SNP rs8099917 ($P = 0.0227$ vs. TG/GG). Thirty-five percent of patients carrying the CC haplotype and 26% with the TT genotype at SNP rs8099917 showed spontaneous clearance of HCV infection ($P = 0.00262$ vs. CT/TT; and $P = 0.00371$ vs. TG/GG respectively). The C-allele frequency was exceptionally high (71%) in immigrants from the Asian republics of Russia. In HCV-infected haemophilia patients, SVR was more commonly achieved among patients who had the CC (rs12979860) or TT (rs8099917) genotype. Likewise, patients who possess harbour the CC or TT genotypes were more likely to clear HCV infection spontaneously. A unique distribution of the CC genotype was observed in some ethnic groups.

Stulhofer, A., A. Chetty, R. A. Rabie, I. Jwehan and A. Ramlawi. "**The prevalence of HIV, HBV, HCV, and HIV-related risk-taking behaviors among Palestinian injecting drug users in the East Jerusalem Governorate.**" *J Urban Health* 2012 89(4): 671-676.

The objective of the study was to determine HIV, HBV, HCV seroprevalence and to assess HIV risks among Palestinian injecting drug users (IDUs) in the East Jerusalem Governorate. Following formative research, a bio-behavioral survey using respondent-driven sampling was carried out in 2010 among 199 IDUs aged 19-56 years ($M=41.33$, $SD=8.09$). Venous blood was drawn for biological testing. Data on drug abuse and sexual behaviors were collected by face-to-face interviewing. No HIV+ cases were found. Five participants were infected with Hepatitis B and 84 participants (estimated population proportion of 40.3 %) tested positive for Hepatitis C. A great majority of the surveyed IDUs (90.4 %) reported using sterile injecting equipment the last time they injected. In a multivariate assessment, age ($OR=2.52$, $pG.05$), education ($OR=6.67$, $pG.01$), personal network size ($OR=.18$, $pG.001$), and the frequency of drug injecting in the past month ($OR=.20$, $pG.001$) were

associated with using sterile injecting equipment in the past week. Condom use at most recent sexual intercourse was reported by about a third (34.2 %) of IDUs. The study documented substantial exposure to HIV risks among Palestinian IDUs whose vulnerability is inseparable from sociopolitic and socioeconomic characteristics of their social environment [corrected].

Stulhofer, A., A. Chetty, R. A. Rabie, I. Jwehan and A. Ramlawi. "**Erratum to: The prevalence of HIV, HBV, HCV, and HIV-related risk-taking behaviors among Palestinian injecting drug users in the East Jerusalem Governorate.**" J Urban Health **2012** 89(4): 677.

The objective of the study was to determine HIV, HBV, HCV seroprevalence and to assess HIV risks among Palestinian injecting drug users (IDUs) in the East Jerusalem Governorate. Following formative research, a bio-behavioral survey using respondent-driven sampling was carried out in 2010 among 199 IDUs aged 19-56 years (M = 41.33, SD = 8.09). Venous blood was drawn for biological testing. Data on drug abuse and sexual behaviors were collected by face-to-face interviewing. No HIV + cases were found. Five participants were infected with Hepatitis B and 84 participants (estimated population proportion of 40.3%) tested positive for Hepatitis C. A great majority of the surveyed IDUs (90.4%) reported using sterile injecting equipment the last time they injected. In a multivariate assessment, age (OR = 2.52, $p < .05$), education (OR = 6.67, $p < .01$), personal network size (OR = .18, $p < .001$), and the frequency of drug injecting in the past month (OR = .20, $p < .001$) were associated with using sterile injecting equipment in the past week. Condom use at most recent sexual intercourse was reported by about a third (34.2%) of IDUs. The study documented substantial exposure to HIV risks among Palestinian IDUs whose vulnerability is inseparable from sociopolitic and socioeconomic characteristics of their social environment.

Carmiel-Haggai, M. "**[Two decades of liver transplantation in Israel].**" Harefuah **2012** 151(12): 679-683, 721.

INTRODUCTION: During the years 1991-2011, 769 liver transplantations were registered in the Israeli National Transplantation Center. METHODS: Data from the Israeli Transplantation Center and from the Collaborative Transplantation Study was used. RESULTS: The majority of liver transplantations were adult cadaveric transplantation. There is an increase in adult-adult living donation during the last decade (9%) compared with the previous decade (1.7%). Pediatric transplantations increased from 3.3% to 15%, while up to 30% are from living donors. Simultaneous liver-kidney transplantations (SLK) account for 6% of all transplantations, regardless of the change in the allocation scheme to the Model for End-Stage Liver Disease (MELD) score during 2005. The most common primary liver disease among liver transplant patients is hepatitis C virus (HCV) (34%) and the leading cause for liver transplantation since 2006 is hepatocellular carcinoma (31%). One year patient survival did not change significantly during two decades: 74.8 and 79.1%, respectively, although 5 years survival has increased during that period, from 54.9% to 67.3% ($p = 0.05$). Average annual mortality beyond the first year stands at 2.47%. The use of old donors (> 50) increased from 36.6% during 1991-1999 to 46% in the years 2005-2009. IN CONCLUSION: During two decades of liver transplantation in Israel, facing a severe shortage of organs, there is increased usage from old donors, as well as living donations for pediatric and adult patients. The use of living donors for urgent adult liver transplantation is common. Survival after liver transplantation has improved.

Peles, E., S. Schreiber, V. Rados and M. Adelson. "Low risk for hepatitis C seroconversion in methadone maintenance treatment." *J Addict Med* 2011 5(3): 214-220.

OBJECTIVES: To study the risk factors for seroconversion to hepatitis C virus (HCV) infection since admission to methadone maintenance treatment (MMT) and to characterize the seronegative admitted group. **METHODS:** All 657 patients admitted to our MMT clinic in Tel Aviv, Israel, between 1993 and 2008 were prospectively followed up. Those who were HCV negative (n = 271) with >1 HCV tests (n = 207) were included for seroconversion analyses. **RESULTS:** Proportions of ever drug injectors, benzodiazepine abuse, and former USSR immigrants were higher among HCV sera-positive versus sera-negative patients on admission to MMT. The incidence of HCV seroconversion in MMT was 2/100 person years [py] (25 seroconversions, 1133.9 py). Seroconversion rates were higher among 44 younger patients (<30 years: 9.6/100 vs 1.4/100 py, P < 0.0005), among 103 patients with positive urine results to benzodiazepines (3.6/100 vs 1/100 py, P = 0.005), among 118 patients who injected the drugs (3.9/100 vs 1/100 py, P = 0.003), and among 43 patients who dropped out and were readmitted to the MMT (4.3/100 vs 1.7/100 py, P = 0.04). There was a trend of higher seroconversion among 61 females (P = 0.1), among 62 patients with no children (P = 0.1), and among those having hepatitis B antigen (n = 7; P = 0.09). Variables that predicted seroconversion were drug injection, benzodiazepine abuse, and being younger at admission to MMT. Being a former USSR immigrant did not predict seroconversion. **CONCLUSIONS:** The HCV seroconversion rate of patients in MMT is low, also, for former USSR immigrants. The predictors for seroconversion were only admission variables (younger age at admission to MMT, ever drug injector, and having positive urine to benzodiazepines at MMT admission). Specific intervention to eliminate seroconversion is needed for these high-risk groups.

Cornberg, M., H. A. Razavi, A. Alberti, E. Bernasconi, M. Buti, C. Cooper, O. Dalgard, J. F. Dillon, R. Flisiak, X. Forns, et al. "A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel." *Liver Int* 2011 31 Suppl 2: 30-60.

BACKGROUND AND AIM: Decisions on public health issues are dependent on reliable epidemiological data. A comprehensive review of the literature was used to gather country-specific data on risk factors, prevalence, number of diagnosed individuals and genotype distribution of the hepatitis C virus (HCV) infection in selected European countries, Canada and Israel. **METHODOLOGY:** Data references were identified through indexed journals and non-indexed sources. In this work, 13,000 articles were reviewed and 860 were selected based on their relevance. **RESULTS:** Differences in prevalence were explained by local and regional variances in transmission routes or different public health measures. The lowest HCV prevalence (<= 0.5%) estimates were from northern European countries and the highest (>= 3%) were from Romania and rural areas in Greece, Italy and Russia. The main risk for HCV transmission in countries with well-established HCV screening programmes and lower HCV prevalence was injection drug use, which was associated with younger age at the time of infection and a higher infection rate among males. In other regions, contaminated glass syringes and nosocomial infections continue to play an important role in new infections. Immigration from endemic countries was another factor impacting the total number of infections and the genotype distribution. Approximately 70% of cases in Israel, 37% in Germany and 33% in Switzerland were not born in the country. In summary, HCV epidemiology shows a high variability

across Europe, Canada and Israel. **CONCLUSION:** Despite the eradication of transmission by blood products, HCV infection continues to be one of the leading blood-borne infections in the region.

Safir, A., A. Levy, E. Sikuler and E. Sheiner. "**Maternal hepatitis B virus or hepatitis C virus carrier status as an independent risk factor for adverse perinatal outcome.**" *Liver Int* 2010 30(5): 765-770.

OBJECTIVE: To examine the impact of maternal hepatitis B virus (HBV) or hepatitis C virus (HCV) carrier status on pregnancy outcomes. **METHODS:** A population-based study was performed by comparing all pregnancies of HBsAg and/or anti-HCV seropositive women who delivered during the years 1988-2007 with all other pregnant women who delivered in the same period. Multivariable logistic regression models were constructed to control for confounders. **RESULTS:** Seven hundred and forty-nine hepatitis seropositive pregnant women were identified out of 186 619 deliveries (0.4%). Maternal characteristics, as well as perinatal outcomes, were comparable between the HBV and HCV carriers. HBV/HCV carriers had higher rates of preterm deliveries (<37 weeks gestation; 11.5 vs. 7.9%, $P<0.001$), premature rupture of membranes (8.9 vs. 6.9%, $P=0.026$), placental abruption (1.5 vs. 0.7%, $P=0.018$), labour induction (33.9 vs. 28.1%, $P<0.001$) and Caesarean deliveries (19.0 vs. 13.2%, $P<0.001$). Higher rates of perinatal mortality (2.3 vs. 1.3%, $P=0.016$), congenital malformations (7.2 vs. 5.1%, $P=0.01$) and low birth weight (<2500 kg; 10.4 vs. 7.8%, $P=0.009$) were noted in newborns of hepatitis carriers compared with the control group. Controlling for possible confounders such as maternal age and parity by using multivariable analyses, the significant association between HBV or HCV carrier status and perinatal mortality, congenital malformations and low birth weight remained significant. **CONCLUSIONS:** Maternal HBV or HCV carrier status is an independent risk factor for adverse perinatal outcome and careful surveillance is warranted.

Mor, Z., S. Srur, R. Dagan and S. Rishpon. "**Hepatitis A disease following the implementation of universal vaccination: who is at risk?**" *J Viral Hepat* 2010 17(4): 293-297.

The incidence of acute hepatitis A in Israel has decreased 25 folds in less than a decade, following the introduction of a two-dose universal toddler's hepatitis A immunization in July 1999. This retrospective study describes demographic data and behavioural determinants of hepatitis A patients following the implementation of a vaccination programme. All records of hepatitis A patients reported to the Ministry of Health during the years 2003 through 2005 were reviewed, and an epidemiological investigation was conducted. During the study period, 420 hepatitis A patients were reported, representing an average annual incidence of two per 100,000 population. Case fatality rate was 0.5%. The majority of the patients were younger than 15 years of age, males and non-Jewish. The highest incidence was recorded in east Jerusalem, where vaccine coverage is relatively low. After exclusion of 165 east Jerusalem patients, 133 (52.2%) patients were available for an interview. Of those, 16 (6%) had possible occupational exposure, 37 (27.8%) travelled to endemic areas, 44 (17%) were contacts of hepatitis A cases, and 3 male patients had sex with men. No known risk determinant was identified in 33 (24.8%) patients. Four patients (3%) were previously immunized with one dose, and none had two doses. The introduction of universal toddler hepatitis A vaccination decreased morbidity. Most of the patients who were detected 4-6 years after the implementation of the vaccination programme could be classified into one of the known risk groups for hepatitis A infection or living in a partly vaccinated community.

Edelstein, M., D. Turbitt, K. Balogun, J. Figueroa and G. Nixon. "**Hepatitis A outbreak in an Orthodox Jewish community in London, July 2010.**" Euro Surveill **2010** 15(37).

A cluster of hepatitis A cases in the Orthodox Jewish community in London, United Kingdom in July 2010 has triggered extensive contact tracing and vaccination. Two primary cases imported from a common source in Israel and three secondary cases have resulted in immunisation of over 900 contacts to date. Rapid response by local public health, primary care services and a dedicated community health team, and active hepatitis A vaccination rather than immunoglobulin treatment were used to avert a larger outbreak.

Lawental, E. "**HCV, HBV and HIV in drug addicts.**" Isr Med Assoc J **2009** 11(3): 193-194; author reply 194.

Ashkenazi, M., N. Fisher, L. Levin and M. M. Littner. "**Seroepidemiology of hepatitis C antibodies among dentists and their self-reported use of infection control measures.**" Community Dent Health **2009** 26(2): 99-103.

OBJECTIVES: To determine the prevalence of hepatitis C virus (HCV) antibodies among dentists graduated from various countries and assess the use of infection control measures in their dental practice. **RESEARCH DESIGN:** The study included 301 Israeli dentists who attended an annual dental conference. Participants filled out a structured questionnaire regarding demographic (age, gender, number of siblings, number of children) and occupational characteristics. Venous blood was examined for presence of HCV antibodies by enzyme immunoassay and confirmed by a third generation line immunoassay, which assesses antibodies to HCV-core antigens (INN-LIA HCV Ab III update, 100% sensitivity, 100% specificity). **RESULTS:** The prevalence of HCV antibodies among Israeli dentists was 1/301 (0.33%), similar to the prevalence range (0.1-0.5%) among the general Israeli population. The studied population included dentists (30.6%) who immigrated from Asia, Eastern Europe and the former USSR, where HCV prevalence ranges from 3.1% to 26.5%. Dentists routinely used gloves (99.6%), gown (93.3%), autoclaves (90.3%), dry heat (29.1%) and mask (81%). Dentists who graduated after 1985 used a mask or gown significantly more often than dentists who graduated before 1985 ($p < 0.001$ and $p = 0.004$, respectively). **CONCLUSION:** It seems that dentists who usually adhere to basic infection control measures are not at an increased risk for HCV.

Agmon-Levin, N., M. Ram, O. Barzilai, B. S. Porat-Katz, R. Parikman, C. Selmi, M. E. Gershwin, J. M. Anaya, P. Youinou, N. Bizzaro, et al. "**Prevalence of hepatitis C serum antibody in autoimmune diseases.**" J Autoimmun **2009** 32(3-4): 261-266.

OBJECTIVE: To evaluate the prevalence of serum antibodies against hepatitis C virus and other infectious agents in a large cohort of well-characterized patients with autoimmune diseases (AID). **METHODS:** We utilized 1322 sera from patients with 18 different AID and 236 sera from healthy controls from the same countries and with similar age and sex distribution. All sera were tested for the presence of serum anti-hepatitis C virus (HCV) antibodies as well as antibodies directed at other infectious agents and autoantibodies. **RESULTS:** Anti-HCV antibody was detected in 115/1322 (8.7%) of patients with AID and 0.4% of matched healthy controls ($P < 0.0001$). The prevalence of anti-HCV antibody was significantly higher in 7/18 different AID (i.e. cryoglobulinemia, mixed cryoglobulinemia pemphigus vulgaris, vasculitis, secondary anti-phospholipid syndrome, Hashimoto's

thyroiditis, and inflammatory bowel disease) compared to controls. Patients with AID and serum anti-HCV positivity had an increased prevalence of antibodies against hepatitis B virus, *Toxoplasma gondii* and Cytomegalovirus as opposed to a lower frequency of serum autoantibodies. **CONCLUSIONS:** The enhanced prevalence of anti-HCV serum antibodies in AID may suggest a role for HCV in tolerance to breakdown, similarly to its established role in mixed cryoglobulinemia. This immune mediated effect does not rule out the role of other infectious agents.

Loebstein, R., R. Mahagna, Y. Maor, D. Kurnik, E. Elbaz, H. Halkin, D. Olchovsky, D. Ezra and S. Almog. "**Hepatitis C, B, and human immunodeficiency virus infections in illicit drug users in Israel: prevalence and risk factors.**" Isr Med Assoc J **2008** 10(11): 775-778.

BACKGROUND: Infections with blood-borne viruses are a major health problem among illicit drug users. There is little information about infection rates and risk factors for hepatitis virus B, C or the human immunodeficiency virus in drug users in Israel. **OBJECTIVES:** To determine the prevalence of HCV, HBV and HIV infections in a large cohort of drug users in Israel; to compare rates of HCV, HBV and HIV between injecting versus non-injecting drug users and between different countries of origin; and to identify risk factors for HCV among illicit drug users. **METHODS:** We conducted a cross-sectional study using an interviewer-administered questionnaire and serological screening for HCV, HBV and HIV in 1443 consecutive drug users diagnosed at the Israeli National Center for Diagnosis of Drug Addicts between January 2003 and December 2005. **RESULTS:** Fourteen (0.9%), 51 (3.5%) and 515 (35.7%) subjects tested positive for HIV, HBV and HCV, respectively. All three infections (HIV, HBV and HCV) were significantly more common among injecting drug users and immigrants from the former Soviet Union and other East European countries compared to native Israelis. Multivariate analysis showed that HCV infection was associated with age (> 40 years) (OR=2.06, 95% CI 1.40-3.03), immigration from East European countries and the former Soviet Union (OR=4.54, 95% CI 3.28-6.28), and injecting drug use (OR=16.44, 95% CI 10.79-25.05). **CONCLUSIONS:** HIV, HBV and HCV prevalence among drug users in Israel is significantly lower than in North America and West Europe. Risk factors for HCV infection in this population include injecting drug use, older age, and immigration from the former Soviet Union.

Shemer-Avni, Y., M. Cohen, A. Keren-Naus, E. Sikuler, N. Hanuka, A. Yaari, E. Hayam, L. Bachmatov, R. Zemel and R. Tur-Kaspa. "**Iatrogenic transmission of hepatitis C virus (HCV) by an anesthesiologist: comparative molecular analysis of the HCV-E1 and HCV-E2 hypervariable regions.**" Clin Infect Dis **2007** 45(4): e32-38.

BACKGROUND: Transmission of hepatitis C virus (HCV) from infected health care workers to patients rarely occurs. In 2003, a cluster of patients with HCV infection was identified at a medical center in Israel. All patients had a common history of various surgical procedures performed during the period 2001-2003. All patients had been anesthetized by an anesthesiologist who was an injection drug user and was infected with genotype 2a HCV. Screening was initiated by the hospital to identify newly infected patients with HCV infection and to determine the source of the iatrogenic HCV infection outbreak using comparative molecular analysis of the HCV E1 and HCV E2 hypervariable regions (HVR1 and HVR2). **METHODS:** A total of 1200 patients who were anesthetized by the anesthesiologist (the related group) and 873 hospital personnel and patients anesthetized by other anesthetists (the

unrelated group) were examined. Serum samples were screened for anti-HCV antibodies, HCV RNA, and genotype. Sequence analysis of HVR1 and HVR2 was performed after reverse-transcriptase polymerase chain reaction. RESULTS: HCV type 2a was found in 33 patients in the related group but in only 1 patient in the unrelated group. The differences between the sequences isolated from the related group serum samples and the sequences isolated from genotype 2a control group serum samples (obtained from 15 patients) were highly statistically significant. The genetic distances from the anesthesiologist sequence were 1.4%-4.4% in the HVR1 and 0%-3% in the HVR2 in the related group serum samples, whereas in the HCV genotype 2a control group serum samples, the genetic distances were 22%-45% and 10%-35%, respectively. CONCLUSIONS: Molecular analysis revealed sequence similarity of HVR1 and HVR2 in the related group, suggesting that the anesthesiologist with chronic HCV infection may have transmitted HCV to 33 patients.

Sarov, B., L. Novack, N. Galai, A. Yaari, M. Orgel, J. Safi, V. Yahalom and E. Shinar. **"Estimation of delay in detecting hepatitis C virus antibodies in pools compared to individual testing on seroconversion panels."** *Clin Microbiol Infect* 2007 13(7): 737-739.

Testing for anti-hepatitis C virus (HCV) antibodies in pools may reduce blood screening costs, making this approach affordable for developing countries, provided that the dilution of infected blood does not significantly increase the number of undetectable viral particles, especially in seroconverters. This study assessed the delay in detection of HCV antibodies in five HCV seroconversion panels, tested in pools of 6-48 samples, and estimated the risk of transfusion-transmitted HCV caused by pooling. The delay in detection of positive samples was 5-12 days for pools of all sizes, adding 7% to the risk of HCV transmission that occurs when blood donors' samples are tested individually.

Sarov, B., L. Novack, N. Beer, J. Safi, H. Soliman, J. S. Pliskin, E. Litvak, A. Yaari and E. Shinar. **"Feasibility and cost-benefit of implementing pooled screening for HCVAg in small blood bank settings."** *Transfus Med* 2007 17(6): 479-487.

To examine the accuracy, feasibility and benefits of screening for hepatitis C virus core antigen (HCVAg) using enzyme-linked immunosorbent assay (ELISA) test in pools. Many countries cannot afford to test blood donations for hepatitis C using molecular methods. Screening individual units using the ELISA HCVAg test is an acceptable, yet still expensive, alternative, especially for small blood bank settings. This study evaluated the option of screening for HCVAg in pools. The sensitivity (Se) and specificity (Sp) of HCVAg in pools of three and six antibody-negative samples were estimated and compared with polymerase chain reaction (PCR). The feasibility and cost-benefit of the assay was assessed on 960 routine samples collected at a hospital blood bank in Gaza. Based on results for 50 PCR-positive pools and 50 and 110 PCR-negative pools of three and six, the Se of testing in pools of three and six samples is 80-82% [95% confidence interval (CI): 66.3-91.4] and Sp \geq 98% (95% CI: 89.4-100.0) compared with PCR. The incidence of antigen in donors in Gaza was 0.1% (95% CI: 0-0.56). Cost analyses suggested significant benefits from implementing screening blood donations for HCVAg when the incidence rate is $>4.2/10,000$, leading to reduction in the expenditures needed to treat patients infected with HCV. The risk of transfusion-transmitted hepatitis C in resource-deprived developing countries can be efficiently reduced by additional screening of antibody-negative blood donations for HCVAg in pools of six.

Lurie, Y., D. A. Landau, L. Blendis, Y. Baruch, E. Veitsman, Z. Ackermann, S. Zelber-Sagie, Z. Halpern and R. Oren. "**Acute hepatitis C in Israel: a predominantly iatrogenic disease?**" J Gastroenterol Hepatol **2007** 22(2): 158-164.

BACKGROUND AND AIMS: Acute hepatitis C virus infection in the era of universal screening of blood products has not disappeared, and is thought to be transmitted primarily via injecting drug use. A growing body of evidence supports iatrogenic transmission as an important mode of transmission. The aim of this study was to examine transmission routes and clinical characteristics in a group of patients with acute hepatitis C in Israel. **METHODS:** A retrospective chart review was conducted in three different liver clinics in Israel, of all new hepatitis C patients. Patients identified as possible acute hepatitis C were re-interviewed and all other sources such as blood bank records and pre-employment check-ups reviewed in order to establish the diagnosis of acute hepatitis C infection and to identify the transmission route. **RESULTS:** Twenty-nine patients were found to have acute hepatitis C, representing 0.75% of all new referrals for hepatitis C. The most frequent (65%) mode of transmission was iatrogenic involving several, often minimal, procedures and clinical settings. The group in which iatrogenic transmission was suspected was older and the patients more often in monogamous relationship compared with other transmission routes groups. Injecting drug use was the second most common route of infection. Spontaneous seroconversion has occurred in approximately one third of the patients. **CONCLUSIONS:** Acute hepatitis C in the post universal blood products screening era was found to be predominantly an iatrogenic disease in the investigated localities. This finding should direct attention and resources towards the development and implementation of preventive measures.

Kerzman, H., M. S. Green and E. Shinar. "**Risk factors for hepatitis C virus infection among blood donors in Israel: a case-control study between native Israelis and immigrants from the former Soviet Union.**" Transfusion **2007** 47(7): 1189-1196.

BACKGROUND: The annual hepatitis C virus (HCV) seropositivity prevalence among blood donors (BDs) in Israel is 0.1 percent. Although only 10 percent of the BD population are immigrants from the former Soviet Union (FSUs), they represent 80 percent of the HCV-seropositive cases. This study aimed to identify HCV risk factors among Native Israeli (NI) and FSUI BDs, to determine if specific interventions are needed. **STUDY DESIGN AND METHODS:** Two case-control studies were designed, interviewing 178 HCV-positive cases (128 FSUs, 50 NIs) and 256 HCV-negative controls (128 FSUs, 128 NIs). All participants were volunteer BDs of Magen David Adom (MDA) Blood Services. **RESULTS:** A total of 434 BDs of 985 mailed letters consented to be interviewed (44% response rate), without differences in compliance between the study populations. In both, intravenous drug use (IVDU) was the strongest HCV seropositivity-associated risk factor. After IVDU adjustment, important risk factors were age, blood transfusion before 1990, first-time donation, and not practicing teeth cleaning. Close contact with people at risk for HCV (odds ratio [OR], 7.2; 95% confidence interval [CI], 1.9-27.8) and surgery (OR, 7.3; 95% CI, 1.6-34.4) were strong risk factors among NIs, whereas gum surgery (OR, 7.6; 95% CI, 1.1-52.3), hospitalization without surgery (OR, 2.6; 95% CI, 1.1-6.5), and therapy in injection form (OR, 4.9; 95% CI, 2.4-10.2) were merely found among FSUs, probably resulting from inadequate aseptic conditions. The ORs for age, gum surgery, contact index, and first blood donation differed significantly between the two populations. **CONCLUSION:** Although the strength of risk factors for HCV differs between

Israeli and immigrant BDs, most factors studied did not differ between the groups. Therefore, changes in screening of all BDs are considered.

Isralowitz, R., A. Reznik, S. E. Spear, M. L. Brecht and R. A. Rawson. "**Severity of heroin use in Israel: comparisons between native Israelis and former Soviet Union immigrants.**" *Addiction* **2007** 102(4): 630-637.

AIMS: This study examined drug use patterns and severity among native-Israeli and former Soviet Union (FSU) immigrants in Israel who reported heroin use. DESIGN, SETTING AND PARTICIPANTS: a total of 272 native Israelis and 300 FSU heroin users were interviewed from 2002 to 2006 as part of a large drug use surveillance study in Israel. Individuals were sampled at an intake centre, a methadone clinic and a day-treatment facility in the Negev region of Israel. Participants were assessed using the Addiction Severity Index, fifth edition. Native Israeli and FSU users were compared within two groups: those interviewed at intake and those interviewed in treatment. FINDINGS: Overall, ASI composite scores suggested generally comparable levels of addiction severity between the two ethnic groups. Native-born Israelis reported more years of heroin use; however, the FSU immigrants reported longer use of other opiates. The FSU reported significantly more heroin use by injection, and a significantly higher rate of hepatitis C and other chronic medical problems. Comparisons by gender within each group revealed higher drug severity scores for females (native-born Israeli and FSU combined). Females in the intake group had significantly higher severity scores in the areas of employment and psychiatric status when compared to individuals who had been in treatment for some time. CONCLUSIONS: Except for higher levels of alcohol use, the FSU did not have more severe drug problems than the native Israelis as measured by ASI severity scores. Injection use among FSU, however, is a critical public health problem, especially given the well-established link between injection drug use, hepatitis C and HIV/AIDS.

Hasin, T., R. Dagan, G. Boutboul, E. Derazne, O. Atias and D. Cohen.

"**Socioeconomic correlates of antibody levels to enteric pathogens among Israeli adolescents.**" *Epidemiol Infect* **2007** 135(1): 118-125.

We examined the association between socioeconomic status and the level of serum antibodies to selected faeco-orally transmitted pathogens among Israeli adolescents. Random samples of eighty volunteers aged 12-15 years from high (HSL), medium (MSL) and low (LSL) standard of living towns were included in the study. Serum samples were examined by radioimmunoassay for HAV and by in-house-developed ELISA systems for IgA and IgG antibody levels against *Shigella sonnei*, *S. flexneri*, *E. coli* O157:H7 lipopolysacchride and *Cryptosporidium parvum* antigens. Seropositivity to HAV was highest (98.8%) in the LSL towns and lowest (25%) in the HSL towns, showing a statistically significant linear trend. Antibody levels to the other enteropathogens had gender variation, with higher titres in females. Significantly lower titres in the HSL towns were found for: IgA anti-*S. sonnei* in females ($P<0.001$); IgG anti-*S. sonnei* in females ($P=0.024$) and males ($P=0.033$); IgG anti-*S. flexneri* in females ($P=0.016$). Inverse linear association with socioeconomic status was found for IgA anti-*C. parvum* in females ($P<0.001$); IgA anti-*E. coli* O157:H7 in females ($P<0.001$) and males ($P=0.024$). A statistically significant association between HAV seropositivity and higher titres of IgA anti-*S. sonnei* and *E. coli* O157:H7 was shown. In conclusion, exposure to enteropathogens transmitted via the faecal-oral route in communities of lower socioeconomic status is reflected in a higher prevalence of lifelong lasting antibodies to HAV, and higher levels of

antibodies to bacterial and protozoan enteropathogens. Among females, the levels of specific serum antibodies are higher and more strongly associated with low socioeconomic status.

Cohen, M., L. Bachmatov, Z. Ben-Ari, Y. Rotman, R. Tur-Kaspa and R. Zemel. **"Development of specific antibodies to an ARF protein in treated patients with chronic HCV infection."** Dig Dis Sci 2007 52(9): 2427-2432.

The hepatitis C virus (HCV) F protein is a recently described, frameshift product of HCV core encoding sequence with unknown biological function. In this study we sought to characterize the prevalence of specific anti-F antibodies in patients with chronic HCV infection and to analyze the anti-F antibody profile before, during, and after antiviral treatment in order to gain a better understanding of the role of F protein in HCV pathogenesis. Serum samples were collected from 44 patients with chronic HCV infection and from 19 healthy controls. Consecutive samples from 27 patients taken before, during, and after treatment with antiviral therapy. The F and the core proteins were cloned from the HCV genome. The recombinant proteins were expressed in *Escherichia coli* and affinity purified. A sensitive and specific enzyme-linked immunosorbent assay was developed to assess the prevalence of anti-F antibodies. Eighty-nine percent of chronic HCV patients had evidence of anti-F antibodies, and 95% of them had anti-core antibodies. No correlation of anti-F antibodies was found with response to treatment, genotype, or seroconversion. We conclude that the F protein elicits specific antibodies in most individuals chronically infected with HCV with no correlation with response to treatment. Our results confirm the expression of F protein during natural HCV infection.

Rosner, G., Y. Lurie, L. Blendis, Z. Halpern and R. Oren. **"Acute hepatitis B in the era of immunisation: pitfalls in the identification of high risk patients."** Postgrad Med J 2006 82(965): 207-210.

BACKGROUND: Since the adoption of a universal hepatitis B immunisation strategy, the reported incidence of acute hepatitis B has declined dramatically worldwide including in Israel. However, new cases of acute hepatitis B still occur. The aim of this study was to describe the incidence of acute hepatitis B in a referral area, routes of transmission, and outcome. **METHODS:** The charts of all new hepatitis B patients, who visited the clinic in the years 2002 and 2003 (January 2002 to December 2003), were reviewed. The main criteria for a diagnosis of acute hepatitis B were transient increase of alanine transaminase activity, and hepatitis B surface antigen seroconversion. **RESULTS:** Twenty nine men and seven women were diagnosed with acute hepatitis B infection during the study period. Two patients were previously vaccinated with hepatitis B vaccine. One case of hepatitis D coinfection was reported. The incidence of acute hepatitis B in the referral area was estimated as 2.25 per 100,000 adult population. Mean age was 36 years (17-75). Twenty one patients (18 men and 3 women) acquired the virus through unprotected sexual contact, and seven patients through iatrogenic exposure. Thirty three patients underwent spontaneous seroconversion while three patients became chronic carriers. **CONCLUSIONS:** Despite a universal immunisation policy, frequent cases of acute hepatitis B in Israel are still seen. High risk heterosexual activity and iatrogenic exposure seem to be the commonest routes of transmission. Further recommendations regarding vaccination policy are discussed.

Maor, Y., D. Bashari, G. Kenet, S. Lalezari, A. Lubetsky, J. Luboshitz, J. M. Schapiro, B. Avidan, S. Bar-Meir and U. Martinowitz. **"Hepatitis C at the Israeli national**

hemophilia center." *Haemophilia* 2006 12(1): 68-74.

Haemophilia patients who received non-virucidally treated large pool clotting factors before 1987 have a high rate of chronic hepatitis C viral infection (HCV). Some patients are coinfecting with HIV. Haemophilia patients and other coagulation disorders were treated at one centre since the beginning of the 1970, and the Israeli National Hemophilia Center (INHC) was officially founded in 1987. To characterize patients with HCV as well as patients with HCV/HIV coinfection at the INHC. Patients with haemophilia and other coagulation disorders positive for HCV antibodies were evaluated between 2001 and 2004. Demographic data, type and severity of coagulation disorder, frequency of coagulation factor usage and treatment with concentrated clotting factors prior to 1987 were recorded. Liver enzymes, viral load, genotype and data supporting advanced liver disease were evaluated. About 179 of 239 haemophilia patients (75%) tested positive for anti-HCV antibodies. Our cohort consisted of 165 patients in whom clinical, biochemical and virological data were available. About 117 patients had active HCV infection with HCV-RNA-positive, and 27 were HCV/HIV coinfecting. Twenty-one patients (13%) persistently tested HCV-RNA-negative, hence were considered to clear their HCV infection. There was no former USSR immigrants among HCV/HIV coinfecting compared with HCV-infected or HCV-RNA-negative groups (0 vs. 30% and 38%, respectively; $P < 0.001$). HCV-RNA-negative patients used concentrated coagulation factor less frequently than HCV or HCV/HIV-infected patients (48% vs. 73%; $P = 0.023$, and 48% vs. 74%; $P = 0.043$, respectively). The use of concentrated clotting factors before 1987 was significantly more frequent in HCV/HIV than in either HCV-infected or HCV-RNA-negative patients (96% vs. 49% and 48%, respectively; $P < 0.001$). Compared with HCV/HIV subjects, patients with HCV mono-infection were characterized by a higher proportion of infection with genotype 1 (80% vs. 61%; $P = 0.027$). The rate of persistently normal liver enzymes in these patients was higher (24% vs. 7%; $P = 0.05$) than in the HCV/HIV-coinfecting patients. Advanced liver disease was significantly more common in patients with HCV/HIV-coinfection than in HCV-mono-infected patients (11% vs. 3%; $P = 0.045$). The majority of haemophilia patients are infected with HCV. Viral clearance occurred in a minority of these patients. HCV mono-infected and HCV/HIV coinfecting differ clinically and prognostically.

Joffe, H., E. Bamberger, S. Nurkin, E. Kedem, Z. Kra-Oz, S. Pollack and I. Srugo. "Sexually transmitted diseases among patients with human immunodeficiency virus in northern Israel." *Isr Med Assoc J* 2006 8(5): 333-336.

BACKGROUND: The co-morbidity of human immunodeficiency virus and other sexually transmitted diseases in Israel has not been established. OBJECTIVES: To compare the prevalence of STDs among HIV-positive patients to HIV-negative patients visiting an STD clinic in northern Israel. METHODS: Between December 2000 and December 2001, 176 HIV-positive individuals (53% males) were screened and compared to 200 HIV-seronegative individuals (76% males). Demographics, symptomatology and risk factors were obtained via questionnaire. First-void urine samples were tested for the detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Serum was tested for type-specific herpes simplex virus-2, hepatitis B and syphilis. RESULTS: Relative to the seronegative STD patients, HIV-positive patients exhibited significantly greater risk-reducing sexual behaviors such as consistent condom use [29/86 (33.7%) vs. 16/187 (8.6%), $P < 0.001$], and abstinence in the previous 6 months [43/125 (34%) vs. 7/185 (3.8%), $P < 0.001$]. Nevertheless, STD prevalence was higher among HIV-positive than

HIV-negative patients (79.5% vs 37.5%, $P < 0.001$). HSV-2, syphilis and HBV were more common among HIV-positive than HIV-negative patients [120/175 (68.8%)] vs. 18/200 (9%), $P < 0.001$], [43/161 (26.7%) vs. 0%, $P < 0.001$], [13/171 (7.6%) vs. 3/200 (1.5%), $P < 0.01$], respectively. In contrast, Chlamydia and gonorrhoea were more common in HIV-negative patients than HIV-positive patients [3/176 (1.7%) vs. 13/200 (6.5%), $P < 0.05$] vs. [0% vs. 5/200 (2.5%), $P < 0.05$], respectively. **CONCLUSION:** Despite the low risk sexual behavior of Israeli HIV patients, they had a high prevalence of chronic STDs (e.g., HSV-2, HBV and syphilis). The lower prevalence of Chlamydia and gonorrhoea among HIV-immunosuppressed patients may be attributed to routine antibiotic prophylaxis against opportunistic infections. Nevertheless, as advocated by international health organizations, it appears prudent to recommend the routine screening of these asymptomatic HIV-positive patients for STD pathogens.

Cwikel, J. G., T. Lazer, F. Press and S. Lazer. "**Sexually transmissible infections among illegal female sex workers in Israel.**" *Sex Health* 2006 3(4): 301-303.

Due to the mobile and clandestine nature of those who enter a country illegally, female sex workers (FSWs) who are working without papers or work permits often have no access to sexual health care. This study reports on the sexually transmissible infection (STI) prevalence among a sample of 43 sex workers working illegally. Brothel workers from republics of the Former Soviet Union (FSU), working in two locales in Israel were tested for the presence of eight pathogens and the presence of pathology by Pap smear. Of these brothel workers, 48.8% had at least one positive STI result, 14% had two STIs and one woman had three STIs. There were no cases of HIV, gonorrhoea or malignancy detected; high rates of ureaplasma (26.8%) and chlamydia were found (16.7%). Four cases of hepatitis C (9%) and three cases of hepatitis B (7%) and mycoplasma (7%) were detected. There was no relationship between reported symptoms and the detection of STIs. The level of STIs is high among this population of FSWs and it is imperative to develop more accessible health services for these women.

Chodick, G., S. Ashkenazi and Y. Lerman. "**The risk of hepatitis A infection among healthcare workers: a review of reported outbreaks and sero-epidemiologic studies.**" *J Hosp Infect* 2006 62(4): 414-420.

All reports of hepatitis A (HA) outbreaks in healthcare settings published between 1975 and 2003 were studied to determine the background immunity or susceptibility of healthcare workers (HCWs) to HA. Twenty-six reports were found. The number of infected personnel ranged from one to 66 and, in most outbreaks, nurses accounted for the majority of personnel infected, reflecting high attack rates reaching 15-41%. In addition, we found 23 sero-epidemiological studies for HA among HCWs that had been performed in 13 different countries. Seroprevalence rates of HCWs with anti-HA antibody ranged between 4% among paramedical workers in Germany to 88% among hospital maintenance workers in Portugal. Effective infection control of HA outbreaks in hospitals demands early recognition, including awareness of atypical presentations of the infection, and strict adherence to universal infection control measures. Education programmes are of special importance for HCWs in neonatal, paediatric and intensive care units. The findings of the current study suggest that a pre-employment screening policy and administration of active vaccination to susceptible HCWs, particularly nurses, should be seriously considered in high-risk settings.

Dagan, R., A. Leventhal, E. Anis, P. Slater, Y. Ashur and D. Shouval. "**Incidence of**

hepatitis A in Israel following universal immunization of toddlers." JAMA 2005 294(2): 202-210.

CONTEXT: In Israel, the mean annual incidence of hepatitis A disease was 50.4 per 100 000 during 1993-1998. A 2-dose universal hepatitis A immunization program aimed at children aged 18 and 24 months (without a catch-up campaign) was started in 1999. OBJECTIVE: To observe the impact of toddlers-only universal vaccination on hepatitis A virus disease in Israel. DESIGN AND SETTING: Ongoing passive national surveillance of hepatitis A cases in Israel has been conducted since 1993 by the Ministry of Health. An active surveillance program in the Jerusalem district in 1999-2003 provided validation for the passive program. MAIN OUTCOME MEASURE: Incidence of reported hepatitis A disease, 1993-2004. RESULTS: Overall vaccine coverage in Israel in 2001-2002 was 90% for the first dose and 85% for the second dose. A decline in disease rates was observed before 1999 among the Jewish but not the non-Jewish population. After initiation of the program, a sharp decrease in disease rates was observed in both populations. The annual incidence of 2.2 to 2.5 per 100 000 during 2002-2004 represents a 95% or greater reduction for each year with respect to the mean incidence during 1993-1998 ($P<.001$). For children aged 1 through 4 years, a 98.2% reduction in disease was observed in 2002-2004, compared with the prevaccination period ($P<.001$). However, a sharp decline was also observed in all other age groups (84.3% [<1 year], 96.5% [5-9 years], 95.2% [10-14 years], 91.3% [15-44 years], 90.6% [45-64 years], and 77.3% [≥ 65 years]). Among the Jewish population in the Jerusalem district, in whom the active surveillance program was successfully conducted, a more than 90% reduction of disease was demonstrated. Of the 433 cases reported nationwide in 2002-2004 in whom vaccination status could be ascertained, 424 (97.9%) received no vaccine and none received 2 doses. CONCLUSION: This universal toddlers-only immunization program in Israel demonstrated not only high effectiveness of hepatitis A vaccination but also marked herd protection, challenging the need for catch-up hepatitis A vaccination programs.

Broide, E., S. Reif, E. Brazovski, R. Shapira, B. Weiss, Y. Bujanover, H. Hager and N. Amir. "**Chronic hepatitis C in Israeli children.**" Fetal Pediatr Pathol 2004 23(4): 231-239.

Natural history, epidemiology, and histopathological features of chronic hepatitis C (CHC) are well established in adults. Data on histopathological findings of CHC in children are still limited and controversial. We aimed to evaluate the histopathological features of CHC in children in Israel. We reviewed, retrospectively, 20 liver specimens from 20 children with CHC for inflammation and fibrosis, hepatocyte necrosis, fatty changes, cholestasis, bile duct damage, sinusoidal lymphocytosis, and glycogen storage. The most common histological feature was portal inflammation (95%) and lobular inflammation (70%). Sinusoidal lymphocytosis was present in 85% and glycogen storage vacuoles in 40%. Most of the children (80%) had no fibrosis, 15% had mild fibrosis and 5% moderate fibrosis. Advanced fibrosis or cirrhosis was not found. No correlation was found between the age at biopsy and any of the histological parameters. Our study shows that children with CHC have a different phenotype of liver disease with slowly progressive natural history irrespective of duration of the disease.

Chodick, G., S. Ashkenazi, H. Aloni, T. Peled and Y. Lerman. "**Hepatitis A virus seropositivity among hospital and community healthcare workers in Israel-the role of occupation, demography and socioeconomic background.**" J Hosp Infect 2003 54(2): 135-140.

Hospital and community-clinic workers were tested for hepatitis A virus antibodies (HAV)-IgG to identify variables associated with presence of (HAV-IgG) and to determine whether sociodemographic background may explain all differences in HAV seropositivity among healthcare workers. Logistic regression analysis was used to identify variable associated with HAV-immunity. Multivariate logistic regression analysis revealed that HAV-seroprevalence correlated significantly ($P < 0.01$) with age, siblings, residence in rural areas and origin. Nurse aides had an increased risk for HAV seropositivity (OR=5.04; 95% CI: 1.49-17.08) whereas physicians had a lower risk (OR=0.54; 95% CI: 0.30-0.98). Age and socioeconomic background were independently correlated with HAV immunity but did not explain all difference in HAV-seroprevalence. The higher susceptibility and elevated incidence of hepatitis A amongst physicians, prioritize primary prevention in this group.

SESSION 5 PREVENTION AND CONTROL OF VIRAL HEPATITIS IN THE COUNTRY (10)

Al-Dabbas, M. and N. M. Abu-Rmeileh. "**Needlestick injury among interns and medical students in the Occupied Palestinian Territory.**" East Mediterr Health J **2012** 18(7): 700-706.

The aim of this study was to determine the prevalence of needlestick injury (NSI) among interns and medical students as well as their knowledge of, attitude towards and their protective strategies against exposure to bloodborne pathogens. A cross-sectional study was conducted among 272 participants using a self-administered questionnaire. Just over 40% of the participants had experienced at least 1 NSI. Wound suturing was the most common cause of injury (33.5%), and the highest incidence (55.5%) was in the emergency room. Failure to report the injury to health representatives was recorded for 48.6% of NSIs. Only 46.7% of the interns had received the hepatitis B vaccine whereas most of the students (76.8%) had completed their vaccination schedule ($P < 0.001$). Participants were found to be at a high risk of NSIs and bloodborne infections.

Cohen-Moreno, R., M. Schiff, S. Levitt, R. Bar-Hamburger, S. Strauss and Y. Neumark. "**Knowledge about Hepatitis-C among methadone maintenance treatment patients in Israel.**" Subst Use Misuse **2010** 45(1-2): 58-76.

Ignorance about Hepatitis-C (HCV) among drug users, treatment staff, and policy makers thwarts treatment uptake and facilitates virus transmission. We assessed knowledge about HCV among methadone patients in Israel, where effective HCV-treatment is provided at low-cost within the national health insurance framework, yet few infected methadone patients are treated. In 2006, 512 patients in two methadone clinics in Israel were interviewed, of whom 53% were HCV-positive. The clinics were purposively selected from the 11 methadone clinics in the country. Respondents exhibited poor knowledge about HCV, particularly about diagnosis and treatment. Lesser-educated respondents were three times more likely to score low on HCV-knowledge compared to those with 12+ years of schooling (AOR = 2.97, 95% CI = 1.5-5.7. HCV-negative patients were also three-times more likely than HCV-positive patients to score low on the HCV-knowledge scale (Adjusted Odds Ratio = 3.0, 95% Confidence Interval = 1.9-4.7). Enhancing HCV-

knowledge may help patients avoid becoming infected and infecting others, allay exaggerated fears about hepatitis, and facilitate HCV-treatment initiation among those infected.

Kerzman, H., M. S. Green and E. Shinar. "**Predictors for non-compliance of notified hepatitis C virus-positive blood donors with recommendation to seek medical counselling.**" *Vox Sang* **2009** 96(1): 20-28.

BACKGROUND: Notification of blood donors represents the commonest method of informing asymptomatic individuals of abnormal test results indicating exposure to hepatitis C virus (HCV) infection. Such notification is therefore important from both health and economic perspectives. This study aimed to identify predictors for non-compliance of HCV-positive blood donors with the National Blood Services recommendation to seek medical counselling. **STUDY DESIGN AND METHODS:** The current research is a cross-sectional study. Telephone interviews were conducted with 201 blood donors identified as HCV positive following blood donation during 2001-2002 (40% response rate). **RESULTS:** About 25% of all the notified blood donors did not seek any counselling; 29% (44/150) of those who requested medical advice from their primary care physicians (general practitioner's) were not referred to specialists. Age, alcohol consumption and non-practice of health-promoting behaviour were independent predictors of non-compliance with the blood services' recommendation. In particular, smoking (odds ratio, 2.0; 95% confidence interval 1.0-4.2) and not undergoing professional teeth cleaning (odds ratio 2.8; 95% confidence interval 1.3-6.1) were found to be significant predictors of non-compliance. **CONCLUSION:** The study provides essential data regarding the extent and risk factors for non-compliance of HCV-positive blood donors with recommendation to seek medical advice. Our results can assist in identifying blood donors who would not seek counselling, based on demographic factors and past exposure to risk factors for HCV. Improvements in the notification process and additional training of general practitioners regarding the management of HCV disease are needed.

Sikuler, E., R. Tur-Kaspa, Y. Shemer-Avni, J. Delgado, D. Zilberman, A. Fich, Y. Baruch and E. Hyam. "**Sustained virologic response to treatment in 100% of patients recently infected, nosocomially, with HCV genotype 2.**" *J Clin Gastroenterol* **2008** 42(6): 730-733.

OBJECTIVE: In 2003, a cluster of hepatitis C virus (HCV)-infected patients with a common history of a surgical procedure, performed during 2001 to 2003, was identified in a medical center. An epidemiologic investigation linked a physician, infected with HCV genotype 2, as the possible source of infection in 35 patients. The evaluation, therapy, and outcome of this unique cohort are presented. **DESIGN:** HCV-RNA was isolated from sera of all patients and the double-stranded phosphorylation homology domain region was sequenced. After a routine clinical investigation 33 patients were offered antiviral therapy. Two patients were not treatment candidates due to old age and comorbidity. **RESULTS:** Twenty-two (66%) were women. The mean age was 48.5+/-16.9 years. Alanine aminotransferase level was 117+/-135 IU/L. Thirty patients were treated with pegylated interferon alpha 2a, 1 with pegylated interferon alpha 2b, and 1 with standard interferon. All received ribavirin 800 mg daily. One patient refused to be treated and was lost for follow-up. Time from acquisition of disease to initiation of therapy was 14.8+/-4.9 month (5.5 to 26). Therapy duration was 24 weeks except for 1 patient who stopped therapy after 16 weeks. Sustained virologic response was achieved in all 32 treated patients. The sequence motif of the phosphorylation homology domain region, studied in all patients, predicted good response to interferon.

CONCLUSIONS: Our excellent results can be explained by a constellation of favorable viral characteristics, a short-term disease and adherence to therapy.

Novack, L., B. Sarov, R. Goldman-Levi, V. Yahalom, J. Safi, H. Soliman, M. Orgel, A. Yaari, N. Galai, J. S. Pliskin, et al. **"Impact of pooling on accuracy of hepatitis B virus surface antigen screening of blood donations."** Trans R Soc Trop Med Hyg **2008** 102(8): 787-792.

Expenditure on screening blood donations in developing countries can be reduced by testing donations in pools. This study evaluated serological screening in pools for hepatitis B virus (HBV) at the Israeli national blood bank and a hospital blood bank in Gaza, the Palestinian Authority. The accuracy of HBV surface antigen (HBsAg) enzyme immunoassay performed on pools of 3-24 samples was compared with individual tests. Delay in detecting positive samples due to dilution in pools and the possibility of antibody-antigen neutralization were analyzed. The sensitivity of pooled testing for HBsAg was 93-99%, prolonging the window period by 5 days (8.3%). Neutralization of HBsAg by hepatitis B surface antibodies (anti-HBs) could be minimized by testing immediately after pooling. Serological testing for HBsAg in pools may be performed using manually created pools of up to six samples, with 5% loss in sensitivity and a risk of neutralization by anti-HBs present in the donor population. Pooling can therefore be considered as an option only in countries with a low prevalence of HBV.

Chemtob, D., S. Levit, H. Mell, A. Margolis, A. Levy and A. Leventhal. **"["Injecting clean or being clean?" The international and Israeli experiences of Syringe Exchange Programs among injecting drug users]."** Harefuah **2008** 147(7): 634-638, 660.

Injecting drug users (IDU) are a hard-to-reach population. The treatment objectives are to reduce their risk factors, to guide them to total abstinence or to antagonist treatment. When IDU are not ready for detoxification, they are referred to Syringe Exchange Programs (SEP). The objective of SEP is harm reduction of blood-borne viruses (of HIV, HBV, HCV). The authors aimed to define the issues related to harm reduction, to discuss the results of SEP in the world, and to describe our experience. We analyzed the world literature and our experience. In this article, we describe the rehabilitation school of thought (which supports complete drug abstinence), the harm reduction school of thought (which refers to drug addiction as a chronic disease), and the possible continuum between these two schools of thought. The AIDS pandemic and the epidemiology of world drug addiction by injection are described, together with the principles of SEP and their evaluation in the world. In addition, we describe drug use in Israel and HIV infection among IDU. Finally, we analyze our preliminary results of the SEP pilot in Israel, during the years 2004-2005, and included 462 IDUs. In conclusion, considering the difficulties that exist with IDUs, most articles emphasize the importance of SEP in this population while sometimes also expressing its effectiveness in preventing transmissions of blood-borne viruses. In Israel, a pilot project has existed since the end of 2003, and has expanded progressively to three cities. An overall evaluation of this program is under preparation.

Novack, L., E. Shinar, J. Safi, H. Soliman, A. Yaari, N. Galai, J. S. Pliskin and B. Sarov. **"Evaluation of pooled screening for anti-HCV in two blood services set-ups."** Trop Med Int Health **2007** 12(3): 415-421.

OBJECTIVE: Screening blood donations for anti-HCV is only partially

performed in many developing countries due to the relatively high costs of testing. The screening expenditures can be reduced by testing donations in pools. This study evaluates the accuracy and feasibility of pooled screening procedure for anti-HCV in blood banks in Israel and the Palestinian Authority. METHODS: The sensitivity and specificity of tests performed on pool sizes of 6-24 samples were compared to singleton immunoassay testing. All negative samples and those positive for anti-HCV were obtained from the routine work of Magen David Adom Blood Services in Israel and Shifa Hospital blood bank in Palestinian Authority. The experiments were run in parallel with different technologies. RESULTS: The sensitivity of pooled-testing for anti-HCV by Magen David Adom was 94-97% for verified samples. In the Shifa Hospital, the sensitivity was estimated as 96-97% for non-verified samples. Cost-analysis showed benefits up to \$2 per donation screened for anti-HCV in Shifa Hospital. CONCLUSIONS: We recommend using manually created pools of up to 6 samples when testing for anti-HCV, but at the cost of 3% loss in sensitivity. Pooling can be considered, in countries which do not perform routine screening, due to their limited economic resources.

Lalazar, G., D. Rund and D. Shouval. **"Screening, prevention and treatment of viral hepatitis B reactivation in patients with haematological malignancies."** Br J Haematol 2007 136(5): 699-712.

The prevalence of hepatitis B virus (HBV) infection in patients with haematological malignancies is increased compared with the general population worldwide. HBV reactivation is common following chemotherapy and is associated with a high mortality despite prompt anti-viral treatment. HBV reactivation may necessitate interruption of chemotherapy with adverse prognostic consequences for the haematological disease. Chemotherapy-induced immune suppression may lead to increased HBV replication. Immune reconstitution within the weeks and months following recovery from chemotherapy may be associated with a flare of hepatitis B manifested by hepatocellular injury. Risk factors associated with HBV reactivation include detectable hepatitis B surface antigen (HBsAg), HBV DNA, Hepatitis B e (HBeAg) antigen, antibodies to hepatitis B core antigen (anti-HBc), treatment with corticosteroids, young age and male gender. Lamivudine is effective during HBV reactivation due to immune suppression. Clinical trials have demonstrated that pre-emptive antiviral treatment with lamivudine is superior to deferred treatment. Current recommendations emphasise screening for HBV infection in all haematology patients, particularly prior to chemotherapy. Patients who are HBsAg positive or HBV DNA positive should receive pre-emptive treatment with lamivudine before chemotherapy. The duration of lamivudine treatment may be prolonged commensurate with the degree of immunosuppression. HBV naive patients should be immunised against hepatitis B, as should haematopoietic stem cell donors. In summary, overt and occult HBV pose a serious, but preventable, threat. Pre-treatment screening of patients at risk should be practiced diligently by all clinicians that treat patients with malignancies.

Kori, M., O. Flidel-Rimon, E. Sigler, E. Shinwell and E. Granot. **"Look-back study of Hepatitis C in teenagers after blood transfusions as neonates."** Acta Paediatr 2007 96(7): 1050-1052.

AIM: To conduct a single-centre "look-back" study of the prevalence of hepatitis C in teenagers who had received blood products as newborns, prior to hepatitis C virus (HCV) blood donor screening. METHODS: Using blood bank records, we identified 732 surviving teenagers aged 14-18 years who had received blood products as neonates during 1986-1990. Letters

recommending HCV antibody testing were sent to 732 surviving teenagers; 581 recipients were contacted and invited to undergo testing, and, of these, 429 consented (59% of the survivors). HCV antibody testing was performed on all and HCV-RNA was tested on those who were antibody positive.

RESULTS: Three teenagers (0.7%, 95% CI 0.54-0.86) tested positive for HCV antibodies and all three were HCV-RNA positive. There were no cases in which antibodies were detected and polymerase chain reaction (PCR) was negative. Two of the three had mildly elevated liver enzymes and all three had mild inflammatory activity and low fibrosis scores on liver biopsy.

CONCLUSIONS: The look-back process, even in a single centre with a stable urban population, is relatively inefficient in screening at-risk populations. Although the prevalence of hepatitis C in this sample was relatively low, paediatricians should offer screening to teenagers and young adults who received blood products in the neonatal period.

Gafter, U. "How to improve anti-hepatitis B vaccination." Nephron Clin Pract **2006** 103(3): c87-88.

SESSION6 Miscellaneous (28)

Nimer, A. and A. Mouch. "**Vitamin D improves viral response in hepatitis C genotype 2-3 naive patients.**" World J Gastroenterol **2012** 18(8): 800-805.

AIM: To examine whether vitamin D improved viral response and predicted treatment outcome in patients with hepatitis C virus (HCV) genotype 2-3. METHODS: Fifty patients with chronic HCV genotype 2-3 were randomized consecutively into two groups: Treatment group [20 subjects, age 48 +/- 14 years, body mass index (BMI) 30 +/- 6, 65% male], who received 180 mug pegylated alpha-interferon-2a plus oral ribavirin 800 mg/d (Peg/RBV), together with oral vitamin D3 (Vitamidyne D drops; 2000 IU/d, 10 drops/d, normal serum level > 32 ng/mL) for 24 wk; and control group (30 subjects, age 45 +/- 10 years, BMI 26 +/- 3, 60% male), who received identical therapy without vitamin D. HCV RNA was assessed by reverse transcription polymerase chain reaction. Undetectable HCV RNA at 4, 12 and 24 wk after treatment was considered as rapid virological response, complete early virological response, and sustained virological response (SVR), respectively. Biomarkers of inflammation were measured. RESULTS: The treatment group with vitamin D had higher BMI (30 +/- 6 vs. 26 +/- 3, P < 0.02), and high viral load (> 400,000 IU/mL, 65% vs. 40%, P < 0.01) than controls. Ninety-five percent of treated patients were HCV RNA negative at week 4 and 12. At 24 wk after treatment (SVR), 19/20 (95%) treated patients and 23/30 (77%) controls were HCV RNA negative (P < 0.001). Baseline serum vitamin D levels were lower at baseline (20 +/- 8 ng/mL) and increased after 12 wk vitamin D treatment, to a mean level of (34 +/- 11 ng/mL). Logistic regression analysis identified vitamin D supplement [odds ratio (OR) 3.0, 95% CI 2.0-4.9, P < 0.001], serum vitamin D levels (< 15 or > 15 ng/mL, OR 2.2, P < 0.01), and BMI (< 30 or > 30, OR 2.6, P < 0.01) as independent predictors of viral response. Adverse events were mild and typical of Peg/RBV. CONCLUSION: Low vitamin D levels predicts negative treatment outcome, and adding vitamin D to conventional Peg/RBV therapy for patients with HCV genotype 2-3 significantly improves viral response.

Daudi, N., D. Shouval, C. Stein-Zamir and Z. Ackerman. "**Breastmilk hepatitis A virus RNA in nursing mothers with acute hepatitis A virus infection.**" Breastfeed Med **2012** 7: 313-315.

Breastmilk specimens from three women with acute hepatitis A virus (HAV) infection were studied. Anti-HAV immunoglobulin M and immunoglobulin G antibodies were detected in serum and breastmilk specimens of the three women. The three women also had serum HAV RNA. However, HAV RNA was detected only in two of the three breastmilk specimens. It is interesting that none of the three infants contracted clinical HAV infection. Furthermore, mothers with HAV infection should not be encouraged to discontinue breastfeeding.

Zemel, R., A. Issachar and R. Tur-Kaspa. "**The role of oncogenic viruses in the pathogenesis of hepatocellular carcinoma.**" Clin Liver Dis **2011** 15(2): 261-279, vii-x.

HBV and HCV have major roles in hepatocarcinogenesis. More than 500

million people are infected with hepatitis viruses and, therefore, HCC is highly prevalent, especially in those countries endemic for HBV and HCV. Viral and host factors contribute to the development of HCC. The main viral factors include the circulating load of HBV DNA or HCV RNA and specific genotypes. Various mechanisms are involved in the host-viral interactions that lead to HCC development, among which are genetic instability, self-sufficiency in growth signals, insensitivity to antigrowth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasiveness. Prevention of HBV by vaccination, as well as antiviral therapy against HBV and for HCV seem able to inhibit the development of HCC.

Muhanna, N., L. Abu Tair, S. Doron, J. Amer, M. Azzeh, M. Mahamid, S. Friedman and R. Safadi. "**Amelioration of hepatic fibrosis by NK cell activation.**" Gut **2011** 60(1): 90-98.

BACKGROUND AND AIMS: Interactions between hepatic stellate cells (HSCs) and immune cell subsets have emerged as important determinants of liver fibrosis progression and regression. Natural killer (NK) cells have an antifibrotic activity through killing of activated HSCs. In liver injury NK cell expression of activating/inhibitory killer immunoglobulin-related receptors (aKIR/iKIR) and their ratio are significantly increased, while class I major histocompatibility (MHC) expression by activated HSCs is decreased. The aim of this study was to amplify the antifibrotic activity of NK cells and ameliorate hepatic fibrosis by iKIR silencing. **METHODS:** Human lymphocytes from patients with hepatitis C virus (HCV) infection were transfected with specific iKIR small interfering RNAs (siRNAs) or non-silencing control siRNAs, then co-cultured with a human HSC line and assessed for fibrogenic activity. To induce hepatic fibrosis, carbon tetrachloride was administered to BALBc SCID-Beige male mice (lacking B/T/NK cells) for 4 weeks. Splenocytes from naive SCID donors (lacking B/T cells but with preserved NK cells) were transfected in vitro with either iKIR siRNA or non-silencing control siRNA, and then were transferred to the fibrotic SCID-Beige recipients. **RESULTS:** Transfection with iKIR or positive control siRNAs (mice and human) decreased mRNA expression of iKIR and mitogen-activated protein kinase 1 (MAPK1). Consequently, total NK cells and NK cell degranulation were increased ($p=0.01$), consistent with NK cell stimulation. Compared with healthy lymphocytes, when HCV lymphocytes were transfected with non-silencing control siRNA and co-cultured with HSCs there was increased alpha-smooth muscle actin (alphaSMA) expression, reflecting HSC activation. Expression of alphaSMA in co-cultures was attenuated when HCV lymphocytes were transfected with iKIR siRNA. In SCID-Beige recipients, hepatic fibrosis and serum alanine aminotransferase (ALT) levels were significantly attenuated as a result of receiving iKIR siRNA. **CONCLUSIONS:** iKIR knockdown stimulates NK cells and promotes their antifibrogenic activity in mice and human co-cultures. These findings have implications for possible immune therapeutic strategies in patients with advanced liver disease.

Lukasiewicz, E., M. Gorfine, A. U. Neumann and L. S. Freedman. "**Combining longitudinal discriminant analysis and partial area under the ROC curve to predict non-response to treatment for hepatitis C virus.**" Stat Methods Med Res **2011** 20(3): 275-289.

A longitudinal discriminant analysis is applied to build predictive models based on repeated measurements of serum hepatitis C virus RNA. These models are evaluated through the partial area under the receiver operating curve index (PA index) and, the final selection of the best model is based on cross-validated estimates of the PA index. Models are compared by building

95% bootstrap confidence interval for the difference in PA index between two models. Data from a randomised trial, in which chronic HCV patients were enrolled, are used to illustrate the application of the proposed method to predict treatment outcome.

Birkenfeld, S., J. Dreiherr, D. Weitzman and A. D. Cohen. "**A study on the association with hepatitis B and hepatitis C in 1557 patients with lichen planus.**" J Eur Acad Dermatol Venereol 2011 25(4): 436-440.

BACKGROUND: Previous reports have demonstrated contradicting results on the association between lichen planus and hepatitis. **OBJECTIVES:** The aim of this study was to investigate the association between lichen planus and viral hepatitis. **METHODS:** Patients with lichen planus were compared with controls regarding the prevalence of viral hepatitis in a case-control study using logistic multivariate regression models. The study was performed utilizing the medical database of Clalit Health Services. **RESULTS:** The study included 1557 lichen planus patients over the age of 20 years and 3115 age- and gender-matched controls. The prevalence of hepatitis C in patients with lichen planus was higher than that in the control group (1.9%, 0.4% respectively, $P < 0.001$). In a multivariate analysis, lichen planus was associated with hepatitis C (OR 4.19, 95% CI 2.21; 7.93). The prevalence of hepatitis B in patients with lichen planus was similar to that in the control group (0.9%, 0.5% respectively, $P = 0.12$). A multivariate analysis revealed that lichen planus was not associated with hepatitis B (OR 1.69, 95% CI 0.82; 3.47). **CONCLUSION:** Lichen planus is associated with hepatitis C but not with hepatitis B. Physicians who care for patients with lichen planus should consider screening patients with lichen planus for hepatitis C.

Abu-Mouch, S., Z. Fireman, J. Jarchofsky, A. R. Zeina and N. Assy. "**Vitamin D supplementation improves sustained virologic response in chronic hepatitis C (genotype 1)-naive patients.**" World J Gastroenterol 2011 17(47): 5184-5190.

AIM: To determine whether adding vitamin D, a potent immunomodulator, improves the hepatitis C virus (HCV) response to antiviral therapy. **METHODS:** Seventy-two consecutive patients with chronic HCV genotype 1 were randomized into two groups: the treatment group ($n = 36$, 50% male, mean age 47 +/- 11 years) received Peg-alpha-2b interferon (1.5 mug/kg per week) plus ribavirin (1000-1200 mg/d) together with vitamin D3 (2000 IU/d, target serum level > 32 ng/mL), and the control group ($n = 36$, 60% male, mean age 49 +/- 7 years) received identical therapy without vitamin D. HCV-RNA was assessed by real-time polymerase chain reaction (sensitivity, 10 IU/mL). The sustained virologic response (SVR) was defined as undetectable HCV-RNA at 24 wk post-treatment. **RESULTS:** Clinical characteristics were similar in both groups. The treatment group had a higher mean body mass index (27 +/- 4 kg/m²) vs 24 +/- 3 kg/m²; $P < 0.01$), viral load (50% vs 42%, $P < 0.01$), and fibrosis score ($> F2$: 42% vs 19%, $P < 0.001$) than the controls. At week 4, 16 (44%) treated patients and 6 (17%) controls were HCV-RNA negative ($P < 0.001$). At week 12, 34 (94%) treated patients and 17 (48%) controls were HCV-RNA negative ($P < 0.001$). At 24 wk post-treatment (SVR), 31 (86%) treated patients and 15 (42%) controls were HCV-RNA negative ($P < 0.001$). Viral load, advanced fibrosis and vitamin D supplementation were strongly and independently associated with SVR (multivariate analysis). Adverse events were mild and typical of Peg-alpha-2b/ribavirin. **CONCLUSION:** Adding vitamin D to conventional Peg-alpha-2b/ribavirin therapy for treatment-naive patients with chronic HCV genotype 1 infection significantly improves the viral response.

Shouval, D. **"The search for a new endpoint for antiviral prophylaxis in hepatitis B virus transplanted patients."** Dig Liver Dis 2010 42(8): 537-538.

Katz, L. H., R. Tur-Kaspa, D. G. Guy and M. Paul. **"Lamivudine or adefovir dipivoxil alone or combined with immunoglobulin for preventing hepatitis B recurrence after liver transplantation."** Cochrane Database Syst Rev 2010 (7): CD006005.

BACKGROUND: Recurrence of hepatitis B virus (HBV) infection in the liver graft is a grave complication following liver transplantation for HBV cirrhosis. Hepatitis B immunoglobulin (HBIG) seems effective in increasing survival after liver transplantation. HBIG and anti-viral drugs are given alone or in combination for its prevention. **OBJECTIVES:** To assess the benefits and harms of different regimens for preventing HBV reactivation following liver transplantation. **SEARCH STRATEGY:** We searched The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, and Science Citation Index Expanded until February 2010. We attempted to identify further trials by reviewing the reference lists and contacting the principal authors of identified trials. **SELECTION CRITERIA:** Randomised clinical trials addressing benefits and harms of lamivudine or adefovir dipivoxil alone or in combination with hepatitis B immunoglobulins (HBIG) for preventing recurrent HBV infection in patients who are liver transplanted due to HBV infection with or without hepatocellular carcinoma. **DATA COLLECTION AND ANALYSIS:** Two authors independently assessed the trials for risk of bias and extracted data. We contacted study authors whenever information was lacking. We collected information on adverse events. The primary outcomes were all-cause mortality and reappearance of hepatitis B surface antigen in serum after liver transplantation. Relative risks were calculated from individual trials. **MAIN RESULTS:** Four trials, recruiting 136 participants, were included. Two trials compared lamivudine alone versus HBIG alone. Randomisation was performed one week after transplantation in one of the trials and after six months after transplantation in another; from transplantation until randomisation, HBIG alone was given to all patients in the two trials. A third trial compared combination treatment with lamivudine and HBIG versus lamivudine alone after one month of combination treatment, and a fourth trial compared the combination of lamivudine and HBIG versus a combination of lamivudine and adefovir dipivoxil after at least 12-month of lamivudine and HBIG combination treatment. Statistically significant differences were not detected in any of the comparisons and outcomes. All trials were open-labelled, and none of the trials were adequately powered to show a difference in HBV recurrence. No meta-analyses were performed since the identified trials assessed different comparisons. **AUTHORS' CONCLUSIONS:** This review could not derive clear evidence from randomised clinical trials for the treatment of patients with chronic HBV following liver transplantation for preventing recurrence of HBV infection. Large randomised clinical trials comparing long-term combination treatment to each of the monotherapy alone, including the newer antiviral drugs, are needed.

Katz, L. H., M. Paul, D. G. Guy and R. Tur-Kaspa. **"Prevention of recurrent hepatitis B virus infection after liver transplantation: hepatitis B immunoglobulin, antiviral drugs, or both? Systematic review and meta-analysis."** Transpl Infect Dis 2010 12(4): 292-308.

OBJECTIVES: To evaluate antiviral prophylaxis against hepatitis B virus (HBV) following liver transplantation. **METHODS:** Systematic review and

meta-analysis. Clinical trials and comparative cohort studies comparing the use of hepatitis B immunoglobulin (HBIG), antivirals, or both following liver transplantation for HBV infection were included. The primary outcome was reappearance of hepatitis B surface antigen (HBsAg). Other outcomes included all-cause and HBV-related mortality, HB-related active liver disease, and reappearance of HBV DNA after transplantation. Relative risks (RR) with 95% confidence intervals (CIs) are reported. RESULTS: Twenty studies (22 comparisons) were included. Ten studies compared HBIG to combination treatment, 9 compared antivirals to combination treatment, and 3 compared lamivudine (LAM) to HBIG. Combination treatment reduced HBsAg reappearance (RR 0.28; 95% CI 0.12-0.66), and was superior to HBIG alone in all other outcome measures. Combination treatment was significantly better than antivirals in preventing reappearance of HBsAg (RR 0.31; 95% CI 0.22-0.44), even when low-dose HBIG was given. No significant difference was found between HBIG and LAM monotherapy for all measured outcomes. Major limitations with regard to comparability of the study groups in non-randomized trials were revealed. CONCLUSIONS: Combination treatment with HBIG and LAM reduced HBV recurrence following liver transplantation, compared with HBIG or LAM alone, and reduced mortality compared with HBIG alone.

Javed, M., A. Saeed, I. M. Khan, K. Hameed, S. Rehman, A. K. Khattak, I. Ahmad and S. A. Khan. **"Frequency of osteoporosis in patients with cirrhosis due to hepatitis B and hepatitis C: a study of 100 cases."** J Ayub Med Coll Abbottabad 2009 21(3): 51-53.

BACKGROUND: Osteoporosis is the disease of bone that affected King David of Israel 3000 years ago. This condition is no longer considered to be due to aging alone and is increasingly recognised as a major health concern and accounts for about 1.5 million fractures annually in United States. Objective of this study was to see the frequency of osteoporosis in patients with cirrhosis due to Hepatitis B and C, and any correlation between the Bone Mineral Density (BMD) and duration and stage of the liver disease. METHODS: The study was conducted in the Department of Gastroenterology, Postgraduate Medical Institute, Hayatabad Medical Complex, Peshawar, from January 2008 to December 2008. All patients from the OPD or Ward fulfilling the criteria and consenting were included. Physical examination, with special emphasis on any signs of chronic liver disease was performed. Full blood count, platelet count, prothrombin time and INR, liver function tests including serum albumin, and renal function tests were done on all patients. Viral serology was checked for those patients who were either newly diagnosed as cirrhotic or were cirrhotic but not screened for viral markers. Abdominal sonogram was recorded on all patients. The Child's score was calculated for each patient using the clinical and lab parameters. The BMD was calculated for all patients using computer based ultrasound probe. Calcaneum was used for evaluation of BMD. The information collected was entered on structured data collection sheets and was analysed using SPSS version 11. RESULTS: Osteoporosis was found in 26% of subject and osteopenia in 42%, while 32% had BMD in the normal range. The mean T score was -1.483 (+/- 1.29). The mean duration of liver disease was 3.77 (+/- 1.56) year. Majority of the patients (81%) were in Child's Class C, followed by Class B and A (16% and 3% respectively). Fifty-nine percent of the patients were males with a mean age of 37.65 years, while 41% were females with mean age of 37.76 years. CONCLUSION: Osteoporosis is a common finding in patients with cirrhosis due to Hepatitis B and C. Osteoporosis is more frequent in patients with long duration of liver disease but there is no significant correlation between the

aetiology or severity of liver disease and osteoporosis.

Zemer, R., Y. Kitay Cohen, T. Naftaly and A. Klein. "**Presence of hepatitis C virus DNA sequences in the DNA of infected patients.**" Eur J Clin Invest 2008 38(11): 845-848.

BACKGROUND: Hepatitis C virus (HCV) consists of a single positive RNA molecule. In the present study we investigated the possibility that HCV may undergo integration into the genomic DNA of infected cells. MATERIALS AND METHODS: HCV(+) patients (n = 51) and 21 HCV(-) controls were investigated for HCV integration. RNase treated DNA samples of mononuclear cells (MNC) and liver biopsies of the patients were screened by PCR and seminested PCR processes for detection of integration. Positive results were further investigated by means of Southern analysis of patient's DNA as well as sequencing of PCR products of patient's DNA. RESULTS: Positive PCR results were detected in 4/51 of the HCV(+) patients and in none of the control group. Southern analysis showed the presence of HCV sequence in a 23 kbp band of the patient which is much larger than the viral genome itself (9.646 kbp). Sequencing of cloned PCR products showed an identity of over 95.0% to HCV. CONCLUSIONS: As much as we are aware this is the first demonstration of the possible integration of HCV sequences into the DNA of HCV(+) patients.

Shlomai, A. and Y. Shaul. "**The "metabolovirus" model of hepatitis B virus suggests nutritional therapy as an effective anti-viral weapon.**" Med Hypotheses 2008 71(1): 53-57.

Hepatitis B virus (HBV) is a small DNA virus that targets the liver almost exclusively. Chronic infection with HBV might lead to severe liver-related pathologies including chronic hepatitis, cirrhosis and hepatocellular carcinoma. Based on its enhancer composition, which links nutritional signals that control hepatic glucose and fat metabolism in the liver to HBV gene expression and replication, it appears that the virus has adopted a regulatory system that is unique to the major hepatic metabolic genes. This unique virus-host interaction, mediated by metabolic events in the liver, is designated by us the "metabolovirus model". We hypothesize that by mimicking the expression of key genes implicated in glucose homeostasis, HBV sophisticatedly exploits the host resources to ensure its persistence. Specifically, by recruiting transcription factors and coactivators common to essential hepatic metabolic genes the virus avoids a possible resistance by its host, on the one hand, and ensures a timely and proper response to changes in its environment in terms of metabolic milieu, on the other hand. Furthermore, by coupling its gene expression to the expression of hepatic metabolic genes that fluctuate during the day, we predict a fluctuating nature of HBV gene expression. This can serve the virus in its attempts to escape the host immune system in addition to other immune evading strategies adopted by the virus, such as the secretion of the e antigen. Based on our "metabolovirus model", we suggest new mechanisms to previously unexplained clinical phenomena, such as the observed diversity in disease severity between different geographical areas that differ in nutritional habits. Furthermore, given the up-regulatory effect of food deprivation on HBV gene expression and replication, we suggest that conditions of short-term starvation should be completely avoided by HBV-infected individuals, and dietary recommendations such as the ingestion of complex carbohydrates before sleep should be adopted. Thus, our hypothesis sets the stage for viral manipulation by controlling food intake, and opens additional avenues towards food or nutritional therapy as an effective anti-HBV weapon.

Ott, J. J., A. M. Paltiel, V. Winkler and H. Becher. "**Chronic disease mortality associated with infectious agents: a comparative cohort study of migrants from the Former Soviet Union in Israel and Germany.**" BMC Public Health 2008 8: 110.

BACKGROUND: Prevalence of infectious diseases in migrant populations has been addressed in numerous studies. However, information is sparse on their mortality due to chronic diseases that are aetiologically associated with an infectious agent. This study investigates mortality related to infectious diseases with a specific focus on cancers of possibly infectious origin in voluntary migrants from the Former Soviet Union residing in Israel and in Germany. **METHODS:** Both groups of migrants arrived from the Former Soviet Union in their destination countries between 1990 and 2001. Population-based data on migrants in Israel were obtained from the Israel Central Bureau of Statistics. Data for migrants in Germany were obtained from a representative sample of all migrants from the Former Soviet Union in Germany. Cause of death information was available until 2003 for the Israeli cohort and until 2005 for the German cohort. Standardized mortality ratios were calculated relative to the destination country for selected causes of death for which infectious agents may be causally involved. Multivariate Poisson regression was applied to assess differences in mortality by length of residence in the host country. **RESULTS:** Both in Israel and in Germany these migrants have lower overall mortality than the population in their destination countries. However, they have significantly elevated mortality from viral hepatitis and from stomach and liver cancer when compared to the destination populations. Regression analysis shows that in Israel stomach cancer mortality is significantly higher among migrants at shorter durations of residence when compared to durations of more than nine years. **CONCLUSION:** Higher mortality from cancers associated with infection and from viral hepatitis among migrants from the Former Soviet Union might result from higher prevalence of infections which were acquired in earlier years of life. The results highlight new challenges posed by diseases of infectious origin in migrants and call attention to the link between communicable and non-communicable diseases.

Mizrahi, M., G. Lalazar, A. Ben Ya'acov, D. M. Livovsky, Y. Horowitz, L. Zolotarov, R. Adler, D. Shouval and Y. Ilan. "**Beta-glycosphingolipid-induced augmentation of the anti-HBV immune response is associated with altered CD8 and NKT lymphocyte distribution: a novel adjuvant for HBV vaccination.**" Vaccine 2008 26(21): 2589-2595.

BACKGROUND: Non-responsiveness towards the currently used hepatitis B virus (HBV) vaccine is a major problem in attempts to protect against HBV infection. Several methods have been tested to overcome the lack of an effective immune response towards HBV antigens. Adjuvants that augment the immunologic reaction are essential components of the vaccines. Beta-glycosphingolipids exert a natural killer T cell (NKT)-mediated immunomodulatory effect in various disorders. **AIMS:** The aim of the present study was to test the ability of these compounds to augment the immune response towards HBV antigens, making them potential adjuvants for HBV vaccines. Six groups of mice were injected with different formulations of an HBV vaccine, along with various doses of beta-glucosylceramide (beta-GC), beta-lactosylceramide (beta-LC), or a combination of both (IGL) in different doses. The effect of beta-glycosphingolipids on the immune response towards HBV was tested by fluorescence-activated cell sorting analysis of hepatic and splenic NKT and CD8 lymphocytes, and serum cytokine levels.

RESULTS: Beta-sphingolipid treatment altered the hepatic NKT and CD8 lymphocyte distribution. beta-LC, beta-GC, and the combination of both augmented anti-HBV immunity, increasing both the anti-HBs titers and the percentage of mice exhibiting high titers. This effect was associated with altered hepatic NKT and CD8+ lymphocyte distribution. CONCLUSIONS: In summary, beta-glycosphingolipids increased the anti-HBV immune response in association with an altered NKT and CD8 lymphocyte distribution, making beta-glycosphingolipids potential potent adjuvants for overcoming non-responsiveness to HBV vaccination and augmenting the anti-viral immune response.

Kitay-Cohen, Y., L. Goldberg-Bittman, R. Hadary, M. D. Fejgin and A. Amiel. **"Telomere length in Hepatitis C."** Cancer Genet Cytogenet **2008** 187(1): 34-38.

Telomeres are nucleoprotein structures located at the termini of chromosomes that protect the chromosomes from fusion and degradation. Hepatocyte cell-cycle turnover may be a primary mechanism of telomere shortening in hepatitis C virus (HCV) infection, inducing fibrosis and cellular senescence. HCV infection has been recognized as potential cause of B-cell lymphoma and hepatocellular carcinoma. The present study sought to assess relative telomere length in leukocytes from patients with chronic HCV infection, patients after eradication of HCV infection (in remission), and healthy controls. A novel method of manual evaluation was applied. Leukocytes derived from 22 patients with chronic HCV infection and age- and sex-matched patients in remission and healthy control subjects were subjected to a fluorescence-in-situ protocol (DAKO) to determine telomere fluorescence intensity and number. The relative, manual, analysis of telomere length was validated against findings on applied spectral imaging (ASI) in a random sample of study and control subjects. Leukocytes from patients with chronic HCV infection had shorter telomeres than leukocytes from patients in remission and healthy controls. On statistical analysis, more cells with low signal intensity on telomere FISH had shorter telomeres whereas more cells with high signal intensity had longer telomeres. The findings were corroborated by the ASI telomere software. Telomere shortening in leukocytes from patients with active HCV infection is probably due to the lower overall telomere level rather than higher cell cycle turnover. Manual evaluation is an accurate and valid method of assessing relative telomere length between patients with chronic HCV infection and healthy subjects.

Katz, L. H., A. Fraser, A. Gafer-Gvili, L. Leibovici and R. Tur-Kaspa. **"Lamivudine prevents reactivation of hepatitis B and reduces mortality in immunosuppressed patients: systematic review and meta-analysis."** J Viral Hepat **2008** 15(2): 89-102.

To assess the effects of prophylactic lamivudine on reactivation and mortality following immunosuppressive therapy in hepatitis B surface antigen (HBsAg)-positive patients, we performed a meta-analysis. Systematic review and meta-analysis of randomized and nonrandomized prospective controlled trials and retrospective comparative case series were identified through The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and LILACS. The primary outcomes were virological reactivation, clinical reactivation and mortality. Secondary outcomes included hepatitis B virus (HBV)-related mortality, liver histology, discontinuation or disruption of immunosuppressive therapy, lamivudine-resistant HBV strains and adverse events. A total of 21 studies were included, two of which were randomized controlled trials. Clinical and virological reactivation were significantly reduced in the lamivudine group

[odds ratio (OR) 0.09; 95% confidence interval (CI) 0.05-0.15 and OR 0.04; 95% CI 0.01-0.14 respectively]. All-cause mortality was significantly reduced in the lamivudine group (OR 0.36; 95% CI 0.23-0.56) which translates to only 11 patients who need to be treated to prevent one death. Lamivudine significantly reduced HBV-related mortality, and discontinuations or disruptions of the immunosuppressive treatment. No adverse effects of lamivudine were recorded, and resistance to lamivudine occurred in low rates. We demonstrated a clear benefit of lamivudine in terms of clinical and virological HBV reactivation, overall mortality, HBV-related mortality and interruptions or discontinuations in the immunosuppressive treatment. Lamivudine should be administered prophylactically to HBsAg-positive patients who are about to receive immunosuppressive therapy.

Schmilovitz-Weiss, H., M. Cohen, O. Pappo, J. Sulkes, M. Braun, R. Tur-Kaspa and Z. Ben-Ari. **"Serum globulin levels in predicting the extent of hepatic fibrosis in patients with recurrent post-transplant hepatitis C infection."** Clin Transplant 2007 21(3): 391-397.

The progression of HCV-related disease is particularly aggressive in the post-transplantation setting. Recipients with recurrent HCV infection undergo repeated liver biopsies in order to estimate disease progression. A strong association was found between serum immunoglobulins levels and hepatic fibrosis in non-transplanted patients with chronic HCV infection. The aim of this study was to determine if serum globulin and immunoglobulins levels can predict the extent of fibrosis in patients with recurrent HCV infection. The records of 45 patients (mean age 51.6 +/- 10.5 yr; 53.3% men) with biochemical, serologic, virologic, and histological evidence of recurrent HCV infection were reviewed. Recurrence developed after a median interval of 11.7 months (range: 3-106); in 14 patients (31.1%), the recurrent infection was severe. The mean duration of follow-up was 51.4 +/- 35.4 months. A total of 96 liver biopsies were performed. The mean fibrosis score increased significantly with an increase in the number of biopsies ($p < 0.0001$, $r = 0.44$). On multivariate analysis, the only predictors of severe fibrosis were serum levels of globulin (OR: 5.97, 95% CI: 1.82-19.53; $p = 0.0004$) and IgG (OR: 1.003, 95% CI: 1.001-1.006; $p = 0.018$). On linear regression analysis, for each 0.5-g/dL increase in serum globulin level, there was a 0.22-point increase in fibrosis stage. In conclusion, serum levels of globulin and IgG can serve as a noninvasive marker of the extent of hepatic fibrosis in patients with post-transplant recurrent HCV infection, thus avoiding the need for repeated liver biopsies. These findings, if confirmed, have important implications for the prevention and treatment of fibrosis in this patient group.

Galun, E., N. A. Terrault, R. Eren, A. Zauberman, O. Nussbaum, D. Terkieltaub, M. Zohar, R. Buchnik, Z. Ackerman, R. Safadi, et al. **"Clinical evaluation (Phase I) of a human monoclonal antibody against hepatitis C virus: safety and antiviral activity."** J Hepatol 2007 46(1): 37-44.

BACKGROUND/AIMS: HCV-AB68, a human monoclonal antibody against the envelope protein of hepatitis C virus (HCV), neutralizes HCV in cell-culture and in the HCV-Trimera mouse model. A Phase 1 clinical trial was designed to test safety, tolerability, and antiviral activity of HCV-AB68 in patients with chronic HCV-infection. METHODS/RESULTS: Single doses of HCV-AB68, 0.25-40 mg, administered to 15 patients were well tolerated with no moderate or serious adverse events (SAEs) reported. In six patients, HCV-RNA levels transiently decreased by 2- to 100-fold immediately following infusion and rebound to baseline in 24-48 h. Multiple doses of HCV-AB68, 10-120 mg, were administered to 25 patients. Doses were given weekly for 3 weeks, then

3x a week during the fourth week, after which patients were followed for 3 months. No drug-related SAEs were reported and no specific pattern of adverse events was evident. Eight out of 25 patients had at least a 1-log reduction and 17 had at least a 0.75-log reduction in HCV-RNA levels from baseline at one or more time points following HCV-AB68 infusion.

CONCLUSIONS: These data support the investigation of HCV-AB68 in the prevention of recurrent HCV-infection in patients who had received hepatic allografts for end-stage liver disease.

Yaari, A., D. Tovbin, M. Zlotnick, M. Mostoslavsky, Y. Shemer-Avni, N. Hanuka, Z. Burbea, Z. Katzir, S. Storch and M. Margalith. "**Detection of HCV salivary antibodies by a simple and rapid test.**" J Virol Methods **2006** 133(1): 1-5.

Hepatitis C (HCV) is common in developing countries, where blood sampling and expensive sophisticated methods for detection are less available. Hemodialysis patients have high prevalence of HCV and may resemble sick populations in developing countries in relation to immunosuppression and antibodies production. For these reasons anti-HCV antibodies were assayed in saliva of hemodialysis patients by ImmunoComb II assay that is less laborious, relatively inexpensive and easy to perform. If the findings are confirmed by larger studies this method may be useful especially in developing countries. Serum and saliva samples were obtained from 37 hemodialysis patients and assayed by ImmunoComb II kit. In positive PCR patients the saliva test had 100% sensitivity, which was as good as serum anti-HCV Axsym testing. Saliva testing had a similar or better specificity than the serum method.

Shlomai, A., N. Paran and Y. Shaul. "**PGC-1alpha controls hepatitis B virus through nutritional signals.**" Proc Natl Acad Sci U S A **2006** 103(43): 16003-16008.

Hepatitis B virus (HBV) is a 3.2-kb DNA virus that replicates preferentially in the liver. Liver-enriched nuclear receptors (NRs) play a major role in the HBV life cycle, operating as essential transcription factors for viral gene expression. Notably, these NRs are also key players in metabolic processes that occur in the liver, serving as central transcription factors for key enzymes of gluconeogenesis, fatty acid beta-oxidation, and ketogenesis. However, the association between these metabolic events and HBV gene expression is poorly understood. Here we show that peroxisome proliferator-activated receptor-gamma coactivator 1alpha (PGC-1alpha), a major metabolic regulator and a coactivator of key gluconeogenic genes, robustly coactivates HBV transcription. We further demonstrate that the liver-enriched NR hepatocyte nuclear factor 4alpha that binds HBV plays an important role in this process. Physiologically, we show that a short-term fast that turns on the gluconeogenic program robustly induces HBV gene expression in vivo. This induction is completely reversible by refeeding and depends on PGC-1alpha. We conclude that HBV is tightly regulated by changes in the body's nutritional state through the metabolic regulator PGC-1alpha. Our data provide evidence for nutrition signaling to control viral gene expression and life cycle and thus ascribe to metabolism an important role in virus-host interaction.

Shitrit, A. B., M. R. Kramer, I. Bakal, G. Morali, Z. Ben Ari and D. Shitrit. "**Lamivudine prophylaxis for hepatitis B virus infection after lung transplantation.**" Ann Thorac Surg **2006** 81(5): 1851-1852.

BACKGROUND: Several reports have shown the efficacy of prophylactic lamivudine treatment for hepatitis B virus (HBV) infection in liver and renal transplantations. No data are available, however, after lung transplantation.

We report our experience with prophylactic lamivudine treatment in lung transplant recipients with HBV infection or when the donor was HBc antibody positive. **METHODS:** All our 120 lung transplant recipients and their donors were routinely screened for HBV markers. All recipients who tested positive for hepatitis B surface antigen and negative for HBV-DNA, or had organs from donors who tested positive for hepatitis B core antibody, were treated prophylactically with lamivudine for 12 months after lung transplantation. Patients whose liver functions became abnormal during follow-up were tested for HBV serology and HBV-DNA. **RESULTS:** Eleven of 120 lung transplant recipients (9.2%) were treated with prophylaxis lamivudine. Four recipients were hepatitis B surface antigen positive, and 7 recipients received organs from donors positive for HBc antibodies. Median follow-up after treatment was 24 months. All patients had normal alanine transaminase and undetectable levels of HBV-DNA before treatment. No side effects of lamivudine therapy were reported by any of the patients. Reactivation with alanine transaminase elevation and high HBV-DNA levels occurred in 2 patients. Both of them were recipients positive for hepatitis B surface antigen. In the first patient, lamivudine-resistant strain was detected and adefovir dipivoxil was started. In the other, reactivation developed 2 months after the end of lamivudine treatment. Lamivudine treatment was resumed, with rapid normalization of the HBV-DNA. **CONCLUSIONS:** Use of lamivudine is considered safe for suppressing HBV infection after lung transplantation.

Katz, L. H., E. Mor, M. Brown, N. Bar-Nathan, E. Shaharabani, J. Sulkes, O. Pappo, R. Tur-Kaspa and Z. Ben-Ari. **"Recurrent hepatitis C virus disease after liver transplantation and concurrent biliary tract complications: poor outcome."** Clin Transplant **2006** 20(4): 465-470.

Recurrent hepatitis C virus (HCV) infection is particularly aggressive in the post-liver transplantation setting, with rapid progression of liver fibrosis. Biliary complications remain a significant cause of morbidity following liver transplantation. Post-cholecystectomy biliary strictures are associated with advanced hepatic fibrosis. The aim of this retrospective study was to determine whether the presence of biliary complications affects survival in liver transplant recipients with recurrent HCV disease. The files of liver transplant recipients (53.7% male; mean age 52.7±10.3 yr) were reviewed for incidence, type and treatment of biliary complications, and findings were compared between those who developed recurrent HCV disease (n=47, 83.9%) and those who did not (n=9). Twenty-one biliary complications developed in 12 patients with recurrent HCV (25.5%). Treatment with endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography with balloon dilatation and stent placement or surgical revision was successful in nine (75%). Three biliary complications developed in three patients with no recurrence (p=NS). There was no statistically significant association between recurrent HCV disease and biliary complications. However, among those with recurrent disease, the recurrence was severe in nine of 12 recipients with biliary complications (75%) but in only nine of 35 without biliary complications (26%) (p=0.001). Death was documented in eight patients with severe recurrence (44.4%), including three (37.5%) with biliary complications and two (7%) with non-severe recurrence, neither of whom had biliary complications (p=0.003). Antiviral treatment was successful in nine of 25 patients (36%) who received it. On multivariate analysis, biliary complications were a significant predictor of severe recurrence (OR 27.0, 95% confidence interval 2.07-351.4) (p=0.012). Fibrosis stage in the second biopsy was significantly correlated with serum alanine aminotransferase (p=0.01) and with duration of biliary obstruction (p=0.07). In

conclusion, biliary complications of liver transplantation strongly affect outcome in patients with recurrent HCV disease despite attempts to relieve the biliary obstruction and to treat the recurrent HCV disease.

Reif, S., R. Somech, E. Brazovski, R. Reich, A. Belson, F. M. Konikoff and A. Kessler. **"Matrix metalloproteinases 2 and 9 are markers of inflammation but not of the degree of fibrosis in chronic hepatitis C."** *Digestion* 2005 71(2): 124-130.

BACKGROUND: The degree of liver fibrosis and inflammation is important in patients with chronic hepatitis C (CHC) in terms of therapy as well as prognosis. To obviate the need of liver biopsy, serum markers such as procollagen I, III and hyaluronic acid have been proposed but were found to be inaccurate. Controversy still exists regarding the role of matrix metalloproteinases (MMPs) as valid markers of liver fibrosis. AIM: To assess liver and serum MMP-2 and -9 as markers of fibrosis and inflammation in patients with CHC. METHODS: Thirty-five CHC patients and 8 non-hepatitis C patients with normal liver enzymes underwent liver biopsy. Activities of inflammation and fibrosis stage were determined by the Desmet score on a scale of 0-4. Serum and liver tissue MMP-2 and -9 activities were measured by zymography using substrate impregnated gels. RESULTS: Patient and control groups were similar in terms of age (50.8 +/- 15.1 vs. 50.6 +/- 15.2) and male/female ratio (18/17 vs. 4/4). In serum, MMP-9 activity was increased in patients compared to controls (308 +/- 110 vs. 163.5 +/- 35, $p < 0.05$). In liver tissue, MMP-9 was also higher in patients than in controls (21 +/- 4.5 vs. 17.1 +/- 5.1, $p < 0.05$), whereas MMP-2 did not differ between patients and controls. Serum MMP-9 values correlated with liver histologic inflammatory grade (290.4 +/- 83 in grade 2 vs. 562.1 +/- 128 in grade 3, $p < 0.05$) but not with fibrosis stage. The highest rising in serum MMP-9 levels was observed between grade 2 to grade 3 and was superior to the rising in serum transaminase levels, indicating its advantage in assessing the progression of disease activity. No correlation between liver MMP activities and liver fibrosis or inflammation was observed. CONCLUSION: Serum MMPs, in particular MMP-9, can serve as markers of disease activity rather than fibrosis stage in chronic HCV patients.

Shibolet, O., R. Alper, L. Zlotogarov, B. Thalenfeld, D. Engelhardt, E. Rabbani and Y. Ilan. **"Suppression of hepatocellular carcinoma growth via oral immune regulation towards tumor-associated antigens is associated with increased NKT and CD8+ lymphocytes."** *Oncology* 2004 66(4): 323-330.

BACKGROUND: Oral immune regulation towards viral proteins was previously shown to modulate the anti-HBV immune response. Adoptive transfer of orally immunomodulated lymphocytes suppressed the growth of hepatocellular carcinoma (HCC) expressing HBsAg in athymic mice. NKT lymphocytes play a role in the defense against tumor growth. AIM: To evaluate the effect of oral immune regulation towards HCC-associated antigens or HBV proteins on growth of HBsAg-expressing HCC, and to determine the role of NKT lymphocytes in immune modulation. METHODS: Sublethally irradiated athymic Balb/c mice were injected with 10^7 human hepatoma cells followed 10 days later by transplantation of 2×10^6 splenocytes from naive donor mice. Immune modulation was performed via feeding of HCC-extracted proteins or HBV antigens (HBsAg + Pre S1 + Pre S2). The control group was fed with bovine serum albumin (BSA). Mice were followed for survival, tumor volume, and serum alpha-fetoprotein levels. To determine the role of NKT cells in tumor suppression, cytokine expression and FACS analysis for CD4+, CD8+, and NK1.1+ T lymphocyte subsets were performed. RESULTS: Oral immune regulation towards HCC-extracted

proteins induced complete tumor suppression in recipient mice. Mortality rates were 0% in HCC-immune-regulated mice, compared with an 80% mortality rate using HBV antigens and a 100% mortality rate in control mice. Oral immune regulation towards HCC prevented weight loss. No visible tumor mass was observed in orally immune-regulated mice as compared with 112 mm³ in controls. Serum alphaFP levels were 0.9, 378 and 1,358 ng/ml in HCC, HBV immune-regulated and controls, respectively. Immune regulation towards HCC antigens significantly increased the NK1.1+ T lymphocytes/CD4+ and CD8+/CD4+ ratios. IFN γ production increased two-fold. CONCLUSION: Oral immune regulation towards HCC antigens effectively enhanced the anti-tumor immune response, thus suppressing the growth of HCC in mice. This effect was associated with an increased NKT, CD8+/CD4+ lymphocyte ratio and may be mediated via enhancement of IFN γ production.

Rosner, I., M. Rozenbaum, E. Toubi, A. Kessel, J. E. Naschitz and E. Zuckerman.

"The case for hepatitis C arthritis." Semin Arthritis Rheum 2004 33(6): 375-387.

OBJECTIVE: To present the data available supporting the existence of an arthropathy associated with hepatitis C infection. METHODS: The MEDLINE database was searched for "arthritis" intersecting with "hepatitis C" in addition to the authors' investigations and experience on this subject. RESULTS: Arthritis, not otherwise explained, has been noted in 2% to 20% of hepatitis C virus (HCV) patients. This arthritis is rheumatoid-like in two thirds of the cases and a waxing/waning oligoarthritis in the rest. Cryoglobulinemia alone does not explain the arthritis, and there is difficulty in differentiating it from rheumatoid arthritis. The arthropathy is nonerosive/nondeforming. Whereas nonsteroidal anti-inflammatory drugs, low-dose corticosteroids, and hydroxychloroquine may be helpful, conventional treatment of arthritis may be problematic in the context of viral hepatitis arthropathy. Antiviral therapy is most effective, even without viral clearance, but rheumatic complications may ensue. CONCLUSIONS: HCV arthropathy should be considered in the differential diagnosis of new-onset arthritis.

Ben-Ari, Z., Y. Ashur, N. Daudi, H. Shmilovitz-Wiess, M. Brown, J. Sulkes, A. Klein, E. Mor, R. Tur-Kaspa and D. Shouval. **"Genotype prevalence, viral load and outcome of hepatitis B virus precore mutant infection in stable patients and in patients after liver transplantation."** Clin Transplant 2004 18(4): 415-422.

OBJECTIVE: The precore mutant is detectable in most Israeli patients with persistent hepatitis B virus (HBV) infection. The aim of this study was to determine the prevalence of HBV genotypes, viral load and outcome of precore mutant infection in stable patients and in patients after liver transplantation. METHODS: The prevalence of HBV genotype and viral load were investigated in 81 patients with HBV precore mutant infection. Of these, 50 patients (40 males, 10 females; mean age 43.4 +/- 11.0 yr) underwent liver transplantation and were serum HBV DNA-negative by hybridization at the time of transplantation. Patients received long-term HBV immunoprophylaxis and immunosuppression, and lamivudine in cases of graft HBV recurrence. The remaining 31 patients were stable, with serum anti-HBe-positivity. Genotypes were tested by restriction fragment length polymorphism of an S gene amplicon. Precore mutations were studied with an INNO-LiPA probe assay. RESULTS: Follow-up was 46.6 +/- 37.7 months. Most of the transplanted group was of Middle Eastern origin (53.6%); the remainder were from Eastern Europe (21.4%), Western Europe and the USA (10.8%), Africa (7.1%), and Asia (7.1%). In the transplanted group, the pre-transplant HBV genotype D was the most prevalent (96%), while genotype A was found in

only 4%. Eleven patients (22%) developed recurrent HBV infection post-transplantation. There were no differences in genotype distribution between patients with graft reinfection or lamivudine resistance and patients without recurrence. Mean viral load at recurrence was $148.4 \times 10^6 \pm 60.4 \times 10^6$ copies/mL. The stable group had a similar origin and HBV genotype prevalence, but a lower mean viral load of $12.4 \times 10^6 \pm 29.4 \times 10^6$ copies/mL ($p = 0.007$). The prevalence of mutations at the precore region and codon 28 was similar in both groups. **CONCLUSIONS:** The chronic precore mutant HBV-infected patients were characterized as follows: (i) genotype D was the most frequent genotype, (ii) the HBV genotype distribution was similar in patients with stable infection and after liver transplantation, (iii) viral load at recurrence was significantly higher than in stable infection, and (iv) HBV genotype was unrelated to the development of recurrence or lamivudine resistance in the tested population

SESSION 7 VACCINATION PROGRAMMES (25)

Mor, Z., Y. Lurie and E. Katchman. "A case of hepatitis A vaccination failure in an HIV-positive man who had sex with men in Israel." *Int J STD AIDS* 2012 23(7): 529-530.

Hepatitis A virus (HAV) vaccination is recommended for men who have sex with men (MSM) and other susceptible populations, who are at increased risk for HAV infection, such as HIV-positive persons. Vaccine failures are uncommon, and in HIV-positive individuals whose CD4 count is ≥ 500 cells/mm², seroconversion is achieved in 73-94% of vaccinees following the second dose. Data were retrieved from the patient's file at the sexually transmitted disease clinic and the AIDS clinic describing this rare case of vaccine failure. A 35-year-old, HIV-positive MSM was vaccinated against HAV on 2007, while his CD4 count was 551 cells/mm². Two years later, he was hospitalized due to acute HAV. The patient's serum drawn two months prior to the onset of acute HAV was retrospectively tested and showed no response to the vaccine. The source of the HAV infection was not identified. The patient's partner who was HIV-negative and had been vaccinated simultaneously with the same batch developed protective antibodies. In conclusion, HIV-positive patients and their providers should be informed about HAV vaccine failure, and post-immunization serologies to hepatitis should be considered to evaluate immunization response. Alternative approaches to develop immunity are needed for non-responders.

Michaël, R., R. C. Margalit, E. Shteyer, Y. Ashur and R. Safadi. "[Vertical HBV transmission in Jerusalem in the vaccine era]." *Harefuah* 2012 151(12): 671-674, 722, 721.

We evaluated the vertical transmission of hepatitis B virus (HBV) in the vaccine era after 1992. **METHODS:** A cross-sectional descriptive study was conducted in the year 2005-2006 at Clalit Health Services, Jerusalem. Children at age ≥ 1 year born after 1992, with HBsAg positive mothers, were evaluated. **RESULTS:** A total of 22,683 HBsAg tests were performed for 20,415 patients (11,186 Jewish and 9,229 Arabs). The prevalence of positive

HBsAg was 2.64% (95% CI, 2.43-2.87] among the general Jerusalem population. It was 3.9% among the Arab population (95% CI, 3.34-4.34), compared to 1.59% [95% CI, 1.37-1.84) among the Jewish population. Data from fertile women aged 18-44 years, showed a prevalence of HBV carrier state of 1.7% (total); 2.84% (95%CI, 2.43-3.3) in Arab women as compared to 0.66% [95% CI, 0.48-0.9) among Jewish women. Of 164 Arab positive HBsAg women, we identified 157 mothers for 409 children at age > or = 1 year born after 1992. Data for 188 children of 70 mothers was collected. The prevalence of vertical infection among the child cohort (positive anti-HBc) as well as the prevalence of chronic infection [positive HBsAg) were 8.4% (95% CI, 4.71-13.1) and 4.4% (95% CI, 1.8-7.6], respectively; 37.1% of these children had negative anti-HBs titers, compared to 41.4% with antiHBs 11-100 mIU/ml and only 21.5% with titers above antiHBs 100 mLU/mL; 48% (23/48) children received passive-active vaccine combination; 35% (17/48) children received only active vaccination; 12.5% (6/48) were born to mothers prior to HBV infection diagnosis and received only the active vaccine; 4.5% (2/48) received no vaccination at all. CONCLUSION: HBV vertical transmission is highly prevalent in our tested Arab cohort, in spite of the universal vaccination program, suggesting its failure. Improvement of physician awareness and double vaccination of infants of carrier mothers will likely reduce the vertical transmission.

Bar-On, E. S., E. Goldberg, S. Hellmann and L. Leibovici. "**Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB).**" Cochrane Database Syst Rev 2012 4: CD005530.

BACKGROUND: Advantages to combining childhood vaccines include reducing the number of visits, injections and patient discomfort, increasing compliance and optimising prevention. The World Health Organization (WHO) recommends that routine infant immunisation programmes include a vaccination against Haemophilus influenzae (H. influenzae) type B (HIB) in the combined diphtheria-tetanus-pertussis (DTP)-hepatitis B virus (HBV) vaccination. The effectiveness and safety of the combined vaccine should be carefully and systematically assessed to ensure its acceptability by the community. OBJECTIVES: To compare the effectiveness of combined DTP-HBV-HIB vaccines versus combined DTP-HBV and separate HIB vaccinations. SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 4), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (January 1966 to week 1, November 2011), EMBASE (January 1990 to November 2011) and www.clinicaltrials.gov (up to April 2011). SELECTION CRITERIA: Randomised controlled trials (RCTs) or quasi-RCTs comparing vaccination with any combined DTP-HBV-HIB vaccine, with or without three types of inactivated polio virus (IPV) or concomitant oral polio vaccine (OPV) in any dose, preparation or time schedule, compared with separate vaccines or placebo, administered to infants up to two years old. DATA COLLECTION AND ANALYSIS: Two review authors independently inspected references identified by the searches and evaluated them against the inclusion criteria, extracted data and assessed the methodological quality of included trials. MAIN RESULTS: Data for the primary outcome (prevention of disease) were lacking. We performed a meta-analysis to pool the results of 20 studies with 5874 participants in an immunogenicity analysis and 5232 participants in the reactogenicity analysis. There were no data on clinical outcomes for the primary outcome (prevention of disease) and all studies used immunogenicity and reactogenicity (adverse

events). The number of vaccine doses differed significantly between the studies. Heterogeneous interventions, study location, healthcare environment and combining research across disparate geographical locations, may have lead to bias. The risk of bias was unclear across most of the included studies. Comparisons found little heterogeneity. In two immunological responses the combined vaccine achieved lower responses than the separate vaccines for HIB and tetanus. No significant differences in immunogenicity were found for pertussis, diphtheria, polio and hepatitis B. Serious adverse events were comparable with mainly hospitalisation and acute bronchiolitis cases. Minor adverse events such as pain and redness were more common in children given the combined vaccine. Overall, the direction shown by the results is in favour of the DTPw (diphtheria-tetanus-whole cell pertussis)-HBV-HIB vaccine rather than the DTPa (diphtheria-tetanus-acellular pertussis)-HBV-HIB vaccine when compared to the separate vaccines (size of effect: risk ratio (RR) 1.43; 95% confidence interval (CI) 0.98 to 2.10, for 5269 participants). **AUTHORS' CONCLUSIONS:** We could not conclude that the immune responses elicited by the combined vaccine were different from or equivalent to the separate vaccines. There was significantly less immunological response for HIB and tetanus and more local reactions in the combined injections. However, these differences rely mostly on one study each. Studies did not use an intention-to-treat (ITT) analysis and we were uncertain about the risk of bias in many of the studies. These results are therefore inconclusive. Studies addressing clinical end points whenever possible, using correct methodology and a large enough sample size should be conducted.

Dagan, R., J. Poolman and C. A. Siegrist. "**Glycoconjugate vaccines and immune interference: A review.**" *Vaccine* **2010** 28(34): 5513-5523.

Bacterial polysaccharide-protein conjugate vaccines (Haemophilus influenzae type b [Hib], pneumococcal and meningococcal conjugates) have revolutionized pediatric vaccination strategies. The widely used carrier proteins are tetanus toxoid (TT), diphtheria toxoid (DT) and diphtheria toxoid variant CRM197 protein, DT conjugates being in general less immunogenic. Multivalent conjugates using TT were found to be at risk for reduced polysaccharide responses, whilst multivalent CRM197 conjugates are at lower risk for this, but may be at higher risk of inducing bystander interference, particularly affecting Hib and hepatitis B immune responses. Novel carriers avoiding these issues could enable the further development of pediatric schedules and combinations.

Orbach, H. and A. Tanay. "**Vaccines as a trigger for myopathies.**" *Lupus* **2009** 18(13): 1213-1216.

Vaccines are considered to be among the greatest medical discoveries, credited with the virtual eradication of some diseases and the consequent improved survival and quality of life of the at-risk population. With that, vaccines are among the environmental factors implicated as triggers for the development of inflammatory myopathies. The sporadic reports on vaccine-induced inflammatory myopathies include cases of hepatitis B virus, bacillus Calmette-Guerin, tetanus, influenza, smallpox, polio, diphtheria, diphtheria-pertussis-tetanus, combination of diphtheria with scarlet fever and diphtheria-pertussis-tetanus with polio vaccines. However, a significant increase in the incidence of dermatomyositis or polymyositis after any massive vaccination campaign has not been reported in the literature. In study patients with inflammatory myopathies, no recent immunization was recorded in any of the patients. Moreover, after the 1976 mass flu vaccination, no increase in the incidence of inflammatory myopathies was observed. Although rare,

macrophagic myofasciitis has been reported following vaccination and is attributed to the aluminium hydroxide used as an adjuvant in some vaccines. Prospective multicenter studies are needed to identify potential environmental factors, including vaccines, as potential triggers for inflammatory myopathies.

Bar-On, E. S., E. Goldberg, A. Fraser, L. Vidal, S. Hellmann and L. Leibovici. **"Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)."** Cochrane Database Syst Rev 2009 (3): CD005530.

BACKGROUND: Advantages to combining childhood vaccines include reducing the number of visits, injections and patient discomfort, increasing compliance, and optimizing prevention. The World Health Organization recommends that routine infant immunization programs include a vaccination against Haemophilus influenza type B (HIB) in the combined diphtheria, tetanus, pertussis (DTP)-hepatitis B (HBV) vaccination. The effectiveness and safety of the combined vaccine should be carefully and systematically assessed to ensure their acceptability by the community. **OBJECTIVES:** To compare the effectiveness of combined DTP-HBV-HIB vaccine with DTP-HBV and HIB vaccinations. **SEARCH STRATEGY:** We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2009, issue 1) which contains the Acute Respiratory Infection Group's Specialized Register; MEDLINE (January 1966 to March 2009) and EMBASE (January 1990 to March 2009). **SELECTION CRITERIA:** Randomized or quasi-randomized controlled trials comparing vaccination with any combined DTP-HBV-HIB vaccine, with or without three types of inactivated poliovirus (IPV) or concomitant oral polio vaccine (OPV) in any dose, preparation or time schedule, compared with separate vaccines or placebo, administered to infants aged up to two years. **DATA COLLECTION AND ANALYSIS:** Two review authors independently inspected references identified by the searches and evaluated them against the inclusion criteria, extracted data and assessed the methodological quality of included trials. **MAIN RESULTS:** Meta-analysis was performed to pool the results of 18 studies. There were no data on clinical outcomes for the primary outcome and all studies used immunogenicity and reactogenicity (adverse events). In two immunological responses the combined vaccine achieved lower responses than the separate vaccines for HIB and HBV. Comparison found little heterogeneity. No significant differences in immunogenicity were found for pertussis, diphtheria, polio and tetanus. Serious adverse events were comparable. Minor adverse events were more common in children given the combined vaccine. **AUTHORS' CONCLUSIONS:** We could not conclude that the immune responses elicited by the combined vaccine were different from, or equivalent to, the separate vaccines. Data for the primary outcome (prevention of disease) were lacking. There was significantly less immunological response for HIB and HBV, and more local reactions in the combined injections. However, these differences rely mostly on one study each. Studies did not use an intention-to-treat analysis and we were uncertain about the risk of bias in many of the studies. These results are therefore inconclusive. Studies addressing clinical end-points whenever possible, using correct methodology and a large enough sample size should be conducted.

Barkai, G., I. Belmaker, N. Givon-Lavi and R. Dagan. **"The effect of universal toddlers-only hepatitis A virus vaccination program on seropositivity rate in unvaccinated toddlers: evidence for reduced virus circulation in the community."** Pediatr Infect Dis J 2009 28(5): 391-393.

BACKGROUND: In July 1999, a national toddler-only hepatitis A virus (HAV) vaccination program was introduced in Israel. Passive and active surveillance showed a large reduction in disease rate, but an objective measurement was needed. We hypothesized that toddler's vaccination in a population living in an endemic area would reduce virus circulation, resulting in reduced HAV seropositivity rates in unvaccinated toddlers. **METHODS:** The study was conducted among Bedouin children in southern Israel, for whom HAV vaccine coverage reached 85.5% and 74.9% for first and second HAV vaccine doses, respectively, in 2000. Toddlers received 2 doses of HAV vaccine at 18 and 24 months. Data on vaccine coverage was received from well-baby clinics. Sera were obtained from healthy unvaccinated 16- to 20-month-old toddlers. Anti-HAV immunoglobulin (Ig)G concentrations were tested by enzyme-linked immunosorbent assay. **RESULTS:** A total of 629 sera were tested (209 obtained in 1991-2000 and 420 obtained in 2001-2002). Seropositivity rates of ≥ 100 mIU/mL ranged from 16.2% to 19.6% in 1991 through 2000 (children born before immunization program). These rates dropped to 2% in 2001-2002 and to 0% in 2003 through 2007. Furthermore, IgG concentrations were significantly lower ($P < 0.001$) in samples taken in 2000, only a few months after beginning of vaccination, than in those taken before initiation of the HAV immunization program (1991-1998), suggesting a marked reduction in circulating HAV resulting in natural boosting. **CONCLUSIONS:** Because HAV vaccines are licensed in children ≥ 12 months old, rates of anti-HAV seropositivity in unvaccinated toddlers can be an objective and sensitive tool to evaluate the effect of immunization program on virus circulation. This method is of special value in communities where no appropriate surveillance is in place.

Stein-Zamir, C., H. Shoob, N. Nubani and G. Zentner. "**Hepatitis A in Jerusalem--the exception that proves the rule?**" Vaccine **2008** 26(41): 5241-5243.

Chodick, G., A. D. Heymann, S. Ashkenazi, E. Kokia and V. Shalev. "**Long-term trends in hepatitis A incidence following the inclusion of Hepatitis A vaccine in the routine nationwide immunization program.**" J Viral Hepat **2008** 15 Suppl 2: 62-65.

For many years hepatitis A was one of the most common vaccine preventable diseases in Israel. In 1999, Israel became the first country to introduce an inactivated hepatitis A vaccine into its national childhood vaccination program. The objectives of the present study were to study trends in disease incidence after the implementation of the new vaccination policy and to assess vaccination coverage among children and adults in Israel. We used the databases of the second largest HMO in Israel (1.7 million members) to identify patients who had evidence of hepatitis A in 1998 and 2007 and to collect information on all subjects who received at least one dose of hepatitis A vaccine during the study period. Hepatitis A vaccination coverage in children < 5 years and 5-14 years of age increased from 9% and 15% in 1998 to 89% and 68% in 2007, respectively. During this period the annual incidence of hepatitis A dropped from 142.4 per to 7.6 per 100 000. The most prominent reduction in the age-specific annual incidence rates was calculated in children < 5 years from 239.4 per 100 000 in 1998 to 2.2 per 100 000 in 2007 and from 310.3 per 100 000 to 3.0 per 100 000 in children aged 5-14 years. In endemic areas, vaccination of infants and children against hepatitis A can greatly reduce the total burden of the disease.

Arya, S. C., N. Agarwal and S. Gupta. "**Apropos "hepatitis A in Jerusalem--the exception that proves the rule"?"**" Vaccine **2008** 26(51): 6494.

Wilson, J. N., D. J. Nokes, G. F. Medley and D. Shouval. **"Mathematical model of the antibody response to hepatitis B vaccines: implications for reduced schedules."** Vaccine 2007 25(18): 3705-3712.

One of the cardinal features of the immune response is immune memory: the size of the secondary antibody response to vaccination reflects the amount of immune memory that has been generated in an individual by the priming dose. We construct a mathematical model of the generation of immune memory and antibody in response to hepatitis B vaccines. The model predictions are compared to post-vaccination antibody titres from eight adult vaccine trials. The model demonstrates significant differences between different vaccines in both the time taken to generate immune memory and the amount of memory generated. The model provides theoretical support for the hypothesis that a single vaccine dose can generate protective immune memory.

Stein-Zamir, C., I. Volovik and S. Rishpon. **"Control of Hepatitis A outbreaks in an endemic community: the role of sustained immunization coverage."** Public Health 2007 121(3): 199-201.

Rubin, L., E. Hefer, Y. Dubnov, S. Warman and S. Rishpon. **"An evaluation of the efficacy of the national immunization programme for hepatitis B."** Public Health 2007 121(7): 529-533.

We report an evaluation of the Israeli national immunization programme for hepatitis B in the Haifa subdistrict. We used a convenience sample of blood tests reported positive for HBsAg over a 6-year period from children who were born after routine immunization began in 1992. We identified 11 children with presumed chronic hepatitis B virus infection who were residents of the Haifa subdistrict, three of whom were born in Israel. All three were immunized at the appropriate age and are thus considered vaccination failures rather than failure to vaccinate. The remaining eight were born abroad, had emigrated to Israel as children and were not immunized at birth. We estimate the rate of chronic hepatitis B virus infection for children born since 1998 to be 0.24/10,000 births. For all children resident in the subdistrict under the age of 12 years, the period prevalence is estimated to be 1.26/10,000. The rate of chronic infection in children younger than 12 years was significantly less than that of older cohorts and less than that of historical controls before the start of immunization. Although the reported rates are probable underestimates of actual rates, the fact that they are based on testing carried out in clinical settings increases the likelihood of positive findings and thus reduces the degree of error. The fact that most young carriers are foreign born points to the importance of timely catch-up programmes. In countries with low and intermediate rates of chronic infection, serosurveys of immunized children need to be large and are therefore costly. Monitoring HBsAg positive tests from routine testing carried out in clinical settings is an inexpensive way to monitor chronic infection rates.

Dagan, R., J. Amir, G. Livni, D. Greenberg, J. Abu-Abed, L. Guy, S. Ashkenazi, G. Foresner, F. Tewald, H. M. Schatzl, et al. **"Concomitant administration of a virosome-adjuvanted hepatitis a vaccine with routine childhood vaccines at age twelve to fifteen months: a randomized controlled trial."** Pediatr Infect Dis J 2007 26(9): 787-793.

BACKGROUND: The objectives of this trial were to test for noninferiority of a virosomal hepatitis A virus (HAV) vaccine (Epaxal) coadministered with routine childhood vaccines compared with Epaxal given alone and to an

alum-adsorbed HAV vaccine (Havrix Junior) coadministered with routine childhood vaccines. METHODS: Healthy children 12- to 15-month-old were randomized to receive either a pediatric dose (0.25 mL) of Epaxal coadministered with DTPaHibIPV, oral polio vaccine, and measles-mumps-rubella vaccine (n = 109; group A), or Epaxal given alone (n = 105; group B), or Havrix Junior coadministered with DTPaHibIPV, oral polio vaccine, and measles-mumps-rubella vaccine (n = 108; group C). A booster dose was given 6 months later. Anti-HAV antibodies were tested before and 1 month after each vaccination. Safety was assessed for 1 month after each vaccination. Solicited adverse events were assessed for 4 days after each vaccination. RESULTS: : HAV seroprotection rates (≥ 20 mIU/mL) at 1 and 6 months after first dose were: A: 94.2% and 87.5%, B: 92.6% and 80.0%, C: 78.2% and 71.3%, respectively (A versus C: $P < 0.001$ and $P = 0.017$ at month 1 and 6, respectively). The respective geometric mean concentrations were: A: 51 and 64 mIU/mL, B: 49 and 59 mIU/mL, C: 33 and 37 mIU/mL (A versus C: $P < 0.001$ at both time points). All groups achieved 100% seroprotection after the booster dose. The geometric mean concentrations after the booster dose were 1758, 1662, and 1414, for groups A, B and C, respectively (A versus C: $P = 0.15$). No clinically significant reduction in immune response to all concomitant vaccine antigens was seen. All vaccines were well tolerated. CONCLUSIONS: : Coadministration of pediatric Epaxal with routine childhood vaccines showed immunogenicity and safety equal to Epaxal alone as well as to Havrix Junior. After first dose, Epaxal was significantly more immunogenic than Havrix Junior.

Chodick, G., M. S. Green, A. D. Heymann, L. Rosenmann and V. Shalev. "The shifting epidemiology of hepatitis A following routine childhood immunization program in Israel." *Prev Med* 2007 45(5): 386-391.

OBJECTIVES: In 1999 Israel became the first country to introduce immunization against hepatitis A to its national childhood vaccination program. The study objectives were to assess the uptake of hepatitis A vaccine following the new policy and to examine the incidence of hepatitis A and the number of prevented cases. METHODS: Data on incidence of hepatitis A and vaccination rates were obtained from a large health maintenance organization in Israel covering 1.6 million members. We identified all members that were diagnosed by a primary care physician as suffering from hepatitis A, had a positive hepatitis A virus-IgM test result, or were hospitalized due to hepatitis A between 1998 and 2004. RESULTS: The results indicate that 5 years following its inclusion in the national childhood immunization program, vaccination coverage levels with at least one dose of hepatitis A vaccine for children aged under 5 years and 5-14 years were 87% and 51%, respectively. During this period the annual incidence rates declined by 88% from 142.4 to 17.3 per 100,000. The most significant reduction in morbidity was observed among children. CONCLUSIONS: In endemic areas, vaccination of infants and children against hepatitis A may be efficient to greatly reduce the total burden of the disease.

Belmaker, I., L. Dukhan, Y. Yosef, A. Leventhal and R. Dagan. "Elimination of hepatitis a infection outbreaks in day care and school settings in southern Israel after introduction of the national universal toddler hepatitis a immunization program." *Pediatr Infect Dis J* 2007 26(1): 36-40.

BACKGROUND: In 1999, Israel became the first country to begin universal toddler immunization against hepatitis A infection with a 2-dose schedule at 18 and 24 months. The effect of the Israeli program on outbreaks of Hepatitis A in day care and school settings was studied. METHODS: The records of all

hepatitis A illness outbreaks in day care and school settings reported to the Ministry of Health in Southern Israel during 1993 through 2005 were reviewed. The number of exposed contacts for whom postexposure prophylaxis was administered was retrieved from records of epidemiologic investigations. Rates of immunization coverage were extracted from records of Maternal and Child Health Clinics. RESULTS: Three hundred nineteen cases of hepatitis A illness during the years 1993 through 2005 were associated with 113 outbreaks in day care and school settings of which 92% occurred before the institution of universal toddler immunization. Since 2000, no hepatitis A infection outbreaks have been reported in any day care and school settings in the region. An average of 732 children received immunoglobulin prophylaxis yearly because of exposure to an outbreak in an educational setting during the preimmunization period, 106 in 2000 and zero in the 5 years since 2001. The data showed marked herd immunity since school-aged children born before 1999 were not immunized, but elimination of outbreaks occurred equally in that age group. Immunization coverage was 86.4% for one dose of hepatitis A vaccine by age 3 years and 77.3% for 2 doses among the birth cohort of 2000. CONCLUSIONS: Universal hepatitis A immunization of toddlers was associated with disappearance of outbreaks in educational settings. This included cohorts of nonimmunized children representing marked herd immunity.

Elinav, E., I. Z. Ben-Dov, Y. Shapira, N. Daudi, R. Adler, D. Shouval and Z. Ackerman. "**Acute hepatitis A infection in pregnancy is associated with high rates of gestational complications and preterm labor.**" Gastroenterology 2006 130(4): 1129-1134.

BACKGROUND & AIMS: Hepatitis A virus (HAV) infection is the most common cause of acute hepatitis but is rarely reported during pregnancy. Our aim was to evaluate the impact of acute HAV infection on pregnancy outcome. METHODS: Consecutive admissions of 79,458 pregnant females during a 25-year period were retrospectively reviewed. RESULTS: Thirteen cases of second and third trimester HAV infection were found and evaluated. Nine of the 13 patients (69%) developed gestational complications, including premature contractions (n = 4), placental separation (n = 2), premature rupture of membranes (n = 2), and vaginal bleeding (n = 1). In 8 of these patients, complications led to preterm labor, at a median of 34 gestational weeks (range, 31-37 weeks). Delivery was vaginal in 12 of the 13 cases; fetal distress was noted in a single case, and meconium in amniotic fluid in 2 cases. Median birth weight was 1778 grams and 3040 grams in preterm and term deliveries, respectively (P < .05). Child outcome was favorable in all cases. In 4 cases, neonatal serum HAV RNA levels were measured and found negative. The presence of fever and hypoalbuminemia were associated with delivery at an earlier gestational week. There was a positive relation between gestational week at diagnosis of HAV infection and birth week (r = 0.68, P = .02), suggesting a causality relationship. All mothers featured full recovery from HAV infection. CONCLUSIONS: Acute HAV infection during pregnancy is associated with high risk of maternal complications and preterm labor. HAV serology and maternal vaccination during prepregnancy evaluation should be considered in areas of the world in which susceptible adult populations exist.

Orr, N., E. Klement, D. Gillis, T. Sela, R. Kayouf, E. Derazne, I. Grotto, R. Balicer, M. Huerta, L. Aviram, et al. "**Long-term immunity in young adults after a single dose of inactivated Hepatitis A vaccines.**" Vaccine 2006 24(20): 4328-4332.

We evaluated in a prospective study the immune response of naive subjects

to a single dose of inactivated Hepatitis A vaccine. Ninety-seven percent of the vaccinees sero-converted 1 month after vaccination and 93% were still positive 2 years later. All of the vaccinees had a strong booster response 2 years after the single dose. Avaxim was more immunogenic than Vaqta for the primary dose ($p = 0.01$ for sero-positivity, $p < 0.001$ for antibody level) but no differences were found after boosting with Avaxim. Performance of intense physical activity during the first month after a single vaccine dose was associated with lower antibody levels ($p = 0.004$). This study indicates that a single dose of inactivated HAV vaccine elicits protective immune memory for at least 2 years.

Mitchell, L. A., A. Joseph, E. Kedar, Y. Barenholz and E. Galun. "**Mucosal immunization against hepatitis A: antibody responses are enhanced by co-administration of synthetic oligodeoxynucleotides and a novel cationic lipid.**" *Vaccine* 2006 24(25): 5300-5310.

Hepatitis A caused by hepatitis A virus (HAV) transmitted by the fecal-oral route, results in considerable morbidity and economic loss. Mucosal immunization can be more effective than conventional injection at inducing both local and systemic immunity to HAV. Here we show that co-administration of killed HAV with synthetic oligodeoxynucleotides (ODNs) containing CpG sequences, and a novel polycationic sphingolipid (CCS)/cholesterol liposomal delivery system, markedly enhances the HAV-specific antibody response at the intestinal interface, particularly when delivered intrarectally or intranasally, to Balb/c mice at low HAV doses. A mucosally delivered, antigen-sparing HAV vaccine that is easily administered without specialized equipment or personnel, is an attractive alternative for facilitating mass immunization in hepatitis A outbreaks.

Mimouni, D., Y. Bar-Zeev, N. Davidovitch and S. Zarka. "**Disease-modifying effects of postexposure hepatitis A active immunization.**" *Mil Med* 2006 171(12): 1196-1197.

BACKGROUND: Several studies have demonstrated the efficacy of hepatitis A virus (HAV) active vaccine in the prevention of secondary HAV infection when administered shortly after exposure. **METHODS:** We describe six new recruits with unknown HAV infection, of whom three received late postexposure prophylaxis with the active HAV vaccine and three were not vaccinated. **RESULTS:** Results indicated that the vaccinated patients had a longer period from exposure to onset of symptoms ($p < 0.05$), shorter hospitalization, and lower liver enzyme levels. **CONCLUSIONS:** It appears that late administration of the active HAV vaccine has a disease-modifying effect. These findings, combined with earlier reports, may have important implications for immunization policies.

Samuels, N. "**Routine testing for IgG antibodies against hepatitis A virus in Israel.**" *BMC Public Health* 2005 5: 60.

BACKGROUND: Viral hepatitis is highly endemic in Israel, with the hepatitis A virus (HAV) responsible for most cases. Improved socioeconomic factors, as well as the universal vaccination of infants (introduced in 1999) has resulted in a decline in infection rates in Israel. This study examines the benefits of routine testing for anti-HAV IgG in high-risk population. **METHODS:** A retrospective examination of the files of teenage and adult patients (aged 16-99 years; mean 33.9) in two primary care clinics found 1,017 patients who had been tested for anti-HAV IgG antibodies for either general healthcare screening or ongoing follow-up for chronic illness. Seropositive patients were then asked regarding recall of past hepatitis (i.e. jaundice, regardless of viral

etiology); post-exposure prophylaxis with immune serum immunoglobulin (ISG); and active immunization with inactivated virus. Seronegative patients were subsequently sent for active immunization. RESULTS: Of the 1,017 patient records studied (503 male, 514 female), a total of 692 were seropositive (354 males, 338 females; $P = 0.113$). Seropositivity rates increased with age ($p < 0.005$), and were highest among those born in Middle Eastern countries other than Israel (91.3%) and lowest among immigrants from South America (44.1%; $P < 0.005$). 456 of the seropositive patients were interviewed, of whom only 91 recalled past illness while 103 remembered receiving post-exposure prophylaxis (ISG) and 8 active vaccination. Those who were unaware of past infection were more likely to have been vaccinated with ISG than those who were aware (26.3% vs. 7.7%; $p < 0.005$). CONCLUSION: The relatively high prevalence rate of anti-HAV seropositivity in our study may be due to the fact that the study was conducted in a primary care clinic or that it took place in Jerusalem, a relatively poor and densely populated Israeli city. Most of the seropositive patients had no recollection of prior infection, which can be explained by the fact that most hepatitis A infections occur during childhood and are asymptomatic. Routine testing for anti-HAV IgG in societies endemic for HAV would help prevent seropositive patients from receiving either post-exposure or preventive immunization and target seronegative patients for preventive vaccination.

Maayan-Metzger, A., P. Kedem-Friedrich and J. Kuint. "To vaccinate or not to vaccinate--that is the question: why are some mothers opposed to giving their infants hepatitis B vaccine?" *Vaccine* 2005 23(16): 1941-1948.

OBJECTIVE: To identify the characteristics of mothers who prevent their newborn babies from receiving the hepatitis B vaccine. METHODS: Women who gave birth and prevented the administration of routine hepatitis B vaccine to their newborn infants (study group) were compared to women who complied with vaccination (control group). During their hospital stay, both groups were asked to answer a questionnaire constructed to evaluate relevant demographic data, knowledge and attitudes liable to differ between the two groups. RESULTS: The 51 women in the Prevent (study) group were more educated and had a higher income level. They expressed more knowledge about the vaccine, and held more naturalistic and less conventional medical attitudes than did the women in the Comply (control) group (153 women). Some of the reasons given by the Prevent group for vaccine rejection included the following: "The child is too young"; "vaccines are dangerous"; "Doctors vaccinate without consideration"; "Vaccines causes trauma to the baby". The Comply group's reasons for giving the vaccine were mainly "to protect the baby" and "trust in the doctors". Differences between the groups were also found with respect to their future intended behavior. The study group planned to breastfeed for a longer period than the control group. Only 16% of the study group compared to 98% of the control group stated they intended to comply with the full vaccination program offered to developing children. On the basis of the answers to the questionnaire, the Comply group was further subdivided into two groups: those with knowledge and those lacking knowledge (determined by subjective evaluation). This subdivision showed that the differences between the Prevent Group and the Comply group exist, even though knowledge was controlled for. CONCLUSIONS: Mothers prevent administration of the hepatitis B vaccine to their newly born children based upon their overall approach, and not due to ignorance. In order to overcome this harmful trend, the medical community must supply counter information that encourages vaccinations.

Dagan, R., D. Greenberg and F. Weber. **"Immunogenicity of an inactivated hepatitis A pediatric vaccine: three-year post-booster follow-up."** Vaccine **2005** 23(44): 5144-5148.

The persistence of anti-hepatitis A virus antibody concentrations was followed over 3 years in 177 healthy children following primary and booster vaccination with an inactivated hepatitis A vaccine, Avaxim 80 pediatric. Seroconversion rates (post-immunization anti-HAV antibody concentration ≥ 20 mIU/mL) and geometric mean concentrations (GMC) were estimated for each of three age groups: 18 month--3 years, 4--8 years, and 9--15 years. Only subjects who were initially HAV-seronegative at inclusion (< 20 mIU/mL) were analyzed. Follow-up visits at years 1, 2, and 3 involved 177, 149, and 135 children, respectively. A decline in GMCs of about 74% occurred during the first year, from 3,060 to 814 mIU/mL overall, but did not continue during years 2 and 3. All subjects remained seropositive (antibody concentration ≥ 20 mIU/mL), with overall GMCs of 814, 891, and 924 mIU/mL in years 1--3, respectively. The inactivated hepatitis A study-vaccine resulted in sustained seroprotective antibody concentrations in 100% of these children, without a significant decline in antibody concentrations over the 3 years following booster injection, thus demonstrating the long-term protection expected with this vaccine.

Weinstein, T., A. Chagnac, M. Boaz, Y. Ori, M. Herman, D. Zevin, H. Schmilovitz-Weiss and U. Gafer. **"Improved immunogenicity of a novel third-generation recombinant hepatitis B vaccine in patients with end-stage renal disease."** Nephron Clin Pract **2004** 97(2): c67-72.

Hepatitis B (HBV) infection remains a significant epidemiological problem in the end-stage renal disease (ESRD) population. Vaccination programs using second-generation vaccines lead to effective seroprotection in only 50-60% of these patients. The purpose of this case series was to describe our experience with a novel third-generation vaccine, Bio-Hep-B, in ESRD patients who had not developed protective anti-HBs titers following a second-generation HBV vaccination protocol. Twenty-nine ESRD patients who had not responded in the past to a standard second-generation HBV vaccination protocol were included in this series. Each patient received 10 microg of Bio-Hep-B intramuscularly at 0, 1 and 6 months. A month after completion of the vaccination protocol, anti-HBs antibody levels were measured. Following immunization, 25 of 29 patients (86%) developed seroprotective anti-HBs levels ≥ 10 mIU/ml. There was a significant difference in the titers of anti-HBs antibodies prior to and following vaccination ($p < 0.0001$). Statistical analysis of the variables age, gender, diagnosis, dialysis mode, weight, hemoglobin, albumin, and KT/V failed to detect predictors of antibody response. A retrospective analysis of the results of a second-generation vaccination program for the years 1999-2001 in our department showed that 19 of 36 (56.4%) ESRD patients developed seroprotection. In conclusion, the results of this study show that the third-generation HBV vaccine Bio-Hep-B is highly immunogenic in the population of ESRD patients who did not respond in the past to a second-generation vaccine. This enhanced seroprotection offers hope that the new vaccine will reduce the rate of non-responders and help to eliminate HBV infection from dialysis centers.

Passwell, J. H. **"[Vaccines for all occasions]."** Harefuah **2004** 143(8): 576-577, 622.

The strategy of immunizing a population at risk of infectious disease has been enormously successful medically and has also proven to be cost effective. Development of effective immunogens, that induce active immunization, is a

long process that requires careful monitoring and assurance of short and long term safety, induction of protective immunity and proven efficacy in preventing the disease. A successful immunization program is also dependent on delivery of the vaccine to as many susceptible individuals as possible, so as to attain herd immunity. Passive immunization with antibodies, usually used prior to the development of active vaccines has also been remarkably effective. The special circumstances of the field and crowded conditions have demanded that the Medical Corps of the Israeli army cater for the needs of our soldiers. In this issue, the past achievements and current immunization policy are outlined for the first time. Their contribution to the health of our soldiers is commendable. Close monitoring of the epidemiology of infectious disease in the special circumstances of field conditions has prompted successful programs to markedly reduce infectious hepatitis A by passive immunization with gamma globulin in the past and, nowadays, with the killed active viral vaccine. In addition, prevention of influenza by killed viral vaccine and invasive bacterial disease by *Neisseria meningitidis* with multivalent polysaccharide vaccines are being used. This group has also improved hygienic conditions in the field to cope with shigellosis and salmonella infections. Research in the development of effective vaccines for protection of shigellosis has also been addressed by this group. New challenges posed by the emerging infectious diseases and the possible effects of bioterrorism are certain to keep this group on their toes.

Gold, Y., R. Somech, D. Mandel, Y. Peled and S. Reif. "**Decreased immune response to hepatitis B eight years after routine vaccination in Israel.**" *Acta Paediatr* **2003** 92(10): 1158-1162.

BACKGROUND AND AIM: Although immunization of infants against hepatitis B virus (HBV) is the most effective way to prevent infection, duration of the afforded protection is unknown. Titers of anti-HBV antibodies decline with time, especially during the first few years after vaccination. Anti-HBV antibody levels were measured in the serum of vaccinated children in order to determine the duration of the response afforded by the primary course of HBV vaccine. **METHODS:** The immunity derived from the HBV vaccine was assessed by measuring antibody levels in 122 healthy children who were vaccinated in a routine vaccination program in Israel. **RESULTS:** Ninety-four children (77.1%) had detectable antibodies levels (HBsAb titer \geq 10 mIU/ml): 59 (48.4%) of the children had high antibodies levels (HBsAb titer $>$ 100 mIU/ml). Twenty-eight children (22.9%) had undetectable antibodies levels (HBsAb titer $<$ 10 mIU/ml). When the children were divided into three groups according to the time elapsed since vaccination, it was found that the antibody levels declined with time ($p < 0.009$). Most of the children with undetectable antibody levels belonged to the 5 to 8-y post-vaccination group (36.1% vs 20% and 14.6% for the 2.5 to 5-y and 1 to 2.5-y groups, respectively, $p < 0.01$). The mean HBsAb declined in relation to the length of time post-vaccination (226.9 \pm 248.2 mIU/ml for 1-2.5 y post-vaccination, 199.0 \pm 235.7 mIU/ml for 2.5-5 y and 90.4 \pm 138.5 for 5-8 y, $p < 0.05$). No correlation was found between HBsAb titers and gestational age, birthweight and parental origin, although females generated higher mean antibody levels than males (207.3 \pm 217 mIU/ml vs 141.9 \pm 218.9 mIU/ml, $p < 0.05$). **CONCLUSION:** Our data demonstrate a steady decline in anti-HBV titers over time after routine vaccination against HBV in Israel. The most significant decline occurred 5-8 y post-vaccination.

3. Hepatitis Bibliography of the Speakers

List of publications was achieved via the speakers when the speakers 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.
Non hepatitis related references are formatted in grey.

Emilia Anis, Director, Division of Epidemiology, Ministry of Health

1. **Anis E**, Leventhal A, Slater PE, Shinar E, Yahalom V, Smetana Z, Zach R, Reznikovich S, Mendelson E, Danon Y, Lev B. (2009) Smallpox revaccination of 21,000 first responders in Israel: lessons learned. International Journal of Infectious Diseases 13: 403-409.
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5. **Anis E**, Leventhal A, Grotto I, Gandacu D, Warshavsky B, Shimshony A, Israeli A. (2011) Recent trends in human brucellosis in Israel. IMAJ 13: 359-362.
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