Most biological systems have developed complex mechanisms to maintain the stability of their genetic information. Exceptions to this include viruses that can undergo rapid and substantial genetic sequence changes and alterations. The hepatitis B virus (HBV) has evolved a unique life cycle resulting in the production of enormous viral loads during active replication without actually directly killing the infected cell. Because the virus uses reverse transcription to copy its DNA genome, mutant viral genomes are frequently found. Particular selection pressures, both endogenous (host immune clearance) and exogenous (vaccines and antivirals), readily select out these escape mutants. It is still not known which particular viral mutations or combination of mutations directly affects the clinical presentation of the liver disease, the nature of the viral persistence, or the course and outcome of chronic infection. Further studies are needed to identify the pathogenic basis for the selection of these mutants. Such research should help improve the basic understanding of this unique virus-host relationship and provide new strategies for complete control of HBV infections.

The relationship of e antigen (eAg) and its antibody (anti-e) to vertical transmission of hepatitis B surface antigen (HBsAg) from chronic asymptomatic HBsAg carrier women to their children was investigated in Taiwan. Sera from 20 of the 62 women studied were positive for eAg (32%); serum from only one woman was positive for anti-e (2%). A total of 85% of the babies born to eAg positive mothers became HBsAg carriers, while only 31% of the babies became carriers when the mother was eAg negative. Maternal e antigenemia correlated with a high HBsAg titer, and both parameters were equally good predictors of vertical transmission.

Yupik Eskimos of southwestern Alaska have the highest known prevalence of hepatitis B virus infection of any general population in the United States. Prospective serological surveys of 1,280 seronegative Yupik Eskimos, performed between 1971 and 1976, identified 189 (14.8%) who developed serological evidence of hepatitis B virus infection. Twenty-six (13.8%) developed clinical hepatitis during the interval when seroconversion occurred. The proportion of patients with clinically apparent hepatitis increased with age (P less than .01), ranging from 9.5% of infections in patients who were four years of age or less to 33.3% of infections in patients who were 30 years of age or older. Twenty-five (13.3%) of the 188 individuals who were studied became chronic carriers of hepatitis B surface antigen. The risk of becoming a carrier was inversely related to the age of the patient at the time of infection (P = .02). Among patients who were four years of age or less when infected, 28.8% became chronic carriers of hepatitis B, as compared with 7.7% of those who were 30 years of age or older.


Viral hepatitis B is an enigmatic disease in which the host's own immune response to persistent viral infection may bring about host destruction through antiviral inflammatory responses which might otherwise present as a benign or inapparent disease. The simple solution to the hepatitis B problem is by immunoprophylaxis using the vaccine licensed in 1981, which prevents both infection and the late sequelae of liver cirrhosis and hepatocarcinoma. Immunotherapeutic vaccines against persistent hepatitis B infection have not been successful and new explorations are being directed to therapies which include antisense, ribozymes, gene silencing by RNA interference (RNAi) and aptamer approaches. Limited benefits from nucleoside therapy and limitations in opportunity for liver transplantation have left a large void of curative treatments. Findings with respect to e antigen tolerance provide a basis for exploration to determine whether passively administered e antigen might suppress cell-mediated immunity, creating a commensal state in which virus persists but without pathologic damage to the host. Therapy of hepatocarcinoma by conventional chemotherapy, radiation, or surgical resection and ablation gives little hope for restoration of health unless the tumor is detected very early. The large engagement of the world medical science community to develop therapeutic vaccines against cancer is now in major clinical trials to determine the hope and credibility for the immunization approach. Vaccines based on tumor peptides which are linked to heat shock proteins and directed to host dendritic cells give reason for excitement and may be the "best show in town". A new era of tumor therapy will need to be based on new discoveries in immune function which are required to pursue immunotherapy on a more rational basis. The many facets of current hepatitis B virology, pathogenesis, immunoprophylaxis, immunotherapeutasis, chemotherapy, and tumor pathogenesis and therapy are discussed here, in depth, but in keeping with needed brevity.
Control and the possible elimination of transmission of HBV infection is possible with the appropriate use of hepatitis B vaccines. The prevention of chronic HBV infection has the potential of reducing the association burden of chronic liver disease and primary hepatocellular carcinoma. Worldwide, strategies for the effective use of hepatitis B vaccine have been developed and are being implemented in those areas where childhood transmission is the predominant source of chronic HBV infections. However, in the United States and other areas with "low" rates of HBV infection, current vaccination strategies have not been effective and have not fully taken into account the multifaceted epidemiology of HBV infection in those areas. Unfortunately, the majority of infections occur among adults who have been the most difficult to access, who acquire infection before they realize they are at risk, and where the changing epidemiology of HBV infections among the various risk groups only emphasizes the problems of vaccine delivery. In addition, the majority of persons receiving vaccine as a result of the current strategy to immunize adult high-risk groups have been persons who acquire HBV infection through occupational exposure, a group that accounted for no more than 5% of cases even before vaccine was introduced. The failure of the current immunization strategy to prevent a disease with significant health care and economic consequences is beginning to cause a reevaluation of this approach. A comprehensive approach to eliminating HBV transmission must address infections acquired during early childhood as well as those acquired by teenagers and adults. (ABSTRACT TRUNCATED AT 250 WORDS)


It has been estimated that presently hepatitis B kills more people every day than AIDS kills in a year world-wide. Infection with hepatitis B produces a wide range of manifestations ranging from asymptomatic carriers to persistent infections leading to chronic liver diseases and hepatocellular carcinoma. Availability of effective and safe vaccine has made all this preventable. To formulate on appropriate vaccination strategy for India the epidemiology of hepatitis B needs to be defined. This report critically reviews the available data. The burden of long term sequelae of HBV infection is probably under-diagnosed and under-reported in India. Prevalence studies of HBV markers indicate that India falls under the area of intermediate endemicity. Limited data on age-specific prevalence of HBV markers suggests that the majority of the infection seems to take place below 15 years of age, and most of it under one year. Perinatal transmission appears to contribute significantly to the carrier pool. Childhood vaccination for HB among the general population is the obvious strategy of choice. But more information is required to decide on the timing of the first dose.
OBJECTIVES: to identify the risk factors for hepatitis B (HBV) and hepatitis C (HCV) virus infections in drug users attending two drug treatment centres in Northwest England, and to evaluate the effect of both needle exchange and hepatitis B vaccination on the prevalence of hepatitis B and hepatitis C infections. METHODS: a retrospective, cross-sectional study performed at the Regional Infectious Disease Unit and a Primary Care Centre for drug users in Liverpool. The study population included 773 drug users who had hepatitis serology performed between January 1992 and April 1996. Information on risk factors was obtained from clinical records; hepatitis serology data were obtained from the Liverpool Public Health Laboratory database. RESULTS: the overall seroprevalences of exposure markers for HBV (anti-HBc antibody) and HCV (anti-HCV antibody) were 48% and 67%, respectively. Duration of injecting drug use was the strongest predictor of HCV infection, with a crude odds ratio of 8.9 (95% confidence interval (CI): 4.5-17) for >10 compared to <3 years of injecting, and was also a strong predictor of HBV infection, with an adjusted odds ratio (controlled for the effects of HBV vaccination) of 5.7 (95% CI: 3.2-10) for >10 compared to <3 years' injecting. Vaccination against HBV was associated with greatly reduced HBV seroprevalence (crude odds ratio 0.11, 95% CI: 0.06-0.18). Overall, HCV was acquired earlier in the injecting career than HBV, but drug users who were not vaccinated against HBV acquired markers for HBV even more rapidly than for HCV. We found no independent protective effect for either anti-HBc or anti-HCV acquisition after the introduction of a needle-exchange scheme. CONCLUSIONS: hepatitis C is highly prevalent among Merseyside drug users and is likely to prove difficult to control because of rapid acquisition early in the injecting career. Vaccination against hepatitis B is the best means of protecting drug users from hepatitis B, and should be offered before injecting is commenced.

Hepatitis B vaccine


The synthesis of the hepatitis B surface antigen (HBsAg) in cells of Saccharomyces cerevisiae and its subsequent isolation, purification and analysis is described. The final, purified HBsAg particle exhibits close structural and biochemical similarities to particles derived from the plasma of chronically infected humans. Particles of yeast and human origin have been found, by chimpanzee efficacy studies and by various in vitro analyses, to be immunologically equivalent. The antigenic expression of a determinant-specific epitopes, as measured by antibody binding to synthetic peptides, has also been shown to be equivalent.

Hepatitis B vaccine is a key tool for the prevention of hepatitis B infection. Age-associated changes in immune function may contribute to decreased vaccine efficacy in older individuals, although research related to this topic has yielded contradictory findings. We performed a meta-analysis of 24 published trials and studies that evaluated the association of age with response to hepatitis B vaccine, using a random-effects model. Pooling of study results suggested a significantly increased risk of nonresponse to hepatitis B vaccine among older individuals (relative risk [RR], 1.76; 95% confidence interval [CI], 1.48-2.10). An elevated risk of nonresponse persisted even after exclusion of poor-quality studies (RR, 1.63; 95% CI, 1.23-2.15) and adjustment for publication bias (RR, 1.52; 95% CI, 1.26-1.83), and it was present even when "older" individuals were defined as being as young as 30 years. These findings have important implications for individuals at risk for hepatitis B infection, including health care workers and travellers.


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

The long term protective efficacy of recombinant hepatitis B vaccine, administered alone or concomitantly with hepatitis B immunoglobulin, was assessed in 263 healthy neonates of hepatitis B e antigen-positive mothers. Infants received the first dose of vaccine at birth; additional doses were given at either Months 1, 2 and 12 or Months 1 and 6. During the follow-up period, which ranged from 2 to 4 years, protective titers (> or = 10 mIU/ml) of anti-hepatitis B surface antibodies were found in virtually all infants who had responded to the primary course of vaccination. "Natural boosts," without persistent infection, were observed in only a small number of children. All children who were shown to have become chronic carriers were infected within the first year of life. No statistical difference in long term protective efficacy could be shown between the two vaccination schedules used or between the use of vaccine alone or vaccine plus hepatitis B immunoglobulin for either schedule.


BACKGROUND: A nationwide hepatitis B vaccination program was implemented in Taiwan in July 1984. To assess the effect of the program on the development of hepatocellular carcinoma, we studied the incidence of this cancer in children in Taiwan from 1981 to 1994. METHODS: We collected data on liver cancer in children from Taiwan's National Cancer Registry, which receives reports from each of the country's 142 hospitals with more than 50 beds. Data on childhood liver cancer were also obtained from Taiwan's 17 major medical centers. To prevent the inclusion of cases of hepatoblastoma, the primary analysis was confined to liver cancers in children six years of age or older. Data were also obtained on mortality from liver cancer among children. RESULTS: The average annual incidence of hepatocellular carcinoma in children 6 to 14 years of age declined from 0.70 per 100,000 children between 1981 and 1986 to 0.57 between 1986 and 1990, and to 0.36 between 1990 and 1994 (P<0.01). The corresponding rates of mortality from hepatocellular carcinoma also decreased. The incidence of hepatocellular carcinoma in children 6 to 9 years of age declined from 0.52 for those born between 1974 and 1984 to 0.13 for those born between 1984 and 1986 (P<0.001). CONCLUSIONS: Since the institution of Taiwan's program of universal hepatitis B vaccination, the incidence of hepatocellular carcinoma in children has declined.
Preterm (PT) infants are at increased risk of experiencing complications of vaccine-preventable diseases but are less likely to receive immunizations on time. Medically stable PT and low birth weight (LBW) infants should receive full doses of diphtheria, tetanus, acellular pertussis, Haemophilus influenzae type b, hepatitis B, poliovirus, and pneumococcal conjugate vaccines at a chronologic age consistent with the schedule recommended for full-term infants. Infants with birth weight less than 2000 g may require modification of the timing of hepatitis B immunoprophylaxis depending on maternal hepatitis B surface antigen status. All PT and LBW infants benefit from receiving influenza vaccine beginning at 6 months of age before the beginning of and during the influenza season. All vaccines routinely recommended during infancy are safe for use in PT and LBW infants. The occurrence of mild vaccine-attributable adverse events are similar in both full-term and PT vaccine recipients. Although the immunogenicity of some childhood vaccines may be decreased in the smallest PT infants, antibody concentrations achieved usually are protective.


Maternal immunization embraces the concepts that vaccines given to pregnant women enhance their resistance to vaccine-preventable diseases and passive antibodies that cross the placenta protect the neonate for the first 3 to 6 months of life. It is a great public health move to get excellent protection at a small cost. Because all recommended vaccines for use in pregnancy are safe, it makes good sense to bring patients up to date on vaccines.


Hepatitis B viral infection is transmitted in adults by transfer of body fluids containing the virus. The outcomes following infection can be significant in terms of both health and employment. It is for these reasons that effective preventative health care is the goal of occupational health practitioners. This evidence-based review of the literature provides a basis upon which practice can be established and highlights some of the issues that may confront practitioners of the future.


OBJECTIVE: To determine the duration of protection from hepatitis B vaccine given
in infancy and early childhood. DESIGN: Cross sectional serological study of hepatitis B virus infection in children of various ages 14 years after the start of a trial of vaccination regimens. SETTING: Two villages in the Gambia. PARTICIPANTS: Children and adolescents given hepatitis B vaccine in infancy or early childhood: 232 were aged 1-5 years, 225 aged 5-9 years, 220 aged 10-14 years, and 175 aged 15-19 years. MAIN OUTCOME MEASURES: Vaccine efficacy against infection and against chronic infection in the different age groups. RESULTS: Vaccine efficacy against chronic carriage of hepatitis B virus was 94% (95% confidence interval 89% to 97%), which did not vary significantly between the age groups. Efficacy against infection was 80% (76% to 84%). This was significantly lower in the oldest age group (65%, 56 to 73). Of the uninfected participants in this age group, 36% had no detectable hepatitis B virus surface antibody. Time since vaccination and a low peak antibody response were the most powerful risk factors for breakthrough infection (P<0.001 in each case). Low peak antibody response was also a risk factor for chronic carriage (odds ratio 95, 19 to 466). CONCLUSIONS: Children vaccinated in infancy are at increased risk of hepatitis B virus infection in the late teens. The risk of chronic carriage after sexual exposure needs further assessment to determine if booster vaccines are necessary.


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


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

Zuckerman J. The place of accelerated schedules for hepatitis A and B vaccinations. Drugs. 2003;63(17):1779-84.

The availability of accelerated schedules of vaccination, as well as the development of combination vaccines, has enhanced the methods of protection against infectious disease, in particular that of hepatitis A and B viruses. The benefits of using accelerated schedules include: (i) enhanced adherence to and subsequent completion of vaccine courses; (ii) convenience for the recipient of the vaccine; (iii) reduced administration costs of providing the vaccine; and, most importantly, (iv) the ability to provide protection against these serious infections to those who will be imminently exposed to the risk and so require protection as quickly as possible. Active immunisation against both hepatitis A and B viruses has only been recognised within the last 20 years. During this time clinical studies have demonstrated the safety and efficacy of administering the monovalent hepatitis B vaccine by way of accelerated schedules. There are now several accelerated schedules of administration of hepatitis B vaccine which can be tailored to the needs of the individual at risk of exposure to infection. One such schedule allows the primary course to be administered within a period of 1 month. This schedule of day 0, 7 and 21, with a booster at 12 months, is licensed for use with the recombinant hepatitis B vaccine Engerix B and results in a seroprotection rate of 65% at day 28 which increases to 99% at month 13. In more recent years, the development of a multivalent or combination vaccine against hepatitis A and B (Twinrix) has been a welcome advance in the protection against viral hepatitis, and has been of particular benefit to those who are at risk of infection with both viruses. The advantages of accelerated schedules have also been recognised with this combination vaccine. The primary course may be administered within a period of 1 month so providing protection for those at risk and, in particular, the last minute traveller.

**Vaccine associated adverse events**


Since the early 1990s, several cases of demyelinating diseases were reported in France in association with the vaccination against hepatitis B. A large scientific, regulatory, and public debate took place to reassure the growing concern of the population. The
objective of this paper is to examine the decision process undertaken both in France and in Italy; to outline the main findings of the studies conducted before and after the French decision to suspend the vaccination campaign among adolescents; and to describe the contribution of systematic review and causality criteria in the evaluation of the risk-benefit profile of vaccines. Even on the basis of the early findings, which appeared to be compatible with a low increase in the risk associated with the vaccination, it was apparent that the risk-benefit profile was unchanged for newborns, and was essentially unchanged for adolescents and for high-risk adults. The availability of subsequent negative association studies provided further reassurance. It is essential to rely on well-conducted systematic reviews to produce valid and reliable estimates of the risk-benefit profile.


Hepatitis B vaccines (HBVs) are composed of highly purified preparations of hepatitis B virus surface antigen (HBsAg). An adjuvant, either aluminium phosphate or aluminium hydroxide, is added to the vaccines, which are sometimes preserved with thiomersal. In placebo-controlled studies, common side effects other than local reactions were reported no more frequently among vaccine recipients than among individuals receiving a placebo. A number of controversial adverse events have, however, been purported to be associated with HBVs, including rheumatoid arthritis (RA), diabetes, demyelinating diseases (e.g., multiple sclerosis [MS]), chronic fatigue syndrome, and more recently, lymphoblastic leukaemia. In addition, the safety of the thiomersal and aluminium contained in the vaccine has also been under close scrutiny. These issues have been reviewed by a number of country-specific or international independent review committees such as that of the US Institute of Medicine (IOM) and the World Health Organization's (WHO) Global Advisory Committee on Vaccine Safety (GACVS). Upon review of the scientific evidence, none of the serious allegations have so far been confirmed. On the contrary, scientific evidence has accumulated to disprove many of the allegations. In particular, the IOM committee has concluded that the evidence favoured rejection of a causal relationship between HBV administered to adults and incident MS or MS relapse. Whilst it is important to continue monitoring some of the safety issues, there is no evidence to suggest that the WHO should consider altering its recommendation that all countries should have universal infant and/or adolescent immunisation programmes. The risks of hepatitis B vaccination are only theoretical in comparison with clear benefits in terms of cirrhosis and cancer prevention, and the HBV remains one with an excellent safety profile.


The possibility that hepatitis B vaccine may cause or exacerbate multiple sclerosis stems from several case reports of onset or recurrence of symptoms of CNS demyelination shortly following vaccination. It is difficult, however, to infer causation from individual case reports since they may simply represent coincidental temporal
associations with vaccination. There is only weak, nonspecific evidence to support the biological plausibility of an association between hepatitis B vaccine and multiple sclerosis. Epidemiological studies have found that hepatitis B vaccine does not increase the risk of developing multiple sclerosis or cause exacerbations. The US Institute of Medicine and other review panels have concluded that the evidence favors rejection of a causal association between hepatitis B vaccine and multiple sclerosis.

Cost-effectiveness of immunization against Hepatitis B


The methods that have been used to estimate the clinical and economic impact of vaccination programmes are not always uniform, which makes it difficult to compare results between economic analyses. Furthermore, the relative efficiency of vaccination programmes can be sensitive to some of the more controversial aspects covered by general guidelines for the economic evaluation of healthcare programmes, such as discounting of health gains and the treatment of future unrelated costs. In view of this, we interpret some aspects of these guidelines with respect to vaccination and offer recommendations for future analyses. These recommendations include more transparency and validation, more careful choice of models (tailored to the infection and the target groups), more extensive sensitivity analyses, and for all economic evaluations (also nonvaccine related) to be in better accordance with general guidelines. We use these recommendations to interpret the evidence provided by economic evaluation applied to viral hepatitis vaccination. We conclude that universal hepatitis B vaccination (of neonates, infants or adolescents) seems to be the most optimal strategy worldwide, except in the few areas of very low endemicity, where the evidence to enable a choice between selective and universal vaccination remains inconclusive. While targeted hepatitis A vaccination seems economically unattractive, universal hepatitis A vaccination strategies have not yet been sufficiently investigated to draw general conclusions.