

Prevention and control of perinatal hepatitis B virus transmission in the WHO European Region

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Guido François

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Part I Prevention and control of perinatal hepatitis B virus transmission in the WHO European Region

– bibliography (in alphabetical order) –

Abe K, Hayakawa E, Sminov AV, Rossina AL, Ding X, Huy TT, Sata T, Uchaikin VF. Molecular epidemiology of hepatitis B, C, D and E viruses among children in Moscow, Russia. *J Clin Virol* 2004; 30:57-61.

Department of Pathology, National Institute of Infectious Diseases, Toyama 1-23-1, Shinjuku-ku, Tokyo 162-8640, Japan. kenjiabe@nih.go.jp

It is known that the prevalence of HBV and HCV infections vary according to geographical areas. However, in Russia, an adequate level of information on the molecular epidemiology of hepatitis viruses has not been available so far. The objectives were to investigate the characterization of various hepatitis viruses in Russia, we conducted molecular-based epidemiological survey of hepatitis viruses including hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV) and hepatitis E virus (HEV) among children in Moscow, Russia. The study population of 374 subjects (ranging in age from 1 to 14 years old) consisted of 195 patients with liver diseases and 179 patients without liver diseases. Viral DNA/RNA was determined by nested PCR. Genotyping of HBV and HCV were examined by PCR using type-specific primers. Anti-HEV antibody was assayed by ELISA. The infection rate of each virus among patients with liver diseases including acute hepatitis, chronic hepatitis or cirrhosis was 65.6% for HBV and 15.9% for HCV. In contrast, among non-liver disease patients, the infection rates were 14.4% for HBV and 0.6% for HCV, respectively. The most common viral genotypes were type D (85%) of HBV and type 1b (79.3%) of HCV. HDV RNA was detected in 7 of 149 (4.7%) HBV DNA-positive children tested. Moreover, testing for HEV among 341 subjects resulted in the detection of anti-HEV IgG in 62 cases (18.2%). Our results suggest that HBV infection is widespread in Moscow and have led to a high incidence of acute and chronic liver diseases among children in this region.

Aggarwal R, Naik SR. Prevention of hepatitis B infection: the appropriate strategy for India. *Natl Med J India* 1994; 7:216-220.

Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.

Hepatitis B infection is a major global health problem with a high morbidity and mortality. With safe and effective vaccines available, it is now possible to prevent it. Many countries have started national hepatitis B control programmes but no attempt has been made to do this in our country. An analysis of the available data on the epidemiology of hepatitis B infection in India reveals that perinatal maternofetal transmission accounts for only a minority of hepatitis B virus carriers in India. Therefore, a policy of screening pregnant mothers for the presence of hepatitis B surface antigen and selective immunization of babies born to those who are surface antigen positive will have very little effect on the hepatitis B carrier rate in our population. Universal immunization of all newborns will have a much greater impact, it will be logistically simpler and more cost-effective--the cost of preventing one hepatitis B carrier being nearly one-fourth of that with selective immunization. We recommend that hepatitis B vaccine should be included in our country's expanded programme of immunization.

Ahn YO. Strategy for vaccination against hepatitis B in areas with high endemicity: focus on Korea. *Gut* 1996; 38(Suppl 2):S63-S66.

Department of Preventive Medicine, Seoul National University College of Medicine, Korea.

Hepatitis B vaccination strategies may vary from country to country depending on hepatitis B virus (HBV) endemicity, predominant modes of infection, age of infection, and health care resources. In areas with high endemicity like Korea, transmission of virus from carrier mothers to infants during the perinatal period, and from other horizontal sources to infants and children, account for most cases of HBV infection. The consequences of HBV infection at an early age are serious, as more than 70% remain chronic carriers of the virus. These chronic carriers are the principal source of infection for other susceptible people, and are themselves at high risk of developing other serious diseases, such as chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. Theoretically, therefore, routine infant immunisation supplemented with prenatal screening of pregnant women for HBsAg or HBeAg and mass immunisation of children is the appropriate strategy for control of hepatitis B in these countries. To prevent primary liver cancer associated with HBV infection, however, immunisation of adults at high risk would also be prudent. Mandatory vaccination of all neonates is recommended in highly endemic areas, together with hepatitis B immune globulin in babies born to HBsAg carrier mothers.

Aiken KD, Clark SJ, Cabana MD. Reasons hospitals give for not offering hepatitis B vaccine to low-risk newborns. *Clin Pediatr (Phila)* 2002; 41:681-686.

Child Health Evaluation and Research Unit, Division of General Pediatrics, University of Michigan Health System, Ann Arbor, Michigan 48109-0718, USA

After a temporary suspension of hepatitis B vaccination (HBV) for low-risk newborns in July 1999, some hospitals still do not offer HBV to these infants. A semi-structured telephone survey of medical directors from a national random sample of 296 hospital nurseries was completed from August 2000 to April 2001 and analyzed using qualitative techniques. Directors of 201 of 290 eligible nurseries (71%) participated. Twenty-eight nurseries have never offered HBV to low-risk newborns ('Never Offered HBV') and 37 nurseries had offered HBV to low-risk newborns before July 1999, but discontinued this practice after the temporary suspension ('Discontinued HBV'). Common reasons for not offering HBV to low-risk newborns were difficulty with reimbursement and convenience of outpatient administration. In addition, directors of 'Never Offered HBV' nurseries cited low disease incidence in their patient population, whereas directors of 'Discontinued HBV' cited preference for the combination hepatitis B - *Haemophilus influenzae* type b vaccine as important factors. Multi-faceted interventions may be necessary to increase HBV use in the nursery.

Alvarez-Muñoz MT, Vázquez-Rosales JG, Torres-López FJ, Arredondo-García JL, Bustamante-Calvillo ME, Del Rey-Pineda G, Garduno-Espinosa J, Muñoz-Hernandez O. Infection of pregnant women with hepatitis B and C viruses and risks for vertical transmission. *Arch Med Res* 1997; 28:415-419.

Unidad de Investigacion Medica en Enfermedades Infecciosas y Parasitarias, Coordinacion de Investigacion Medica, IMSS, Mexico, D.F.

Pregnant women infected with hepatitis B and C viruses pose a risk for infecting their newborn infants by vertical transmission. We studied 6,253 pregnant women aged 12-49 years for infection with hepatitis B (HBV) and C (HCV) viruses. Infection was diagnosed by measuring IgG antibodies against HBc, HBs, HBe, as well as IgM-HBc and HCV viral antigens with commercially available immunoassay kits. HBV infection was detected in 113 cases (1.8%), and

prevalence was significantly higher (2.4%) in a group of women with a high-risk pregnancy who were attending a perinatology hospital than in healthy pregnant women (1.67%, $p < 0.05$). Infection with HBV was significantly higher in women older than 30 years old ($p < 0.05$). HBsAg was found in blood, colostrum and vaginal exudate of two pregnant women; HBsAg was detected in the gastric aspirate but not in the blood of the two newborn infants. HBeAg and IgM-HBc were not detected in any of the samples. DNA-HBV was detected in serum of seven women, and DNA-HBV was detected in the gastric aspirate of only one of the newborns. HCV infection was diagnosed in three out of 111 women with markers for HBV infection (2.7%), and in 6 out of 1,000 women without these markers (0.6%). Anti-HCV antibodies were found in the serum of six of their infants during up to six months of age. Infants were monitored for one year and none of them developed any sign of hepatic disease. These results suggest that special attention should be paid to women older than 30 years and with a high-risk pregnancy, as they are at a higher risk of HBV and HCV infections.

André FE, Zuckerman AJ. Review: protective efficacy of hepatitis B vaccines in neonates. *J Med Virol* 1994; 44:144-151. *Enclosed in Annex.*

SmithKline Beecham Biologicals, Rixensart, Belgium.

A literature search was carried out to investigate the factors that influence the protective efficacy (PE) of hepatitis B vaccines when given to neonates of hepatitis B surface antigen and e antigen positive mothers. Hepatitis B vaccines with either high or low antigen doses are very effective in preventing chronic hepatitis B infection in neonates at risk, but there is evidence that with lower dosages simultaneous use of hepatitis B immune globulin (HBIG) administration is more important than with higher dosages to elicit good protection ($PE > \text{or} = 90\%$). There is also a tendency for lower dosages to confer high PE less consistently, with noticeably greater numbers of chronic surface antigen carriers in neonates who received a complete vaccination course. Furthermore vaccination courses with higher vaccine dosages give high PEs, without concomitant HBIG administration at birth, provided that the first vaccine dose is given at birth and that the second dose follows within 2 months.

Arora NK, Ganguly S, Agadi SN, Irshad M, Kohli R, Deo M, Paul VK, Deorari AK, Chellani H, Prasad MS, Sharma D. Hepatitis B immunization in low birthweight infants: do they need an additional dose? *Acta Paediatr* 2002; 1:995-1001.

Department of Pediatrics, All India Institute of Medical Sciences, New Delhi.
nkmanan@hotmail.com

The aim was to determine the influence of gestation and weight on the development of protective anti-HB levels and geometric mean titres after three doses of HBV vaccine and to ascertain the need for a fourth dose in low birthweight infants. Hepatitis B vaccine (Enivac HB, Panacea Biotech Ltd., India) was given to 82 preterm (PT) and 60 term intrauterine growth-retarded (T-IUGR) infants at birth and at 6, 10 and 14wk of life. Protective anti-HB levels ($> 10 \text{ mIU/ml}$) were reached in 86.6% (71/82) of PT infants and 96.7% (58/60) of T-IUGR infants after three doses of HBV vaccine ($p = 0.044$). The odds of having a protective response after the third dose of HBV vaccine was 1.25 (95% CI 1.02-1.53) with every one-week increase in gestation ($p = 0.032$). Birthweight was not associated with the development of a protective immune response. After the third dose, only 66.7% (8/12) of the PT infants whose mothers had anti-HB antibodies, developed protective anti-HB levels compared with 90% (63/70) of those with no maternal antibodies ($p = 0.028$). In PT infants after the fourth dose, there was a significant increase in the proportion of infants with protective antibody levels (8.6%, 95% CI 0.6-16.6%) among those with no maternal antibodies and 12.2% overall (95% CI 6.0-21.3) ($p = 0.031$ to 0.002) over that reached with the third dose. Administration of the fourth dose to T-IUGR infants did not confer such a benefit. In

HBV-endemic areas, PT infants, irrespective of their birthweights, may benefit from an additional dose of hepatitis B vaccine in a schedule starting at birth. This approach will prevent vertical transmission and bring their immune response up to par with term infants. Term intrauterine growth-retarded infants should be vaccinated as per the schedule recommended for normal term infants. However, studies in other settings with different vaccine formulations and a longer follow-up period will be required before this strategy can be practised more widely.

Asratian AA, Melik-Andreasian GG, Mkhitarian IL, Aleksanian IuT, Shmavonian MV, Kazarian SM, Mkhitarian RG, Kozhevnikova LK. Seroepidemiological characterization of virus hepatitis in the Republic of Armenia. *Zh Mikrobiol Epidemiol Immunobiol* 2005; 5:93-96. [Article in Russian]

The survey of the population immunological structure with respect to parenteral hepatitis showed a wide circulation of hepatitis B (HB) and hepatitis C (HC) viruses among the adult population of Armenia. During the 5 year period of observation the number of persons having antibodies to HC virus increased 2.7-fold. High occurrence of antibodies to HBsAg of HB virus among the healthy population in 2002 (12.0%) in comparison with 1997 (5.4%) reflected a decreased infection rate with HB virus as well. Antibodies to hepatitis A (HA) virus were isolated, on the average, in 64 % of persons. Simultaneously with a decrease in the proportion of HA cases an increased number of HC patients was registered. No circulation of hepatitis E virus was detected. A high percentage of hepatitis cases of mixed etiology was established, as well as an increased number of combined parenteral hepatitis cases was registered (57.1%).

Asratian AA, Isaeva OV, Mikhailov MI. Tendency and analysis of the epidemic situation in parenteral virus hepatitis B and C in the Russian Federation and a number of its regions. *Zh Mikrobiol Epidemiol Immunobiol* 2005; 4:40-45. [Article in Russian]

As revealed in the present survey, during the last 3 years, against a background of decreased number of registered cases of acute hepatitis B (HB) and acute hepatitis C (HC), an increase in the proportion of patients with the chronic forms of these diseases was observed. The incidence rate of carriership of hepatitis B (HBV) and hepatitis C viruses (HCV) is many times greater than morbidity rates in acute and chronic forms of the disease. Such differences could be due to imperfect laboratory and clinical diagnosis. The registered statistics on HBV and HCV carriership included newly detected HBsAg and anti-HCV in the absence of clinical manifestations, which did not reflect the true spread of HBV and HCV in a given territory. The group of HBV and HCV carriers was found to include a considerable proportion of patients with asymptomatic form of HB and HC. It was testing for HBsAg, anti-HCV only without determination of virus replication markers (anti-HBc IgM, HBV DNA, anti-HCV IgM, HCV RNA) that seemingly determined the category of carriers greatly exceeding the true incidence. To obtain reliable epidemiological information, the complex detection of HB and HC infection markers is necessary.

Balan A, Beldescu N, Popa R. The prevalence of viral hepatitis B in pregnant women in an area of southern Romania. *Bacteriol Virusol Parazitol Epidemiol* 1998; 43:254-260. [Article in Romanian]

Institutul de Sanatate Publica Bucuresti.

In Romania, the acute hepatitis B virus (HBV) infections are considered to be a public health problem. One of the most effective routes of transmission is from infected mothers to newborns both perinatal and in early childhood. That for, this study objective was to estimate the prevalence of hepatitis B in pregnant women. We used the cluster sampling method with a sample size of 1356 pregnant women. Finally our study was based on 1298 blood samples coming from 19

clusters (obstetrics wards/hospitals) selected from those 108 obstetrics wards/hospitals in the south of Romania. Overall, 31.8% (95% C.I. 27.3%-36.4%) of pregnant women admitted for birth in southern Romania had the evidence of past or current HBV infection (anti-HBc, AgHBs). In a study done in 1990, Bradley A. Woodruff *et al.* have reported a prevalence of past or current HBV infection of 36.7% among pregnant women in northeastern Romania.

Bart PA, Jacquier P, Zuber PL, Lavanchy D, Frei PC. Seroprevalence of HBV (anti-HBc, HBsAg and anti-HBs) and HDV infections among 9006 women at delivery. *Liver* 1996; 16:110-116.

Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

Serum samples from 9006 women, who delivered in Switzerland in 1990 and 1991, were collected around the country. Of these women, 62.7% were Swiss and 37.3% originated from foreign countries. Samples were first screened for anti-HBc and those found positive were further tested for HBsAg, anti-HBs and anti-HDV. Anti-HBc was found in 640 of the 9006 women (overall prevalence, 7.1%; Swiss, 3.3%; foreigners, 13.5%). Of these 640 positive samples, 61 (9.5%) were positive for HBsAg (without anti-HBs), 467 (73.0%) positive for anti-HBs (without HBsAg) and 8 (1.3%) positive for both HBsAg and anti-HBs. The remaining 104 were thus anti-HBc positive without HBsAg or anti-HBs. These 104 specimens with the so-called 'isolated anti-HBc' reactivity represented 1.2% of the whole population or 16.3% of the 640 anti-HBc positive mothers. All were HBV DNA negative (PCR). Anti-HDV antibody was found in only five women. HBsAg was seen in 38 of the cord-blood samples from the anti-HBc positive mothers. In this large sampling, we observed a relatively high seroprevalence of HBV infection. Cases with isolated anti-HBc reactivity, being HBV DNA negative by PCR, were probably non-infectious at the time of blood collection.

Belloni C, Chirico G, Pistorio A, Orsolini P, Tinelli C, Rondini G. Immunogenicity of hepatitis B vaccine in term and preterm infants. *Acta Paediatr* 1998; 87:336-338.

Division of Neonatal Intensive Care, IRCCS Policlinico San Matteo, Pavia, Italy.

Some studies have suggested that decreased seroconversion rates might be found in premature infants with low birthweight (< 2000 g) following administration of hepatitis B vaccine at birth. The aim of the present investigation was to evaluate possible differences in seropositive rates between full-term and preterm infants after primary vaccination, in particular when gestational age or birthweight is very low. Two-thousand and nine neonates born to HBsAg-negative mothers were vaccinated with 10 microg of recombinant hepatitis B virus (HBV) vaccine, from May 1991 to October 1994. Children with infections, congenital malformations or serious illnesses were excluded. HBV vaccine was administered intramuscularly, on the fourth day of life and again at 1 and 6 months of age. A 1-ml blood sample was drawn from each infant 1 month after the third vaccine dose for determination of the level of anti-HBs antibody. The response to HBV vaccination was evaluated in 241 preterm (gestational age < 38 weeks) infants and 1727 term neonates. No statistical difference was observed in the distribution of anti-HBs antibody level, either between preterm infants (< 38 weeks) and newborns of normal gestational age, or between low birthweight (< 2500 g) and normal weight infants. The results suggest that preterm and low birthweight infants (< 2500 g) respond to HBV vaccine in the same measure as normal-term infants.

Beutels P, Musabaev EI, Van Damme P, Yasin T. The disease burden of hepatitis B in Uzbekistan. *J Infect* 2000; 40:234-241.

Centre for the Evaluation of Vaccination, Department of Epidemiology and Community Medicine, University of Antwerpen, Belgium. philippe.beutels@ua.ac.be

The objective was to describe the burden of hepatitis B illness in Uzbekistan by means of model-based estimates. A mathematical simulation model was developed to mimic the disease evolution of hepatitis B and calculate the size and age of specific HBV patient groups, defined according to the severity of their illness. The calculations indicate that of 678,000 neonates in Uzbekistan, 159,185 (235 per 1000) would incur an HBV infection at some time during their lives. About 55,095 persons (81 per 1000) would become chronic carriers of hepatitis B and 6307 persons (9.3 per 1000) are expected to die due to hepatitis B before they would die from another cause. In the overall population, we calculated that about 3074 Uzbeki die each year from the consequences of hepatitis B. Only 3.2% of these premature HBV-deaths are due to acute hepatitis B, whereas 96.8% are due to chronic hepatitis B. It was calculated that 2.1% of all deaths (or 1 in 47 deaths), and nearly 25% of deaths (or one in four deaths) between 30 and 40 years of age in Uzbekistan are due to hepatitis B. Vaccination seems easily defensible on the basis of rudimentary but very conservative cost-effectiveness calculations (\$84 per carrier prevented; \$735 per death prevented and \$22 per life-year gained). Hepatitis B represents a huge health problem in Uzbekistan, especially in young adults. The potential for prevention by vaccination seems very high, but demands a long-term vision if chronic hepatitis, in particular, is to be reduced. Routine hepatitis B vaccination was found to be a relatively cost-effective intervention in Uzbekistan.

Beutels P, Shkedy Z, Mukomolov S, Aerts M, Shargorodskaya E, Plotnikova V, Molenberghs G, Van Damme P. Hepatitis B in St Petersburg, Russia (1994-1999): incidence, prevalence and force of infection. *J Viral Hepat* 2003; 10:141-149.

Centre for the Evaluation of Vaccination, WHO Collaborating Centre for the Prevention and Control of Viral Hepatitis, Epidemiology and Community Medicine, University of Antwerpen, Antwerpen, Belgium. philippe.beutels@ua.ac.be

Hepatitis B (HB) is thought to be an expanding health problem in Russia. The incidence of infection was estimated from mandatorily reported HB cases in St Petersburg. The two-sided t-test for independent samples and the LOESS (locally-weighted regression) smoother were used to compare the age at infection for symptomatic, asymptomatic and chronic infections, by gender. The force of infection was estimated from seroprevalence data (907 sera taken in 1999) using a newly developed nonparametric method based on local polynomials, as well as an earlier method based on isotonic regression and kernel smoothers. With the local polynomial method, pointwise confidence intervals (95%) were constructed by bootstrapping. On average, men contracted HB infection at a significantly younger age than women (in 1999, 21.8 vs 22.7 years, respectively). The overall male to female ratio was 1.92. In 1999 the overall incidence almost doubled compared with the preceding years and tripled among the age groups with highest incidence (15-29-year olds: 85% of cases in 1999). The incidence increase was associated with a lower average age at infection (24.1 years in 1994 vs 22.1 years in 1999). The age and gender-specific force of infection estimates generally confirmed the incidence estimates and emphasized the usefulness of local polynomials to do this. Hence HB transmission in St Petersburg occurs mainly in young adults. The dramatic increase of infections in 1999 was probably due to injecting drug use. Without intervention, HB virus is expected to continue to spread rapidly with a greater proportion of female infections caused by sexual transmission. These trends may also provide an indication for HIV transmission.

Boxall E. Screening of pregnant women for hepatitis B. *Vaccine* 1998; 16(Suppl):S30-S33.

Public Health Laboratory, Birmingham Heartlands Hospital, Bordesley Green East, UK.
lboxall@cdscwmid.demon.co.uk

Neonatal infection with hepatitis B virus carries a very high risk of resulting in a persistent infection. Babies born to hepatitis B carrier mothers are at risk of infection through exposure to blood and body fluids during birth. These 'at risk' babies can only be identified through screening of all mothers during pregnancy. Prevention of infection in this group is a key element in any nation's strategy to reduce the incidence and eventually eliminate hepatitis B infection in its population as the persistently infected infants are a reservoir of infection throughout their lives. The infected adult carries a relatively low risk of becoming a chronic carrier (< 10%). Various strategies for screening in pregnancy have been adopted. These include attempts to identify women with a history of 'risk behaviour', testing only women who were born in areas of high endemicity, pooling of sera and universal antenatal screening. The advantages and disadvantages of the various strategies will be discussed.

Boxall EH, Smith N. Antenatal screening for HIV; are those who refuse testing at higher risk than those who accept testing? *J Public Health (Oxf)* 2004; 26:285-287.

National Blood Service, Vincent Drive, Edgbaston, Birmingham B15 2SG, UK.
elizabeth.boxall@nbs.nhs.uk

The UK Department of Health recommends that all pregnant women are offered screening for infection with human immunodeficiency virus (HIV) and had encouraged maternity units to achieve uptake targets of 90 per cent by the end of 2002. Many maternity units fail to meet this target and there is concern that those women who are still refusing testing may include a higher proportion of women at high risk of infection. In consequence, those infected with HIV are not being identified and are not receiving the antiviral treatment, which would be of benefit to them and reduce the risk of transmission of HIV to their babies. A retrospective audit of HIV screening uptake in women who were found to be infected with hepatitis B virus (HBV) and in those who were not infected with HBV was carried out in order to explore further the characteristics of 'acceptors' and 'refusers' of HIV screening. The overall uptake rate of HIV screening in the West Midlands population served by the National Blood Service was 60 per cent in 2001 and 74 per cent in 2002. The prevalence of HBV infection was found to be twice as high (0.39 per cent) in those who had refused an HIV test compared with those who had accepted a test (0.21 per cent) ($p = 0.022$). There is good evidence that women refusing HIV antenatal screening have a higher prevalence of another blood-borne virus, indicating clearly that further effort must be made to increase the screening uptake and fully integrate HIV screening with other antenatal tests.

Burk RD, Hwang LY, Ho GY, Shafritz DA, Beasley RP. Outcome of perinatal hepatitis B virus exposure is dependent on maternal virus load. *J Infect Dis* 1994; 170:1418-1423.

Marion Bessin Liver Research Center, Albert Einstein College of Medicine, Bronx, New York 10461.

To evaluate the role of maternal hepatitis B virus (HBV) DNA levels in perinatal infection, two nested case-control studies were done within a cohort of 773 hepatitis B surface antigen (HBsAg)-positive Taiwanese women and their infants. As serum HBV DNA levels increased from < 0.005 to ≥ 1.4 ng/ml among the hepatitis B e antigen (HBeAg)-positive mothers, the odds ratio (OR) for having a persistently infected infant increased from 1.0 to 147.0 (P for trend < 0.001). Among HBeAg-negative mothers, the OR for having a persistently infected infant was 19.2 (95% confidence interval, 2.3-176.6) in mothers with high versus low levels of serum HBV DNA. A

logistic regression analysis identified maternal HBV DNA to be a stronger independent predictor of persistent infection than HBeAg status. Thus, perinatal exposure to high levels of maternal HBV DNA is the most important determinant of infection outcome in the infant.

Cacciola I, Cerenzia G, Pollicino T, Squadrito G, Castellaneta S, Zanetti AR, Mieli-Vergani G, Raimondo G. Genomic heterogeneity of hepatitis B virus (HBV) and outcome of perinatal HBV infection. *J Hepatol* 2002; 36:426-432.

Department of Internal Medicine, University of Messina, Messina, Italy.

Data regarding hepatitis B virus (HBV) genomic heterogeneity in perinatal infection are incomplete, although HBV variants might be involved in neonatal fulminant hepatitis (ALF). We investigated HBV variability in infected babies showing different clinical courses. We analyzed HBV genomes isolated from nine vertically infected babies and the mothers of four of them. Two infants born to HBe-antigen (HBeAg)-positive women developed a chronic infection; seven babies (six born to anti-HBe mothers) developed acute hepatitis that had a fulminant course in four cases and a benign course in three. Two babies developing ALF received anti-HBV immunoprophylaxis at birth. Viruses carrying no significant mutation infected infants born to HBeAg-positive women. HBeAg-defective viruses were detected both in children with benign and fulminant hepatitis and their mothers. A double nucleotide mutation at positions 1762 and 1764 of the HBV core-promoter was found in two of the four infants with ALF, although it was not detected in isolates from the mother of one of them. No significant S gene mutation was found in HBV from any of the babies. This study indicates that HBV genomic heterogeneity is not primarily involved either in the evolution of the infection or the failure of neonatal HBV immunoprophylaxis.

Chakravarti A, Rawat D, Jain M. A study on the perinatal transmission of the hepatitis B virus. *Indian J Med Microbiol* 2005; 23:128-130.

Department of Microbiology, Maulana Azad Medical College and Associated Lok Nayak Hospital, New Delhi - 110 019, India. anita_chakravarti@yahoo.com

The purpose of this study was to determine the age wise prevalence of Hepatitis B virus (HBV) in children under five years and to analyze the relative importance of horizontal or vertical transmission. This study included 400 children in the age group of less than five years attending the outpatient department of pediatrics with minor complaints. History of HBV immunization was taken as the exclusion criteria. All the samples were tested for Hepatitis B surface antigen (HBsAg) and anti HBs using commercial ELISA kits. Liver function tests were performed on all the HBsAg positive patients. Hepatitis B nucleocapsid antigen (HBeAg) was detected in few HBsAg positive mothers. Overall HBsAg positivity in children below five years was 2.25%. There was no statistically significant difference in HBsAg positivity in the different age groups by chi square test. HBsAg positivity in mothers was 4.25%. However only in three cases the pair of mother and child were both positive for HBsAg. The mean anti HBs positivity in children was 23.75%. There was no statistically significant difference in the anti HBs positivity in different age groups of children. The observation that there is no statistically significant difference in the prevalence of HBV infection (HBsAg and HBs) amongst different age groups of children below five years signifies that a large proportion of HBV infection in children of this age is acquired via vertical transmission. It is also indicated that this mode of disease transmission is responsible for the majority of chronic carriers. Universal immunization of all infants is desirable to decrease the carrier pool and it is inferred from the present study that Hepatitis B immunization should begin at birth to have greater impact.

Chang MH, Hsu HY, Huang LM, Lee PI, Lin HH, Lee CY. The role of transplacental hepatitis B core antibody in the mother-to-infant transmission of hepatitis B virus. *J Hepatol* 1996; 24:674-679.

Department of Pediatrics and Obstetrics, College of Medicine, National Taiwan University, Taipei, Taiwan.

The aim was to investigate the influence of transplacental hepatitis B core antibody (anti-HBc) on perinatal hepatitis B virus (HBV) transmission, we studied the anti-HBc titers in 294 mother-neonate pairs. The anti-HBc titer was highest (10(5.13 +/- 0.80) to 10(4.36 +/- 0.97) in mothers, 10(5.13 +/- 0.76) to 10(5.52 +/- 0.98) in infants) in the 200 hepatitis B e antigen (HBeAg) positive hepatitis B surface antigen (HBsAg) carrier mothers and their infants, second highest (10(4.51 +/- 0.76) and 10(4.68 +/- 0.76)) in the 60 HBeAg-negative HBsAg carrier mothers and their infants, and lowest (10(3.11 +/- 0.76) and 10(3.24 +/- 0.83)) in the 34 non-carrier mothers and their infants ($p < 0.05$). One hundred and ninety-two infants of HBeAg-positive carrier mothers received hepatitis B immunoglobulin as well as hepatitis B vaccines, and were followed prospectively from birth. Ten infants became HBsAg carriers, and their mothers had significantly lower anti-HBc titers than those of the mothers of 182 infants who did not become carriers ($p = 0.003$), while maternal serum hepatitis B virus DNA levels (29.9 +/- 23.6 versus 39.9 +/- 58.1 pg/10 ml) did not differ in those two groups ($p > 0.25$). The same trend was observed in the infants' anti-HBc titers in those two groups ($p = 0.0006$). The association of lower anti-HBc titers in HBeAg-positive carrier mother-infant pairs and the development of carrier status in the infants suggests a positive role of anti-HBc in the modulation of mother-to-infant transmission of HBV. A high maternal anti-HBc level in serum may be a negative predictor of immunoprophylaxis failure in high-risk infants.

Chen HL, Chang MH, Ni YH, Hsu HY, Lee PI, Lee CY, Chen DS. Seroepidemiology of hepatitis B virus infection in children: Ten years of mass vaccination in Taiwan. *JAMA* 1996; 276:906-908.

Department of Pediatrics, National Taiwan University Hospital, Taipei Taiwan.

The objective was to study the seroepidemiology of hepatitis B virus (HBV) infection in children 10 years after a mass hepatitis B vaccination program was begun in Taiwan. Design: cross-sectional seroprevalence survey. Setting: Cheng-Chung/Chung-Cheng District, Taipei, Taiwan, 1994. Serum samples from 1515 healthy children younger than 12 years were tested for HBV markers. The results were compared with a baseline seroepidemiologic study conducted just before the vaccination program was launched in 1984 and with a subsequent study in 1989 in the same area. Eighty-seven percent of the children had received at least 3 doses of HBV vaccine. The overall prevalence rate of hepatitis B surface antigenemia decreased from 9.8% in 1984 to 1.3% in 1994. A statistically significant decrease was observed in every age group from 1 to 10 years. The overall prevalence rate of hepatitis B core antibody was 26% in 1984, 15% in 1989, and 4.0% in 1994. This suggests that the risk of horizontal HBV infection has decreased over time, not only because of the protective effect of the vaccine but also because the infection source has diminished. A high prevalence rate of hepatitis B surface antibody (79%) was noted in 1994 as anticipated. The Taiwanese mass vaccination program has protected most children younger than 10 years from becoming carriers, reducing both perinatal and horizontal HBV transmission. Mass HBV vaccination has proved to be a successful method to control HBV infection in this hyperendemic area.

Chen WH, Yin CS, Chang YK, Yan JS, Chu ML. Neonatal gastric aspirates as a predictor of perinatal hepatitis B virus infections. *Int J Gynaecol Obstet* 1998; 60:15-21.

Department of Obstetrics and Gynecology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan.

The objective was to elucidate possible routes and predictors of perinatal transmission of hepatitis B virus (HBV). This was a prospective follow-up study. One hundred and forty-seven out of 1762 pregnant women who were screened in the antenatal clinic of a university teaching hospital were HBsAg carriers. Enzyme immunoassay was used for determination of hepatitis B markers. Occurrence of HBsAg in newborns' gastric aspirates, newborns' and infants' blood, and maternal milk samples were determined. Their relationship with delivery routes and duration of the first stage of labor were analyzed by chi square test. The presence of HBsAg in newborns' gastric aspirates was strongly associated with the acquisition of HBsAg by the babies. There was no correlation between the rate of infant antigenemia and the duration of the first stage of labor, nor did cesarean section decrease the rate of vertical transmission of HBV. This is the first report to provide direct evidence for the major role of the oral route in vertical transmission of HBV during delivery. In addition to maternal serum HBeAg, HBsAg status in newborn's gastric aspirates is another important determinant for vertical transmission of HBV.

Clements CJ, Baoping Y, Crouch A, Hipgrave D, Mansoor O, Nelson CB, Treleaven S, van Konkelenberg R, Wiersma S. Progress in the control of hepatitis B infection in the Western Pacific Region. *Vaccine* 2006; 24:1975-1982.

Centre for International Health, The Macfarlane Burnet Institute for Medical Research and Public Health Ltd., GPO Box 2284, Commercial Road, Melbourne, Vic. 3004, Australia.

Hepatitis B virus infection is a serious problem globally, and particularly in the Western Pacific Region where the population suffers disproportionately from the infection and its sequelae. By 2001, every immunization programme in the Region had included hepatitis B vaccine in their schedule. However, many challenges remain if every one of the 26 million children born in the 37 countries and areas of the Region each year is to be protected against hepatitis B infection. In 2003, the Regional Committee of the World Health Organization's Western Pacific Region resolved to improve hepatitis B control by making it one of two new pillars for strengthening the Expanded Programme on Immunization. The Committee endorsed the strategies of the Regional Plan to improve hepatitis B control through immunization, reducing chronic HBV infection (chronic carriage rate) to less than 1%, and aiming for coverage of at least 80% of the birth cohort in every district with three doses of hepatitis B vaccine by 2005. To help guide this process, an assessment was made of the progress to date, and is reported in this paper. Coverage data used in this evaluation were not independently verified, and could over-estimate progress made in some countries. Whilst there has indeed been great progress in the Region, a number of national programmes still lack the ability to reach all children with immunization services. Other major issues that need to be addressed are the challenges of delivering a timely birth dose, and for certain countries, the affordability of the vaccine over the short- and long-term.

Corrarino JE. Perinatal hepatitis B: update & recommendations. *MCN Am J Matern Child Nurs* 1998; 23:246-252.

Suffolk County Department of Health Services, Hauppauge, New York, USA.
janecorarrino@yahoo.com

The hepatitis B virus (HBV) is the most prevalent chronic infectious disease in the world, and should be better understood by nurses caring for families. Perinatal acquisition is the major cause

of infection in infants and children. Without vaccine during infancy, 90% of infants born to women positive for the virus will go on to become lifelong carriers. There are significant sequelae associated with HBV infection, ranging from fulminant HBV to chronic liver disease to an increased risk for carcinoma. A comprehensive prevention and treatment strategy has been developed by the Centers for Disease Control and Prevention, which includes screening of all pregnant women for the presence of HBV, the administration of hepatitis B immunoglobulin (HBIG) at birth, and the administration of hepatitis B vaccine at birth, at 1 month of age, and at 6 months of age. Nurses working in the perinatal and pediatric specialties must understand the implications of HBV to help prevent transmission and to assist in the coordination of care and advocacy for affected populations. The community health implications for the care of women and children with HBV are clear, giving nurses the opportunity to develop a closer linkage between hospital- and community-based nursing practice.

Da Villa G. Rationale for the infant and adolescent vaccination programmes in Italy. *Vaccine* 2000; 18(Suppl 1):S31-S34.

Italian Institute for the Prevention of Liver Diseases, Institute "Fernando de Ritis", Via Generale Orsini, 42-80132, Naples, Italy.

In Italy in the 1980s, the incidence of acute hepatitis B was about 13 per 100,000, corresponding on average to 7500 new symptomatic cases per year was about 3%, making Italy an area of intermediate endemicity. HBV infection was also associated with 12 per 100,000 deaths from cirrhosis and with 5.1 per 100,000 deaths from hepatocellular carcinoma. In view of the large numbers of pregnant women who were hepatitis B surface antigen (HBsAg)-positive, selective hepatitis B vaccination of all newborns to these mothers and of other high-risk groups was introduced in 1983. Compliance was high among the newborns but low in other high-risk groups. Hepatitis vaccination was adopted in Italy in 1991, including each year all newborns, all adolescents aged 12 years and other high-risk groups. Compliance has been nearly 95% for newborns and 80% for adolescents. Since the introduction of vaccination, both the incidence of acute hepatitis B and the prevalence of HBV carriage have fallen, the latter from 3.4% in 1985 to 0.9% in 1996. There is good evidence that these decreases are mainly the result of the vaccination programmes. Although the full economic impact cannot yet be assessed, about 18,000 cases of acute HBV infection have been prevented over the 6 years since starting the mass vaccination programme, with cost savings of about US\$ 244,308,000.

Del Canho R, Grosheide PM, Schalm SW, de Vries RR, Heijtkink RA. Failure of neonatal hepatitis B vaccination: the role of HBV-DNA levels in hepatitis B carrier mothers and HLA antigens in neonates. *J Hepatol* 1994; 20:483-486.

Department of Internal Medicine II, University Hospital Dijkzigt, Rotterdam, The Netherlands.

In a hepatitis B vaccination program (1982-1992), 705 infants born to HBsAg-positive mothers received HBIG within 2 h of birth and were vaccinated according to a three- or four-dose vaccination schedule, starting either at 3 months or directly after birth. Eight children HBsAg-positive during the first year of life (group 1: infected nonresponders). To determine whether failure of the hepatitis B vaccination was due to perinatal high-level maternal viraemia or genetically determined infant nonresponsiveness to the vaccine, we measured HBsAg and anti-HBs levels in infants and HBeAg and hepatitis B virus-DNA levels in maternal serum, and determined the HLA type of the infants. Controls included 14 infants with a normal anti-HBs response 1 year after vaccination (group 2: noninfected responders) and all eight infants without HBsAg and anti-HBs 1 year after vaccination (group 3: noninfected low responders). HBsAg, HBeAg and anti-HBs were measured by radioimmunoassay (Abbott Laboratories), hepatitis B virus-DNA was measured quantitatively by solution hybridization for groups 1, 2, and 3 (Abbott

hepatitis B virus-DNA assay, Abbott Laboratories), and HLA was characterized by microcytotoxicity test for groups 1 and 3. All infants in groups 1 and 2 were born to HBeAg carrier mothers, and those in group 3 to HBeAg-negative mothers. Hepatitis B virus-DNA levels in maternal serum in group 1 were significantly higher than in group 2 (Wilcoxon rank-sum test: $p < 0.01$). Hepatitis B virus-DNA was not observed in group 3 maternal serum samples.

Drobeniuc J, Hutin YJ, Harpaz R, Favorov M, Melnik A, Iarovoi P, Shapiro CN, Woodruff BA. Prevalence of hepatitis B, D and C virus infections among children and pregnant women in Moldova: additional evidence supporting the need for routine hepatitis B vaccination of infants. *Epidemiol Infect* 1999; 123:463-467.

National Centre for Scientific and Applied Preventive Medicine, Chisinau, Republic of Moldova.

Rates of acute hepatitis B are high in Moldova, but the prevalence of chronic infection is unknown. In 1994, we surveyed children and pregnant women, collected demographic information, and drew blood for laboratory testing. Among the 439 children (mean age, 5 years), the prevalence of antibody to hepatitis B core antigen (anti-HBc) and hepatitis B surface antigen (HBsAg) were 17.1 and 6.8%, respectively. Among the 1098 pregnant women (mean age, 26 years), 52.4% were anti-HBc-positive and 9.7% were HBsAg-positive. Of the HBsAg-positive pregnant women, 35.6% were hepatitis B e antigen (HBeAg) positive and 18.3% had antibodies to hepatitis D virus. The prevalence of antibody to hepatitis C virus was 1.4% in children and 2.3% in pregnant women. The high HBeAg prevalence among HBsAg-positive pregnant women and the high anti-HBc prevalence among children indicate that both perinatal and early childhood transmission contribute to the high hepatitis B virus endemicity in Moldova.

Elefsiniotis IS, Glynou I, Magaziotou I, Pantazis KD, Fotos NV, Brokalaki H, Kada H, Saroglou G. HBeAg negative serological status and low viral replication levels characterize chronic hepatitis B virus-infected women at reproductive age in Greece: a one-year prospective single center study. *World J Gastroenterol* 2005; 11:4879-4882.

Department of Internal Medicine, Faculty of Nursing, University of Athens, Helena Venizelou Maternal Hospital, Greece. ielefs@acn.gr

The aim was to evaluate the seroprevalence of hepatitis B surface antigen (HBsAg) in 13 581 women at reproductive age and the hepatitis B e antigen (HBeAg)/anti-HBe status as well as serum hepatitis B virus (HBV)-DNA levels in a subgroup of HBsAg(+) pregnant women at labor in Greece. Serological markers were detected using enzyme immunoassays. Serum HBV-DNA was determined by a sensitive quantitative PCR assay. Statistical analysis of data was based on parametric methodology. Overall, 1.156% of women were HBsAg(+) and the majority of them (71.3%) were Albanian. The prevalence of HBsAg was 5.1% in Albanian women, 4.2% in Asian women and 1.14% in women from Eastern European countries. The prevalence of HBsAg in African (0.36%) and Greek women (0.29%) was very low. Only 4.45% of HBsAg(+) women were also HBeAg(+) whereas the vast majority of them were HBeAg(-)/anti-HBe(+). Undetectable levels of viremia (< 200 copies/ml) were observed in 32.26% of pregnant women at labor and 29.03% exhibited extremely low levels of viral replication (< 400 copies/ml). Only two pregnant women exhibited extremely high serum HBV-DNA levels ($> 10\,000\,000$ copies/ml), whereas 32.26% exhibited HBV-DNA levels between 1 500 and 40 000 copies/ml. The overall prevalence of HBsAg is relatively low among women at reproductive age in Greece but is higher enough among specific populations. The HBeAg(-)/anti-HBe(+) serological status and the extremely low or even undetectable viral replicative status in the majority of HBsAg(+) women of our study population, suggest that only a small proportion of HBsAg(+) women in Greece exhibit a high risk for vertical transmission of the infection.

Eriksen EM, Perlman JA, Miller A, Marcy SM, Lee H, Vadheim C, Zangwill KM, Chen RT, DeStefano F, Lewis E, Black S, Shinefield H, Ward JI. Lack of association between hepatitis B birth immunization and neonatal death: a population-based study from the vaccine safety datalink project. *Pediatr Infect Dis J* 2004; 23:656-662.

UCLA Center for Vaccine Research, Harbor-UCLA Medical Center, Torrance, CA 90502, USA.

There have been no population-based studies of the potential association between neonatal death and newborn immunization with hepatitis B vaccine (HBV). As part of the Vaccine Safety Datalink Project, we defined a birth cohort at Southern and Northern California Kaiser Permanente Health Plans of more than 350,000 live births from 1993 to 1998 and ascertained all deaths occurring under 29 days of age. We compared the proportions of deaths among birth HBV-vaccinated and unvaccinated newborns and reviewed the causes and circumstances of their deaths. We performed detailed clinical reviews of all HBV-vaccinated neonates who died and a sample of unvaccinated neonates who died and who were matched to vaccinated deaths for days of life, sex, birth year and site of care. To avoid confounding, we categorized the causes of death as either 'expected' or 'unexpected' and performed a stratified analysis to compare mortality with immunization status. There were 1363 neonatal deaths during the study period. Whereas 67% of the entire birth cohort received HBV at birth, only 72 (5%) of the neonates who died were HBV-vaccinated at birth ($P < 0.01$). We found no significant difference in the proportion of HBV-vaccinated (31%) and unvaccinated (35%) neonates dying of unexpected causes ($P = 0.6$). Further we could not identify a plausible causal or temporal relationship between HBV administration and death for the 22 vaccinated neonates who died unexpectedly. A relationship between HBV and neonatal death was not identified.

Euler GL, Copeland J, Williams WW. Impact of four urban perinatal hepatitis B prevention programs on screening and vaccination of infants and household members. *Am J Epidemiol* 2003; 157:747-753.

Epidemiology and Surveillance Division, National Immunization Program, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA. gle0@cdc.gov

During 1992-2000, the authors studied compliance with perinatal hepatitis B prevention recommendations, including vaccination of household contacts, at four metropolitan sites in Connecticut, Georgia, Texas, and Michigan. Demographic and hepatitis B-related knowledge, attitudes, practices, and barrier data were collected on pregnant women testing positive for hepatitis B surface antigen and on their infants, children, and household and sexual contacts. Generalized estimating equations with repeated measures in a multivariable model were used to obtain adjusted relative risks of household noncompliance. In 1,458 households studied, 1,490 infants and 3,502 other contacts were identified. Among infants, vaccination start/finish rates were 92%/72%, and 73% were serotested postvaccination. Prevacination serotesting rates among contacts were 22% preenrollment and 47% postenrollment. Among 2,519 contacts whose immunity status was susceptible or unknown, the vaccination start/finish rate was 45%/41%. Site-specific adjusted relative risks of household noncompliance compared with Texas were 2.14 (Michigan), 1.96 (Georgia), and 1.30 (Connecticut). Mother's birth in the United States increased the relative risk of household noncompliance (1.32). Home visits, implemented only in Texas, most likely account for higher compliance rates in that state. Findings may indicate that many perinatal programs could achieve higher overall rates of infant and contact identification; pre- and postvaccination serologic testing in contacts and infants, respectively; and contact hepatitis B vaccination.

Gaetskii SA, Seniuta NB, Syrtsev AV, Abdullaev OM, Aliev DA, Kerimov AA, Yamashita M, Hayami M, Kato T, Mizokami M. Analysis of some viral infections, transmitted by parenteral and sexual routes, in the Republic of Azerbaijan. *Vopr Virusol* 1999; 44:232-236. [Article in Russian]

Representatives of various population groups in Azerbaijan were tested for infection with human T-lymphotropic (HTLV-I and HTLV-II) and hepatotropic viruses (HCV and HBV). A total of 835 sera were studied by screening and specific tests for virus-specific antibodies and/or antigens. Thirty-five DNA specimens from peripheral blood lymphocytes were analyzed in the PCR for HTLV-I-specific sequences. No HTLV-I or HIV were detected, but two cases with integration of the HTLV-I LTR gene into cellular DNA genome were detected. A high rate of infection with hepatitis B and C was revealed. The level of anti-HCV was 8.7%, HBsAg 4.1%, and antiHBs 23.4%. Six cases with double HBV-HCV infection were detected. High values of ALT among HBV/HCV-seronegative subjects prompts their testing for other types of hepatitis viruses.

Giles ML, Sasadeusz JJ, Garland SM, Grover SR, Hellard ME. An audit of obstetricians' management of women potentially infected with blood-borne viruses. *Med J Aust* 2004; 180:328-332.

Clinical Microbiology and Infectious Disease, Royal Women's Hospital, 132 Grattan Street, Parkville, Victoria 3050, Australia. michelle.giles@rwh.org.au

The objective was to assess obstetricians' current antenatal screening practices for blood-borne viruses (hepatitis B, hepatitis C and HIV) and how they manage pregnant women infected with a blood-borne virus. Design and participants: national cross-sectional survey conducted between September 2002 and January 2003. All obstetricians (n = 767) registered with the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) were mailed a questionnaire assessing their antenatal screening practices and knowledge of management of women potentially infected with a blood-borne virus. Concordance of clinical practice with RANZCOG recommendations and current evidence-based guidelines. 523 obstetricians (68% response rate) completed the questionnaire. Fifty-one per cent of respondents said they would always offer HIV screening and 60% would always offer HCV screening. For HIV-infected women, 36% of obstetricians would always recommend elective caesarean section and 33% would always avoid rupture of membranes. Despite a lack of evidence, 34% of obstetricians advise patients that the risk of HBV transmission is increased with breastfeeding, and 47% give the same advice about HCV transmission. There is some discordance between the RANZCOG antenatal screening recommendations for HCV and HIV and current practice. Knowledge about the management of HIV-infected women could be improved, and more obstetricians need to be aware that current evidence suggests there is no increased risk of transmission of HBV or HCV with breastfeeding.

Glikberg F, Brawer-Ostrovsky J, Ackerman Z. Very high prevalence of hepatitis B and C in Bukharian Jewish immigrants to Israel. *J Clin Gastroenterol* 1997; 24:30-33.

Department of Family Medicine, Hadassah University Hospital, Mount Scopus, Jerusalem, Israel.

In Israel, the reported prevalence of hepatitis-C virus (HCV) infection among blood donors is 0.44%. As we found a high prevalence of chronic hepatitis-B virus (HBV) and HCV infection in Jewish immigrants from Uzbekistan and Tajikistan (Bukharian Jews) among our general patient population, we determined the prevalence of HBV and HCV infection among 'healthy' Bukharian Jewish immigrants by screening for HBV and HCV markers and risk factors in a population of Bukharian Jews in north Jerusalem. A total of 27 (26.5%) of 102 patients were anti-HCV positive (by ELISA and confirmation tests). The HCV positive patients were older and had a higher rate of

liver enzyme abnormalities than were the HCV-negative patients (56.5 +/- 2.3 versus 47.6 +/- 1.8, $p = 0.003$; and 14 of 27 versus 7 of 75, $p < 0.01$, respectively). HCV-positive patients with liver enzyme abnormalities were younger than HCV-positive patients without liver enzyme abnormalities (52.5 +/- 3.0 versus 62.8 +/- 2.8, $p = 0.02$). Sixteen patients (15.7%) were hepatitis-B surface antigen (HBsAg) carriers, and only two of these HBsAg carriers had liver enzyme abnormalities. None of the HCV-positive patients were HBsAg carriers (0 of 27 among HCV-positive patients versus 16 of 75 among HCV-negative patients, $p = 0.0055$). Past infection with HBV was found in 67 examinees (66%) (45 of 75 HCV-negative patients and 22 of 27 HCV-positive patients, $p = 0.058$). However, similar proportions of patients from both groups had past and present exposure to HBV [61 (81.3%) of 75 among HCV-negative patients versus 22 (81.5%) of 27 among HCV-positive patients]. Only 14 patients (13.7%) had no exposure to either HCV or HBV. Possible risk factors were use of nondisposable needles during mass vaccination in the U.S.S.R. or possible intrafamilial spread. The study concluded that immigrant Jews from former Asiatic U.S.S.R. republics have the highest rate of HCV positivity ever reported, and many of them have past and present HBV infection. Measures to prevent intrafamilial transmission of both viruses should be instituted.

Goldstein ST, Zhou F, Hadler SC, Bell BP, Mast EE, Margolis HS. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. *Int J Epidemiol* 2005; 34:1329-1339.

Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA.
sgoldstein@cdc.gov

Limited data are available regarding global hepatitis B virus (HBV)-related morbidity and mortality and potential reduction in disease burden from hepatitis B vaccination. A model was developed to calculate the age-specific risk of acquiring HBV infection, acute hepatitis B (illness and death), and progression to chronic HBV infection. HBV-related deaths among chronically infected persons were determined from HBV-related cirrhosis and hepatocellular carcinoma (HCC) mortality curves, adjusted for background mortality. The effect of hepatitis B vaccination was calculated from vaccine efficacy and vaccination series coverage, with and without administration of the first dose of vaccine within 24 h of birth (i.e. birth dose) to prevent perinatal HBV infection. For the year 2000, the model estimated 620,000 persons died worldwide from HBV-related causes: 580,000 (94%) from chronic infection-related cirrhosis and HCC and 40,000 (6%) from acute hepatitis B. In the surviving birth cohort for the year 2000, the model estimated that without vaccination, 64.8 million would become HBV-infected and 1.4 million would die from HBV-related disease. Infections acquired during the perinatal period, in early childhood (< 5 years old), and ≥ 5 years of age accounted for 21, 48, and 31% of deaths, respectively. Routine infant hepatitis B vaccination, with 90% coverage and the first dose administered at birth would prevent 84% of global HBV-related deaths. Globally, most HBV-related deaths result from the chronic sequelae of infection acquired in the perinatal and early childhood periods. Inclusion of hepatitis B vaccine into national infant immunization programs could prevent > 80% of HBV-related deaths.

Gong XH, Liu LR, Jia L, Li YH, Xing YL, Wang QY. Epidemiological effect of hepatitis B immunization among newborn babies in Beijing. *Zhonghua Gan Zang Bing Za Zhi* 2003; 11:201-202. [Article in Chinese]

The objective was to evaluate the epidemiological effect of hepatitis B immunization among newborn babies in Beijing. A multistage sampling method was used for the collection of immunization cards, field epidemiological survey on hepatitis B virus (HBV) immunization of children, analysis of infectious disease reports. HBsAg, anti-HBs and anti-HBc levels were detected by solid phase radioimmunoassays (SPRIA). The incidence of hepatitis B in children of 0

to 14 years at the beginning of HBV immunization was 18.59 to 20.52/100,000, and declined to 0.39 to 2.38/100,000 in 2000 ($\chi^2 = 58.26$, $P < 0.01$). The HBsAg carrying rate of the children decreased from 2.82% to 0.60%, about 80.00% after vaccination ($\chi^2 = 10.75$, $P < 0.01$). Hepatitis B vaccination of newborn babies is an effective measure for prevention and control of hepatitis B virus infection.

Grosheide PM, den Ouden AL, Verrips GH, Conyn-van Spaendonck MA, Loeber JG, Verloove-Vanhorick SP. Evaluation of the hepatitis B prevention program in newborn infants. I. National data, 1990. *Ned Tijdschr Geneeskde* 1993; 137:2589-2594. [Article in Dutch]

Centrum voor Infectieziekten Epidemiologie, Rijksinstituut voor Volksgezondheid en Milieuhygiene, Bilthoven.

The aim was to evaluate the effectiveness of the national programme for prevention of perinatal hepatitis B infections. Setting: the regional public health laboratories and provincial immunization administrations in the Netherlands. Design: retrospective evaluation. Starting October 1989 routine screening of pregnant women for HBsAg was performed and passive-active immunisation of infants of HBsAg-positive mothers was added to the national immunisation programme. Infants receive hepatitis B immunoglobulin at birth and hepatitis B vaccine at 3,4,5, and 11 months of age, concomitant with the DTP-polio vaccine. The effectiveness of screening and intervention in 1990 was evaluated. Screening covered about 85% of the pregnant population and the prevalence (0.44%) was less than expected. About 60% of the infants born to HBsAg-positive mothers were registered for vaccination. Of these infants the average coverage was 83% for immunoglobulin, and 90%, 86%, 80% and 55% for the four successive hepatitis B vaccinations. There was considerable delay in vaccine administration; frequently doses were administered later than recommended. Compliance with screening and vaccination appeared incomplete. Recommendations for the simplification of the current programme are made.

Grosheide PM, Klokman-Houweling JM, Conyn-van Spaendonck MA. Programme for preventing perinatal hepatitis B infection through screening of pregnant women and immunisation of infants of infected mothers in The Netherlands, 1989-92. National Hepatitis B Steering Committee. *BMJ* 1995; 311:1200-1202.

Department of Infectious Diseases Epidemiology, National Institute of Public Health and Environmental Protection, Bilthoven, Netherlands.

The objective was to launch a programme for the prevention of perinatal infection with hepatitis B in the Netherlands. Design: Routine antenatal screening and intervention programme. Setting: community antenatal programme, the Netherlands. Subjects: infants of mothers who were carriers of hepatitis B detected by routine screening. Interventions: infants of infected mothers received hepatitis B immunoglobulin at birth and four doses of hepatitis B vaccine in conjunction with routine immunisation at 3, 4, 5, and 11 months of age. Main outcome measures: results of screening and immunisation from 1989-92. The coverage of screening increased from 46% in 1989 to 84% in 1992. Hepatitis B surface antigen was detected in 2145 women (0.44%). The coverage of postnatal immunoprophylaxis in 1645 neonates born to mothers who were carriers of hepatitis B was 85% (1391); in 3% (42) there was a delay in administration of immunoglobulin of over 24 hours. In 1991, 96% (537), 95% (532), 94% (525), and 87% (489) of the infants received the first, second, third, and fourth dose of vaccine, respectively. There was considerable variation in the timing of vaccination; 17% (258) of the infants received their first dose more than two weeks late. Of the 59% (583) of infants who received the fourth dose more than two weeks beyond target age, 14% (141) also received their first dose too late. It was concluded that a prevention programme for perinatal hepatitis B in an area of low prevalence, when incorporated into existing

health care, is feasible and achieves satisfactory coverage rates. Intensive follow up is needed to improve adherence to the immunisation schedule.

Hipgrave DB, Maynard JE, Biggs B-A. Improving birth dose coverage of hepatitis B vaccine. *Bull WHO* 2006; 84:65-70.

UNICEF Indonesia, Wisma Metropolitan 11, Jalan Sudirman 31, Jakarta 12920, Indonesia.
dhipgrave@unicef.org

Administration of a birth dose of hepatitis B vaccine (HepB vaccine) to neonates is recommended to prevent mother-to-infant transmission and chronic infection with the hepatitis B virus (HBV). Although manufacturers recommend HepB vaccine distribution and storage at 2-8 degrees C, recognition of the heat stability of hepatitis B surface antigen stimulated research into its use after storage at, or exposure to, ambient or high temperatures. Storage of HepB vaccine at ambient temperatures would enable birth dosing for neonates delivered at home in remote areas or at health posts lacking refrigeration. This article reviews the current evidence on the thermostability of HepB vaccine when stored outside the cold chain (OCC). The reports reviewed show that the vaccines studied were safe and effective whether stored cold or OCC. Field and laboratory data also verifies the retained potency of the vaccine after exposure to heat. The attachment of a highly stable variety of a vaccine vial monitor (measuring cumulative exposure to heat) on many HepB vaccines strongly supports policies allowing their storage OCC, when this will benefit birth dose coverage. We recommend that this strategy be introduced to improve birth dose coverage, especially in rural and remote areas. Concurrent monitoring and evaluation should be undertaken to affirm the safe implementation of this strategy, and assess its cost, feasibility and effect on reducing HBV infection rates. Meanwhile, release of manufacturer data verifying the potency of currently available HepB vaccines after exposure to heat will increase confidence in the use of vaccine vial monitors as a managerial tool during storage of HepB vaccine OCC.

Hipgrave DB, Nguyen TV, Vu MH, Hoang TL, Do TD, Tran NT, Jolley D, Maynard JE, Biggs BA. Hepatitis B infection in rural Vietnam and the implications for a national program of infant immunization. *Am J Trop Med Hyg* 2003; 69:288-294.

International Health Unit, The Burnet Institute, Alfred Medical Research & Education Precinct, Melbourne, Australia.

To ascertain hepatitis B virus (HBV) infection rates for Vietnam, we surveyed HBV markers in two districts of Thanh Hoa province. We randomly selected 536 infants (9- < or = 18 months old), 228 children (4 to < or = 6 years old), 219 adolescents (14 to < or = 16 years old), and 596 adults (25 to < or = 40 years old). On questioning, none of those surveyed had received vaccine against HBV. Hepatitis B virus surface antigen (HBsAg) and total HBV core antibody (anti-HBc) were measured in all specimens, and HBV e antigen (HBeAg) in those positive for HBsAg, and HBV surface antibody (anti-HBs) were measured in all others. Current infection (HBsAg+) rates were infants = 12.5%, children = 18.4%, adolescents = 20.5%, and adults = 18.8%. Current or previous infection (HBsAg+, anti-HBc+, or anti-HBs+) increased with age (infants = 19.6%, children = 36.4%, adolescents = 55.3%, adults = 79.2%). Rates of HBeAg among those HBsAg+ were infants = 85.1%, children = 88.1%, adolescents = 71.1%, and adults = 30.4%. The epidemiology of HBV in Vietnam resembles that of many southeast Asian nations before introduction of vaccine. Immunization of newborns will have enormous impact on HBV-related morbidity and mortality there.

Hipgrave DB, Tran TN, Huong VM, Dat DT, Nga NT, Long HT, VAN NT, Maynard JE, Biggs BA. Immunogenicity of a locally produced hepatitis B vaccine with the birth dose stored outside the cold chain in rural Vietnam. *Am J Trop Med Hyg* 2006; 74:255-260.

International Health Unit, Burnet Institute, Alfred Medical Research and Education Precinct, Prahran, Victoria, Australia; Department of Medicine (Royal Melbourne Hospital/Western Hospital), University of Melbourne, Royal Melbourne Hospital, Parkville, Australia; Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden; National Institute of Hygiene and Epidemiology, Hanoi, Vietnam; Program for Appropriate Technology in Health, Hanoi, Vietnam.

The heat stability of hepatitis B vaccine (HepB vaccine) should enable its storage outside the cold chain (OCC), increasing access to the birth dose in areas lacking refrigeration. We compared the immunogenicity of a locally produced vaccine among infants who received three doses stored within the cold chain (n = 358) or for whom the first dose was stored OCC for up to one month (n = 748). Serum was collected from these infants at age 9-18 months. The vaccine was protective in 80.3% of all infants. There were no differences in the prevalence of a protective level of antibody or antibody titer among groups of infants according to storage strategy. Differences in antibody titer between certain groups of infants could be explained by different vaccination schedules. Where birth dose coverage will be improved, HepB vaccine can be taken OCC for up to one month without affecting its immunogenicity.

Huang K, Lin S. Nationwide vaccination: a success story in Taiwan. *Vaccine* 2000 18; 18(Suppl 1):S35-S38.

Department of Microbiology, National Cheng Kung University Medical College, Tainan, Taiwan.

In the early 1980s, 15-20% of the population of Taiwan were estimated to be hepatitis B virus (HBV) carriers. A programme of mass vaccination against hepatitis B was therefore launched in 1984. In the first 2 years, newborns of all HBV surface antigen (HBsAg)-positive mothers were vaccinated. Since 1986, all newborns, and then year by year pre-school children, primary school children, adolescents, young adults and others have also been vaccinated. Vaccination coverage is over 90% for newborns, with 79% of pregnant women screened for HBsAg. The proportion of babies born to highly infectious carrier mothers who also became carriers decreased from 86-96% to 12-14%; the decrease was from 10-12% to 3-4% for babies of less infectious mothers. Between 1989 and 1993, the prevalence of HBsAg in children aged 6 years also fell from 10.5 to 1.7%. The average annual incidence of hepatocellular carcinoma in children aged 6-14 years decreased significantly from 0.7 per 100,000 in 1981-1986 to 0.36 per 100,000 in 1990-1994 (P < 0.01). Similarly, the annual incidence of hepatocellular carcinoma in children aged 6-9 years declined from 0.52 per 100,000 for those born in 1974-1984 to 0.13 per 100,000 for those born in 1986-1988 (P < 0.001). The mass vaccination programme is highly effective in controlling chronic HBV infection and in preventing liver cancer in Taiwan. If a coverage rate of 90% of all newborns vaccinated against hepatitis B can be maintained, by the year 2010 the carrier rate in Taiwan is expected to decline to < 0.1%.

Iashina TL, Favorov MO, Shakhgil'dian IV, Firsova SN, Eraliev AE, Zhukova LD, Reznichenko RG. The prevalence of the markers of viral hepatitis B and delta among the population in regions differing in the level of morbidity. *Vopr Virusol* 1992; 37:194-196. [Article in Russian]

From two regions differing by the levels of incidence of hepatitis B, 2019 blood serum specimens from normal population were examined for markers of HBV infection. In Moscow, among 1040 samples examined HBsAg was found in 2.0%, anti-HBs in 10.0%, anti-HBc in the absence of

HBsAg and anti-HBs in 4.5%. In the Osh Province of Kirgizstan, among 979 subjects examined the same markers were found in 10.3%, 22.4%, and 14.0%, respectively. In this area, HBsAg was detected most frequently among infants (14.9% in infants under 1 year), in whom HBs-antigenemia was combined with the presence of HBeAg in 54.5% and with anti-HBc-IgM in 69.2%. Antibody to delta antigen (anti-delta) was found in 24 (25.8%) out of 93 HBsAg-positive subjects in the Osh Province but in none of 21 subjects with HBs-antigenemia in Moscow.

Ikoev VN, Gorbunov IA, Anan'ev VA, Noskova AV, Titov IA. The vaccinal prevention of the HBsAg carrier state among newborn infants. *Vopr Virusol* 1991; 36:452-454. [Article in Russian]

The paper presents the data on the time course of HBsAg carrier state in babies born to mothers with antigenemia indicating the dependence of the pattern of the antigen carrier state in babies upon the time of its primary detection. The stable (chronic) HBsAg carrier state in babies was shown to be formed after the first 3 months of life which attests to the necessity of using a vaccine against hepatitis B (HB) for prevention of HBsAg carrier state in newborns. The results of epidemiological survey in 185 babies developing HB with the analysis of all possible factors of their infection contraction are presented. The efficacy of the national plasma vaccine against hepatitis B is evaluated in observations of the newborn babies whose mothers were carriers of HBsAg. It was established that in vaccinated babies after 3 injections of the vaccine at 0, 1, and 6 months the rate of antigen detection was 3.3% and that of antibody 80% whereas in babies of the control group these values were 23.7% and 8.0%, respectively.

Kant L, Hall AJ. Epidemiology of childhood hepatitis B in India: vaccination related issues. *Indian J Pediatr* 1995; 62:635-653.

Division of Epidemiology and Communicable Diseases, Indian Council of Medical Research, New Delhi.

It has been estimated that presently hepatitis B kills more people every day than AIDS kills in a year world-wide. Infection with hepatitis B produces a wide range of manifestations ranging from asymptomatic carriers to persistent infections leading to chronic liver diseases and hepatocellular carcinoma. Availability of effective and safe vaccine has made all this preventable. To formulate on appropriate vaccination strategy for India the epidemiology of hepatitis B needs to be defined. This report critically reviews the available data. The burden of long term sequelae of HBV infection is probably under-diagnosed and under-reported in India. Prevalence studies of HBV markers indicate that India falls under the area of intermediate endemicity. Limited data on age-specific prevalence of HBV markers suggests that the majority of the infection seems to take place below 15 years of age, and most of it under one year. Perinatal transmission appears to contribute significantly to the carrier pool. Childhood vaccination for HB among the general population is the obvious strategy of choice. But more information is required to decide on the timing of the first dose.

Khukhlovich PA, Shakhgil'dian IV, Narkevich MI, Anan'ev VA, Kuzin SN, Sergeeva NA, Khodzhaev ShKh, Iarovoi PI, Drobeniuk ZhA, Iuldashev AK, Khodzhaeva MA, Makmudova ON, Buriev AI, Rakhimov RA, Tuliaganova GM, Khasanova VA, Tsvainer MI, Eliseeva TS, Tuichibaeva MA, Minecheva LV, Kotsaga EI, Nagachevskaya VI, Rafikova NK, Klimenko SM. The vaccinal prophylaxis of hepatitis B among children born to mothers with persistent HBs-antigenemia. *Zh Mikrobiol Epidemiol Immunobiol* 1996; 2:55-59. [Article in Russian]

In Uzbekistan and Moldova 542 children born of HBsAg carriers were immunized against hepatitis B (with vaccine Engerix B according to the immunization schedule of 4 injections). Anti-

HBs antibodies in protective titers were detected by EIA and RIA techniques in 76.7% of children aged 4-5 months after the 3rd injection, in 95.7% of children aged 15-16 months and in 90.0% of children aged 2-2.5 years after the 4th (booster) injection. In the control group (117 nonimmunized children born of HBs carriers) observed during the same period anti-HBs antibodies were detected significantly less frequently (in 7.3%, 11.6% and 12.9% of these children respectively). 1-2 months after the course of immunization was completed 74.1% of the immunized children had high anti-HBs antibody titers (exceeding 1000 IU/ml) with their subsequent decrease by 2-2.5 years of age. In the control group these figures were 27.1% and 29.0% respectively. The index of immunization effectiveness obtained by the comparison of the hepatitis B morbidity rates in both groups was 7.8. No postvaccinal complications were registered.

Kondili LA, Brunetto MR, Maina AM, Argentini C, Chionne P, La Sorsa V, Resuli B, Mele A, Rapicetta M. Clinical and molecular characterization of chronic hepatitis B in Albania: a country that is still high endemic for HBV infection. *J Med Virol* 2005; 75:20-26.

Department of Infectious, Parasitic, and Immunomediated Diseases, Viral Hepatitis Unit, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy.

Albania is a Mediterranean country, still with a high endemicity level of hepatitis B virus (HBV) infection. The chronic hepatitis B profile was characterized in this geographical area and used as a model to investigate the impact of endemicity level on the prevalence of the two major forms of chronic hepatitis B (HBeAg-positive and HBeAg-negative chronic hepatitis B). A cross-sectional study was conducted among 62 chronic hepatitis B patients consecutively admitted to the most important tertiary health care center for the diagnosis and treatment of liver disease in Albania. HBV-DNA was measured with an in-house PCR with a sensitivity of 10⁴ copies/ml which uses primers encompassing the pre-core/core region. PCR products were subjected to sequencing and oligohybridization assay. Of the 62 patients, 75.8% had HBeAg-negative chronic hepatitis B. Genotype D was found in all 39 patients with detectable HBV viremia, for whom the heterogeneity of the region modulating HBeAg expression was assessed. Basic core promoter (BCP) mutations (1762/1764) were observed more often in anti-HBe-positive and older patients. In more than 90% of the HBeAg-negative chronic hepatitis B patients with detectable viremia, HBV that carries the G to A pre-core mutation at nucleotide 1896 was found. Patients with HBeAg-positive chronic hepatitis B were younger than HBeAg-negative chronic hepatitis B patients, and for symptomatic and asymptomatic liver-disease patients, the age of peak prevalence was at least 10 years lower for HBeAg-positive chronic hepatitis B patients. In conclusion, the virological and clinical pattern of chronic hepatitis B in Albania is similar to that observed in other Mediterranean countries; it seems to be independent of the HBV endemicity level.

Koyama T, Matsuda I, Sato S, Yoshizawa H. Prevention of perinatal hepatitis B virus transmission by combined passive-active immunoprophylaxis in Iwate, Japan (1981-1992) and epidemiological evidence for its efficacy. *Hepatol Res* 2003; 26:287-292.

Health Service Association, Iwate, Japan

In a model area in Iwate, Japan, with a population of 1.4 million, the immunoprophylaxis of perinatal transmission of hepatitis B virus (HBV) was started in 1981 and covered > 60% of all births already in 1986 when it became mandatory by the national program. Babies born to mothers who carried hepatitis B surface antigen (HBsAg) along with hepatitis B e antigen (HBeAg) in serum received hepatitis B immune globulin (HBIG) at birth and 2 months as well as vaccine at 2, 3 and 5 months after birth. In 1985, 39 of 45 (86.7%) babies who received immunoprophylaxis did not develop the HBV carrier state. During 1986-1992, 100286 of 104493 (96.0%) expecting mothers received tests for HBsAg, and it was detected in 1242 (1.2%) of them. Among the mothers carrying HBsAg, 257 (20.7%) were positive for HBeAg and their babies received

immunoprophylaxis. Reflecting effects of immunoprophylaxis, the prevalence of HBsAg decreased from 0.75% (78/10437) in the children born during 1978-1980 to 0.23% (46/20812) in those during 1981-1985 ($P < 0.001$), and further to 0.04% (12/32049) in those during 1986-1990 ($P < 0.001$). The prevalence rates of antibody to HBsAg (anti-HBs) were 1.52, 0.79 and 0.85% in the three groups of children ($P < 0.001$ between those during 1978-1980 and the others). The frequency of antibody to HBV core in the children with anti-HBs diminished remarkably from 76.7% (23/30) in those born in 1971 to 9.0% (6/67) in those born in 1990, thereby indicating a marked decrease in resolved infection and increase in acquired immunity to HBV as the results of immunoprophylaxis.

Kuru U, Turan O, Kuru N, Saglam Z, Ceylan Y, Nurluoğlu M, Agacfidan A. Prevalence of hepatitis B virus infection in pregnant Turkish women and their families. *Eur J Clin Microbiol Infect Dis* 1996; 15:248-251.

Department of Pediatrics, Bakirkoy Maternity and Children's Hospital, Social Insurance Foundation, Bakirkoy, Istanbul, Turkey.

A total of 5,366 pregnant Turkish women were screened for hepatitis B surface antigen (HBsAg) and 225 (4.2%) of them were found to be positive. Hepatitis B e antigen (HBeAg) was detected in 6.2% of HBsAg-positive pregnant women. The overall prevalence of HBsAg and antibody to HBsAg (anti-HBs) among the spouses, previous children, mothers and first degree relatives of the HBsAg-positive pregnant women was 56%, 49%, 79% and 74% respectively. The prevalence of HBsAg is thus high in pregnant Turkish women with familial clustering of hepatitis B virus infection.

Kuzin SN, Ikoev VN, Shakhgil'dian IV, Gorbunov MA, Farber NA, Mikhailov MI, Braginskii DM, Karetnyi IuV, Buriev Ala, Khalitova KA, et al. Patterns in perinatal infection with the hepatitis B virus in areas contrasted by the level of HBsAg and HBeAg carriage. *Vopr Virusol* 1990; 35:304-306. [Article in Russian]

In 1984-1988, the levels of HBsAg carrier state and the status of the 'e'-system components in pregnant women in Moscow and in the Uzbek SSR, as well as the rate of infection with hepatitis B virus (HBV) in babies born to women carriers of HBsAg in regions with different levels of HBsAg and HBeAg carrier state were studied. The levels of HBsAg carrier state among pregnant women were different in Moscow and Uzbekistan (1.1% and 6.9%, respectively). It was noted that in female HBsAg carriers in these regions the rate of HBeAg detection differed greatly: 5.2% in Moscow and 13.9% in Uzbekistan. The frequency of perinatal infection with HBV in Moscow was 26.1%, in Uzbekistan 40.0%, the frequency of persistent carrier state of HBsAg in the infected babies of Uzbekistan was 16.0%. The possibility of formation of HBsAg persistence in babies born to women with HBsAg and anti-HBe in the blood was demonstrated. The problem of the use of specific prophylaxis measures to prevent perinatal transmission of HBV is discussed.

Lazizi Y, Badur S, Perk Y, Ilter O, Pillot J. Selective unresponsiveness to HBsAg vaccine in newborns related with an in utero passage of hepatitis B virus DNA. *Vaccine* 1997; 15:1095-1100.

Unité d'Immunologie Microbienne, Hôpital Antoine Bécclère, WHO Center of Reference and Research for Viral Hepatitis, Clamart, France.

Thirty four out of 158 (22%) newborns to mothers chronically infected by the hepatitis B virus (HBV) did not produce antibodies (Ab) to HBsAg 1 month after the last injection of the HBV vaccine supplemented with HBV specific immunoglobulins. At birth, HBV genome was detected by polymerase chain reaction (PCR) in the peripheral blood mononuclear cells (PBMC) of a large

majority (28 out of 34) of these non-responder newborns but never in the other newborns who responded to the HBsAg vaccine. HBV genome was detected in serum, only in some cases (nine out of 34) and never in the absence of HBV DNA in PBMC. For nine out of 14 followed newborns, the absence of response was transitory since anti-HBs Abs appeared after 15 months, without booster, while the HBV genome had disappeared. Unresponsiveness was specific to the HBV envelope protein since all late responders and 15-months-non-responders to the HBsAg vaccine produced normal levels of Abs to the three poliovirus serotypes, to tetanus toxoid and to the pneumococcus polysaccharides. An in utero induced immune tolerance to low doses of HBsAg appears as the most plausible hypothesis to explain this unresponsiveness to HBV vaccine.

Lee C, Gong Y, Brok J, Boxall EH, Gluud C. Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis. *BMJ* 2006; 332:328-336.

Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Copenhagen University Hospital, Denmark.

The objective was to evaluate the effects of hepatitis B vaccine and immunoglobulin in newborn infants of mothers positive for hepatitis B surface antigen. Design: Systematic review and meta-analysis of randomised clinical trials. Data sources: electronic databases and hand searches. Randomised clinical trials were assessed for methodological quality. Meta-analysis was undertaken on three outcomes: the relative risks of hepatitis B occurrence, antibody levels to hepatitis B surface antigen, and adverse events. 29 randomised clinical trials were identified, five of which were considered high quality. Only three trials reported inclusion of mothers negative for hepatitis B e antigen. Compared with placebo or no intervention, vaccination reduced the occurrence of hepatitis B (relative risk 0.28, 95% confidence interval 0.20 to 0.40; four trials). No significant difference in hepatitis B occurrence was found between recombinant vaccine and plasma derived vaccine (1.00, 0.71 to 1.42; four trials) and between high dose versus low dose vaccine (plasma derived vaccine 0.97, 0.55 to 1.68, three trials; recombinant vaccine 0.78, 0.31 to 1.94, one trial). Compared with placebo or no intervention, hepatitis B immunoglobulin or the combination of plasma derived vaccine and hepatitis B immunoglobulin reduced hepatitis B occurrence (immunoglobulin 0.50, 0.41 to 0.60, one trial; vaccine and immunoglobulin 0.08, 0.03 to 0.17, three trials). Compared with vaccine alone, vaccine plus hepatitis B immunoglobulin reduced hepatitis B occurrence (0.54, 0.41 to 0.73; 10 trials). Hepatitis B vaccine and hepatitis B immunoglobulin seem safe, but few trials reported adverse events. Hepatitis B vaccine, hepatitis B immunoglobulin, and vaccine plus immunoglobulin prevent hepatitis B occurrence in newborn infants of mothers positive for hepatitis B surface antigen.

Lee SS, Young BW, Wong KH, Lim WL. The implication of a reduced-dose hepatitis B vaccination schedule in low risk newborns. *Vaccine* 2002; 20:3752-3754.

Department of Health, Hong Kong SAR Government, Hong Kong, China. ss_lee@dh.gov.hk

Five hundred and seventy-four babies born to HBsAg negative mothers in Hong Kong received either a regular (5 µg) or reduced (2.5 µg) three-dose regimen of recombinant hepatitis B vaccine. A significantly higher anti-HBs positivity rate (> or = 10 mIU/ml), geometric mean titer (GMT) and the maintenance of a high anti-HBs level (> or = 100 mIU/ml) were observed with the regular-dose regimen. The differences persisted, however, only up to 1 year post-vaccination. Over an 8-year period, only 1% of the vaccinees demonstrated anti-HBc seroconversion and none had become HBsAg positive. The long-term efficacy of the reduced-dose regimen was confirmed, even in an HBV endemic population.

Levin CE, Nelson CM, Widjaya A, Moniaga V, Anwar C. The costs of home delivery of a birth dose of hepatitis B vaccine in a prefilled syringe in Indonesia. *Bull World Health Organ* 2005; 83:456-461.

Program for Appropriate Technology in Health, Seattle, WA 98107, USA. clevin@path.org

The objective was to provide global policy-makers with decision-making information for developing strategies for immunization of infants with a birth dose of hepatitis B vaccine, this paper presents a retrospective cost analysis, conducted in Indonesia, of delivering this vaccine at birth using the Uniject prefill injection device. Incremental costs or cost savings associated with changes in the hepatitis B immunization programme were calculated using sensitivity analysis to vary the estimates of vaccine wastage rates and prices for vaccines and injection devices, for the birth dose of hepatitis B vaccine. The introduction of hepatitis B vaccine prefilled in Uniject (HB-Uniject) single-dose injection devices for use by midwives for delivering the birth dose is cost-saving when the wastage rate for multidose vials is greater than 33% (Uniject is a trademark of BD, Franklin Lakes, NJ, USA). The introduction of HB-Uniject for birth-dose delivery is economically worthwhile and can increase coverage of the critical birth dose, improve resource utilization, reduce transmission of hepatitis B and promote injection safety.

Li XM, Shi MF, Yang YB, Shi ZJ, Hou HY, Shen HM, Teng BQ. Effect of hepatitis B immunoglobulin on interruption of HBV intrauterine infection. *World J Gastroenterol* 2004; 10:3215-3217.

Department of Obstetrics and Gynecology, Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou 510630, Guangdong Province, China. tigerlee777@163.net
The aim was to evaluate the efficacy of hepatitis B immunoglobulin (HBIG) in interrupting hepatitis B virus (HBV) intrauterine infection during late pregnancy. We allocated 112 HBsAg positive pregnant women into 2 groups randomly. Fifty seven cases in the HBIG group received 200 IU (unit) HBIG intramuscularly every 4 wk from the 28 wk of gestation to the time of delivery, while 55 cases in the control group received no special treatment. HBsAg, HBeAg, HBcAb, HBeAb, HBsAb and HBV DNA levels were tested in the peripheral blood specimens from all of the mothers at 28 wk of gestation, just before delivery, and in blood from their newborns within 24 h before administration of immune prophylaxis. The intrauterine infection rate in HBIG group and control group were 10.5% and 27.3%, respectively, with significant difference ($P < 0.05$). It showed ascendant trend as HBV DNA levels in the peripheral blood increased before delivery. HBIG is potent to cut down HBV intrauterine infection rate significantly when administered to pregnant women regularly during late pregnancy. The possibility of HBV intrauterine infection increases if maternal blood HBV DNA $> \text{ or } = 10^8$ copies/ml.

Li XM, Yang YB, Hou HY, Shi ZJ, Shen HM, Teng BQ, Li AM, Shi MF, Zou L. Interruption of HBV intrauterine transmission: a clinical study. *World J Gastroenterol* 2003; 9:1501-1503.

Department of Obstetrics and Gynecology, The Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou 510630, Guangdong Province, China. tigerli777@163.com

The aim was to investigate the effect of hepatitis B virus (HBV) specific immunoglobulin (HBIG) and lamivudine on HBV intrauterine transmission in HBsAg positive pregnant women. Each subject in the HBIG group (56 cases) was given 200 IU HBIG intramuscularly (i.m.) every 4 weeks from 28-week (wk) of gestation, while each subject in the lamivudine group (43 cases) received 100 mg lamivudine orally (po.) every day from 28-wk of gestation until the 30th day after labor. Subjects in the control group (52 cases) received no specific treatment. Blood specimens were tested for HBsAg, HBeAg, and HBV-DNA in all maternities at 28-wk of gestation, before delivery, and in their newborns 24 hours before the administration of immune prophylaxis.

Reductions of HBV DNA in both treatments were significant ($P < 0.05$). The rate of neonatal intrauterine HBV infection was significantly lower in HBIg group (16.1 %) and lamivudine group (16.3 %) compared with control group (32.7 %) ($P < 0.05$), but there was no significant difference between HBIg group and lamivudine group ($P > 0.05$). No side effects were found in all the pregnant women or their newborns. The risk of HBV intrauterine infection can be effectively reduced by administration of HBIg or lamivudine in the 3rd trimester of HBsAg positive pregnant women.

Lin HH, Wang LY, Hu CT, Huang SC, Huang LC, Lin SS, Chiang YM, Liu TT, Chen CL. Decline of hepatitis B carrier rate in vaccinated and unvaccinated subjects: sixteen years after newborn vaccination program in Taiwan. *J Med Virol* 2003; 69:471-474.

Department of Gastroenterology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan.
hoholin@ms10.hinet.net

Taiwan was an endemic area for hepatitis B virus (HBV) infection, and related liver diseases cause a significant drain of public resources. To control the endemic, a nation-wide newborn vaccination program was started in 1985. We reviewed the results of the annual survey for HBV surface antigen (HBsAg) performed in freshmen class of two high schools in Hualien, eastern Taiwan, from 1991 to 2001. A total of 10,194 students, most of them 15 years old, were tested for serum HBsAg using enzyme immunoassays. There is a significant trend ($P < 0.0001$) of decreasing HBsAg carrier rate from 20.3 to 4.4% in males and 14.3% to 2.4% in females, respectively, over 11 years. The HBsAg carrier rate was 16.0-20.3% in students surveyed during 1991-1993 (born more than 6 years before the start of the national vaccination program), which decreased to 7.7-11.9% during 1994-1999 (born 1-6 years before the program). It further declined to 4.7% and 3.4% in 2000 and 2001 (born after the start of the program). The HBsAg carrier rate in male students was significantly higher than that in female students in most of the years. The HBV newborn vaccination program not only successfully prevented most of the perinatal transmission of HBV but also reduced horizontal transmission of HBV to children born up to 6 years before the start of the program. Also, the protection persisted for at least 15 years.

Linder N, Vishne TH, Levin E, Handsher R, Fink-Kremer I, Waldman D, Levine A, Ashkenazi S, Sirota L. Hepatitis B vaccination: long-term follow-up of the immune response of preterm infants and comparison of two vaccination protocols. *Infection* 2002; 30:136-139.

Dept. of Neonatology, Schneider Children's Medical Center of Israel, Petah Tiqva.
linderm@netvision.net.il

We conducted a 3-year follow-up study of long-term antibody persistence following vaccination of low-risk preterm infants with recombinant hepatitis B vaccine (HBV). Two three-dose protocols were compared: vaccination beginning within 24 h of birth to initial vaccination delayed until a weight of 2,000 g was reached. The study population included 136 children, divided into three groups: children born prematurely (≤ 35 weeks, $n = 57$), children born at term (≥ 37 weeks, $n = 39$), both groups receiving the first dose of HBV within 24 h of birth, and children born prematurely (≤ 35 weeks, $n = 40$), who received the first dose of HBV when a weight of 2,000 g was reached. All infants received the second hepatitis vaccination 1 month after the first, and the third dose 6 months after the first. Hepatitis B surface antibody (AntiHBs) was measured at an age of 3-3.5 years (at least 2.5 years after completion of the three-dose HBV series). An AntiHBs level of ≥ 10 IU/l was considered positive. At 3-3.5 years of age, a higher percentage of the premature-delayed vaccination group had a positive AntiHBs level (92.5%) compared to both the premature (54.4%, $p < 0.001$) and full-term groups (71.8%, $p < 0.05$) vaccinated soon after birth. The premature-delayed vaccination group also had a significantly higher geometric mean concentration (GMC) (119 vs 14.2 IU/l, $p < 0.001$ and 119 vs 32.7 IU/l, $p < 0.005$, respectively).

Delaying vaccination of premature infants against hepatitis B until a weight of 2,000 g was reached resulted in both a significantly higher percentage of children with positive antibody levels and a significantly higher GMC at 3-3.5 years of age as compared to early-vaccinated preterm and full-term infants. The known short-term advantage of delayed vaccination of preterm infants was shown to persist for at least the first 3 years of life.

Liu Y, Liu X, Kuang J. Comparing immunogenicity and efficacy of two hepatitis B vaccines in newborn infants of hepatitis B surface antigen (+)/hepatitis B e antigen (+) carrier mothers. *Zhonghua Fu Chan Ke Za Zhi* 1999; 34:470-472. [Article in Chinese]

Department of Obstetrics and Gynecology, Sun Sat-Sen Memorial Hospital, Guangzhou 510120, China.

The objective was to investigate a practical diagnostic method in clinic for fetuses infecting with hepatitis B (HBV) and study the mutual effects between fetal infection and clinical factors. Venous blood was drawn from 144 cases of HBV carrier mothers and their neonates. HBV DNA was detected by polymerase chain reaction (PCR) and hybridization, HBV M was detected by enzyme linked immunoadsorbent assay (ELISA), and aspartate aminotransferase/alanine aminotransferase (AST/ALT) was detected by IFCC. Umbilical blood and femoral blood was taken from 40 of 144 neonates for HBV DNA detection. Clinical data, neonatal AST and ALT level were compared between fetal infection group and control group. Results: (1) The fetal infectious rate was 22.9% (33/144). Comparing with peripheral venous blood sample, the sensitivity and positive predictive value of HBV DNA detected in cords was 100.0%, 80.0% respectively. Following up the infants, HBV DNA was found persistently positive in 7 of 28 intrauterine infectious infants 6 approximately 9 months after birth. HBsAg was found changing to be negative 1 month later in the infants with HBsAg positive at birth. (2) The fetal infectious rate in mothers with HBeAg (+) or HBV DNA (+) was 70.5%, 61.1% respectively which was significantly higher than that in mothers with HBeAg (-) or HBV DNA (-). $P < 0.01$. There was no significantly difference in mothers' age, gestational age, delivery way, birth weight (BW), body length (BL), Apgar score between fetal infectious group and control group. (3) The mean value of AST, ALT in fetal infectious group was (61.2 +/- 31.3) IU, (24.7 +/- 14.9) IU respectively, which was significantly higher than that in control group [(55.2 +/- 37.1) IU, (19.0 +/- 10.1) IU]. $P < 0.01$. Conclusions: (1) Detection of HBV DNA in cord blood is a sensitive index for diagnosing fetal infection, however detection of peripheral venous blood is with the significance of making correct diagnosis. (2) HBsAg or HBV DNA positive in mothers is one of the risk factors of intrauterine infection. There is no relationship among fetal infection and mothers' age, gestational age, delivery way, neonates' sex, BW, BL. (3) The liver function of neonates infected with HBV intrauterinely maybe impaired to some extent.

Liu ZH, Men K, Xu D. A follow-up study on correlated factors for intrauterine infection of hepatitis B virus. *Zhonghua Yu Fang Yi Xue Za Zhi* 1997; 31:263-265. [Article in Chinese]

Department of Epidemiology, Fourth Military Medical University, Xi'an.

One hundred and twenty-two pregnant women with positive serum hepatitis B surface antigen (HBsAg) and their infants were followed-up to study the risk factors related to intrauterine infection of hepatitis B virus (HBV). Infants were immunized with three doses of hepatitis B vaccine within 24 hours after birth, one month and six months of age, respectively, and hepatitis B immunoglobulin (HBIG) was injected simultaneously with the first dose. Markers of HBV infection in pregnant women and infants were detected by enzyme linked immunosorbent assay (ELISA). Results showed that 13 infants were detected positive for HBsAg in their sera, eight of them were positive at their birth and the other five converted positive during follow-up. Simple and multiple logistic regression analyses showed that positivity of hepatitis Be antigen (HBeAg) in

mothers and their threatened abortion related to intrauterine infection, with relative risks of 31.27 and 10.87, respectively.

Liu Z, Xu D, Yan Y. The relationship of serum hepatitis B virus DNA load in HBsAg positive pregnant women to the intrauterine infection of newborns. *Zhonghua Fu Chan Ke Za Zhi* 1999; 34:133-134. [Article in Chinese]

Fourth Military Medical University, Xi'an 710033.

The aim was to study the relationship of serum hepatitis B virus (HBV) DNA load in HBsAg positive pregnant women to intrauterine infection of their newborns. Serum HBV DNA were determined by dot-blot hybridization in 185 HBsAg positive pregnant women. Serum HBsAg were tested by ELISA in their newborns within 24 hours after birth. The prevalence of intrauterine HBV infection of the newborns was associated with the HBV DNA level of the mothers. With the increase of serum HBV DNA load, the risk of fetal intrauterine infection was increasing. Fetal exposure to high level of maternal HBV DNA is one of the important determinant of intrauterine infection.

Lolekha S, Warachit B, Hirunyachote A, Bowonkiratikachorn P, West DJ, Pörschke G. Protective efficacy of hepatitis B vaccine without HBIG in infants of HBeAg-positive carrier mothers in Thailand. *Vaccine* 2002; 20:3739-3743.

Department of Pediatrics, Faculty of Medicine, Ramathabodi Hospital, Mahidol University, Bangkok, Thailand.

The primary objective of this study was to estimate the efficacy of a recombinant hepatitis B vaccine (H-B-VAXII) in preventing chronic hepatitis B infection when given alone without concomitant hepatitis B immune globulin (HBIG) to healthy Thai infants born of HBeAg-positive carrier mothers. The infants received a 0.5 ml (5 µg HBsAg) intramuscular injection of H-B-VAXII either at birth, 1, and 6 months of age (Schedule A) or at birth, 1, 2, and 12 months of age (Schedule B). Blood drawings for the determination of hepatitis B virus (HBV) serologic markers were scheduled 4, 9, and 13 months following the initial dose of vaccine. At 13 months, 5 (10%) of 50 infants vaccinated on Schedule A and 7 (14.9%) of 47 infants vaccinated on Schedule B had experienced chronic HBV infection. Based on an expected infection rate in unimmunized infants of either 70 or 90%, the overall efficacy for both schedules combined was estimated to be 82.3% (95% CI: 70.6, 90.6) or 86.2% (95% CI: 77.1, 92.7), respectively. Corresponding schedule-specific estimates were for Schedule A: 85.7% (95% CI: 68.8, 95.3) or 88.9% (95% CI: 75.8, 96.3) and for Schedule B: 78.7% (95% CI: 59.6, 91.1) or 83.4% (95% CI: 68.6, 93.1). These results suggest that in areas of high endemicity, where mothers may not always be screened for HBV infection, routine vaccination of infants at birth with a course of hepatitis B vaccine alone should be highly protective, even for very high-risk infants of HBeAg-positive mothers.

Magdzik WW. Hepatitis B epidemiology in Poland, Central and Eastern Europe and the newly independent states. *Vaccine* 2000; 18(Suppl 1):S13-S16.

Epidemiological Department, National Institute of Hygiene, Chocimska 24 str, 00-791, Warsaw, Poland.

The incidence of hepatitis B virus (HBV) infection varies considerably in countries in Central and Eastern Europe and the Newly Independent States, but data are difficult to compare between countries because of the large differences in levels of diagnosis, particularly serological identification, and levels of notification. Poland has high levels of diagnosis, including laboratory

diagnosis. In the past, the incidence of hepatitis B in Poland was approx. 45 reported cases per 100,000 population, but following the introduction of improved sterilization of medical equipment in 1986 and a selective programme of vaccination in 1991, the incidence fell to about 35 per 100,000 by 1993. In 1993, an intensive vaccination campaign was launched, which has reduced the incidence to under 15 per 100,000. The incidence of HBV infection has decreased across all age groups and in both men and women, and in the under 3 years age group only 32 cases in total were reported in 1997. In 1996 and 1997, there was a slight relative increase in the incidence of HBV infection in men aged 20-24 years. This group may be a target for future vaccination programmes and other activities of control for the infection.

Mast EE, Alter MJ, Margolis HS. Strategies to prevent and control hepatitis B and C virus infections: a global perspective. *Vaccine* 1999; 17:1730-1733.

Hepatitis Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30306, USA. eem1@cdc.gov

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are major causes of acute and chronic liver disease worldwide. Chronic infection with these viruses often leads to chronic liver disease, including cirrhosis or primary hepatocellular carcinoma. Both HBV and HCV are bloodborne viruses; however, HBV is transmitted efficiently by both percutaneous and mucosal exposures, and HCV is transmitted predominantly by percutaneous exposures. Because the relative importance of various modes of transmission of these viruses differs by country, the choice of specific prevention and control strategies depends primarily on the epidemiology of infection in a particular country. Comprehensive hepatitis B prevention strategies should include (1) prevention of perinatal HBV transmission, (2) hepatitis B vaccination at critical ages to interrupt transmission and (3) prevention of nosocomial HBV transmission. The prevention of hepatitis C is problematic because a vaccine to prevent HCV infection is not expected to be developed in the foreseeable future. From a global perspective, the greatest impact on the disease burden associated with HCV infection will most likely be achieved by focusing efforts on primary prevention strategies to reduce or eliminate the risk for transmission from nosocomial exposures (e.g., blood transfusion, unsafe injection practices) and high-risk practices (e.g., injecting drug use).

Mast EE, Hwang LY, Seto DS, Nolte FS, Nainan OV, Wurtzel H, Alter MJ. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. *J Infect Dis* 2005; 192:1880-1889.

Centers for Disease Control and Prevention, Atlanta, GA 30333, USA. emast@cdc.gov

The goal of the present study was to assess risk factors for perinatal hepatitis C virus (HCV) transmission and the natural history of infection among HCV-infected infants. In a cohort study, 244 infants born to HCV-positive mothers were followed from birth until age > or = 12 months. Maternal serum was collected at enrollment and delivery; infant serum was collected at birth and at 8 well-child visits. Testing included detection of antibody to HCV, detection of HCV RNA (qualitative and quantitative), and genotyping. HCV-infected infants were followed annually until age 5 years. Overall, 9 of 190 (4.7% [95% confidence interval (CI), 2.3%-9.1%]) infants born to mothers who were HCV RNA positive at delivery became infected, compared with 0 of 54 infants born to HCV RNA-negative mothers (P = 0.10). Among HCV RNA-positive mothers, the rate of transmission was 3.8% (95% CI, 1.7%-8.1%) from the 182 who were human immunodeficiency virus (HIV) negative, compared with 25.0% (95% CI, 4.5%-64.4%) from the 8 who were HIV positive (P < 0.05). Three infected infants resolved their infection (i.e., became HCV RNA negative). In multivariate analysis restricted to HCV RNA-positive mothers, membrane rupture > or = 6 h (odds ratio [OR], 9.3 [95% CI, 1.5-179.7]) and internal fetal monitoring (OR, 6.7 [95% CI, 1.1-35.9]) were associated with transmission of HCV to infants. If duration of membrane

rupture and internal fetal monitoring are confirmed to be associated with transmission, interventions may be possible to decrease the risk of transmission.

Mast EE, Margolis HS, Fiore AE, Brink EW, Goldstein ST, Wang SA, Moyer LA, Bell BP, Alter MJ, on behalf of the Advisory Committee on Immunization Practices (ACIP). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. *MMWR Recomm Rep* 2005; 54(RR-16):1-23. [Errata: 2006; 54(RR-16). *MMWR* 2006; 55(06):158-159.

Division of Viral Hepatitis, National Center for Infectious Diseases, USA. emast@cdc.gov

This report is the first of a two-part statement from the Advisory Committee on Immunization Practices (ACIP) that updates the strategy to eliminate hepatitis B virus (HBV) transmission in the United States. The report provides updated recommendations to improve prevention of perinatal and early childhood HBV transmission, including implementation of universal infant vaccination beginning at birth, and to increase vaccine coverage among previously unvaccinated children and adolescents. Strategies to enhance implementation of the recommendations include 1) establishing standing orders for administration of hepatitis B vaccination beginning at birth; 2) instituting delivery hospital policies and procedures and case management programs to improve identification of and administration of immunoprophylaxis to infants born to mothers who are hepatitis B surface antigen (HBsAg) positive and to mothers with unknown HBsAg status at the time of delivery; and 3) implementing vaccination record reviews for all children aged 11-12 years and children and adolescents aged < 19 years who were born in countries with intermediate and high levels of HBV endemicity, adopting hepatitis B vaccine requirements for school entry, and integrating hepatitis B vaccination services into settings that serve adolescents. The second part of the ACIP statement, which will include updated recommendations and strategies to increase hepatitis B vaccination of adults, will be published separately.

Mehmet D, Meliksah E, Serif Y, Gunay S, Tuncer O, Zeynep S. Prevalence of hepatitis B infection in the southeastern region of Turkey: comparison of risk factors for HBV infection in rural and urban areas. *Jpn J Infect Dis* 2005; 58:15-19.

Department of Gastroenterology, Medical School of Dicle University, 21280 Diyarbakir, Turkey. mertem@dicle.edu.tr

Although hepatitis B has been well studied, there are still aspects of its epidemiology that remain to be clarified. There are many regions with high seroprevalence, particularly in the developing regions of the world, and these regions are known to have different epidemiologic patterns. Nonetheless, there are currently no data on the differences in hepatitis B seroprevalence between urban and rural areas of Turkey. In the present study, therefore, we used 30-cluster sampling to determine and compare the prevalence of hepatitis B in the urban and rural areas of the least developed region of Turkey, the southeastern region. From 2,888 adults living in the region, blood samples were obtained from house visits, and screened for HBsAg, anti-HBs, and anti-HBcIgG. Factors associated with hepatitis B seroprevalence, particularly living in rural areas, were analyzed with multivariate methods. The seroprevalence of HBsAg was 8.2% in the rural and 6.2% in the urban areas. There was a statistically significant difference between urban and rural regions in terms of HBsAg positivity (crude OR: 0.74; 95% CI: 0.55 - 0.98). Exposure to hepatitis B virus (HBV) increased with age both in urban and rural areas. Lower education level was also an important risk factor for hepatitis B seropositivity in urban areas (adjusted OR: 1.66; 95% CI: 1.26 - 2.19) but not in rural ones (adjusted OR: 0.77; 95% CI: 0.36 - 1.69). Familial jaundice history was a statistically significant risk factor for HBsAg positivity in rural areas (adjusted OR: 2.15; 95% CI: 1.30 - 3.56) but not in urban ones (adjusted OR: 1.48; 95% CI: 0.96 - 2.27). This study

shows that the prevalence of HBV infection in the southeastern region of Turkey is intermediate among the levels reported for the European region of the World Health Organization.

Meng J, Yue Y, Zhang S. Effect of intrauterine hepatitis B virus infection on hepatitis B vaccine inoculation in newborns. *Zhonghua Fu Chan Ke Za Zhi* 2002; 37:136-138. [Article in Chinese]

Department of Obstetrics and Gynecology, First Hospital of Xi'an Jiaotong University, Xi'an 710061, China.

The objective was to study the effect and the mechanism of peripheral blood nuclear cells (PBMC) invaded by hepatitis B virus (HBV) on the artificial immunization in newborns. Fifty-two newborns, whose mothers were hepatitis B surface antigen (HBsAg) positive, were immunized with hepatitis B immunoglobulin and hepatitis B vaccine (HBVac), and then followed for 7 months. The newborns' serum and PBMC HBV DNA was detected by nested-PCR, hepatitis B surface antibody (HBsAb) was tested with solid phase radioimmunoassay. PBMC from newborn were incubated with PHA and HBsAg. The supernatant interleukin 2 (IL-2) level was measured by enzyme linked immunosorbent assay (ELISA). The rate of vaccination failure was higher in the infants with PBMC HBV DNA positive than those with negative ($P < 0.05$). The supernatant IL-2 level was lower in the former than that in the latter and the control ($P < 0.05$). The level of IL-2 in the immunization failure newborns was lower than that in the vaccination success and the control ($P < 0.05$). The intrauterine PBMC HBV invasion is one of the important causes of vaccination failure in the newborns. PBMC IL-2 autocrine down regulation is closely related to HBV invasion, that may lead to the failure of HBVac inoculation in the newborns.

Milne A, West DJ, Chinh DV, Moyes CD, Pörschke G. Field evaluation of the efficacy and immunogenicity of recombinant hepatitis B vaccine without HBIG in newborn Vietnamese infants. *J Med Virol* 2002; 67:327-333.

The Hepatitis Foundation, Whakatane, New Zealand. sandorandfay@extra.co.nz

A study involving more than 2,000 infants was conducted in Vietnam to assess the field effectiveness and immunogenicity of recombinant hepatitis B vaccine given at birth, 1 month, 2 months, without concomitant hepatitis B immune globulin (HBIG). All received a 5 microg dose of H-B-VAX II at birth. Infants born to non-carrier mothers (Group 1; N = 1798) then received 2.5 microg doses at 1 and 2 months of age, while infants of HBeAg-negative (Group 2; N = 125) or HBeAg-positive (Group 3; N = 88) carrier mothers received 5 microg doses. No Group 1 or 2 vaccinees were infected. In Group 3, 12 (14.6%) of 82 infants did become infected (estimated efficacy 84%). 98.0-98.6% of uninfected infants who were tested for anti-HBs developed a seroprotective concentration ≥ 10 IU/l. In hyperendemic Vietnam, where routine maternal screening and passive-active prophylaxis of high-risk infants with vaccine plus HBIG is not feasible, administration of vaccine alone to all newborns may control effectively HBV infection.

Nelson CM, Wibisono H, Purwanto H, Mansyur I, Moniaga V, Widjaya A. Hepatitis B vaccine freezing in the Indonesian cold chain: evidence and solutions. *Bull World Health Organ* 2004; 82:99-105.

Program for Appropriate Technology in Health, Seattle, WA 98107, USA. cnelson@path.org

The objectives were to document and characterize freezing temperatures in the Indonesian vaccine cold chain and to evaluate the feasibility of changes designed to reduce the occurrence of freezing. Data loggers were used to measure temperatures of shipments of hepatitis B vaccine from manufacturer to point of use. Baseline conditions and three intervention phases were monitored.

During each of the intervention phases, vaccines were removed progressively from the standard 2-8 degrees C cold chain. Freezing temperatures were recorded in 75% of baseline shipments. The highest rates of freezing occurred during transport from province to district, storage in district-level ice-lined refrigerators, and storage in refrigerators in health centres. Interventions reduced freezing, without excessive heat exposure. Inadvertent freezing of freeze-sensitive vaccines is widespread in Indonesia. Simple strategies exist to reduce freezing - for example, selective transport and storage of vaccines at ambient temperatures. The use of vaccine vial monitors reduces the risk associated with heat-damaged vaccines in these scenarios. Policy changes that allow limited storage of freeze-sensitive vaccines at temperatures > 2-8 degrees C would enable flexible vaccine distribution strategies that could reduce vaccine freezing, reduce costs, and increase capacity.

Ngui SL, Andrews NJ, Underhill GS, Heptonstall J, Teo CG. Failed postnatal immunoprophylaxis for hepatitis B: characteristics of maternal hepatitis B virus as risk factors. *Clin Infect Dis* 1998; 27:100-106.

Virus Reference Division, Central Public Health Laboratory, London, United Kingdom.

A retrospective case-control study was conducted to determine why some infants born full-term without obstetric intervention to hepatitis B e antigen (HBeAg)-seropositive mothers become infected by hepatitis B virus (HBV) despite having received passive-active immunoprophylaxis. Cases and controls comprised 12 hepatitis B surface antigen (HBsAg)-seropositive infants and 22 HBsAg-seronegative infants, respectively. Infants infected by putative vaccine-escape mutants were excluded. Risk factors, after adjustment for the level of maternal viremia, were the following allelic base changes in maternal HBV:C158, A328, G365, and A479 (P = 0.017, 0.005, 0.003, and 0.005, respectively). High-level maternal viremia (i.e., > or = 10(8) genome equivalents/mL) was a significant factor only after adjustment for G365 (P = 0.027). HBV DNA sequences recovered from one of the cases, the case's mother, and three infected contacts all had the high-risk mutations. Specific allelic mutations in maternal HBV and level of maternal viremia are potential predictors of vertical breakthrough infection.

Niesert S, Messner U, Tillmann HL, Gunter HH, Schneider J, Manns MP. Prevalence of hepatitis B in pregnancy and selective screening. *Geburtshilfe Frauenheilkd* 1996; 56:283-286. [Article in German]

Zentrum Frauenklinik der Medizinischen Hochschule Hannover.

Infants of mothers positive for HBsAg are at risk for peripartur transmission of hepatitis B infection. Active and passive immunisation administered immediately after birth can prevent neonatal hepatitis B. In a prospective study the prevalence of hepatitis B in pregnant women and the efficiency of selective antepartur screening of women with identifiable risk factors for hepatitis B were analysed. From November 1992 to May 1994, 912 women presenting at the department of obstetrics and gynaecology of the Medizinischen Hochschule Hannover were tested for HBsAg, HBeAg, anti HBs, anti HBc, and HBV-DNA. Venous blood samples were taken during the third trimester of pregnancy or immediately post partum. 13 (1.4%) patients were found to be HBsAg positive. The prevalence of HBsAg in German females and women from countries with low endemicity for hepatitis B was 0.38% versus 5.7% for women from endemic areas. HBeAg was detected in two patients. 10 patients with a positive serological result belonged to groups considered to be of increased risk for hepatitis B infection. Nevertheless, 6 of these women had not undergone antepartur screening. These findings support a need for routine screening of all pregnant women for HBsAg, as it has been recently introduced in Germany.

Niu MT, Targonski PV, Stoll BJ, Albert GP, Margolis HS. Prevention of perinatal transmission of the hepatitis B virus. Outcome of infants in a community prevention program. *Am J Dis Child* 1992; 146:793-796.

Hepatitis Branch, Centers for Disease Control, Atlanta, GA 30333.

The objective was to assess the outcome of infants born to hepatitis B surface antigen (HBsAg)-positive mothers who received prenatal and infant care in a large, public health care system. Design: follow-up of a cohort of infants born to HBsAg-positive mothers. Setting: large, urban hospital providing prenatal care and obstetric services to county health departments. Participants: forty-two infants born to HBsAg-positive women. Interventions: prenatal testing of women and immunoprophylaxis of infants with hepatitis B immune globulin at birth and hepatitis B vaccine at birth and ages 1 and 6 months. All 42 infants received hepatitis B immune globulin and the first dose of vaccine. Of forty-one infants (98%) who received the second dose of vaccine, 37 received it by age 4 months. Thirty-two infants (76%) completed the three-dose vaccine series by age 12 months, and 34 infants (81%) completed the series by age 18 months. The rate of completion of the hepatitis B vaccine series was comparable to that of infants receiving the third dose of diphtheria-pertussis-tetanus vaccine. Of 26 infants who completed the hepatitis B vaccine series and had follow-up serologic testing, 24 (92%) had adequate levels of antibody to HBsAg. Only one infant who did not complete the vaccine series had serologic evidence of hepatitis B virus infection. No infant was HBsAg-positive. Public programs serving urban populations can effectively deliver hepatitis B immunoprophylaxis to infants born to HBsAg-positive mothers.

Onishchenko GG, Dement'eva LA. Spread of hepatitis virus as a threat to national security. *Zh Mikrobiol Epidemiol Immunobiol* 2003; 4:93-99. [Article in Russian]

Ministry of Health of the Russian Federation, Moscow.

Information on viral hepatitis A, B and C morbidity in Russia is presented. A distinct trend to decreased viral hepatitis B and C morbidity in 2001-2002 in comparison with the 1990-ies is noted. Nevertheless, there is still unfavorable prognosis regarding high hepatitis B morbidity among the population of reproductive age, as well as among adolescents, which increases the risk for children at an early age. In addition, a new specific feature of hepatitis A spread is observed: morbidity in this infection is shifted to older age groups. The role of vaccinal prophylaxis in the decrease of hepatitis A and B morbidity, virus safety of blood and its components, the quality of the diagnostics of chronic hepatitis, especially hepatitis C, are discussed. The complex of measures for the prophylaxis of viral hepatitis is proposed.

Otto BF, Suarnawa IM, Stewart T, Nelson C, Ruff TA, Widjaya A, Maynard JE. At-birth immunisation against hepatitis B using a novel pre-filled immunisation device stored outside the cold chain. *Vaccine* 1999; 18:498-502.

Macfarlane Burnet Centre for Medical Research, Melbourne, Australia.

We evaluated the immunogenicity of hepatitis B (HB) vaccine in UniJect, a pre-filled, non-reusable injection device, stored at tropical temperatures for up to one month and used to give the first dose of HB vaccine to newborns. Infants in Tabanan district, Bali, Indonesia, were given their first dose of HB vaccine with UniJect stored out of the cold chain, UniJect stored in the cold chain; or standard syringe, needle and multidose vial stored in the cold chain. Subsequent doses were given by usual means and blood samples drawn 4-6 weeks after the third dose. No significant differences were found in seroconversion rates or geometric mean titres of HB surface antibody between the three groups.

Papaevangelou G. Hepatitis B immunization programme: lessons learnt in Greece. *Vaccine* 1998; 16(Suppl):S45-S47.

Faculty of Nursing, University of Athens, Greece.

Historically, Greece has had the highest burden of hepatitis B virus (HBV) infection in the European Union (EU). Heterosexual contact is the primary means of HBV transmission in Greece, accounting for approximately 30% of acute cases in adult males and 50% of acute cases in women of reproductive age [Kattamis C, Papevangelou G. Workshop Group: Greece. *Vaccine* 1995; 13:S97-S98.]. In 1982, Greece implemented a hepatitis B prevention programme aimed at high-risk groups; unfortunately, this approach had little impact on disease incidence or prevalence. At the recommendation of the WHO and the World Health Assembly and after sustained lobbying by several scientific and medical associations in Greece, the Greek government decided to implement a national prevention programme for hepatitis B. The programme, in effect from early 1998, includes the screening of pregnant women, universal infant and adolescent immunization and immunization of high-risk groups.

Poovorawan Y, Chongsrisawat V, Theamboonlers A, Vimolkeij L, Yano M. Is there evidence for intrauterine HBV infection in newborns of hepatitis B carrier mothers? *Southeast Asian J Trop Med Public Health* 1997; 28:365-369.

Viral Hepatitis Research Unit, Faculty of Medicine, Chulalongkorn University and Hospital, Bangkok, Thailand.

It has been proposed that some neonates infected with hepatitis B virus (HBV), acquire their infections in utero as demonstrated by HBV seromarkers in venous blood samples at birth. In this study, paired blood samples from 13 HBsAg-positive, 19 HBsAg- and HBeAg-positive, 2 HBsAg-negative mothers and 34 of their neonates, were drawn 24-72 hours after birth and tested for HBV-DNA in their peripheral blood mononuclear cells (PBMC). The presence of HBV-DNA in PBMC was detected in 69.2% (9/13) of HBsAg-positive mothers, 94.7% (18/19) of HBsAg- and HBeAg-positive mothers, and in none of their neonates. The conclusion from these results is that the evidence for hepatitis B infections occurring in neonates of hepatitis B carrier mothers in utero is uncommon.

Poovorawan Y, Theamboonlers A, Vimolket T, Sinlaparatsamee S, Chaiear K, Siraprapasiri T, Khwanjaipanich S, Owatanapanich S, Hirsch P, Chunsuttiwat S. Impact of hepatitis B immunisation as part of the EPI. *Vaccine* 2000; 19:943-949.

Viral Hepatitis Research Unit, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University and Hospital, 10330, Bangkok, Thailand. yong.p@chula.ac.th

Since 1992, hepatitis B vaccine has been an integrated part of Thailand's expanded programme on immunisation (EPI). Based on the data from five representative provinces, we have evaluated its impact on the countrywide prevalence of HBV infection and carrier rate. The population studied comprised 400-488 healthy and immuno-competent, subjects per area. The subjects' ages ranged from 6 months to 18 years. We examined their sera for viral hepatitis markers using commercially available test kits and established the coverage rate of hepatitis B vaccination after its inclusion into the EPI to be 71.2-94.3%. The number of individuals undergoing the complete course of vaccinations had increased four-fold. Consequently, only 0.7% of the children born after the implementation of this the novel EPI strategy were HBV carriers.

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

Laboratoire de virologie, CHU Dupuytren, 87042, Limoges, France. sylvie.rogez@unilim.fr

The infection by the hepatitis viruses, when appearing during the pregnancy, could result in damages for the infant. However, risks differ according to the implicated virus. Hepatitis B virus infection, for which prevalence varies according to areas, is injurious when the mother is chronic HBsAg carrier. Risk consists of neonate's contamination during the labour, and if contaminated, the neonate becomes a chronic carrier himself in 80 to 90% of cases. When the mother is positive for viral DNA in her serum, transmission rate is estimated at 90%. In the opposite, if the mother is negative for viral DNA in the serum, transmission rate is about 10 to 30%. HBsAg screening is obligatory in France during the sixth month of pregnancy: in case of positivity, serovaccination of the neonate is systematically carried out. Protection rate is 100% if the mother had a low viral load (< 150 pg/ml) at the end of pregnancy, and weaker (about 70%) if the mother had a higher level of viral DNA. Transmission risk of hepatitis C virus (HCV) is much lesser, since it is about 5% for a woman who is positive for viral RNA at the end of her pregnancy, and at least 10% if the woman is moreover positive for the HIV. Risk is more important if the woman had an important plasmatic viral load (> 10⁵ copies/ml) and if the duration between membrane rupture and delivery is long. Vaginal delivery and breast-feeding are not advised. Neonates from mothers who replicate the HCV at the end of pregnancy are serologically evaluated until 12-15 months of age, in order to determine their possible contamination. Delta virus transmission from mother to infant is exceptional and could be avoided by the HBV serovaccination of the new-born. Intra-utero transmission of hepatitis A virus is very rare, but perinatal transmission could occur. Materno-fetal transmission of hepatitis E virus has been reported, but the virus is essentially dangerous for the mother, resulting in a mortality rate of 15 to 25% if the acute infection occurs during the third trimester of the pregnancy.

Ranger-Rogez S, Denis F. Hepatitis B mother-to-child transmission. *Expert Rev Anti-infective Ther* 2004; 2:133-145.

Laboratoire de Virologie, CHU Dupuytren, 2 Avenue Martin Luther King, 87042 Limoges Cedex, France. sylvie.rogez@unilim.fr

Approximately 350 million people are estimated to be chronically infected with hepatitis B virus, leading to an important public health problem. In highly endemic areas where 8 to 15% of people are chronically infected with hepatitis B virus, the risk for the neonate to be perinatally infected by the chronically infected mother, then to become chronically infected themselves, is very high. In those countries, the World Health Organization recommends hepatitis B vaccination systematically at birth, independent of hepatitis B virus maternal status. This vaccination program has begun to induce a rapid decrease in the number of acute hepatitis B virus infections and has also had a secondary effect of a decrease in related sequels. Lamivudine (Zeffix, GlaxoSmithKline), when associated with the immunization of the neonate, was recently demonstrated to dramatically reduce the residual risk of perinatal transmission. In intermediate and low endemicity areas, a systematic hepatitis B surface antigen screening is recommended during pregnancy, allowing, in the case of positivity, a selective hepatitis B virus neonate immunization during the first 12 h of life. Hepatitis B virus vaccination of children born to hepatitis B surface antigen-positive mothers confers long-term immunity.

Rumi MA, Begum K, Hassan MS, Hasan SM, Azam MG, Hasan KN, Shirin M, Khan AK. Detection of hepatitis B surface antigen in pregnant women attending a public hospital for delivery: implication for vaccination strategy in Bangladesh. *Am J Trop Med Hyg* 1998; 59:318-322.

Department of Immunology, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders, Dhaka.

Routine antenatal hepatitis B surface antigen (HBsAg) screening and immunization of risk babies is very effective in preventing perinatal transmission of hepatitis B virus (HBV). We studied 1,800 parturients attending a public hospital to assess the rationale for such vaccination in Bangladesh. In one in every 29 deliveries (63 of 1,800 or 3.5%), the mother was found to be HBsAg positive. All were asymptomatic and many (41 of 63 or 65%) without risk factors would remain undetected if HBsAg screening were performed on selected groups. Most of the HBsAg-positive mothers (54 of 63 or 85.7%) were found to be chronic carriers and 30.2% (19 of 63) were also hepatitis B e antigen (HBeAg) positive, indicating high infectivity. Although 23 cord blood were positive for HBsAg or HBeAg, none were positive for IgM antibody to hepatitis B core antigen (IgM anti-HBc), suggesting transplacental transmission of the antigens rather than intrauterine infection. These findings are discussed in relation to the cost-effectiveness of routine prenatal screening and immunization of risk babies compared with universal infant immunization.

Sanpavat S, Poovorawan Y, Chittinand S, Bhongsvej S, Thaithumyanon P. Immunogenicity of hepatitis B vaccine in premature infants. *Southeast Asian J Trop Med Public Health* 1994; 25:93-95.

Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

The immunogenicity of plasma-derived hepatitis B vaccine was studied in 39 premature neonates, whose weights were 1,800-2,400 g and gestational ages 32-37 weeks. All maternal anti-HBc antibody were negative. Dosage of 5 micrograms of hepatitis B vaccine (Pasteur vaccine) was given at 0, 1, 2 and 12 months after birth. At the ages of 1, 2, 4, 9, 12 and 13 months, anti-HBs antibody was found in 7.7%, 20%, 69.7%, 81.4%, 77.3% and 89.5%, respectively, while the geometric mean titer in this seropositive group, starting at age 2 months was 37, 121, 113, 69 and 1,016 mIU/ml. There was no severe reaction attributed to the vaccination. The result indicated that the vaccine was immunogenic. Although the conversion rate was low after primary injection, a satisfactory response developed at age 4 months after 3 doses of vaccine.

Shakhgil'dian IV, Mikhailov MI, Khukhlovich PA, Anan'ev VA, Romanenko VV, Kuznetsova IO, Esaulkova AIu, Klimenko SM. The vaccinal prophylaxis of hepatitis B in Russia – the achievements, problems and outlook. *Zh Mikrobiol Epidemiol Immunobiol* 2000; 2:44-49. [Article in Russian]

Ivanovsky Research Institute of Virology, Gamaleya Research Institute of Epidemiology and Microbiology, Moscow, Russia.

Certain specific features of the present epidemic situation with hepatitis B (HB) in Russia were established: significant growth of HB morbidity, starting from 1995; the prevalence of persons aged 15-29 years among HB patients, which was linked with the sharp activation of the sexual route of the transmission of HB virus in recent years; an essential increase in the number of patients having contacted this virus in the process of the intravenous use of drugs. The results of the use of vaccine 'Engerix B' among persons belonging to different risk groups were considered (a decrease in HB morbidity among them by 8-19 times was noted), the study demonstrated high immunogenicity anti-HBs antibodies on protective titers were determined in 92.3-95.7% of the

vaccinees) and low reactogenicity of the vaccine, as well as stable postvaccinal immunity (5 years after the course of vaccination was completed anti-HBs antibodies were retained in 70.6-74% of the vaccinees). The study showed that only the vaccination of adolescents in combination, in the presence of opportunity, with the immunization of newborn infants and young children in the first year of their life made it possible to produce an essential effect on the activity of the epidemic process. Already in 2 years such organization of work on the prophylaxis of HB in one of the cities of the Sverdlovsk region led to a decrease in HB morbidity by 2.9 times, and among adolescents 9 times.

Shiraki K. Perinatal transmission of hepatitis B virus and its prevention. *J Gastroenterol Hepatol* 2000; 15(Suppl):E11-E15.

Department of Paediatrics, Faculty of Medicine, Tottori University, Yonago, Japan.
shirakik@hi-ho.ne.jp

In order to prevent liver cirrhosis and hepatocellular carcinoma in later life, it is essential to prevent HBV infection in infants. If the mother is chronically infected with HBV and is also positive for HBeAg, 80-90% of the newborns become chronically infected, whereas if the mother is positive for anti-HBe, only some newborns will develop acute hepatitis or fulminant hepatitis. It is necessary to screen pregnant women for HBsAg and prevent mother-to-infant infection of HBV, treating the infant with hepatitis B hyperimmune globulin at birth, followed by HBV vaccination. In highly endemic areas of HBV, universal HBV vaccination of all newborns is advisable.

Sloan D, Ramsay M, Prasad L, Gelb D, Teo CG. Prevention of perinatal transmission of hepatitis B to babies at high risk: an evaluation. *Vaccine* 2005; 23:5500-5508.

Immunisation Department, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK.

We aimed to determine factors associated with successful vaccination coverage and development of infection in high-risk infants born to hepatitis B infected women. Immunisation of 860/932 (92%) of babies was started within 48 h of birth and three doses of vaccination completed for 794/921 (86%). Only 543 (58%) infants were tested and 26 (4.9%) were found to have evidence of current infection. Delayed start of immunisation was significantly associated with unbooked pregnancy, maternal hepatitis B e-markers and year. Current infection in the baby was strongly associated with maternal hepatitis B e-status, ethnicity and year of vaccination. The proportion of infants developing infection declined after 1998, coinciding with the publication of national recommendations and the wider use of the accelerated schedule.

Söderström A, Norkrans G, Lindh M. Hepatitis B virus DNA during pregnancy and post partum: aspects on vertical transmission. *Scand J Infect Dis* 2003; 35:814-819.

Department of Infectious Diseases, Sahlgrenska University Hospital, Ostra, Göteborg, Sweden.
ann.soderstrom@medfak.gu.se

Little is known about how pregnancy influences viremia levels in women with chronic hepatitis B virus infection. In this study, we first retrospectively analysed changes in HBV DNA levels during and after 55 pregnancies in HBsAg-positive women, of whom 9 were HBeAg-positive. Secondly, HBV DNA levels in 3 HBeAg-positive mothers whose babies became chronic HBV carriers, were compared with levels in 18 mothers whose babies were not infected by HBV. We found that HBV DNA ranged from $10^{8.1}$ to $10^{9.5}$ copies/ml in HBeAg-positive, and from undetectable (< 100) to $10^{6.8}$ copies/ml in HBeAg-negative mothers. HBV DNA increased by a mean of 0.4 log late in

pregnancy or early post partum; in 4 out of 16 HBeAg negative mothers by > 1 log during pregnancy. Post partum ALT increased in both HBeAg-positive and negative women. HBV DNA was $10^{9.4}$ - $10^{10.4}$ copies/ml in 3 HBeAg-positive mothers whose babies were, as compared to < $10^{10.4}$ copies/ml in 18 whose babies were not, vertically infected. Although the majority of HBeAg-negative women had low and relatively stable HBV DNA during pregnancy, viremia was also relatively high in some HBeAg-negative mothers, and both viremia and ALT increased significantly late in pregnancy or shortly after delivery. Vertical transmission was only seen in HBeAg-positive mothers with very high levels of viremia. The value of measuring HBV DNA in the pregnant woman to modify immunoprophylaxis to her infant needs further study.

Sood A, Singh D, Mehta S, Midha V, Kumar R. Response to hepatitis B vaccine in preterm babies. *Indian J Gastroenterol* 2002; 21:52-54.

Department of Medicine, Dayanand Medical College and Hospital, Ludhiana, Punjab.

A well-accepted vaccination schedule for preterm babies is not available. We therefore studied the response to hepatitis B vaccine in preterm babies. Sixty babies born to HBsAg-negative mothers were studied. Group I (n = 20) consisted of term babies with birth weight > 2.5 kg, group II (n = 20) included preterm babies with birth weight between 1.8 and 2.49 kg, and group III (n = 20) included preterm babies with birth weight between 1.2 and 1.79 kg. Mean gestational age in the three groups was 38.5 (1.1), 33.5 (1.4) and 32.7 (2.1) weeks, respectively. All babies received 3 doses (10 µg/0.5 ml) of a recombinant HBV vaccine within 3 days of birth, and at 6 weeks and 6 months of life. Anti-HBs levels were measured one month after the 2nd and 3rd doses each; the immune response was categorized as good responders (anti-HBs > 100 mIU/ml, low responders (anti-HBs 10-100 mIU/ml) and non-responders (anti-HBs < 10 mIU/ml). Good antibody response after the second dose was seen in 95% of babies in group I, 60% of those in group II and 10% of those in group III. This increased to 100%, 90% and 45%, respectively after the third dose. The response was influenced by gestational age (r = 0.73); 94% of babies with gestational age 34-36 weeks attained good antibody response compared to only 55% of babies with gestational age of 31-33 weeks. Birth weight had no independent influence on the antibody response. The response to hepatitis B vaccine is influenced by gestational age. Hence, in preterm babies, it is advisable to check antibody titers one month after the third dose to assess the need for a booster dose.

Sriprakash I, Anil TP. Routine prenatal screening of Indian women for HBsAg: benefits derived versus cost. *Trop Doc* 1997; 27:176-177.

Microbiology Department, MS Ramaiah Medical College, Bangalore, India.

This study finds that pregnant mothers in India should receive prenatal screening for hepatitis B in order to prevent perinatal transmission and spread of the infection within the larger community. Neonates who contract hepatitis B will have an almost 90% risk of developing chronic hepatitis B surface antigen (HBsAg) carriage and chronic liver disease. Infants may spread the disease to siblings and others. Neonatal immunization with HBIG and HBV vaccine interrupts vertical transmission. The US Centers for Disease Control recommend universal screening due to the aforementioned reasons. The study sample included 520 third-trimester pregnant women who attended a prenatal clinic at the Kempegowda Institute of Medical Sciences Hospital in Bangalore, India. Screening was conducted during 1991-92. Serum samples were tested by ELISA using commercial kits from Hoechst India. Positive samples were retested using Abbot's QUANTUM II for final confirmation. A full, detailed medical history of risk factors was collected for each patient. Findings indicate that 24 samples (4.6%) were positive. The positive cases included 8 with blood transfusions, 6 with a bad obstetric history, 4 with experience as health care workers and no immunization, and 6 with no risk factors. The hospital cases fit the pattern among the general population. In India, about 30-40% of pregnant HBsAg carriers are HbeAg positive. The cost of a

single ELISA test is about Rs40. At the rate of 17 pregnant women per 1000 population, total costs for obstetric screening would amount to about Rs70 crores. The cost of managing a single clinical case and its complications would amount to several lakhs of rupees, which makes screening very cost-effective.

Stamouli M, Gizaris V, Totos G, Papaevangelou G. Decline of hepatitis B infection in Greece. *Eur J Epidemiol* 1999; 15:447-449.

Department of Microbiology and Immunology, Naval and Veterans Hospital, Athens, Greece.

Hepatitis B has long been a serious public health problem in Greece. In recent years, a decline in hepatitis B infection is observed ascribable to many factors such as demographic and socioeconomic changes, medical precautions, use of disposable medical equipments, screening of blood donors and vaccination. We studied the prevalence of HBV infection in a sample of 1050 Greek male Navy recruits. 343 subjects (32.6%) had previously been vaccinated and were anti-HBs positive. We observed that during the last decade, the prevalence of immunes declined to 1.33% and the prevalence of any HBV marker declined to 2.28%. The HBsAg carrier rate declined from 3.9% in 1973 to 0.9% in 1986. Since then, it is stable at 0.95% because perinatal and vertical transmissions are still responsible for the majority of HBV chronic infections. Universal prenatal screening and infant immunization will contribute to a further decline of HBV infection.

Stroffolini T, Bianco E, Szklo A, Bernacchia R, Bove C, Colucci M, Coppola RC, D'Argenio P, Lopalco P, Parlato A, Ragni P, Simonetti A, Zotti C, Mele A. Factors affecting the compliance of the antenatal hepatitis B screening programme in Italy. *Vaccine* 2003; 21:1246-1249.

The effectiveness in the prevention of perinatally transmitted HBV infection was assessed in 11858 pregnant women consecutively recruited in public and private hospitals in six Italian regions during a 2 months period in 2001. Of them 10881 (91.8%) attended HBsAg antenatal screening. The overall HBsAg prevalence was 1.7% (CI 95%: 1.4-1.9); it was 1.4% (CI 95%: 1.2-1.7) in pregnant women born in Italy but 5.9% (CI 95%: 4.1-8.1) in those born in Asia, Africa, central and south America, and eastern Europe. Results of multiple logistic regression analysis indicate that birth in foreign countries (OR 2.0; CI 95%: 1.3-3.0), family size with more than 4 members in the household (OR 3.5; CI 95%:2.7-4.6), and birth in a private hospital (OR 1.9; CI 95%: 1.3-2.8) were all independent predictors of lack of adherence to HBsAg screening. Out of the 182 new-borns of HBsAg-positive mothers 172 (95.0%) were given active plus passive immunisation; this figure was 100% in new-borns of foreign mothers. These findings evidence a good effectiveness in the prevention of perinatally transmitted HBV in Italy. More efforts should be addressed to improve the effectiveness of the programme among foreign pregnant women who have high rate of HBsAg and more likely escape HBsAg screening than Italian pregnant women.

Sun Z, Ming L, Zhu X, Lu J. Prevention and control of hepatitis B in China. *J Med Virol* 2002; 67:447-450.

Cancer Institute, Chinese Academy of Medical Sciences, Panjiayuan, Beijing, China.
ztsun@public3.bta.net.cn

About 170 million Chinese are infected chronically with HBV and 10% suffer from chronic hepatitis. Around half a million Chinese die from hepatitis B caused hepatocellular carcinoma and endstage cirrhosis each year. From 1983 to the present, a controlled clinical trial involving 80,000 children on a universal hepatitis B vaccination programme to prevent chronic hepatitis, hepatocellular carcinoma, and endstage cirrhosis was implemented in Qidong, China. A pilot study

demonstrated that the HBsAg rate reached the adult level before the fifth year of age, and neonatal vaccination with either plasma-derived or recombinant hepatitis B vaccines provided a similar 75% protective efficacy against HBV infection. The high rate of follow-up and blood tests coverage of the cohorts provided data to show 75% protection at the tenth to eleventh years of age against serum HBsAg and also against prolonged hepatic dysfunction. The strategy of controlling hepatitis B nationwide was based on the universal immunisation of newborns, beginning in cities and then the rural areas. The large-scale vaccine source was provided by domestic plants through technology transfer, first providing plasma-derived vaccine replaced completely by recombinant DNA vaccine in 1997. An official survey in 1999 using a cluster sampling of 25,878 children from 31 provinces reported an average coverage rate of three dose of hepatitis B vaccination of 70.7%, being higher in urban areas. The Ministry of Public Health of China has planned to integrate hepatitis B vaccination into the nationwide EPI program with Government-provided vaccines starting January 1, 2002.

Sutanto A, Suarnawa IM, Nelson CM, Stewart T, Soewarso TI. Home delivery of heat-stable vaccines in Indonesia: outreach immunization with a prefilled, single-use injection device. *Bull World Health Organ* 1999; 77:119-126.

Disease Prevention and Health Promotion, NTB Province, Ministry of Health, Indonesia.

Extending immunization coverage to underserved populations will require innovative immunization strategies. This study evaluated one such strategy: the use of a prefilled, single-use injection device for outreach immunization by village midwives. The device, UniJect, is designed to prevent refilling or reuse. Stored at ambient temperatures for up to 1 month in midwives' homes, vaccine-filled UniJect devices were immediately available for outreach. Between July 1995 and April 1996, 110 midwives on the Indonesia islands of Lombok and Bali visited the homes of newborn infants to deliver hepatitis B vaccine to the infants and tetanus toxoid to their mothers. Observations and interviews showed that the midwives used the device properly and safely to administer approximately 10,000 sterile injections in home settings. There were no problems with excessive heat exposure during the storage or delivery of vaccine. Injection recipients and midwives expressed a strong preference for the UniJect device over a standard syringe. Use of the prefilled device outside the cold chain simplified the logistics and facilitated the speed and efficiency of home visits, while the single-dose format minimized vaccine wastage.

Tang JR, Hsu HY, Lin HH, Ni YH, Chang MH. Hepatitis B surface antigenemia at birth: a long-term follow-up study. *J Pediatr* 1998; 133:374-377.

Department of Pediatrics, College of Medicine, National Taiwan University, Taipei, Taiwan.

The objective was to investigate the prevalence and outcome of hepatitis B surface antigenemia in newborns of hepatitis B e antigen (HBeAg)-positive hepatitis B surface antigen (HBsAg) carrier mothers under the current immunoprophylaxis program. From 1984 to 1993, 665 high-risk newborns born to HBeAg-positive HBsAg carrier mothers were prospectively recruited. The newborns were tested for HBsAg soon after birth, before hepatitis B immune globulin administration. All newborns received hepatitis B immune globulin within 24 hours after birth plus subsequent hepatitis B vaccination. Those who were seropositive for HBsAg at birth were regularly followed up for their hepatitis B virus (HBV) markers, liver function profiles, and alpha-fetoprotein levels from 1984 to 1996. Sixteen (2.4%) of the 665 subjects were found to be seropositive for HBsAg at birth, and all remained HBsAg-positive at 6 months of age. Twelve of the 16 received long-term follow-up care, and all were confirmed to have chronic HBV infection. Of the 12, 2 had HBeAg seroconversion, and 1 had alanine aminotransferase flares without HBeAg seroconversion. Delayed appearance of hepatitis B core antibody (anti-HBc) occurred in 2 without alanine aminotransferase elevation. Current immunoprophylaxis strategy does not protect

newborns with surface antigenemia, apparently acquired in utero, from becoming HBV carriers. Immunologic attempts to eliminate HBV may occur in carrier children infected in utero, despite their profound immune tolerance to HBV.

Van Damme P, Vorsters A. Hepatitis B control in Europe by universal vaccination programmes: the situation in 2001. *J Med Virol* 2002; 67:433-439.

Centre for the Evaluation of Vaccination, WHO Collaborating Centre for Prevention and Control of Viral Hepatitis, Department of Epidemiology and Social Medicine, University of Antwerpen, Antwerpen, Belgium. pierre.vandamme@ua.ac.be

In the nine years since the Global Advisory Group of the Expanded Programme on Immunisation (WHO) set 1997 as the target for integrating hepatitis B vaccination into national immunisation programmes worldwide, 129 countries have included hepatitis B vaccine as part of their routine infant or adolescent immunisation programmes (June 2001). By the end of 2002, 41 out of the 51 countries of the WHO European Region will be implementing universal hepatitis B immunisation. The rewards of effective implementation of the programmes in countries that started 10 years ago are becoming apparent; and their success offers an exemplary model for other countries. Some other countries, however, have difficulties to incorporate hepatitis B vaccine into universal childhood immunisation programmes, because of major economic constraints and the inability to procure a constant vaccine supply. The next decade will be characterised by expanded use of hepatitis B vaccines and the increasing efforts to sustain vaccine programmes and make the vaccine available to those countries and regions that cannot afford it. In Europe, as well as in the rest of the world, work still remains to be done to support and implement interventions that will bring us closer to the WHO goal and to eradicate hepatitis B.

Vranckx R, Alisjahbana A, Meheus A. Hepatitis B virus vaccination and antenatal transmission of HBV markers to neonates. *J Viral Hepat* 1999; 6:135-139.

Institute of Public Health, Brussels, Belgium.

The high prevalence of hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) in pregnant women is considered to be the most important factor contributing to the high carrier rate of HBsAg in some populations. Several factors, including the age at which infection occurs, predispose to the acquisition and frequency of the carrier state. The proportion of infected people who become chronic carriers ranges from about 80 to 95% for babies born to HBsAg/HBeAg-positive mothers. In this study of Indonesian infants receiving only active immunization against HBV, we measured the HBV markers passively acquired from their HBsAg-positive mothers. The relationship of these markers with vaccination response and with HBV infection status was studied longitudinally in the infants. In the exposed neonates from the HBsAg-positive mothers (n = 61), the seroconversion rate to hepatitis B surface antibody (HBsAb) positivity was 95% after the first booster vaccination, with a geometric mean titre (GMT) of 2017 IU/l. After 60 months, the GMT in this group decreased to 50 IU/l. Four newborns in this group became HBsAg carriers. Of the four vaccination failures, three newborns were HBsAg/HBeAg positive at birth, suggesting that they had been infected in utero. No vaccination strategy (active alone, or passive/active) can prevent this transmission from occurring. One carrier was HBsAg negative at birth and up to month 4 but was HBsAg positive at month 12 and subsequently, suggesting a postnatal infection. Vaccination early in life can, to a large extent, prevent perinatal transmission and hepatitis B virus (HBV) infection later in infancy and childhood. In this study, the protective efficacy of the vaccination was 85% in the subcohort of neonates from HBeAg-positive mothers and 100% in the subcohort of neonates from HBeAg-negative mothers. Lack of maternal antibodies to hepatitis B core antigen (HBcAb) correlated strongly with transmission of HBV infection.

Vryheid RE, Yu ES, Mehta KM, McGhee J. The declining prevalence of hepatitis B virus infection among Asian and Pacific Islander children. *Asian Am Pac Isl J Health* 2001; 9:162-178.

This article provides a review of the literature on the decline of hepatitis B virus (HBV) infection in Asian and Pacific nations having universal hepatitis B immunization programs. Papers on the epidemiology of HBV infection and hepatitis B immunization programs in Asian and Pacific nations were located by searching MEDLINE and libraries for publications in English, and by contacting hepatitis B experts. High endemicity for HBV in Asian and Pacific nations was partly caused by a cycle of high infectiousness, perinatal transmission, and chronic infection from early ages. Higher prevalence of infection has been found in men, some families, communities, and ethnic groups, and in people with high risk behaviors and situations, such as attending day care, getting injections, or sharing personal items. Incidence of acquisition of infection is about 2%-5% per year. Prevalence of HBV infection was declining in some nations before commencing hepatitis B immunization programs, probably because of improvements in medical practices and living conditions. Twenty-seven of 34 Pacific and East and Southeast Asian nations have attained > 70% hepatitis B vaccination coverage in infants, and twelve have documented reducing infection or liver cancer to fractions of their former rates. But the immunization programs may be causing natural selection of mutant hepatitis B viruses, necessitating study of the mutants, and modification of serological tests and vaccines. Practical implications for U.S. health professionals are: increasing HBV screening and hepatitis B vaccination of adolescents and adults from Asian and Pacific nations can prevent many infections and disease cases; most children coming from high coverage Asian and Pacific nations will be immune and few infected; we can learn much from these successful programs; and we should still make efforts to immunize Asian and Pacific children in the United States, and help Asian and Pacific nations which do not yet have highly successful hepatitis B immunization programs.

Wang JS, Chen H, Zhu QR. Transformation of hepatitis B serologic markers in babies born to hepatitis B surface antigen positive mothers. *World J Gastroenterol* 2005; 11:3582-3585.

The aim was to better understand the clinical significance of hepatitis B serologic markers in babies born to hepatitis B surface antigen (HBsAg) positive mothers, the incidence of maternal serologic markers of hepatitis B via placenta and its transformation in these babies were investigated. Mothers with positive HBsAg were selected in the third trimester of pregnancy. Their babies received immunoprophylaxis with hepatitis B immunoglobulin and hepatitis B vaccine after birth, and were consecutively followed up for hepatitis B serologic markers and HBV DNA at birth, mo 1, 4, 7, 12, and 24. Forty-two babies entered the study, including 16 born to hepatitis B e antigen (HBeAg)-positive HBsAg carrier mothers and 26 to HBeAg-negative HBsAg carrier mothers. Apart from four babies born to HBeAg-positive carrier mothers and demonstrated persistent positive HBeAg eventually became HBV carriers, all other babies developed anti-HBs before 12 mo of age. Among the other 12 babies born to HBeAg-positive carrier mothers, HBeAg was detected in 7 at birth, in 4 at mo 1, and in none of them thereafter. No antibody response to the transplacental HBeAg was detected. Among the babies born to HBeAg-negative carrier mothers, anti-HBe was detected 100% at birth and mo 1, in 88.5% at mo 4, in 46.2% at mo 7, in 4.2% at mo 12 and none in mo 24. Among all the immunoprophylaxis-protected babies born to either HBeAg-positive or HBeAg-negative carrier mothers, anti-HBc was detected in 100% at birth, mo 1 and mo 4, in 78.9% at mo 7, in 36.1% at mo 12 and in none at mo 24. HBeAg can pass through human placenta from mother to fetus and become undetectable before 4 mo of age, but no antibodies response to the transplacental HBeAg can be detected till mo 24 in the immunoprophylaxis-protected babies. The sole existence of anti-HBe before 1 year of age or anti-HBc before 2 years of age in babies born to HBsAg carrier mothers may simply represent the transplacental maternal antibodies, instead of indicators of HBV infection status.

Wang Z, Zhang J, Yang H, Li X, Wen S, Guo Y, Sun J, Hou J. Quantitative analysis of HBV DNA level and HBeAg titer in hepatitis B surface antigen positive mothers and their babies: HBeAg passage through the placenta and the rate of decay in babies. *J Med Virol* 2003; 71:360-366.

Department of Infectious Disease, Nanfang Hospital, The First Medical College of PLA, Guangzhou 510-515, PR China.

It is well documented that perinatal transmission is the major cause of chronic HBV infection in China. However, the mechanisms of HBV perinatal transmission are not defined clearly. It is not known whether hepatitis B e antigen can cross the human placenta, and the rate of HBeAg decay in babies with and without HBV breakthrough has not been studied. In this study, HBV serological markers were investigated in 95 hepatitis B surface antigen positive pregnant women. These markers were also studied in the babies at birth and at the age of 6 months and 12 months. The data show that 7.4% (7/95) children were infected with HBV during the first year after birth despite receiving passive-active immunoprophylaxis with hepatitis B immune globulin and hepatitis B vaccine. The surface gene fragment of HBV DNA was cloned and sequenced following PCR amplification in 7 cases of HBsAg positive babies and their mothers. All babies had the same sequences as their mothers, although two babies also had sequences that would produce an amino acid substitution within the 'a' determinant. Furthermore, we measured HBeAg titers and HBV DNA levels by using Abbott AxSYM system and LightCycler-based real-time fluorescence quantitative PCR in 54 mother-infant pairs. Thirty-three mothers were HBeAg positive, and 21 mothers were HBeAg negative. Seventy percent (23/33) of neonates from HBeAg-positive mothers were HBeAg positive at birth compared with 0% (0/21) of neonates from HBeAg negative mothers. HBeAg was present at higher titer in the birth sera of the babies with HBV breakthrough than in babies without breakthrough. HBeAg was cleared from the serum in all 19 babies without breakthrough. In 17 of these 19 babies, the HBeAg was cleared within 6 months, and in two babies clearance took 12 months. The mean serum HBV DNA level in the mothers of the 4 infants with HBV breakthrough was significantly higher than in the mothers of babies who did not become infected. In conclusion, this data suggests that HBeAg can cross the human placenta, and disappears from serum within 6 months in most babies. HBV DNA levels in hepatitis B carrier mothers are associated with the failure of HBIG and vaccine immunization, and the additional influence of transmitted HBeAg cannot be excluded.

Wilson HR. Hepatitis B and you: a patient education resource for pregnant women and new mothers. *J Womens Health (Larchmt)* 2003; 12:437-441.

Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia 30333, USA. hwilson@cdc.gov

An educational tool, Hepatitis B and You, has been designed to encourage women who test positive for hepatitis B virus (HBV) infection during pregnancy to become active participants in the care required to prevent perinatal HBV transmission to their infants. Hepatitis B and You presents information at a sixth-grade reading level and uses educational strategies that are known to work with people who have low literacy skills. Preliminary evaluation shows that 86% of respondents reported that their knowledge about hepatitis B improved after reading the slide set, 85% that the information was helpful, and 95% that the format was easy to follow.

Wong S, Chan LY, Yu V, Ho L. Hepatitis B carrier and perinatal outcome in singleton pregnancy. *Am J Perinatol* 1999; 16:485-488.

Department of Obstetrics & Gynecology, Princess Margaret Hospital, Hong Kong, PR China.

The objective of this article is to evaluate the effect of hepatitis B antigenemia on perinatal outcome. Perinatal outcome of 824 women with hepatitis B surface antigen (HBsAg) was compared with 6281 women without hepatitis B surface antigen (control) from June 1996 to September 1998. The maternal characteristics were comparable between the two groups. Perinatal outcome was comparable between groups. The incidences of preterm birth, premature prelabor rupture of membranes, prelabor rupture of membranes, small for gestational age, neonatal jaundice, fetal distress, perinatal asphyxia, congenital abnormality, gastrointestinal tract abnormality, and perinatal mortality were similar among the two groups. We conclude that the presence of hepatitis B surface antigen in pregnant women does not pose additional risk for the pregnancy.

Xia GL, Gong J, Wang JJ, Meng ZD, Jia ZY, Cao HL, Liu CB. Efficacy of recombinant hepatitis B vaccine and low-dose hepatitis B immune globulin in preventing mother-infant transmission of hepatitis B virus infection. *Zhonghua Liu Xing Bing Xue Za Zhi.* 2003; 24:362-365. [Article in Chinese]

Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 100052, PR China.

The objective was to determine the efficacy of recombinant hepatitis B (rHB) vaccine and low-dose hepatitis B immune globulin (HBIG) in the prevention of mother-infant transmission of hepatitis B virus (HBV) infection. rHB vaccine was administered to two groups of healthy neonates born to mothers with both hepatitis B surface antigen and e antigen positive in Guangxi, Hunan and Hebei province. Two hundred eighty-nine subjects were included in active immunization group, receiving triple doses of rHB vaccine given i.m. at 0, 1 and 6 month intervals; while 186 subjects receiving 50 IU HBIG at birth with triple doses of rHB vaccine in the low-dose HBIG group. Efficacy of active immunization alone was 87.8% (95% CI: 83.6 - 91.9). Efficacy of rHB vaccine and HBIG was 91.2% (95% CI: 86.7 - 95.6). No significant differences in efficacy by type of rHB vaccine ($P = 0.7072$), immunoprophylaxis programs ($P = 0.2955$) and regions of living ($P = 0.9987$) were noticed. Seroprotection rates (anti-HBs ≥ 10 mIU/ml) were detected in 91.1% and 93.5% in rHB vaccine alone recipients and rHB vaccine plus HBIG recipients, with geometric mean titer (GMT) of 153 mIU/ml and 164 mIU/ml at 1 year of age, respectively. Anti-rHBs decreased significantly with years after vaccination ($\chi^2 = 60.47$, $P = 0.0001$). Seroprotection rates of anti-rHBs antibodies decreased to 65.0% and 66.6% at 4 years of age in rHB vaccine alone recipients and rHB vaccine plus HBIG recipients, with GMT of 55 mIU/ml and 56 mIU/ml, respectively. These results suggested that the effectiveness of rHB vaccine plus low-dose HBIG was much better than only active plasma-derived vaccine; however, methods used for anti-rHBs assay need to be evaluated and verified.

Xu DZ, Yan YP, Choi BC, Xu JQ, Men K, Zhang JX, Liu ZH, Wang FS. Risk factors and mechanism of transplacental transmission of hepatitis B virus: a case-control study. *J Med Virol* 2002; 67:20-26.

Department of Epidemiology, Fourth Military Medical University, Xi'an, PR China.
xudezh@fmmu.edu.cn

Intrauterine hepatitis B virus (HBV) infection has been suggested to be caused by transplacental transmission that cannot be blocked by hepatitis B vaccine. This would decrease the effectiveness

of hepatitis B vaccine. This study examined the risk factors and mechanism of transplacental HBV transmission. A case-control study included 402 newborn infants from 402 HBsAg-positive pregnant women. Among these, 15 newborn infants infected with HBV by intrauterine transmission were selected as cases, and the rest as controls. A pathology study included 101 full-term placentas from the HBsAg-positive pregnant women above and 14 from HBsAg-negative pregnant women. Immunohistochemistry staining and HBV DNA in situ hybridization were used to estimate the association of intrauterine HBV infection and HBV infection in the placentas. HBeAg positivity in mothers' sera (OR = 17.07, 95%CI 3.39-86.01) and threatened preterm labor (OR = 5.44, 95%CI 1.15-25.67) were found to be associated with transplacental HBV transmission. The intrauterine infection rate increased linearly and significantly with maternal serum HBsAg titers (trend test $P = 0.0117$) and HBV DNA concentration (trend test $P < 0.01$). Results of the pathology study showed that HBV infection rates decreased gradually from the maternal side to the fetal side (trend test $P = 0.0009$) in the placental cell layers. There was a significant association between intrauterine HBV transmission and HBV infection in villous capillary endothelial cells (VCEC) in the placenta (OR = 18.46, $P = 0.0002$). The main risk factors for intrauterine HBV infection are maternal serum HBeAg positivity, history of threatened preterm labor, and HBV in the placenta especially the villous capillary endothelial cells. Previous reports of transplacental leakage of maternal blood causing intrauterine infection are confirmed. In addition, there appears to be a 'cellular transfer' of HBV from cell to cell in the placenta causing intrauterine infection. This latter hypothesis needs to be confirmed.

Xu D, Yan Y, Xu J. A molecular epidemiology study on risk factors and mechanism of HBV intrauterine transmission. *Zhonghua Yi Xue Za Zhi* 1999; 79:24-27. [Article in Chinese]

Department of Epidemiology, Fourth Military Medical University, Xi'an 710032, PR China.

The aim was to clarify the risk factors and mechanism of HBV intrauterine infection by molecular epidemiology method. We performed a case-control study. 402 HBsAg-positive pregnant women and their infants were collected as subjects. 15 infants infected by HBV intrauterine transmission were selected as case group and others as controls. Besides, HBsAg titer in 182 maternal sera and HBV DNA concentration in 185 maternal sera were determined. To identify the HBV infection in the placentas, immunohistochemistry stain and HBV DNA hybridization in situ were conducted. The data from both laboratory and epidemiological fields were analysed. The findings indicated that the positiveness of HBeAg in mother's sera (OR = 17.07) and the history of threatened premature labour (OR = 5.44) were the main risk factors. Intrauterine transmission was significantly related to HBsAg titers and HBV DNA concentration in mother's sera ($P = 0.01$). The results of immunochemistry stain and HBV DNA situ in hybridization in the placentas from 101 full-term pregnancy women showed that HBV infection rates had a decreasing trend ($P = 0.0009$) from mother's side to fetus's in placenta and there was a significant association between HBV intrauterine transmission and HBV infection in villous capillary endothelial cells in placenta (OR = 18.46, $P = 0.0002$). There might be a 'cellular transfer' of HBV infection in the placenta. With regard to the mechanism of HBV intrauterine transmission; there are two transmission routes, namely, hemogenous route and cellular route.

Yang YJ, Liu CC, Chen TJ, Lee MF, Chen SH, Shih HH, Chang MH. Role of hepatitis B immunoglobulin in infants born to hepatitis B e antigen-negative carrier mothers in Taiwan. *Pediatr Infect Dis J* 2003; 22:584-588.

Department of Pediatrics, Institute of Clinical Medicine, College of Medicine, National Cheng Kung University and Hospital, Tainan, Taiwan.

The efficacy of hepatitis B immunoglobulin (HBIG) in infants of hepatitis B e antigen (HBeAg)-negative hepatitis B surface antigen (HBsAg) carrier mothers in Taiwan is not clear. The objective

was to describe the responses of infants born to HBeAg-negative carrier mothers receiving HBIg combined with hepatitis B vaccine. Term babies born to HBeAg-negative carrier mothers were assigned based on chart number to 1 of the 2 treatment groups. Group A infants (n = 94) received 0.5 ml (145 IU) of HBIg within 24 h of birth and 3 subsequent doses of recombinant hepatitis B virus (HBV) vaccine at 3 to 5 days, 1 month and 6 months of age. Group B infants (n = 122) received 3 doses of vaccines only. Infants (n = 19) born to HBeAg-positive carrier mothers were treated like those in Group A and are referred to as Group C. Sera obtained from infants at 2 and 7 months of age were tested for hepatitis B virus (HBV) markers. There were 2 (1%; one in Group A and one in Group B) subclinical breakthrough hepatitis B infections among studied infants. One (5%) child of Group C had asymptomatic HBV infection at the age of 7 months and became a chronic carrier. The rate of protective anti-hepatitis B surface antibody (anti-HBs) titers achieved (> 10 mIU/ml) by 2 months of age was significantly higher in Group A than that in Group B (98% vs. 57%, $P < 0.001$). However, it was not different by 7 months of age. Infants (Group A) immunized with HBIg and vaccine had a significantly higher geometric mean titer (GMT, milli-International Units/ml) of anti-HBs than those (Group B) with vaccines only at 2 months of age ($P < 0.001$). Conversely at 7 months of age, the GMT of anti-HBs was significantly higher in infants who received vaccine only ($P = 0.001$). A protective level of antibodies was achieved earlier in those infants receiving both passive and active immunizations. However, infants receiving active immunizations alone achieved a higher GMT at 7 months of age. There was no clear benefit of passive-active vs. active immunization alone for chronic HBV infection in infants of HBsAg-positive, HBeAg-negative mothers.

Yao JL. Perinatal transmission of hepatitis B virus infection and vaccination in China. *Gut* 1996; 38(Suppl 2):S37-S38.

Department of Infectious Diseases, Sun Yat-Sen University of Medical Sciences, Guangzhou, PR China.

Hepatitis B remains one of the most important infectious diseases in China. In 1980, an overall hepatitis B virus (HBV) infection rate of 42.6% was reported and a hepatitis B surface antigen (HBsAg) carrier rate of 10.3%. HBsAg positivity among children under 1 year of age ranged from 5.1% in Beijing to 7% in Guangdong. A peak in carrier rate was observed in 7 to 14 year olds, reaching 24% in Guangdong. During the past decade, there has been no significant change in overall HBV carrier rates. However, in areas where hepatitis B vaccination for all neonates has been introduced, a decline in HBsAg positivity in lower age groups has been observed. Perinatal transmission is believed to account for 35-50% of carriers although horizontal transmission is also important, particularly within families. Infants born to HBeAg positive carrier mothers are at even greater risk of infection. HBV infection during childhood leads to an increased risk of serious longterm sequelae, including hepatocellular carcinoma (HCC). It is hoped that universal childhood immunisation will allow control of HBV infections in China within a few generations.

Yao GB. Importance of perinatal versus horizontal transmission of hepatitis B virus infection in China. *Gut* 1996; 38(Suppl 2):S39-S42.

Jingan Clinical Immunology Research Centre, Jingan Qu Central Hospital, Shanghai, PR China.

China has one of the highest rates of hepatitis B virus (HBV) endemicity in the world. In a survey of five provinces, the overall HBV infection rate in the general population was found to be 42.6%, with 10.3% testing positive for hepatitis B surface antigen (HBsAg). Higher rates were found in rural than in urban areas. The prevalence of HBsAg among children under 1 year of age is quite low but increases rapidly thereafter, reaching a peak among 5 to 9 year olds. The pattern of age distribution suggests that horizontal transmission is an important route of HBV infection during early childhood, and the proportion of chronic HBsAg carriage attributable to perinatal

transmission has been estimated at only 13-20%. Contact with infected family members probably accounts for much of the horizontal transmission in children. In a nationwide survey, 27.2% of families were found to have one or more HBsAg positive members and a strong tendency for family clustering has been identified. The strategy for prevention of HBV infection includes vaccination of all newborns, whether their mothers are HBsAg positive or negative, together with vaccination of high risk populations, and improved control measures in clinics and blood transfusion centres.

Yu XL, Chen CH, Zhong M. Reasons of failure in blocking mother-infant transmission of HBV by using vaccine and related strategies. *Zhonghua Hu Li Za Zhi* 1997; 32:69-71. [Article in Chinese]

Nanfang Hospital, First Medical College of PLA, Guangzhou, PR China.

We have detected the serum marker of HBV of 32 mothers whose HBsAg present positive and their children whom were given Hepatitis B vaccine immunization throughout duration of their mothers' pregnancy, altogether making up 66 cases. In 3 of these 32 families, Hepatitis B vaccine failed to block transmission between mother and infant. Direct nucleotide sequence analysis of HBV were carried out in 7 HBsAg-positive infected persons. To confirm the possibility of HBV transmission between mother and infant on molecular level, we used PCR technique and DNA sequencing method. The reasons of which HBV vaccine failed in blocking transmission were discussed at the point of views of virus variation. Besides, we make and emphasized discussion on how to tighten up the measurement of controlling the course of infection and protecting susceptible population.

Yue YF, Jiang H, Shi L, Li LF, Xi BS, Yu YL, Chen GF. Study on the mechanism of intrauterine infection of hepatitis B virus. *Zhonghua Fu Chan Ke Za Zhi* 2004; 39:224-226. [Article in Chinese]

Department of Obstetrics and Gynecology, First Hospital, Xi'an Jiaotong University, Xi'an 710061, PR China.

The aim was to study the possible mechanism of intrauterine infection of hepatitis B virus (HBV). HBV DNA was examined in amniotic fluid, and vaginal secretion of 59 HBsAg positive mothers and in cord blood of their neonates by PCR. Ten negative hepatitis B virus marker (HBVM) mothers and their neonates were served as control. HBsAg and HBcAg in placenta were examined by avidin biotin complex (ABC) method. The detection rate of HBV DNA in amniotic fluid, vaginal secretion and neonatal cord blood of the study group were 47.5% (28/59), 52.5% (31/59) and 45.8% (27/59) respectively. HBsAg and HBcAg in placenta was distributed in the following descending order: maternal decidual cells, trophoblastic cells, villous mesenchymal cells and villous capillary endothelial cells. But the distribution was in reverse order in 4 placentas. HBsAg and HBcAg were detected in amniotic epithelial cells in 32 mothers. The main route of HBV transmission from mother to fetus is transplacental, from maternal side of placenta to fetal side. However, HBV intrauterine infection may take place through other routes.

Yue Y, Yang X, Zhang S. Prevention of intrauterine infection by hepatitis B virus with hepatitis B immune globulin: efficacy and mechanism. *Chin Med J (Engl)* 1999; 112:37-39.

Department of Obstetrics and Gynecology and Lab of Hepatitis, First Clinical College of Xi'an Medical University, Xi'an 710061, PR China.

The objective was to evaluate the efficacy of hepatitis B immune globulin (HBIG) in preventing

intrauterine infection by hepatitis B virus (HBV) and to investigate its mechanism. Forty-eight pregnant women positive for hepatitis B surface antigen (HBsAg) were randomly divided into 2 groups. The 34 women in the study group were injected with HBIg during pregnancy; the other 14 women were controls. Maternal blood samples were taken before HBIg injection and at delivery. Neonatal blood samples were taken within 24 hours after birth before HBIg and hepatitis B vaccine were given. HBsAg and antibody to HBsAg (anti-HBs) were tested by radioimmunoassay. None of the 35 newborns (including 2 twins) in the study group was positive for HBsAg, but 3 (21%) in the control group were positive ($P = 0.02$). The HBsAg titers in the women in the study group decreased after HBIg injection. Of the 35 newborns in the study group, 32 (91%) were positive for anti-HBs. Systematic injections of HBIg during pregnancy may prevent intrauterine HBV infection, the mechanism of which may be reduction of maternal HBV viremia and production of fetal passive immunity.

Zamir C, Dagan R, Zamir D, Rishpon S, Fraser D, Rimon N, Ben Porath E. Evaluation of screening for hepatitis B surface antigen during pregnancy in a population with a high prevalence of hepatitis B surface antigen-positive/hepatitis B e antigen-negative carriers. *Pediatr Infect Dis J* 1999; 18:262-266.

Sub-District Health Office, Hadera, Israel. hdrzamir@matat.health.gov.il

Universal hepatitis B vaccination in infancy was implemented in Israel in 1992. The program consists of active vaccination at birth and at 1 and 6 months of age, without hepatitis B surface antigen (HBsAg) screening during pregnancy. Infants of HBsAg carrier mothers do not receive specific hepatitis B immunoglobulin in addition to vaccine at birth. The recently arrived Jewish immigrants from Ethiopia are the group with the highest rate of HBsAg carriage (approximately 10%) in Israel. The objective of this study was to evaluate whether the present policy is effective against perinatal HBV transmission from mothers of Ethiopian origin to their infants. The study group included 411 Israeli born children, offspring of mothers of Ethiopian origin. All infants were fully vaccinated starting at birth. Sera were collected from the children at the age of 9 to 36 months and from their mothers. Tests for HBsAg, antibodies to HBsAg (anti-HBs) and antibodies to hepatitis B core antigen (anti-HBc) were performed. Eighty-nine percent of the children had detectable anti-HBs, including 82.2% with protective anti-HBs concentrations ($> \text{ or } = 10 \text{ mIU/ml}$). Although 24 mothers (6.2%) were HBsAg carriers, none of the children was HBsAg-positive. Seven of 394 infants (1.7%) tested positive for anti-HBc. This test became negative in 5 of 6 who were followed for 12 months. The percentage of infants with protective anti-HBs concentrations decreased significantly from 91.4% at 9 to 12 months to 70.1% at 31 to 36 months of age. The mother's infection status was not associated with the infant's response to vaccine. Calculation based on the above data suggests that screening for HBsAg in pregnancy in that group is not cost-effective. Our results suggest that the Israeli vaccination program against HBV infection is effective, even in a high risk population, and additional measures are not cost-effective.

Zhu Q, Yu G, Yu H, Lu Q, Gu X, Dong Z, Zhang X. A randomized control trial on interruption of HBV transmission in uterus. *Chin Med J (Engl)* 2003; 116:685-687.

Department of Infection Diseases, Children's Hospital, Fudan University, Shanghai 200032, PR China. qrzhu@shmu.edu.cn

The aim was to study the interruptive effect of hepatitis B virus (HBV) specific immunoglobulin (HBIg) before delivery in attempt to prevent intrauterine transmission of HBV. Nine hundred and eighty HBsAg carrier pregnant women were randomly divided into HBIg group and control group. Each subject in the HBIg group received 200 IU or 400 IU of HBIg intramuscularly at 3, 2, and 1 month before delivery. The subjects in the control group did not receive any specific treatment. All newborn infants received 100 IU of HBIg intramuscularly after venous blood samples were taken

at birth and 2 weeks after birth, followed by 30 micro g plasma-derived HB vaccine or 5 µg recombinant yeast-derived hepatitis B vaccine at 1, 2 and 7 months of age. Blood tests were performed for all the lying-in women and their neonates. Blood specimens were tested for HBsAg and HBeAg by enzyme immunoassay. All infants were followed up for 1 year. In the HBIG group, 491 neonates were born to 487 HBV carrier mothers; and in the control group, 496 neonates were born to 493 HBV carrier mothers. The rates of intrauterine transmission in the two groups were 14.3% and 5.7% respectively ($\chi^2 = 20.280$, $P < 0.001$), and the rates of chronic hepatitis B in the two groups were 2.2% and 7.3% respectively ($\chi^2 = 13.696$, $P < 0.001$). The high risk factors of intrauterine HBV infection included HBsAg HBeAg double positive and HBV DNA positive in the peripheral blood of pregnant women. HBV infection in the uterus may be interrupted by injecting multiple intramuscular HBIG injections before delivery without causing any side-effects.

Zimmerman RK, Ruben FL, Ahwesh ER. Hepatitis B virus infection, hepatitis B vaccine, and hepatitis B immune globulin. *J Fam Pract* 1997; 45:295-315.

Hepatitis B virus (HBV) infection is a major health problem in the United States; in 1995, approximately 128,000 cases occurred. Transmission of HBV occurs primarily by blood exchange (e.g., by shared needles during injection drug use) and by sexual contact. Persons infected early in life are much more likely to become chronically infected than those infected during adulthood: as many as 90% of infants infected perinatally develop chronic infection and up to 25% will die of HBV-related chronic liver disease as adults. Clinical signs of acute hepatitis occur in about 50% of infected adults but in only 5% of infected preschool-aged children. In the United States, hepatitis B vaccine is currently made by recombinant DNA technology using baker's yeast. Preexposure vaccination results in protective antibody levels in almost all infants and children (> 95%) and healthy adults younger than 40 years of age (> 90%). The most common adverse event following administration of hepatitis B vaccine is pain at the injection site, which occurs in 13% to 29% of adult and 3% to 9% of children. A comprehensive hepatitis B vaccination policy is now recommended that includes (1) routine infant vaccination; (2) catch-up vaccination of 11- to 12-year-olds who were not previously vaccinated; (3) catch-up vaccination of young children at high risk for infection; (4) vaccination of adolescents and adults based on lifestyle or environmental, medical, and occupational situations that place them at risk; and (5) prevention of perinatal HBV infection.

Part II Additional bibliographical sources and websites

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