18

Hepatitis B

NOTIFIABLE

The disease

Hepatitis B is an infection of the liver caused by the hepatitis B virus (HBV). Many individuals with a new infection with hepatitis B may have a sub-clinical or 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 acute 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. 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), hepatitis B core IgM antibody (anti-HBc 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 through percutaneous exposure (e.g. sharing of needles and other equipment by people who inject drugs (PWID), '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 donors and 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. 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. 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 around 250 million people worldwide are chronically infected with HBV (WHO 2017). 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. Since 1987, the WHO has recommended universal infant or adolescent hepatitis B immunisation. As of 2008, 177 countries had incorporated hepatitis B vaccine as an integral part of their national infant immunisation programmes (WHO 2009). In 2016 the World Health Assembly adopted WHO's first Global Health Sector Strategy on viral hepatitis with elimination as its overarching vision. Scaling up hepatitis B vaccination coverage in infant immunisation programmes is highlighted as a successful prevention intervention.

The importance of the various modes of transmission varies according to the prevalence in a particular country. In areas of high endemicity (and 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 people who inject drugs (PWID) 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.

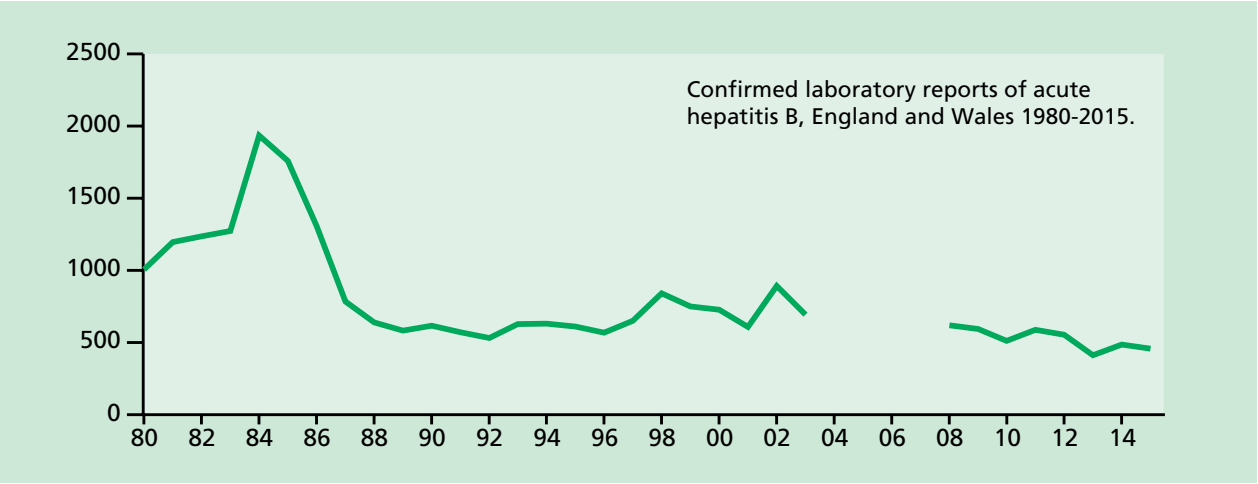

Figure 18.1 Laboratory reports of confirmed acute hepatitis B, England and Wales.
From 2008 cases reported on HPZone and matched to laboratory data for England only. No data between 2004-7 due to the inability to distinguish between acute and chronic cases

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 where populations with origins in endemic countries are higher. Overall, the prevalence in antenatal women in the UK is around 0.4% (National Antenatal Infections Screening Monitoring https://www.gov.uk/government/publications/national-antenatal-infections-screening-monitoring-annual-data-tables).

In the UK, the incidence of acute infection is low but is higher among those with certain behavioural or occupational risk factors. Vaccination has therefore been recommended for individuals at higher risk since the 1980s. Laboratory reports of acute hepatitis B 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 PWIDs (figure 18.1). The decrease was also seen in other risk groups, most probably linked to a modification of risk behaviours, such as condom use, in response to the HIV/AIDS epidemic. Higher vaccination coverage in those at risk may have contributed to the more recent low incidence with the numbers of reports fluctuating at around 500 to 600 cases per year since 2009. Whereas in the past, most reports of acute infection in the UK were associated with injecting drug use, they now occur most commonly as heterosexual exposure, followed by sex between men. Periodic surveys in PWID indicate that hepatitis B prevalence is less than 1% following introduction of harm reduction policies including vaccination (Public Health England 2016).

As the UK is a very low prevalence and incidence country, a programme using monovalent hepatitis B vaccine, either in infancy or in adolescence, was previously found not to be cost-effective (Siddiqui *et al.,* 2011). In addition, there had been concern that the available infant combination vaccines (those including a 2- or 3-component acellular-pertussis vaccine) that included hepatitis B could produce inferior Hib responses. Combinations with 3-component acellular-pertussis have now been used widely in the UK for some years. Experience suggests that with the current UK schedule, with a Hib booster at one year of

age, adequate protection will be achieved and control of Hib sustained. In 2014, therefore, the Joint Committee on Vaccination and Immunisation re-evaluated their earlier advice and recommended that a universal hepatitis B infant programme was highly likely to be cost-effective using an infant combination vaccine (JCVI, October 2014). A suitable vaccine has been procured to commence routine infant immunisation from late 2017.

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 vaccines

The Hepatitis B vaccine is given as a single or combined product:

- monovalent hepatitis B vaccine (HepB)
- bivalent combination vaccine: hepatitis A and B (HepA/HepB)
- hexavalent combination vaccine containing diphtheria/tetanus/acellular pertussis/inactivated polio vaccine/*Haemophilus influenzae* type b/hepatitis B (DTaP/IPV/Hib/HepB)

Specific monovalent hepatitis B containing vaccines are also available for patients with renal insufficiency and dialysis patients.

Hepatitis B vaccines contain HBsAg prepared from yeast cells using recombinant DNA technology. The antigen is adsorbed onto aluminium hydroxide, aluminium phosphate or aluminium hydroxphosphate sulphate adjuvant. Fendrix®, for patients with renal insufficiency, is adjuvanted by monophosophoryl lipid A, and adsorbed onto aluminium phosphate. Hepatitis B-containing vaccines are inactivated, do not contain live organisms and cannot cause the diseases against which they protect. Thiomersal is not used as a preservative in hepatitis B vaccines available in the UK.

The available vaccines are highly effective in preventing infection in children and most adults through the production of specific antibodies to HBsAg (anti-HBs). Hepatitis B vaccine is also highly effective at preventing infection if given shortly after exposure (see below). Ideally, immunisation should commence within 24 hours of exposure, although it should still be considered up to a week after exposure.

Hepatitis B immunoglobulin

Specific hepatitis B immunoglobulin (HBIG) is obtained from the plasma of immunised and screened human donors. All donors are screened for HIV, hepatitis B and hepatitis C, and all plasma pools are tested for the presence of nucleic acid from these viruses. A solvent-detergent inactivation step for envelope viruses is included in the production process. 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.

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. As vaccine alone is highly effective, the use of HBIG in addition to vaccine is only recommended 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 necessary, HBIG should also be given at the same time as vaccine, ideally within 24 hours of vaccine, although it may still be considered up to a week after exposure.

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

Table 18.1 Presentation of hepatitis B vaccines

Vaccine	Product	Pharmaceutical presentation	Instructions on handling vaccine
Monovalent hepatitis B (HepB)	Engerix B® Fendrix® HBvaxPRO®	Suspension for injection	Shake the vaccine well to obtain a slightly opaque, white suspension
Combined hepatitis A and B vaccine (HepB/HepA)	Twinrix Adult® Twinrix Paediatric®	Suspensions for injection	Shake the vaccine well to obtain a slightly opaque suspension
	Ambirix®	Suspension for injection in a prefilled syringe	Shake the vaccine well to obtain a slightly opaque suspension
Hexavalent hepatitis B (DTaP/IPV/Hib/HepB)	Infanrix hexa®	Powder (Hib) in vial and suspension DTaP/IPV/HepB for injection in pre-filled syringe	Reconstitute powder in liquid suspension in accordance with manufacturer's instructions

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

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 or reinforcing dose in individuals who have previously received another hepatitis B vaccine (Bush *et al.*, 1991).

Table 18.2 Dosage of monovalent 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 18.3 Dosage of combined containing hepatitis B vaccines by age

Vaccine product	Ages	Dose of other antigens	Dose HBV	Volume
Twinrix Adult®	16 years or over	720 ELISA units HAV	20µg	1.0ml
Twinrix Paediatric®	1–15 years	360 ELISA units HAV	10µg	0.5ml
Ambirix®	1–15 years	720 ELISA units HAV	20µg	1.0ml
Infanrix hexa®	6 weeks – 2 years	30 International Units (IU) diphtheria toxoid; 40 IU tetanus toxoid; 25 µg pertussis toxoid (PT); 25 µg filamentous haemagglutinin (FHA); 8 µg pertactin (PRN); 40 D-antigen units (DU) of type 1, 8 DU type 2, and 32 DU type 3 poliovirus; 10 µg of adsorbed purified capsular polysaccharide of Hib covalently bound to approximately 25 µg of tetanus toxoid	10µg	0.5ml

Table 18.4 Dosage of HBIG

Age group	Dose	Approximate volume	Ampoules required
Newborn and children aged 0–4 years	200IU	1.5.ml	200IU
Children aged 5–9 years	300IU	2 ml	2 x 200IU
Adults and children aged 10 years or over	500IU	3.5 ml	500IU

Schedule

There are many different immunisation schedules for hepatitis B vaccine which depend on the vaccine product used and how quickly protection is needed for pre or post exposure. These schedules are discussed in detail under each indication.

Administration

Hepatitis B-containing 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 including diphtheria, tetanus, pertussis, poliomyelitis, *Haemophilus influenzae* type b conjugate, 4CMenB, hepatitis A, MMR, pneumococcal conjugate, oral rotavirus and with 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 into 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 Health Technical Memorandum 07-01: Safe management of healthcare waste (Department of Health, 2013).

Recommendations for the use of the vaccine

The objective of the immunisation programme is to provide a minimum of three doses of hepatitis B vaccine for:

- infants, as part of the routine childhood immunisation programme, to protect against future exposure risks (pre-exposure immunisation)
- individuals at high risk of exposure to the virus or complications of the disease (pre-exposure immunisation).
- individuals who have already been exposed to the virus (post-exposure immunisation) including infants born to hepatitis B infected mothers

Routine childhood immunisation programme

In the routine immunisation programme, a total of **three** doses of vaccine at the appropriate intervals (8, 12 and 16 weeks of age) are considered to give satisfactory long-term protection. The appropriate intervals are determined by the need to also protect individuals against diphtheria, tetanus, pertussis, polio and Hib.

Selective neonatal immunisation programme

Post-exposure immunisation is provided to infants born to hepatitis B infected mothers, identified through antenatal screening, to prevent mother to child transmission at or around the time of birth. Immunisation of the infant should start as soon as possible after birth, and no later than 24 hours, and be followed by a dose four and eight weeks later and a further dose at one year of age. From late 2017, as hepatitis B is included in the routine childhood immunisation programme, the dose at eight weeks in the selective neonatal programme will be provided in DTaP/IPV/Hib/HepB as part of the routine programme, as will additional doses given at 12 and 16 weeks..

Selective immunisation programme

Immediate post-exposure vaccination is used to prevent infection following exposure, for example needlestick injuries (see below), followed by a dose one and two months later. Pre-exposure vaccination is also used to protect individuals at high risk of exposure to the virus or of the complications of the disease.

Pre-exposure immunisation

Primary Immunisation

Infants and children under ten years of age

From late 2017, the routine childhood programme consists of three doses of a hepatitis B-containing product with an interval of one month between each dose, before the age of one year. If the primary course is interrupted it should be resumed but not repeated, allowing an interval of four weeks between the remaining doses.

Children of one to ten years of age who have completed a primary course of diphtheria, tetanus, pertussis, Hib and polio, but who have not received hepatitis B-containing vaccines do not require any hepatitis B-containing vaccine unless they are in a high-risk group or are exposed to hepatitis B (see below).

Individuals at high risk of exposure or of the complications of the disease

Pre-exposure immunisation is used for individuals who are at increased risk of hepatitis B or complications of the disease because of their lifestyle, occupation, co-existing medical conditions or other factors (see below). 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.

Where testing for markers of current or past infection is clinically indicated, e.g. for household contacts of infected persons, 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.

People who inject drugs (PWID)

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

- all current PWID, 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, children, other household and close family contacts of PWID

Individuals who change sexual partners frequently

Those who change sexual partners frequently, men who have sex with men (MSM), and male and female commercial sex workers are at particular risk of infection and should be offered vaccination.

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

Sexual partners are most at risk of transmission, and they and close family and 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.

Newborn infants born to a hepatitis B negative woman but known to be going home to a household with another hepatitis B infected person may be at immediate risk of hepatitis B infection. In these situations, a monovalent dose of hepatitis B vaccine should be offered before discharge from hospital. They should then continue on the routine childhood schedule commencing at eight weeks.

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 later section).

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 of the risks and hepatitis B vaccination recommended. 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 infected with 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). Testing is advised in this patient group (see later section on testing).

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 e.g. dialysis
- 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 percutaneous 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.

Pre-exposure immunisation schedule

Infants and children

DTaP/IPV/Hib/HepB is recommended to be given at eight, twelve and sixteen weeks of age but can be given at any stage from six weeks to ten years of age.

Vaccination of pre-term babies

It is important that premature infants have their immunisations at the appropriate chronological age (i.e. age since birth, not corrected), according to the schedule.

Pre-exposure immunisation schedule for high risk individuals

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. Higher completion rates are achieved with the accelerated schedule (at zero, one and two months) in groups where compliance is difficult (e.g. in PWID and genitourinary 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 the opportunistic use of a fourth dose after 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. If the primary course is interrupted it should be resumed but not repeated.

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 to provide longer term protection. 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, PWIDs and prisoners. In teenagers under 18 years of age, response to vaccine is usually better than in older adults (Plotkin and Orenstein, 2004). Although not licensed for this age group, the very rapid 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. PWIDs 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 to provide longer term protection.

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

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.

Reinforcing doses for those who have received pre-exposure 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, Poovorawan *et al*., 2010, Bruce *et al*., 2016, Simons *et al*., 2016). Although some evidence suggests that not all individuals make this amnestic response (Williams *et al*., 2003; Boxall *et al*., 2004), the clinical significance of this is unclear. The WHO has concluded that, although knowledge about the duration of protection against infection and disease is still incomplete, studies demonstrate that, among successfully vaccinated immunocompetent individuals, protection against chronic infection persists for 20-30 years or more. Therefore WHO conclude that there is no compelling evidence for recommending a booster dose of hepatitis B vaccine in routine immunisation programmes (WHO 2017).

Based on this conclusion, the current UK recommendation is that those who have received a primary course of immunisation, including children vaccinated according to the routine childhood schedule and individuals at high risk of exposure, do not require a reinforcing dose of HepB-containing vaccine, except in the following categories:

- healthcare workers (including students and trainees), who should be offered a single booster dose of vaccine, once only, around five years after primary immunisation
- patients with renal failure (see later section)
- at the time of a significant exposure (see next section)

Post-exposure immunisation

Post-exposure prophylaxis should be initiated rapidly to protect the following groups.

Babies born to hepatitis B infected mothers (selective neonatal immunisation programme)

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 immediately at birth.

Since 1998, the Department of Health and now the UK National Screening Committee (UK NSC) have recommended population screening for hepatitis B in pregnancy (Department of Health, 1998). The main objective of the programme is to reduce the risk of mother-to-child transmission by providing prompt post-exposure vaccination of the baby. Early identification in pregnancy will also facilitate appropriate assessment and management of the mother and their baby. Women with hepatitis B in pregnancy should have care provided by a multidisciplinary team to ensure all aspects are reviewed and managed. An appropriate care plan and neonatal alert should be put in place for the birth of their baby.

Those mothers shown to be infected, should have confirmatory testing and testing for hepatitis B e-markers and viral load. Where an unbooked mother presents in labour, an urgent HBsAg test should be performed to ensure that vaccine can be appropriately given to babies born to hepatitis B infected mothers within 24 hours of birth. Hepatitis B e-markers and/or viral load should also be undertaken rapidly to advise on whether HBIG is also required.

All babies born to these mothers should receive a complete course of vaccine on time; the first dose of vaccine should be given as soon as possible, ideally within 24 hours of birth. 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 18.5). Management of the infant should be based on the results of e-markers and hepatitis B viral load testing of the mother. HBIG should ideally be ordered well in advance of the birth and given simultaneously with vaccine but at a different site. If this is not possible, HBIG should be ordered to be given within 24 hours of the birth dose of vaccine.

Table 18.5 Vaccination of 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 had acute hepatitis B during pregnancy	Yes	Yes
Mother is HBsAg positive and anti-HBe positive	Yes	No
Mother is HBsAg positive and known to have an HBV DNA level equal or above $1x10^6$IUs/ml in any antenatal sample during this pregnancy (regardless of HBeAg and anti-HBe status)	Yes	Yes
Mother is HBsAg positive and baby weighs 1500g or less	Yes	Yes

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 born to mothers infected with hepatitis B, with a birthweight of 1500g or less, should receive HBIG in addition to the vaccine, regardless of the e-antigen status or viral load of the mother. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Post-exposure schedule and follow-up for the selective neonatal programme

Babies born to hepatitis B infected mothers should be vaccinated using an accelerated immunisation schedule with a dose of hepatitis-B containing vaccine at birth, 4 weeks and 8 weeks of age. From late 2017, the routine childhood immunisation programme includes

hepatitis B, and therefore these infants will receive monovalent vaccine at birth and 4 weeks, but hexavalent hepatitis B-containing vaccine instead of monovalent vaccine at 8 weeks. They should then receive additional hexavalent vaccine doses at 12 and 16 weeks (see table 18.6).

A further dose of monovalent HepB vaccine is given at one year of age, alongside a test for HBsAg. Testing at one year of age is important to identify babies who have become chronically infected with hepatitis B despite vaccination, and will allow prompt referral for further management. This testing can be carried out at the same time as the dose at one year of age is given, or soon after. A further dose of hepatitis B-containing vaccine at 3 years and 4 months is no longer recommended for those children who have completed their routine primary immunisations with the hexavalent hepatitis B-containing vaccine. However the pre-school booster visit (for MMR and DTaP/IPV or dTaP/IPV vaccinations) provides an opportunity to check the child has been appropriately managed, i.e. fully immunised against hepatitis B and tested for infection.

Where immunisation has been delayed beyond the recommended intervals, the vaccine course should be resumed, 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.

Table 18.6 Hepatitis B immunisation schedule for routine childhood and selective neonatal immunisation programmes following the introduction of hexavalent hepatitis B-containing vaccine

Age	Routine childhood programme	Babies born to hepatitis B infected mothers
Birth	✗†	✓ Monovalent HepB
4 weeks	✗	✓ Monovalent HepB
8 weeks	✓ DTaP/IPV/Hib/HepB	✓ DTaP/IPV/Hib/HepB
12 weeks	✓ DTaP/IPV/Hib/HepB	✓ DTaP/IPV/Hib/HepB
16 weeks	✓ DTaP/IPV/Hib/HepB	✓ DTaP/IPV/Hib/HepB
1 year of age	✗*	✓ Monovalent HepB ✓ Test for HBsAg
3 years and 4 months	✗*	✗*

† Newborn infants born to a hepatitis B negative woman but known to be going home to a household with another hepatitis B infected person may be at immediate risk of hepatitis B infection. In these situations, a monovalent dose of hepatitis B vaccine should be offered before discharge from hospital. They should then continue on the routine childhood schedule commencing at eight weeks.

* Give the recommended non-hepatitis B containing vaccines as per the routine schedule

Other groups potentially exposed to hepatitis B

Any individual potentially exposed to hepatitis B-infected blood or body fluids should be offered immediate protection against hepatitis B. A summary of existing guidance on post-exposure prophylaxis, depending on prior vaccination status and the status of the source is given in Table 18.7. (derived from PHLS Hepatitis Sub-committee, 1992) (https://www.gov.uk/government/collections/hepatitis-b-guidance-data-and-analysis).

Sexual partners

Any sexual partner of individuals suffering from acute hepatitis B should be offered protection with vaccine, and if seen within one week of last contact should also be offered HBIG. Sexual contacts of an individual with newly diagnosed chronic hepatitis B should be offered vaccine; HBIG may be considered if unprotected sexual contact with the new partner first occurred in the past week. Individuals should be advised on the appropriate use of condoms, at least until after the second dose, and on the importance of completing the course to minimise the risk of infection.

Persons who are accidentally inoculated or contaminated

This includes those who contaminate their eyes or mouth, or fresh cuts or abrasions of the skin (e.g. community or occupational needlestick injuries and bites), 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 and hospital infection control officer.

Post-exposure schedule and follow-up for other groups

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. If HBIG is also indicated, it should be given as soon as possible, ideally at the same time or within 24 hours of the first dose of vaccine, but not after seven days have elapsed since exposure.

Guidance on follow up testing for infection is summarised elsewhere (PHLS Hepatitis Sub-committee, 1992) (https://www.gov.uk/government/collections/hepatitis-b-guidance-data-and-analysis).

Reinforcing immunisation

Those who have receive post-exposure prophylaxis with a zero, one and two months accelerated schedule, do not require a further dose at 12 months unless they remain at continued high risk. Thereafter, these individuals do not require a reinforcing dose of hepatitis B-containing vaccine, except in the following categories:

- healthcare workers, including students and trainees, who should be offered a single booster dose of vaccine, once only, around five years after primary immunisation
- patients with renal failure (see later section)
- at the time of a subsequent significant exposure (Table 18.7)

Table 18.7 Hepatitis B prophylaxis for reported exposure incidents

	Significant exposure			Non-significant exposure	
HBV status of person prior to exposure	**HBsAg positive source**	**Unknown source**	**HBsAg negative source**	**Continued risk**	**No further risk**
Unvaccinated	Accelerated course of HepB vaccine plus HBIG with first dose	Accelerated course of HepB vaccine	Consider course of HepB vaccine	Initiate course of HepB vaccine	No HBV prophylaxis Reassure
Partially vaccinated	One dose of HepB vaccine and finish course	One dose of HepB vaccine and finish course	Complete course of HepB vaccine	Complete course of HepB vaccine	Complete course of HepB vaccine
Fully vaccinated with primary course	Booster dose of HepB vaccine if last dose ≥ 1year ago	Consider booster dose of HepB vaccine if last dose ≥ 1year ago	No HBV prophylaxis. Reassure	No HBV prophylaxis Reassure	No HBV prophylaxis Reassure
Known non-responder to HepB vaccine (anti-HBs < 10mIU/ml 1-2 months post-immunisation)	HBIG Booster dose of HepB vaccine A second dose of HBIG should be given at one month	HBIG Consider booster dose of HepB vaccine A second dose of HBIG should be given at one month	No HBIG Consider booster dose of HepB vaccine	No HBIG Consider booster dose of HepB vaccine	No HBV prophylaxis Reassure

Adapted from: PHLS Hepatitis Subcommittee (1992).

Testing for response to vaccination

Hepatitis B vaccines are highly effective; around 90% of adults respond to vaccines adequately. 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 people who have alcohol dependency, 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.

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-HBc) infection. However, immunisation should not be delayed while awaiting any test results for current or past infection.

Testing for evidence of immunity post immunisation (anti-HBs) is not routinely recommended, except in certain groups as described below.

Those at risk of occupational exposure

In those at risk of occupational exposure, particularly healthcare and laboratory workers, anti-HBs titres should be checked one to two 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. 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. Current advice is that healthcare and laboratory workers should be offered a single booster dose of vaccine, once only, five years after the primary immunisation.

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 two 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.

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 the relevant specialist consultant, the local screening and immunisation team 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.

Children who have had a systemic or local reaction following a previous immunisation with DTaP/IPV/Hib/HepB or DTaP/IPV/Hib can continue to receive subsequent doses of hepatitis B containing vaccine. Such reactions include:

- fever, irrespective of its severity
- hypotonic-hyporesponsive episodes (HHE)
- persistent crying or screaming for more than three hours, or
- severe local reaction, irrespective of extent

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 (Kroger *et al*., 2013). 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

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 premature infant 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.

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 or using a higher antigen content dose may improve the anti-HBs response in HIV-infected individuals (Rey *et al.*, 2000; Fonseca *et al.*, 2005).

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, 2015) and the Children's HIV Association (CHIVA) immunisation guidelines http://www.chiva.org.uk/guidelines/immunisation/).

Neurological conditions

The presence of a neurological condition is not a contraindication to immunisation but if there is evidence of current neurological deterioration, deferral of the hexavalent DTaP/IPV/Hib/HepB combination vaccine may be considered, to avoid incorrect attribution of any change in the underlying condition. The risk of such deferral should be balanced against the risk of the preventable infection, and vaccination should be promptly given once the diagnosis and/or the expected course of the condition becomes clear.

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. This does not apply to yellow fever vaccine since HBIG does not contain significant amounts of antibody to this virus. Other live virus vaccination should be deferred or repeated after three months.

Adverse reactions

Monovalent hepatitis B vaccine

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.

Numerous epidemiological studies have studied the alleged association between hepatitis B vaccination and multiple sclerosis and demyelinating diseases of the peripheral nervous system such as Guillain-Barré syndrome (Shaw *et al.*, 1988; McMahon *et al.*, 1992), and the weight of evidence does not support an association with the vaccine. The Global Advisory Committee on Vaccine Safety (GACVS) issued a statement in 2002 and concluded that there is no association between administration of the hepatitis B vaccine and multiple sclerosis (MS). For further information please see: http://www.who.int/vaccine_safety/committee/topics/hepatitisb/multiple_sclerosis/en/

Hexavalent DTaP/IPV/Hib/HepB vaccine

Fever, and pain, swelling or redness at the injection site commonly occurs and are seen more frequently following subsequent doses. A small, painless nodule may form at the injection site; this usually disappears and is of no consequence. Convulsions, high-pitched screaming, and episodes of pallor, cyanosis and limpness (HHE) occur rarely (Tozzi and Olin, 1997). Studies have shown that when hepatitis B vaccine is added to DTaP/IPV/Hib vaccine, the frequency and type of adverse reactions experienced are similar to those seen when the DTaP/IPV/Hib vaccine is given alone or with monovalent hepatitis B vaccine. (Dhillon S, 2010).

Confirmed anaphylaxis occurs extremely rarely. Data from the UK, Canada and the US point to rates of 0.65 to 3 anaphylaxis events per million doses (Bohlke *et al.*, 2003; Canadian Medical Association, 2002). Other allergic conditions may occur more commonly and are not contraindications to further immunisation.

Hepatitis B Immunoglobulin (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

Monovalent 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 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).

Hexavalent DTaP/IPV/Hib/HepB vaccine

- Infanrix hexa®

This vaccine is centrally purchased for the NHS as part of the national immunisation programme and can only be ordered via ImmForm. Vaccines for use as part of the national childhood immunisation programme are provided free of charge. Vaccines for private prescriptions, occupational health use or travel are NOT provided free of charge and should be ordered from the manufacturers. Further information about ImmForm is available at https://www.gov.uk/government/collections/immform, from the ImmForm helpdesk at helpdesk@immform.org.uk or Tel: 0844 376 0040. The vaccine is distributed by Movianto UK Ltd (Tel: 01234 248631).

In Scotland, supplies should be obtained from local childhood vaccine holding centres. Details of these are available from Procurement, Commissioning & Facilities of NHS National Services Scotland (Tel: 0131 275 6725).

In Northern Ireland, supplies should be obtained from local childhood vaccine holding centres. Details of these are available from the Regional Pharmaceutical Procurement Service (Tel: 028 9442 2089).

Hepatitis B immunoglobulin

England:
Public Health England (PHE) Rabies and Immunoglobulin Service
0208 327 6204

Wales:
Department of Virology, Public Health Wales, Microbiology, Cardiff
029 20 742178

Scotland:
In Scotland, HBIG should be obtained from local hospital pharmacy departments. Details of these are available from Procurement, Commissioning & Facilities of NHS National Services Scotland
0131 275 6725

Northern Ireland:
HBIG is held by blood banks in each Hospital Trust in Northern Ireland, with HBIG for neonatal use also held in hospitals with maternity units. HBIG is supplied to hospitals by the Northern Ireland Blood Transfusion Service
028 9032 1414

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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