Hepatitis B Vaccination in Childhood
A briefing from the Board of Science
Updated May 2010

Background
There have been a number of BMA resolutions regarding hepatitis B vaccination, the most recent at the 2007 ARM:

That this Meeting acknowledges the call by the World Health Organisations to provide hepatitis B vaccines to all children and calls upon the Department of Health to introduce the hepatitis B vaccine into the childhood schedule without further delay. (ARM, 2007)

The BMA Board of Science produced a briefing paper in 2005, Hepatitis B Vaccination in Childhood, which outlined the case for universal vaccination of infants against hepatitis B. This report is an update of the 2005 briefing note.

The Board of Science wrote to the Joint Committee on Vaccination and Immunisation (JCVI) in 2005 and 2007 calling for universal hepatitis B vaccination in the UK. The JCVI reviewed the case for universal hepatitis B vaccination in 2005 and 2009, and concluded that there was insufficient evidence for the cost-effectiveness of a national hepatitis B vaccination programme. In April 2010, Board of Science representatives met with Sir Mike Richards, National Clinical Director for Cancer, to discuss hepatitis B vaccination in children, and the feasibility of implementing local vaccination programmes, particularly in areas of high incidence, as a means of reducing local hepatitis B prevalence and gathering further evidence on the effectiveness of a hepatitis B vaccination programme.

What is hepatitis B?
Hepatitis B (HBV) is a bloodborne viral infection that affects the liver. Many people with HBV infection have no symptoms at all and do not know that they are infected. Others have ‘flu-like’ symptoms and develop yellowing of the skin and eyes (jaundice). In most cases HBV infection can only be identified by a serological test. A person will go on to develop chronic HBV infection if they fail to clear the infection after six months, and will be at risk of cirrhosis and liver cancer. Two billion people worldwide have serological evidence of past or current infection.¹

Acute hepatitis B incidence is proportional to age, and occurs in one per cent of infant, 10 per cent of early childhood (1-5 years) and 30 per cent of late (>5 years old) HBV infections. Chronic HBV infection is inversely related to age and occurs in 90 per cent of infant, 30 per cent of early childhood and six per cent of late infections. Risk of premature death is 15-25 per cent in people with chronic HBV infection.² Treatment for HBV infection is with interferon alpha 2-b antiviral drug. The drug is very expensive, has severe side effects, high relapse rates, and not all patients are suitable for treatment.³

How is hepatitis B infection spread?
¹Hepatitis B virus is transmitted by contact with blood or body fluids of an infected person in the same way as human immunodeficiency virus (HIV), the virus that causes AIDS. HBV is 50 to 100 times more infectious than HIV⁴.

Transmission can occur in the following ways: mother-to-infant, child-to-child, unsafe injection practices, blood transfusions, and sexual contact. In the UK, those most at risk are health care workers, dialysis patients, injecting drug users, household and sexual contacts of people with chronic HBV infection, people with multiple sexual partners, and people whose country of birth has high HBV prevalence.⁵

Why is hepatitis B infection serious for babies?
Without vaccination, many babies born to mothers who are HBV carriers will become infected. As many as 9 out of 10 babies infected at birth develop long lasting infection and these babies are at risk of developing serious liver disease in adult life. Once infected, they can pass on infection to their close family and other contacts.⁴
**How can hepatitis B be prevented?**

Vaccines to prevent HBV (HepB vaccines) have been available since 1982 and are highly immunogenic.\(^5\) The complete vaccine course of three doses is effective in over 95 per cent of infants, children and adolescents, 90 per cent of adults over 40 years of age and in 65-75 per cent of adults over 60 years of age.\(^5\) Worldwide surveillance data confirms that the vaccine is very safe and has very few side effects. The cumulative data indicate that the vaccine confers lifelong protection.

The HepB vaccine is available as a monovalent vaccine or in combination with other vaccines: DTwP or DTaP (diphtheria, tetanus and pertussis), Hib (Haemophilus influenzae type b), hepatitis A or IPV (polio). There is evidence that Hib immunity is reduced in the combined HepB/Hib vaccine (Infanrix-Hexa) compared to the monovalent Hib vaccine (Pediacel) currently in use.

In 1992, the World Health Organisation (WHO) recommended that all countries implement universal HepB vaccination programmes as part of national infant immunization schedules. By 2008, 177 (84%) of WHO member states include HepB vaccination in national infant immunization schedules, compared with only 31 countries in 1992.\(^5\) This is an important part of the global effort to eradicate an infection that causes liver failure and cancer.

Low prevalence countries (with <2% chronic HBV infection) that have already implemented the HepB vaccine for infants include:
- Andorra, Australia, Austria, Belgium, Canada, Czech Republic, Estonia, France, Germany, Germany, Greece, Israel, Italy, Latvia, Luxembourg, Malta, Monaco, New Zealand, Poland, Portugal, San Marino, Slovakia, Spain, Switzerland, Turkey, and the United States.\(^7,8\)

Low prevalence countries that have not introduced universal HepB vaccination of infants include:
- Denmark, Netherlands, Switzerland, Sweden, Norway, Finland, Ireland, Iceland, Japan and the UK.\(^6,8\)

**What is the hepatitis B vaccination status for children in the UK?**

The UK is one of the few developed countries that have not implemented universal neonatal HBV immunisation. Because the burden of HBV in the UK is relatively low, a policy of immunisation of newborns of carrier mothers and those in high-risk groups has been followed. This approach has limited impact as it fails to identify a large proportion of those at risk and it also ignores the increase in international travel, the rise of HBV and the high rates in some areas of this country. It is time that the policy is reviewed in the light of experience with this selective immunisation policy, the data on efficacy of universal immunisation from other countries, and the proven safety of recombinant vaccines.\(^9\)

Both the rise in the incidence of HBV infection in high risk groups, particularly evident in outbreaks among injecting drug users,\(^10\) and the increase in prevalence of HBV attributable to immigrants and asylum seekers, suggest that greater attention to prevention of infection is required.\(^11\)

Health Protection Agency (HPA) Cover of Vaccination Evaluated Rapidly (COVER) data from 2007 indicate 90 per cent of infants whose mothers are HBV carriers received the birth vaccine dose, but only 30-40 per cent completed the vaccine course.\(^12\)

**When should babies have the hepatitis B vaccine?**

Babies born to mothers who are known carriers should have the first dose of vaccine within 24 hours of birth. Under a universal immunisation policy all other babies should complete a course of vaccine during the first year of life. It is essential that babies receive the full course of vaccine for it to be effective.

**Is the hepatitis B vaccine safe?**

The vaccine is safe and millions of doses have been given to infants worldwide without serious side effects. In some babies the site of the injection may become red and swollen, but this does not last for long.
In the last two decades concerns have been raised that HepB vaccine may be associated with the development of the neurological disorder multiple sclerosis (MS). These concerns have been investigated at length, and numerous scientific studies and expert panel reviews have failed to find a link between the HepB vaccine and MS.

The studies on HepB vaccine and MS have been reviewed by the World Health Organisation Global Advisory Committee on Vaccine Safety. It states that ‘multiple studies and review panels have concluded that there is no link between MS and HBV vaccination’. The WHO also affirms that the recent study by Hernán and colleagues does not provide sufficient evidence to link HBV vaccination to MS, and does not justify discontinuation or modification of HBV vaccination programmes.

In addition, a review by the Institute of Medicine Immunisation Safety Review Committee in 2003 found that there was no link found between HepB vaccine and certain neurological disorders such as MS. A systematic review from the Cochrane Vaccines Field in 2003, also found no evidence of an association between HepB vaccine and MS. Recent statements by the US Centres for Disease Control, and the National Network for Immunisation Information support this position.

For further detail on this and other references relating to HepB vaccine safety please refer to the briefing from the National Centre for Immunisation Research and Surveillance (NCIRS).

Introduction of hepatitis B vaccine: Italy
Italy was the first low prevalence country to introduce universal vaccination against HBV. Following the collection of epidemiological data on age-specific incidence rates of infection, a law was passed in 1991, which established mandatory immunisation of neonates and 12-year-old adolescents. The first data on compliance with vaccination, both in infants and in adolescents, indicated the success of the programme, which was helped by good vaccination delivery services and awareness of the risks of HBV both in physicians and the public.

After ten years of routine HepB vaccine introduction in Italy, evidence on the epidemiological impact of universal immunisation indicated that the universal immunisation strategy was successful. Coverage is on average >90% and is >or=95% in many areas of Italy. Incidence of acute HBV, already declining before 1991, was further decreased by the routine vaccination programme. Furthermore, passive surveillance of adverse events following HepB vaccination supported the excellent safety record of HepB vaccines.

Universal vaccination
WHO recommends universal HepB vaccination in infants, including in low prevalence countries as a significant proportion of chronic HBV infections are acquired through transmission in childhood. The UK is one of only a few countries in the world that does not have a universal HepB vaccination programme in the infant immunization schedule.

There are also positive reasons for low-incidence countries such as the UK to implement a programme of universal vaccination, based on the ethical presumption that where a potentially devastating disease is easily preventable, those at potential risk should be protected, particularly where the infection is on the increase and will carry on in that direction unless a universal immunisation programme is introduced.

Cost effectiveness of universal vaccination
As of April 2009, the Secretary of State for Health in England is required to accept the recommendations of the JCVI, under the Health Protection (Vaccination) Regulations 2009. The recommendations must "be based on an assessment which demonstrates cost effectiveness".

The JCVI recognise universal HepB vaccination of infants over selective targeting as the optimal vaccination strategy for the UK, but do not recommend it due to its cost effectiveness. Their view is that universal vaccination may become cost effective if it is delivered as part of the childhood vaccination programme, and if a suitable combined vaccine becomes available. Central purchase of vaccine would also further reduce costs. They also note that any factors perceived by the public as a possible risk (the link to MS, for example) had the potential to compromise the infant programme.
In 2005 the JCVI reviewed the evidence on cost effectiveness of a universal HepB vaccine programme, and concluded that there was insufficient evidence. The committee reviewed the evidence again in 2009, and concluded that a universal infant or child vaccination policy would not be cost effective, but neither is the current selective infant vaccination strategy:

“The committee was presented with a paper, peer review comments and a response from the authors on the introduction of a hepatitis B vaccine programme. The authors of the paper concluded that at current vaccine prices neither a universal infant programme, universal adolescent programme nor selective infant vaccination programme (i.e. one targeting geographically intermediate/high risk ethnic populations – similar to that in place for BCG) would be considered cost-effective in the UK.

“The committee agreed that at this point in time it could not recommend the use of hepatitis B vaccines in a universal infant, universal adolescent or selective infant vaccination programme.”

The costs associated with the selective vaccination programme in the UK – in terms of delivery of the vaccination programme and the treatment of patients with chronic HBV – are substantial but difficult to assess. In addition, the JCVI note that the selective programme may be necessary to continue in parallel with the universal vaccine approach for approximately 20 years after the universal approach was adopted.

**Peer-reviewed studies**

There are very few published studies that have assessed the cost effectiveness of a universal HepB vaccination programme. The NHS Economic Evaluation Database notes that no existing study designs match the situation in the UK exactly. Most studies found that universal vaccination of either infants or children was the most cost effective option, compared to selective or no vaccination strategies, but results are heavily dependent on modelling assumptions.²¹

In a 2008 study using data from Ireland, Tilson et al concluded that universal vaccination would be cost effective, in particular if using the combination vaccines (€37,000 cost per life year gained).²²

In a study using UK data, published in 1996, Fenn et al reported that 80 per cent of deaths from HBV infection could be avoided through an infant vaccination programme in the UK, using the Engerix B monovalent HepB vaccine. The researchers compared universal infant, child and adolescent vaccination strategies to the current selective strategy, and found that universal infant vaccination was the most cost effective option (£37,000 – 102,000 cost per life year gained, depending on the assumptions in the model). The authors noted that administrative saving from incorporating the vaccine into current infant immunization procedures might also contribute to cost effectiveness.²³

In an Australian study, Harris et al (2001) also found that a universal vaccination strategy using the combined Hib/HepB vaccine would reduce HBV infection by 77%, and was cost effective compared to selective vaccination ($12,000 cost per life year gained).²⁴

Zurn et al (2000) compared several universal vaccination strategies (infants, children, adolescent, all) to selective vaccination and found that vaccination of children was the most cost effective option.²⁵

Williams et al (1996) evaluated different vaccination scenarios based on UK HBV incidence data, and concluded that universal infant vaccination was less cost effective per dose than vaccination of infants after antenatal serological screening of HBV infection mothers.²⁶

**The selective targeting vaccination approach**

Evidence from the HPA and JCVI indicate that the selective targeting approach in the UK is not effective in controlling HBV infection. There are difficulties in identifying and targeting people at risk of HBV infection in the UK on an individual and regional level. A significant number of new infections are not covered by the selective targeting approach, and the effectiveness of the selective approach varies significantly across PCTs.²⁷

Pregnant women at greatest risk of infection and transmission to their infants often fail to attend prenatal clinics, and their infants fail to complete the HepB vaccination course. Vaccination in other high
risk groups is underused, and failure rates for completing the vaccination course are high. In 2005, 16 per cent of births registered in England were to mothers born in countries with high HBV prevalence, and four per cent to fathers from high prevalence countries (HPA). A quarter of PCTs in England have over 20 per cent of births registered to one or more parent born outside of the UK, and these PCTs are more likely to benefit from a universal HepB vaccination programme locally.\(^{19}\)

In the Netherlands, the HepB vaccine is given to children where one or both parents come from countries with high HBV infection prevalence, and the JCVI have shown interest in this approach for the UK.

**Epidemiological data: Worldwide**

An estimated 350 million people worldwide (5\% of the world’s population) are chronic carriers. About a quarter of these carriers will develop serious liver disease, including chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma\(^{28,30}\) which results in more than one million deaths each year.\(^{24,25}\) HBV also causes 16 million healthcare related infections in the tropics every year, and 620,000 deaths annually worldwide.\(^{31,32}\)

HBV is prevalent in Africa and South East Asia, with rates of current or past infection as high as 50-80 per cent. Death from cirrhosis or hepatoma occurs in up to one third of carriers who acquired HBV perinatally.\(^{33}\)

‘High rates of chronic HBV infection are also found in the Amazon and the southern parts of Eastern and Central Europe. In the Middle East and Indian sub-continent, about five per cent are chronically infected. Infection is less common in Western Europe and North America, where less than one per cent are chronically infected. Young children who become infected with HBV are the most likely to develop chronic infection. About 90 per cent of infants infected during the first year of life and 30 to 50 per cent of children infected between 0 to 4 years of age develop chronic infection. The risk of death from HBV-related liver cancer or cirrhosis is approximately 25 per cent for persons who become chronically infected during childhood’.\(^{34}\)

**Epidemiological data: UK**

The Department of Health estimates that the prevalence of chronic HBV infection is 0.3 per cent, and there are approximately 180,000 people chronically infected with HBV in the UK.\(^{35}\) Ethnic minorities and immigrant populations have prevalence similar to their country of origin. ‘In addition, there are at least 1,300 cases of symptomatic acute hepatitis B each year and 7,700 new cases of chronic hepatitis B. Of these new chronic cases, around 300 people were infected within this country, while the remainder, some 96 per cent, have entered this country, generally from areas of high prevalence where HBV is frequently transmitted from mother to child. Many people with asymptomatic infections are also infectious, and quite often remain undiagnosed until they present with overt disease’.\(^{36}\)

The HPA estimate that 3,780 new HBV infections occur per year, with 269 progressing to chronic carrier status in England and Wales (HPA). In addition, the HPA estimate a net immigration of 6,571 people with chronic HBV infection annually. Rates of infection are likely to rise with increases in foreign travel and the impact of migration.\(^{37}\)

Of infections acquired in the England and Wales, under 50 per cent are acquired from injecting drug users and men who have sex with men (MSM). The cause of transmission in the remainder of new infections is unknown, but is likely to be mother-to-infant, heterosexual transmission, and travel to countries with high HBV infection prevalence.

**England and Wales – HBV notifications**\(^{38}\)

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<tr>
<th>Year</th>
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<tr>
<td>1992</td>
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<td>2003</td>
<td>1151</td>
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**Northern Ireland (laboratory reports of Hepatitis B)**\(^{39}\)

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<th>Year</th>
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<tr>
<td>1992</td>
<td>34</td>
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<td>2003</td>
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**Scotland**
In 2002, 354 cases of HBV infection were reported by laboratories to the Scottish Centre for Infection and Environmental Health (SCIEH); in 2000 and 2001, 360 and 357 cases were reported respectively. Of the 354 reports in 2002, 37 mentioned injecting drug use as the patient’s principal risk factor.

There are no robust estimates of how much treatment of chronic hepatitis B (CHB) costs the NHS. Of countries for which burden of disease estimates are available, the country with prevalence and population closely matching that of the UK is Germany. Harbarth et al (2000) estimated the total cost of HBV in Germany to be £589 million. The burden of CHB to any country depends crucially, however, on its population and the prevalence of hepatitis B.40

Hepatitis B and travel
As destinations become more diverse, with people increasingly travelling outside Europe the opportunity for HBV transmission is much greater. As such, HepB vaccine should also be considered for a wider range of travellers, including those who may travel to areas endemic for HBV, may be exposed by virtue of their sexual practices, or may be exposed to unscreened or inadequately screened blood or blood products or inadequately sterilised medical and surgical equipment.41

Summary: the case for universal vaccination against hepatitis B
Worldwide, over 2 billion people have past or current HBV infection. 350 million people are chronic carriers, are infectious and at risk of cirrhosis and liver cancer, and premature death. Treatment options for patients with acute or chronic HBV infection are limited and expensive.

The WHO recommends universal infant vaccination in all countries as the most effective method to reduce the burden of HBV infection. While chronic HBV infection is relatively low in the UK, there are still significant health care costs associated with treatment, and in identifying and targeting people most at risk. Selective targeting strategies for HepB vaccination have not been effective in the UK.

As of April 2009, the Secretary of State for Health in England is required to accept the recommendations of the JCVI, under the Health Protection (Vaccination) Regulations 2009. The recommendations must “be based on an assessment which demonstrates cost-effectiveness”. The JCVI recognises universal vaccination of infants as the preferred method of vaccination in the UK, but do not recommend this approach due to cost effectiveness. There is limited data regarding cost effectiveness of universal vaccination relative to selective vaccination strategies, but data suggest that universal vaccination of infants is a more cost effective option than selective targeted vaccination of high risk groups.

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A briefing from the BMA Board of Science

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