18

Hepatitis B

NOTIFIABLE

The disease

Hepatitis B is an infection of the liver caused by the hepatitis B virus (HBV). Many new infections with hepatitis B are sub-clinical or may have a flu-like illness. Jaundice only occurs in about 10% of younger children and in 30 to 50% of adults. Acute infection may occasionally lead to fulminant hepatic necrosis, which is often fatal.

The illness usually starts insidiously – with anorexia and nausea and an ache in the right upper abdomen. Fever, when present, is usually mild. Malaise may be profound, with disinclination to smoke or to drink alcohol. As jaundice develops, there is progressive darkening of the urine and lightening of the faeces. In patients who do not develop symptoms suggestive of hepatitis, the illness will only be detected by abnormal liver function tests and/or the presence of serological markers of hepatitis B infection (e.g. hepatitis B surface antigen (HBsAg), antiHBc IgM).

The virus is transmitted by parenteral exposure to infected blood or body fluids. Transmission mostly occurs:

- through vaginal or anal intercourse
- as a result of blood-to-blood contact (e.g. sharing of needles and other equipment by injecting drug users (IDUs), 'needlestick' injuries)
- through perinatal transmission from mother to child.

Transmission has also followed bites from infected persons, although this is rare. Transfusion-associated infection is now rare in the UK as blood donations are screened. Viral inactivation of blood products has eliminated these as a source of infection in this country.

The incubation period ranges from 40 to 160 days, with an average of 60 to 90 days. Current infection can be detected by the presence of HBsAg in the serum. Blood and body fluids from these individuals should be considered to be infectious. In most individuals, infection will resolve and HBsAg disappears from the serum, but the virus persists in some patients who become chronically infected with hepatitis B.

Chronic hepatitis B infection is defined as persistence of HBsAg in the serum for six months or longer. Individuals with chronic infection are sometimes

referred to as chronic carriers. Among those who are HBsAg positive, those in whom hepatitis B e-antigen (HBeAg) is also detected in the serum are the most infectious. Those who are HBsAg positive and HBeAg negative (usually anti-HBe positive) are infectious but generally of lower infectivity. Recent evidence suggests that a proportion of chronically infected people who are HBeAg negative will have high HBV DNA levels, and may be more infectious.

The risk of developing chronic hepatitis B infection depends on the age at which infection is acquired. Chronic infection occurs in 90% of those infected perinatally but is less frequent in those infected as children (e.g. 20 to 50% in children between one and five years of age). About 5% or less of previously healthy people, infected as adults, become chronically infected (Hyams, 1995). The risk is increased in those whose immunity is impaired.

Around 20 to 25% of individuals with chronic HBV infection worldwide have progressive liver disease, leading to cirrhosis in some patients. The risk of progression is related to the level of active viral replication in the liver. Individuals with chronic hepatitis B infection – particularly those with an active inflammation and/or cirrhosis, where there is rapid cell turnover – are at increased risk of developing hepatocellular carcinoma.

History and epidemiology of the disease

The World Health Organization (WHO) has estimated that over 350 million people worldwide are chronically infected with HBV. The WHO has categorised countries based upon the prevalence of HBsAg into high (more than 8%), intermediate (2 to 8%) and low (less than 2%) endemicity countries. In many high-prevalence countries, 10% or more of the population have chronic hepatitis B infection. High-prevalence regions include sub-Saharan Africa, most of Asia and the Pacific islands. Intermediate-prevalence regions include the Amazon, southern parts of Eastern and Central Europe, the Middle East and the Indian sub-continent. Low-prevalence regions include most of Western Europe and North America (see Figure 18.1).

The importance of the various modes of transmission varies according to the prevalence in a particular country. In areas of high prevalence, infection is acquired predominantly in childhood – by perinatal transmission or by horizontal transmission among young children. In low-endemicity countries, most infections are acquired in adulthood, where sexual transmission or sharing of blood-contaminated needles and equipment by injecting drug users accounts for a significant proportion of new infections. In areas of intermediate endemicity, the pattern of perinatal, childhood and adult infection is mixed, and nosocomial infection may be important.

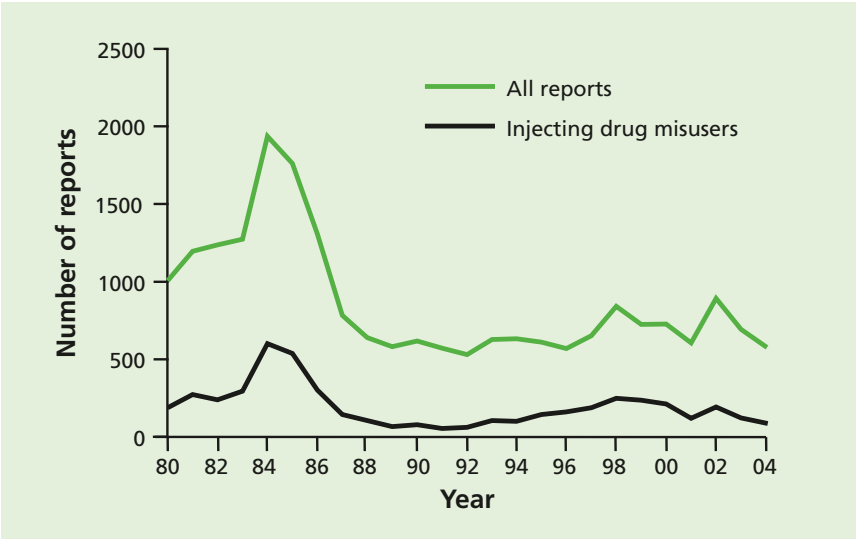

Figure 18.1 Laboratory reports of confirmed acute hepatitis B, England and Wales

The UK is a very low-prevalence country, but prevalence of HBsAg varies across the country. It is higher in those born in high-endemicity countries, many of whom will have acquired infection at birth or in early childhood (Boxall *et al*.,1994; Aweis *et al.*, 2001). This is reflected in the prevalence rates found in antenatal women, which vary from 0.05 to 0.08% in some rural areas but rise to 1% or more in certain inner city areas. Overall, the prevalence in antenatal women in the UK is around 0.14%.

The incidence of acute infection is high among those with certain lifestyle or occupational risk factors. Most reports of acute infection in the UK occur as a result of injecting drug use or sexual exposure.

Laboratory reports of acute hepatitis B to the Health Protection Agency fell from a peak of just below 2000 reports from England and Wales in 1984 to 531 reports in 1992, mainly due to a decline in cases in IDUs. The decrease was also seen in other risk groups, most probably linked to a modification of risk behaviours in response to the HIV/AIDS epidemic. Since then there has been no further fall; reports have fluctuated between around 600 and 800 cases per year. In recent years, there has been a fall in the number of reports in men who have sex with men (MSM), but a rise among IDUs. In Scotland in 2003, 87 acute infections were reported; the commonest risk factor was injecting drugs.

The hepatitis B vaccination

There are two classes of products available for immunisation against hepatitis B: a vaccine that confers active immunity and a specific immunoglobulin that provides passive and temporary immunity while awaiting response to vaccine.

The hepatitis B vaccine

Hepatitis B vaccine contains HBsAg adsorbed onto aluminium hydroxide adjuvant. It is prepared from yeast cells using recombinant DNA technology. Fendrix®, for patients with renal insufficiency, is adjuvanted by monophosophoryl lipid A, and adsorbed onto aluminium phosphate.

A combined vaccine containing purified inactivated hepatitis A virus (HAV) and purified recombinant HBsAg, separately adsorbed onto aluminium hydroxide and aluminium phosphate, is also available where protection against both hepatitis A and hepatitis B infections is required.

Thiomersal is not used as a preservative in hepatitis B vaccines available in the UK. However, thiomersal is still used in the production process for Engerix B®, Twinrix®, Ambirix® and Fendrix® and therefore, residues are present in the final product.

Hepatitis B-containing vaccines are inactivated, do not contain live organisms and cannot cause the diseases against which they protect.

There are vaccines that are effective in preventing infection in individuals who produce specific antibodies to HBsAg (anti-HBs). However, it is important that immunisation against hepatitis B does not encourage relaxation of other measures designed to prevent exposure to the virus, for example condom use and needle exchange. Healthcare workers giving immunisation should use the opportunity to provide advice on other preventative measures or to arrange referral to appropriate specialist services.

Around 10 to 15% of adults fail to respond to three doses of vaccine or respond poorly. Poor responses are mostly associated with age over 40 years, obesity and smoking (Roome *et al.*, 1993). Lower seroconversion rates have also been reported in alcoholics, particularly those with advanced liver disease (Rosman *et al.*, 1997). Patients who are immunosuppressed or on renal dialysis may respond less well than healthy individuals and may require larger or more frequent doses of vaccine.

Hepatitis B vaccine is highly effective at preventing infection if given shortly after exposure (see below). Ideally, immunisation should commence within 48 hours, although it should still be considered up to a week after exposure.

The vaccine is not effective in patients with acute hepatitis B, and is not necessary for individuals known to have markers of current (HBsAg) or past (anti-HB) infection. However, immunisation should not be delayed while awaiting any test results.

Hepatitis B immunoglobulin

Specific hepatitis B immunoglobulin (HBIG) provides passive immunity and can give immediate but temporary protection after accidental inoculation or contamination with hepatitis B-infected blood. HBIG is given concurrently with hepatitis B vaccine and does not affect the development of active immunity. If infection has already occurred at the time of immunisation, virus multiplication may not be inhibited completely, but severe illness and, most importantly, development of the carrier state may be prevented.

HBIG is used after exposure to give rapid protection until hepatitis B vaccine, which should be given at the same time, becomes effective. The use of HBIG in addition to vaccine is recommended only in high-risk situations or in a known non-responder to vaccine. Whenever immediate protection is required, immunisation with the vaccine should be given. When appropriate, this should be combined with simultaneous administration of HBIG at a different site. HBIG should be given as soon as possible, ideally within 48 hours, although it should still be considered up to a week after exposure.

HBIG is obtained from the plasma of immunised and screened human donors. Because of a theoretical risk of transmission of vCJD from plasma products, HBIG used in the UK is now prepared from plasma sourced from outside the UK, and supplies are scarce.

All donors are screened for HIV, hepatitis B and hepatitis C, and all plasma pools are tested for the presence of RNA from these viruses. A solvent-detergent inactivation step for envelope viruses is included in the production process. There is no evidence associating the administration of HBIG with acquisition of HIV infection. Not only does the processing of the plasma from which it is prepared render it safe, but the screening of blood donations is routine practice.

Storage

Vaccines should be stored in the original packaging at +2˚C to +8˚C and protected from light. All vaccines are sensitive to some extent to heat and cold. Heat speeds up the decline in potency of most vaccines, thus reducing their shelf life. Effectiveness cannot be guaranteed for vaccines unless they have been stored at the correct temperature. Freezing may cause increased reactogenicity and loss of potency for some vaccines. It can also cause hairline cracks in the container, leading to contamination of the contents.

HBIG should be stored in a refrigerator at +2˚C to +8˚C. These products are tolerant to ambient temperatures for up to one week. They can be distributed in sturdy packaging outside the cold chain if needed.

Presentation

HBIG is a clear, pale yellow fluid or light brown solution dispensed in vials containing 200IU or 500IU in approximately 2ml and 4ml respectively.

Vaccine	Product	Pharmaceutical presentation	Instructions on handling vaccine
Hepatitis B	Engerix B® Fendrix® HBvaxPRO®	Suspension for injection	Shake the vaccine well to obtain a slightly opaque, white suspension
Combined hepatitis A and B vaccine	Twinrix Adult® Twinrix Paediatric®	Suspensions for injection	Shake the vaccine well to obtain a slightly opaque
	Ambirix®	Suspension for injection in a prefilled syringe	Shake the vaccine well to obtain a slightly opaque suspension

Dosage

Currently, licensed vaccines contain different concentrations of antigen per millilitre. The appropriate manufacturer's dosage should be adhered to.

Different hepatitis B vaccine products can be used to complete a primary immunisation course or, where indicated, as a booster dose in individuals who have previously received another hepatitis B vaccine (Bush *et al.*, 1991).

Table 18.1 Dosage of hepatitis B vaccines by age

Vaccine product	Ages and group	Dose	Volume
Engerix B®	0–15 years*	10µg	0.5ml
Engerix B®	16 years or over	20µg	1.0ml
Fendrix®	Patients with renal insufficiency aged 15 years and over	20µg	0.5ml
HBvaxPRO Paediatric®	0–15 years	5µg	0.5ml
HBvaxPRO®	16 years or over	10µg	1.0ml
HBvaxPRO40®	Adult dialysis and pre-dialysis patients	40µg	1.0ml

* 20µg of Engerix B may be given to children 11–15 of years age if using the two-dose schedule (see below)

Table 18.2 Dosage of combined hepatitis A and hepatitis B vaccines by age

Vaccine product	Ages	Dose HAV	Dose HBV	Volume
Twinrix Adult®	16 years or over	720 ELISA units	20ìg	1.0ml
Twinrix Paediatric®	1–15 years	360 ELISA units	10ìg	0.5m
Ambirix®	1–15 years	720 ELISA units	20ìg	1.0ml

Table 18.3 Dosage of HBIG

Age group	Dose
Newborn and children aged 0–4 years	200IU
Children aged 5–9 years	300IU
Adults and children aged 10 years or over	500IU

HBIG is available in 2ml ampoules containing approximately 200IU or 500IU.

Schedule

There are many different immunisation regimes for hepatitis B vaccine (see page 175). Generally the schedule for hepatitis B or combined hepatitis A and hepatitis B vaccine consists of three doses, with or without a fourth booster dose. One exception involves the use of adult strength vaccines in children, where two doses of Ambirix® or adult strength Engerix B® (given at zero and six to twelve months) are acceptable in those aged 1-15 years and 11-15 years respectively.

Administration

Hepatitis B vaccines are routinely given intramuscularly in the upper arm or anterolateral thigh. The buttock must not be used because vaccine efficacy may be reduced.

Hepatitis B-containing vaccines can be given at the same time as other vaccines such as DTaP/IPV/Hib, hepatitis A, MMR, MenC, Td/IPV and other travel vaccines. The vaccines should be given at a separate site, preferably in a different limb. If given in the same limb, they should be given at least 2.5cm apart (American Academy of Pediatrics, 2003). The site at which each vaccine was given should be noted in the individual's records.

For individuals with a bleeding disorder, vaccines should be given by deep subcutaneous injection to reduce the risk of bleeding.

HBIG can be administered in the upper outer quadrant of the buttock or anterolateral thigh (see Chapter 4). If more than 3ml is to be given to young children and infants, or more than 5ml to older children and adults, the immunoglobulin should be divided into smaller amounts and administered to different sites. HBIG may be administered, at a different site, at the same time as hepatitis B vaccine.

Disposal

Equipment used for vaccination, including used vials, ampoules, or partially discharged vaccines should be disposed of at the end of a session by sealing in a proper, puncture-resistant 'sharps' box according to local authority regulations and guidance in the technical memorandum 07-01 (Department of Health, 2006).

Recommendations for the use of the vaccine

Pre-exposure vaccination

The objective of the immunisation programme is to provide a minimum of three doses of hepatitis B vaccine for individuals at high risk of exposure to the virus or complications of the disease.

Pre-exposure immunisation is used for individuals who are at increased risk of hepatitis B because of their lifestyle, occupation or other factors. Immediate post-exposure vaccination is used to prevent infection, especially in babies born to infected mothers or following needlestick injuries (see below).

Where testing for markers of current or past infection is clinically indicated, this should be done at the same time as the administration of the first dose. Vaccination should not be delayed while waiting for results of the tests. Further

doses may not be required in those with clear evidence of past exposure. Pre-exposure immunisation is recommended for the following groups.

Injecting drug users

IDUs are a group at particular risk of acquiring hepatitis B infection. Vaccination is recommended for the following:

- all current IDUs, as a high priority
- those who inject intermittently
- those who are likely to 'progress' to injecting, for example those who are currently smoking heroin and/or crack cocaine, and heavily dependent amphetamine users
- non-injecting users who are living with current injectors
- sexual partners of injecting users
- children of injectors.

Individuals who change sexual partners frequently

Those who change sexual partners frequently, particularly MSM and male and female commercial sex workers.

Close family contacts of a case or individual with chronic hepatitis B infection

Sexual partners are most at risk, and they and close household contacts should be vaccinated. Blood should be taken at the time of the first dose of vaccine to determine if they have already been infected. Contacts shown to be HBsAg, anti-HBs or anti-HBc positive do not require further immunisation. Advice regarding the appropriate use of condoms should be given; a reasonable level of protection can be assumed following the second dose, provided that completion of the schedule can be assured.

Contacts who have had recent unprotected sex with individuals who have acute hepatitis B or who are HBsAg positive require post-exposure prophylaxis, including HBIG (see below).

Families adopting children from countries with a high or intermediate prevalence of hepatitis B

Members of such families may be at risk, as these children could be chronically infected (Christenson, 1986; Rudin *et al.*, 1990). When the status of the child to be adopted is not known, families adopting children from any high or intermediate-prevalence country should be advised as to the risks and hepatitis B vaccination recommended. In due course, testing such children is advisable because there could be benefits from referring an infected child for further management.

Foster carers

Some children requiring fostering may have been at increased risk of acquiring hepatitis B infection. Emergency placements may be made within a few hours: foster carers who accept children as emergency placements should be made aware of the risks of undiagnosed infection and how they can minimise the risks of transmission of all blood-borne virus infections. All short-term foster carers who receive emergency placements, and their families, should be offered immunisation against hepatitis B. Permanent foster carers (and their families) who accept a child known to be at high risk of hepatitis B should also be offered immunisation.

Individuals receiving regular blood or blood products and their carers

Those individuals receiving regular blood products, such as people with haemophilia, should be vaccinated. Those receiving regular blood transfusions, for example people with thalassaemia or other chronic anaemia, should be vaccinated against hepatitis B. Carers responsible for the administration of such products should also be vaccinated.

Patients with chronic renal failure

Patients with renal failure may need haemodialysis, at which time they may be at increased risk of hepatitis B. The response to hepatitis B vaccine among patients with renal failure is lower than among healthy adults. Between 45 and 66% of patients with chronic renal failure develop anti-HBs responses and, compared with immunocompetent individuals, levels of anti-HBs decline more rapidly. However, increased response rates have been reported in vaccines formulated for use in patients with chronic renal failure (Tong *et al*., 2005).

Immunisation against hepatitis B is recommended for patients already on haemodialysis or renal transplantation programmes and for other patients with chronic renal failure as soon as it is anticipated that they may require these interventions. The vaccines formulated for use in patients with chronic renal insufficiency should be used.

Patients with chronic liver disease

Individuals with chronic liver disease may be at increased risk of the consequences of hepatitis B infection. Immunisation against hepatitis B is therefore recommended for patients with severe liver disease, such as cirrhosis, of whatever cause. Vaccine should also be offered to individuals with milder liver disease, particularly those who are chronically infected with hepatitis C virus, who may share risk factors that mean that they are at increased risk of acquiring hepatitis B infection.

Inmates of custodial institutions

Immunisation against hepatitis B is recommended for all sentenced prisoners and all new inmates entering prison in the UK.

Individuals in residential accommodation for those with learning difficulties

A higher prevalence of chronic hepatitis B infection has been found among individuals with learning difficulties in residential accommodation than in the general population. Close, daily living contact and the possibility of behavioural problems may lead to residents being at increased risk of infection. Vaccination is therefore recommended.

Similar considerations may apply to children and adults in day care, schools and centres for those with severe learning disability. Decisions on immunisation should be made on the basis of a local risk assessment. In settings where the individual's behaviour is likely to lead to significant exposure (e.g. biting or being bitten) on a regular basis, immunisation should be offered to individuals even in the absence of documented hepatitis B transmission.

People travelling to or going to reside in areas of high or intermediate prevalence

Travellers to areas of high or intermediate prevalence who place themselves at risk when abroad should be offered immunisation. The behaviours that place them at risk will include sexual activity, injecting drug use, undertaking relief aid work and/or participating in contact sports. Travellers are also at risk of acquiring infection as a result of medical or dental procedures carried out in countries where unsafe therapeutic injections (e.g. the re-use of contaminated needles and syringes without sterilisation) are a risk factor for hepatitis B (Kane *et al.*, 1999; Simonsen *et al.*, 1999). Individuals at high risk of requiring medical or dental procedures in such countries should therefore be immunised, including:

- those who plan to remain in areas of high or intermediate prevalence for lengthy periods
- children and others who may require medical care while travelling to visit families or relatives in high or moderate-endemicity countries
- people with chronic medical conditions who may require hospitalisation while overseas
- those travelling for medical care.

Individuals at occupational risk

Hepatitis B vaccination is recommended for the following groups who are considered at increased risk:

- **healthcare workers in the UK and overseas (including students and trainees):** all healthcare workers who may have direct contact with patients' blood, blood-stained body fluids or tissues, require vaccination. This includes any staff who are at risk of injury from blood-contaminated sharp instruments, or of being deliberately injured or bitten by patients. Advice should be obtained from the appropriate occupational health department.
- **laboratory staff:** any laboratory staff who handle material that may contain the virus require vaccination.
- **staff of residential and other accommodation for those with learning difficulties:** a higher prevalence of hepatitis B carriage has been found among certain groups of patients with learning difficulties in residential accommodation than in the general population. Close contact and the possibility of behavioural problems, including biting and scratching, may lead to staff being at increased risk of infection.

  Similar considerations may apply to staff in day-care settings and special schools for those with severe learning disability. Decisions on immunisation should be made on the basis of a local risk assessment. In settings where the client's behaviour is likely to lead to significant exposures on a regular basis (e.g. biting), it would be prudent to offer immunisation to staff even in the absence of documented hepatitis B transmission.
- **other occupational risk groups:** in some occupational groups, such as morticians and embalmers, there is an established risk of hepatitis B, and immunisation is recommended. Immunisation is also recommended for all prison service staff who are in regular contact with prisoners.

Hepatitis B vaccination may also be considered for other groups such as the police and fire and rescue services. In these workers an assessment of the frequency of likely exposure should be carried out. For those with frequent exposure, pre-exposure immunisation is recommended. For other groups, post-exposure immunisation at the time of an incident may be more appropriate (see below). Such a selection has to be decided locally by the occupational health services or as a result of appropriate medical advice.

Post-exposure immunisation

Post-exposure prophylaxis is recommended for the following groups.

Babies born to mothers who are chronically infected with HBV or to mothers who have had acute hepatitis B during pregnancy

Hepatitis B infection can be transmitted from infected mothers to their babies at or around the time of birth (perinatal transmission). Babies acquiring

infection at this time have a high risk of becoming chronically infected with the virus. The development of the chronic infection after perinatal transmission can be prevented in over 90% of cases by appropriate vaccination, starting at birth, of all infants born to infected mothers.

UK guidelines (Department of Health, 1998) recommend that all pregnant women should be offered screening for hepatitis B infection during each pregnancy. Confirmatory testing and testing for hepatitis B e-markers of those mothers shown to be infected should follow. Where an unbooked mother presents in labour, an urgent HBsAg test should be performed to ensure that vaccine can be given to babies born to positive mothers within 24 hours of birth.

Management of the infant should be based on the results of these markers and, if available, HBV viral load testing of the mother. www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1223019399138

All babies born to these mothers should receive a complete course of vaccine on time. Arrangements should be in place to ensure that information is shared with appropriate local agencies to facilitate follow up.

Babies born to highly infectious mothers should receive HBIG as well as active immunisation (see Table 18.4). HBIG should preferably be given within 24 hours of delivery, and should be ordered well in advance of the birth. HBIG may be given simultaneously with vaccine but at a different site.

Table 18.4 Vaccination of term babies according to the hepatitis B status of the mother

Hepatitis B status of mother	Baby should receive	
	Hepatitis B vaccine	HBIG
Mother is HBsAg positive and HBeAg positive	Yes	Yes
Mother is HBsAg positive, HBeAg negative and anti-HBe negative	Yes	Yes
Mother is HBsAg positive where e-markers have not been determined	Yes	Yes
Mother had acute hepatitis B during pregnancy	Yes	Yes
Mother is HBsAg positive and anti-HBe positive	Yes	No
A woman who is HBsAg seropositive and known to have an HBV DNA level equal or above $1x10^6$IUs/ml in an antenatal sample*	Yes	Yes

* Where viral load testing has been performed to inform the management of the mother.

Vaccination of pre-term babies

There is evidence that the response to hepatitis B vaccine is lower in pre-term, low-birth weight babies (Losonsky *et al*., 1999). It is, therefore, important that premature infants receive the full paediatric dose of hepatitis B vaccine on schedule. Babies with a birthweight of 1500g or less, born to mothers infected with hepatitis B, should receive HBIG in addition to the vaccine, regardless of the e-antigen status of the mother.

It is important that premature infants have their immunisations at the appropriate chronological age, according to the schedule. The occurrence of apnoea following vaccination is especially increased in infants who were born very prematurely.

Very premature infants (born ≤ 28 weeks of gestation) who are in hospital should have respiratory monitoring for 48-72 hrs when given their first immunisation, particularly those with a previous history of respiratory immaturity. If the child has apnoea, bradycardia or desaturations after the first immunisation, the second immunisation should also be given in hospital, with respiratory monitoring for 48-72 hrs Pfister *et al*., 2004; Ohlsson *et al*., 2004; Schulzke *et al*., 2005; Pourcyrous *et al*., 2007; Klein *et al*., 2008).

As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Vaccination schedule and follow-up

For post-exposure prophylaxis in babies born to mothers infected with hepatitis B, the accelerated immunisation schedule is preferred. For these babies this will mean an initial dose of vaccine at birth, with further doses at one and two months of age and a fourth dose at one year of age.

Testing for HBsAg at one year of age will identify any babies for whom this intervention has not been successful and who have become chronically infected with hepatitis B, and will allow them to be referred for assessment and any further management. This testing can be carried out at the same time as the fourth dose is given.

Where immunisation has been delayed beyond the recommended intervals, the vaccine course should be completed, but it is more likely that the child may become infected. In this instance, testing for HBsAg above the age of one year is particularly important.

Other groups potentially exposed to hepatitis B

Any individual potentially exposed to hepatitis B-infected blood or bodyfluids should be offered protection against hepatitis B, depending on their prior vaccination status and the status of the source

www.hpa.org.uk/cdr/archives/CDRreview/1992/cdrr0992.pdf. Guidance on post-exposure prophylaxis following exposure to hepatitis B has been issued by the former PHLS Hepatitis Subcommittee (PHLS Hepatitis Subcommittee, 1992). A summary of this guidance is given in Table 18.5.

Sexual partners

Any sexual partner of individuals suffering from acute hepatitis B, and who are seen within one week of last contact, should be offered protection with HBIG and vaccine. Sexual contacts of an individual with newly diagnosed chronic hepatitis B should be offered vaccine; HBIG may be added if unprotected sexual contact occurred in the past week.

Persons who are accidentally inoculated or contaminated

This includes those who contaminate their eyes or mouth, or fresh cuts or abrasions of the skin, with blood from a known HBsAg-positive person. Individuals who sustain such accidents should wash the affected area well with soap and warm water, and seek medical advice. Advice about prophylaxis after such accidents should be obtained by telephone from the nearest public health laboratory or from the local Health Protection Team or virologist on call. Advice following accidental exposure may also be obtained from the occupational health services, hospital control of infection officer.

Primary immunisation

Pre-exposure prophylaxis

For pre-exposure prophylaxis in most adult and childhood risk groups, an accelerated schedule should be used, with vaccine given at zero, one and two months. Only for those infants who are at continued risk, a fourth dose is recommended at 12 months. An alternative schedule at zero, one and six months should only be used where rapid protection is not required and there is a high likelihood of compliance.

Higher completion rates are achieved with the accelerated schedule (at zero, one and two months) in groups where compliance is difficult (e.g. in IDUs and genito-urinary medicine clinic attenders) (Asboe *et al*., 1996). This improved compliance is likely to offset the slightly reduced immunogenicity when compared with the zero-, one- and six-month schedule, and similar response rates can be achieved by opportunistic use of a fourth dose after 12 months.

In addition to the schedules outlined above, for children under 15 years of age, a two-dose schedule of a vaccine containing adult strength hepatitis B, (Ambirix® for those aged one to 15 years or Engerix B® for those aged 11 to 15 years) at zero and six months provides similar protection to three doses of the childhood hepatitis B vaccines (see page 167).

Table 18.5 HBV prophylaxis for reported exposure incidents

	Significant exposure			Non-significant exposure	
HBV status of person exposed	**HBsAg positive source**	**Unknown source**	**HBsAg negative source**	**Continued risk**	**No further risk**
≤ 1 dose HB vaccine pre-exposure	Accelerated course of HB vaccine* HBIG × 1	Accelerated course of HB vaccine*	Initiate course of HB vaccine	Initiate course of HB vaccine	No HBV prophylaxis. Reassure
≥ 2 doses HB vaccine pre-exposure (anti-HBs not known)	One dose of HB vaccine followed by second dose one month later	One dose of HB vaccine	Finish course of HB vaccine	Finish course of HB vaccine	No HBV prophylaxis. Reassure
Known responder to HB vaccine (anti-HBs >10mIU/ml)	Consider booster dose of HB vaccine	Consider booster dose of HB vaccine	Consider booster dose of HB vaccine	Consider booster dose of HB vaccine	No HBV prophylaxis. Reassure
Known non-responder to HB vaccine (anti-HBs < 10mIU/ml 2–4 months post-immunisation)	HBIG × 1 Consider booster dose of HB vaccine A second dose of HBIG should be given at one month	HBIG × 1 Consider booster dose of HB vaccine A second dose of HBIG should be given at one month	No HBIG Consider booster dose of HB vaccine	No HBIG Consider booster dose of HB vaccine	No prophylaxis. Reassure

*An accelerated course of vaccine consists of doses spaced at zero, one and two months.
A booster dose may be given at 12 months to those at continuing risk of exposure to HBV.
Source: PHLS Hepatitis Subcommittee (1992).

Engerix B® can also be given at a very rapid schedule with three doses given at zero, seven and 21 days (Bock *et al*., 1995). When this schedule is used, a fourth dose should be administered 12 months after the first dose for the individual to be considered protected. This schedule is licensed for use in circumstances where adults over 18 years of age are at immediate risk and where a more rapid induction of protection is required. This includes persons travelling to areas of high endemicity, IDUs and prisoners. In teenagers under 18 years of age, response to vaccine is as good or better than in older adults (Plotkin and Orenstein, 2004). Although not licensed for this age group, this schedule can be used in those aged 16 to 18 years where it is important to provide rapid protection and to maximise compliance (e.g. IDUs and those in prison).

Twinrix Adult® vaccine can also be given at zero, seven and 21 days. This will provide more rapid protection against hepatitis B than other schedules but full protection against hepatitis A will be provided later than with vaccines containing a higher dose of hepatitis A (see Chapter 17). When this schedule is used, a fourth dose should be administered 12 months after the first dose for the individual to be considered protected.

Fendrix® is recommended to be given at zero, one, two and six months.

Post-exposure prophylaxis

For post-exposure prophylaxis, an accelerated schedule of monovalent hepatitis B vaccine (or a combined vaccine of equivalent strength) should be used, with vaccine given at zero, one and two months. For those who are at continued risk, a fourth dose is recommended at 12 months. If HBIG is also indicated, it should be given as soon as possible, ideally at the same time as the first dose of vaccine.

Reinforcing immunisation

The full duration of protection afforded by hepatitis B vaccine has yet to be established (Whittle *et al*., 2002). Levels of vaccine-induced antibody to hepatitis B decline over time, but there is evidence that immune memory can persist in those successfully immunised (Liao *et al.*, 1999). However, recent evidence suggests that not all individuals may respond in this way (Williams *et al*., 2003; Boxall *et al*., 2004). It is, therefore, recommended that individuals at continuing risk of infection should be offered a single booster dose of vaccine, once only, around five years after primary immunisation. Measurement of anti-HBs levels is not required either before or after this dose. Boosters are also recommended after exposure to the virus (as above).

Because of the continued presence of infection in other family members, a single booster dose of hepatitis B vaccine, given with the pre-school booster for other childhood immunisations, is advised for the children born to hepatitis B infected-mothers. This will also provide the opportunity to check whether the child was properly followed up in infancy.

Reinforcing immunisation in travellers

For travellers who have completed a primary course of vaccination, a single booster dose of vaccine at five years is not required, unless they are considered to be at continuing risk of infection.

Response to vaccine and the use of additional doses

Except in certain groups (see below), testing for anti-HBs is not recommended.

Those at risk of occupational exposure

In those at risk of occupational exposure, particularly healthcare and laboratory workers, antibody titres should be checked one to four months after the completion of a primary course of vaccine. Under the Control of Substances Hazardous to Health (COSHH) Regulations, individual workers have the right to know whether or not they have been protected. Such information allows appropriate decisions to be made concerning post-exposure prophylaxis following known or suspected exposure to the virus (see above).

Antibody responses to hepatitis B vaccine vary widely between individuals. It is preferable to achieve anti-HBs levels above 100mIU/ml, although levels of 10mIU/ml or more are generally accepted as enough to protect against infection. Some anti-HBs assays are not particularly specific at the lower levels, and anti-HBs levels of 100mIU/ml provide greater confidence that a specific response has been established.

Responders with anti-HBs levels greater than or equal to 100mIU/ml do not require any further primary doses. In immunocompetent individuals, once a response has been established further assessment of antibody levels is not indicated. They should receive the reinforcing dose at five years as recommended above.

Responders with anti-HBs levels of 10 to 100mIU/ml should receive one additional dose of vaccine at that time. In immunocompetent individuals, further assessment of antibody levels is not indicated. They should receive the reinforcing dose at five years as recommended above.

An antibody level below 10mIU/ml is classified as a non-response to vaccine, and testing for markers of current or past infection is good clinical practice. In non-responders, a repeat course of vaccine is recommended, followed by retesting one to four months after the second course. Those who still have anti-HBs levels below 10mIU/ml, and who have no markers of current or past infection, will require HBIG for protection if exposed to the virus (see below).

Patients with renal failure

The role of immunological memory in patients with chronic renal failure on renal dialysis does not appear to have been studied, and protection may persist only as long as anti-HBs levels remain above 10mIU/ml. Antibody levels should, therefore, be monitored annually and if they fall below 10mIU/ml, a booster dose of vaccine should be given to patients who have previously responded to the vaccine.

Booster doses should also be offered to any haemodialysis patients who are intending to visit countries with a high endemicity of hepatitis B and who have previously responded to the vaccine, particularly if they are to receive haemodialysis and have not received a booster in the last 12 months.

Contraindications

There are very few individuals who cannot receive hepatitis B-containing vaccines. When there is doubt, appropriate advice should be sought from a consultant paediatrician, immunisation co-ordinator or local Health Protection Team rather than withholding vaccine.

The vaccine should not be given to those who have had:

- a confirmed anaphylactic reaction to a previous dose of a hepatitis B-containing vaccine or
- a confirmed anaphylactic reaction to any component of the vaccine.

Precautions

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation. If an individual is acutely unwell, immunisation may be postponed until they have fully recovered. This is to avoid confusing the differential diagnosis of any acute illness by wrongly attributing any signs or symptoms to the adverse effects of the vaccine.

Pregnancy and breast-feeding

Hepatitis B infection in pregnant women may result in severe disease for the mother and chronic infection of the newborn. Immunisation should not be withheld from a pregnant woman if she is in a high-risk category. There is no evidence of risk from vaccinating pregnant women or those who are breast-feeding with inactivated viral or bacterial vaccines or toxoids (Plotkin and Orenstein, 2004). Since hepatitis B is an inactivated vaccine, the risks to the foetus are likely to be negligible, and it should be given where there is a definite risk of infection.

Premature infants

There is evidence that the response to hepatitis B vaccine is lower in pre-term, low-birthweight babies (Losonsky *et al*., 1999). It is, therefore, important that premature infants receive the full paediatric dose of hepatitis B vaccine on schedule. Babies with a birthweight of 1500g or less, born to mothers infected with hepatitis B, should receive HBIG in addition to the vaccine, regardless of the e-antigen status of the mother.

HIV and immunosuppressed individuals

Hepatitis B vaccine may be given to HIV-infected individuals and should be offered to those at risk, since infection acquired by immunosuppressed, HIV-positive patients can result in higher rates of chronic infection (Bodsworth *et al.*, 1991). Response rates are usually lower depending upon the degree of immunosuppression (Newell and Nelson, 1998; Loke *et al.*, 1990). Increasing the number of doses may improve the anti-HBs response in HIV-infected individuals (Rey *et al.*, 2000).

Further guidance is provided by the Royal College of Paediatrics and Child Health (www.rcpch.ac.uk) the British HIV Association (BHIVA) *immunisation guidelines for HIV-infected adults* (BHIVA, 2006) and the Children's HIV Association of UK and Ireland (CHIVA) immunisation guidelines (www.chiva.org.uk).

Precautions for HBIG

When HBIG is being used for prevention of hepatitis B, it must be remembered that it may interfere with the subsequent development of active immunity from live virus vaccines. If immunoglobulin has been administered first, then an interval of three months should be observed before administering a live virus vaccine. If immunoglobulin has been given within three weeks of

administering a live vaccine, then the vaccine should be repeated three months later. This does not apply to yellow fever vaccine since HBIG does not contain significant amounts of antibody to this virus.

Adverse reactions

Hepatitis B vaccine is generally well tolerated and the most common adverse reactions are soreness and redness at the injection site. Other reactions that have been reported but may not be causally related include fever, rash, malaise and an influenza-like syndrome, arthritis, arthralgia, myalgia and abnormal liver function tests.

Serious suspected neurological reactions such as Guillain-Barré syndrome and demyelinating disease have been reported, although these have been very rare and a causal relationship with hepatitis B vaccine has not been established (Shaw *et al.*, 1988; McMahon *et al.*, 1992). The results of recent studies indicate no association between hepatitis B immunisation and the development of multiple sclerosis (Ascherio *et al.*, 2001) and that immunisation against hepatitis B does not increase the short-term risk of a relapse in patients with multiple sclerosis (Confavreux *et al.*, 2001).

All suspected reactions in children and severe suspected reactions in adults should be reported to the Commission on Human Medicines using the Yellow Card scheme.

Adverse reactions to HBIG

HBIG is well tolerated. Very rarely, anaphylactoid reactions occur in individuals with hypogammaglobulinaemia who have IgA antibodies, or those who have had an atypical reaction to blood transfusion.

No cases of blood-borne infection acquired through immunoglobulin preparations designed for intramuscular use have been documented in any country.

Supplies

Hepatitis B vaccine

- Engerix B®
- Fendrix®

These vaccines are available from GlaxoSmithKline (Tel: 0808 100 9997).

- HBvaxPRO®
- HBvaxPRO Paediatric®
- HBvaxPRO® 40

These vaccines are available from Sanofi Pasteur MSD (Tel: 0800 0855511).

Combined hepatitis A and hepatitis B vaccine

- Twinrix Paediatric®
- Twinrix Adult®
- Ambirix®

These vaccines are available from GlaxoSmithKline (Tel: 0808 100 9997).

Hepatitis B immunoglobulin

England:
Public Health England
Centre for Infectious Disease Surveillance and Control Tel: 020 8200 6868

Wales:
Department of Virology NPHS Microbiology Cardiff Tel: 029 20 742178

Scotland:
HBIG is held by the Blood Transfusion Service:

Aberdeen	Tel: 01224 685685
Dundee	Tel: 01382 645166
Edinburgh	Tel: 0131 5365300
Glasgow	Tel: 0141 357 7700
Inverness	Tel: 01463 704212/3

Northern Ireland:
HBIG is held by the Public Health Laboratory
Belfast City Hospital
Belfast (Tel: 028 9032 9241 ext 2417)

Note: Supplies of HBIG are limited and demands should be restricted to patients in whom there is a clear indication for its use.

HBIG for use in hepatitis B-infected recipients of liver transplants should be obtained from:

Bioproducts Laboratory
Dagger Lane
Elstree
Herts WD6 3BX
(Tel: 020 8258 2342)

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