

## Position Paper on Hepatitis B Vaccines, Oct 2009

### **Key references in alphabetic order with summaries, when available**

**Amirzargar AA, Mohseni N, Shokrgozar MA, Arjang Z, Ahmadi N, Yousefi Behzadi M, Amanzadeh A, Shokri F. HLA-DRB1, DQA1 and DQB1 alleles and haplotypes frequencies in Iranian healthy adult responders and non-responders to recombinant hepatitis B vaccine. Iran J Immunol. 2008 Jun;5(2):92-9.**

**BACKGROUND:** Different studies have demonstrated that a small proportion of healthy individuals receiving the hepatitis B (HB) vaccine do not produce protective levels of anti-HB antibody, a phenomenon which could be linked to certain human leukocyte antigen (HLA) class-II alleles or haplotypes. **OBJECTIVES:** The present study was undertaken to determine the frequency of HLA class-II alleles in Iranian healthy adult responders and non-responders to HB vaccine. **METHODS:** Twelve non-responders (anti-HBs antibody < 10 IU/L) and 46 responders (anti-HBs antibody > 100 IU/L) were tissue typed for HLA class-II. HLA-DRB1, DQB1 and DQA1 alleles were determined using polymerase chain reaction based on sequence specific primers (PCR-SSP) technique. Accessibility to excess amount of genomic DNA was possible using Epstein-Barr virus (EBV)-transformed B-cells established from all vaccinees. **RESULTS:** Our results demonstrated increased frequencies of HLA- DRB107, DRB103, DRB104, DQB10201, DQA10201 alleles and HLA- DRB107/DQB10201/DQA10201 and DRB104/DQB10302/DQA103011 haplotypes in the non-responder group. Comparison between responders and non-responders revealed only a significant difference for DQB10201 allele ( $p < 0.05$ ). **CONCLUSION:** These findings confirm the association of certain HLA alleles and haplotypes with the lack of antibody response to HB vaccine in an Iranian population.

**Averhoff F, Mahoney F, Coleman P, Schatz G, Hurwitz E, Margolis H. Immunogenicity of hepatitis B Vaccines. Implications for persons at occupational risk of hepatitis B virus infection. Am J Prev Med. 1998 Jul;15(1):1-8**

**OBJECTIVE:** To assess risk factors for decreased immunogenicity among adults vaccinated with hepatitis B vaccine and to determine the importance of differences in immunogenicity between vaccines among health care workers (HCWs). **DESIGN:** Randomized clinical trial and decision analysis. **PARTICIPANTS:** HCWs. **MAIN OUTCOME MEASURES:** Development of seroprotective levels of antibody to hepatitis B surface antigen (anti-HBs) and the number of expected chronic hepatitis B virus (HBV) infections associated with lack of protection. **RESULTS:** Overall, 88% of HCWs developed seroprotection. Risk factors associated with failure to develop seroprotection included increasing age, obesity, smoking and male gender ( $P < .05$ ). Presence of a chronic disease was associated with lack of seroprotection only among persons  $\geq 40$  years of age ( $P < .05$ ). The two vaccines studied differed in their overall seroprotection rates (90% vs. 86%;  $P < .05$ ), however, this difference was restricted to persons  $\geq 40$  years of age (87% vs. 81%;  $P < .01$ ). Among HCWs  $\geq 40$  years of age, the decision analysis found 44 (0.34/100,000 person-years) excess chronic HBV infections over the working life of the cohort associated with use of the less immunogenic vaccine compared to the other. **CONCLUSIONS:** Hepatitis B vaccines are highly immunogenic, but have decreased immunogenicity associated with increasing age, obesity, smoking, and male gender; and among older adults, the presence of a chronic disease. One of the two available vaccines is more

immunogenic among older adults; however, this finding has little clinical or public health importance. Hepatitis B vaccines should be administered to persons at occupational risk for HBV infection early in their career, preferably while they are still in their training.

**Banatvala JE, Van Damme P. Hepatitis B vaccine -- do we need boosters? J. Viral Hepat. 2003 Jan;10(1):1-6.**

This review analyses the cumulated data from a number of long-term follow-up studies among infants, children and adults vaccinated against hepatitis B in industrialised and developing countries. Despite low or undetectable antibody responses years after vaccination, the development of HBsAg was a rarity and, if present, only transient. Some vaccinees developed anti-HBc responses but none developed an HB carrier state or clinical manifestations of disease. Studies demonstrating anamnestic responses among those with low or undetectable anti-HBs levels following challenge with HB vaccine, together with the production of anti-HBs in circulating B-cells by spot ELISA, confirmed the presence of immune memory among vaccinees. Anamnestic anti-HBs responses all correlate close in kinetics and magnitude with proliferative T-cell responses. The accumulated data from studies assessed in this Review indicate that protection is dependent on immune memory, rather than declining anti-HBs responses and add additional weight to the European Consensus recommendations (12) that following a complete course of vaccination, booster doses are unnecessary in immunocompetent persons. If implemented, this recommendation will have considerable cost benefits world-wide.

**Bavdekar SB, Maiya PP, Subba Rao SD, Datta SK, Bock HL. Immunogenicity and safety of combined diphtheria tetanus whole cell pertussis hepatitis B/ Haemophilus influenzae type b vaccine in Indian infants. Indian Pediatr. 2007 Jul;44(7):505-10.**

**OBJECTIVE:** To evaluate the immunogenicity of the Hepatitis B and Haemophilus influenzae type b components and the overall safety and reactogenicity of the DTPw-HBV/Hib vaccine when given as primary vaccination to Indian infants. **DESIGN AND METHODS:** At 3 centers in India, 225 healthy infants (who had received HBV at birth) received three doses of DTPw-HBV/Hib vaccine at 6, 10 and 14 weeks of age. Serum anti-HBs and anti-PRP antibody levels were measured prior to vaccination and one month post dose 3. Solicited local and general symptoms reported during the 4-day follow-up period and unsolicited adverse event reported during the 30-day follow-up period after each dose were recorded. Serious adverse events were recorded throughout the study. **RESULTS:** A total of 219 subjects completed the study. 2.7% and 11.5% of all administered doses led to redness and swelling >20 mm, respectively; only 3.6% of doses were followed by severe pain (cried when limb was moved, spontaneously painful) within 4 days after vaccination. Fever exceeding 39.5C was recorded following only one dose in one subject. The percentage of doses followed by severe solicited general symptoms (symptoms that prevented normal activity) did not exceed 0.8%. Two SAEs were reported, neither of which were considered as related to vaccination. One month post-dose 3, all subjects had seroprotective antiPRP antibody concentrations (> or =0.15 microgram/mL) and 98.6% had concentrations > or =1 microgram/mL; 99% were seropositive for antiHBs (concentrations > or = 3 mIU/mL) and 99% were seroprotected (concentrations > or = 10 mIU/mL). **CONCLUSION:** The combination DTPw-HBV/Hib vaccine is immunogenic (for the antigens tested), safe and well tolerated in Indian infants.

**Beasley RP, Hwang LY. Overview of the epidemiology of hepatocellular carcinoma. In: Hollinger FB, Lemon SM, Margolis HS, eds. Viral hepatitis and liver disease: proceedings of the 1990 International Symposium on Viral Hepatitis and Liver**

**Disease: contemporary issues and future prospects. Baltimore, Williams & Wilkins,1991: 532–535. (No summary)**

**Beasley RP, Hwang LY, Lee GC, Lan CC, Roan CH, Huang FY, Chen CL. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. Lancet. 1983 Nov 12;2(8359):1099-102.**

A randomised blind controlled trial of hepatitis B immune globulin (HBIG) plus hepatitis B vaccine for the prevention of the perinatally transmitted HBsAg carrier state was conducted in Taipei. Infants of e-antigen-positive HBsAg carrier mothers were given HBIG immediately after birth, and then one of three schedules of vaccination. There was no difference in efficacy between the three schedules; the combined efficacy was 94%, compared with that of HBIG alone (71%) or of vaccination alone (75%). Persistent HBs antigenaemia developed in only 9 (6%) of the 159 infants receiving prophylaxis, but in 88% of the controls. Antibodies developed in all those who did not become antigenaemic and presumably will provide long-term protection from hepatitis B virus infection. HBIG should be given as soon as possible after birth and need not be given again if the infant is subsequently vaccinated. With HBIG coverage from birth, the timing of the start of vaccination does not seem to be of importance within the first month of life, but to maximise compliance and minimise costs hepatitis B vaccination should be initiated during the confinement.

**Beran J. Safety and immunogenicity of a new hepatitis B vaccine for the protection of patients with renal insufficiency including pre-haemodialysis and haemodialysis patients. Expert Opin Biol Ther. 2008 Feb;8(2):235-47.**

**BACKGROUND:** High susceptibility to infections including the hepatitis B virus (HBV) causes increased morbidity and mortality in patients with end stage renal disease. HBV vaccination is recommended for all patients undergoing dialysis; however, antibody response is much lower than in healthy individuals. **OBJECTIVE:** This review discusses the clinical experience with HBV vaccine with a novel adjuvant system among dialysed patients. **METHOD:** A new adjuvanted HBV vaccine (Fendrix(), GlaxoSmithKline Biologicals, Rixensart, Belgium) contains as active substance 20 microg recombinant hepatitis B surface antigen produced in *Saccharomyces cerevisiae* and the novel adjuvant system composed of aluminum salt and 3-O-desacyl-4'-monophosphoryl lipid A (AS04). **CONCLUSION:** HBV-AS04 vaccine has a good safety profile with clinically acceptable reactions similar to standard HBV vaccines and has elicited earlier antibody response and higher antibody titres in pre and haemodialysis patients as compared with four double doses of standard HBV vaccine.

**Beutels P, Edmunds WJ, Antonanzas F, De Wit GA, Evans D, Feilden R, Fendrick AM, Ginsberg GM, Glick HA, Mast E, Pechevis M, Van Doorslaer EK, van Hout BA; Viral Hepatitis Prevention Board. Economic evaluation of vaccination programmes: a consensus statement focusing on viral hepatitis. Pharmacoeconomics. 2002;20(1):1-7.**

The methods that have been used to estimate the clinical and economic impact of vaccination programmes are not always uniform, which makes it difficult to compare results between economic analyses. Furthermore, the relative efficiency of vaccination programmes can be sensitive to some of the more controversial aspects covered by general guidelines for the economic evaluation of healthcare programmes, such as discounting of health gains and the treatment of future unrelated costs. In view of this, we interpret some aspects of these guidelines

with respect to vaccination and offer recommendations for future analyses. These recommendations include more transparency and validation, more careful choice of models (tailored to the infection and the target groups), more extensive sensitivity analyses, and for all economic evaluations (also nonvaccine related) to be in better accordance with general guidelines. We use these recommendations to interpret the evidence provided by economic evaluation applied to viral hepatitis vaccination. We conclude that universal hepatitis B vaccination (of neonates, infants or adolescents) seems to be the most optimal strategy worldwide, except in the few areas of very low endemicity, where the evidence to enable a choice between selective and universal vaccination remains inconclusive. While targeted hepatitis A vaccination seems economically unattractive, universal hepatitis A vaccination strategies have not yet been sufficiently investigated to draw general conclusions.

**Bialek SR, Bower WA, Novak R, Helgenberger L, Auerbach SB, Williams IT, Bell BP. Persistence of protection against hepatitis B virus infection among adolescents vaccinated with recombinant hepatitis B vaccine beginning at birth: a 15-year follow-up study. *Pediatr Infect Dis J.* 2008 Oct;27(10):881-5.**

**BACKGROUND:** Long-term follow-up studies of populations that received recombinant hepatitis B (HB) vaccination beginning at birth are limited. **METHODS:** Micronesian adolescents who had received 3 doses of recombinant HB vaccine (Recombivax 5 microg at birth, 2.5 microg at 2 months, 2.5 microg at 6 months) and tested negative for antibody to HB core antigen (anti-HBc) 2 years after primary vaccination (baseline testing) were followed up 15 years after primary vaccination. After testing for anti-HBc, HB surface antigen (HBsAg), and antibody to HBsAg (anti-HBs), participants received a booster dose of HB vaccine. An anamnestic response was defined as an increase in anti-HBs concentrations to a level  $\geq$  10 mIU/mL 14 days postbooster. **RESULTS:** Of the 105 participants, 42 (40.0%) had anti-HBs concentrations  $\geq$  10 mIU/mL on baseline testing. At 15 years, 8 (7.6%) were anti-HBc positive; none were HBsAg positive. Of the remaining 97, 7 (7.3%) had anti-HBs concentrations  $\geq$  10 mIU/mL. Of the 96 who received a booster dose, 46 (47.9%) had an anamnestic response; final antibody concentrations were 10-99 mIU/mL for 17 (17.7%) and  $>$  100 mIU/mL for 29 (30.2%). Participants with anti-HBs concentrations  $\geq$  10 mIU/mL on baseline testing were more likely to have an anamnestic response at 15 years [26/39 (66.7%) versus 20/57 (35.1%);  $P = 0.003$ ]. **CONCLUSIONS:** Fifteen years after primary vaccination starting at birth, 8% of participants had evidence of past HB virus infection, but none had chronic infection. Absence of an anamnestic response to an additional vaccine dose, seen in half of participants, might indicate waning immunity.

**Centers for Disease Control and Prevention (CDC). Implementation of newborn hepatitis B vaccination--worldwide, 2006. *MMWR Morb Mortal Wkly Rep.* 2008 Nov 21;57(46):1249-52**

Globally, hepatitis B virus (HBV) infections are a major cause of cirrhosis and liver cancer and result in an estimated 620,000 deaths annually. In 1992, the World Health Organization (WHO) set a goal for all countries to introduce hepatitis B (HepB) vaccine into national routine infant immunization programs by 1997. In countries where a high percentage of HBV infections are acquired perinatally (where general population prevalence of chronic HBV infection is  $\geq$  8%), WHO recommends administering the first HepB vaccine dose  $<$  24 hours after birth to prevent perinatal HBV transmission. To assess implementation of newborn HepB vaccination, the most recently available data were examined from the Joint Reporting Form used by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) to track worldwide vaccine coverage for WHO-recommended infant immunizations. In 2006, a total of 162 (84%)

of 193 countries had introduced HepB vaccine into their national infant immunization schedules. Among the 193 countries, 81 (42%) reported using a schedule with a HepB vaccine birth dose (defined as a dose administered within 24 hours of birth). Worldwide, 27% of newborns received a HepB vaccine birth dose in 2006. In the 87 countries with  $\geq 8\%$  chronic HBV infection prevalence, HepB vaccine birth dose coverage was 36%. These findings highlight the global need to implement this key hepatitis B prevention strategy more widely.

**Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, Liang DC, Shau WY, Chen DS. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. N Engl J Med. 1997 Jun 26;336(26):1855-9.**

**BACKGROUND:** A nationwide hepatitis B vaccination program was implemented in Taiwan in July 1984. To assess the effect of the program on the development of hepatocellular carcinoma, we studied the incidence of this cancer in children in Taiwan from 1981 to 1994. **METHODS:** We collected data on liver cancer in children from Taiwan's National Cancer Registry, which receives reports from each of the country's 142 hospitals with more than 50 beds. Data on childhood liver cancer were also obtained from Taiwan's 17 major medical centers. To prevent the inclusion of cases of hepatoblastoma, the primary analysis was confined to liver cancers in children six years of age or older. Data were also obtained on mortality from liver cancer among children. **RESULTS:** The average annual incidence of hepatocellular carcinoma in children 6 to 14 years of age declined from 0.70 per 100,000 children between 1981 and 1986 to 0.57 between 1986 and 1990, and to 0.36 between 1990 and 1994 ( $P < 0.01$ ). The corresponding rates of mortality from hepatocellular carcinoma also decreased. The incidence of hepatocellular carcinoma in children 6 to 9 years of age declined from 0.52 for those born between 1974 and 1984 to 0.13 for those born between 1984 and 1986 ( $P < 0.001$ ). **CONCLUSIONS:** Since the institution of Taiwan's program of universal hepatitis B vaccination, the incidence of hepatocellular carcinoma in children has declined.

**Cornejo-Juárez P, Volkow-Fernández P, Escobedo-López K, Vilar-Compte D, Ruiz-Palacios G, Soto-Ramírez LE. Randomized controlled trial of Hepatitis B virus vaccine in HIV-1-infected patients comparing two different doses. AIDS Res Ther. 2006 Apr 6;3:9.**

**BACKGROUND:** Co-infection with hepatitis B virus (HBV) and human immunodeficiency virus (HIV) is not infrequent as both share same route of exposure. The risk of developing chronic hepatitis B virus is 6%, in general population but can reach 10-20% in HBV/HIV co-infected patients. When compared to general population, the response rate to HBV vaccine in HIV-infected patients is diminished, so previous studies have tried to improve this response using variety of schedules, doses and co-administration of immunomodulators. The purpose of this study was to evaluate two doses of recombinant HBV vaccine (10 or 40 microg), IM at 0, 1 and 6 months. Vaccination response was measured 30-50 days after last dose; titers of  $> 9.9$  IU/L were considered positive. **RESULTS:** Seventy-nine patients were included, 48 patients (60.7%) seroconverted. Thirty-nine patients (49.3%) received 10 microg vaccine dose, 24 patients (61.5%) seroconverted. Forty patients (50.7%) received 40 microg vaccine dose, 24 (60%) seroconverted. There were no differences between two doses. A statistically significant higher seroconversion rate was found for patients with CD4 cell counts at vaccination  $>$  or = 200 cel/mm<sup>3</sup> (33 of 38 patients, 86.8%), compared with those with CD4  $<$  200 cel/mm<sup>3</sup> (15 of 41, 36.6%), [OR 11.44, 95% IC 3.67-35.59,  $p = 0.003$ ], there were no differences between two vaccine doses. Using the logistic regression model, CD4 count  $<$  200 cel/mm<sup>3</sup> were significantly

associated with non serologic response ( $p = 0.003$ ). None other variables such as gender, age, risk exposure for HIV, viral load, type or duration of HAART or AIDS-defining illness, were associated with seroconversion. **CONCLUSION:** In this study, an increase dose of HBV vaccine did not show to increase the rate of response in HIV infected subjects. The only significant findings associated to the response rate was that a CD4 count  $\geq 200$  cel/mm<sup>3</sup>, we suggest this threshold at which HIV patients should be vaccinated.

**de la Hoz F, Perez L, de Neira M, Hall AJ. Eight years of hepatitis B vaccination in Colombia with a recombinant vaccine: factors influencing hepatitis B virus infection and effectiveness. *Int J Infect Dis.* 2008 Mar;12(2):183-9.**

**OBJECTIVE:** To evaluate the effectiveness of a recombinant hepatitis B vaccine used in endemic areas of Colombia, as well as risk factors associated with hepatitis B virus (HBV) infection and carriage after vaccine introduction. **METHODS:** A cross-sectional study was carried out in urban and rural areas of the Colombian Amazon, a highly endemic area for hepatitis B infection. Children under 12 years of age and their mothers were selected for the study using one-stage cluster sampling ( $N=2145$ ) and were examined for HBV serological markers and antibodies against surface antigen (anti-HBs). **RESULTS:** There has been a reduction of 60-75% in the prevalence of HBV infection and hepatitis B surface antigen (HBsAg) carriage since HBV vaccination was introduced. Receiving the first dose of HBV vaccine at more than two months after birth was one of the factors associated with HBV carrier status. Maternal HBV infection was also associated with infection in the child. **CONCLUSIONS:** The recombinant Cuban hepatitis B vaccine has contributed to the reduction of the infection in this highly endemic area, though further efforts are required to improve timely vaccination for children at high risk.

**Duclos P. Safety of immunisation and adverse events following vaccination against hepatitis B. *Expert Opinion on Drug Safety,* 2003,2:225-231. (No summary)**

**Dumolard L et al. Implementation of newborn hepatitis B vaccination--worldwide, 2006. *MMWR Morb Mortal Wkly Rep.* 2008 Nov 21;57(46):1249-52**

Globally, hepatitis B virus (HBV) infections are a major cause of cirrhosis and liver cancer and result in an estimated 620,000 deaths annually. In 1992, the World Health Organization (WHO) set a goal for all countries to introduce hepatitis B (HepB) vaccine into national routine infant immunization programs by 1997. In countries where a high percentage of HBV infections are acquired perinatally (where general population prevalence of chronic HBV infection is  $\geq 8\%$ ), WHO recommends administering the first HepB vaccine dose  $<24$  hours after birth to prevent perinatal HBV transmission. To assess implementation of newborn HepB vaccination, the most recently available data were examined from the Joint Reporting Form used by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) to track worldwide vaccine coverage for WHO-recommended infant immunizations. In 2006, a total of 162 (84%) of 193 countries had introduced HepB vaccine into their national infant immunization schedules. Among the 193 countries, 81 (42%) reported using a schedule with a HepB vaccine birth dose (defined as a dose administered within 24 hours of birth). Worldwide, 27% of newborns received a HepB vaccine birth dose in 2006. In the 87 countries with  $\geq 8\%$  chronic

HBV infection prevalence, HepB vaccine birth dose coverage was 36%. These findings highlight the global need to implement this key hepatitis B prevention strategy more widely.

**EASL Clinical Practice Guidelines: Management of chronic hepatitis B. *Journal of Hepatology*, 2009, 50:227-242.** (No summary)

**European Consensus Group on Hepatitis B Immunity. Are booster immunisations needed for lifelong hepatitis B immunity? *European Consensus Group on Hepatitis B Immunity. Lancet*. 2000 Feb 12;355(9203):561-5.**

Long-term protection against clinically significant breakthrough hepatitis B (HB) virus infection and chronic carriage depends on immunological memory, which allows a protective anamnestic antibody response to antigen challenge. Memory seems to last for at least 15 years in immunocompetent individuals. To date there are no data to support the need for booster doses of HB vaccine in immunocompetent individuals who have responded to a primary course. All adequately vaccinated individuals have shown evidence of immunity in the form of persisting anti-HBs and/or in vitro B-cell stimulation or an anamnestic response to a vaccine challenge. Nonetheless several countries and individuals currently have a policy of administering booster doses to certain risk groups. Boosters may be used to provide reassurance of protective immunity against benign breakthrough infection. For immunocompromised patients, regular testing for anti-HBs, and a booster injection when the titre falls below 10 mIU/mL, is advised. Long-term monitoring should continue, to confirm the absence of clinically significant breakthrough episodes of hepatitis B and to find out if a carrier state develops after 15 years. Also, non-responders to a primary course should continue to be studied.

**Floreani A, Baldo V, Cristofolletti M, Renzulli G, Valeri A, Zanetti C, Trivello R. Long-term persistence of anti-HBs after vaccination against HBV: an 18 year experience in health care workers. *Vaccine*. 2004 Jan 26;22(5-6):607-10.**

The aim of the present study was to evaluate the long-term persistence of seroprotection after hepatitis B virus (HBV) vaccination. A total of 422 health care workers (HCWs) were evaluated 4.8-18.8 years after primary immunization (mean follow-up 11.8 years); 241 of them had received plasma-derived vaccines and 181 had been given yeast-derived vaccines; 107 subjects received a booster dose of yeast-derived vaccine 6 years after primary immunization with either plasma-derived or yeast-derived vaccines. Seroprotection was assumed when the anti-HBs titers were >10 mIU/ml. The overall response after primary immunization was 98.8%. Among subjects who reached a 10 year follow-up, those treated with plasma-derived vaccine had a seroprotection rate of 87.8 compared to 81.6% of those vaccinated with yeast-derived vaccines ( $P<0.001$ ). Anti-HBs geometric mean titers (GMTs) after primary immunization were similar in the two groups, but were significantly lower at 10 years follow-up in the group that had received a yeast-derived vaccine (104 mIU/ml versus 244 mIU/ml in those who used a plasma-derived vaccine,  $P<0.05$ ). Anti-HBs GMTs in the 107 subjects given the booster dose were 242 mIU/ml pre-booster titer, and rose to 35,171 mIU/ml after the booster dose. A mean 10.1 years after the booster dose, GMTs were 952 mIU/ml. Overall, the anti-HBs seroprotection rate was 95.4% (102 subjects). Based on GMT results, no booster dose is necessary in healthy adults for at least 10 years after primary immunization.

**Global and regional immunization profile. Geneva, World Health Organization, Vaccine-preventable diseases monitoring system, 2009.**  
[http://www.who.int/immunization\\_monitoring/en/globalsummary/GS\\_GLOProfile.pdf](http://www.who.int/immunization_monitoring/en/globalsummary/GS_GLOProfile.pdf), accessed 4 September 2009).

**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 Dec;34(6):1329-39.**

**BACKGROUND:** Limited data are available regarding global hepatitis B virus (HBV)-related morbidity and mortality and potential reduction in disease burden from hepatitis B vaccination. **METHODS:** 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. **RESULTS:** 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 > or = 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. **CONCLUSION:** 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.

**Goldstein ST, Alter MJ, Williams IT, Moyer LA, Judson FN, Mottram K, Fleenor M, Ryder PL, Margolis HS. Incidence and risk factors for acute hepatitis B in the United States, 1982-1998: implications for vaccination programs. *J Infect Dis.* 2002 Mar 15;185(6):713-9.**

From 1982-1998, enhanced sentinel surveillance for acute hepatitis B was conducted in 4 counties in the United States to determine trends in disease incidence and risk factors for infection. During this period, the reported incidence of acute hepatitis B declined by 76.1% from 13.8 cases per 100,000 in 1987 to 3.3 cases per 100,000 in 1998. Cases associated with injection drug use (IDU) decreased by 90.6%, men who have sex with men (MSM) by 63.5%, and heterosexual activity by 50.7%. During 1994-1998, the most commonly reported risk factor for infection was high-risk heterosexual activity (39.8%) followed by MSM activity (14.6%) and IDU (13.8%). Over half of all patients (55.5%) reported treatment for a sexually transmitted disease (STD) or incarceration in a prison or jail prior to their illness, suggesting that more than half of the acute hepatitis B cases might have been prevented through routine hepatitis B immunization in STD clinics and correctional health care programs.

**Griffiths UK, Hutton G, Das Dores Pascoal E. The cost-effectiveness of introducing hepatitis B vaccine into infant immunization services in Mozambique. Health Policy Plan. 2005, Jan;20(1):50-9.**

**OBJECTIVE:** To estimate the cost-effectiveness of introducing hepatitis B vaccine into routine infant immunization services in Mozambique, which took place in the year 2001. **METHODS:** A decision analytic model was used to estimate the impact of hepatitis B vaccination. This model was developed for the WHO to estimate the global burden of disease from hepatitis B. Cost data of vaccine delivery and medical treatment related to hepatitis B infection were collected for the analysis. **FINDINGS:** The introduction of hepatitis B vaccine has increased the annual budget for immunization services by approximately 56%. It is predicted that more than 4000 future deaths are averted annually by the intervention. In the base case scenario, the incremental costs per undiscounted deaths averted amount to US\$436, and the costs per undiscounted DALY averted amount to US\$36. Since the major impact of hepatitis B vaccination will not start to be evident for at least another 40 years (deaths from hepatitis B mainly occur between 40-60 years of age), the cost per DALY averted rises to US\$47, when using a discount rate of 3% on health effects. We found that the monovalent hepatitis B vaccine was considerably more cost-effective than the hepatitis B vaccine in combination with DTP. **INTERPRETATION:** If policy makers value future health benefits equal to current benefits, the cost-effectiveness of infant hepatitis B vaccination is in the range of other primary health care interventions for which similar analysis has been undertaken.

**Hammitt LL, Hennessy TW, Fiore AE, Zanis C, Hummel KB, Dunaway E, Bulkow L, McMahon BJ. Hepatitis B immunity in children vaccinated with recombinant hepatitis B vaccine beginning at birth: a follow-up study at 15 years. Vaccine. 2007 Sep 28;25(39-40):6958-64.**

**BACKGROUND:** The duration of protection after hepatitis B vaccination of infants is unknown. We determined antibody to hepatitis B surface antigen (anti-HBs) and response to a booster dose 15 years after vaccination among Alaskan children born to hepatitis B surface antigen-negative mothers. These children had protective anti-HBs concentrations when tested after receiving a three-dose series of 2.5 microg recombinant hepatitis B vaccine starting at birth. **METHODS:** Participants received 5 microg of recombinant hepatitis B vaccine. Sera were collected at baseline, 10-14 days and 1 month after vaccination, and tested for antibody to hepatitis B core antigen (anti-HBc) and anti-HBs. An anamnestic response was defined as an anti-HBs increase within 15 days, from either undetectable to  $\geq 10$  mIU/mL, or, if the baseline concentration was detectable, a 4-fold increase. **RESULTS:** None of 37 participants (mean age 14.6 years) were anti-HBc positive. An anamnestic response (GMC=254 mIU/mL, range 16-2767 mIU/mL) was observed in 18 (51%) of 35 participants who had sera collected within 15 days after the booster. **CONCLUSIONS:** In this small study, half of children who had received hepatitis B vaccine starting at birth did not have evidence of immune memory as measured by development of anamnestic responses to booster vaccination. Additional studies are needed to assess whether this indicates susceptibility to infection and whether persons vaccinated starting at birth may benefit from a hepatitis B vaccine booster to maintain long-term protection.

**Harris A, Yong K, Kermode M. An economic evaluation of universal infant vaccination against hepatitis B virus using a combination vaccine (Hib-HepB): a decision analytic approach to cost effectiveness. Aust N Z J Public Health. 2001 Jun;25(3):222-9.**

**OBJECTIVE:** To evaluate the health impact and cost effectiveness of two infant vaccination strategies for protection against hepatitis B virus (HBV) infection in the Australian population.

Vaccinating only high-risk infants, assuming 65% compliance, was compared with universal vaccination of infants using a combination Hib-HepB vaccine, with 87.4% compliance. **METHOD:** A Markov model simulated the natural history of HBV infection and disease in an Australian birth cohort. The cohort was divided into those at high risk of infection (infants born into high-risk families) and low-risk infants. Clinical and epidemiological data used were obtained from published reports and a survey of clinical experts. The model included the health costs associated with acute and chronic HBV infection, and the sequelae of chronic HBV infection. **RESULTS:** The model predicted that universal hepatitis B vaccination of an Australian birth cohort (260,000 births) would result in a 77% reduction in cases of HBV infection. The incremental cost per life year gained was \$11,862, which is low compared with many other health care interventions. With no discounting of costs or consequences, universal vaccination with the combination vaccine was predicted to save lives and reduce costs. **CONCLUSION:** There is no socially accepted threshold value for cost per life year gained to guide decisions about funding Australian health care interventions. Nevertheless, based on these results, universal hepatitis B vaccination of Australian infants using a combination Hib-HepB vaccine would almost certainly be regarded as a worthwhile investment of public funds.

**Heininger U; DTP-HBV-IPV-059 Study Group; DTP-HBV-IPV-096 Study Group, Sanger R, Jacquet JM, Schuerman L. Booster immunization with a hexavalent diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus vaccine and Haemophilus influenzae type b conjugate combination vaccine in the second year of life: safety, immunogenicity and persistence of antibody responses. Vaccine. 2007 Jan 22;25(6):1055-63.**

The immunogenicity and reactogenicity of booster vaccination with GSK Biologicals' hexavalent DTPa-HBV-IPV/Hib vaccine was assessed in toddlers aged 12-18 months previously primed with the same combination (N=341), or with DTPa-IPV/Hib and HBV administered separately (N=102; Trials 217744/059 and 217744/096). Antibody persistence at age 4-6 years was also assessed in children who had received a 4th consecutive dose of DTPa-HBV-IPV/Hib vaccine or separate DTPa-IPV/Hib and HBV vaccines in this study and in another study conducted under similar conditions in Germany. Prior to booster vaccination in the second year of life, antibody concentrations and seroprotection rates were similar irrespective of the primary vaccine used. One month after boosting with DTPa-HBV-IPV/Hib, substantial antibody increases were observed against all vaccine antigens indicative of previous immune priming. Seropositivity and booster response rates against all antigens were 97.4-100%. Reactogenicity following booster vaccination with DTPa-HBV-IPV/Hib was similar regardless of the primary regimen used. Three to four years after administration of the 4th DTPa-HBV-IPV/Hib dose, >90% vaccinees had persistent protective antibody concentrations against diphtheria, hepatitis B, Hib and the three poliovirus types. Anti-tetanus antibody concentrations were  $\geq 0.1$  IU/ml in 76.4% subjects and seropositivity for pertussis antibodies ranged from 34.5% for PT to 98.9% for FHA. In conclusion, the combined hexavalent DTPa-HBV-IPV/Hib vaccine is immunogenic and safe when used for boosting in the second year of life, regardless of the primary vaccine used, and offers sustained protection during early childhood and beyond.

**Hyams KC. Risks of chronicity following acute hepatitis B virus infection: a review. Clin Infect Dis. 1995 Apr;20(4):992-1000.**

A bibliographic search was conducted of English-language articles dealing with chronic hepatitis B virus (HBV) infection to evaluate the risk of chronicity following acute infection. Chronic HBV infection was defined as carriage of hepatitis B surface antigen (HBsAg) for at least 6 months. On the basis of incidence studies employing standard serological test methods,

the highest risk (80%-90%) of chronic infection was found to be among infected neonates born to hepatitis B e antigen-positive carrier mothers. Of children infected before 6 years of age, chronic infection was reported to develop in approximately 30%. A relatively wide range of risks (< 1%-12%) was found among diverse populations of older children and adults. However, most of the 10 identified incidence studies of generally healthy adults indicated that the risk of chronicity is very low: < or = 5% in eight studies. In addition, the pooled incidence of chronicity was < 5% among two different adult population groups: initially uninfected subjects, who usually experienced asymptomatic infection, and patients presenting with acute hepatitis B. In addition to the primary influence of age, the studies revealed a higher risk of chronic HBV infection among males and among patients with impaired immunity due to various causes.

**Jack AD, Hall AJ, Maine N, Mendy M, Whittle HC. What level of hepatitis B antibody is protective? J Infect Dis. 1999 Feb;179(2):489-92.**

This study assessed the level of vaccine-induced hepatitis B surface antibody that is protective against hepatitis B infection and carriage in The Gambia. Sera from 700 of a cohort of 1041 children vaccinated against hepatitis B in infancy were serially tested for markers of hepatitis B until age 7 years. No absolute level of protection against infection was found, but all children who attained a peak antibody response to vaccination of  $\geq 10$  IU/L were protected against carriage of hepatitis B surface antigen. Two-thirds of 45 infected children experienced brief infection (determined by loss of core antibody). This transient infection was likely related to surface antibody level. The data support the use of the peak antibody response as the best indicator of protection against carriage and suggest that most infections after vaccination are short-lived.

**Kim SY, Salomon JA, Goldie SJ. Economic evaluation of hepatitis B vaccination in low-income countries: using cost-effectiveness affordability curves. Bull World Health Organ. 2007 Nov;85(11):833-42.**

**OBJECTIVE:** We sought to describe a method that explicitly considers both a health-care programme's cost-effectiveness and its affordability. For illustration, we apply the method to the programme to vaccinate infants against hepatitis B in the Gambia. **METHODS:** We synthesized selected data and developed a computer-based model from the societal and payer perspectives to evaluate the cost-effectiveness of routine infant vaccination against hepatitis B in the Gambia compared with no vaccination. The primary outcome measure was cost per averted disability-adjusted life year (DALY), which was expressed in 2002 US dollars. We used Monte Carlo methods for uncertainty analysis to examine the affordability of the programme from the payers perspective, and we derived an affordability curve and cost-effectiveness affordability curves for the programme. **FINDINGS:** In the Gambia, vaccinating infants against hepatitis B is highly cost-effective. Compared with offering no intervention, the vaccination programme would cost US\$ 28 per DALY averted from the societal perspective or US\$ 47 per DALY averted from the payers perspective. The programme also has the potential to be affordable, starting at a relatively low budget of US\$ 160,000 per year. Combining the two dimensions of the outcome measure, the probability that vaccinating infants would be both cost-effective and affordable is 40% at an annual programme budget of US\$ 182,000 (the estimated total programme cost from the payers perspective), given a threshold cost-effectiveness value of US\$ 47 per DALY averted. **CONCLUSION:** In the face of uncertainties about both the health and economic consequences of a vaccine programme, as well as the availability and magnitude of resources needed to fund the programme, cost-effectiveness affordability curves can provide information

to decision-makers about the probability that a programme will be both cost-effective and affordable: these are distinct but equally relevant considerations in resource-poor settings.

**Kong NC, Beran J, Kee SA, Miguel JL, Sánchez C, Bayas JM, Vilella A, Calbo-Torrecillas F, López de Novales E, Srinivasa K, Stoffel M, Hoet B. A new adjuvant improves the immune response to hepatitis B vaccine in hemodialysis patients. *Kidney Int.* 2008 Apr;73(7):856-62.**

Prehemodialysis and hemodialysis patients are at an increased risk of hepatitis B infection and have an impaired immune response to hepatitis B vaccines. We evaluated the immune response to the new adjuvant of hepatitis B vaccine AS04 (HBV-AS04) in this population. We measured antibody persistence for up to 42 months, and the anamnestic response and safety of booster doses in patients who were no longer seroprotected. The primary vaccination study showed that HBV-AS04 elicited an earlier antibody response and higher antibody titers than four double doses of standard hepatitis B vaccine. Seroprotection rates were significantly higher in HBV-AS04 recipients throughout the study. The decline in seroprotection over time was significantly less in the HBV-AS04 group with significantly fewer primed patients requiring a booster dose over the follow-up period. Solicited/unsolicited adverse events were rare following booster administration. Fifty-seven patients experienced a serious adverse event during the follow-up; none of which was vaccine related. When HBV-AS04 was used as the priming immunogen, the need for a booster dose occurred at a longer time compared to double doses of standard hepatitis B vaccine. Hence, in this population, the HBV-AS04 was immunogenic, safe, and well-tolerated both as a booster dose after HBV-AS04 or standard hepatitis B vaccine priming.

**Lee C, Gong Y, Brok J, Boxall EH, Glud C. Hepatitis B immunisation for newborn infants of hepatitis B surface antigen-positive mothers. *Cochrane Database Syst Rev.* 2006 Apr 19;(2):CD004790.**

**BACKGROUND:** Hepatitis B vaccine and hepatitis B immunoglobulin are considered for newborn infants of HBsAg-positive mothers to prevent hepatitis B infection. **OBJECTIVES:** To assess the beneficial and harmful effects of hepatitis B vaccines and hepatitis B immunoglobulin in newborn infants of HBsAg-positive mothers. **SEARCH STRATEGY:** Trials were identified through The Cochrane Neonatal Group Controlled Trials Register, The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Central Register of Controlled Trials in The Cochrane Library, MEDLINE, and EMBASE (until February 2004), authors of trials, and pharmaceutical companies. **SELECTION CRITERIA:** Randomised clinical trials comparing: plasma-derived vaccine (PDV) or recombinant vaccine (RV) versus no intervention, placebo, or other active vaccines; hepatitis B immunoglobulin versus no intervention, placebo, or other control immunoglobulin; as well as PDV or RV plus hepatitis B immunoglobulin versus no intervention, placebo, or other control vaccines or immunoglobulin. **DATA COLLECTION AND ANALYSIS:** Outcomes are assessed at maximal follow-up. The primary outcome measure was hepatitis B occurrence, based on a blood specimen positive for HBsAg, HBeAg, or antibody to hepatitis B core antigen (anti-HBc). Binary outcomes are reported as relative risks (RR) with 95% confidence interval (CI). Subgroup analyses were performed with regard to methodological quality of the trial, mother's HBe-Ag status, and time of immunisation after birth. **MAIN RESULTS:** We identified 29 randomised clinical trials, five of which were considered high quality. Only three trials reported inclusion of hepatitis B e-antigen negative mothers. Compared with placebo/no intervention, vaccine reduced hepatitis B occurrence (RR 0.28, 95% confidence interval (CI) 0.20 to 0.40, 4 trials). No significant differences of hepatitis

B occurrence were found comparing recombinant vaccine (RV) versus plasma-derived vaccine (PDV) (RR 1.00, 95% CI 0.71 to 1.42, 4 trials) and high-dose versus low-dose vaccine (PDV: RR 0.97, 95% CI 0.55 to 1.68, 3 trials; RV: RR 0.78, 95% CI 0.31 to 1.94, 1 trial). Compared with placebo/no intervention, hepatitis B immunoglobulin or the combination of vaccine plus hepatitis B immunoglobulin reduced hepatitis B occurrence (hepatitis B immunoglobulin: RR 0.50, 95% CI 0.41 to 0.60, 1 trial; PDV plus hepatitis B immunoglobulin: RR 0.08, 95% CI 0.03 to 0.17, 3 trials). Compared with vaccine, vaccine plus hepatitis B immunoglobulin reduced hepatitis B occurrence (RR 0.54, 95% CI 0.41 to 0.73, 10 trials). Hepatitis B vaccine and hepatitis B immunoglobulin seem safe, but few trials reported on adverse events. AUTHORS' CONCLUSIONS: Vaccine, hepatitis B immunoglobulin, and vaccine plus hepatitis B immunoglobulin prevent hepatitis B occurrence in newborn infants of HBsAg positive mothers.

**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 Jun;83(6):456-61.**

**OBJECTIVE:** 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. **METHODS:** 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. **FINDINGS:** 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). **CONCLUSION:** 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.

**Liaw YF, Leung N, Kao JH, Piratvisuth T, Gane E, Han KH, Guan R, Lau GK, Locarnini S; for the Chronic Hepatitis B Guideline Working Party of the Asian-Pacific Association for the Study of the Liver. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. Hepatol Int. 2008 Sep;2(3):263-283.**

Large amounts of new data on the natural history and treatment of chronic hepatitis B virus (HBV) infection have become available since 2005. These include long-term follow-up studies in large community-based cohorts or asymptomatic subjects with chronic HBV infection, further studies on the role of HBV genotype/naturally occurring HBV mutations, treatment of drug resistance and new therapies. In addition, Pegylated interferon alpha2a, entecavir and telbivudine have been approved globally. To update HBV management guidelines, relevant new data were reviewed and assessed by experts from the region, and the significance of the reported findings were discussed and debated. The earlier "Asian-Pacific consensus statement on the management of chronic hepatitis B" was revised accordingly. The key terms used in the statement were also defined. The new guidelines include general management, special indications for liver biopsy in patients with persistently normal alanine aminotransferase, time to start or stop drug therapy, choice of drug to initiate therapy, when and how to monitor the patients during and after stopping drug therapy. Recommendations on the therapy of patients in special circumstances, including women in childbearing age, patients with antiviral drug resistance, concurrent viral infection, hepatic decompensation, patients receiving immune-

suppressive medications or chemotherapy and patients in the setting of liver transplantation, are also included.

**Lok AS and McMahon BJ, AASLD Practice Guidelines: Chronic Hepatitis B: Update 2009. *Hepatology*, 2009, 50:1-36. (No summary)**

**Losonsky GA, Wasserman SS, Stephens I, Mahoney F, Armstrong P, Gumper K, Dulkerian S, West DJ, Gewolb IH. Hepatitis B vaccination of premature infants: a reassessment of current recommendations for delayed immunization. *Pediatrics*. 1999 Feb;103(2):E14.**

**OBJECTIVE:** Current American Academy of Pediatrics and United States Public Health Service Immunization Practices Advisory Committee recommendations for hepatitis B immunization in premature infants weighing <2 kg at birth born to hepatitis B surface antigen (HBSAg)-negative mothers are to delay the initiation of vaccination until such infants reach 2 kg or until 2 months of age. This proposal to delay vaccination at birth in these low-risk infants was based on limited studies not conducted in the United States. We sought to reassess current recommendations to delay administration of hepatitis B vaccine in low-risk premature infants by determining the immunogenicity of early hepatitis B vaccination in a US population and identifying variables associated with poor immunogenicity. **METHODS:** A total of 148 infants <37 weeks' gestation born to mothers negative for HBSAg were recruited at birth and stratified to three birth weight groups: <1000 g, 1000 to 1500 g, and >1500 g. Recombinant hepatitis B vaccine was administered within the first week of life, at 1 to 2 months of age, and at 6 to 7 months of age. Serum obtained at birth and after the second and third doses of vaccine was tested for antibody to HBSAg. Variables associated with poor response were sought prospectively by collecting demographic and clinical data. **RESULTS:** A total of 118 subjects (83%) completed the study. Postsecond dose sera were available for 117 infants and postthird dose sera were available for 112 infants. The seroprotection rate (attaining  $\geq 10$  mIU/mL HBS antibody) after two doses was low (25%) regardless of birth weight; infants weighing <1000 g at birth had the poorest response (11%). The seroprotection response rate after three doses of vaccine increased with birth weight; infants weighing  $\leq 1500$  g at birth (groups 1 and 2) had lower rates of response (52% and 68%, respectively) than did infants weighing >1500 g at birth (group 3; 84% response rate). The seroprotection response rate of group 3 infants after three doses of vaccine, although low, could not be differentiated from the response rates reported for full-term infants using 95% confidence intervals. Of all infants who did not achieve protective levels of antibody after three doses of vaccine, 96% (26/27) weighed <1700 g at birth. The geometric mean HBS antibody levels in responders were 88 and 386 mIU/mL after two and three doses, respectively. Of 36 children with a birth weight >1500 g, 33 (91%) achieved levels of HBS antibody >100 mIU/mL after three doses of vaccine, compared with 25/35 (71%) of infants with birth weight <1500 g. Using logistic regression analysis, nonresponders were more likely than were responders to have been treated with steroids (26% vs 9%) and to have had a low birth weight (1037 g vs 1455 g). In addition, the seroresponse rate of black infants was more likely than that of white infants to be associated with poor weight gain (falling off 2 percentile ranks in weight) in the first 6 months of life: 22% of black and 60% of white children who failed to gain weight adequately responded to vaccination, compared with 92% of black and 70% of white children who were growing adequately. Of interest, the only infant with a birth weight of >1700 g who did not make protective levels of specific antibody after three doses of vaccine was 2300 g at birth, but had inadequate weight gain in the first 6 months of life. **CONCLUSIONS:** This study supports current recommendations of the American Academy of Pediatrics and the Centers for Disease Control and Prevention for delaying the initiation of hepatitis B immunization beyond the first week of life for premature infants at low risk for hepatitis B infection, particularly in newborns weighing <1700 g at birth. In addition, we have

identified variables other than birth weight that were associated with an inadequate immune response to early hepatitis B vaccination in premature infants, such as poor weight gain in the first 6 months of life.

**Lu CY, Ni YH, Chiang BL, Chen PJ, Chang MH, Chang LY, Su IJ, Kuo HS, Huang LM, Chen DS, Lee CY. Humoral and cellular immune responses to a hepatitis B vaccine booster 15-18 years after neonatal immunization. J Infect Dis. 2008 May 15;197(10):1419-26.**

**BACKGROUND:** Whether hepatitis B (HB) vaccine-conferred immunity persists into adulthood is unknown. We aimed to investigate long-term HB immunity in adolescents. **METHODS:** In 2004-2005, 6156 high school students (15-21 years old) who had been vaccinated with plasma-derived HB vaccine as infants were recruited for HB seromarker screening. The immune response to an HB vaccine booster was evaluated in 872 subjects who were seronegative. HB surface antibody (anti-HBs) titers and levels of HB surface antigen (HBsAg)-specific interferon (IFN)-gamma- or interleukin (IL)-5-secreting peripheral blood mononuclear cells (PBMCs; measured by enzyme-linked immunospot assay) were determined 4 weeks later. **RESULTS:** Although the vaccine remained highly efficacious in reducing the HBsAg positivity rate, 63.0% of the vaccinees had no protective anti-HBs. After the booster, anti-HBs remained undetectable in 28.7% (158/551) of the subjects who had received complete HB vaccination (4 doses) during infancy. We estimated that 10.1% of the total population had lost their HB vaccine-conferred booster response. HBsAg-specific IFN-gamma- or IL-5-secreting PBMCs remained negative in 27.2% (25/92) of subjects after the booster. **CONCLUSIONS:** A notable proportion of fully vaccinated adolescents had lost immune memory conferred by a plasma-derived HB vaccine 15-18 years later. This decay of immune memory may raise concerns about the need for a booster vaccine for high-risk groups in the long run.

**Mangione R, Stroffolini T, Tosti ME, Fragapani P, Mele A. Delayed third hepatitis B vaccine dose and immune response. Lancet. 1995 Apr 29;345(8957):1111-2. (No summary)**

**Margolis HS, Coleman PJ, Brown RE, Mast EE, Sheingold SH, Arevalo JA. Prevention of hepatitis B virus transmission by immunization. An economic analysis of current recommendations. JAMA. 1995 Oct 18;274(15):1201-8.**

**OBJECTIVE--**To evaluate the outcome of immunization strategies to prevent hepatitis B virus (HBV) transmission. **DESIGN AND SETTING--**A decision model was used to determine the incremental effects of the following hepatitis B immunization strategies in a birth cohort receiving immunization services in the public sector: (1) prevention of perinatal HBV infection, (2) routine infant vaccination, or (3) routine adolescent vaccination. **MAIN OUTCOME MEASURES--**Over the lifetime of the cohort, the reduction in infections and medical and work-loss costs of HBV-related liver disease were determined for each strategy and compared with the outcome without immunization. **RESULTS--**Prevention of perinatal infection and routine infant vaccination would lower the 4.8% lifetime risk of HBV infection by at least 68%, compared with a 45% reduction for adolescent vaccination. From a societal perspective, each strategy was found to be cost saving, but was not cost saving with respect to direct medical costs. The estimated cost per year of life saved was \$164 to prevent perinatal HBV infection, \$1522 for infant vaccination, and \$3730 for adolescent vaccination. **CONCLUSIONS--**Routine vaccination of infants in successive birth cohorts to prevent HBV transmission is cost-effective

over a wide range of assumptions. While economically less attractive than infant vaccination, adolescent vaccination could serve to protect those children who were not vaccinated as infants.

**Marion SA, Tomm Pastore M, Pi DW, Mathias RG. Long-term follow-up of hepatitis B vaccine in infants of carrier mothers. Am J Epidemiol. 1994 Oct 15;140(8):734-46.**

A program of immunization against hepatitis B, consisting of one dose of hepatitis B immune globulin within 12 hours of birth and three doses of hepatitis B vaccine at 0, 1, and 6 months of age for all infants of carrier mothers, has been operating in British Columbia, Canada, since 1984. The authors report on a survey conducted in 1992 of children immunized between 1984 and 1989. The survey included blood tests obtained from the children and interviews of the mothers. A total of 770 of 1,135 eligible children participated. Thirty-one percent of the mothers had been positive for hepatitis B e antigen prior to the birth of the child. At follow-up, the overall antibody against hepatitis B surface antigen seropositivity rate for children was 87.9 percent. A total of 5.1 percent of children had evidence of previous hepatitis B infection, and 2.3 percent were hepatitis B surface antigen positive. In multiple logistic regression analysis, a delay in the initial dose of vaccine was associated with increased risk of infection, but the age of the child was not, even though antibodies against hepatitis B surface antigen declined with age. The authors conclude that most infections occurred early and resulted from prenatal infection, initial nonresponse, or a delay in the initial dose of vaccine, not from waning immunity. A booster dose of vaccine, at least up to age 8 years, is not necessary.

**Mast EE, Ward JW. Hepatitis B vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines, 5th ed., Saunders Elsevier, 2008: 205-241. (No summary)**

**Mikaeloff Y, Caridade G, Rossier M, Suissa S, Tardieu M. Hepatitis B vaccination and the risk of childhood-onset multiple sclerosis. Arch Pediatr Adolesc Med. 2007 Dec;161(12):1176-82.**

**OBJECTIVE:** To investigate whether vaccination against hepatitis B (HB) increases the risk of incident multiple sclerosis (MS) in childhood in the short and long terms. **DESIGN:** Case-control study. **SETTING:** Population-based study conducted in France from January 1, 1994, to December 31, 2003. **PARTICIPANTS:** The case patients had incident MS with onset before age 16 years. Each case was individually matched for age, sex, and geographic location (current place of residence) to 12 control participants randomly selected from the general population of France. **EXPOSURE:** Hepatitis B vaccine. **MAIN OUTCOME MEASURE:** The risk of MS associated with HB vaccine exposure. **RESULTS:** One hundred forty-three case patients with MS were matched to 1122 control participants. The rate of HB vaccination in the 3 years before the index date was approximately 32% for both cases and controls. Vaccination against HB within the 3-year study period was not associated with an increased rate of a first episode of MS (adjusted odds ratio, 1.03; 95% confidence interval, 0.62-1.69). The rate was also not increased for HB vaccination within 6 months of the index date or at any time since birth or as a function of the number of injections or the brand of HB vaccine. **CONCLUSION:** Vaccination against HB does not seem to increase the risk of a first episode of MS in childhood.

**Nikolopoulos GK, Paraskevis D, Hatzitheodorou E, Moschidis Z, Sypsa V, Zavitsanos X, Kalapothaki V, Hatzakis A. Impact of hepatitis B virus infection on the progression of**

**AIDS and mortality in HIV-infected individuals: a cohort study and meta-analysis. Clin Infect Dis. 2009 Jun 15;48(12):1763-71**

**BACKGROUND:** The effect of hepatitis B virus (HBV) infection on the natural history of human immunodeficiency virus (HIV) disease remains uncertain. Therefore, a retrospective cohort study was conducted to examine the influence of HIV-HBV coinfection on AIDS development and overall mortality. Moreover, our results were added to those of previous studies in a literature-based meta-analysis. **METHODS:** Serum samples obtained from HIV-seropositive patients from 1984 through 2003 were retrospectively tested for hepatitis B surface antigen. Multivariable analyses were performed using Poisson and logistic regression models. For meta-analytic purposes, eligible articles were identified and relevant data were abstracted. Pooled estimates of effect were calculated applying fixed and random effects models. **RESULTS:** The prevalence of chronic HBV infection (documented hepatitis B surface antigen seropositivity for >6 months) among 1729 HIV-positive patients was approximately 6%. The multivariable analyses in our primary study revealed no significant impact of concomitant HIV-HBV infection on progression to AIDS and all-cause mortality. However, a meta-analysis performed on data from 12,382 patients enrolled in 11 studies revealed a significant effect of HIV-HBV coinfection on overall mortality (pooled effect estimate, 1.36; 95% confidence interval, 1.12-1.64). The increased rate of death among coinfecting individuals was observed in the meta-analyses of studies conducted both before (pooled effect estimate, 1.60; 95% confidence interval, 1.07-2.39) and after (pooled effect estimate, 1.28; 95% confidence interval, 1.03-1.60) commencement of highly active antiretroviral therapy. **CONCLUSIONS:** HIV-HBV coinfection seems to affect all-cause mortality, and strategies to reduce liver damage in patients coinfecting with HIV and HBV are justified.

**Pichichero ME, Blatter MM, Reisinger KS, Harrison CJ, Johnson CE, Steinhoff MC, Senders SD, Rothstein EP, Willems P, Howe BJ. Impact of a birth dose of hepatitis B vaccine on the reactogenicity and immunogenicity of diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-Haemophilus influenzae type b combination vaccination. Pediatr Infect Dis J. 2002 Sep;21(9):854-9.**

**OBJECTIVES:** To assess the impact of a birth dose of hepatitis B vaccine (HepB) on the reactogenicity and immunogenicity of a novel diphtheria-tetanus-acellular pertussis (DTaP)-HepB-inactivated poliovirus (IPV)/ type b (Hib) combination vaccine administered subsequently at 2, 4 and 6 months of age. **METHODS:** Neonates (= 550) were randomized into two groups with regard to receipt of HepB at birth. All subjects in both groups received DTaP-HepB-IPV/Hib at 2, 4 and 6 months of age. Solicited local and general adverse events were recorded for 8 days after each dose. Antibodies to hepatitis B surface antigen were measured 1 month after the third dose of DTaP-HepB-IPV/Hib in a subset of 170 infants; titers of at least 10 mIU/ml were considered protective. **RESULTS:** The DTaP-HepB-IPV/Hib combination vaccine was well-tolerated in both groups. Of the infants who received a birth dose of HepB, 22.6% had severe (Grade 3) reactions after any of the three doses of DTaP-HepB-IPV/Hib combination vaccine compared with 23.2% of subjects who did not receive a birth dose of HepB (difference, -0.5%; 90% confidence interval, -7.4 to 6.1). Antibody to hepatitis B surface antigen titers were > or =10 mIU/ml for all tested infants. Geometric mean titers were 2996.2 and 1240.1 mIU/ml with and without a birth dose of HepB, respectively. **CONCLUSIONS:** A HepB birth dose does not increase the reactogenicity of a combination DTaP-HepB-IPV/Hib vaccine administered at 2, 4 and 6 months of age, and all tested subjects achieved protective anti-HBs titers (> or =10 mIU/ml), although geometric mean titers were higher when a birth dose of HepB was given.

**Rich JD, Ching CG, Lally MA, Gaitanis MM, Schwartzapfel B, Charuvastra A, Beckwith CG, Flanigan TP. A review of the case for hepatitis B vaccination of high-risk adults. Am J Med. 2003 Mar;114(4):316-8.**

The sequelae of hepatitis B virus infection include fulminant liver failure, chronic liver disease, hepatocellular carcinoma, and death. The hepatitis B vaccine is efficacious, safe, and cost-effective, but has been consistently underutilized in high-risk adults despite long-standing recommendations. Instituting routine hepatitis B vaccination for high-risk adults in settings such as prisons and jails, sexually transmitted disease clinics, drug treatment centers, and needle exchange programs could prevent up to 800 cases of hepatitis, and 10 deaths from hepatitis, per 10,000 vaccinations, with an overall cost savings. Low rates of completion of the three-dose series and lack of funding for adult immunizations have always been challenges to offering hepatitis B vaccines to high-risk adults. However, there is benefit to an incomplete vaccination series, and high-risk populations are accessible for follow-up vaccination outside of traditional medical settings. A clear national objective and federal funding for vaccinating high-risk adults are needed.

**Saari TN; American Academy of Pediatrics Committee on Infectious Diseases. Immunization of preterm and low birth weight infants. American Academy of Pediatrics Committee on Infectious Diseases. Pediatrics. 2003 Jul;112(1 Pt 1):193-8.**

Preterm (PT) infants are at increased risk of experiencing complications of vaccine-preventable diseases but are less likely to receive immunizations on time. Medically stable PT and low birth weight (LBW) infants should receive full doses of diphtheria, tetanus, acellular pertussis, Haemophilus influenzae type b, hepatitis B, poliovirus, and pneumococcal conjugate vaccines at a chronologic age consistent with the schedule recommended for full-term infants. Infants with birth weight less than 2000 g may require modification of the timing of hepatitis B immunoprophylaxis depending on maternal hepatitis B surface antigen status. All PT and LBW infants benefit from receiving influenza vaccine beginning at 6 months of age before the beginning of and during the influenza season. All vaccines routinely recommended during infancy are safe for use in PT and LBW infants. The occurrence of mild vaccine-attributable adverse events are similar in both full-term and PT vaccine recipients. Although the immunogenicity of some childhood vaccines may be decreased in the smallest PT infants, antibody concentrations achieved usually are protective.

**Schroth RJ, Hitchon CA, Uhanova J, Noreddin A, Taback SP, Moffatt ME, Zacharias JM. Hepatitis B vaccination for patients with chronic renal failure. Cochrane Database Syst Rev. 2004;(3):CD003775.**

**BACKGROUND:** Chronic renal failure patients are at particular risk of hepatitis B virus infection. Early studies have demonstrated that renal failure patients benefit from vaccination; however, not all studies have consistently shown benefit. **OBJECTIVES:** To determine the beneficial and harmful effects of hepatitis B vaccine and of a reinforced vaccination series in chronic renal failure patients. **SEARCH STRATEGY:** We searched The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Renal Group Controlled Trials Register, The Cochrane Controlled Trials Register on The Cochrane Library (Issue 1, 2002), PubMed/MEDLINE (1966 to July 2003), EMBASE (1985 to November 2003), Current Clinical Practice Guidelines (Canadian Immunization Guide and Vaccine Preventable Diseases Surveillance Manual), and Science Citation Index as well as journals, published abstracts, and reference lists of articles. **SELECTION CRITERIA:** Randomised clinical trials comparing plasma vaccine with placebo, recombinant vaccine with placebo, recombinant vaccine with plasma vaccine, and a reinforced vaccination series (ie, more than three inoculations) with three inoculations of vaccine in chronic renal failure patients. **DATA COLLECTION AND**

**ANALYSIS:** Primary outcome measures included incidence of patients developing hepatitis B virus antibodies and infections while secondary outcomes included adverse events, liver-related morbidity, and mortality. Random effects models were used and reported relative risks and 95% confidence intervals (RR and 95% CI). **MAIN RESULTS:** We included seven randomised clinical trials. None of them had high quality. Plasma vaccine was significantly more effective than placebo in achieving hepatitis B antibodies (RR 23.0, 95% CI 14.39 to 36.76, 3 trials). We found no statistically significant difference between plasma vaccine or placebo regarding hepatitis B virus infections (RR 0.50, 95% CI 0.20 to 1.24). We found no statistically significant differences between recombinant vaccine and plasma vaccine in achieving hepatitis B antibodies (RR 0.65, 95% CI 0.28 to 1.53, 2 trials). Heterogeneity was significant and appeared to be attributable to the dose of vaccine. Two trials examined a reinforced recombinant vaccine strategy, which was not statistically more effective than three inoculations of recombinant vaccine regarding development of hepatitis B antibodies (RR 1.36, 95% CI 0.85 to 2.16). **REVIEWERS' CONCLUSIONS:** Plasma derived vaccines are more effective than placebo in achieving hepatitis B antibodies, while no statistically significant difference was found between recombinant and plasma vaccines. No statistically significant difference of effectiveness was observed between a reinforced vaccination series versus routine vaccinations of three inoculations of recombinant vaccine.

**Tan KL, Goh KT, Oon CJ, Chan SH. Immunogenicity of recombinant yeast-derived hepatitis B vaccine in nonresponders to perinatal immunization. JAMA. 1994 Mar 16;271(11):859-61.**

**OBJECTIVE--**Nonresponse to hepatitis B vaccine in the perinatal period occasionally occurs. This report documents the results of reimmunization of nonresponders to perinatal immunization. **DESIGN--**From a cohort of 1154 infants immunized with plasma-based vaccine in the perinatal period and followed up for more than 8 years, 45 nonresponders were identified. These children were reimmunized at 4 years of age. Each child received a yeast-derived recombinant hepatitis B vaccine on a 0-, 1-, and 5-month schedule, 33 children with 10-micrograms and 12 with 5-micrograms doses. Blood was sampled 1 month after the third vaccination and thereafter at 1, 2, and 4 years. **SETTING--**The follow-up clinic where the cohort of children was regularly seen. **PATIENTS--**Forty-five 4-year-old children who had no antibody to hepatitis B despite perinatal immunization. **MAIN OUTCOME MEASURE--**Antibody levels to hepatitis B surface antigen. **RESULTS--**Seroconversion with titers higher than 10 mIU/mL occurred in all children. More than 70% still had titers higher than 10 mIU/mL 4 years after vaccination. **CONCLUSION--**Nonresponders to perinatal hepatitis B vaccination respond well to subsequent vaccination.

**van der Sande MA, Waight P, Mendy M, Rayco-Solon P, Hutt P, Fulford T, Doherty C, McConkey SJ, Jeffries D, Hall AJ, Whittle HC. Long-term protection against carriage of hepatitis B virus after infant vaccination. J Infect Dis. 2006 Jun 1;193(11):1528-35.**

**BACKGROUND:** Carriage of hepatitis B virus (HBV) is a major risk factor for liver cirrhosis and hepatocellular carcinoma. Infant vaccination has been effective in preventing horizontal transmission during early childhood. It is unknown whether protection is maintained into early adulthood. **METHODS:** In 1984, early childhood vaccination was introduced in 2 rural Gambian villages. In 2003, serological assessment of 81.5% of 1,350 eligible participants 1-24 years old was done, to determine vaccine efficacy against infection and carriage. **RESULTS:** Overall vaccine efficacy against infection and carriage was 83.4% (95% confidence interval [CI], 79.8%-86.6%) and 96.5% (85% CI, 93.9%-98.9%), respectively. Vaccine efficacy against infection was similar when restricted to primary responders (85.3%), but a significant effect of

peak antibody concentration was found. Both vaccine efficacy and levels of hepatitis B surface antibody (anti-HBs) decreased with age, resulting in a vaccine efficacy against infection and carriage among 20-24-year-old participants of 70.9% (95% CI, 60.4%-80.5%) and 91.1% (95% CI, 75.8%-100%), respectively. Fifteen years after vaccination, fewer than half of the vaccinees had detectable anti-HBs. The prevalence of carriage in the unvaccinated population was similar to the prevalence 20 years earlier. CONCLUSIONS: HBV vaccination early during life can provide long-lasting protection against carriage, despite decreasing antibody levels. The role played by subclinical boosting and the necessity of a booster need to be evaluated.

**Viviani S, Jack A, Hall AJ, Maine N, Mendy M, Montesano R, Whittle HC. Hepatitis B vaccination in infancy in The Gambia: protection against carriage at 9 years of age. Vaccine. 1999 Aug 6;17(23-24):2946-50.**

To estimate the efficacy in The Gambia (West Africa) of infant hepatitis B vaccination against infection and carriage with the virus at the age of 9 years. The HBV status of 9-year old children vaccinated in infancy was compared to that of unvaccinated children of the same age. Eight percent of the vaccinated children had been infected by HBV compared to 50% of the unvaccinated control group; HBV carrier status was 0.6 and 10% respectively, resulting in a vaccine efficacy of 83% against infection and of 95% against chronic carriage. The results show that infant vaccination provides a high level of protection at the age of nine years against both HBV infection and chronic carrier status and no booster dose of vaccine is required in the first decade. These findings support the WHO recommendation for the introduction of HBV vaccination into the Expanded Programme on Immunization in Africa.

**(WHO) Global and regional immunization profile. Geneva, World Health Organization, Vaccine-preventable diseases monitoring system, 2009**  
**[http://www.who.int/immunization\\_monitoring/en/globalsummary/GS\\_GLOProfile.pdf](http://www.who.int/immunization_monitoring/en/globalsummary/GS_GLOProfile.pdf), accessed 4 September 2009).**

**WHO Scientific Advisory Group of Experts. Report in Weekly Epidemiological Record 2009, 84, 213-236.**

**WHO. International travel and health. 2009, p 106. ISBN-13 9789241580427**  
**<http://www.who.int/topics/travel/en/>**

**WHO. Global Plan of Action on Workers' Health 2008–2017, Objective 1.10**  
**(WHA60/A60\_R26): [http://apps.who.int/gb/ebwha/pdf\\_files/WHA60/A60\\_R26-en.pdf](http://apps.who.int/gb/ebwha/pdf_files/WHA60/A60_R26-en.pdf).**

**(WHO) [http://www.who.int/vaccine\\_safety/topics/hepatitisb/en/index.html](http://www.who.int/vaccine_safety/topics/hepatitisb/en/index.html)**

**Wong VC, Ip HM, Reesink HW, Lelie PN, Reerink-Brongers EE, Yeung CY, Ma HK. Prevention of the HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg by administration of hepatitis-B vaccine and hepatitis-B immunoglobulin. Double-blind randomised placebo-controlled study. Lancet. 1984 Apr 28;1(8383):921-6.**

Newborn infants of Chinese HBeAg-carrier mothers in Hong Kong were randomly assigned to one of four study groups. Group I was treated with 3 micrograms heat-inactivated hepatitis B (HB) vaccine at birth and at 1, 2, and 6 months thereafter, in conjunction with seven monthly HBIg injections; group II was treated according to the same vaccine schedule but received only one HBIg injection at birth; group III received only the vaccine, at months 0, 1, 2, and 6; and group IV received placebos for both vaccine and HBIg. The first set of injections was given within 1 h after birth. Comparisons were made in the 140 children who were at least six months old at the close of the trial (495 days). In all three treatment groups development of the persistent carrier state was significantly ( $p$  less than or equal to 0.0001) less frequent than in controls (2.9%, 6.8%, and 21.0% versus 73.2%). Although vaccination alone was significantly less protective than vaccination plus multiple HBIg injections ( $p = 0.03$ ), the degree of protection was still remarkable. 12 months after the first set of injections 96-100% of the infants in the three treatment groups were anti-HBs positive; the geometric mean titres of anti-HBs in the three groups did not differ significantly. This indicates that even high doses of HBIg do not interfere with the anti-HBs response to the vaccine. Probable intra-uterine HB infections were observed in 3 infants. No serious side-effects were observed from the interventions, even in the babies with intra-uterine infections who had received HBIg and HB-vaccine at birth. To prevent development of the persistent HBsAg carrier state, and thereby the consequent chronic liver disease and/or primary carcinoma of the liver, HB vaccine and HBIg should be administered as soon as possible after birth to all newborn infants at risk of perinatal hepatitis B infection.

**Yu O, Bohlke K, Hanson CA, Delaney K, Rees TG, Zavitskovsky A, Ray P, Mullooly J, Black SB, Benson P, Thompson WW, Davis RL, Jackson LA. Hepatitis B vaccine and risk of autoimmune thyroid disease: a Vaccine Safety Datalink study. *Pharmacoepidemiol Drug Saf.* 2007 Jul;16(7):736-45.**

**PURPOSE:** Hepatitis B vaccine has been postulated as a possible cause of autoimmune disorders, including autoimmune thyroid diseases (ATD). Cases of Graves' disease and Hashimoto's thyroiditis, following hepatitis B vaccine have been reported to the Vaccine Adverse Events Reporting System (VAERS). To test the hypothesis that hepatitis B vaccine increases the risk of ATD, we conducted a case-control study, within the Vaccine Safety Datalink project. **METHODS:** We identified potential cases of Graves' disease and Hashimoto's thyroiditis, among persons aged 18-69 years from administrative data recorded by three health maintenance organizations (HMOs) and verified cases by medical record review. Controls were frequency-matched to cases by birth year, sex, and study site. Vaccine information was collected from administrative records, chart review, and telephone interviews with study subjects. We enrolled 355 Graves' disease cases, 418 Hashimoto's thyroiditis cases, and 1102 controls. We assessed the association between ever-receipt of hepatitis B vaccine, as well as receipt of hepatitis B vaccine less than 1 year, 1-5 years and at least 5 years prior to the index date, and the risk of ATD. **RESULTS:** Ever-receipt of hepatitis B vaccine was not associated with risk of Graves' disease (odds ratio (OR), 0.90; 95% confidence interval (CI), 0.62-1.32) or Hashimoto's thyroiditis (OR, 1.23; 95%CI, 0.87-1.73). There was also no association between the time interval since receipt of hepatitis B vaccination and either outcome. **CONCLUSIONS:** We did not observe an increased risk of Graves' disease or Hashimoto's thyroiditis, following receipt of hepatitis B vaccine.

**Yuen MF, Lim WL, Chan AO, Wong DK, Sum SS, Lai CL. 18-year follow-up study of a prospective randomized trial of hepatitis B vaccinations without booster doses in children. *Clin Gastroenterol Hepatol.* 2004 Oct;2(10):941-5.**

**BACKGROUND & AIMS:** The long-term immunogenicity and efficacy of hepatitis B virus (HBV) vaccination remain to be defined. We aimed to examine the long-term immunogenicity and efficacy of HBV vaccination with 3 different regimens over 18 years of follow-up.

**METHODS:** A total of 318 Chinese subjects receiving 3 different regimens of HBV vaccination (2-dose recombinant vs. 3-dose recombinant vs. 3-dose plasma-derived vaccines) without receiving a booster dose were recruited. The HBV serologic markers, including hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), and antibody to hepatitis B core antigen (anti-HBc), were determined at yearly follow-up. After 18 years, 88 subjects were still being followed up.

**RESULTS:** Compared with subjects receiving the 2-dose regimen, subjects receiving the 3 dose regimens had a significantly higher geometric mean titer of anti-HBs and a higher proportion had anti-HBs titers  $\geq 10$  mIU/mL during the 18 years of follow-up. There were no differences in these 2 parameters between subjects receiving the 3-dose recombinant and subjects receiving the 3-dose plasma-derived vaccines. A total of 88 anamnestic responses were documented in 70 subjects (8 with initial anti-HBs titers  $< 100$  mIU/mL at 12 months and 7 with anti-HBs titers  $< 10$  mIU/mL before the anamnestic responses). No subject became positive for HBsAg. Three subjects had benign breakthrough HBV infection without leading to chronicity indicated by isolated anti-HBc positivity.

**CONCLUSIONS:** There was less long-term immunogenicity associated with the 2-dose regimen when compared with the 3-dose regimens of HBV vaccination. Because of the highly effective anamnestic responses, a booster dose was not necessary at least up to 18 years after the primary vaccination.