Strategies for hepatitis B immunisation

There are an estimated 300 million hepatitis B virus (HBV) carriers world wide. In areas of high prevalence such as SE Asia and Africa up to 20% of the population are carriers, whereas in Western Europe and North America the carrier rate is 0.5% or less. Chronic HBV infection is an important cause of death from chronic liver disease and hepatocellular carcinoma.1

In the last decade, two hepatitis B vaccines have been licensed for use in Great Britain. The plasma derived vaccine proved efficacious2 and became commercially available in 1982. Studies of the molecular biology of the hepatitis B genome led to the development of a recombinant vaccine3 which was licensed in 1986. Both vaccines are similar in cost, safety and efficacy. There was considerable optimism after the introduction of immunisation that the prevalence of this world wide infection problem and its complications of chronic liver disease and hepatocellular carcinoma would be reduced. Indeed, in developing countries where immunisation has been introduced the prevalence of hepatitis B infection is falling,4 when in some industrialised countries the incidence has recently increased in certain groups.5

There is a continuing need to reassess appropriate immunisation strategies which will vary according to the HBV prevalence rates in different parts of the world. The current trend in developing countries is mass immunisation of infants, and in industrialised countries to target and immunise high risk groups. New approaches are required for those who fail to respond to the vaccine and guidance is also needed on the timing of booster doses.

Zones of high hepatitis B endemicity
Vaccination strategies in highly endemic countries depend on the indigenous pattern of hepatitis B transmission. There are two main transmission patterns.

SOUTH EAST ASIA
In SE Asia, where the HBV carrier rate is approximately 15%, the predominant mode of transmission is vertical (from mother to child at or around the time of birth) and this accounts for 30 to 50% of the HBV carrier pool.6 This high transmission rate occurs because up to 40% of HBV positive mothers show active viral replication (HBV DNA and HBeAg positive) and in these mothers HBV transmission to their infants approaches 90%. Horizontal transmission is less frequent and occurs especially among young children. It is obvious that immediate protection of the newborn infant is essential and can be achieved by a combination of hyperimmune hepatitis B globulin and vaccination. The incidence of hepatitis B in the children of HBeAg positive mothers can be reduced from the expected value of 90% to 5%.7 In Taiwan a nationwide vaccine programme was introduced in 1984.4 This involved screening mothers for HBV surface antigen (HBsAg) and vaccinating infants born to HBsAg carrier mothers either with the plasma derived vaccine (administered at one, five, nine weeks and 12 months of age), or the combination of hyperimmune globulin (within 24 hours of birth) and vaccine if mothers were HBsAg and HBeAg positive. This was extended to all newborn infants in 1986, as mass vaccination of infants without previous screening was shown to be cost effective in Taiwan. The programme is now being extended to other susceptible groups such as school children, medical personnel, and close contacts of HBsAg carriers.

A fall in prevalence of hepatitis B in Taiwan has been documented following mass immunisation. Epidemiological studies in Taipei (Taiwan) showed a fall in HBsAg carrier rates among children from 10% to 2% after a five-year vaccination programme.4 A major limiting factor is expense, particularly the hyperimmune hepatitis B globulin. Although initial studies have shown that the combination of vaccination and hyperimmune hepatitis B globulin was superior at preventing perinatal transmission than vaccination alone, high protective rates of 91% have recently been achieved with vaccine alone.8 In contrast with the Taiwan programme the first dose of vaccine was administered within 12 hours of birth and subsequent doses at one, two, and 12 months.

What about the need for booster doses of vaccine? A five year follow up study in Taipei of 1000 immunised infants born to HBeAg positive mothers showed a low rate of infection with <1% children becoming chronic hepatitis B carriers.9 Most of the acute infections were subclinical and characterised by a natural anti-HBs booster phenomenon and seroconversion to anti-HBc. In this population at least with a high natural background of HBV infection, booster doses of vaccine are likely to be of little benefit and probably not cost effective. After introduction of mass immunisation in Taiwan, more than 20 other countries of high endemicity have developed similar programmes. A fall in the incidence of cirrhosis and hepatocellular carcinoma can be anticipated.

AFRICA AND MIDDLE EAST
Hepatitis B is highly endemic in all parts of sub Sahara Africa, North Africa, and the Middle East and the predominant mode of transmission is horizontal amongst infants and young children.10 The limited data available indicate that perinatal transmission occurs less frequently (10–20%) because a smaller percentage of carrier mothers show active viral replication (HBeAg and HBV DNA positive). Infection rates increase rapidly from the age of six months, however, and by two years of age, 40% of children in one study had already been infected with the hepatitis B virus.11 The precise modes of transmission are not fully understood, but cuts and serous exudates have been implicated12 and circumcision, scarification and insect vectors (although not confirmed) are other possibilities. There is, therefore, no need for immediate immunisation at birth that is essential in SE Asia, and administration of expensive hyperimmune hepatitis B globulin is inappropriate.

The WHO sponsored Expanded Programme of Immunisation aims to immunise all infants against the common infectious diseases of childhood. Hepatitis B vaccine was previously too expensive for inclusion in this programme. Recent production of local vaccines in some countries and bulk government purchase in others, however, has resulted in falling costs, and a highly cost effective $1 per dose will soon be achieved. Recent data demonstrate that polio, diphtheria, tetanus, pertussis and hepatitis B vaccines can all
be effectively immunogenic when administered together. Incorporating the hepatitis B vaccine into the Expanded Programme of Immunisation should help to ensure widespread acceptance and compliance.

Gambia was the first African country to initiate a major vaccination programme and incorporate the vaccination schedule into the Expanded Programme of Immunisation. The first dose of vaccine was administered about one week after birth. Access to infants before this proved difficult as most births occurred unsupervised at home. Ninety eight per cent of children received the first dose and 74% completed the course of four injections. At one year of age only two of 710 children had become chronic HBV carriers, 57 had HBC antibody probably indicative of natural infection. The uptake and protective immunisation of this programme in Gambia is comparable to those achieved in the Taiwan programme.

The Middle East and North Africa have similar epidemiological patterns of HBV infection to sub Sahara Africa, where horizontal transmission among young children is common. Therefore hepatitis B immunisation should be integrated into the Expanded Programme of Immunisation. An important consideration here is the high prevalence of schistosomiasis. The immune response to hepatitis B vaccination of neonates born to mothers infected with schistosomiasis is impaired.

EUROPE AND NORTH AMERICA

There are marked regional variations in the prevalence of hepatitis B carriers necessitating different strategies at a regional level. In the United Kingdom and northern Europe the prevalence is <0.1%, whereas in southern Europe it is 1–15% with southern Italy having the largest pool of hepatitis B carriers. In the UK and North America immunisation is currently aimed at ‘high risk groups.’ These include homosexuals, intravenous drug abusers, health care workers in contact with patients with hepatitis B or their blood, individuals working in institutions for the mentally handicapped, infants born to HBsAg positive mothers, immigrants from high prevalence areas and family members of HBsAg carriers. Guidelines for immunisation are published annually. Uptake of the vaccine by at risk groups in the UK, however, has been less than satisfactory. Many health care workers are still not being immunised because of anxiety about adverse reactions and unfounded fear of HIV transmission. Improved educational programmes and counselling are required. A case has been made for routine screening of pregnant mothers in the UK for HBsAg, so that infants born to HBsAg or HBV DNA positive mothers can be immunised. Only 0.5% of mothers tested were HBsAg positive, however, and many were from endemic areas or belonged to an at risk group. Such an approach is unlikely to be cost effective except in certain inner city areas where the prevalence of HBV carriers is high.

Since the introduction of vaccination, the incidence of acute hepatitis B has fallen in all at risk groups in the UK. Acute hepatitis B in the United States, however, is increasing among intravenous drug abusers and homosexuals. The control of hepatitis B in the college and university populations and in educational programmes, but undoubtedly the AIDS epidemic has led to a reduction in high risk sexual behaviour. In health care workers the change is probably related to vaccination although more stringent precautions with blood products may have played a part. The increase in drug addicts and homosexuals in the United States reflect that little change has occurred in high risk behaviour among drug addicts despite educational programmes and in addition this group of individuals is difficult to identify and approach for vaccination. Heterosexual transmission of hepatitis B is increasing in the United States. Those with multiple partners and those with a history of other sexually transmitted diseases are at increased risk independent of other risk factors. This group is particularly difficult to target for vaccination as heterosexuals do not regard themselves as being at high risk. Even if all high risk groups could be successfully targeted and immunised, there are still 30 to 40% of hepatitis B carriers who have no apparent risk factors. Therefore mass vaccination of the whole population is being discussed.

Southern Europe has a higher prevalence of hepatitis B (1 to 15%). Cost benefit analysis has shown that where the prevalence of HBV carriage exceeds 2% then mass vaccination of infants becomes cost effective. Italy instituted a national programme against hepatitis B in 1988. This included vaccination of all newborn babies of HBsAg carrier mothers, household contacts of HBsAg carriers and all neonates in communities such as Naples where the prevalence of hepatitis B carriers exceeds 8%. In this area the government provides vaccination free of charge and all newborn infants are being vaccinated.

HEPATITIS B MUTANT

One important new factor in the Mediterranean is the recent discovery of a hepatitis B escape mutant. Healthy individuals including infants, who responded adequately to vaccination with anti-HBs titres greater than 10 IU/ml became infected with hepatitis B. Sequencing of the viral genome in one infant who developed serious liver disease revealed a point mutation in the S region of the genome, which is normally highly conserved. Recombinant vaccines including the sequence of this mutant strain will be required to prevent further emergence of this virus.

Areas for improvement

DOSE AND FREQUENCY

The optimum dosage and frequency of vaccination need to be formulated. The dosage depends on the type of vaccine used: 10 µg of the recombinant and 20 µg of the plasma derived are currently recommended for adults with half dosage for infants. Two frequency regimes are practised in the UK: immunisation at 0, 1, 6 months and 0, 1, 2 and 12 months. The latter is given when a quicker antibody response is required – for example, travellers visiting endemic areas. Different regimens, however, are being practised throughout the world. More up to date immunogenic vaccines may help compliance by reducing the number of injections required. Hepatitis B vaccine is administered intramuscularly into the deltoid muscle. Intradermal injection has the cost advantage of using a much smaller dose. It is more difficult to administer, however, and the antibody response is unreliable. Also the same dose of intramuscular vaccine is of comparable immunogenicity.

POOR RESPONDERS TO VACCINATION

There are a small number of hypo and non-responders to hepatitis B vaccination. Approximately 5% of healthy individuals under the age of 40 and up to 50% of individuals with chronic renal failure, alcoholic liver disease, HIV disease and the elderly, will fail to mount a sufficient antibody response. A more immunogenic vaccine may improve the seroconversion rate. The different mechanisms underlying non-respondiveness are not yet well understood. A T-cell abnormality has been postulated and the inclusion of the pre-S2 protein in the vaccine (see below) may activate T-cells and circumvent non-respondiveness. A metabolic monocyte defect preventing interleukin-2 production in an immunosuppressed population may account for non-
responsiveness. Antibody response in haemodialysis patients may be augmented by the addition of interleukin 2. Genetic predisposition to non-responsiveness has been shown in association with the haplotype HLA B8 SC01 DR3 possibly because of an absent dominant immune response gene in the major histocompatibility complex. IMPROVED VACCINES

The current vaccines, plasma derived and recombinant contain only the S protein of the hepatitis B virus. Recent data suggest that the pre-S2 and pre-S1 domains induce protective antibodies. Immunisation of mice with the S and pre-S2 protein showed the pre-S2 to be significantly more immunogenic than the S region and the combination of the S and pre-S2 protein can circumvent non-responsiveness to the S region. Similarly the pre-S1 is immunogenic at the T cell level in man. Trials are under way to evaluate the immunogenicity of vaccines containing various combinations of pre-S1, pre-S2 and S proteins. Other vaccine developments have been reviewed recently.

NEED FOR BOOSTER VACCINATIONS

The duration of protection is unknown. After a full vaccination course, there is a decline in the anti-HBs titre which is related to the original peak titre of anti-HBs obtained. Attempts to predict the rate of decline have not been wholly successful, hence the timing of booster vaccinations is uncertain. This is because hepatitis B infection has occurred with low levels of anti-HBs, but fortunately seldom leads to clinical disease or a chronic carrier state. Booster doses are associated with a brisk antibody response within a few days, even when antibody levels have fallen below 10 IU. Strategies for booster doses need to be formulated. Options include (i) no booster and reliance on immunological memory, (ii) give booster doses to all vaccinated individuals at three to five year intervals or (iii) test anti-HBs levels and give booster doses when antibody levels fall below 10 IU. At present only options two and three are justifiable and the third option is the most appropriate but the most expensive. The option selected will vary in different parts of the world according to available resources.

Optimism for the future control of hepatitis B in developing countries where mass vaccination programmes have been implemented is justified. In some such areas the incidence of hepatitis B is already declining but an effect on chronic liver disease and hepatic carcinoma may take several decades to become apparent. Unless current vaccination strategies in Europe and North America are improved it is unlikely that the disease incidence will fall in these areas.

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Addendum

Since this article was written, further data have appeared. Two further studies from areas of high HBV prevalence have assessed the long term follow up (four to seven years) of HBV vaccines, and confirm the very low rate of chronic HBV infection in vaccinees and that the occurrence of acute HBV infection was subclinical.

Schoub et al reported the practical difficulties encountered in distributing HBV vaccine in Transvaal, South Africa, using the vaccination schedule corresponding to the standard Expanded Programme of Immunisation, adding further support for a multivalent vaccine which includes hepatitis B.

Coursaget et al suggested a schedule of revaccination based on the anti-HBs titre at the time of the booster dose at month 13 of a primary vaccination schedule. The anti-HBs titre decline with time was found to be a logarithmic function. It remains unclear, however, whether booster doses are in fact necessary as the incidence of overt or chronic HBV infection appears extremely low in the presence of low or undetectable titres of anti-HBs.

33. Stevens CE, Buynak EB.
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