“Hepatitis B vaccination: a completed schedule ... enough to control HBV lifelong?.”

Viral Hepatitis Prevention Board Meeting
Milan, Italy, 17-18 November 2011.

Greet Hendrickx
VHPB Secretariat
Content

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

1. Meeting subjects............................................pag.3

Pubmed MEDLINE search on { (Booster OR long term imm*) AND (Hepatitis) } in all fields and published since 2005 was performed. In Endnote the relevant references were selected and classified in the different meeting subjects.

Session 2: Vaccine efficacy and long-term immunogenicity ........................................pag.3
Session 3: Immune response/ Immune memory..............................pag.20
Session 4: Effectiveness of Universal hepatitis B Vaccination.................................................................pag.31
Session 5: Breakthrough infections (vaccine escape mutants).......................................................... pag.43
Session 6: hepatitis B Booster vaccination.................................pag.51

Not included in the meeting session:
Vaccination in immunocompromised and haemodialysis patients.....................................................pag.62

2. Hepatitis Bibliography of the Speakers. pag.78

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

Pubmed MEDLINE search on {(Booster OR long term imm*) AND (Hepatitis)) in all fields and published from 2005 on, was performed. After a manual search of the 342 references only the references and the abstracts really related to the meeting were selected and classified in the different meeting subject. The references are ranged by publication year (most recent first) and for each year in alphabetical order of the first author’s name.

Session 2: Vaccine efficacy and long-term immunogenicity (41)


BACKGROUND: A potential problem of hepatitis B immunization is that vaccine-induced antibody to hepatitis B surface antigen (anti-HBs) declines to low levels with age. This study investigated the persistence of anti-HBs in vaccinated children in a low hepatitis B virus (HBV) endemic area. METHODS: Plasma samples of 938 children between ages of 8 months and 15 years were tested for the presence of anti-HBs. RESULTS: The seroprotection rate was 60%. Protective antibody level was detected in 65% of children one year after vaccination, and in 30%, 29% and 24% 5, 10 and 15 years after vaccination, respectively. The mean anti-HBs titer declined with post-vaccination time (to 66 mIU/mL in 1 year, 60 mIU/mL in 5 years, 40 mIU/mL in 10 years to 37 mIU/mL in 15 years after vaccination). CONCLUSIONS: Children vaccinated against HBV during infancy may show low levels of antibody during adolescence. Our data suggest that a booster dose of vaccine may be required in low HBV endemic areas.


INTRODUCTION: Vaccination is the main tool for preventing hepatitis B virus (HBV) infection; however, following the completion of the vaccination series, the concentrations of anti-HBs can decline over the years and reach levels less than 10mIU/mL. The persistence of protection in these individuals is still unknown. The present study aimed to determine the anti-HBs antibody levels among children and adolescents who had received a complete vaccination course for hepatitis B. METHODS: Antibodies against HBV surface antigen (anti-HBs) were tested in 371 individuals aged 10 to 15 years-old. RESULTS: Volunteers who showed undetectable quantities of anti-HBs accounted for 10.2% of the population studied and 39.9% presented antibody titers of less than 10mIU/mL. Anti-HBs >/= 10mIU/mL were verified in 49.9%. CONCLUSIONS: These results corroborate other studies indicating levels of anti-HBs below 10mIU/mL in vaccinated individuals. Additional studies are required to assess whether this indicates susceptibility to HBV infection and the need and age for booster doses.


Long-term persistence of antibodies against hepatitis A and B (anti-HAV and anti-HBs) were evaluated in 1- to 11-year-old children following 2 doses (0, 6 months) of hepatitis A and B vaccine. Ten years postvaccination, all subjects were anti-HAV seropositive (> or =15 mIU/mL), 81.7% had anti-HBs antibody concentrations > or =10 mIU/mL. All subjects with anti-HBs concentrations <10 mIU/mL, mounted a vigorous anamnestic response to an HBV vaccine challenge dose indicating the presence of immunologic memory against hepatitis B.


300 adolescents aged 12-15 years were randomised (1:1) into two groups to compare the long-term (10 years) immunogenicity profile of two doses of an Adult formulation [Group HAB_2D: 150; 0-6 months] vs. three doses of a Paediatric formulation [Group HAB_3D: 150; 0-1-6 months] of a combined hepatitis A and B (HAB) vaccine. At Year 10, anti-HAV seropositivity rate was 100% in both groups, while 85.9% and 85.1% subjects in the HAB_2D and HAB_3D groups, respectively, had anti-HBs antibody concentrations > or =10 mIU/mL. The anti-HAV antibody GMCs (HAB_2D: 429.3 mIU/mL; HAB_3D: 335.5 mIU/mL) and anti-HBs antibody GMCs (HAB_2D: 50.6 mIU/mL; HAB_3D: 60.1 mIU/mL) were similar in both groups. No vaccine-related serious adverse events were reported. Hence, with respect to long-term antibody persistence, the two-dose schedule of the combined HAB vaccine Adult formulation is an effective alternative to the conventional three-dose schedule of the Paediatric formulation in adolescents.


The objective of this study was to determine long-term immunity to hepatitis B virus (HBV) in a cohort of adolescents who received plasma-derived HBV vaccine in 1989 and 1990 in a remote Australian Aboriginal community. This was done using a serological survey; primary outcome measures were cut-off titres of HBsAb, and the presence of HBeAb and/or HBsAg. Of 37 adolescents in the cohort, 4 (11%) had evidence of active infection, one with abnormal liver enzymes, 7 (19%) had evidence of past infection, 15 (41%) were HBsAb positive in low titre and 11 (30%) were classed as immune. It was concluded that there was relatively poor long-term serological immunity to HBV vaccination in this group; a finding which is in keeping with similar studies in Indigenous and remote populations elsewhere. This finding raises the concern that a significant proportion of Aboriginal adolescents in other remote communities (vaccinated in 1989 and 1990) were not adequately protected by the vaccine. If so, there will be an unexpected burden of chronic HBV infection in these settings and a substantial group who are non-immune, despite having received complete HBV vaccination courses as infants. The authors recommend followup serosurveys in remote Aboriginal communities to identify people with low HBsAb titres, especially those without an adequate anamnestic response to another dose of HBV vaccine. In addition, community-based active surveillance programs will be required to detect people with chronic HBV infection and provide access to monitoring and appropriate treatment.


BACKGROUND: Hepatitis B vaccination in children born to hepatitis B surface antigen
(HBsAg)-positive mothers considerably decreases the risk of vertical transmission. However, whether this protection against carriage of hepatitis B virus is maintained into early adulthood is as yet unknown. PATIENTS AND METHODS: A combined passive-active immunization programme for newborns of HBsAg-positive mothers was initiated in the north-eastern part of the Czech Republic in 1988. The number of immunized newborns had reached 665 newborns by the end of 2006. All mothers of immunized infants were HBsAg-positive during pregnancy, and 34 (5%) were also hepatitis B e antigen (HBeAg)-positive. The immunization programme consists of providing newborns with protection at birth with hepatitis B immunoglobulin, followed by three 10-mug doses of plasma-derived or, since 1990, recombinant vaccine administered at 0, 1 and 6 months of life. Only 29 children of HBeAg-positive mothers received vaccine at 0, 1 and 2 months of life. Blood samples were obtained after immunization, at 2 years of age, and biennially thereafter. Samples were tested for HBsAg and hepatitis B surface and core antibodies (anti-HBs, anti-HBc). RESULTS: The immunization schedules were completed in 640 children. A protective anti-HBs level after immunization was proven in 574 of 620 children (93%). Persistence of protective anti-HBs antibodies was detected in 70, 40 and 25% of children at 5, 10 and 15 years of age. Vertical transmission with chronic HBsAg carrier status was detected in two infants. Anti-HBc seroconversion was proven in ten children from 3 to 15 years of age. Natural boosting with an anti-HBs increase was detected in 38 children (twice in one child). CONCLUSION: Our results show that combined active-passive immunization of newborns against hepatitis B provides persistent protection up to adolescence despite a frequent waning of anti-HBs antibodies, suggesting there is no need for booster vaccination during adolescence.


BACKGROUND: The standard three-dose schedule of hepatitis B vaccines is frequently not completed, especially in adolescents. A primary study has confirmed the equivalence of a two-dose schedule of an Adult formulation of hepatitis B vaccine [Group HBV_2D] to a three-dose schedule of a Paediatric formulation in adolescents (11-15 years) [Group HBV_3D]. This follow-up study evaluated the five year persistence of antibody response and immune memory against the hepatitis B surface (anti-HBs) antigens five years after completion of primary vaccination. METHODS: A total of 234 subjects returned at the Year 5 time point, of which 144 subjects received a challenge dose of hepatitis B vaccine. Blood samples were collected yearly and pre- and post-challenge dose to assess anti-HBs antibody concentrations. RESULTS: At the end of five years, 79.5% (95% confidence interval [CI]: 71.7 - 86.1) and 91.4% (95% CI: 82.3 - 96.8) of subjects who received the two-dose and three-dose schedules, respectively had anti-HBs antibody concentrations >/= 10 mIU/mL. Post-challenge dose, all subjects had anti-HBs antibody concentration >/= 10 mIU/mL and >/= 94% subjects had anti-HBs antibody concentration >/= 100 mIU/mL. All subjects mounted a rapid anamnestic response to the challenge dose. Overall, the challenge dose was well-tolerated. CONCLUSION: The two-dose schedule of hepatitis B vaccine confers long-term immunogenicity and shows evidence of immune memory for at least five years following vaccination. TRIAL REGISTRATION: Clinical Trials NCT00343915, NCT00524576.

Zinke, M., J. Disselhoff, B. Gartner and J. M. Jacquet. "Immunological persistence in 4-6 and 7-9 year olds previously vaccinated in infancy with hexavalent DTPa-HBV-IPV/Hib." Hum Vaccin 2010 6(2).

Background: The combined diphtheria-tetanus-pertussis-hepatitis B-inactivated poliomyelitis-Haemophilus influenzae conjugate vaccine (DTP a-HBV-IPV/Hib, Infanrix Hexa() GlaxoSmithKline Biologicals, Rixensart, Belgium) is the only hexavalent vaccine currently licensed for primary and booster vaccination of infants and provides simultaneous
protection against six major diseases of childhood. The persistence of the immune response in children aged 4-6 and 7-9 years of age previously vaccinated with four doses of DTP a-HBV-IPV/Hib vaccine was assessed (www.clinicaltrials.gov.au 106744 NCT00356564 and 106745 NCT00335881). Methods: A blood sample was collected from 403 children, all of whom had received 3-dose primary vaccination and a booster dose in the second year of life with DTP a-HBV-IPV/Hib, in previous clinical vaccine trials in Germany. Results: Mean time from the fourth DTP a-HBV-IPV/Hib dose until serological follow-up ranged between 3.6 and 6.4 years. After the 4th DTP a-HBV-IPV/Hib dose, in subjects who had not received additional booster doses, seroprotective antibody levels persisted up to 9 years of age in >/=90% of subjects for diphtheria, Hib and poliomyelitis, in 77.2% subjects for Hepatitis B and in 64.7% of subjects for tetanus. Anti-pertussis toxin antibodies remained detectable in no more than 38.2% of subjects. Conclusion: With the exception of PT, the combined DTP a-HBV-IPV/Hib induces long lasting immune response against all vaccine antigens. Falling seropositivity against PT over time supports the recommended administration of a pertussis booster dose in 5-6 year old children in Germany.


A total of 465 children aged 8 to 10 years were vaccinated with 2 doses of Recombivax-HB 2.5 microg (RB) or Twinrix-Junior 10 microg/360 EL.U (TX), according to a 0 and 6 months schedule. Seven years postsecond dose, a challenge dose of vaccine was given. All vaccinees in the TX and 98% in the RB group showed an anamnestic response. Vaccination at the age of 8 to 10 years with two-pediatric doses of TX or RB given with a 6 months interval induces a long-lasting immunity in most vaccinees.


Poly lactic acid (PLA) is one of widely used biodegradable polymer in vaccine delivery. However, the use is restricted due to hydrophobic nature and generation of acidic micro-environment upon its degradation, rendering it unfavorable to the encapsulated antigen. In the present study we have synthesized PEG derivatized block copolymers of PLA for development of nanoparticles encapsulating HBsAg for mucosal vaccination against hepatitis B. The copolymers of compositions AB, ABA and BAB (PLA as A-block and PEG as B-block) were synthesized and characterized by 1H NMR spectroscopy and gel permeation chromatography. Nanoparticles were characterized to determine the effect of copolymer. Among all, BAB produced nanoparticles of smallest size and lowest zeta potential, suggesting highest PEG density on their surface. The in vitro release experiments were performed in PBS (pH7.4). SDS-PAGE analysis confirmed the structural stability and integrity of the released antigen. Results were compared for immunogenicity with plain PLA nanoparticles and conventional alum-HBsAg based vaccine. BAB nanoparticles produced better humoral response as compared to other polymeric nanoparticles. The extent of humoral response obtained in single dose of BAB nanoparticles was comparable to the response produced by alum based vaccine (which received a booster dose). Block copolymeric nanoparticles also produced better sIgA level at all local and distal mucosal sites as compare of PLA nanoparticles, where alum based formulation failed to give any considerable response. Additionally, IgG1 and IgG2a isotype were determined to confirm the T(H)1/T(H)2 mixed immune response. These data demonstrate the potential of BAB nanoparticles as mucosal vaccine delivery system capable of eliciting high and prolonged immune response.

AIMS: To assess the differences of long-term efficacy between plasma-derived and recombinant hepatitis B virus (HBV) vaccines and the effectiveness of catch-up vaccination in adolescents with undetectable anti-HBs. METHODS: Before 1992, infants born in Taiwan were immunized using plasma-derived HB vaccine, and thereafter, by using recombinant HB vaccine. From the only junior middle school of a rural township in central-southern Taiwan, 1788 (93.7%) students from five cross-sectional screenings, grouping into three birth cohorts (Group I: born during 1984-1986, II: 1986-1992 and III: 1992-1995), were enrolled for checking HBsAg, anti-HBs and anti-HBc. Students with undetectable HBsAg and anti-HBs underwent a booster dose (2.5µg) of recombinant HB vaccine (Engerix-B; GlaxoSmithKline, Rixensart, Belgium) and had anti-HBs re-checked 3 weeks later. Individuals who had remained undetectable for anti-HBs completed the other two doses of HB vaccines at 1 and 6 months later. RESULTS: The prevalence of HBsAg (11.4, 5.4 and 1.2%), anti-HBs (64.5, 44.1 and 36.0%) and anti-HBc (29.5, 12.5 and 4.4%) decreased from Group I to III (P<0.001 for trends). After a booster dose, the positive rates of anti-HBs increased up to 80.5% (16% increase) in Group I, 81.0% (36.9% increase) in Group II, and 94.4% (58.4% increase) in Group III. The percentages of anamnestic response increased with a trend (P<0.001). A total of 110 non-responders completed 3 doses of catch-up HB vaccination, but 3 cases (2.7%) of Group II, evoked primary vaccination response. CONCLUSION: Recombinant vaccine showed predominant disappearance rate (62.7%) of anti-HBs 12-15 years after vaccination, but provided better anamnestic response after a booster dose. It also showed high success rate (97.3%) in catch-up vaccination in adolescents.


BACKGROUND: The duration of protection in children and adults (including health care workers) resulting from the hepatitis B vaccine primary series is unknown. METHODS: To determine the protection afforded by hepatitis B vaccine, Alaska Native persons who had received plasma-derived hepatitis B vaccine when they were >6 months of age were tested for antibody to hepatitis B surface antigen (anti-HBs) 22 years later. Those with levels <10 mIU/mL received a dose of recombinant hepatitis B vaccine and were evaluated on the basis of anti-HBs measurements at 10-14 days, 30-60 days, and 1 year. RESULTS: Of 493 participants, 60% (298) had an anti-HBs level ≥10 mIU/mL. A booster dose was administered to 164 persons, and 77% responded with an anti-HBs level >or=10 mIU/mL at 10-14 days, reaching 81% by 60 days. Response to a booster dose was positively correlated with younger age, peak anti-HBs response after primary vaccination, and the presence of detectable anti-HBs before boosting. Considering persons with an anti-HBs level >or=10 mIU/mL at 22 years and those who responded to the booster dose, protection was demonstrated in 87% of the participants. No new acute or chronic hepatitis B virus infections were identified. CONCLUSIONS: The protection afforded by primary immunization with plasma-derived hepatitis B vaccine during childhood and adulthood lasts at least 22 years. Booster doses are not needed.


Immune stimulating complexes (ISCOMs) incorporating recombinant hepatitis B surface antigen (rHBsAg) were prepared for induction of humoral and cellular immunity by subcutaneous administration. Prepared ISCOMs were characterized for their size, shape, incorporation efficiency, zeta potential, antigen integrity, antigen conformation and immunogenicity by biophysical and immunological techniques including transmission electron microscopy (TEM), Dynamic light scattering (DLS), SDS-PAGE, fluorescence spectroscopy, in vitro potency test and in vivo humoral and cellular immune stimulatory
efficacy in Balb/c mice. Prepared ISCOM particles show characteristic cage like morphology with average size of 44 approximately nm, polydispersity index 0.1, negative zeta potential (-21.7 mV) and antigen association efficiency approximately 39%. Tryptophan emission fluorescence and in vitro potency assay data suggest that association of rHBsAg with ISCOMs results in local electrostatic interactions, motional restriction of tryptophan residues of the protein resulting in reduction of anti-rHBsAg monoclonal antibodies binding affinity. Immunization with rHBsAg ISCOMs resulted in upregulation of specific cellular (IFN-gamma and IL-2) as well as IgG response (IgG2a isotype biased) humoral response in Balb/c mice. Immune responses were significantly higher than those produced by of alum-adsorbed antigen (alum-rHBsAg) after (one booster) (p < 0.001). These data demonstrate that although the conformation of rHBsAg after incorporation into ISCOMs was moderately altered but due to strong adjuvant ability, rHBsAg ISCOMs were highly immunogenic as compared to marketed rHBsAg formulations by subcutaneous route of administration.

BACKGROUND: Transmission of hepatitis B virus (HBV) from carrier mothers to their babies appears to be one of the most important factors influencing the prevalence of chronic HBV infection in areas of high hepatitis B endemicity. METHODS: Infants born to HBV surface antigen (HBsAg)-positive mothers who were or were not positive for HBV e antigen (HBeAg) or to mothers who were negative for both HBsAg and HBeAg have been followed for 17 years for serological evidence of HBV infection. These infants were divided into 2 groups on the basis of their hepatitis B vaccination protocols: group 1 received vaccine at birth and 1, 2, and 12 months later, and group 2 received vaccine at birth and 1 and 6 months later. Follow-up involved annual clinic visits, during which a blood sample was taken and analyzed for the presence of HBsAg, antibody to HBsAg, and antibody to HBV core antigen (HBcAg). Selected blood samples that tested positive for HBV markers during 2 consecutive visits separated by a long interval were further investigated by polymerase chain reaction to detect HBV DNA. RESULTS: Transient presence of HBsAg or transient and/or long-term presence of antibody to HBcAg suggested that this population was heavily exposed to HBV during the follow-up period. Despite these findings, no new cases of chronic HBV infection were observed. None of the subjects with transient presence of HBsAg had any clinical symptoms of liver disease. CONCLUSIONS: This study demonstrates the efficacy of the HBV vaccine and its ability to protect against symptomatic disease.

Vaccination with recombinant hepatitis B vaccines is highly effective in preventing hepatitis B infection. Recently, a preservative-free (PF) formulation of hepatitis B vaccine [GlaxoSmithKline (GSK) Biologicals, Rixensart, Belgium] has been licensed. The immunogenicity of the PF hepatitis B vaccine and antibody persistence 6 years later was assessed in this study. This formulation was compared with the preservative- containing (PC) formulation of the vaccine and a low-preservative (LP) content formulation. Five hundred forty-one healthy adult subjects were evaluated in the primary study. Over 94% of the subjects in the three study groups had seroprotective anti-HBs antibody concentrations (>or=10 mIU/ml) 1 month after completing primary vaccination. Antibody measurements in 242 healthy adults who returned for the follow-up study and who had received primary vaccination 6 years earlier showed that over 81% of subjects in the three study groups still had anti-HBs antibody concentrations >or=10 mIU/ml. No apparent differences in antibody decline or distribution between the study groups were observed. These results indicate that
the removal of preservatives from the hepatitis B vaccine does not affect adversely its immunogenicity both in the short and in the longer term.


The combined HB-Hib vaccine candidate Hebervac HB-Hib (CIGB, La Habana), comprising recombinant HBsAg and tetanus toxoid conjugate synthetic PRP antigens has shown to be highly immunogenic in animal models. A phase I open, controlled, randomized clinical trial was carried out to assess the safety and immunogenicity profile of this bivalent vaccine in 25 healthy adults who were positive for antibody to HBsAg (anti-HBs). The trial was performed according to Good Clinical Practices and Guidelines. Volunteers were randomly allocated to receive the combined vaccine or simultaneous administration of HB vaccine Heberbiovac-HB and Hib vaccine QuimiHib (CIGB, La Habana). All individuals were intramuscularly immunized with a unique dose of 10 mcg HBsAg plus 10 mcg conjugated synthetic PRP. Adverse events were actively recorded after vaccine administration. Total anti-HBs and IgG anti-PRP antibody titers were evaluated using commercial ELISA kits at baseline and 30 days post-vaccination. The combined vaccine candidate was safe and well tolerated. The most common adverse reactions were local pain, febricula, fever and local erythema. These reactions were all mild in intensity and resolved without medical treatment. Adverse events were mostly reported during the first 6-72 hours post-vaccination. There were no serious adverse events during the study. No severe or unexpected events were either recorded during the trial. The combined vaccine elicited an anti-HBs and anti-PRP booster response in 100% of subjects at day 30 of the immunization schedule. Anti-HBs and anti-PRP antibody levels had at least a two-fold increase compared to baseline sera. Even more, anti-HBs antibody titer showed a four-fold increase in 100% of volunteers in the study group. The results indicate that the combined HB-Hib vaccine produces increased antibody levels in healthy adults who have previously been exposed to these two antigens. To our knowledge, this is the first demonstration of safety and immunogenicity for a combined vaccine comprising recombinant HBV and synthetic Hib antigens. The present results support phase I-II clinical trial in the target population, two months old healthy infants.


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 mcg at birth, 2.5 mcg at 2 months, 2.5 mcg ug 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 > or = 10 mIU/mL 14 days postbooster. RESULTS: Of the 105 participants, 42 (40.0%) had anti-HBs concentrations > or = 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 > or = 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 > or = 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 =
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.


Long-term immunogenicity and efficacy of HBV vaccination with different regimens of HBV vaccines (A: 2-dose recombinant vs. B: 3-dose recombinant vs. C: 3-dose plasma-derived vaccines) without booster dose were examined in 318 Chinese children. Geometric mean titer (GMTs) of anti-HBs of group A subjects was significantly lower than that of groups B and C subjects at years 1, 5, 10 and 15. At year 22, the proportion of subjects with anti-HBs > or = 10 mIU/mL for groups A, B and C were 35.3%, 76.5% and 52.4%, respectively (p < 0.05 between groups A and B) in 55 subjects. In the 22 years study period, none was found to be HBsAg positive, and 72 subjects had > or = 1 episodes of anamnestic response. In conclusion, the 3-dose regimens have a better long-term immunogenicity. In terms of protection against HBV infection, the 2-dose and 3-dose vaccines had equal efficacies.


BACKGROUND: In 2001, two hexavalent vaccines were licensed in Italy (Hexavac, Infanrix Hexa), and since 2002 were extensively used for primary immunization in the first year of life (at 3, 5, 11/12 months of age). In 2005, the market authorization of Hexavac was precautionary suspended by EMEA, because of doubts on long-term protection against hepatitis B virus. The objectives of this study were to evaluate the persistence of antibodies to anti-HBs, in children in the third year of life, and to investigate the response to a booster dose of hepatitis B vaccine. METHODS: Participant children were enrolled concomitantly with the offering of anti-polio booster dose, in the third year of life. Anti-HBs titers were determined on capillary blood samples. A booster dose of hepatitis B vaccine was administered to children with anti-HBs titers < 10 mIU/mL, with the monovalent precursor product of the previously received hexavalent vaccine. HBsAb titers were tested again one month after the booster. RESULTS: Sera from 113 children previously vaccinated with Hexavac, and from 124 vaccinated with Infanrix Hexa were tested for anti-HBs. Titers were > or = 10 mIU/ml in 69% and 96% (p < 0.0001) respectively. The proportion of children with titers > or = 100 mIU/ml did also significantly differ among groups (27% and 78%; p < 0.0001). Post-booster, 93% of children achieved titers > or = 10 mIU/ml, with no significant difference by vaccine group. DISCUSSION: Fifteen months after third dose administration, a significant difference in anti-HBs titers was noted in the two vaccine groups considered. Monovalent hepatitis B vaccine administration in 3-year old children induced a proper booster response, confirming that immunologic memory persists in children with anti-HBs titers < 10 mIU/ml. However, long-term persistence of HBV protection after hexavalent vaccines administration should be further evaluated over time.


OBJECTIVE: To investigate the dynamic changes of the anti-HBs level among immunized newborn infants born to HBsAg-positive and HBsAg-negative mothers in hyper-endemic area of Hepatitis B. METHODS: Infants who were regularly vaccinated with Hepatitis B vaccine and tested to be anti-HBs positive were divided into two groups according to HBsAg-positive or negative mothers in Long-an, Guangxi. Each subject was followed up 3
times during age 5 to 8. SPRIA was used to test HBsAg, anti-HBs and anti-HBc. Results
During the follow-up period, positive rates of anti-HBs in children born to HBsAg-positive
mothers ranged between 52.00% and 78.00%, and those with HBsAg-negative mothers was
between 43.84% and 54.74%. GMT in two groups was between 55.36 mIU/ml and 95.66
mIU/ml as well as between 39.90 mIU/ml and 65.47 mIU/ml, respectively. There was no
statistical significance in both positive rates and GMT between age groups. The anti-HBs
level in the follow-up period of children born to HBsAg-positive mothers was higher than
that of those born to HBsAg-negative mothers in the same age group. In the age group of 6-
8 years with HBsAg-negative mothers, the positive rates in the follow-up period of children
with high anti-HBs titers in the primary vaccination were 2.29-2.84 times of those with low
titers. The anti-HBs titer of children in a follow-up period was lower than that in the
primary vaccination, no matter whether they were born to HBsAg-positive mothers.
However, the decline rate of children born to HBsAg-negative mothers was significantly
higher than those born to HBsAg-positive mothers (84.91% vs. 61.54%; chi2 = 28.7982, P
= 0.000). The incidence rate (25.64%) of a 4-fold increase in antibody titers of children
born to HBsAg-positive mothers was significantly higher than that of children born to
HBsAg-negative mothers (7.37%) from the primary vaccination to the follow-up period
(chi2 = 6.7661, P = 0.009) with was 3.5 times of the latter. Subjects with HBsAg
seroconversion were those with low anti-HBs titers in primary vaccination.
CONCLUSION: The anti-HBs level decreased slowly in successfully immunized children
from age 5 to 8. The chance of natural booster yielded by natural infection increased in
immunized children born to HBsAg-positive mothers. The anti-HBs level in the primary
vaccination played an important role in prevention of seroconversion of HBsAg.

Hennig, B. J., K. Fielding, J. Broxholme, M. Diatta, M. Mendy, C. Moore, A. J. Pollard, P. Rayco-
Solon, G. Sirugo, M. A. van der Sande, et al. "Host genetic factors and vaccine-induced
BACKGROUND: Vaccination against hepatitis B virus infection (HBV) is safe and
effective; however, vaccine-induced antibody level wanes over time. Peak vaccine-induced
anti-HBs level is directly related to antibody decay, as well as risk of infection and
persistent carriage despite vaccination. We investigated the role of host genetic factors in
long-term immunity against HBV infection based on peak anti-HBs level and
seroconversion to anti-HBc. METHODS: We analyzed 715 SNP across 133 candidate
genes in 662 infant vaccinees from The Gambia, assessing peak vaccine-induced anti-HBs
level and core antibody (anti-HBc) status, whilst adjusting for covariates. A replication
study comprised 43 SNPs in a further 393 individuals. RESULTS: In our initial screen we
found variation in IFNG, MAPK8, and IL10RA to affect peak anti-HBs level (GMRatio of
< 0.6 or > 1.5 and P < or = 0.001) and lesser associations in other genes. Odds of core-
conversion was associated with variation in CD163. A coding change in ITGAL (R719V)
with likely functional relevance showed evidence of association with increased peak anti-
HBs level in both screens (1st screen: s595_22 GMRatio 1.71, P = 0.013; 2nd screen:
s595_22 GMRatio 2.15, P = 0.011). CONCLUSION: This is to our knowledge the largest
study to date assessing genetic determinants of HBV vaccine-induced immunity. We report
on associations with anti-HBs level, which is directly related to durability of antibody level
and predictive of vaccine efficacy long-term. A coding change in ITGAL, which plays a
central role in immune cell interaction, was shown to exert beneficial effects on induction
of peak antibody level in response to HBV vaccination. Variation in this gene does not
appear to have been studied in relation to immune responses to viral or vaccine challenges
previously. Our findings suggest that genetic variation in loci other than the HLA region
affect immunity induced by HBV vaccination.

Kabir, A., M. Keshvari, A. H. Kashani and S. M. Alavian. "Predicting response to HBV
vaccination in people with positive anti-HBc but negative HBsAg and anti-HBs." Hum Vaccin
OBJECTIVE: There are 5.1-6.5% of people with positive anti-HBc in Iran. The aim of this
study was to assess the predicting factors of response to hepatitis B vaccination in anti-HBc positive subjects. RESULTS: Total response rate to vaccination was 79.8% (75 cases) and 67.9% (38 cases) in cases and controls, respectively. Nineteen persons (20.2%) in cases and 18 persons (32.1%) of controls had negative anti-HBs even after three doses of HB vaccination. Factor associated with decreased response to vaccination was prior history of being HBsAg positive (OR = 1.3, p = 0.01). METHODS: In a quasi-experimental study, 94 people with negative HBsAg, negative anti-HBs and positive anti-HBc (cases) and 56 persons with negative HBsAg, anti-HBs and anti-HBc (controls) were vaccinated at zero, one and six months with recombinant hepatitis B vaccine. Successful immunization was defined by anti-HBs antibody titer > or =10 mIU/mL. CONCLUSION: The rate of response to hepatitis B vaccination is nearly like other studies but somewhat different. Higher percent of married cases together with higher percent of positive HBsAg in spouses may explain the slight difference in the response to vaccination in cases in comparison with controls as a result of booster like effect that seldom happens because of recurrent contacts between the subjects and the HBsAg positive spouses spontaneously.


AIM OF THE STUDY: To evaluate the immunogenicity, safety, and reactogenicity of a seven-valent pneumococcal conjugate vaccine (PCV7) when given concomitantly with a fully liquid DTaP-IPV-HBV-Hib combination vaccine. METHODS: Two hundred and sixty-six healthy infants in France (n=136) and Germany (n=130) were randomized to receive DTaP-IPV-HBV-Hib and PCV7 (test group) at the age of 2, 3 and 4 months (primary series) and 12-15 months (booster dose), or to receive DTaP-IPV-HBV-Hib at the same time points but PCV7 at the ages of 5, 6, 7 and 13-16 months (control group). Antibody levels to all vaccine antigens were measured before dose 1, 1 month after dose 3, at the time of booster, and 1 month later. Safety data were collected after each vaccine dose. RESULTS: Two hundred and fifty-seven infants (test group, 131; control group, 126) completed the primary immunization series and two hundred and forty-five received the booster dose (test group, 125; control group, 120). Depending on the serotype, 92.8-100% of subjects in the test group achieved antibody levels >or=0.15 microg/mL for PCV7 antigens at 5 months of age, and 89.7-99.1% of them antibody levels >or=0.50 microg/mL 1 month after booster. For DTaP-IPV-HBV-Hib, there was no statistically significant difference between the two groups in the proportion of infants that achieved pre-defined seroprotective levels for each antigen at 5 months and 1 month after booster. Frequency of local and systemic reactions was similar in both groups except for fever above 38.0 degrees C, which was more frequent in the test group after dose 1, 2 or 4. Fever >39.0 degrees C was only reported from three children in each group. CONCLUSION: The PCV7 vaccine was highly immunogenic, well tolerated, and safe when coadministered with the DTaP-IPV-HBV-Hib vaccine at 2, 3, and 4 months of age and a booster dose at 12-15 months. In this study, PCV7 did not show any relevant influence on the immunogenicity and safety of the concurrently administered DTPa-IPV-HBV-Hib vaccine.


In 1992, 620 adolescents were vaccinated against hepatitis B. Anti-HBs concentrations were measured in 480 (77.4%) adolescents 1 month after completion of the primary course of vaccination. To assess the persistence of anti-HBs, 347 and 228 of such vaccinees were retested for anti-HBs in 1999 and for anti-HBs and anti-HBe in 2003. More than 10 years after vaccination, individuals with anti-HBs >or=10 mIU/ml were considered protected while those with antibody <10 mIU/ml were given a booster dose and retested 2 weeks later. Check performed in 2003 showed that 208/228 (91.2%) vaccinees retained protective
concentrations of anti-HBs. All vaccinees were anti-HBc negative. 11 of the 12 (91.7%) individuals who were given a booster dose of vaccine showed a vigorous anamnestic response while the remaining one showed a weak response (10.6 mIU/ml). These data suggests that hepatitis B vaccination can confer long-term immunity and that immunological memory can outlast the loss of antibody. Hence, the use of routine booster doses of vaccine does not appear necessary to maintain long-term protection in successfully vaccinated immunocompetent individuals.


OBJECTIVE: The purpose of study was to evaluate the immune response in a sample of vaccinated children aged 6 years. BACKGROUND: Although immunization of infants against hepatitis B virus (HBV) is the most effective way to prevent infection, duration of the afforded immunization is unknown. METHODS: The immunity derived from the HBV vaccine was assessed by measuring the antibody in 3752 children who were vaccinated in a routine vaccination program in three cities of Iran (Isfahan, Khoramabad, Shahrekord). RESULTS: Seven hundred and twenty-three (19.3%) children had antibodies levels <10 MIU/mL and 1096 (29.2%) had antibodies levels ≥100 MIU/mL. The total GMT was 34.5+-0.66, and GMT was statistically different in non-immune and immune children (3.1+-0.36 versus 49.1+-0.52). No correlation was found between HbsAb titers and growth pattern during the first and sixth years of life, number of vaccine, time of vaccination and drug use. The predictors were low birth weight and chronic disease. CONCLUSION: It is recommended that high risk children should be monitored regularly for anti-HBS, and booster must be administrated, if necessary.


OBJECTIVE: To investigate the status of vaccination against hepatitis B among postgraduate students of medical institutions of higher education in Guangzhou. METHODS: HBsAg and anti-HBs in the serum samples from 1139 postgraduate students were detected by ELISA. Data on hepatitis B vaccine inoculation were investigated by using a questionnaire. Statistical analyses were performed by using SAS software. RESULTS: The HBsAg positive rate among the 1139 postgraduate students was 2.90 percent. The HBsAg positive rates in hepatitis B vaccine inoculated (1.15 percent) and non-inoculated (21.69 percent) postgraduate students were significantly different (x2=119.11, P<0.0001). The positive rates of HBsAb between the two groups were also significantly different (x2=62.05, P<0.0001). Among the hepatitis B vaccine inoculated students, 17.31 percent were negative for HBsAb. The positive rate of HBsAb among those inoculated the vaccine within the past 3 years was higher than that among those inoculated the vaccine earlier (0-3 years vs. 4-6 year, P=0.0089) (0-3 years vs. 7-9 years, P=0.0172) (0-3 years vs. >9 years, P=0.0474). The positive rate of HBsAb among the students who received hepatitis B vaccine booster dose was higher than that of the students who did not receive any booster dose (P=0.0093). CONCLUSION: With the increase of ages, the effect of vaccination for hepatitis B decreased. Male populations may be more susceptible to hepatitis B virus than female. It is necessary to monitor HBsAb levels for those who were inoculated with HBV vaccine more than 3 years ago to give booster dose in time to prevent HBV infection.


We assessed the long-term immunity to hepatitis B among 242 Egyptian children aged 6-12 years who had received a full vaccination course in infancy, and investigated the factors associated with immunity. Only 39.4% of the children had protective (> or = 10 IU/L)
hepatitis B surface antibody levels (HBsAb). This proportion decreased with age but the
decrease was not statistically significant. The mean level of HBsAb decreased significantly
with increasing age (P = 0.026). A significant negative correlation was found between
current age and HBsAb levels (r = -0.31, P = 0.041). Age and weight-for-age were found to
be significant predictors of non-protective HBsAb levels.

Van Damme, P. and K. Van Herck. "A review of the long-term protection after hepatitis A and
Vaccine-preventable viral hepatitis continues to be a cause of considerable morbidity and
mortality: on worldwide basis, approximately 1.4 million cases of hepatitis A are reported
every year. The true incidence, however, has been estimated to be 3-10 times higher.
Regarding hepatitis B, more than a third of the world's population has been infected. The
World Health Organization has estimated (2000) that there are 367 million chronic carriers
of hepatitis B worldwide, and approximately 1 million deaths per year as a consequence of
chronic complications and acute fulminant disease. Hepatitis B vaccines have been licensed
came available. An update on the long-term protection conferred by hepatitis A
and hepatitis B vaccines as well as the combined hepatitis A and B vaccine is offered in this
paper. Long-term efficacy and booster policy for hepatitis B vaccines have often been
a topic of discussion. Based on current data and field experience there is, in general, no
necessity for booster doses for fully vaccinated immunocompetent individuals. Long-term
protection has been demonstrated by the rapid (5-7 days) development of anamnestic
antibody responses among vaccinees who no longer have detectable anti-HBs. Anamnestic
responses correlate with lymphoproliferative T-cell responses following challenge with
hepatitis B vaccine. Furthermore, employing Spot-ELISA techniques, circulating B-cells
were shown to be able to produce anti-HBs in vaccinees who lost their detectable
antibodies. The accumulated data from a large number of studies indicate that despite
antibody decline or loss, immune memory exhibits long-term persistence. There is
somewhat less information available for hepatitis A vaccines, yet an increasing number of
studies indicate that the findings for hepatitis B vaccines are also applicable to hepatitis A
vaccines. The necessity to provide a booster dose was based on early projections of
observed antibody levels. However, recent follow-up studies with up to 12 year
observation, as well as studies employing mathematical models predict that following
primary vaccination, antibodies will persist for at least 25 years. In addition, experimental
studies confirm that vaccination against hepatitis A induces immunological memory.
Therefore hepatitis A booster vaccination is presently considered as unnecessary in fully
vaccinated individuals. The above findings are of importance in the context of
administering combined hepatitis A and B vaccine for which similar long-term data have
been observed. All available data on monovalent and combined hepatitis A and hepatitis B
can indicate that there is no support for a hepatitis A or hepatitis B booster when a
complete primary vaccination course is offered to immunocompetent individuals.

van der Sande, M. A., M. Mendy, P. Waight, C. Doherty, S. J. McConkey, A. J. Hall and H. C.
Whittle. "Similar long-term vaccine efficacy of two versus three doses of HBV vaccine in early
WHO currently recommends three vaccinations against hepatitis B to provide optimal
protection against infection and carriage. However, immunological theory and
mathematical modelling suggest that similar protection could be induced with two doses,
and trials among adolescents and adults have shown comparable rates for both primary
seroprotection and geometric mean titres following vaccination. We determined vaccine
efficacy among 60 children who only received two doses of hepatitis B vaccine as infants
and among 463 children who had received three doses after 4-7 years of follow-up. Vaccine
efficacy among the two-dose group was 86.3% against anti-HBc positivity (infection) and
92.3% against HBsAg positivity (carriage), which was similar to the vaccine efficacy found
among the participants who had received three doses. To confirm this comparable vaccine
efficacy a randomised controlled non-inferiority trial with long-term follow-up is needed.


BACKGROUND: To evaluate immunogenicity, reactogenicity, and safety of a hexavalent combination vaccine diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio virus-Haemophilus influenzae type b (DTPa-HBV-IPV/Hib) when coadministered with a 7-valent pneumococcal conjugate vaccine (PCV7). METHODS: Infants received either a hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio virus-H. influenzae type b vaccine concomitantly with PCV7 or DTPa-HBV-IPV/Hib alone infants were vaccinated at 2, 3 and 4 months (primary immunization) and 12-15 months of age (booster dose). Local and systemic reactions and adverse events were monitored following each dose and compared between groups. Blood was obtained prior to dose 1, one month after dose 3, immediately prior to and 1 month following the booster dose to measure antibody responses to each of the antigens. RESULTS: Two hundred and fifty-three subjects (PCV7, 127; Control, 126) were enrolled. Antibody responses were compared in 226 subjects for the primary immunization and 212 for the booster dose (per-protocol (PP) population). Although there were some differences in geometric mean concentrations (GMCs) to the DTPa-HBV-IPV/Hib antigens after the primary series, GMCs for all antigens after the booster dose were similar in both groups, except for diphtheria which was significantly higher in the PCV7 group (PCV7, 7.41 IU/mL; Control, 5.78 IU/mL). Reactogenicity and safety data were compared in 252 infants receiving primary immunization and 235 children receiving the booster dose. Site reactions were similar in both groups. Fever $\geq$38.0 degrees C following each vaccination was reported more frequently in the PCV7 group (28.3-50.0%) than in the Control group (15.6-33.6%) whereas fever $\geq$39.0 degrees C occurred only in a few cases and to the same extent in both groups (PCV7, 0.8-2.7%; Control, 1.6-4.1%). Only one reported serious adverse event was characterized as being related to the study vaccines: control subject was hospitalized with a fever. CONCLUSION: DTPa-HBV-IPV/Hib and PCV7 were highly immunogenic, well-tolerated and safe when coadministered at 2, 3 and 4 months of age with a booster dose at 12-15 months of age. These results support the coadministration of PVC7 with DTPa-HBV-IPV/Hib as part of the routine immunization schedule for infants and children.


AIM: This trial studied the effectiveness of early hepatitis B (HepB) immunisation in babies weighing less than 1800 grams, born of HepB surface-antigen-negative mothers. METHODS: The first vaccine dose was given once clinical stability was achieved, with second and third doses given 1 and 6 months later, respectively. HepB serology, done using Abbott EIA (phase 1) and Abbott Axsym (phase 2) before and after June 2001, respectively, was checked at birth (Sero1), prior to (Sero2) and 6 months after (Sero3) the third dose. A booster dose was recommended when Sero3 showed a non-immune status (< 10 mIU/mL). RESULTS: Median birth weight and gestational age (n = 118) were 1295 [range 475, 1780] g and 31 [range 24, 37] completed weeks, respectively. Sero1 (median age of 4 [range 1, 34] days) showed 64% (n = 113) to be non-immune. The first dose of vaccine was administered at a median weight of 1268 [range 530, 1790] g, median age of 6 [range 1-63] days and median post-menstrual age of 32 [range 24-37] completed weeks. Sero2 (median age of 179 [range 112-260] days), for 110 babies (93.2%) showed immunity in 48.2% (median titres--Phase 1: 26 [range 10, 150] mIU/mL; Phase 2: 34 [range 10, 1000] mIU/mL). Sero3 revealed seroprotection in 77.8% (median titres--Phase 1: 102 [range 12, 150] mIU/mL; Phase 2: 162 [range 16, 1000] mIU/mL). The more mature the baby at time of first dose, the more likely he is to achieve seroprotection (85% amongst those administered at and beyond 33 weeks; 91% among those administered at and beyond Day
CONCLUSIONS: Early HepB immunisation in infants < 1800 g can be safely recommended, with booster doses necessary at 1 year for some infants.


The objective of this work was to estimate the effectiveness of DNA recombinant anti-HBV vaccines in a retrospective cohort study of 1,012 Brazilian blood donors who completed the vaccination schedule (3 doses + booster of antibody titer < 10IU/L) during the period 1998-2002. The results showed that seroconversion rates were significantly lower among the donors whose antibody titers was measured six months after completing the vaccination scheme and among older donors, particularly those aged over 50. Overall vaccine effectiveness was 88.7%, ranging from 80.6% in the oldest (50 years or over) to 91.4% among the youngest (18-30 years) donors. The booster regimen was effective at reducing the percentage of non-responders. We conclude that vaccine effectiveness was significantly better in younger blood donors and that the anti-HBs testing interval influenced the vaccine effectiveness.


BACKGROUND: Health care workers are at increased risk of occupational exposure to hepatitis B virus (HBV) infection. Reassessment for revaccination of such high-risk persons after 10 years may be appropriate if anti-HBs antibody titers declined below 10 mlU/mL. This study was conducted to evaluate the long-term efficacy of HBV vaccine in health care workers and the need for their reassessment for revaccination. METHODS: We interviewed 600 health care workers in a referral hospital in Shiraz, southern Iran. They were asked to complete a confidential questionnaire including information on their age, gender, vaccination date, number of doses of vaccine, their job description in hospital, previous history of needlestick injury, and educational level. Anti-HBs antibodies were determined by the ELISA method and titers of >10 mlU/mL were considered protective. Those with a positive HBsAg or anti-HBcAb were excluded from the study. RESULTS: Among 600 health care workers interviewed, 339 subjects who accepted to participate in the study, were vaccinated with three doses of HBV vaccine. Anti-HBsAb titers were >100 mlU/mL in 211 subjects (62.2%), 10 - 100 mlU/mL in 85 (25.1%), and <10 mlU/mL in 43 (12.7%) persons. Among 339 subjects who received three doses of vaccine, 273 were vaccinated less than 5 years, 47 cases between 5 - 10 years, and 19 cases were vaccinated more than 10 years before the study. The majority of them had an antibody concentration above the protective level (88.1%, 88.9%, and 60.9%, respectively, P = 0.001). CONCLUSION: Reassessment for revaccination in health care workers should be considered according to their anti-HBsAb levels 10 years after vaccination. In our health care workers, we think that due to the existence of low immunity against HBV, reassessment for revaccination after 10 years is mandatory.


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.


BACKGROUND: Alaska Native (AN) children were at high risk of acquiring hepatitis B virus (HBV) infection before vaccination began in 1983. We evaluated the long-term protection from hepatitis B (HB) vaccination among AN children immunized when infants.

METHODS: During 1984-1995, we recruited a convenience sample of AN children who had received a three dose series of HB vaccine starting at birth and had serum antibody to hepatitis B (anti-HBs) concentrations of >/= 10 mIU/mL at 7-26 months of age. We evaluated anti-HBs concentrations and the presence of anti-HBc in participants' sera every other year up to age 16 years. Anti-HB core antigen (anti-HBc)-positive specimens were tested for hepatitis B surface antigen and for HBV DNA. RESULTS: We followed 334 children for 3151 person-years (median, 10 years per child) with 1610 specimens collected. Anti-HBs concentrations dropped rapidly among all participants. Among children 2, 5 and 10 years of age, 37 of 79 (47%), 33 of 176 (19%) and 8 of 95 (8%), respectively, had anti-HBs concentrations of >/= 10 mIU/mL. Receipt of recombinant vaccine was significantly associated with a more rapid antibody decline (P < 0.001). Six (1.8%) children acquired anti-HBc, 3 of whom had definite breakthrough infections (at least 2 consecutive anti-HBc-positive specimens or at least 1 anti-HBc-positive specimen and HBV DNA detection by PCR). None of these children had detectable hepatitis B surface antigen, and none had symptoms of hepatitis. CONCLUSIONS: Anti-HBs concentrations declined over time among AN infants successfully immunized with HB vaccine starting at birth. Transient anti-HBc appeared in a small percentage of children; however, none developed clinical signs of hepatitis or chronic HBV infection.


Combination vaccines decrease the number of injections and improve parental satisfaction and vaccination schedule compliance. In a phase 1, randomized, partially-blinded, single-dose booster study, we evaluated two formulations of an investigational liquid hexavalent vaccine containing diphtheria, tetanus, acellular pertussis (5-component), inactivated poliovirus, Haemophilus influenzae b conjugate and hepatitis B surface antigen (DTaP-IPV-Hib-HBV) in 60 healthy toddlers, 15 to 18 months of age, who had been primed with three doses of a licensed pentavalent diphtheria, tetanus, acellular pertussis (5-component), inactivated poliovirus, Haemophilus influenzae b conjugate (DTaP-IPV/PRP-T) vaccine. The DTaP-IPV//PRP-T vaccine was used as a control in 30 subjects. The investigational formulations, which contained the same DTaP-IPV components, differed only in Hib (content and conjugate) and HBV (content) (PRP-T/HBV10 = 12 mug Hib tetanus toxoid conjugate with 10 microg HBsAg; PRP-OMP/HBV15 = 6 microg Hib Neisseria meningitidis outer membrane protein complex with 15 microg HBsAg). Injection-site pain,
redness and swelling were reported by 46.7%, 46.7%, and 20.0% of the licensed vaccine recipients, 43.3%, 43.3%, and 26.7% of PRP-T/HBV10 recipients and 70.0%, 46.7%, and 46.7% of PRP-OMPC/HBV15 recipients, respectively. Fever \( \geq 37.8 \) degrees C and irritability were reported by 0% and 16.7% of licensed vaccine recipients, 10.3% and 23.3% of PRP-T/HBV10 recipients and 30.0% and 16.7% of PRP-OMPC/HBV15 recipients, respectively. There were no apparent differences between the groups in the proportion of participants achieving predefined, threshold or seroprotective immune responses. Geometric mean antibody levels for all antigens were similar except for anti-PRP levels, which were 19.0 microg/mL in recipients of the licensed vaccine, 40.8 microg/mL in PRP-T/HBV10 recipients and 9.4 microg/mL in PRP-OMPC/HBV15 recipients. We conclude that the hexavalent formulations appear generally well tolerated and immunogenic as a booster dose in these toddlers.


BACKGROUND: The duration of protection afforded by hepatitis B vaccination is unknown. OBJECTIVE: To determine antibody persistence and protection from hepatitis B virus (HBV) infection. DESIGN: Prospective cohort study. SETTING: 15 villages in southwest Alaska. PARTICIPANTS: 1578 Alaska Natives vaccinated at age 6 months or older. INTERVENTION: During 1981-1982, participants received 3 doses of plasma-derived hepatitis B vaccine. This cohort was followed annually over the first 11 years, and 841 (53%) persons were tested at 15 years. MEASUREMENTS: Antibody to hepatitis B surface antigen (anti-HBs), markers of HBV infection, and testing to identify HBV variants. RESULTS: Levels of anti-HBs in the cohort decreased from a geometric mean concentration of 822 mIU/mL after vaccination to 27 mIU/mL at 15 years. Initial anti-HBs level, older age at vaccination, and male sex were associated with persistence of higher anti-HBs levels at 15 years when analyzed by a longitudinal linear mixed model. After adjustment for initial anti-HBs level and sex, those vaccinated at age 6 months to 4 years had the lowest anti-HBs level at 15 years. Asymptomatic breakthrough infections were detected in 16 participants and occurred more frequently in persons who did not respond to vaccination than those who responded (\( P = 0.01 \)). Among infected persons with viremia, 2 were infected with wild-type HBV and 4 had HBV surface glycoprotein variants, generally accompanied by wild-type HBV. LIMITATIONS: The loss of participants to follow-up at 15 years was 47%. However, characteristics of persons tested were similar to those of persons lost to follow-up. CONCLUSIONS: Hepatitis B vaccination strongly protected against infection for at least 15 years in all age groups. Antibody levels decreased the most among persons immunized at 4 years of age or younger.


A survey of persistence of anti-HBs after hepatitis B vaccination has shown that five years after vaccination on a sample of 152 persons, or 82.53%, stands at >10 IU/I. Long term immunogenicity of vaccinated children remained at 88.89%, health workers 79.41% and drug addicts 64.28%. The results of these studies in Bosnia and Herzegovina show the high level of protection hepatitis B vaccine against HBV infection. Vaccination against viral hepatitis B results in immunologic memory response among the vaccinated, and even after a decrease of anti-HB level following the third vaccine dose inoculation, a booster dose is not needed. Immunity remains steady and a booster dose is not recommended.


Although vaccination against hepatitis B virus (HBV) is highly successful, 5% to 10% of individuals do not experience a response with an adequate antibody level to hepatitis B surface antigen (anti-HBs). Contributing causes for nonresponse to the vaccine are genetic
predisposition, immunosuppression, and certain chronic illnesses. The distinction between true nonresponse (after adequate immunization) and waning anti-HBs levels is important. The latter is not uncommon in populations in areas of the world with low endemicity for HBV infection. Data from subjects with waning anti-HBs levels show that immunologic memory may still protect these individuals against acute HBV infection or may prevent chronic infection with HBV for < or =10 years after immunization. Recent reports from Asia and Alaska describe cases of chronic HBV infection 15 years after immunization in subjects who have very low levels of anti-HBs. Thus, nonresponders or those with waning immunity who may be at risk of HBV infection in subsequent years may require a booster dose. Clinical algorithms to reimmunize nonresponders have been described and are discussed in this article. Experimental hepatitis B vaccines have shown some promise in nonresponders but are not commercially available in the United States.


BACKGROUND: Universal anti-hepatitis-B vaccination of infants and adolescents was implemented in Italy in 1991. We undertook a multicentre study in previously vaccinated individuals to assess the duration of immunity and need for booster, over 10 years after vaccination. METHODS: In 1212 children and 446 Italian Air Force recruits vaccinated as infants and adolescents, respectively, we measured the concentrations of antibodies to hepatitis-B surface antigen (anti-HBs) and the presence of antibodies to hepatitis-B core antigen (anti-HBc) at enrollment; postimmunisation values were not available. Individuals positive for anti-HBc were tested for hepatitis B surface antigen (HBsAg) and hepatitis B viral DNA. Individuals with anti-HBs concentrations at 10 IU/L or more were regarded as protected; those with antibody less than 10 IU/L were given a booster dose and retested 2 weeks later. Individuals showing postbooster anti-HBs concentrations of less than 10 IU/L were offered two additional vaccine doses and retested 1 month after the third dose. FINDINGS: Protective anti-HBs concentrations were retained in 779 (64%, 95% CI 61.6-67) children and 398 (89%, 86.4-92.1) recruits. We recorded antibody amounts of less than 10 IU/L in 433 children (36%, 33-38.4) and 48 (11%, 7.9-13.6) recruits. One child and four recruits were positive for anti-HBc, but negative for HBsAg and hepatitis B viral DNA. Antibody concentrations were higher in recruits than in children (geometric mean titre 234.8 IU/L vs 32.1 IU/L, p=0.0001). 332 (97%) of 342 children and 46 (96%) of 48 recruits who received a booster showed an anamnestic response, whereas ten (3%) children and two (4%) recruits remained negative for anti-HBs or had antibody concentrations of less than 10 IU/L. Prebooster and postbooster antibody titres were strongly correlated with each other in both groups. All individuals given two additional vaccine doses (eight children and two recruits) showed anti-HBs amounts of more than 10 IU/L at 1 month after vaccination. INTERPRETATION: Strong immunological memory persists more than 10 years after immunisation of infants and adolescents with a primary course of vaccination. Booster doses of vaccine do not seem necessary to ensure long-term protection.

BACKGROUND: Incidence of hepatitis B in Poland decreased significantly after implementation of routine immunization in infants. Natural boosters may influence the long-term post vaccination immunity in countries, where endemicity is high. In areas of low incidence this influence may be limited. The aim of the study was to analyze the influence of risk factors for HBV infection (potential natural boosters) on long-term post vaccination immunity against hepatitis B and the possibility of HBV infection in previously vaccinated individuals. PATIENTS AND METHODS: In 130 children aged 10-12 years, vaccinated with 4 doses of recombinant vaccine against hepatitis B in infancy, exposure to risk factors for HBV infection (infection in family members including mother, hospitalization, surgical interventions, blood transfusion, dental treatment, piercing, tattooing) was analyzed. Markers of HBV infection (anti-HBc and HBsAg) and humoral immunity against hepatitis B were determined. Protective level of anti-HBs antibodies was defined as \( \geq 10 \) IU/l.

RESULTS: Statistically significant influence of dental treatment \((p<0.02)\) and surgical interventions \((p<0.05)\) on possessing very high anti-HBs titer \((\geq 1000 \text{ IU/l})\) was revealed, which indicates that these factors act as natural boosters. Children, who previously received blood transfusion, statistically more frequently did not have protective level of anti-HBs \((p<0.01)\). In all 6 children with confirmed HBV infection there was exposure to risk factors for infection in anamnesis. In children with chronic hepatitis B (positive HBsAg) statistically significantly more frequently surgical interventions were performed \((p<0.05)\).

CONCLUSIONS: 1. Despite of low incidence of hepatitis B in Poland, natural boosters, especially dental and surgical treatment, may stimulate the post vaccination immunity. 2. Blood transfusion is currently not a source of infection, however, children who received blood transfusion in the neonatal period, may require control of immunization efficacy or a booster dose. 3. HBV infection and chronic hepatitis B may occur in previously vaccinated children, especially if they underwent surgical intervention.


The immunogenicity of a vaccine is conventionally measured through the level of serum Abs early after immunization, but to ensure protection specific Abs should be maintained long after primary vaccination. For hepatitis B, protective levels often decline over time, but breakthrough infections do not seem to occur. The aim of this study was to demonstrate whether, after hepatitis B vaccination, B-cell memory persists even when serum Abs decline. We compared the frequency of anti-hepatitis-specific memory B cells that remain in the blood of 99 children five years after priming with Infanrix-hexa (GlaxoSmithKline) \((n=34)\) or with Hexavac (Sanofi Pasteur MSD) \((n=65)\). These two vaccines differ in their ability to generate protective levels of IgG. Children with serum Abs under the protective level, \(<10 \text{ mIU/mL}\), received a booster dose of hepatitis B vaccine, and memory


Long-term persistence of antibodies against hepatitis A and B (anti-HAV and anti-HBs) were evaluated in 1- to 11-year-old children following 2 doses \((0, 6 \text{ months})\) of hepatitis A and B vaccine. Ten years postvaccination, all subjects were anti-HAV seropositive \((\geq 15\)
mIU/mL), 81.7% had anti-HBs antibody concentrations ≥10 mIU/mL. All subjects with anti-HBs concentrations <10 mIU/mL, mounted a vigorous anamnestic response to an HBV vaccine challenge dose indicating the presence of immunologic memory against hepatitis B.


The duration of protection of hepatitis B vaccine remains incompletely understood. To assess the long-term protection provided by a primary vaccine series, the current study again recruited all subjects of a previous randomized placebo-controlled trial cohort 23 years after vaccination. Two hundred and sixty-one healthy children aged 5-9 years living in a highly HBV-endemic country were enrolled in the primary trial and received three doses of plasma-derived vaccine or placebo. The primary placebo receivers who did not receive any immunization against hepatitis B were used as non-vaccinated controls in the current study. After eliminating the interference of an early booster dose and vaccines outside the study, 48.1% (39/81) vaccinees still maintained anti-HBs titers ≥ 10 mIU/mL at Year 23, higher than 34.7% (26/75) in non-vaccinated controls (P=0.088). 75-100% of vaccinees with anti-HBs titer <10 mIU/mL at Year 23 in different sub-groups divided according to early immune backgrounds developed a rapid and robust antibody anamnestic response after a booster dose, highly significantly different from non-vaccinated controls who received the same dose of vaccine (7.5%, P<0.01). No case of clinically significant HBV infection was found in the primary cohort during the whole 23 years, but 10 transient HBsAg seroconversions in the primary placebo group and one in the primary vaccine group were determined. Anti-HBc positive rate obviously tended to be lower in vaccinees compared with non-vaccinated controls at Year 23. These results suggest a persisting immune memory and certain protection for 23 years after primary vaccination in children living in highly HBV-endemic areas. Clinically insignificant infections, which cannot be avoided and may often occur in vaccinees, play a positive role in the maintaining of immunity to HBV. Booster doses should be unnecessary for more than 20 years after a full primary immunization in children (as catch-up vaccination) and, also likely, in newborns living in highly HBV-endemic areas.


Neonatal vaccination against hepatitis B virus (HBV) infection was launched in the 1980s in Qidong, China, where HBV and hepatocellular carcinoma were highly prevalent. Presence of immune memory and immunity against HBV in adults needs to be clarified. From a cohort of 806 who received plasma-derived Hep-B-Vax as neonates and were consecutively followed at ages 5, 10, and 20 years, 402 twenty-four-year-old adults were recruited for booster test. Among them 4 (1%) were found to be HBsAg(+), 27 (6.7%) were HBsAg(-)anti-HBc(+), 121 (30.2%) were HBsAg(-)anti-HBc(-)anti-HBs(+), and 252 (62.4%) were HBsAg(-)anti-HBc(-)anti-HBs(-). Of them, 141 subjects with HBsAg(-)anti-HBc(-) were boosted with 10-μg recombinant HBV vaccine on day-0 and 1-month. The conversion rates of anti-HBs ≥10 mIU/ml on D10-12 and 1-month post-booster were 71.4% and 87.3% respectively in the vaccinees who were anti-HBs(+) at age 5, higher than in those who were anti-HBs(-) at age 5, 57.5% and 80.0% respectively, but no statistically significant. After the second dose of booster, all subjects with anti-HBs(+) at age 5 had anti-HBs >500 mIU/ml. However, 6/40 subjects, with anti-HBs(-) at age 5, had anti-HBs <10 mIU/ml, geometric mean concentration was 3.6 (95% CI 2.0-7.7). Of the subjects received booster, 44 subjects were determined the presence of T cell immunity on D10-12, 41 had HBsAg-specific T cells detectable, including 7/10 subjects whose anti-HBs were <10 mIU/ml 10-12 days post-booster. Among 27 HBsAg(-)anti-HBc(+) subjects, 19 had detectable serum HBV-DNA, and an "a" epitope mutation was found in 1/5 HBV isolates.
One subject who was anti-HBc(+) at age 20 converted into HBsAg(+) 4 years later. The adults received neonatal HBV vaccination had immune memory and immunity against HBV infection. However, 31.9% of neonatal HBV vaccinees who responded weakly at an early age might be susceptible to HBV infection after childhood.


Persistent immunity to hepatitis A and hepatitis B antibodies six years after vaccination of adolescents (aged 12-15 years) with a combined hepatitis A and B (HAB) vaccine following a 0, 6 month or a 0, 12 month schedule was assessed. Yearly (Year-2-6) serum samples were tested for anti-HAV and anti-HBs using EIA. Subjects with anti-HBs concentrations <10 mIU/mL (14/23) at Year-5 or Year-6, received an additional HBV vaccine dose approximately 12 months after Year-6. Blood samples were collected pre-booster and 1 month post-booster to assess booster response. 240 subjects were vaccinated in the study; at Year-6, data were available from 88 subjects. At that time 84.8% (39/46; 0, 6 month) and 92.9% (39/42; 0, 12 month) of subjects had anti-HBs concentrations > or = 10 mIU/mL. All but one of the 14 boosted subjects responded to the additional HBV vaccine dose with anti-HBs concentrations > or = 100 mIU/mL. All seroconverted subjects who returned at Year-6 were seropositive for anti-HAV. Simplification, reduced number of doses and similar long-term persistence of immunity make the 0, 6 month and 0, 12 month schedule preferable for immunization against HAV/HBV in this population.


The long-term protection of hepatitis B (HB) vaccination has been debated for years. The purpose here was to evaluate the kinetic changes of antibody to HB surface antigen (anti-HBs) and define immune memory of the HB vaccine among college students who had previously received full neonatal immunization against HB. In all, 127 college students aged 18-23 years born after July 1984 who had completed HB vaccination and were seronegative for all three HB viral markers, including HB surface antigen (HBsAg), antibody to HB core protein (anti-HBc), and anti-HBs, were recruited. They received three doses of HB vaccine at enrollment, 1 month and 6 months after enrollment. Their anti-HBs titers were assayed at enrollment, 7-10 days, 1 month, 6 months, and 7 months following the first dose of HB vaccine. The anti-HBs seroprotective rates for subjects 7-10 days, 1 month, 6 months, and 7 months postvaccination were 20.5%, 75.6%, 94.5%, and 99.2%, respectively. Those who were seroprotective at 7 to 10 days after one dose of HB vaccine booster developed significantly higher levels of anti-HBs at 1 and 6 months than those not developing seroprotective anti-HBs response at an earlier timepoint. CONCLUSION: At least one-quarter of HB vaccinees have lost their immune memory to the HB vaccine when entering college. Immune memory to HB vaccine was identified by early seroconversion, which was present in only 20% of vaccinees in the present study. To ensure higher than 90% anti-HBs seroconversion rates, at least 2 doses of HB booster vaccines are recommended for at-risk youths who received complete HB vaccinations in neonatal or infant periods but are seronegative for HBsAg, anti-HBs, and anti-HBc in adolescence.


BACKGROUND: Immunization is the best method of protection against hepatitis B. Routine vaccination for newborns and infants was introduced in Poland in 1994-96. Although duration of protection afforded by vaccination remains unknown, no routine boosters are recommended. According to references, up to 50% of 15-year old children had lost the post vaccination immune memory protecting against HBV infection. The aim of the study was to determine the immunity against hepatitis B in 10-12-year old children and to
establish indications for routine booster doses. MATERIAL AND METHODS: In 130 children aged 10-12 years, immunized against hepatitis B with recombinant vaccine in infancy (10 microg, according to schedule: 0-1-2-12 months, first dose given at birth) humoral immunity (anti-HBs antibodies) as well as cellular memory (anamnestic response to booster given in children without protective titers of anti-HBs) were determined. Titers of anti-HBs > or = 10 IU/l were considered protective. Anamnestic response was defined as increase in anti-HBs concentration from < 10 IU/l to > or = 10 IU/l 4 weeks after receiving a booster dose. MARKERS OF HBV INFECTION: hepatitis B surface antigen (HBsAg - marker of chronic hepatitis) and antibodies to core antigen (anti-HBc--marker of past HBV infection) were additionally determined. RESULTS: Protective level of anti-HBs was found in 102/130 (78%) children, including 43/130 (33%) with high (100-999 IU/l) and 16/130 (12%) with very high (> or = 1000 IU/l) titers. 28/ 130 (22%) did not have protective level of anti-HBs, in 9/130 (7%) antibodies were undetectable. Immune memory was determined in 9 children--anamnestic response was revealed in eight of them (89%). In 6/130 (4.5%) of participants HBV infection was confirmed according to positive anti-HBc, including 2 (1.5% of the study group) with positive HBsAg. CONCLUSIONS: Most children in the studied group had seroprotection and immune memory against hepatitis B 10-12 years after vaccination. No routine booster seems to be necessary.


Booster vaccination against hepatitis B (HBV) is not currently recommended, although debate continues on the duration of protection after priming. We assessed antibody persistence and immune memory to hepatitis B 20 years after priming with a recombinant HBV-vaccine during infancy. Infants were vaccinated at birth, 1, 2 and 12 months of age. A subset received a booster dose at Year 5. Antibody persistence was measured approximately yearly until Year 20. Immune memory was assessed by administration of HBV booster dose. At Year 20, anti-HBs seroprotection rates and GMCs tended to be higher in Year 5 boosted than unboosted recipients (83.9% versus 60.5%). After the Year 20 booster dose, anti-HBs anamnestic responses were within the same range 95.8% of subjects in both groups. Primary and booster vaccination with HBV-vaccine in infants induces sustained seroprotection and immune memory against hepatitis B for up to 20 years. Higher persisting seroprotection rates in subjects boosted at Year 5 did not translate into apparent differences in immune memory in a high endemic country.


OBJECTIVE: To investigate the immunization status of hepatitis B vaccine who were inoculated at birth, HBV infections and the vaccine booster effect in the first-year middle school students (12 - 14 years old). METHODS: A cluster, stratified simplified random sampling method was administrated. The sample size was at least 218, which was calculated by Epi Info 3.3.2 software at 53% the minimum acceptable anti-HBs positive rate and 95% confidence level. A total of 250 and 236 students participated in the infection status and booster immunization effects investigation. The HBsAg, anti-HBs and anti-HBc IgG were detected by Enzyme-linked immunosorbent assay (ELISA). HBV DNA was detected by fluorescein quantitative PCR, and the diagnostic test kit were produced respectively by ABBOTT, Diasorin and Beijing Wantai Biological Pharmacy Enterprise Co. RESULTS: For the immunization status before booster: the positive rate of anti-HBs was 62.80% (157/250), the GMT was 73.79 IU/L; the currently HBV infection rate (HBsAg and anti-HBc positive) was 2.80% (7/250). After injection, the anti-HBs positive rate was 94.92% (224/236). Compared with the before booster results, the significant difference was observed (chi(2) = 73.92, P = 0.00). The GMT was 521.15 IU/L, comparing with the before booster results, there was significant difference (t = 15.98, P = 0.00). The anti-HBs
conversion rate (from negative to positive) was 91.86% (79/86) after immune-enhancement; of which, 11 students got the second dose of booster vaccine who are non-responders after first injection, in addition 8 students got the anti-HBs. CONCLUSION: It is an effective method to put the first-year middle school students into the immune-enhancement program, so as to improve the immunization memory effect and avoid the loss of protective antibodies.


Gene-based hepatitis B virus (HBV) vaccines have been proposed as a novel approach to improve the immunogenicity toward non-responders and to allow for protection against potential viral escape mutants. Furthermore, there is significant interest in using DNA or viral vector vaccines to serve as therapeutic agents to treat chronic HBV infections that are resistant to existing drug therapies. However, the key protective antigen of HBV, the surface protein (HBsAg), can be expressed in three different sizes due to its multiple translational initiation sites: small, middle, and large forms of HBsAg. It is not clear whether the immunogenicity of these HBsAg is same, especially their ability to elicit HBsAg-specific B cell and T cell immune responses in addition to the traditional serum HBsAg-specific antibody responses. In the current study, the immunogenicity of three forms of HBsAg DNA vaccines was analyzed individually in a mouse model. Our results indicated that different forms of the HBsAg have unique immunogenicity profiles and this information is useful for the selection of optimal gene-based HBV vaccines for further improved prophylactic and therapeutic applications.


BACKGROUND: In 2000, hexavac and infanrix hexa were licensed in Europe for primary immunisation of children against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive infections caused by Haemophilus influenzae b. In 2005, hexavac was suspended because of concerns about the long-term immunogenicity of its hepatitis B component. We aimed to assess the duration of immunity and need for booster injections in children primed with these vaccines. METHODS: In an open-label, randomised, controlled, multicentre study in six local health units and at the Bambino Gesu Paediatric Research Hospital in Italy, antibody concentrations were measured 5 years after immunisation of infants with hexavac or infanrix hexa. Children with concentrations of antibodies to hepatitis B surface antigen (anti-HBs) lower than 10 mIU/mL were randomly assigned by simple randomisation to receive a booster of HBVaxPro or engerix B monovalent hepatitis B vaccine and tested 2 weeks later. Primary endpoints were the proportion of children with anti-HBs concentrations of at least 10 mIU/mL, geometric mean concentrations (GMCs) of antibody 5 years after vaccination, and the proportion of children with anti-HBs concentrations lower than 10 mIU/mL who had anamnestic response to booster. The study is registered with Agenzia Italiana del Farmaco, code FARM67NFPN. FINDINGS: 1543 children were enrolled, 833 had received hexavac and 710 infanrix hexa. 831 children who received hexavac and 709 who received infanrix hexa were included in the analysis. 319 children who received hexavac and 709 who received infanrix hexa were included in the analysis. 319 children who received hexavac and 709 who received infanrix hexa were included in the analysis. 319 children who received hexavac and 709 who received infanrix hexa were included in the analysis. 319 children who received hexavac and 709 who received infanrix hexa were included in the analysis. 319 children who received hexavac and 709 who received infanrix hexa were included in the analysis. 319 children who received hexavac and 709 who received infanrix hexa were included in the analysis. 319 children who received hexavac and 709 who received infanrix hexa were included in the analysis. 319 children who received hexavac and 709 who received infanrix hexa were included in the analysis. 319 children who received hexavac and 709 who received infanrix hexa were included in the analysis. 319 children who received hexavac and 709 who received infanrix hexa were included in the analysis. 319 children who received hexavac and 709 who received infanrix hexa were included in the analysis. 319 children who received hexavac and 709 who received infanrix hexa were included in the analysis. 319 children who received hexavac and 709 who received infanrix hexa were included in the analysis. 319 children who received hexavac and 709 who received infanrix hexa were included in the analysis. 319 children who received hexavac and 709 who received infanrix hexa were included in the analysis. 319 children who received hexavac and 709 who received infanrix hexa were included in the analysis. 319 children who received hexavac and 709 who received infanrix hexa were included in the analysis. 319 children who received hexavac and 709 who received infanrix hexa were included in the analysis. 319 children who
years after immunisation with hexavalent vaccines, immunological memory seems to
persist in children with anti-HBs concentrations lower than 10 mIU/mL, suggesting that
booster doses are not needed. Additional follow-up is needed. FUNDING: Agenzia Italiana
del Farmaco.

Bagnato, B., M. G. Marino, F. Ruggiero, L. Zaratti and E. Franco. "[Persistence of protection
Universal mass vaccination against hepatitis B virus in infants and adolescents, together
with targeted prophylaxis for risk groups, is recommended since almost twenty years all
over the world to prevent infection and related diseases. Safety and effectiveness of the
vaccine have been clearly demonstrated while unambiguous data about long term protection
and need of booster administration are not yet available, especially for high risk subjects
like health care workers and dialysis patients. By means of new vaccines and new adjuvants
better results could be obtained in a next future.

Chinchai, T., C. Chirathaworn, K. Praianantathavorn, A. Theamboonlers, Y. Hutagalung, P. H.
to hepatitis B vaccine in high-risk children 18-20 years after neonatal immunization." Viral
Eighty-seven high-risk individuals in Thailand who had received a complete course of
recombinant HBV vaccine 18-20 y ago were investigated with regard to their
immunological memory. To evaluate humoral immunity, anti-HBs antibody titers were
measured. Cellular immunity was determined by ELISPOT to detect HBV-specific IFN-
gamma-producing cells. Overall 83.9% of participants developed circulating anti-HBs (titer
> or = 1 mIU/mL) and 58.6% were seroprotected (titer > or = 10 mIU/mL). As for cellular
immunity, 50.6% were positive on ELISPOT. Moreover, there was no correlation between
the level of anti-HBs and positive ELISPOT results. However, the majority of participants
(81.8%) who were positive for IFN-gamma-producing cells were seropositive, but only
50% of seropositive participants were ELISPOT-positive. Thus, 18-20 y after
immunization, it appears that a second booster dose should be considered, especially in
high-risk groups.

Grunert, K. H. Laakmann, R. Gunasekaran, et al. "Immune memory to hepatitis B virus in 4-9-
year old children vaccinated in infancy with four doses of hexavalent DTPa-HBV-IPV/Hib
vaccine." Hum Vaccin 2009 5(9): 592-598.
The combined hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated
polio Haemophilus influenzae type b (DTPa-HBV-IPV/Hib) vaccine produces similar
hepatitis B responses as the HBV monovalent vaccine. Booster vaccination of
immunocompetent individuals primed against hepatitis B in infancy is currently not
recommended. We investigated persisting immunity to hepatitis B in 4-6 (Study A; 106745)
and 7-9 (Study B; 106744) year-old children primed in infancy and boosted in the second
year of life with DTPa-HBV-IPV/Hib. Immunity was assessed by measuring persisting
anti-HBs antibodies and evaluating the response to a challenge dose of HBV vaccine. At 4-
6 years of age 86.0% of 186 subjects had persisting anti-HBs > or =10 mIU/ml increasing
to 98.4% after the challenge. At 7-9 years of age, 78.0% of 186 subjects continued to have
anti-HBs antibody concentrations > or =10 mIU/ml, increasing to 98.9% after
the challenge. In both studies anti-HBs antibody GMC rose >80-fold. An anamnestic response
to the HBV challenge was observed in 95.7% and 98.9% of subjects in Studies A and B,
respectively. In both studies, 87% of 38 subjects with initially undetectable circulating anti-
HBs antibodies (>3.3 IU/ml) achieved the 10 mIU/ml threshold after challenge; > or
=97.0% of subjects with detectable antibodies before the challenge at least quadrupled their
concentration. Post-vaccination anti-HBs concentrations were directly related to persisting
antibody concentrations and the concentrations achieved after the booster dose in the
second year of life. The HBV vaccine challenge dose was well tolerated. These studies
show that primary and booster vaccination with combined DTPa-HBV-IPV/Hib (Infanrix hexa) induces sustained immune memory against hepatitis B up to age 9 years.


The duration of protection after hepatitis B vaccination in children is unknown. We determined the serum level of antibody to hepatitis B surface antigen (anti-HBsAg) in 273 randomly selected 7-9-year-old schoolchildren from Zanjan City, Islamic Republic of Iran, who had been fully vaccinated against hepatitis B starting at birth. Titres < or = 10 mlU/mL were considered unprotective. Just over half of the children (52%) had titres < or = 10 mlU/mL with no difference between the sexes, while 81 (29.7%) had no anti-HBsAg (0 mlU/mL). Three of the children had antibodies to hepatitis B core protein. More studies are needed to determine the necessity for or timing of booster doses.


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.


BACKGROUND: The frequency of protective antiviral memory B cells after hepatitis B virus (HBV) vaccination is unknown. METHODS: A novel 2-step immunomagnetic protocol to assess the ex vivo frequency of protective HBV surface antigen (HBsAg)-specific memory B cells was used. RESULTS: HBsAg-specific memory B cells were detected in vaccinated individuals, although at very low frequency (median, 0.2% of CD19(+) cells [range, 0%-4% of CD19(+)]). No correlation existed between the frequency of HBsAg-specific memory B cells and the corresponding serum antibody titer or B cell enzyme-linked immunosorbsent spot findings. CONCLUSION: Our results indicate sustained B cell-mediated protection against HBV despite waning antibody titers, which is consistent with clinical observations.


OBJECTIVE: To study the immune memory in vaccinees after the completion of a full
schedule hepatitis B immunization. METHODS: One thousand and two hundred one infants born in 1987-1989 were immunized with 3 doses of plasma derived hepatitis B vaccine, while 2484 newborn babies during 1996-1999 were injected with 3 doses of the yeast recombinant hepatitis B vaccine. All of the infants under observation were tested for HBsAg, anti-HBs and anti-HBc, in 2005. Of 959 individuals negative for anti-HBs (< 10 mIU/ml), HBsAg and anti-HBc, 228 were immunized with plasma-derived vaccine and 731 with yeast recombinant vaccine after birth. All of them were detected for anti-HBs 15 days after a booster of 10 Ipg yeast recombinant vaccine. In addition, interleukin-2 (IL-2) was detected in 11 non-responders and 22 responders after boosting, using an enzyme-linked immunospot (ELISPOT). The anti-HBs levels of 190 individuals (91 with plasma derived vaccine and 99 with yeast recombinant vaccine) who had had quantitative data on their antibody status after the primary hepatitis B vaccination, were compared with that after the boosting. RESULTS: Among the individuals who received plasma derived vaccine 16-18 years ago, 79.82% of them showed the signs of immune memory after one booster, with a geometric mean titer (GMT)of 325.69 mIU/ml. Of the individuals who received the yeast recombinant vaccine 6-9 years ago, 95.62% showed immune memory after one booster, with its GMT of 745.18 mIU/ml. Anti-HBs levels induced by the booster were associated with that after the primary immunization. The positive rate of IL-2 was 40.91% in subjects with good immune memory. However, IL-2 was not detected in non-responders after the booster (P < 0.01). CONCLUSION: Most of the individuals who had received a completed schedule of primary hepatitis B vaccination and seroconverted from anti-HBs positive to negative, showed the signs of having immune memory after the booster. Only a small proportion of the vaccinees had lost their immune memory during the long term follow-up period, suggesting that these individuals should receive a booster of hepatitis B vaccine in the highly endemic areas of hepatitis B. Hepatitis B virus; Immune memory; Booster immunization


Antibodies to influenza virus and human immunodeficiency virus are detectable in B cells during the early stages of the immune response, prior to their occurrence in plasma. To investigate similar phenomena in a model of immunization against hepatitis B virus (HBV) infection, medical students in Ghana were screened for HBV markers, HBV surface (HBs) antigen (HBsAg), and HBV core antibodies (anti-HBc). Consenting volunteers, 24 of whom were seronegative (susceptible) and 2 of whom were positive for anti-HBc (prior infection), were vaccinated on day 0, day 40, and 6 months. Two sets of 10 blood samples, sequentially collected at intervals of 2 days following each immunization on days 0 and 40, were processed into B-cell lysates and plasma. Solid-phase HBsAg coated on microtiter plates for enzyme immunoassay or nitrocellulose membranes for dot blot assay was used to detect anti-HBs activity by an indirect antiglobulin assay. A commercially procured sandwich immunoassay was used, along with an enzyme-linked immunosorbent assay and a dot blot assay, for the detection of anti-HBs in B-cell lysates and plasma. Following the first injection of vaccine, a single sample of B-cell lystate collected between 5 and 21 days revealed anti-HBs in 18/21 subjects with no plasma antibodies detectable by sandwich immunoassay. After the booster dose was injected on day 40, a single sample of B-cell lystate collected between 44 and 49 days showed anti-HBs in 16/19 subjects, and this was accompanied by plasma antibodies in 8 subjects. In contrast, between 8 and 13 days, both subjects with prior HBV infection showed anti-HBs in B-cell lysates and plasma. Thus, primary immunization with the HBV vaccine appears to transiently elicit low-affinity anti-HBs in B-cell lysates into plasma.

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


Long-term protection after hepatitis B vaccination is dependent on the persistence of a strong immunologic memory. In search of reliable markers for a hepatitis B surface antigen (HBsAg)-specific immunological memory we studied the cellular and humoral immune responses of 15 healthy individuals who were successfully vaccinated but had lost anti-HBs titers. To determine the reactivity of vaccine-induced HBsAg-specific T cells of both effector and memory phenotype CD4+/CD45RA+ and CD4+/CD45R0+ T cells, respectively, were isolated, stimulated with HBsAg and tested for IFN-gamma and IL-5-secretion by enzyme-linked immunospot assays (Elispot). To detect even small numbers of specific T cells, we enriched the appropriate subpopulation from the entire PBMC population. B cell memory was analysed by cocultivation of isolated B cells with CD4+ T cells and identification of anti-HBs-secreting cells by Elispot. All individuals were revaccinated and humoral and cellular responses were determined. The results showed significant numbers of HBsAg-specific memory T and B cells present in all vaccinees despite the absence of specific antibodies. Our data suggest that individuals who had lost their anti-HBs seropositivity still show immunologic T cell memory and that these T cells are able to trigger anti-HBs production of B cells activated by revaccination.


BACKGROUND: Vaccination with the hepatitis B surface antigen (HBsAg) induces protective levels of antibody (anti-HBs = 10 IU/L) in majority of vaccinees. It has been shown that the levels of anti-HBs antibody do wane after vaccination. The aim of this study was to evaluate the persistence of anti-HBs antibodies in healthy Iranian children at 10 years after primary vaccination and the response to a booster dose using recombinant hepatitis B vaccine. METHODS: Blood samples were collected from 146 healthy 10-11 years old children who received primary course of Hepatitis B vaccine at 0, 1.5 and 9 months of age. The sera were tested for anti-HBs, antibody to Hepatitis B core antigen (anti-HBc) and HBsAg by ELISA technique. A single booster dose of recombinant hepatitis B vaccine was administered intramuscularly to a total of 94 children, whose anti-HBs antibody was less than 50 IU/L (70 children with anti-HBs < 10 IU/L and 24 subjects with anti-HBs 10-50 IU/L). The sera of children were re-tested for anti-HBs antibody levels at 4 weeks after booster vaccination. RESULTS: At 10 years after primary vaccination 70/146 (47.9%) of children had protective levels of antibody with geometric mean titer (GMT) of 68.12 IU/ml. All children were negative for HBsAg, although anti-HBc antibody was positive in 11 (7.5%) of children. In the 94 subjects who received the booster dose the seroprotection and the GMT of anti-HBs antibody were 25.5% and 9.58 IU/L at pre-booster time and rose to 95.75% and 575.6 IU/L after the booster vaccination, respectively. Seroprotection rates and mean titer of antibody similarly expressed in males and females. CONCLUSION: The results of present study showed that at 10 years after primary vaccination with recombinant HB vaccine, 47.9% of the children had protective levels of anti-HBs antibody. Moreover we have demonstrated an anamnestic response to booster vaccination that confirms the persistence of an effective immunological memory in
OBJECTIVE: To explore the relationship between calendar month of administration and antibody (Ab) response to vaccination in subjects from The Gambia and Pakistan, two countries with distinct patterns of seasonality. METHODS: Three cohorts were investigated: Responses to rabies and pneumococcal vaccine were assessed in 472 children (mean age 8 years, males 53%) from rural Gambia. Responses to tetanus, diphtheria and hepatitis B (HBsAg) were investigated in 138 infants also from The Gambia (birth to 52 weeks of age, males 54%). Responses to rabies and Vi typhoid vaccines were assessed in 257 adults from Lahore, Pakistan (mean age 29.4 years, males 57%). RESULTS: In Gambian children, significant associations were observed between month of vaccination and Ab response for the pneumococcal and rabies vaccines. As no consistent pattern by month was observed between the responses, it is assumed that different immunomodulatory stimuli or mechanisms were involved. In Pakistani adults, a significant pattern by month of vaccination was observed with both rabies and typhoid vaccine. No monthly influences were observed in the infant study to the tetanus, diphtheria or the HbsAg vaccines. CONCLUSIONS: Antibody responses to certain specific vaccines are influenced by month of administration. Further research is required to elucidate the precise mechanisms explaining these observations, but a co-stimulatory effect of seasonally variable environmental antigens is a likely cause. Future studies of Ab response to vaccination in countries with a seasonally dependent environment should consider month of vaccination when interpreting study findings.


AIM: To evaluate in vitro T lymphocyte proliferation and specific antibody response to hepatitis B vaccination in two groups of rats fed with normal and marginal zinc content. METHODS: Twenty-two Wistar-Albino rats were randomly assigned into two groups and were fed with constant diet. Zinc was suplemented 10mg/kg dry weight in group I (marginal zinc content) (n=14) and 30mg/kg dry weight in group II (n=8). Hepatitis B vaccine (Engerix B, 4mug) was administered intramuscularly after 8 weeks on feeding and a booster dose was applied 4 weeks after the first injection. Rats were killed 3 weeks after the second injection. Peripheral blood mononuclear cells were stimulated in vitro by PHA (2.5mug/ml) and hepatitis B surface antigen (2.5, 5, 10mug/ml). Proliferation was evaluated by ELISA (celltiter-96 aqueous one solution cell proliferation assay). Serum zinc, anti-HBs titer and zinc per dry liver weight were also measured. Two groups were compared with respect to antigen specific antibody and lymphocyte proliferation responses. Proliferation response to HbsAg were expressed as net percent increase (pci) in lymphocyte proliferation from the baseline activity. RESULTS: Rats' mean body weight and weight gain per month were similar. Median serum zinc was 39 (23-75) and 76(64-115)mug/dl of groups I and II rats, respectively (p<0.05), while there was no difference in liver zinc content between the two groups (37mug/g dry weight versus 32mug/g dry weight). Median anti-HBs levels of groups I and II were 741 (0-10,000)IU/l, 5791 (558-10,000)IU/l, respectively (p<0.05). In lymphocyte proliferation assays, mean net pci with HbsAg of 5 and 10mug/ml were 9.4% and 11.3% in group I rats; while they were 25.3% and 26.1% in group II rats (p<0.01 and p<0.01, respectively). CONCLUSION: In vitro cell-mediated immune response and in vivo specific antibody response to hepatitis B vaccine was decreased in rats fed a diet with marginal zinc content. These observations have shown that marginal Zn deficiency might influence the efficacy of hepatitis B vaccination in humans.


To assess persistence of anti-HBs and immunologic memory of non-responders after revaccination, 40 healthy non-responder children were given a three-dose recombinant hepatitis B vaccine revaccination randomly by intramuscular (10 microg per dose) or intradermal (2 microg per dose) route and followed up to five years. All 17 intramuscular and 22 of 23 intradermal children developed a seroprotective antibody response (anti-HBs≥10 mIU/mL) after revaccination. Children of intramuscular group had significantly higher seroprotection rates and anti-HBs geometric mean titers than the intradermal group. At year 5, 50% of children in intramuscular group, but only 18.2% of intradermal group still maintained seroprotection (P=0.075). By the end of follow-up, a booster dose (5 microg) was given to those who had lost seroprotection. All the eight intramuscular children developed an anamnestic response with increase of anti-HBs level by 215 times, but two of the 18 intradermal children failed to produce seroprotective level. Three-routine-dose intramuscular revaccination was significantly more effective than low-dose intradermal revaccination with the same number of injections. No child seroconverted to HBsAg, and 11 had transient infections indicated by seroconversion to anti-HBc. These results demonstrated that non-responders could benefit from three doses intramuscular revaccination not only in high proportion of anti-HBs conversion but also in long-term persistence of seroprotection, and more importantly in preservation of the immunologic memory years after loss of protective anti-HBs.


Currently, there is a need for therapeutic vaccines that are effective in inducing robust T helper type 1 (Th1) immune responses capable of mediating viral clearance in chronic hepatitis B infection. Hepatitis B therapeutic vaccines were designed and formulated by loading the hepatitis B core antigen (HBcAg) into poly(D,L-lactic-acid-co-glycolic acid) (PLGA) nanoparticles with or without monophospholipid A (MPLA), a Th1-favoring immunomodulator. These particles were around 300 nm in diameter, spherical in shape and had approximately 50% HBcAg encapsulation efficiency. A single immunization with a vaccine formulation containing (MPLA+HBcAg) coformulated in PLGA nanoparticles induced a stronger Th1 cellular immune response with a predominant interferon-gamma (IFN-gamma) profile than those induced by HBcAg alone, free (HBcAg+MPLA) simple mixture or HBcAg-loaded nanoparticles in a murine model. More importantly, the level of HBcAg-specific IFN-gamma production could be increased further significantly by a booster immunization with the (HBcAg+MPLA)-loaded nanoparticles. In summary, these results demonstrated that codelivery of HBcAg and MPLA in PLGA nanoparticles promoted HBcAg-specific Th1 immune responses with IFN-gamma production. These findings suggest that appropriate design of the vaccine formulation and careful planning of the immunization schedule are important in the successful development of effective HBV therapeutic vaccines.


OBJECTIVE: This study looks into the immune response to hepatitis B vaccine (HBV) among children who completed the 3 doses of vaccine 7-years after inclusion of HBV vaccination to the National Extended Program for Immunizations (EPI) in Yemen. METHODS: Between March 2002 and October 2002, a total of 170 children, aged 13-73 months with a mean age of 43.64 ± 17.42 SD months; and have completed the 3 HBV vaccine doses were investigated for immune response to HBV vaccine by quantifying anti-HBs. Past infection was investigated by testing children to total anti-HBc. RESULTS: Of all children, 49.4% were males and 50.6% were females. One hundred and forty-two
(83.5%) responded to the vaccine (antibody level > or = 10 mIU/ml). Only 3 children of 153 (2%) were reactive to anti-HBc indicating that the response was due to vaccination rather than combined effect of vaccine and HBV past-infections. There was a trend of decreasing antibody level with an increasing age. However, the difference in antibody levels between age groups was not statistically significant (p=0.40). Significantly lower antibody level (p=0.02) was found among children with a low economic status.

CONCLUSION: This study has revealed a high response rate to HBV vaccine. However, a considerable proportion (32.4%) of vaccinated children remains to be reconsidered for either revaccination or booster doses due to lack, inadequate or low response. The trend of decreasing antibody level with increasing age suggests a need of careful monitoring of HBV vaccine efficacy in Yemen. Demographic factors such as gender number of inhabitants per room and educational level of father did not significantly affect the immune response to HBV vaccine.

Session 4: Effectiveness of (Universal) hepatitis B vaccination (29)


OBJECTIVES: The study was undertaken, first, to determine the coverage rate of hepatitis B (HB) vaccine and second to evaluate the immune response to HB vaccine among children under 10 years old by measuring the level of circulating anti-HB surface antigen (anti-HBs) antibodies after immunisation with three doses. METHODS: First, 840 children were randomly selected from 4 randomly selected sites in Sana'a city to study the coverage rate of the vaccine; of these, 504 children vaccinated against HBV prior to the study, were tested (56% males and 44% females). Sera were tested for anti-HBs antibodies by ELISA quantitative technique. Each individual's data was collected in a pre-designed questionnaire including: vaccination date, sex, and age at the time of the study. RESULTS: The coverage rate of HBV vaccine was only 69.9%, being slightly higher among male children (72.1%) than female children (66.8%). A total of 276 (54.8%) of the 504 children responded to the vaccine with anti-HBs antibody level >/= 10 mIU/ml, while 228 (45.2%) of the 504 children had non-protective anti-HBs antibodies levels (<10IU/ml). Children of ages 3-5 years had the highest protective rate (63.6%), and the lowest protective rate was in the 9-10 years age group. CONCLUSION: This study revealed a low coverage rate of HBV vaccine and a low protective rate against HBV infection. A considerable proportion of vaccinated children should be considered for either revaccination or booster doses. There is also the need to complete HBV vaccine coverage among the child population in San'a, Yemen.


INTRODUCTION: Vaccination is the main tool for preventing hepatitis B virus (HBV) infection; however, following the completion of the vaccination series, the concentrations of anti-HBs can decline over the years and reach levels less than 10mIU/mL. The
persistence of protection in these individuals is still unknown. The present study aimed to determine the anti-HBs antibody levels among children and adolescents who had received a complete vaccination course for hepatitis B. METHODS: Antibodies against HBV surface antigen (anti-HBs) were tested in 371 individuals aged 10 to 15 years-old. RESULTS: Volunteers who showed undetectable quantities of anti-HBs accounted for 10.2% of the population studied and 39.9% presented antibody titers of less than 10mIU/mL. Anti-HBs >/= 10mIU/mL were verified in 49.9%. CONCLUSIONS: These results corroborate other studies indicating levels of anti-HBs below 10mIU/mL in vaccinated individuals. Additional studies are required to assess whether this indicates susceptibility to HBV infection and the need and age for booster doses.


Vaccination against hepatitis B virus (HBV) immediately after birth prevents neonatal infection by vertical transmission from HBV carrier mothers. There is an ongoing debate whether infant vaccination is sufficient to protect against infection when exposed to HBV later in life. We studied 222 Thai infants born to HBsAg +/- and HBeAg +/- mothers who were vaccinated with recombinant hepatitis B vaccine at 0-1-2-12 months of age. A subset of 100 subjects received a booster dose at age 5 years. Blood samples collected yearly for 20 years were examined for anti-HBs antibodies and serological markers of hepatitis B infection (anti-HBc, HBsAg, and in selected cases HBeAg, anti-HBe, HBV DNA). During the 20-year follow-up, no subject acquired new chronic HBV infection or clinical hepatitis B disease. During the first decade, possible subclinical breakthrough HBV infection (anti-HBc seroconversion) was only observed in subjects born to HBsAg +/-HBeAg + mothers (6/49 [12.2%]). During the second decade, breakthrough HBV infections were detected in all groups (18/140 [12.8%]). Increases in anti-HBs concentrations that were unrelated to additional HBV vaccination or infection were detected in approximately 10% of subjects in each decade. Primary infant vaccination with a recombinant hepatitis B vaccine confers long-term protection against clinical disease and new chronic hepatitis B infection despite confirmed hepatitis B exposure.


BACKGROUND: This study is aimed to investigate if there was increased risk of HBV acquisition among first graders in Taiwan during a 3-year follow-up period. METHODS: A total of 1545 healthy first graders, who were vaccinated against HBV in infancy, were recruited in 2005. All subjects were checked for hepatitis B surface antigens (HBsAg), antibodies to HBsAg (anti-HBs), and to the hepatitis B core antigen (anti-HBc). Nucleotide sequence of the "a" determinant of HBsAg was determined by polymerase chain reaction and direct sequencing in the HBsAg carriers. RESULTS: Among 1545 subjects, 0.78% were HBsAg seropositive, 54.30% were anti-HBs seropositive, and 1.68% anti-HBc seropositive. Three of the 10 HBV carriers (30%), whose HBV DNA were sequenced for the S gene, had surface antigen mutants at the "a" determinant. CONCLUSION: There were no new chronic HBV infections in this cohort of children for two consecutive years. HBV S gene vaccine escape mutants did exist in the vaccine-failure population, but they may not have made a major health impact.


The objective of this study was to determine long-term immunity to hepatitis B virus (HBV) in a cohort of adolescents who received plasma-derived HBV vaccine in 1989 and
1990 in a remote Australian Aboriginal community. This was done using a serological survey; primary outcome measures were cut-off titres of HBsAb, and the presence of HBeAb and/or HBsAg. Of 37 adolescents in the cohort, 4 (11%) had evidence of active infection, one with abnormal liver enzymes, 7 (19%) had evidence of past infection, 15 (41%) were HBsAb positive in low titre and 11 (30%) were classed as immune. It was concluded that there was relatively poor long-term serological immunity to HBV vaccination in this group; a finding which is in keeping with similar studies in Indigenous and remote populations elsewhere. This finding raises the concern that a significant proportion of Aboriginal adolescents in other remote communities (vaccinated in 1989 and 1990) were not adequately protected by the vaccine. If so, there will be an unexpected burden of chronic HBV infection in these settings and a substantial group who are nonimmune, despite having received complete HBV vaccination courses as infants. The authors recommend followup serosurveys in remote Aboriginal communities to identify people with low HBsAb titres, especially those without an adequate anamnestic response to another dose of HBV vaccine. In addition, community-based active surveillance programs will be required to detect people with chronic HBV infection and provide access to monitoring and appropriate treatment.


BACKGROUND: Mutants of the a determinant of hepatitis B surface antigen (HBsAg) can escape neutralization by vaccine-induced antibodies and prevail in an immunized population. METHODS: We evaluated the a mutants in a pediatric population surveyed in 2004 and compared these findings with the data of previous surveys. RESULTS: There were 38 children and 74 adolescents who were HBsAg positive, and serum hepatitis B virus (HBV) DNA was obtained and tested from 31 and 34 of them, respectively. The a mutants were found in 7 (22.6%) of 31 HBV DNA-positive children and in 7 (0.10%) of 7234 children, the entire population that was surveyed in 2004. After the beginning of universal immunization, the very low prevalence of mutants has remained unchanged for 20 years. More a mutants were found in immunized than in nonimmunized HBV DNA-positive children aged 1-4 years old (31% vs 4%, P = .016) but not in those children aged 5-12 years old. Approximately 68% of immunized, mutant-infected children had carrier mothers. More a mutants emerged in children immunized with plasma-derived vaccines than in those immunized with recombinant vaccines (14 of 5166 vs 3 of 4970, respectively; P = .04). HBV DNA levels were significantly lower in hepatitis B e antigen-positive sera containing the G145R mutant than were levels in sera containing wild-type virus. HBsAg-negative sera containing a mutants had very low HBV DNA levels. CONCLUSIONS: Less infectivity of G145R, recombinant vaccine use, and mutant loss with older age seem to decrease the a mutant prevalence in an immunized population over time.


The success of childhood vaccination against hepatitis B relies on persistence of immunity into adolescence and adulthood. In 2000, two hexavalent vaccines with a hepatitis B component (Hexavac, Infanrix hexa) were introduced in Germany. Hexavac was withdrawn in 2005 amidst concerns about its long-term hepatitis B protection. We compared hepatitis B surface antibody (anti-HBs) levels in children fully vaccinated with Hexavac or Infanrix hexa (n=477) in a secondary data analysis of a large cross-sectional health survey in Germany. On average 2.4 years after vaccination, 25.3% of Hexavac vaccinees had anti-HBs levels <10 mIU/ml (95% CI 19.0-32.8) compared to 4.7% of Infanrix hexa vaccinees (95% CI 2.4-8.9). These findings suggest that short-term hepatitis B immunogenicity in
Hexavac vaccinees may also be weaker. Further studies are warranted to assess whether Hexavac vaccinees should be re-vaccinated or receive a booster vaccination before these birth cohorts reach adolescence.


The world's first nationwide hepatitis B virus (HBV) universal vaccination program for infants was launched in Taiwan in July, 1984. All infants received three to four doses of plasma or recombinant HBV vaccines. In addition, infants of HBeAg-positive mothers received 0.5ml of hepatitis B immunoglobulin within 24 hours after birth. The vaccination coverage rate is as high as 97%. Seroprevalence of hepatitis B surface antigen (HBsAg) declined from 9.8% (prevaccination period) to 0.6% in children in Taipei City after 20 years of mass vaccination. The seropositive rates for HBsAg, antibody to HBsAg, and antibody to hepatitis B core antigen were 1.2%, 50.5%, and 3.7%, respectively, in those born after the vaccination program (<20 years old) in 2004. In line with the decrease of chronic HBV infection, the incidence of hepatocellular carcinoma (HCC) also decreased in children in Taiwan. From 1981 to 1994, the incidence of HCC in 6- to 9-year-olds declined from 0.52/100,000 for those born between 1974 and 1984 to 0.13 for those born between 1984 and 1986 (p<0.001). We extended the observation to 2000, the incidence of HCC per 100,000 children decreased from 0.54 to 0.20. The prevalence of a determinant mutants (amino acids 121-149 of HBsAg) in Taiwanese carrier children was 7.8% (eight out of 103) in 1984, increased to 19.6% (10 out of 51) in 1989, peaked at 28.1% (nineteen out of 32) in 1994, and remained stationary at 23.1% (three out of 13) and about 25% in 1999 and 2004, respectively; it was higher in those fully vaccinated compared with those not vaccinated. The other group of subjects who are susceptible to vaccine failure is the immunocompromized hosts. We observed some de novo HBV infection in children after liver transplantation. Despite the success of hepatitis B immunization, childhood chronic HBV infection and HCC were not eliminated by the universal vaccination program. Among those HBsAg carriers born after the vaccination program, 89% of their mothers were found to be positive for HBsAg, indicating the importance of maternal transmission. This was also true in the mothers of children with HCC, of them 96% were HBsAg positive. After two decades of universal infant HBV vaccination, we found this program provides long-term protection for up to more than 20 years, and a universal booster is not required for the primary HBV vaccinees before adulthood. Mother-to-child transmission, although largely diminished, is still the main cause for immunoprophylaxis failure. The emergence of escape mutants did not impose increased risk of chronic infection at present. Nevertheless, development of new vaccines may overcome the vaccine failure.


Hepatitis B vaccine is one of the best human vaccines ever developed; it is safe, cheap, and highly immunogenic, stimulates long lasting protective efficacy, and is the first human cancer vaccine. Remarkably, HBV vaccine works even when administered to newborns, timing which is necessary because of mother to infant transmission. Countrywide HBV immunization programs were initiated in Taiwan and Thailand in the 1980s. HBV vaccine has been part of the WHO global immunization since 199x and with at-birth immunization programs in xxx countries resulting in major declines in acute sequelae of HBV infection. Of far greater significance, HBV vaccination prevents hepatocellular carcinoma (HCC) and its use is reducing mother to infant transmission, the driving force behind the HBV carrier state worldwide. These benefits are just being realized since decades elapse between perinatal transmission at birth and the onset of HCC decades later. Studies in Taiwan and Thailand are showing declines in HCC incidence as a result of country wide at-birth HBV immunization programs initiated in the 1980s. Many investigators from many countries have contributed to the understanding of HBV and its role as the major cause of HCC. This article briefly summarizes the work of my University of Washington laboratory in Taipei,
Taiwan where I lived and worked from 1972 and 1986 because of the very high HBV carrier rates of HBV in Taiwan. During those 14 years we discovered vertical transmission, its timing and mechanism, and the predictive value of HBeAg. We went on to establish the efficacy of HBIG for prevention of vertical transmission. In later studies we established the efficacy and timing of HBV vaccine and HBIG and HBV vaccine in combination for optimum preventive efficacy. Of greatest significance, our studies showed that chronic HBV infection is the commonest cause of HCC. Worldwide, mothers are the driving force behind the infections that lead to HCC because the HBV carrier state is inversely proportional to the age of the infant when infected. We were able persuade WHO to adopt HBV as the 7th immunogen in the EPI, its global infant immunization program. In some ways enormous progress has been made but measured against its potential, progress in most countries, including the United States has been far too slow.


BACKGROUND: Preventive measures remain the best approach to control the spread of hepatitis B virus (HBV) infection. PATIENTS AND METHODS: To evaluate the effectiveness of vaccination against HBV, we conducted a 20-year retrospective study on 100 subjects, born to hepatitis B surface antigen (HBsAg)-positive mothers, who had received postexposure prophylaxis at the Clinic of Infectious Diseases (Siena University, Italy) during 1984-2004. All patients were tested for the presence of HBsAg, anti-HBs and anti-HB core antigen (anti-HBc). RESULTS: Two subjects (2%) acquired the infection as shown by the presence of anti-HBc. Of the 98 patients who did not acquire the infection, 62 of these (63.3%) had an anti-HBs concentration considered protective (> or =10 mIU/ml). The percentage of protected subjects decreased in relation to time from vaccination with a significant reduction (p = 0.009) of anti-HBs geometric mean titre (GMT) after 5 years, which reached the level of 10 mIU/ml after about 15 years. No patients without protective concentration have acquired the infection as of today. Only 12% of the HBsAg-positive mothers were followed in specialized structures after pregnancy, reflecting the scarce knowledge of the problem in the general population. CONCLUSION: Our data, while confirming the effectiveness of anti hepatitis B vaccination, highlight the need for postvaccination follow-up, particularly in high-risk categories, to prolong protection, through booster doses if necessary. We show, moreover, the importance of maintaining active surveillance in the territory to improve follow-up to chronic carriers and to sensitize families.


Hepatitis B virus infection is a global health problem. Worldwide, about 360 million people are chronically infected with the virus. They continue to spread the virus to others and are themselves at risk of chronic liver diseases and hepatocellular carcinoma. The infection can now be treated by antivirals or interferons and the transmission route can be interrupted. Nevertheless, the most effective means is to immunize all susceptible individuals, especially young children, with safe and efficacious vaccines. The combined efforts of vaccination, effective treatment and interruption of transmission make elimination of the infection plausible and may eventually lead to eradication of the virus. Because hepatitis B vaccination has a key role in the control of hepatitis B, properties of this vaccine, its effectiveness in pre-exposure and post-exposure settings, duration of protection after vaccination and the need of booster doses are discussed. Mass hepatitis B vaccination in children decreases the carriage of the virus, and the diseases associated with acute and chronic infection, including hepatocellular carcinoma. Challenges that need to be solved to expand mass vaccination, and the strategies towards elimination and eventual eradication of hepatitis B in the world are also discussed.

INTRODUCTION: This is the third evaluation study of the hepatitis B virus (HBV) vaccination program, initiated in 1989 in Saudi Arabia. AIMS: This study sought to assess the efficacy and long-term protection of the hepatitis B vaccine among Saudi adolescents. METHODS: School students between the ages of 16 and 18 years were randomly chosen from high endemic (Aseer), intermediate endemic (Madinah), and low endemic (Al-Qaseem) areas of the country. Hepatitis B surface antigen (HBsAg), hepatitis B core IgG antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs) were measured using standard techniques. RESULTS: A total of 1355 students (689 males and 666 females) were selected randomly from the three areas. No cases of positive HBsAg or anti-HBc were detected among the study population. Five hundred and ten students (38%) showed protective anti-HBs titers (≥ 10mIU/ml), while 528 (39%) students had undetectable anti-HBs titers (<1 mIU/ml). CONCLUSIONS: This study shows the excellent efficacy of the HBV vaccination program in Saudi Arabia 18 years after its launch. Based on this study and others, a booster dose for the adult population appears to be unnecessary.


Hepatitis B virus (HBV) infection and its sequelae remain a major health problem for Taiwan. The national hepatitis B (HB) vaccination programme was first launched in 1984 to combat the spread of this infection. This study examined the status of HBV infection amongst students at a Taiwanese university in 2005, 18 years after the implementation of a nation-wide mass HB vaccination programme. In 2005, 5875 new university entrants, who were born during the period 1 July 1976 to 30 June 1988, were subdivided into one of 12 one-year-interval birth-year cohorts. Each student was individually tested for serum hepatitis B surface antigen (HBsAg), Antibody to hepatitis B surface antigen (anti-HBs) and antibody to hepatitis B core antigen (anti-HBc) status. We observed a declining trend of past exposure to HB infection from 48.7% (1976 birth-year cohort) to 5.2% (1987 birth-year cohort). The prevalence of chronic HB infection also declined from 14.5% (1976 birth-year cohort) to 1.9% (1987 birth-year cohort). The prevalence of persistent HB immunity through (earlier) active vaccination declined from 72% (1984 birth-year cohort) to 41.6% (1987 birth-year cohort). The prevalence of HB infection-naive individuals increased from 18.2% (1984 birth-year cohort) to 53.1% (1987 birth-year cohort). This study demonstrates that as the implementation of the mass HB vaccination programme in 1984, the incidence of HB infection in Taiwan has declined, although a 'waning-off' effect of serum anti-HBs to low or undetectable levels, which may not provide protection, amongst this student population has arisen, 18 years following the implementation of the nation-wide HB vaccination programme. Such a situation may mean that these individuals may not be effectively protected against future HB infection. A booster dose of HB vaccine, given 18 years following HB vaccination, perhaps even earlier, should be considered.


Primary hepatocellular carcinoma is the commonest cancer in The Gambia. The Gambia Hepatitis Intervention Study (GHIS) was established in 1986 to evaluate the protective effectiveness of infant hepatitis B immunization in the prevention of chronic liver disease, particularly, hepatocellular carcinoma and cirrhosis later in adult life. This program was designed based on a series of assumptions. Here, we used data from observational and epidemiologic studies developed since 1986 to examine the validity of these assumptions. We found that (a) hepatitis B vaccine coverage was 15% more than originally assumed, (b)
protection against hepatitis B virus (HBV) infection was not dependent on the number of vaccine doses received, (c) perinatal infection with HBV was of negligible importance, and (d) the HBV attributable risk of hepatocellular carcinoma at age < 50 was 70% to 80%, lower than initially assumed. Based on these data, the final outcome of the GHIS should be measurable from 2017, sooner than originally assumed. The GHIS strategy takes into account-specific patterns of virus epidemiology and natural history of hepatocellular carcinoma in Africa and provides a model for integrating and evaluating new vaccines into the Expanded Programme of Immunization of sub-Saharan African countries.


BACKGROUND: Hepatitis B virus infection is one of the most important risk factors for hepatocellular carcinoma. Hepatitis B vaccination has been obligatory in the Expanded Program on Immunization (EPI) in Khon Kaen since 1990. OBJECTIVE: To compare the incidence of hepatocellular carcinoma in children in Khon Kaen province before and after the introduction of national hepatitis B vaccination program. METHODS: Cases of liver tumors in children under 18, diagnosed during 1985-2007, were retrieved from the population-based cancer registry of Khon Kaen. Patients were divided into 2 groups, vaccinated and non-vaccinated with hepatitis B vaccine regarding the year of birth before or after 1990. Patients with diagnosis of liver cancer from any basis of diagnosis in population-based registration, except hepatoblastoma, were included. Patients without verified histology were assumed as having hepatocellular carcinoma if the age at diagnosis was over 10. Age-standardized incidence rates (ASRs) were analyzed and expressed as numbers per 1,000,000 population. RESULTS: Fifteen patients aged 13 to 18 years were included in this study. The mean and median ages at diagnosis were 15.7 and 15 years respectively. Four children had a verified histology (age 14 to 18 years, median and mean = 16). The remaining 11 patients were diagnosed based on history and physical examination, radiology and death certificate, at the aged of 13 to 18 years. The ASRs for liver cancer in children over 10 years of age of non-vaccinated and vaccinated children were 0.88 and 0.07 per million respectively (p = 0.039). When calculated by including children at or older the 5 years of age, the ASRs for non-vaccinated and vaccinated cases were 0.97 and 0.24 per million respectively (p = 0.007). CONCLUSIONS: The incidence of hepatocellular carcinoma is significantly lower in Thai children who receive hepatitis B vaccine at birth.


BACKGROUND/PURPOSE: The nationwide hepatitis B vaccination program in Taiwan was well known for its efficacy in reducing the carrier rate of hepatitis B and the morbidity and mortality of hepatitis B-related diseases among children. The aim of this study was to investigate the seroprevalence of hepatitis B 20 years after this program was implemented. METHODS: A total of 7592 freshmen from one university in Northern Taiwan participated in this study during their school entry health exam in September 2003 and September 2004. Basic data including gender, birthday, family history and vaccination history of hepatitis B by self-reported questionnaire were collected. Hepatitis B serum markers, including hepatitis B surface antigen, antibody against hepatitis B surface antigen, and antibody against hepatitis B core antigen were all checked. The differences in the seroprevalence of hepatitis B between two groups of subjects born before July 1984 and after July 1984 were examined. Multiple logistic analyses were performed for identifying the odds ratio (OR) of family history and other variables for each hepatitis B serum marker. RESULTS: Subjects born after July 1984 were found to have a lower rate of hepatitis B surface antigen of 2.2% (95% confidence interval [CI], 1.8-2.6%) vs. 7.4% (95% CI, 5.9-8.9%), and core antibody against hepatitis B of 6.7% (95% CI, 6.0-7.3%) vs. 23.5% (95% CI, 21.1-25.9%), but a higher rate of surface antibody against hepatitis B of 74.3% (95% CI, 73.2-75.4%).
69.1% (95% CI, 66.5-71.7%) compared with those born before July 1984 (all p < 0.001).
Subjects with a family history of hepatitis B had higher risk of being infected by hepatitis B
(OR, 4.07; 95% CI, 3.18-5.12) and becoming carriers (OR, 7.26; 95% CI, 5.05-10.44) after
adjustment for sex, age, birth year, and self-reported hepatitis B vaccination history.
CONCLUSION: The seroprevalence of hepatitis B surface antigen continued to decline 20
years after neonatal hepatitis B vaccination program. It is strongly recommended that those
who have a family history of hepatitis B should receive early check-up of hepatitis B status
after complete vaccination or closely follow up their hepatitis B status after neonatal
hepatitis B vaccination.

Hammitt, L. L., T. W. Hennessy, A. E. Fiore, C. Zanis, K. B. Hummel, E. Dunaway, L. Bulkow and
B. J. McMahon. "Hepatitis B immunity in children vaccinated with recombinant hepatitis B
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
candidate at birth. METHODS: Participants received 5 microg of recombinant
hepatitis B vaccine. Sera were collected at baseline, 10-14 days and 1 month after
vaccination, and tested for antibody to hepatitis B core antigen (anti-HBc) and anti-HBs.
An anamnestic response was defined as an anti-HBs increase within 15 days, from either
undetectable to >/=10 mIU/mL, or, if the baseline concentration was detectable, a 4-fold
increase. RESULTS: None of 37 participants (mean age 14.6 years) were anti-HBc
positive. An anamnestic response (GMC=254 mIU/mL, range 16-2767 mIU/mL) was
observed in 18 (51%) of 35 participants who had sera collected within 15 days after the
booster. CONCLUSIONS: In this small study, half of children who had received hepatitis B
vaccine starting at birth did not have evidence of immune memory as measured by
development of anamnestic responses to booster vaccination. Additional studies are needed
to assess whether this indicates susceptibility to infection and whether persons vaccinated
starting at birth may benefit from a hepatitis B vaccine booster to maintain long-term
protection.

Chen, H. Y. Hsu, et al. "Two decades of universal hepatitis B vaccination in taiwan: impact and
BACKGROUND & AIMS: Following the world's first successful implementation of a
universal hepatitis B virus (HBV) vaccination program for infants in Taiwan 20 years ago,
we performed this study to evaluate the long-term protection afforded by HBV vaccination
and to rationalize further prevention strategies. METHODS: HBV seromarkers, including
hepatitis B surface antigen (HBsAg) and antibodies to HBsAg (anti-HBs) and core antigen
(anti-HBc), were studied in 18,779 subjects from neonates to adults below 30 years of age
in 2004. The birth cohort effect was evaluated by comparing the results of the same birth
cohorts at different ages among this survey and the previous 1984, 1989, 1994, and 1999
surveys. RESULTS: The seropositive rates for HBsAg, anti-HBs, and anti-HBc were 1.2%,
50.5%, and 3.7%, respectively, in those born after the vaccination program (<20 years of
age) in 2004. A positive maternal HBsAg status was found in 89% of the HBsAg
seropositive subjects born after the vaccination program. The absence of an increase in
HBsAg seropositive subjects at different ages in the same birth cohorts born after the
vaccination program implied no increased risk of persistent HBV infection with aging.
CONCLUSIONS: Universal HBV vaccination provides long-term protection up to 20
years, and a universal booster is not indicated for the primary HBV vaccinees before
adulthood. Maternal transmission is the primary reason for vaccine failure and is the
challenge that needs to be addressed in future vaccination programs. This may include an
appropriate hepatitis B immunoglobulin administration strategy for high-risk infants and
involve efforts to minimize noncompliance.


AIMS: To analyze the prevalence of hepatitis B virus infection markers and hepatitis B vaccination in a representative sample of the juvenile and adult population of Catalonia and to evaluate the changes with respect to seroepidemiological surveys carried out in 1989 and 1996. DESIGN: In all subjects anti-HBc and anti-HBs antibodies and HBsAg were determined using an ELISA test. The possible association between sociodemographic variables and the prevalence of markers was analysed by calculating the adjusted odd ratio (simple logistic regression). SETTING: The study was carried out in 2002 in representative samples of the juvenile (5-14 years) and adult population (>or= 15 years) of Catalonia (Spain). MAIN RESULTS: In 2002 the global prevalence of HBsAg+ was 0.7% (95% CI: 0.4-1.0) and that of anti-HBc+ 8.7% (95% CI: 7.6-9.8), values higher than those obtained in 1989 of 1.5% (95% CI: 1.0-2.1) and 15.6 (95% CI: 13.9-17.3). The prevalence of markers of infection increased with age. The only sociodemographic variable significantly associated with the prevalence of hepatitis B virus infection was the place of birth. The risk of infection was twice as high in subjects born outside Catalonia (p<0.01), adjusted OR 2.0 (95% CI: 1.34-2.98) compared with those born in Catalonia. CONCLUSIONS: The results of this study show that the prevalence of hepatitis B virus infection (anti-HBc+) in Catalonia (Spain) is currently the lowest it has ever been and suggest that there has been a change in the pattern of endemicity of hepatitis B virus infection in Catalonia, which has become a country of low endemicity.


In Taiwan, the nation-wide Hepatitis-B virus (HB) vaccination program was first launched in July 1984 and was directed to those infants born to hepatitis B surface antigen (HBsAg) carrier mothers in Taiwan. From July 1986 onwards, all infants born in Taiwan were immunized against HB. This study examined the HB-infection status amongst students at a Taiwanese university 18 years subsequent to the implementation of universal HB vaccination. A total of 1,969 new university entrants in 2005 were grouped into 1 of 3 distinct birth cohorts according to their HB-vaccination schedule (cohort-1 students born prior to July 1, 1984; cohort-3 students born subsequent to June 30, 1986) and were examined for their serum HBsAg, antibody to hepatitis B surface antigen (anti-HBs), and antibody to hepatitis B core antigen (anti-HBc) status. Immunity arising from vaccination was defined as an anti-HBs level 10 mIU/ml. We observed a trend toward a decreasing anti-HBc-positive rate and a decreasing HBsAg carrier rate from, respectively, 26.5 and 8.7% for cohort-1 to 4.7 and 1.7% for cohort-3 students. The prevalence of students featuring seronegativity for all three HB markers increased from 12.3% for cohort-1 to 48.8% for cohort-3 individuals. Amongst the 1,695 subjects revealing seronegativity for HBsAg and anti-HBc, their anti-HBs level was analyzed according to their birth year. The prevalence of students featuring a non-protective anti-HBs level increased from 11.9% for birth-year 1984 individuals to 48.2% for birth-year 1987 students. The introduction of HB vaccine has effectively reduced the transmission of HBV infection in Taiwan, 18 years subsequent to the commencement of the universal HB-vaccination program. A "waning-off" effect of anti-HBs seropositivity acquired from the HB vaccination program has also been observed.

The long-term protective effect of hepatitis B virus (HB) vaccination against HB infection and the necessity for routine booster vaccination in young-adult age subsequent to full HB immunization at birth remain issues of some debate currently. This study is aimed at evaluating the seroprevalence of HB infection and the response to HB booster vaccination amongst young-adult university students who had previously undergone full vaccination during their infancy. Eight hundred and forty-three subjects (mean age 18.7 +/- 0.4 years), 492 males and 351 females, with a complete HB vaccination during infancy were enrolled into this study. The prevalence of natural HB infection, chronic HB-carrier status, and HB-naive group was, respectively, 4.1%, 1.4%, and 62.3%. Amongst 316 study subjects who were naive to HB infection and had received one HB booster at time of university entrance health examination, 49.6%, 91.4%, and 97.5% of the participants with a serum anti-HBs level <0.1, 0.1 to <1.0 and 1.0 to <10.0mIU/mL prior to the booster vaccination, respectively, developed an anamnestic response (i.e., >/=10mIU/mL) to a booster dose of HB vaccine. Full implementation of national-wide HB vaccination program in 1986 has significantly reduced the incidence of HB infection and associated carrier rate in Taiwan. Approximately three-quarter of the subjects who were naive to HB infection and had received one HB booster demonstrated an anamnestic response to a booster HB vaccine. The higher the anti-HBs titers remained for an individual subsequent to primary vaccination, the greater the anamnestic response observed. Additional long-term follow-up studies are needed for young adults initially vaccinated for HB in their infancy.


Hepatitis B virus (HBV) infection is highly prevalent in Asia, Africa, southern Europe and Latin America, HBV vaccination has effectively reduced the acute and chronic infection rates as well as related complications in the vaccinated children. The incidence of hepatocellular carcinoma in children has been reduced to approximately 25% of the incidence before the vaccination program, and fulminant hepatitis in children has also been reduced after universal hepatitis B vaccination. HBV DNA sero-positive rate was 98-100% in HBsAg positive vaccinated children, while the positive rate was only 11-20% in those vaccinees with a negative HBsAg but positive anti-HBc reaction. Hepatitis B surface gene mutants in HBV DNA positive children increased gradually from 7.8% before the vaccination program, to 19.6%, 28.1% and 23.1% at 5, 10 and 15 years after the vaccination program. Long-term follow-up of vaccinated children has confirmed that universal HBV vaccination in infancy has produced adequate protection up to 14 years of age. The annual decay rate of hepatitis B surface antibody (anti-HBs) was 10.2% in children who did not receive a booster dose. The new HBV infection rate was not different between those who did and those who did not receive a booster dose of HBV vaccine. During a follow-up period of seven years for 1200 vaccinated 7-year-old children in Taiwan, the mean annual hepatitis B core antibody sero-conversion rate was 0.2%. All were negative for HBV DNA. No new chronic HBV infections developed. A booster dose of HBV vaccine is not recommended in children under 15 years of age. Systematic HBV DNA screening of a large population such as blood donors may be instrumental in following the long-term effect of the universal vaccination program on the incidence of silent HBV infection and vaccine escape mutants.


The national hepatitis B vaccination program in Taiwan is considered one of the most successful and effective public health programs to control chronic hepatitis B infection in the past 20 years. This review illustrates how to implement a successful hepatitis B vaccination program based on Taiwan's experience. Several important controlled randomized clinical trials on hepatitis B immunoglobulin and vaccine in Taiwan demonstrated an 80-90% protective effect among infants of mothers who were positive for
either hepatitis B envelope antigen or hepatitis B surface antigen. A series of prevalence surveys on children born before and after the national vaccination program began disclosed a steady decrease in seroprevalence of hepatitis B surface antigen in Taiwan, with 78-87% effectiveness after the national vaccination program was launched. Studies on the secular trend of liver disease risk also documented a 68% decline in mortality from fulminant hepatitis in infants and a 75% decrease in the incidence of hepatocellular carcinoma in children 6-9 years of age after the national vaccination program began. In conclusion, since 1984, the national hepatitis B vaccination program has been successful in preventing acute and chronic liver diseases in Taiwan.


OBJECTIVES: To evaluate the impact of the universal hepatitis B (HB) vaccination programme on the prevalence of hepatitis B surface antigen (HBsAg) carriers and immunity to HB virus infection among children <18 years and to determine the HB seroprevalence in the Thai population. METHODS: We enrolled people in four provinces, including Chiangrai, Udon Thani, Chonburi and Nakhon Si Thammarat to geographically represent populations in the North, Northeast, Center and South of the country respectively. Serology for HBsAg, anti-hepatitis B surface (anti-HBs), and anti-hepatitis B core (anti-HBc) was tested using ELISA commercial kits. In total, 6213 subjects aged 6 months to 60 years from the four provincial hospitals and two to three district hospitals of each participating province participated. RESULTS: Overall HBsAg, anti-HBs, and anti-HBc seropositive rates amounted to 4%, 41.6% and 26.5% respectively. Of 2887 participants aged 6 months to 18 years, 2303 were born after (group I) and 584 prior to (group II) HB vaccine integration into the expanded programme on immunization of each participating province. The HBsAg seropositive rate was 0.7% among group I children and 4.3% among group II children. The prevalence rate of anti-HBc was 2.9% in group I and 15.8% in group II. In children under 18 years, the HBsAg carrier rate was 0.98% among complete vaccinees and 1.36% among participants without vaccination. CONCLUSIONS: This finding supports the efficacy of universal HB immunization in reducing the prevalence of HB infection in Thailand which is a highly endemic country.


In Taiwan, decrease of both infection and carrier rates of hepatitis B virus (HBV) have been documented especially in metropolitan areas after universal HBV vaccination. This study investigated HBV infection status in a rural township 15 years after the program began. Three cross-sectional studies were conducted in 1999, 2000 and 2003, to recruit all the students of the only junior middle school, born from July 1984 to June 1991, in a township in central Taiwan. Serum samples were tested for HBsAg, anti-HBs and anti-HBc. Subjects identified to be neither positive for HBsAg nor anti-HBs were given a booster dose of HBV vaccine. Subjects lacking an anamnestic anti-HBs response were given a complete 3-dose vaccination. A total of 1454 (98.5%) students responded. The prevalence rate of HBsAg decreased 57% [from 12.5% in 1984 to 5.4% in 1991, P < 0.005 (chi2-test for linear trends)], and anti-HBc positive rate dropped 68% (from 31.9 to 10.2%, P < 0.001). An anamnestic anti-HBs response developed after a vaccine booster among 433 (72%) anti-HBs negative and 12 (66.7%) anti-HBc alone subjects. And 93 (94.9%) anti-HBs negative and 1 (16.7%) anti-HBc alone subject developed a primary anti-HBs response after catch-up vaccination. Viremia was detected for two anti-HBc alone subjects without anamnestic or primary response. The vaccination program has decreased the number of those infected and carrier rates in either urban or rural areas in Taiwan. However, the prevalence of HBsAg and anti-HBc in rural area were much higher than urban area.

OBJECTIVES: Hawaii implemented routine infant hepatitis B vaccination in 1992 and required it for school entry in 1997. Previously, in 1989, a serologic survey among Hawaii school children in grades 1 to 3 indicated that 1.6% had chronic hepatitis B virus infection, and 2.1% had resolved infection. We conducted a follow-up survey to examine changes in hepatitis B virus infection rates. PATIENTS AND METHODS: This study was performed in Oahu, Hawaii, during the 2001-2002 school year among children in grades 2 and 3. Consenting parents/guardians provided demographic information including place of birth. Participants were tested for serologic evidence of hepatitis B virus infection and their vaccination status was determined by reviewing school records. Rates of symptomatic acute hepatitis B among persons aged < or = 19 years were calculated from cases reported from Hawaii to the Centers for Disease Control and Prevention between 1990 and 2004.

RESULTS: Completed hepatitis B vaccination series were documented for 83% of the 2469 participants by age 18 months and for 97% by age 5 years. Past or present hepatitis B virus infection was detected among 6 participants (0.24%), including 1 (0.04%) with chronic infection and 5 (0.20%) with resolved infections. Compared with the 1989 survey, these prevalences represent declines of 97% and 90% in chronic and resolved hepatitis B virus infections, respectively. The incidence of symptomatic acute hepatitis B in Hawaii children and adolescents aged < or = 19 years decreased from 4.5 cases per 100,000 in 1990 to 0.0 during 2002-2004. To date, the last reported case in a child aged < 15 years in Hawaii occurred in 1996. CONCLUSIONS: Hepatitis B virus infection has nearly been eliminated in Hawaii children born after universal infant hepatitis B vaccination was implemented. These findings suggest that hepatitis B prevention goals are being met through routine immunization and related prevention programs among US children.


Sero-epidemiological studies on herd immunity following the vaccination against hepatitis B virus may contribute to assess the needs and the optimal calendar of some booster vaccinations against hepatitis B. Such studies are quite uncommon. In order to evaluate the immune protection at community scale we performed a seroprevalence study using a sample of 360 volunteer subjects stratified in 9 groups of age. Sterile sera were obtained and preserved as frozen at -20 degrees C, and antibodies against HBsAg were measured using ELISA kits made by Dia Sorin, Italy. Data base and statistical processing of data have been made using Access, Epi Info and Excel software. 60.3% of subjects proved having protective seric levels of Anti-HBs, significantly prevailing in female subjects (68.8%; p < 0.001) and in urban population (62.8%; p <0.001). The general trend of Anti-HBs by age varied insignificantly (correlation coefficient 0.6%); the values were significantly lower in the groups of 10-14 years of age (39.4%; p<0.001) and in 15-19 years of age (40%; p<0.001). The serum levels of Anti-HBs varied between maximum a of 1.970 mUI/ml and a minimum of 1 mUI/ml, the geometric average being of 41 mUI/ml (standard deviation 27.3 ; IC 95% : (38.18-43.82)). The vaccine efficacy for the level considered as protective (10 mUI/ml) has been 81.9% (IC 95% : (76.1-87.7)). The protection against hepatitis B viral infection assessed by measuring the prevalence of Anti-HBs is significantly more frequent in female subjects and in urban population. The trend of serum level of Anti-HBs by age, having irrelevant variations by age, has been induced by vaccination against hepatitis B virus starting 1995. The efficacy of vaccinations in newborns and health care personnel, in the field populations, was as high as 81.9%.


This study aimed to determine the protective efficacy of hepatitis B vaccine against infection and chronic carriage in 720 children aged 10 years who were vaccinated in infancy. All children were tested for hepatitis B 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) using 3rd generation ELISA technique. Only 37.9% of vaccinated children had protective anti-HBs indicating its decay with time. Hepatitis B infection occurred in 6.8% of the vaccinated children and it induced a boosting effect on anti-HBs level. HBsAg was detected in 0.6% only of the vaccinated children. Thus we could conclude that up to 10 years, booster doses are unnecessary possibly due to protective anamnestic response to antigenic challenge. Further follow-up studies for longer duration than 10 years are needed especially during adolescence with the onset of sexual activity to monitor the vaccine efficacy in preventing chronic carriage and the possible necessity for booster doses.

Session 5: Breakthrough infections (vaccine escape mutants)(25)


AIM: To evaluate the impact of mass vaccination against the hepatitis B virus (HBV) in Egypt, and to search for vaccinee asymptomatic breakthrough HBV infection and its genotype. METHODS: Seven hundred serum samples from vaccinated children and adults (aged 2-47 years) were used for quantitative and qualitative detection of HBsAb by ELISA. Three hundred and sixty serum samples representing undetectable or low or high HBsAb were screened for markers of active HBV infection (HBsAg, HBcAb (IgG) and HBeAb by ELISA, plus HBsAg by AxSYM) and HBV-DNA genotyping by nested multiplex PCR and by DNA sequencing. RESULTS: It was found that 65% of children aged 2-4 years, and 20.5% aged 4-13 years, as well as 45% adults were good responders to HBV vaccination mounting protective level HBsAb. Poor responders were 28%, 59.5% and 34%, and non-responders were 7%, 20% and 21% respectively, in the three studied groups. Markers of asymptomatic HBV infections were HBsAg detected by ELISA in 2.5% vs 11.39% by AxSYM. Other markers were HBcAb (IgG) in 1.38%, HBeAb in 0.83%, and HBV-DNA in 7.8%. All had HBV genotype E infection. CONCLUSION: It is concluded that HBV vaccine is efficient in controlling HBV infection among children and adults. The vaccine breakthrough infection was by HBV genotype E. A booster dose of vaccine is recommended, probably four years after initial vaccination.


We report a case of acute hepatitis B virus genotype A vaccine escape mutant infection with loss of HBV vaccine-induced seropositivity in a HIV-1 infected patient. His HBV is unresponsive to tenofovir/emtricitabine treatment demonstrated by persistent viremia despite lacking known resistance mutations and while having an undetectable HIV-1 viral load.

Genotypes B and C are the major hepatitis B virus (HBV) genotypes in Taiwan, and genotype C is associated with more severe liver disease than genotype B. Whether the implementation of the hepatitis B immunization program has affected the secular trend of the HBV genotype distribution remains unknown. We thus investigated the HBV genotypes in hepatitis B surface antigen (HBsAg)-carrier children born before the implementation of the universal infant immunization program and in those born afterward. One hundred seven children who were infected with HBV despite appropriate immunization were enrolled as immunized cases with HBV breakthrough infection. Each case was matched with two unimmunized HBsAg carriers according to the age at enrollment. HBV genotypes were determined with molecular methods. Compared with unimmunized HBsAg carriers, more immunized children had HBsAg-positive mothers (65.9% versus 100%, P < 0.001) and were infected with genotype C (16.4% versus 42.1%, P < 0.001). Among the children born to HBsAg-positive mothers, the mothers' and children's HBV genotypes were highly concordant in both unimmunized (kappa = 0.97, 95% confidence interval (CI) = 0.90-1.00) and immunized children (kappa = 0.97, 95% CI = 0.92-1.00). After adjustments for gender, maternal age, and delivery mode, immunized HBsAg-carrier children born to HBsAg-positive mothers had a higher likelihood of genotype C infection than unimmunized children (odds ratio = 3.03, 95% CI = 1.62-5.65, P = 0.001). However, the increased genotype C to genotype B ratio was not seen in the HBsAg-carrier mother pool in the postimmunization era. CONCLUSION: In the postimmunization era, most HBV breakthrough infections are due to maternal transmission, and immunized children born to genotype C mothers may have a higher rate of breakthrough infection than those born to genotype B mothers.


Combined passive and active immunization for newborns very effectively prevents perinatal hepatitis B virus (HBV) infections. In the Netherlands, babies born to hepatitis B surface antigen (HBsAg)-positive women receive passive immunization with hepatitis B and at least three active HBsAg vaccinations. Serological testing for the presence of HBV markers was offered for all infants born to HBsAg-positive mothers between January 2003 and July 2007, after completion of their vaccination schedule. About 75% of the infants (n = 1743) completed their HB-vaccination schedule and participated in the serologic evaluation. Twelve of them (0.7%) were found to be HBV infected. Furthermore, we identified three older children with high levels of anti-HBc, anti-HBs and anti-HBe, while they were HBsAg and HBV DNA negative. This serologic profile is evidence for a resolved HBV infection. In the group of older children (1.5-5 years of age, n = 728), about half of the HBV-infected children (3 of 7) had already cleared their infection at the time of sampling. For a proper evaluation of the efficacy of a new intervention programme to prevent vertical HBV transmission, it is also important to analyse the HBV markers in serum collected when the children are older than 1.5 years. In a programmatic setting, all children born to HBV-infected mothers should be tested not only for the level of anti-HBs but also for the absence of HBsAg, because 2 of the 12 HBV-infected children (17%) had a high level of anti-HBs.


The universal HBV vaccination programme in Taiwan has effectively led to the reduction of acute and chronic hepatitis B, and of hepatocellular carcinoma among vaccinated children. Seropositivity rates for hepatitis B surface antigen (HBsAg) decreased from 10-17% in those born before the start of the vaccination programme to the current 0.5-1.7%.
Nonetheless, breakthrough infection continues to be observed. The main causes include high maternal viral load, intrauterine infection, emergence of S gene mutants and immunosuppression. Among vaccinated individuals with breakthrough HBV infection, sG145R & sT126A/S mutations (which account for 48% of the mutants detected) have become prominent. However, owing to the marked reduction in the HBsAg carrier rate, the prevalence rate of S gene mutants in the total vaccinated population has not increased. With limited evidence of spread, S gene mutants do not need to be incorporated into the HBV vaccine. Further studies are required to design better strategies to prevent breakthrough HBV infection of both wild-type and S gene mutants.


A high rate of viral turnover, combined with an error-prone polymerase, results in a very high frequency of mutational events during HBV replication. Not surprisingly, particular selection pressures, both endogenous (host immune clearance) and exogenous (vaccines and antivirals), readily select out new 'escape' mutants. The introduction of nucleoside/nucleotide analogue (NA) therapy for chronic hepatitis B has witnessed the emergence of antiviral drug resistance as the major factor limiting drug efficacy. Furthermore, because of the overlap of the viral polymerase and envelope reading frames in the HBV DNA genome, NA resistance-associated mutations selected in the catalytic domains of the polymerase frequently result in important changes to the neutralizing antibody-binding domains of the hepatitis B surface antigen, including the emergence of antiviral drug-associated potential vaccine escape mutants (ADAPVEMs). The public health significance of ADAPVEMs is considerable in terms of the global programme for control of hepatitis B via universal infant immunization. Thus, prevention of resistance requires the adoption of strategies that not only effectively control HBV replication, but also prevent the emergence of ADAPVEMs.

Immune pressure exerted on HBV by anti-HBV antibodies and long-term therapy with drugs that mutagenize the viral P gene can select for mutations in its S gene, leading to vaccine escape and evasion from serological detection. Although transmissibility of these mutants is poor and their evolution towards heightened virulence appears slow, the situation could change as vaccination coverage increases, and treatment of patients with chronic hepatitis B and those coinfected by HIV and HBV becomes widespread. Enhanced surveillance programmes to track changes in the genotype and phenotype of the mutants are needed.


We present a case of a clinical manifest hepatitis B virus infection and a potentially misleading HBV serological profile in an HIV-1 positive patient despite previous HBV vaccination. The patient presented with an acute hepatitis B and there was no indication of chronic HBV infection or the presence of a mutation in the 'a' determinant. Remarkably, simultaneously with high HBV surface antigen and HBV viral load, high anti-HBs antibodies were present. If, due to previous HBV vaccination only anti-HBs was tested in this patient, the result of the high anti-HBs antibodies could be very misleading and offering a false sense of security. Our findings contribute to the ongoing discussion on how to assess HBV specific immunological memory and determining the role of HBV booster vaccinations in immunocompromised individuals.


BACKGROUND: Individuals who reach the antibody threshold level of 10IU/l against the surface protein of the hepatitis B virus (HBV) after completion of a series of hepatitis B vaccination are considered to be long-term protected against a clinically manifest HBV infection. CASE REPORT: Here we describe an acute hepatitis B infection in a patient who received five hepatitis B vaccinations. Although his initial response to vaccination was moderate, he finally reached an excellent hepatitis B surface antibody level (anti-HBs) titres of more than 1000 IU/l in response to a booster vaccination with a recombinant DNA vaccine. Nevertheless, he developed full-blown acute hepatitis due to an HBV infection 14years after this booster vaccination. A DNA analysis of the surface protein encoding region followed by phylogenetic analysis showed that our patient was infected with a normal HBV strain that is circulating among men who have sex with men. To our knowledge, this is the first report of a genuine hepatitis B vaccination failure in someone who acquired a high anti-HBs level in response to a recombinant DNA hepatitis B vaccine. CONCLUSION: Healthcare workers whose response to the initial hepatitis B vaccination is moderate might be vulnerable to hepatitis B virus infection.


BACKGROUND/AIMS: Presence of occult HBV infection in HBV vaccinated children remains largely unknown. The aim of this study was to investigate the prevalence of occult HBV infection among HBV vaccinated children in Taiwan. METHODS: Forty-six HBsAg negative sera from vaccinated children were enrolled randomly. HBV serum markers were detected by ELISA, and the titers of HBV DNA were determined by quantitative real-time PCR. Pre-S, S and pre-core/core genes were amplified by nested PCR and analyzed. RESULTS: Anti-HBs was detected in 23 (50%) children, and the positivity decreased according to age. Five (10.9%) children were classified into occult HBV infection by positivity of nested PCR in at least two regions; they had a low titer (mean titer
Sequence analyses of S gene showed occult isolates were variants; no G145R but C139S vaccine escape mutant was found. Variation and deletion were found in pre-S region; pre-S deletion was more frequent in 3' terminus of pre-S1 which leads to loss of immune epitopes and function sites. CONCLUSIONS: This pilot study indicates that the prevalence of occult HBV infection is 10.9% in HBV vaccinated children. Since this is a small study, a study of a large population is needed to confirm the findings herein.


The hepatitis B virus (HBV) polymerase and envelope genes overlap in such a way that resistance mutations to antiviral agents in the reverse transcriptase gene may affect the antigenicity of the HBV surface antigen. Mutant viruses may escape serological diagnosis using specific anti-HBV surface antigen antibodies, causing occult forms of chronic hepatitis B. Moreover, these HBV strains may evade vaccine protection, representing a public health challenge. Thus, the circulation of HBVs encoding envelope mutations selected by antiviral agents requires close monitoring.


Hepatitis B virus (HBV) infection has a major effect on health care systems, with about one-third of the world's population currently infected with the virus. There is an effective vaccine against HBV, which contains a recombinant "surface antigen" produced in an expression vector. Vaccination has proved to be successful in Hungary: the number of acute HBV cases has decreased in the past 10 years. Although an increasing number of publications report on "vaccine-escape" HBV variants which can infect HBV-vaccinated individuals, such mutant HBV strains have not yet been detected in Hungary. We therefore surveyed two risk groups for vaccine-escape or immunoglobulin-escape HBV mutations in Hungary: 28 actively and/or passively HBV-immunized children of HBV carrier mothers who proved to be HBsAg and/or anti-HBc positive and 40 symptomless HBV carrier pregnant women (presumably carrying genotype B or C). We focused on the coding sequences of the "a" immundominant region of the surface protein. We could not detect the G145R amino acid substitution associated with vaccine escape mutant virus. However, we
could map other mutations potentially affecting the immunodominant "a" region of the HBV surface protein.


BACKGROUND: Hepatitis B virus (HBV) often persists after resolution, but its replication is suppressed by antiviral T cells. Immunosuppressive treatment may lead to viral reactivation and severe hepatitis. Early antiviral therapy prevents reactivation but some occult HBV infections are not easily detectable. RESULTS: Here we describe a patient with a progressive non-Hodgkin lymphoma who had probably not been vaccinated against HBV and, before immunosuppression, showed antibodies (anti-HBs) against the viral surface antigen (HBsAg) as the only possible marker of occult HBV infection. Under immunosuppression he developed viremia (>10(8)copies/mL). The virus exhibited three S gene mutations (L109R, C137W, G145R) which led to false negative HBsAg results and diminished binding of vaccine-induced anti-HBs. CONCLUSIONS: Reliable screening and monitoring of severely immunosuppressed patients for HBV should include, in addition to anti-HBc and HBsAg, anti-HBs and sensitive HBV DNA assays. Furthermore, active vaccination or hepatitis B immune globulin may not protect against such mutants.


BACKGROUND: Given the overlap between envelope and polymerase in the hepatitis B virus (HBV) genome, changes in antigenic sites of the HBV surface antigen may occur as a result of selection of drug-resistance mutations. METHODS: Serum HBV-DNA was isolated from 71 patients with chronic hepatitis B receiving anti-HBV drugs for longer than 12 months, 52 of whom were HIV-positive. The reverse transcriptase/envelope gene from each HBV isolate was amplified using a nested polymerase chain reaction (PCR) covering 720 bp (aa 48 to 288), which includes all known nucleos(t)ide analogue resistance mutations in HBV. RESULTS: All but 13 patients had received lamivudine. Of the rest, 10 HBV-monoinfected subjects had received adefovir and 3 HBV/HIV-coinfected patients had been treated with tenofovir. Only lamivudine-resistance-associated mutations produced changes in the HBV envelope antigenic sites. Lamivudine resistance mutations were more frequent in HBV genotype A than D (P = 0.014). Contrary to monoinfected individuals, HBV genotype A was the predominant genotype among HBV/HIV-coinfected patients. The triple-HBV mutant rtV173L + rtL180M + rtM204V, which has been shown to produce a diminished hepatitis B surface (HBs) antigen-antibody binding, was found in 3 individuals, all coinfected with HIV and HBV. CONCLUSION: Circulation of HBV encoding envelope mutations with diminished HBsAg-antigen-antibody binding as result of selection of drug-resistance mutations may occur, particularly in patients infected with HBV genotype A, the most prevalent genotype among HBV/HIV-coinfected patients. Such mutations might represent a public health concern because of the potential risk of transmission of HBV drug- and vaccine-resistant strains.

Chang, M. H. "Hepatitis B virus mutation in children." Indian J Pediatr 2006 73(9): 803-807. Due to the lack of proof reading activity of hepatitis B virus (HBV) polymerase, mutation/variation of the viral sequence is frequently found during long term follow-ups. In the majority of children with chronic HBV infection, wild type HBV is the dominant viral strain during the natural course of chronic HBV infection. During long-term follow-up, HBV precore mutants developed spontaneously in approximately 10 to 24% of children before HBeAg seroconversion and in around 50% of children after HBeAg seroconversion mutants. Occasionally, children may be infected primarily by mutant strains of HBV. Approximately 36% of children with fulminant hepatitis and 30% of children with acute
hepatitis B were infected by precore mutants of HBV transmitted by their mothers or blood donors. In addition, after universal HBV vaccination, HBV surface gene variants emerge or are selected under the immune pressure generated by the host or by administration of hepatitis B immune globulin and hepatitis B vaccination. In HBV DNA positive children from four sequential surveys in Taiwan, the prevalence of hepatitis B surface gene determinant mutants increased from 7.8% before the vaccination program, to 19.6%, 28.1% and 23.1% at 5, 10 and 15 years after the program. Nucleoside analogue may also induce mutant strains, which reduces the antiviral effects. The most common example is the YMDD mutation of the HBV polymerase gene after antiviral therapy with lamivudine. It developed in 19% of the treated children. In conclusion, children may be infected primarily by mutant strains of HBV either naturally during acute HBV infection. Those infected with wild type HBV initially may develop mutant strains gradually during the course of chronic infection under the host immune pressure. Vaccine escape mutants may develop after immunoprophylaxis. In addition, antiviral therapy with nucleoside analogues may also induce drug resistant mutant strains. Understanding the viral mutation status will help to design accurate strategies of immunoprophylaxis and antiviral therapy against HBV infection.


A nation-wide hepatitis B virus (HBV) immunization program of all newborn babies was launched in Mongolia in 1991. However, the continuation of clinical icteric viral hepatitis infections in children led to the investigation to determine whether HBV breakthrough infections were occurring and if any were due to hepatitis B surface antigen (HBsAg) mutants. Hepatitis A virus (HAV) infections accounted for most of these cases with 3% of the jaundiced children shown to have acute hepatitis B. Hepatitis B vaccine protection was 93% against HBV infection and 97% against HBV carriage. A G145A "escape mutant" was found in one HBV carrier child only. Anti-HBs levels, however, were low with 85% having titers less than 100 IU/L, 46% of whom had levels less than 10 IU/L. The results from this study demonstrate that the HBV immunization program in Mongolia provides an effective level of protection. However, continued surveillance of breakthrough infections and close monitoring of "vaccine escape" mutants is required.


Genotype E hepatitis B virus (HBV) was detected in two Argentine sisters exhibiting an African mitochondrial lineage. One of them (who had been vaccinated against HBV) exhibited anti-HBs cocirculating antibodies without HBsAg escape mutants, while her unvaccinated sister showed a D144A HBsAg escape mutant without anti-HBs antibodies. Both sisters carried an unusual L209V substitution within HBsAg.


BACKGROUND: Little is known about the prevalence and pattern of hepatitis B virus (HBV) mutations in HIV/HBV co-infected individuals on long-term lamivudine (3TC) therapy. METHODS: HBV polymerase/envelope/basal core promoter/pre-core sequences from 81 HIV-HBV co-infected persons who received at least 6 months 3TC were compared to HBV reference sequences. Host and viral characteristics associated with HBV mutations were determined. RESULTS: HBV viraemia was detected in 53 persons (65%) and was
associated with lower CD4 cell count nadir and higher HIV RNA at the time of testing but not with 3TC duration. Known 3TC-resistant mutations occurred in 50% and 94% of viremic patients with < 2 years and > 4 years 3TC, respectively. The CD4 cell count at testing was significantly higher in those with 3TC-resistant mutations. The triple polymerase mutant (rtL173V, rtL180M, rtM204V), which behaves as a vaccine escape mutant in vitro, occurred in 17% of viremic patients. Polymerase mutations that may confer resistance to other anti-HBV agents were also detected. CONCLUSIONS: In HIV-HBV co-infected patients, greater immunocompromise is associated with continued HBV viraemia while on 3TC, and development of 3TC-resistant mutations are inevitable with prolonged 3TC use. These mutant viruses may limit future therapeutic options due to cross-resistance or may produce HBV vaccine escape mutants. Thus, timing and selection of antiretroviral therapy is critical in this population.


Hepatitis B virus (HBV) mutants have usually been studied in patients in Asia because of the wider use of HBV immunization there and the resultant emergence of viral mutants. Nevertheless, HBV surface antigen (S) gene mutants also are found in Europe and North America. In Europe and North America, HBV with mutations in the portion of the S gene coding the "a" determinant of the hepatitis B surface antigen (HBsAg) have been documented in small numbers of infants born to HBV-infected mothers following postnatal HBV vaccine and hepatitis B immune globulin (HBIG) prophylaxis and in many liver transplant recipients who develop HBV re-infection despite HBIG prophylaxis. In some cases, these mutations have included a glycine to arginine substitution at position 145 (G145R), which results in a conformational change and different reactivity to monoclonal antibody reagents than that of the wild-type virus. Mutations in the a determinant (but not G145R) also have been reported in European patients with chronic HBV infection who have not received HBV vaccine or HBIG. However, it appears that such mutations are only responsible for a small proportion of "occult" or "silent" HBV infections, which are characterized by the presence of HBV DNA in serum in the absence of detectable HBsAg. However, some of these mutant forms of HBV in cases of occult HBV may theoretically escape detection and could present a risk to blood safety.


OBJECTIVE: To investigate whether the presence of HBV mutant in vaccinees simply reflects the prevalence of HBV mutant in a specific geographic area or is indeed due to the immune pressure induced by vaccination. METHODS: HBV S genes were amplified by using polymerase chain reaction (PCR) and DNA sequence analysis of the "a" determinant was performed on sera from 30 childhood patients with immunoprophylaxis and 30 patients without vaccinations. RESULTS: Mutations of the "a" determinant were detected in 8 of the 60 patients. They were all of the adw subtype. The prevalence of amino acid substitutions as detected by direct sequencing was higher in those fully-vaccinated than of those not vaccinated. In all 8 vaccinated and also with detectable mutants, the mean age was older than the other vaccinated children. CONCLUSION: The prevalence of mutants is related to HBV subtypes and genotypes. Universal vaccination has accelerated an accumulation of HBsAg "a" determinant mutants with amino acid changes critical for immune escape in vaccinated children who became carriers. This suggests that new vaccination strategies should be considered.


BACKGROUND: Mutants of the hepatitis B virus (HBV) following vaccination (escape
mutants) have been isolated over the course of the last decade. They consist most commonly of an aminoacid change from glycine to arginine at position 145 of the highly antigenic a determinant of the surface antigen (HBsAg). OBJECTIVE: Description of an escape mutant of HBV identified in the course of the post-exposure follow-up of a percutaneous exposure. Methods: The viral DNA was extracted from serum samples of a dialysed patient vaccinated against hepatitis B, who developed an acute infection. A direct sequencing was performed on the amplified DNA followed by a sequence analysis. RESULTS AND CONCLUSIONS: A threonine to lysine substitution at position 118 of HBsAg (Thr118Lys) was observed in the analysed viral aminoacid sequence. Such mutation could have significantly changed the antigenic profile of the HBsAg compared to that of the wild type.


Hepatitis B virus (HBV) reverse transcriptase is an error-prone enzyme, and this results in a large number of nucleotide substitutions during replication. As a result, HBV has a "quasispecies" distribution in infected individuals, meaning that HBV circulates as a complex mixture of genetically distinct but closely related variants that are in equilibrium at a given time point of infection in a given replicative environment. The quasispecies distribution of HBV implies that any newly generated mutation conferring a selective advantage to the virus in a given replicative environment will allow the corresponding viral population to overtake the other variants. Such selection processes occur at any step of infection to allow the emergence of variant viruses, such as precore and core promoter mutants during the natural course of infection, HBs antigen mutants under the pressure of active or passive anti-HBs immunization, or HBV mutants that are resistant to the antiviral action of specific HBV inhibitors.

Session 6: hepatitis B Booster vaccination (29)


OBJECTIVE: To study the efficiency of booster immunization with different recombinant hepatitis B vaccines. METHODS: 2789 children aged over 10 years who had completed the basic immunization of hepatitis B vaccine under 1 year old were selected. All the sampled children were classified into four groups (A, B, C and D) and immunized with different hepatitis B vaccines produced by different companies respectively. Before booster immunization, their blood plasma specimens were detected for hepatitis B virus (HBV) surface antigen (HBsAg), antibodies to HBV surface antigen (anti-HBs) and antibodies to HBV core antigen (anti-HBc) by chemiluminescence. In each group, the anti-HBs positive children were immunized with one dosage and anti-HBs negative children were immunized three dosages of the same vaccine. Their blood specimens were collected again after 1 month, and detected for anti-HBs. RESULTS: The anti-HBs positive rates of A, B, C and D group were 36.43%, 37.59%, 42.91% and 46.46% respectively before immunization while 89.20%, 91.52%, 90.96% and 85.45% respectively after immunization with one dosage, 99.12%, 99.47%, 98.87% and 98.85% respectively after immunization with three dosages. The differences of anti-HBs positive rates in the four respective groups showed statistical significances between any two rates of pre-immunization, post-immunization with one dosage and post-immunization with three dosages (all P < 0.05). The anti-HBs positive
The conversion rates of four groups were 83.01%, 86.41%, 84.16% and 72.82% respectively after immunization with one dosage. The anti-HBs positive conversion rate of four groups were 98.62%, 99.16%, 98.03% and 97.84% respectively after immunization with three dosages and the difference of positive conversion rates in each group showed statistical significances between booster immunization with one dosage and booster immunization with three dosages. The average GMTs in anti-HBs positive children in the four groups were 2853.21, 6254.23, 3581.40 and 3021.32 mIU/ml respectively after immunization with one dosage. The average GMTs of anti-HBs negative children in the four groups were 273.08, 648.52, 387.87 and 245.36 mIU/ml respectively after immunization with one dosage, and were 632.30, 2341.14, 563.97 and 394.08 mIU/ml respectively after immunization with three dosages. CONCLUSION: Our data showed that it would be suitable to anyone to use the four vaccines for anti-HBs positive children aged over 10 years with one dosage and for anti-HBs negative children aged over 10 years with three dosage booster immunization.


After several decades of vaccination against hepatitis B virus in newborns, infants, adolescents, and adults, the question remains whether a booster dose is ever needed. Long-term protection is most commonly measured through 4 methods: the anamnestic response after administration of a booster dose, infection rate in vaccinated populations, in vitro B and T cell activity testing, and seroepidemiological studies. Long-term protection is present despite a decrease in anti-hepatitis B surface antibodies over time. The exact mechanism of long-term protection, however, is not yet fully understood. There is no need for boosters in immunologically potent persons as long as a full course was adequately administered that respected the recommended timelines, as evidenced by studies conducted up to 20 years after the original immunization course. However, a booster dose should be planned for immunocompromised patients, based on serological monitoring.


BACKGROUND: The national hepatitis B virus (HBV) vaccination program was launched in Taiwan in 1984. After November 1992, a recombinant HBV vaccine replaced the plasma-derived HBV vaccine. METHODS: A total of 1,812 nursing and medical technology freshman students was tested to evaluate their waning immunity toward hepatitis B. In the 2007 (2008) academic year, 438 (382) students testing nonprotective antibodies received 3 (1) booster doses of HBV vaccine according to suggestions from Taiwan's Center for Disease Control (CDC). RESULTS: The seroprevalences of hepatitis B surface antigen (+) were 0.8% and 0.7% in the plasma-derived and recombinant group, respectively; for antibody to hepatitis B surface antigen (anti-HBs) (+), they were 43.2% and 33.3% (P < .001), respectively. In the 2007 freshman group, 99.1% of the students previously vaccinated with plasma-derived HBV vaccine exhibited anti-HBs seroconversion. In the 2008 freshman group, the booster dose induced anti-HBs seroconversions of 92.1% and 95.9% in the students who had received the plasma-derived and recombinant HBV vaccine, respectively (P = .370). CONCLUSION: Most students exhibited signs of immune memory after receiving the booster, regardless of having received plasma-derived or recombinant HBV. Only a small number of vaccinees lost their immune memory after 16 years, suggesting that some students might benefit from boosting before proceeding to clinical practice.


The twin aims of this study were to investigate the changes in anti-HBs IgG levels after booster vaccinations and to compare the effects of different vaccine doses in children aged 11-15 years who were both negative for HBsAg and had an Anti-HBs < 10.0 mIU/mL after primary vaccination. Children who were born between 1993 and 1998 and who had completed their Hepatitis B vaccination program in infancy were randomly recruited to the study. The participants were divided into three groups according to their anti-HBs IgG levels: group I had a level < 0.1 mIU/mL; group II 0.1 - < 1.0 mIU/mL, and group III 1.0 - < 10.0 mIU/mL. The booster vaccination program comprised three (20mug) doses of HepB (CHO) vaccine administered at zero, one and six months after they are join this program: anti-HBs levels were measured one month after the first and third vaccinations. Among 448 HBsAg-negative infants, anti-HBs seroconversion rates (defined as an anti-HBs >= 10 mIU/mL) after the first and third vaccinations were 85.5% and 98.6% respectively - these observed differences were statistically significant (chi2 [1dof] = 50.11, p< 0.05). Seroconversion rates and GMTs after the first and third doses were significantly lower for group I children than the other two groups (p< 0.05). Compared, the OR of being negative (anti-HBs< 10mIU/ml) in group I after the first and the third dose were 7.66 (95%CI: 4.35-13.47, P< 0.05) and 20.48 (95% CI: 2.36-177.67, P< 0.05). So the anti-HBs titer levels decay to 10mIU/ml in 11-15 years of age children completed HepB Basic immunization, which need for booster immunization. The effect is better for those children with a relatively higher antibody titer before booster, and the effect of three doses booster is best.


Some hepatitis B vaccine booster studies have suggested waning of vaccine-induced immunity in adolescents vaccinated starting at birth. Those studies, however, used a pediatric formulation of the hepatitis B vaccine as a booster to detect anamnestic response. We compared adolescents boosted with an adult dose of hepatitis B vaccine with those boosted with a pediatric dose. Among adolescents who had lost protective antibody levels against hepatitis B, a higher proportion had an anamnestic response when boosted with the adult dose (60.0% vs. 43.8%). Thus, higher antigen concentrations may be required to elicit an adequate immune memory response. Despite improved anamnestic response, our study still raises concerns about whether children immunized in early infancy will remain protected from hepatitis B as they age into adulthood.


Health care workers (HCW) are at increased risk for acquisition of hepatitis B virus (HBV) infection from occupational exposure. This can be prevented by active immunization. We performed a retrospective chart review of HCW who were persistent low (anti-HBs antibody values <100 U/L) or non responders (<10 U/L) after 6 active immunizations and demonstrate successful immunization (anti-HBs >/=100 U/L) after a total of 8-14 vaccine doses in 13 such HCW by use of various vaccination schedules. This "proof of principle" should encourage occupational health care providers to convince HCW to accept further vaccine doses until the targeted threshold considered to be the correlate of immunity has been reached. Prospective studies should be performed to determine the optimal schedule of further booster doses for HCW who are persistent non or low responders.


The long-term protection of hepatitis B (HB) vaccination has been debated for years. The purpose here was to evaluate the kinetic changes of antibody to HB surface antigen (anti-HBs) and define immune memory of the HB vaccine among college students who had previously received full neonatal immunization against HB. In all, 127 college students aged 18-23 years born after July 1984 who had completed HB vaccination and were seronegative for all three HB viral markers, including HB surface antigen (HBsAg), antibody to HB core protein (anti-HBc), and anti-HBs, were recruited. They received three doses of HB vaccine at enrollment, 1 month and 6 months after enrollment. Their anti-HBs titers were assayed at enrollment, 7-10 days, 1 month, 6 months, and 7 months following the first dose of HB vaccine. The anti-HBs seroprotective rates for subjects 7-10 days, 1 month, 6 months, and 7 months postvaccination were 20.5%, 75.6%, 94.5%, and 99.2%, respectively. Those who were seroprotective at 7 to 10 days after one dose of HB vaccine booster developed significantly higher levels of anti-HBs at 1 and 6 months than those not developing seroprotective anti-HBs response at an earlier timepoint. CONCLUSION: At least one-quarter of HB vaccinees have lost their immune memory to the HB vaccine when entering college. Immune memory to HB vaccine was identified by early seroconversion, which was present in only 20% of vaccinees in the present study. To ensure higher than 90% anti-HBs seroconversion rates, at least 2 doses of HB booster vaccines are recommended for at-risk youths who received complete HB vaccinations in neonatal or infant periods but are seronegative for HBsAg, anti-HBs, and anti-HBc in adolescence.


BACKGROUND: Antibodies against hepatitis B surface antigen (HBs) wane over time after vaccination for hepatitis B (HB); hence, the duration of protection provided by the vaccine is still unknown but may be evaluated indirectly by measuring the anamnestic immune response to booster doses of vaccine. OBJECTIVES: To assess the benefits and harms of booster dose hepatitis B vaccination for preventing HB infection. SEARCH STRATEGY: We searched The Cochrane Hepato-biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 4, 2010) in The Cochrane Library, MEDLINE, EMBASE, Science Citation Index Expanded, conference databases, and reference lists of articles to May 2010. We also contacted authors of articles and manufacturers. SELECTION CRITERIA: Randomised clinical trials addressing anamnestic immune response to booster of HB vaccine five years or more after primary vaccination in apparently healthy participants, vaccinated in a 3-dose or 4-dose schedules of HB vaccine without receiving additional dose or immunoglobulin. DATA COLLECTION AND ANALYSIS: Two authors made the decisions if the identified publications on studies met the inclusion criteria or not. Primary outcome measures included the proportion with anamnestic immune response in non-protected participants and signs of hepatitis B virus infection. Secondary outcomes were the proportion with local and systemic adverse event events developed following booster dose injection. Weighted proportion were planned to be reported with 95% confidence intervals. MAIN RESULTS: There were no eligible randomised clinical trials fulfilling the inclusion criteria of this review. AUTHORS' CONCLUSIONS: We were unable to identify randomised clinical trials on the topic. We need randomised clinical trials to formulate future booster policies for preventing hepatitis B infection.


The duration of protection provided by hepatitis B vaccine is still unknown but can be estimated through long-term follow-up studies. Electronic databases and conference
databases to December 2008 were searched. Reference lists of articles were screened and the studies authors and manufacturers were contacted for additional unpublished references. Randomized clinical trials and prospective cohort studies addressing the long-term protective effect of hepatitis B vaccine were included in this meta-analysis. We assessed 42 separate cohorts involving overall 11,090 subjects; 34 cohorts involving 9356 subjects were included in the final meta-analysis. Results indicate that the overall cumulative incidence of HBV breakthrough infection 5-20 years post-primary vaccination was 0.007 [95% CI: 0.005 to 0.010] with a variation among studies from 0 to 0.094. Available data do not allow us to exclude an increased risk for infection with time since vaccination. We conclude that the protection provided by three or four doses of monovalent HB vaccine persists for at least two decades in the great majority of immunocompetent individuals. Additional studies are needed for assessing vaccine efficacy for longer periods of time and the need of booster doses in different subgroups of population.


Hepatitis B virus infection is a global health problem. Worldwide, about 360 million people are chronically infected with the virus. They continue to spread the virus to others and are themselves at risk of chronic liver diseases and hepatocellular carcinoma. The infection can now be treated by antivirals or interferons and the transmission route can be interrupted. Nevertheless, the most effective means is to immunize all susceptible individuals, especially young children, with safe and efficacious vaccines. The combined efforts of vaccination, effective treatment and interruption of transmission make elimination of the infection plausible and may eventually lead to eradication of the virus. Because hepatitis B vaccination has a key role in the control of hepatitis B, properties of this vaccine, its effectiveness in pre-exposure and post-exposure settings, duration of protection after vaccination and the need of booster doses are discussed. Mass hepatitis B vaccination in children decreases the carriage of the virus, and the diseases associated with acute and chronic infection, including hepatocellular carcinoma. Challenges that need to be solved to expand mass vaccination, and the strategies towards elimination and eventual eradication of hepatitis B in the world are also discussed.


Few data are available concerning the persistence of anti-HBs and the effect of booster doses given several years post-vaccination against hepatitis B during preadolescence. The objective of this open-labelled clinical trial was to evaluate the persistence of antibodies after vaccination with three paediatric doses of Engerix-B at the age of 8-10 years and the effect of a booster dose given 5 (Group Y5) or 10 (Group Y10) years later. Anti-HBs were measured before and one month post-primary vaccination, then 5 and 10 years later, before the booster dose, as well as one month and 1 year post-booster. The anamnestic response was defined as a >or=fourfold increase of anti-HBs post-booster (>or=10 IU/L) when compared to pre-booster. Ten years post-primary vaccination, 559 of the 652 initially randomized subjects (86%) were eligible for analysis. Group Y5, 5 years post-booster results: 99% of subjects had detectable levels of antibodies and 96% a titer >or=10 IU/L. The anti-HBs GMTs decreased from 114,489 IU/L one month post-booster to 3354 IU/L 5 years later. Group Y10 results: 10 years post-primary vaccination 96% of subjects had a detectable level of anti-HBs and 85% were above the threshold of 10 IU/L. The GMTs one month post-booster were 31,030 IU/L. The challenge with a booster demonstrated an anamnestic response in 99% of subjects in group Y5 and 100% of subjects in group Y10. All subjects were anti-HBc negative. The booster doses were well tolerated. The excellent anamnestic response observed after the booster dose demonstrates the persistence of immunity in virtually all young adults vaccinated at the age of 8-10 with three paediatric
doses of Engerix-B.


BACKGROUND: The duration of protection in children and adults (including health care workers) resulting from the hepatitis B vaccine primary series is unknown. METHODS: To determine the protection afforded by hepatitis B vaccine, Alaska Native persons who had received plasma-derived hepatitis B vaccine when they were >6 months of age were tested for antibody to hepatitis B surface antigen (anti-HBs) 22 years later. Those with levels <10 mIU/mL received 1 dose of recombinant hepatitis B vaccine and were evaluated on the basis of anti-HBs measurements at 10-14 days, 30-60 days, and 1 year. RESULTS: Of 493 participants, 60% (298) had an anti-HBs level ≥10 mIU/mL. A booster dose was administered to 164 persons, and 77% responded with an anti-HBs level ≥10 mIU/mL at 10-14 days, reaching 81% by 60 days. Response to a booster dose was positively correlated with younger age, peak anti-HBs response after primary vaccination, and the presence of detectable anti-HBs before boosting. Considering persons with an anti-HBs level ≥10 mIU/mL at 22 years and those who responded to the booster dose, protection was demonstrated in 87% of the participants. No new acute or chronic hepatitis B virus infections were identified. CONCLUSIONS: The protection afforded by primary immunization with plasma-derived hepatitis B vaccine during childhood and adulthood lasts at least 22 years. Booster doses are not needed.


Almost all current vaccines work by the induction of antibodies in serum or on the mucosa to block adherence of pathogens to epithelial cells or interfere with microbial invasion of the bloodstream. However, antibody levels usually decline after vaccination to undetectable amounts if further vaccination does not occur. Persistence of vaccine-induced antibodies usually goes well beyond the time when they should have decayed to undetectable levels because of ongoing "natural" boosting or other immunologic mechanisms. The production of memory B and T cells is of clear importance, but the likelihood that a memory response will be fast enough in the absence of a protective circulating antibody level likely depends on the pace of pathogenesis of a specific organism. This concept is discussed with regard to Haemophilus influenzae type b, Streptococcus pneumoniae, and Neisseria meningitidis; hepatitis A and B; diphtheria, tetanus, and pertussis; polio, measles, mumps, rubella, and varicella; rotavirus; and human papilloma virus. With infectious diseases for which the pace of pathogenesis is less rapid, some individuals will contract infection before the memory response is fully activated and implemented. With infectious diseases for which the pace of pathogenesis is slow, immune memory should be sufficient to prevent disease.


To explore contemporarily genetic and non-genetic determinants of long-term immunological memory to hepatitis B (HB) vaccination, we conducted a case-control study nested in an adolescent cohort of booster recipients who had received primary infantile HB vaccination but with residual anti-HBs titers <10 mIU/mL at 15-18 years of age. High-resolution phenotypes of human leukocyte antigen (HLA)-A, -B, and -DRB1 loci were determined by sequence-specific oligonucleotide probe hybridization. After controlling for pre-booster anti-HBs levels, the absences of HLA-A*02 and -DRB1*08, simply expressed as A*02(-) and -DRB1*08(-), and the presence of B*15 were significantly associated with elevated risks of non-response (post-booster anti-HBs titers<10 mIU/mL) to booster vaccination. The adjusted odds ratios (ORs) were 3.85 (CI, 1.82-8.33), 4.55 (CI, 1.23-
57

16.67), 3.59 (CI, 1.40-9.17), respectively. There was multiplicative synergism between A*02 and B*15 on the risk of non-response to booster vaccination. The multivariate-adjusted ORs for A*02(-)/B*15, A*02(-)/B*15(-), A*02/B*15, and A*02/B*15(-) haplotypes were 20.39 (p=0.0003), 3.29 (p=0.007), 1.32 (p>0.05), and 1.0, respectively. Recent cigarette smoking and/or betel-quid chewing was associated with a 12-fold risk of non-response to booster vaccination. Further comparisons between responders and adolescents who had undetectable post-booster anti-HBs titers (<0.1 mIU/mL) demonstrated similar results. Our results indicated that response to booster HB vaccination as well as long-term immunological responses to HB vaccination are closely related with host genetic factors, and probably modified by recent substance use.


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.


OBJECTIVES: The influence of booster vaccination on hepatitis B surface antigen (HBsAg)-specific B lymphocytes in humans has not been well characterized. Considering the low frequency of circulating B cells specific for HBsAg in vaccine high responder subjects, determination of this frequency at different time intervals after booster dose injection may provide invaluable information for evaluation of immune response to rHBsAg and identification of the most appropriate timing for isolation of specific B cells and generation of human monoclonal antibodies. METHODS: Peripheral blood mononuclear cells (PBMCs) were isolated from 7 healthy high responder adults at 1, 2, 4, 8 and 16 weeks following administration of booster vaccination with an rHBsAg. The cells were transformed with Epstein-Barr virus and cultured at different cell densities over a feeder of human fetal foreskin fibroblasts. Following transformation, total IgG and HBsAg-specific antibody were screened in culture supernatant using ELISA, and primary frequency of specific B cells was calculated by limiting dilution assay based on Poisson analysis. Actual frequency was determined taking into consideration the percent of B cells in each PBMC population and efficiency of EBV transformation. RESULTS: The mean frequencies of specific B cells after booster vaccination were found to be 1/13,462, 1/3,318, 1/5,224, 1/8,861 and 1/10,714 for the specified time intervals, respectively. Significant differences were observed between the frequencies of samples collected at all time intervals with the exception of week 1 versus weeks 8 and 16, week 2 versus week 4, and week 8
versus week 16. CONCLUSIONS: Our results may provide an indirect measure for immunological memory and may help optimize immunization strategies for novel vaccines and generate human monoclonal antibodies.


BACKGROUND AND AIM: The risk of acquiring hepatitis B virus (HBV) infection through exposure to blood or its products is highest amongst health care workers (HCWs). Despite potential risks, a proportion of HCWs never get vaccinated. India is second to China in the numbers of people with chronic HBV. This study aimed to investigate the vaccination practices and the prevalence of HBV infection in HCWs in India. METHODS: A total of 2162 HCWs were screened for the presence of serological markers of HBV and hepatitis C virus (HCV). Occult HBV infection was tested by detection of HBV-DNA for surface and core regions by nested polymerase chain reaction in HBsAg-negative and IgG anti-hepatitis core antigen-positive subjects. RESULTS: Only 1198 (55.4%) of the 2162 HCWs screened had been vaccinated; and 964 (44.6%) were not vaccination-status conscious; of these HCWs, 600 (27.7%) had never been vaccinated and 364 (16.4%) were unaware of their vaccination status. Protective (> 10 IU/mL) anti-hepatitis B surface (anti-HBs) antigen titers were seen in only 61.7%. The anti-HBs titers were found to be lower with the passage of time; the median anti-HBs titers in subjects who were vaccinated > 10 years ago were significantly lower than those who had been vaccinated < 5 years ago (P < 0.001). One percent of HCWs were HBsAg-positive, and 24.7% of 700 HCWs screened had past exposure (IgG-anti-HBc-positive). Occult HBV was detected in 5% of 120 positive subjects with past exposure; all had anti-HBs titers > 10 IU/mL. CONCLUSIONS: Even today, 28% HCWs in India are unvaccinated and 17% are unaware of their vaccination status. This data suggests that use of hepatitis B immune globulin be mandatory in needle-pricked HCWs in India, and that implementation of awareness strategies is urgent. Since the anti-HBs titers decline in a fair proportion, there is justification for giving a booster dose of vaccine 10 years after primary vaccination to HCWs in India.


BACKGROUND: The duration of protection provided by hepatitis B vaccination is unknown, but the presence of immune memory can be evaluated indirectly by measuring the immune response to a booster dose of vaccine. METHODS: Participants included 74 adolescents (aged 11.7-14.9 years) who had received a plasma-derived 3-dose primary vaccine series and 138 adolescents (aged 10.0-14.7 years) and 166 children (aged 5.0-7.0 years) who received a recombinant 3-dose primary vaccine series. All were born to hepatitis B surface antigen-negative mothers and had received the first dose of hepatitis B vaccine within 7 days of birth. The proportion of participants with serologic evidence of protective immunity (antibody to hepatitis B surface antigen > or = 10 mIU/mL) at baseline (prebooster), the proportion who developed an anamnestic response (increase to > or = 10 mIU/mL at or at more than fourfold increase in antibody to hepatitis B surface antigen to > 10 mIU/mL), and the geometric mean concentration by 1, 2, and 4 weeks after a 5-microg recombinant vaccine booster dose were determined. RESULTS: No participant had evidence of chronic hepatitis B virus infection. Overall, 99% of the group of children who received recombinant hepatitis B vaccine, 83% of the group of adolescents who received recombinant hepatitis B vaccine, and 69% of the group of adolescents who received the plasma-derived vaccine had an anamnestic response to a booster dose; among responders, the geometric mean concentration at 2 weeks postbooster was 3360 and 128 mIU/mL among adolescents who received recombinant hepatitis B vaccine and 369 mIU/mL among adolescents who received recombinant hepatitis B vaccine and
5091 and 696 mIU/mL for children who received recombinant hepatitis B vaccine. The anamnestic response rate at 2 weeks postbooster among participants with antibodies to hepatitis B surface antigen < 10 mIU/mL at baseline was inversely associated with age; 97% of 5-year-olds responded compared with 60% of 14-year-olds. CONCLUSIONS: Although most participants responded to a booster dose of hepatitis B vaccine, the significance of the increased proportion of nonresponses among older adolescents might indicate waning immune memory.


BACKGROUND: Chronic infection with hepatitis B virus (HBV) arising in childhood is associated with hepatocellular carcinoma in adult life. Between 1986 and 1990, approximately 120,000 Gambian newborns were enrolled in a randomised controlled trial to assess the effectiveness of infant HBV vaccination on the prevention of hepatocellular carcinoma in adulthood. These children are now in adolescence and approaching adulthood, when the onset of sexual activity may challenge their hepatitis B immunity. Thus a booster dose in adolescence could be important to maintain long-term protection. METHODS: Fifteen years after the start of the HBV infant vaccination study, 492 vaccinated and 424 unvaccinated children were identified to determine vaccine efficacy against infection and carriage in adolescence. At the same time, 297 of the 492 infant-vaccinated subjects were randomly offered a booster dose of HBV vaccine. Anti-HBs was measured before the booster, and two weeks and 1 year afterwards (ISRCTN71271385). RESULTS: Vaccine efficacy 15 years after vaccination was 67.0% against infection as manifest by anti-HBc positivity (95% CI 58.2-74.6%), and 96.6% against HBsAg carriage (95% CI 91.5-100%). 31.2% of participants had detectable anti-HBs with a GMC of 32 IU/l. For 168 boosted participants GMC anti-HBs responses were 38 IU/l prior to vaccination, 524 IU/l two weeks after boosting, and 101 IU/l after 1 year. CONCLUSIONS: HBV vaccination in infants confers very good protection against carriage up to 15 years of age, although a large proportion of vaccinated subjects did not have detectable anti-HBs at this age. The response to boosting persisted for at least a year. TRIAL REGISTRATION: Controlled-Trials.com ISRCTN71271385.


BACKGROUND/AIMS: In this revaccination study, we explored the determinants of response to booster hepatitis B (HB) vaccination in anti-HBs-seronegative adolescents who had received primary HB vaccination 15-18 years before. RESULTS: After controlling for prebooster anti-HBs levels, cigarette smoking, betel-quid chewing, alcohol drinking, and indigenous ethnicity were significantly associated with elevated risks of non-response to booster HB vaccination. The adjusted odds ratios (aORs) were 3.21 (CI: 1.33-7.84), 8.78 (CI: 2.03-37.94), 2.64 (CI: 1.15-6.02), and 2.46 (CI: 1.28-4.72), respectively. Among adolescents with undetectable prebooster anti-HBs titers, only indigenous ethnicity significantly associated with elevated risk, with an adjusted OR of 2.57 (CI: 1.20-5.54), of non-response to booster HB vaccination. On the contrary, the influences of cigarette smoking, betel-quid chewing, and alcohol drinking were restricted to adolescents with prebooster anti-HBs titers of 0.1-9.9mIU/mL. The corresponding multivariate-adjusted ORs were 5.70, 17.41, and 3.72, respectively. Adolescents who smoked cigarettes and chewed betel-quid were at highest risk of non-response (aOR, 25.3; CI: 2.97-215.7).

CONCLUSIONS: A booster dose of HB vaccine may be insufficient to induce immunological response in healthy adolescents who had undetectable prebooster anti-HBs titers or who were of Malay-Polynesian ethnicity. Responses to booster vaccination are probably modified by recent cigarette smoking and/or betel-quid chewing.

We conducted a revaccination study to investigate the short-term response to booster hepatitis B (HB) vaccination in seronegative adolescents who had received primary infantile HB vaccination. A booster dose of recombinant HB vaccine was administered to 395 adolescents 15-18 years of age whose serum titers of antibody against hepatitis B surface antigen (HBsAg) (anti-HBs) were <10 mIU/mL. Seventy-seven percent of the booster recipients converted to anti-HBs seropositivity (postbooster titers> or =10 mIU/mL). As compared with adolescents who had undetectable prebooster anti-HBs titers (<0.1 mIU/mL), the seropositive rates and geometric mean titers (GMTs) of 2-month and 1-year postbooster were significantly higher for those of prebooster titers of 0.1-0.9 and 1.0-9.9 mIU/mL (all p<0.0001). Postbooster titers declined significantly more rapidly for those with undetectable prebooster anti-HBs titers than for those with prebooster titers of 0.1-0.9 and 1.0-9.9 mIU/mL. Our observations indicate that a booster dose of HB vaccine maybe unable to induce sufficient immunological response in adolescents who had undetectable residual anti-HBs titers.


BACKGROUND: Few data are available concerning the long term immunogenicity of the pediatric doses of hepatitis B vaccines given to preteenagers. The long term effect of the booster dose in teenagers is unknown. We evaluated the immunogenicity of 2 pediatric hepatitis vaccines after primary vaccination and after a booster dose. METHODS: A prospective 15-year follow-up study of the immunogenicity of 2 hepatitis B vaccines was initiated in 1995 in Quebec City, Canada. One year apart, 1129 children 8-10 years old received Engerix-B 10 microg (EB), and 1126 received Recombivax-HB 2.5 microg (RB) vaccine after a 0-, 1-, 6-month schedule. After 5 years, one-third of the 2 cohorts were randomly selected. A booster dose of EB 10 microg or RB 5 microg was administered according to the vaccine used in the primary immunization. Antibodies were measured before, 1 month after and 1 year after the booster injection. RESULTS: Before the booster dose, anti-HB surface antibody (HBs) was detected in 94.7% of the EB subjects and in 95.2% of the RB subjects (P = 0.85). The geometric mean titer (GMT) was higher in the EB than in the RB group (252 mIU/mL versus 66 mIU/mL, P < 0.0001). One month after the booster, 99.7% of subjects in the EB group and 99.6% in the RB group had a detectable anti-HBs, and 99.0 and 99.3%, respectively, had anti-HBs > or =10 mIU/mL. The anti-HBs GMT was 113,201 mIU/mL in the EB and 16,623 mIU/mL in the RB groups (P < 0.0001). One year after the booster, 99.3% of subjects in the EB group and 100% in the RB group had detectable anti-HBs, and 97.9 and 98.5% respectively, had anti-HBs > or =10 mIU/mL. The anti-HBs GMT was 14,028 mIU/mL in the EB and 3437 mIU/mL in the RB group (P < 0.0001). CONCLUSIONS: The immunity persists for at least 5 years after the primary vaccination with both pediatric vaccines in 99% of children vaccinated at the age of 8-10 years. It confirms that no booster is needed at that point.


The long-term efficacy of hepatitis B vaccine, long-term effectiveness of hepatitis B immunisation programmes, immune memory induced by hepatitis B vaccine, current booster policies, and impact of hepatitis B virus mutants on immunisation programmes were reviewed at the Viral Hepatitis Prevention Board (VHPB) meeting in Sevilla, Spain, March 2004. The main focus was on universal vaccination programmes with data being
presented from Italy, Saudi Arabia, Singapore, Spain, Taiwan, Thailand, The Gambia, and USA (Alaska).

John, T. J. and G. Cooksley. "**Hepatitis B vaccine boosters: is there a clinical need in high endemicity populations?**" *J Gastroenterol Hepatol* 2005 20(1): 5-10.

The Steering Committee for the Prevention and Control of Infectious Diseases in Asia recently conducted a survey of primary-care physicians in Asia, which revealed that many physicians administer boosters in their clinical practice and that there is considerable variation and uncertainty among physicians regarding this practice. This paper serves as a response to physicians' uncertainties by reviewing the literature regarding the administration of hepatitis B vaccine boosters in high endemicity areas and presenting the Steering Committee's guidelines for booster administration. While there are few data to support a need for routine hepatitis B vaccine boosters as a public health measure, they help to provide reassurance of immunity against breakthrough infection in certain risk groups. In clinical practice, primary-care physicians must exercise their judgment regarding the need for booster vaccination on an individual basis. This paper examines the available literature on the administration and value of hepatitis B vaccine boosters, explores the differences between the public health approach and clinical practice, and provides guidelines for those who use boosters in high endemicity Asian populations. Relevant articles were identified through searches of MEDLINE (1975-2003) and the Cochrane Library, using 'hepatitis B' and 'booster' as primary search terms. Guidelines for those who decide to administer hepatitis B vaccine boosters include: boosting approximately 10-15 years after primary vaccination; boosting rather than not when monitoring of antibody levels is not feasible; boosting immunocompromised patients when the antibody to hepatitis B surface antigen titer falls below 10 mIU/mL; and boosting healthcare workers based on the endemicity of the particular country.

Kao, J. H. and D. S. Chen. "**Hepatitis B vaccination: to boost or not to boost?**" *Lancet* 2005 366(9494): 1337-1338.


**BACKGROUND:** Universal anti-hepatitis-B vaccination of infants and adolescents was implemented in Italy in 1991. We undertook a multicentre study in previously vaccinated individuals to assess the duration of immunity and need for booster, over 10 years after vaccination. **METHODS:** In 1212 children and 446 Italian Air Force recruits vaccinated as infants and adolescents, respectively, we measured the concentrations of antibodies to hepatitis-B surface antigen (anti-HBs) and the presence of antibodies to hepatitis-B core antigen (anti-HBc) at enrollment; postimmunisation values were not available. Individuals positive for anti-HBc were tested for hepatitis B surface antigen (HBsAg) and hepatitis B viral DNA. Individuals with anti-HBs concentrations at 10 IU/L or more were regarded as protected; those with antibody less than 10 IU/L were given a booster dose and retested 2 weeks later. Individuals showing postbooster anti-HBs concentrations of less than 10 IU/L were offered two additional vaccine doses and retested 1 month after the third dose. **FINDINGS:** Protective anti-HBs concentrations were retained in 779 (64%, 95% CI 61.6-67) children and 398 (89%, 86.4-92.1) recruits. We recorded antibody amounts of less than 10 IU/L in 433 children (36%, 33-38.4) and 48 (11%, 7.9-13.6) recruits. One child and four recruits were positive for anti-HBc, but negative for HBsAg and hepatitis B viral DNA. Antibody concentrations were higher in recruits than in children (geometric mean titre 234.8 IU/L vs 32.1 IU/L, p=0.0001). 332 (97%) of 342 children and 46 (96%) of 48 recruits who received a booster showed an anamnestic response, whereas ten (3%) children and two (4%) recruits remained negative for anti-HBs or had antibody concentrations of less than 10 IU/L. Prebooster and postbooster antibody titres were strongly correlated with each other in
both groups. All individuals given two additional vaccine doses (eight children and two recruits) showed anti-HBs amounts of more than 10 IU/L at 1 month after vaccination. INTERPRETATION: Strong immunological memory persists more than 10 years after immunisation of infants and adolescents with a primary course of vaccination. Booster doses of vaccine do not seem necessary to ensure long-term protection.

Zuckerman, J. N., B. A. Connor and F. von Sonnenburg. "Hepatitis A and B booster recommendations: implications for travelers." Clin Infect Dis 2005 41(7): 1020-1026. Hepatitis A and B are serious vaccine-preventable diseases with a predominantly overlapping epidemiological distribution. Travelers, a term encompassing a range of individuals, are at risk of contracting these diseases if they are unvaccinated. Although the benefits of the primary vaccination course of hepatitis A and B vaccines are clear, the administration of hepatitis A and B boosters varies worldwide. Recommendations on the need for booster vaccinations have recently been published, and the implications of these recommendations for travelers are discussed in this review. Until a greater understanding is reached on the immunogenicity of hepatitis A and B vaccines in certain special groups (e.g., immunocompromised persons), there will be a need to monitor antibody levels to assess whether booster vaccinations are required. However, for the majority of immunocompetent travelers, the full primary vaccination course will provide protection from both hepatitis A and B infection in the long term, without the need for boosters.

Not included in the meeting session: Vaccination in immunocompromised and haemodialysis patients


The long-term antibody responses to re-immunization in recipients of allogeneic haematopoietic stem cell transplantation (allo-HSCT) have not been well studied. We prospectively and longitudinally evaluated the antibody responses to eight vaccine antigens (diphtheria, tetanus, pertussis, measles, mumps, rubella, hepatitis B, and poliovirus) and assessed the factors associated with negative titres in 210 allo-HSCT recipients at St. Jude Children's Research Hospital. Antibody responses lasting for more than 5 years after immunization were observed in most patients for tetanus (95.7%), rubella (92.3%), poliovirus (97.9%), and, in diphtheria-tetanus-acellular pertussis (DTaP) recipients, diphtheria (100%). However, responses to pertussis (25.0%), measles (66.7%), mumps (61.5%), hepatitis B (72.9%), and diphtheria in tetanus-diphtheria (Td) recipients (48.6%) were less favourable, with either only transient antibody responses or persistently negative titres. Factors associated with vaccine failure were older age at immunization; lower CD3, CD4 or CD19 counts; higher IgM concentrations; positive recipient cytomegalovirus serology; negative titres before immunization; acute or chronic graft-versus-host disease; and radiation during preconditioning. These response patterns and clinical factors can be used to formulate re-immunization and monitoring strategies. Patients at risk for vaccine failure should have long-term follow-up; those with loss of antibody response or no seroconversion should receive booster immunizations.

Lao-Araya, M., T. Puthanakit, L. Aupribul, S. Taecharoenkul, T. Sirisanthana and V. Sirisanthana. "Prevalence of protective level of hepatitis B antibody 3 years after revaccination in HIV-infected children on antiretroviral therapy." Vaccine 2011 29(23): 3977-3981. After responding to highly active antiretroviral therapy (HAART), HIV-infected children had a good response to hepatitis B immunization. However, there are limited data on the
durability of antibody to hepatitis B surface antigen (anti-HBs) in these children. The primary objective of this study is to determine the prevalence of protective anti-HBs level 3 years after a 3-dose HBV revaccination among HIV-infected children with immune recovery (CD4 cell ≥ 15%) while on HAART. The secondary objective is to assess immunologic memory among children who had waning of anti-HBs. An anti-HBs level of ≥ 10 mIU/mL was defined as a protective antibody level. Sixty-nine HIV-infected children who had history of a 3-dose HBV revaccination while receiving HAART were enrolled. The mean (SD) of CD4 cell and duration of HAART at time of revaccination was 27.2% (6.7) and 5.9 years (0.4), respectively. The proportion of children with protective anti-HBs level 3 years after the revaccination was 71.0% [95% CI, 58.8-81.3]. The geometric mean titer was 114(SD 5)IU/mL. By multivariate logistic analysis, the predictors for protective anti-HBs level 3 years after revaccination were CD4 cell count ≥ 500 cells/mm(3) at the time of vaccination (p = 0.04) and anti-HBs level ≥ 100 IU/mL at 1 month after completion of the 3-dose vaccination (p < 0.001). Anamnestic response after one booster dose was demonstrated among 14 of 17 children who had waning protective anti-HBs level (82.4% [95% CI, 62.2-102.6]). Our findings support the recommendation of giving a 3-dose HBV vaccination to HIV-infected children with immune recovery while receiving HAART.


OBJECTIVES:Hepatitis B virus (HBV) reactivation has been described in patients treated with infliximab for inflammatory bowel disease (IBD). This has resulted in a "black box" warning. Although universal vaccination against hepatitis B was implemented in the United States in 1991, up to 10% of vaccine recipients fail to respond with adequate anti-hepatitis B surface antibodies (anti-HBs) levels after a primary series of vaccinations. In addition, anti-HBs levels are expected to decline with time. The objectives of this study were to determine HBV immunity in children with IBD on infliximab therapy and to determine response to a booster dose of the HBV vaccine in patients who were found to be non-immune.METHODS:This was a prospective cross-sectional, single-center study that included 100 pediatric IBD patients on infliximab. Serologic specimens were tested for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and anti-HBs. Patients with an anti-HBs level ≥ 10 mIU/ml were considered to be immune. One booster dose was given to non-immune patients and a serum sample was collected after 4 weeks to assess the presence of anamnestic response (anti-HBs level ≥ 10 mIU/ml after booster).RESULTS:The mean age of the patients was 17.9 (+/- 4.0) years. None of the patients were positive for HBsAg or anti-HBc. In all, 87 patients were vaccinated against HBV and 49/87 (56%) had immunity to HBV as defined by anti-HBs level ≥ 10 mIU/ml. The mean concentration of anti-HBs levels in immune patients was 295.6 (+/- 350.6) mIU/ml. Older age, lower albumin levels, and the presence of pancolitis were associated with the absence of protective antibodies; however, infliximab dose, frequency, duration, and the concurrent use of immunomodulators were not significantly different between immune and non-immune patients. Thirty-four patients received booster immunization and 26/34 (76%) had an anamnestic response. Interestingly, non-responders were given infliximab with higher frequency (every 5.9 +/- 1.2 weeks vs. every 7.1 +/- 1.8 weeks, P=0.01). Overall, 75/87 (86%) of previously immunized patients were considered immune against HBV infection.CONCLUSIONS:In pediatric IBD patients seen at a large, urban tertiary care facility in the United States, a significant minority (13%) have not been vaccinated against HBV. Nearly one-half of all patients (and 44% of previously vaccinated patients) did not have protective anti-HBs levels. Moreover, of those previously vaccinated, a significant minority (14%) appear at risk for HBV because protective anti-HBs levels were absent and could not be elicited through booster immunization. Given the high risk for severe HBV infection in this group, efforts should be made to screen for HBV immunity at...
the time of IBD diagnosis. Booster immunization should be considered in patients without protective antibodies. Am J Gastroenterol advance online publication, 30 August 2011; doi:10.1038/ajg.2011.295.


Background: Three doses of the investigational AS02v-adjuvanted hepatitis B virus (HBV) vaccine HB-AS02 have been shown to induce more rapid seroprotection and higher anti-HBs antibody concentrations in patients with renal insufficiency than four doses of FENDrix (HB-AS04), an adjuvanted HBV vaccine licensed in Europe for use in this population. This study evaluated persistence of immune response up to 36 months after primary vaccination. Methods: In this open, international, Phase III follow-up study, 151 patients with renal insufficiency were vaccinated with 3 doses of HB-AS02. Of these, 99 and 80 returned at Month 36, 76 and 62 of whom were eligible for inclusion in the Long-Term According-To-Protocol (LT-ATP) cohort for descriptive analysis of antibody persistence (mean age: 65.6 years). Results: At Month 36, 89.5% of subjects in the HB-AS02 group and 72.6% of those in the HB-AS04 group had anti-HBs antibody concentrations (>100 mIU/ml). Anti-HBs antibody concentrations were (3)100 mIU/ml in 82.9% and 35.5% of subjects, respectively. Anti-HBs geometric mean antibody concentrations were higher in the HB-AS02 group over the 36 months of follow-up. An exploratory "time to boost" analysis confirmed that subjects who received HB-AS02 were 2.54 times more likely than those who received HB-AS04 to have anti-HBs antibody concentrations (>10 mIU/ml at Month 36 (p=0.013 [95% CI: 1.22, 5.31]). Conclusion: HB-AS02 candidate vaccine induces high and persistent anti-HBs antibody levels in pre-dialysis, peritoneal dialysis and hemodialysis patients, potentially reducing the need for booster doses in this population.


An investigational AS02(v)-adjuvanted hepatitis B (HB-AS02) was compared with a licensed conventional recombinant hepatitis B vaccine (HBVAXPRO; Sanofi Pasteur MSD, Lyon, France) in pre-dialysis, peritoneal dialysis and hemodialysis patients aged >/=18 years who had failed either to respond to prior vaccination with a conventional hepatitis B vaccine (Study A; n=251) or to maintain protective antibody concentrations after prior hepatitis B vaccination (Study B; n=181). These were open, randomized, comparative trials. Mean (range) age was 65.9 (31-92) and 64.6 (29-92) years in the two studies, respectively. In Study A, two doses of HB-AS02 given one month apart were found to be superior to two doses of the licensed vaccine in terms of seroprotection rate (76.9% versus 37.6%) and anti-HBs geometric mean antibody concentrations (GMC; 139.3 versus 6.9mIU/ml), with antibody concentrations >/=100mIU/ml in 61.1% and 15.4% of subjects in the two groups, respectively. In Study B, one month after administration of a single booster dose, seroprotection rates were 89.0% in the HB-AS02 group and 90.8% in the licensed vaccine group, 81.3% and 60.9% of subjects had antibody concentrations >/=100mIU/ml, and anti-HBs GMCs were 1726.8 and 189.5mIU/ml. HB-AS02 was found to be more reactogenic than the licensed vaccine. In summary, the investigational HB-AS02 vaccine induced higher seroprotection rates and anti-HBs GMCs than a licensed conventional hepatitis B vaccine in uremic patients who had failed to respond or to maintain protective antibody titers after prior hepatitis B vaccination.

Zingone, F., F. Morisco, A. Zanetti, L. Romano, G. Portella, P. Capone, P. Andreozzi, R. Tortora

64

Aim of this study was to investigate the anti-HBs antibody persistence and immune memory to hepatitis B virus in adult celiacs vaccinated as adolescents and the effect of a booster administration in non-protected individuals. Eleven years after primary vaccination, the proportion of vaccinees with titres $\geq 10$ mIU/ml and antibody geometric mean concentrations (GMCs) were lower among celiac patients than among controls (68.6% vs 91.7%, $p<0.01$; GMCs 29.38 mIU/ml vs 250.6 mIU/ml, $p<0.001$). Participants with anti-HBs below 10 mIU/ml received a booster dose and were retested 2 weeks later to assess the anamnestic response. Post-booster anti-HBs levels were still <10 mIU/ml in 71.4% celiacs and 25% controls ($p<0.01$). Our findings indicate that the prevalence of seroprotective levels of anti-HBs detected eleven years after primary immunization as well as the frequency of response to a booster dose of vaccine are lower in celiac patients compared to healthy controls.


AIM: To assess tolerability and immunological activity of Bubo-M vaccine and hepatitis B vaccine in patients with chronic obstructive pulmonary disease (COPD). MATERIALS AND METHODS: Sixty-three patients with moderate and severe COPD aged 35-65 years were immunized against diphtheria, tetanus, and hepatitis B. Bubo-M vaccine as well as vaccine against hepatitis B were used for immunization. Immunologic effect of vaccination was assessed by measurement of serum antibody level to HBsAg as well as to diphtheria and tetanus toxoids. Assessment of antibody level to HBsAg was performed by ELISA, and levels of antibodies to diphtheria and tetanus toxoids--by micromethod in direct hemagglutination assay. Reactogenicity of Bubo-M vaccine was measured according to duration and intensity of local and systemic reactions. RESULTS: The local and systemic reactions were infrequent, serious adverse events after vaccination were not observed. Six months after vaccination, protective antibody titers to hepatitis B, diphtheria and tetanus were determined in all immunized persons--either healthy, or with COPD. During completion of vaccination schedule, significant reduction of acute respiratory infections rate and main disease exacerbations was noted in patients with COPD. CONCLUSION: Good tolerability and high immunogenicity of Bubo-M and hepatitis B vaccines were demonstrated in both groups of vaccinees. These vaccines could be recommended for booster vaccination of adults with COPD.


A range of schedules are recommended for hepatitis B vaccination of premature infants. This open-label study (217744/083) compared the immune response of premature (N = 94) and full-term infants (N = 92) to hepatitis B antigen following primary administration of hexavalent DTPa-HBV-IPV/Hib vaccine at 2-4-6 months and a booster dose at 18 months. Anti-HBsAg antibodies were determined before and one month after primary and booster doses. There were no significant differences in postprimary seroprotection rates (anti-HBsAg $>10$ mIU/mL; preterm 93.4%; full-term 95.2%) or geometric mean concentrations (634 versus 867 mIU/mL), and neither appeared to be related to gestational length or birth weight. Prebooster seroprotection rates were 75 and 80.6%, respectively. Six premature infants did not respond to primary and booster doses. Primary and booster vaccinations with DTPa-HBV-IPV/Hib elicit satisfactory anti-HBsAg responses in preterm infants, which are not influenced by gestational age or birth weight. This schedule and vaccine will greatly facilitate the immunisation of premature infants.

The first cases of transient hepatitis B surface antigenemia (HBsAg) in adults following hepatitis B virus (HBV) immunization were reported in the 1990s. HBV immunization is mandatory for all hemodialysis (HD) patients. Ly et al. who demonstrated transient HBsAg in eight out of nine HD patients following HBV vaccine concluded that HD patients should not be screened for HBV within a week of HBV immunization and that positive HBsAg within a month of HBV immunization must be interpreted with caution. We present an 81-year-old woman on HD, who needed a booster Recombivax (Merck, Whitehouse Station, NJ, USA) vaccine after remaining hepatitis B surface antibody (HBsAb) negative from previous vaccinations. The HD Unit had switched to Engerix B (GlaxoSmithKline, Atlanta, GA, USA) HBV vaccine. Two days after the first Engerix B vaccine, HBsAg was detected. She was asymptomatic; ALT was 25 U/L. Repeat testing for HBsAg, HBsAb, hepatitis B E antigen (HB E Ag), and hepatitis B DNA (HB DNA), a week later, all returned negative. Previous reports of transient HBsAg following HBV vaccines were after Engerix B vaccination. Our patient is unusual since she had received both brands of HBV vaccines, sequentially, at different times. Twice, HBsAg tests completed as early as 5 days following Recombivax vaccine were negative. We submit that positive HBsAg tests are more likely following Engerix B vaccines. We reemphasize previous recommendations that patients should not be screened for HBsAg < 4 weeks following HBV immunization. This is particularly important in HD units where hepatitis B screening is carried out routinely all year round and hepatitis B vaccinations are commonplace. Very strict schedules must be adopted to avoid false positive HBsAg tests.


The adjuvanted hepatitis B vaccine, HB-AS04, elicits more rapid and persistent protective antibody concentrations than double doses of conventional recombinant vaccines in patients with renal insufficiency. We compared the immunogenicity, reactogenicity, and safety of the AS02(V)-adjuvanted hepatitis B vaccine HB-AS02 with that of HB-AS04. In this phase III, open, randomized study, 151 hepatitis B vaccine-naive pre-dialysis, peritoneal dialysis, and hemodialysis patients aged 15 years and older received three doses of HB-AS02 at 0, 1, and 6 months. Another 149 similar patients received four doses of HB-AS04 at 0, 1, 2, and 6 months, and all were followed up for 12 months. HB-AS02 elicited more rapid and persistent seroprotection than HB-AS04, with rates of 77 and 39%, respectively, 1 month after the second vaccine dose, and 94 and 79%, respectively, at 12 months. Superiority of HB-AS02 over HB-AS04 in anti-hepatitis B geometric mean concentrations was found at all time points. HB-AS02 was more reactogenic than HB-AS04, but adverse events were mainly transient, of mild to moderate intensity with no reportable vaccine-related serious events. We conclude that a three-dose primary course of HB-AS02 induced more rapid, enhanced, and persistent protection in patients with renal insufficiency than the licensed four-dose primary schedule of HB-AS04. This adjuvanted vaccine affords greater protection with reduced need for booster doses in patients at high risk of hepatitis B infection.


BACKGROUND: Hepatitis B virus (HBV) is an important cause of comorbidity in human immunodeficiency virus (HIV)-infected individuals. The immunogenicity of HBV vaccination in children receiving highly active antiretroviral therapy (HAART) was
investigated. METHODS: HIV-infected children receiving HAART who had low to moderate HIV loads and who had previously received 3 doses of HBV vaccine were given an HBV vaccine booster. Concentrations of antibody to hepatitis B surface antigen (anti-HBs) were determined before vaccination and at weeks 8, 48, and 96. A subset of subjects was administered a subsequent dose, and anti-HBs was measured before and 1 and 4 weeks later. RESULTS: At entry, 24% of 204 subjects were seropositive. Vaccine response occurred in 46% on the basis of seropositivity 8 weeks after vaccination and in 37% on the basis of a 4-fold rise in antibody concentration. Of 69 subjects given another vaccination 4-5 years later, immunologic memory was exhibited by 45% on the basis of seropositivity 1 week after vaccination and by 29% on the basis of a 4-fold rise in antibody concentration at 1 week. Predictors of response and memory included higher nadir and current CD4 cell percentage, higher CD19 cell percentage, and undetectable HIV load. CONCLUSIONS: HIV-infected children frequently lack protective levels of anti-HBs after previous HBV vaccination, and a significant proportion of them do not respond to booster vaccination or demonstrate memory despite receiving HAART, leaving this population insufficiently protected from infection with HBV.


BACKGROUND: Thalassemia is hereditary anemia with lifelong transfusion as treatment and hepatitis B virus (HBV) infection is one of the transfusion transmitted infections (TTI). HBV vaccination is obligatory for these patients by 3 double-dose injections. The authors studied the HBV status and immune response to vaccination by hepatitis B surface antibody (HBsAb) titration in their thalassemic patients. They also compared these results with their previous study to find out the effectiveness of a booster dose in the immunity of patients against HBV. MATERIALS AND METHODS: Hepatitis B surface antigen (HBsAg), HBsAb, and hepatitis B core antibody (HBCaAb) were detected in sera of 416 patients at the Tehran Adult Thalassemia Clinic. The immune status was classified into 4 categories: (1) immune to HBV via the vaccination (positive vaccinal)--if HBs Ag: negative, HBsAb: positive, HBCaAb: negative; (2) immune to HBV via the natural disease (past infection)--if HBs: negative, HBsAb and HBCaAb: both positive; (3) nonimmune to HBV (negative)--if all three parameters were negative; (4) carrier of HBV (carrier state)--if HBs Ag was positive and HBsAb and HBCaAb: both negative. Also grading of immunity done by HBsAb titration as positive if HBsAb titer was more than 100 IU/mL, negative if HBsAb titer was less than 10 IU/mL, and weakly positive if antibody level was 10-100 IU/mL. RESULTS: There were 416 patients: 302 (72.5%) with thalassemia major (TM), 104 (25%) thalassemia intermedia (TI), 7 (1.6%) sickle thalassemia (ST), and 3 (0.7%) alpha-thalassemia (HbH disease). The mean age was 25.6 +/- 8.3 yr and median age was 24 yr; there were 247 (59.4%) males and 169 (40.6%) females. A total of 257 patients (61.7%) were splenectomized. According to our classification 289 (69.4%) were immunized by vaccination; 80 (19.2%) were immunized by past infection; 44 (10.5%) were negative, and 3 (0.7%) were in carrier state of HBV. In grading of immunity to HBV vaccination, 319 (76.6%) patients had HBsAb > 100 IU/mL (positive), 77 (18.5%) between 10 and 100 IU/mL (weakly positive), and 20 (4.8%) less than 10 IU/mL (negative). There was no significant correlation between the level of HBsAb and splenectomy or type of thalassemia. CONCLUSION: Response rate to vaccination is more than 95% after complete course (3 doses) in healthy individuals but failure to fulfill vaccination seems a problem in chronic transfused patients. These results reflect advantages of a booster dose of vaccine, which increased the protection level among these high-risk patients from 46.9% (in the authors' previous data) up to 69.4% in this study.

Several life-threatening infections, a major risk to adult solid organ transplant (SOT) recipients on immunosuppressive therapy, can be prevented by immunization. We analyzed sociodemographic parameters and the immunization status of adult liver transplant recipients (LTX-R, n=267) and renal transplant recipients (RTX-R, n=197) SOT recipients at the Transplantation Center, Berlin, Germany. Date, number, and provider of recommended vaccines were recorded and seroprotection rates determined. The social status in both groups was similar. Most patients (89%) were not adequately informed about immunizations; and if informed, main sources were physicians (47%) and the media (40%). Vaccinations were predominantly provided by family doctors (LTX-R, 66%; RTX-R, 31%) or hemodialysis centers (RTX-R, 37%). Before transplantation, RTX-R had significantly more often received booster vaccinations against tetanus and diphtheria (P<0.005), and a primary hepatitis B immunization (55%); whereas in LTX-R, post-transplant vaccinations against hepatitis A (16%) and pneumococcal disease (13%) were more frequent. Seroprotection rates against tetanus were fairly high in LTX-R (85.3%) and RTX-R (86.8%), and considerably lower for diphtheria, hepatitis A, and influenza. Immunization rates are too low in SOT recipients. Improvement will depend on a more active role of health care providers.


The mortality in inflammatory bowel disease (IBD) has been reported similar or slightly increased as compared to that of the general population. However, deaths related to infectious and parasitic diseases have been repeatedly reported in clinical trials, open series and registries. The IBD patients are exposed to the same infections affecting the community, added to opportunistic infectious related to the immunosuppression. Some of these infectious diseases may be prevented by the appropriate use of a vaccination program. Thus, vaccination status should be assessed at IBD diagnosis, and from time to time, and vaccination should be updated to every patient as soon as possible, since deaths due to preventable diseases should never occur. Present recommendations include vaccination for influenza (annually), for pneumococcal disease with the 23-valent strain (every 5 years), for hepatitis B virus (in patients with no detectable hepatitis B surface antibodies), combined vaccination against tetanus, diphtheria and inactivated poliomyelitis (every 10 years). The role of human papillomavirus vaccine preventing cervical dysplasia and neoplasia in IBD women taking immunosuppressive are at present unknown. In patients lacking varicella immunization, specific vaccination should be considered. Nevertheless, it should be taken into account that varicella vaccine contains live attenuated virus that cannot be administered in patients taking immunosuppressive. The same consideration should be kept in mind for patients travelling to endemic areas for yellow fever. Finally, IBD patients on immunosuppressive may have an altered response to vaccine immunization. Decreased response has been reported for hepatitis B and pneumococcal vaccination. In those cases, testing for serological responses to vaccine should be performed and booster doses may be required.


BACKGROUND: Hepatitis B vaccine is effective in protection against hepatitis B virus (HBV) infection in haemodialysis (HD) patients, but the antibody response is variable in this population and the persistence of immunity in them remains largely unknown. In this study we aimed to evaluate the efficacy and long-term immunogenicity of hepatitis B vaccine in HD patients. METHODS: In this study, we initially offered HBV vaccination as double dose, four vaccine series schedule (40 microg injections intramuscularly in the deltoid muscle at 0, 1, 2 and 6 months) to 54 HD patients who were negative for hepatitis B core antibody and did not receive any dose of HBV vaccine previously. Serum levels of hepatitis B surface antibody (anti-HBs) tested 1-2 months after completion of vaccination.
Then we follow the patients up to 1 year after primary vaccination to evaluate the persistence of immunity (as indicated by serum levels of anti-HBs higher than or equal to 10 IU/l). RESULTS: After primary vaccination, 87% of patients developed anti-HBs levels above 10 IU/l. 27.8% and 59.2% of them were weak responders and high responders respectively. 13% of patients were non-responders. After 1-year follow-up, 18.18% of responders had lost their anti-HBs (transient responders). All of them were initially in weak responders group and had lower anti-HBs levels. CONCLUSION: We found an average percentage of seroconversion after primary HBV vaccination in HD patients. Our study also supported this fact that an antibody titre above 100 IU/l following primary vaccination is necessary to maintain that level of antibody 1 year later.


BACKGROUND: Hepatitis B virus (HBV) immunization protocols are routinely followed in dialysis units. Recommendations for retesting and booster dose administration are variable and less well known. DESIGN: Quality improvement report. SETTING & PARTICIPANTS: Provincial dialysis cohort in all 5 regional centers in British Columbia (n = 1,055). QUALITY IMPROVEMENT PLAN: (1) Describe the variations in HBV testing practice patterns between centers and modalities of dialysis, (2) propose an evidence-based protocol for HBV follow-up testing, and (3) compare the current practice for HBV follow-up testing with the protocol. MEASURES: (1) Number of HBV tests performed based on geographic center and dialysis modality; (2) tabulation of local, national, and international guidelines to determine concordance and develop British Columbian protocol, and (3) percentage of patients who received recommended HBV testing based on protocol. RESULTS: (1) Significant variation noted in HBV testing frequency among the 5 regional centers and between hemodialysis and peritoneal dialysis patients (P < 0.001); (2) current available guidelines generally are concordant, but vary in regard to frequency of follow-up testing; and (3) comparing recommended testing frequency with actual testing, 50% of patients were tested as recommended; 13%, less than recommended; and 37%, more than recommended. Hemodialysis patients often were tested more than recommended (hemodialysis, 47% versus peritoneal dialysis, 16%; P < 0.01). Patients with current or past HBV infection were tested more than recommended (P < 0.01). All variability remained significant when adjusted for age, sex, and dialysis therapy duration in a multivariate model. LIMITATIONS: The cohort was ascertained from laboratory data; therefore, information for vaccination and booster dose administration was not available. CONCLUSION: In a cohort of dialysis patients initially screened for hepatitis B, 50% of patients are being appropriately monitored with retesting compared with an evidence-based protocol. Patients with known HBV infection and hemodialysis patients are being tested more than recommended. Adherence to a protocol for retesting would ensure appropriate follow-up and reduce unnecessary retesting, potentially leading to significant cost savings.


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.


OBJECTIVE: Patients with celiac disease, who often carry human leukocyte antigen-DR3;DQ2, are prone to inadequate response to hepatitis B immunization. We evaluated vaccine response in relation to disease activity and whether previous treatment with a gluten-free diet influences the achievement of protective antibody titers. PATIENTS AND METHODS: We studied 128 children and adolescents with celiac disease and 113 age-matched control subjects. Twenty-two patients with celiac disease were prospectively immunized after diagnosis during dietary treatment (group 1). A total of 106 (group 2) and the control subjects received vaccination by mass immunization in schools at 14 years of age regardless of diet status and when celiac disease was still undiagnosed in 27 of these children. Diet compliance and celiac disease activity were monitored by measurement of antibodies against transglutaminase and endomysium. Vaccine response was determined by measuring antihepatitis B antibodies from serum. RESULTS: The seroconversion after hepatitis B vaccination was 95.5% in group 1. All of these patients carried human leukocyte antigen DQ2. The response rate in group 2 was 50.9% and correlated with gluten intake (untreated patients: 25.9%, non-strict diet: 44.4%, strict diet: 61.4%). Treated and compliant patients did not significantly differ from control subjects (75.2%). Thirty-seven antihepatitis B-negative patients with celiac disease received a booster during a controlled gluten-free diet, and 36 (97.3%) seroconverted, irrespective of the presence of human leukocyte antigen DQ2. CONCLUSIONS: Nonresponse to recombinant hepatitis B surface antigen may be a sign of undiagnosed celiac disease. However, there is a good vaccine response in adequately treated patients. Human leukocyte antigen DQ alleles do not seem to have a primary role. Revaccination is recommended during a controlled gluten-free diet.


BACKGROUND: A hepatitis B virus (HBV) universal vaccination program for infants was implemented for 24 years in Taiwan. Most of the children who received organ transplantation were primarily vaccinated before transplantation. This study investigated the efficacy of HBV vaccination and booster responses in children after liver transplantation (LT). METHODS: Totally 31 children were enrolled. They were clinically stable for more than 1 year after LT. Twenty of them kept a titer of antibody to hepatitis B surface antigen (anti-HBs) more than 10 mIU/mL and received no booster, while 11 received one booster because their anti-HBs titers were less than 10 mIU/mL. Cellular immunity was checked by enzyme-linked immunospot assay with interferon-gamma surrogated for T-helper 1 cells and interleukin-5 for T-helper 2 before and after booster vaccine. RESULTS: One of the non-boosters had de novo HBV infection after LT and recovered to be anti-HBs positive. The first booster restored an adequate titer in 64% (7/11) of those with anti-HBs titer less than 10 mIU/mL after LT. The four patients who failed the first booster responded well to the second dose. After the booster, the mononuclear cells of all 11 had more than one spot-forming cell for interferon-gamma or interleukin-5. Transplanted girls maintained a higher antibody titer than boys. CONCLUSION: Primary HBV vaccination or the booster dose(s) of HBV vaccine could provide adequate humoral and cellular immunity in children with LT.
Aim: The aim of this study was to investigate whether haemodialysis (HD) patients suffering from diabetes mellitus could be considered at risk for the development of the protective antibodies to hepatitis B (HB) vaccination and, to evaluate the effectiveness of tetanus toxoid (TT) administrated 2 days before HB vaccination. METHODS: Forty-nine HD patients were divided into two groups: group A (19 diabetic patients) and group B (30 non-diabetic patients). A dose of 40 microg recombinant HB vaccine was injected intramuscularly to the patients at 0, 1, 2 and 6 months. RESULTS: After the completion of the course, the patients in group A were found to have a lower protective antibody rates than the patients in group B (57.8% vs 70%) (P > 0.05). After the administration of additional booster doses during 12 months, the protective antibody to hepatitis B surface antigen (HBsAb) levels were detected in 78.9% and 96.6% of the patients in group A and group B, respectively (P > 0.05). The patients not having protective HBsAb levels were administered TT and HB vaccines, and after course, all of them have produced protective HBsAb levels. CONCLUSION: The present study showed that diabetic patients on HD may carry a greater risk of not seroconverting than non-diabetic ones for antibody response to HB vaccination. The use of TT 2 days before HB vaccination may be a useful and effective method of enhancing the immune response to HB vaccination, especially in the patients with diabetes mellitus on HD.


After liver transplantation for hepatitis-B-related diseases, patients currently receive lifelong treatment with hepatitis B immunoglobulin to prevent endogenous re-infection with hepatitis B virus (HBV). Active immunization with hepatitis B vaccine would be a preferable alternative; however, most attempts to immunize these patients with standard vaccine have failed. A recent study with a new adjuvanted hepatitis B vaccine was exceptionally successful, leading to a high-titered long-lasting antibody response in 80% of all vaccinees. To identify the immunological mechanisms behind these unexpected results, the successfully vaccinated participants were tested for hepatitis B surface antigen (HBsAg)-specific T and B cells, and their cellular responses to revaccination with conventional vaccine were studied. HBsAg-specific CD4(+) T lymphocytes could be detected in 13 of 16 patients after immunization with the new vaccine. Unexpectedly, these T cells produced almost exclusively interleukin (IL)-10 and had a CD4(+)CD25(+) phenotype. They were functionally active, suppressing cytokine secretion in HBsAg-specific (Th1) cells, thus representing antigen-specific regulatory T cells (T(Reg)). Following a booster dose with conventional vaccine 22-31 months after completion of the initial vaccination series, the T-cell pattern in the revaccinated individuals changed substantially: 7 days after revaccination 9 of 11 individuals showed a switch to a Th1-type immune response with HBsAg-specific T cells secreting IL-2, interferon gamma and tumor necrosis factor alpha as observed in healthy controls. Four weeks after the booster, 4 patients still showed a Th1-type cytokine pattern, whereas in 5 patients only IL-10-secreting cells were detectable. After 1 year, in 3 of 4 revaccinated individuals only IL-10-secreting cells could be found, whereas the specific T cells of the fourth patient still showed a Th1-type of response. HBsAg-specific T(Reg) cells could be demonstrated in HBV-positive liver transplant recipients successfully immunized with a new adjuvanted vaccine. Revaccination led to immediate disappearance of the these cells and the appearance of HBsAg-specific T cells with a Th1-type cytokine profile, which in most cases were replaced by the IL-10-secreting regulatory cells during the following months. The specific induction of T(Reg) cells could contribute to the poor response of liver transplant recipients to conventional vaccine. In conclusion, for successful vaccination of these patients, a
vaccine with a strong inhibitory effect on T(Reg) cells would be desirable.


OBJECTIVES: The aim of the study was to evaluate the efficacy of vaccination against hepatitis B in HIV infected individuals and the influence of the stage of HIV infection and antiretroviral therapy (HAART). Response for additional doses of hepatitis B vaccine among the patients who do not develop protective anti-HBs level after routine vaccination schedule was analysed. METHODS: Fifty-four HIV infected individuals, 20 women (37%) and 34 men (63%), 20 to 64 years old (mean age 32 years) were analysed. 32 patients (59.6%), 22 men and 10 women were treated with antiretroviral drugs. Stage of HIV infection was assessed on the basis of data derived from medical records (lowest CD4 cells count, highest viral load), and immunological status at the moment of introduction of vaccination (CD4 cells count, viral load). Efficacy of vaccination was compared with control group, which consisted of 56 healthy volunteers. In both groups hepatitis B virus infection was excluded by serologic tests. HBvaxPro vaccine produced by Merck Sharp & Dohme Company, dose registered for adults (10 ug) was injected at month 0-1-6. Patients with anti-HBs <10 IU/l have received booster doses of vaccine month intervals, no more then three. RESULTS: Protective level of antibodies was found in 52 (92.9%) persons from control group and 32 (63%) HIV infected individuals. Anti-HBs > 100 IU/l was twice more common in control group (80%) than in investigated group (46.3%) (p < 0.001). Protective level of anti-HBs had 14.3% patients with CD4 below 200 cells/pl, none of them had anti-HBs > 100 IU/l. Patients with higher CD4 cell count had better response for vaccination (p = 0.015). Differences between patients with high and low viral load were not statistically significant (p = 0.015). Patients with viral load below 10,000 copies/ml had slightly better response then those with higher viral load. Efficacy of vaccination was also associated with the level of distraction of immunological system before introduction of HAART. Patients with CD4 < 200 cells/microl or HIV-RNA > 50,000 copies/ml had worst immunological response for vaccination. After the fist additional dose of vaccine anti-HBs >10 IU/l had 79.7% patients, 87.1% after the second dose and 90.7% after the third dose. Anti-HBs >100 IU/l had subsequently 57.4%, 66.7%, 79.6% patients. CONCLUSIONS: We concluded that efficacy of the routine vaccination schedule was lower among HIV individuals in comparison with healthy volunteers. Influence of the progression of HIV infection on the response for vaccination was detected. Additional vaccine's doses have improved efficacy of immunisation which was comparable with general population.


Despite a history of hepatitis B virus (HBV) vaccination prior to highly active antiretroviral therapy (HAART), most of HIV-infected children do not have protective antibody to HBV infection. The efficacy of an additional booster dose in children with immune recovery on HAART remains unknown. This study was conducted to determine the response rate of HBV antibody after re-vaccination in HIV-infected children with immune recovery on HAART. Sixty-three successfully HAART-treated HIV-infected children with history of prior HBV vaccination received 10microg doses of recombinant HBV vaccine (Government Pharmaceutical Organization-Merieux Biological Product, Bangkok, Thailand) intramuscularly at 0, 2 and 6 months. The vaccine response rates were 17.4, 82.5, and 92.1% at 2, 6 and 7 months after the first dose of vaccine, respectively. Plasma HIV RNA level below the limit of detection at the time of re-vaccination was associated with successful vaccine response. HIV-infected children with immune recovery after HAART are likely to benefit from three-dose HBV re-vaccination.

Omenaca, F., J. Garcia-Sicilia, R. Boceta, A. Sistiaga-Hernando and P. Garcia-Corbeira. "Antibody persistence and booster vaccination during the second and fifth years of life in a cohort of
children who were born prematurely." Pediatr Infect Dis J 2007 26(9): 824-829.

BACKGROUND: These studies assessed the immunogenicity and reactogenicity of booster vaccination with diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-adsorbed conjugated Haemophilus influenzae type b (DTaP-HBV-IPV/Hib) at 18-20 months, and with DTaP during the fifth year of life in children who had been born prematurely (<37 weeks gestation). METHODS: Open-label, parallel group studies in which preterm and full-term subjects primed with DTaP-HBV-IPV/Hib received booster vaccination with DTaP-HBV-IPV/Hib (Infanrix hexa) at 18-20 months and DTaP (Infanrix) at 4 years of age. Immunogenicity was assessed before and 1 month after DTaP-HBV-IPV/Hib dose and 1 month after DTaP administration. Local and general symptoms were recorded for 4 days, unsolicited symptoms for 31 days after each dose. RESULTS: Before the second year booster, Hib, hepatitis-B, and polio type 3 seroprotection rates were higher in the full-term group (antipolyribosyl ribitol phosphate > or =0.15 microg/mL observed in 76.2%/83.6% preterm/full term respectively, anti-HBs > or =10 mIU/mL in 75.0%/80.6% respectively). One month after the DTaP-HBV-IPV/Hib booster, > or =98% in both groups were seroprotected/seropositive for all vaccine antigens, except hepatitis-B in preterms (seroprotection rate 91.6%). By the fifth year hepatitis-B seroprotection rates were 85.3%/70.5% (seroprotective/full term) in subjects who had previously responded to hepatitis-B vaccination, and seroprotection rates for polio and polyribosyl ribitol phosphate were >95%. No differences between groups were observed after the DTaP booster. Both booster doses were generally well tolerated with minimal differences observed between groups. Local symptoms occurred more frequently after the fifth vaccination at 4 years of age. CONCLUSIONS: Despite trends for lower immune responses to some vaccine antigens in preterm subjects, these findings support undelayed primary and booster vaccination in infants and children born before term. Booster vaccinations with DTaP-HBV-IPV/Hib and DTaP were well tolerated in this susceptible group.


AIM: The aim of our study was the long-term evolution of hepatitis B immunity and the titers of antibodies against the surface antigen (anti-HBs) acquired either naturally or after vaccination in hemodialysis (HD) patients with no history of hepatitis C virus (HCV) infection. METHODS: 36 HD patients were vaccinated with 4 doses of 40 microg recombinant B vaccine (Engerix, Rixensart, Belgium), intramuscularly at 0, 1, 2 and 6 months. 21 patients (60%) seroconverted developing anti-HBs titers > or = 10 IU/ml. Two patients were transferred to another unit before completion of 6 months after the last vaccine dose. We followed-up 19 HD patients who were immune against HBV after vaccination (Group A), and 30 immune patients (anti-HBs titers > or = 10 IU/ml) who had never been vaccinated and had antibodies against the core antigen (anti-HBc), diagnostic of natural HBV infection (Group B). In all patients of Groups A and B, anti-HBs were determined every 6 months, starting 6 months after the last dose in the vaccinated patients. Follow-up period lasted from October 2002 - April 2006. RESULTS: The mean follow-up in Group A was 21 +/- 12 months (range 6 - 36) and in Group B 29 +/- 12 months (range 6 - 42). Age, sex, presence of diabetes mellitus and duration of dialysis did not differ between the two groups. Five patients in Group A (26%) and 2 patients in Group B (9%) lost immunity (anti-HBs < 10 IU/ml) (p = 0.07). The median time to loss of immunity in Group A patients was 12 months (interquartile range 6 - 18 months), while in Group B patients it was 15 months (interquartile range 12 - 18 months). No booster dose was administered during the study. The 2 patients of Group B who lost immunity were the oldest of the group and redeveloped anti-HBs 6 and 12 months after they had lost it. During the first 6 months of the follow-up period, Group A had significantly higher anti-HBs titers than Group B (p < 0.05). However, this difference was lost later on, and after the first year of follow-up, anti-HBs titers were decreased significantly in Group A (p < 0.05), but remained unchanged in Group B throughout the follow-up period. CONCLUSIONS: In conclusion, HD patients
lost hepatitis B immunity both after natural infection or vaccination, but naturally infected patients easily redeveloped protective anti-HBs titers. Anti-HBs titers decreased faster in vaccinated patients than in those with natural acquired immunity who held stable titers for a longer period. It is suggested that HD patients should be followed-up regularly for loss of HBV immunity after vaccination and receive a boosting dose when this occurs. In contrast, patients who acquired natural immunity do not need any anamnestic vaccination.


The protective power of two booster dose vaccination against hepatitis B virus (HBV) infection has not been previously studied in patients with acute lymphoblastic leukemia (ALL) who remained unresponsive to immunization. The aim of this study was to determine the HBV infection rate in vaccinated and unvaccinated patients with or without seroconversion and to compare these groups in respect to HBV infection rate. The study group included 111 male and 85 female ALL patients with a mean age of 6.23+/-.4.10 years. Patients were divided into three groups as follows: Group 1 included 82 patients who were vaccinated during maintenance chemotherapy, Group 2 included 87 unvaccinated patients, and Group 3 included 27 patients who were vaccinated prior to the diagnosis of ALL. Seroconversion was obtained in 35.4% (29/82) of patients in Group 1. The incidence of HBV infection was significantly lower in Group 1 (4/82, 4.8%) than in Group 2 (25/87, 28.7%). When we compared only the seronegative patients in Group 1 with Group 2 in respect to HBV infection rate, Group 1 still had a significantly lower HBV infection rate than Group 2 (7.5% versus 28.7%) (p<0.001). No patients in Group 3 (n=27) had HBV infection. In addition to the seroconversion level, infection rate is also important in the evaluation of the effectiveness of vaccination. Our study results suggest that a high protective role of HBV vaccination was also observed in non-seroconversion ALL patients. The effect of cellular immunity on the protection against infection should also be investigated in such patients with further studies.


Patients after orthotopic liver transplantation (OLT) due to hepatitis B virus (HBV)-related disease are at risk of endogenous hepatitis B reinfection and may receive life long prophylaxis with hepatitis B hyperimmunoglobulin (HBIG). In a previous study 16 of 20 OLT patients were immunized successfully with an adjuvant hepatitis B vaccine. To maintain protective antibody levels under immunosuppressive therapy, 11 of these patients were revaccinated with a double dosed conventional hepatitis B vaccine. Median interval between last vaccination and booster was 24 months (range 22-31 months). Antibody titres against hepatitis B surface antigen (anti-HBs) were monitored at the day of booster vaccination (day 0), at day 7 and day 28. At day 0, all vaccinees but one had anti-HBs titres greater than 500 IU/L (median 1,925 IU/L, range 196-7,612 IU/L). Maximum antibody titres after previous vaccination declined by a median of 82% (range 47-96%). After booster vaccination the anti-HBs titre increased significantly by a median factor of 2.42 (P<0.05). In conclusion, the majority of liver transplant recipients who previously had responded to adjuvant hepatitis B vaccine exhibited sufficient immunocompetence to produce a substantial antibody response after booster immunization with a conventional vaccine.


BACKGROUND: Isolated antibody to hepatitis B core antigen (anti-HBc) is frequently found in HIV-infected patients. The present study aimed to determine the prevalence and
risk factors of isolated anti-HBc and the anamnestic response to hepatitis B vaccination in this population. MATERIAL AND METHOD: HIV-infected patients who visited Ramathibodi Hospital in May 2006 were included to test hepatitis B serology. Subjects with isolated anti-HBc were given hepatitis B vaccine and tested for anti-HBs. RESULTS: Of 140 patients, 28 (20%) had isolated anti-HBc. From multivariate analysis, IVDU (OR 30.8, p < 0.001) and anti-HCV seropositive (OR 6.7, p = 0.002) were independent risk factors for isolated anti-HBc. Two from 28 (7%) patients who received vaccine had a response to vaccination. CONCLUSION: Prevalence of isolated anti-HBc among Thai HIV-infected patients was 20%. Risk factors of isolated anti-HBc were IVDU and anti-HCV seropositive. Anamnestic response to hepatitis B vaccination was low. Further study with strategies to improve the response of vaccination is needed.


Reinforced hepatitis B (HB) vaccination schedules have been tested in nonresponsive hemodialysis (HD) patients. Primary high-dose intradermal (ID) vaccination in HD has been proposed in one study with higher seroconversion rate, but no cost analysis was made. The aim of this prospective study was to confirm this previous report and focus on a cost-effectiveness evaluation of the thorough vaccination with a maintenance program. Thirty-five chronic incident HD patients received primary ID HB vaccination with a reinforced schedule (20 microg Engerix-B every 2 weeks). Revaccination with a monthly single ID dose of 20 microg was performed whenever anti-HBs titer fell under 20 IU/L and continued until a titer of 20 U/L was reached. Outcome measures were cumulative seroconversion rates, mean levels of anti-HBs, maintenance booster doses, rate of seroprotection at the end of the 2-year follow-up and subsequent costs. The present study was associated with an earlier peak of anti-HBs titer (3.9 +/- 1.7 months) and a higher cumulative seroconversion rate (96.9%) after 1 year. Moreover, a low-booster shot (17.4 microg) of ID Engerix-B/year/patient confers a 100% seroprotection for all responders for a second-year period. The mean cost of our schedule is 127.7 euro/patient for a 2-year period, revaccination included. This current study demonstrates that primary reinforced ID HB vaccination with a maintenance program for a 2-year period warrants the best cost-effectiveness ratio with rapid and sustained seroprotection in almost all HD patients.


HIV-infected children had a lower seroconversion rate to hepatitis B immunization and a more rapid antibody decline when compared to healthy children. Whether re-immunization or additional booster dose is necessary after immune recovery remains unknown. This study was conducted to determine the prevalence of hepatitis B virus protective antibody in HIV-infected children with immune recovery after highly active antiretroviral therapy (HAART). Serum hepatitis B viral markers were measured. An antibody level of > or =10 mIU/mL was defined as a protective antibody level. Only one out of 69 children (1%) had a protective antibody level. We concluded that despite the history of hepatitis B immunization and despite evidence of immune recovery after HAART, most HIV-infected children are still susceptible to HBV infection.


OBJECTIVE: Patients with end-stage renal failure are at high risk of hepatitis B virus (HBV) infection. They have impaired immune response to HBV intramuscular (i.m.) vaccine. Non-response (anti HBs titer < 100mIU/ml) hemodialysis patients (HD) with the previous three-dose i.m. vaccination were examined with booster dose vaccine by i.m., intradermal
MATERIAL AND METHOD: Thirty-four HD patients who had been vaccinated with three-dose vaccine (40 microgram, 2 ml, Engerix B, i. m.) and had anti-HBs titer less than 100mIU/ml were selected. They were randomly divided into three groups and received a fourth dose of vaccine by i.m. (40 microgram, 2 ml), i.d (10 microgram. 0. 5 ml) and s.c. (10 microgram, 0. 5 ml). Then, serum anti-HBs titer was determined after 45 days and 6 months. RESULTS: Forty five days after completion of the re-vaccination course, anti-HBs titer was above 100 mlU/ml in 6/11, 3/11 and 4/12 of i.m. s.c and i. d groups, respectively (p > 0.05). After six months, 4/11, 3/11 and 2/12 of patients had anti-HBs titer above 100mIU/ml (p > 0.05). CONCLUSION: With lower dose of vaccine (10 microgram) in s.c. groups, these patients had lower change in their anti-HBs titer. Therefore, it is cost effective and practical to offer other vaccination schemes.


OBJECTIVES: As interleukin (IL)-2 therapy increases CD4 cell counts in HIV infected subjects, it emerged as a candidate for the partial restoration of immune competence in this disease. METHODS: We studied the frequencies of antigen-specific T cells using single cell resolution cytokine ELISPOT assays and titers of specific antibodies before and after immunization of HIV infected subjects who were treated with HAART or HAART plus IL-2. RESULTS: Subjects seronegative to hepatitis A were vaccinated with hepatitis A antigen. In the non-IL-2 treated group, hepatitis A-specific T cells producing IL-2 and IL-4 along with specific antibodies were induced, showing that these subjects are immune competent and capable of mounting a primary immune response. Additional IL-2 treatment had no significant effect on this primary T cell response; however, booster immunizations with tetanus toxoid or the gp120 depleted HIV vaccine Remune induced higher frequencies of specific interferon (IFN)-gamma producing T cells in IL-2 treated subjects. No impact of IL-2 treatment on these secondary B cell responses was seen. CONCLUSION: Overall, our study showed that IL-2 therapy had no immune enhancing effect on the induction of a primary response, but increased the frequency of IFN-gamma producing memory cells after booster immunization.


The doses of hepatitis B vaccine given to peritoneal dialysis (PD) patients are currently based on responsiveness data from hemodialysis (HD) patients. To determine whether the doses are also appropriate from PD patients, we did a head-to-head comparison of short-term and 2-year responses to hepatitis B vaccination of HD patients and PD patients. We evaluated serum titers of the antibody to hepatitis B surface antigen (anti-HBs) after the patients had completed a course of four consecutive intramuscular vaccinations (40 microg of Engerix-B administrated into the deltoid muscle at 0, 1, 2, and 6 months) in 69 dialysis patients (47 HD and 22 PD patients) who were both hepatitis B surface antigen (HBsAg) and anti-HBs negative. No patients had received a hepatitis B vaccination prior to the study. There was no significant difference in response to hepatitis B vaccination between the HD and PD groups (78.7% versus 77.3%, p=0.33). The seroconversion rate defined as anti-HBs > or = 10mIU/L was influenced only by age (p=0.011). There was also no significant difference in responsiveness between the HD and PD groups (60% versus 50%, p=0.41) at a 2-year follow-up. We conclude that doses of HBV vaccine being used for HD patients are also appropriate for PD patients and a booster dose of vaccine is required to maintain seroprotection for those who lost protecting anti-HBs.

**B vaccine in pre-hemodialysis and hemodialysis patients.** *Kidney Int* **2005** 68(5): 2298-2303.

BACKGROUND: Due to their impaired immune system, patients with renal insufficiency have a suboptimal response to hepatitis B (HB) vaccination and frequent boosters are needed to maintain protection. GlaxoSmithKline Biologicals has developed a HB vaccine containing a new adjuvant system AS04 for use in this immunocompromised patient population. METHODS: In an open, randomized clinical trial conducted in pre-hemodialysis (documented creatinine clearance < or =30 mL/min) and hemodialysis patients, over 15 years of age and naive for HB, the immunogenicity and safety of single doses of HB-AS04 (Fendrix, GlaxoSmithKline Biologicals) were compared to double doses of commercially available HB vaccine (Engerix, GlaxoSmithKline Biologicals) administered at 0, 1, 2, and 6 months, and followed-up for 36 months. RESULTS: The HB-AS04 vaccine elicited a more rapid onset of protection than the currently licensed vaccine for this particular population, with 74% versus 52% of subjects seroprotected at month 3. After the vaccination course, seroprotection rates increased to 91% versus 84% in the HB-AS04 and standard vaccine groups, respectively. Differences persisted up to 36 months post-vaccination (73% vs. 52%, respectively). Antibody concentrations were higher following the HB-AS04 vaccine at all post-vaccination time points. During the follow-up, significantly fewer subjects primed with the HB-AS04 vaccine needed a booster dose as a consequence of anti-HBs loss below seroprotective levels (11/62 subjects in the HB-AS04 group vs. 22/57 subjects in the standard vaccine group, respectively, *P* = 0.014). The HB-AS04 was more locally reactogenic than the standard immunization regimen, with pain at the injection site occurring with 41% of HB-AS04 doses versus 19% of standard vaccine doses. The occurrence of grade 3 pain was less than 1% in both groups and all events resolved within the 4-day follow-up period. CONCLUSION: The improved immunogenicity profile and clinically acceptable reactogenicity of HB-AS04 vaccine are of key importance to provide a more rapid, enhanced, and longer seroprotection to these immunocompromised patients at risk for HB infection.
2. Hepatitis Bibliography of the Speakers

Yong Poovorawan, Center of Excellence in Clinical Virology, Faculty of Medicine, Chulalongkorn University, Bangkok Thailand


8. Tharmaphornpilas P, Rasdjarmrearnsook AO, Plianpanich S, Sa-nguanmoo P, Poovorawan Y. Increased risk of developing chronic HBV infection in infants born to chronically HBV infected mothers as a result of delayed
second dose of hepatitis B vaccination. Vaccine. 2009 Oct
19;27(44):6110-5.


(refernece list from speakers-form)

ALESSANDRO ZANETTI, Department of Public Health, Microbiology, Virology University of Milan, Italy


*(reference list from Pubmed search { (Author name)AND( Hepatitis)}

**BRIAN McMAHON**, Centers for Disease Control and Prevention And Alaska Native Medical Center, Alaska


*(reference list from speakers-form)


(reference list from Pubmed search { (Author name)AND( Hepatitis)}

**Geert Leroux-Roelis,** Center for Vaccinology (CEVAC) – Ghent University and Hospital, Ghent, Belgium


(reference list from speakers-form)

**WOLFGANG JILG** Institute for Medical Microbiology and Hygiene, University of Regensburg, Germany


RITA CARSETTI, Research Center Ospedale Bambino Gesu, Roma, Italy


MARIO CLERICI, Immunology, University of Milano, Italy


9. LUDEK ROZNOVSKY, Department of Infectious Diseases, University Hospital, Ostrava, Czech Republic

CHYI-FENG JAN, National Taiwan University Hospital, Taipei, Taiwan


HILTON WHITTLE, London School Hygiene and Tropical Medicine, London, UK


**ANGELA DOMINGUEZ**. Department of Public Health, University of Barcelona, Spain


3. Lopalco PL, Salleras L, Barbuti S, Germinario C, Bruguera M, Buti M, Domínguez A. Hepatitis A and B in children and adolescents – What can we learn from Puglia (Italy) and Catalonia (Spain)? Vaccine 2001; 19: 478-482.


(reference list from Pubmed search { (Author name)AND( Hepatitis)}

---

MIRA KOJOUHAROVA. National Centre of Infectious and Parasitic Diseases, Sofia, Bulgaria


3. Kojouharova M. Vaccine-prevention of viral hepatitis A and B in Bulgaria. Practical Pediatria, 2006, 8, 12-16 (in Bulgarian)


**TRUDY MURPHY, Centers for Disease Control and Prevention, USA**


5. Dorell CG, Yankey D, Byrd KK, Murphy TV. **Hepatitis A vaccination coverage among adolescents in the United States.** *Pediatrics* (Accepted for publication)

6. Zhen Z, Murphy TV, Jacques-Carroll L. **Progress in Newborn Hepatitis B Vaccination by Birth Year Cohorts – 1998-2007, USA.** *Vaccine* (Accepted for publication)


YEN-HSUAN NI, Department of Pediatrics, Children’s Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan


(reference list from speakers-form)


(Reference list from speakers-form)

Richard Tedder, Health Protection Agency, London, UK


**JAMIE WILSON, Department of Biological Sciences, University of Warwick, UK**


(reference list from Pubmed search { (Author name)AND( Hepatitis)}

**JOHN WARD.** Centers for Disease Control and Prevention, USA


(reference list from Pubmed search { (Author name)AND( Hepatitis)}


{reference list from Pubmed search { (Author name)AND( Hepatitis)}}
DAVID FITZSIMONS, rapporteur, Prévessin, France


