

06

Hepatitis B

NOTIFIABLE

Introduction

Hepatitis B virus (HBV) is an important cause of serious liver disease including acute and chronic hepatitis, cirrhosis and primary hepatocellular carcinoma. People with chronic HBV infection can transmit the infection for many years. A safe and effective vaccine is available for the prevention of HBV infection.

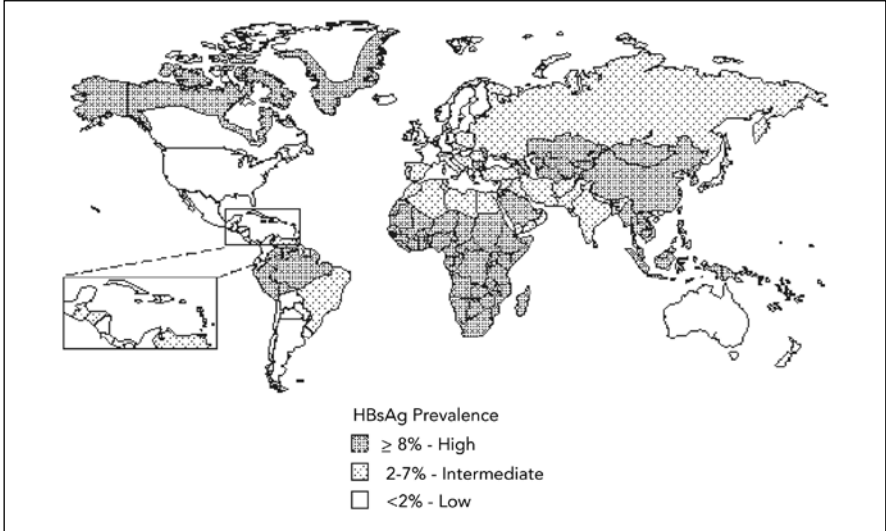
Epidemiology

The World Health Organization (WHO) estimates that over 350 million people worldwide are chronically infected with HBV (Figure 6.1). The WHO has categorised countries based upon the prevalence of hepatitis B surface antigen (HBsAg) into:

- High endemicity ($\geq 8\%$): sub-saharan Africa, most of Asia and the Pacific Islands
- Intermediate endemicity (2-7%): Southern parts of Eastern and Central Europe, Middle East and Indian sub-continent, Central and South America
- Low endemicity ($< 2\%$): Most of Western Europe and North America, Australia.

In Ireland the prevalence of serological markers of hepatitis B infection is low. A national study in the general population in 1999 estimated the prevalence of past exposure to hepatitis B (anti-core antibody, anti-HBc) to be 0.51%. Between 2003 and 2006, a prevalence of HBsAg of 0.01% was detected in new blood donors tested by the Irish Blood Transfusion Service donor screening programme. One in 2,000 to 1 in 6,000 pregnant Irish-born women are HBsAg positive, depending on the population surveyed.

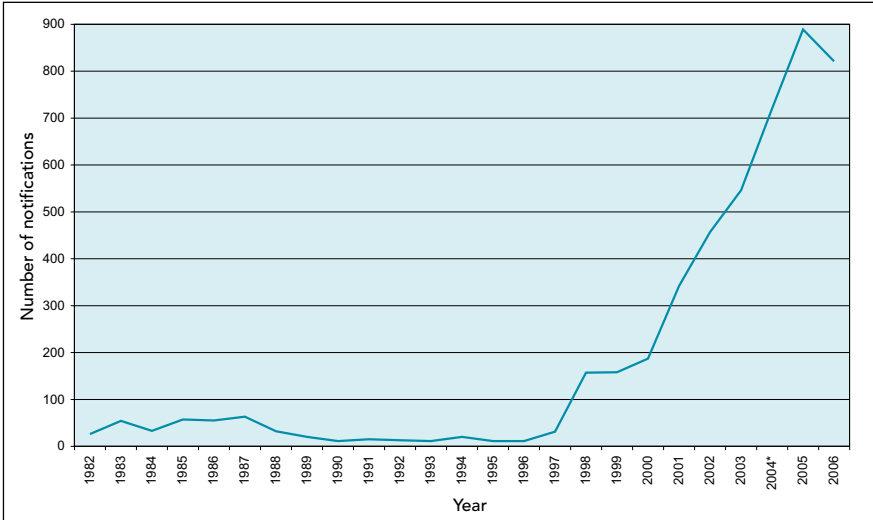
Figure 6.1 Geographic distribution of hepatitis B prevalence. Source: WHO



A higher HBV prevalence is seen in some population groups in Ireland. The prevalence of anti-HBc in Irish prisoners in 1998 was 8.7% overall and in injecting drug-using prisoners was 18.5%. Homeless people also have evidence of increased exposure to hepatitis B, with a prevalence of anti-HBc of 9% in a study performed in Dublin in 1999-2000.

Figure 6.2 shows the number of statutory notifications of hepatitis B infection in Ireland, 1982-2006. The increase in notifications since 1998 may be largely attributed to changes in immigration patterns and the introduction of active screening in high-risk populations. Most of these notifications are cases of chronic infection. For HBV notifications received by the Health Protection Surveillance Centre in 2006, 90% of the chronic HBV cases, where country of birth was known, were born in a country of either high or intermediate prevalence.

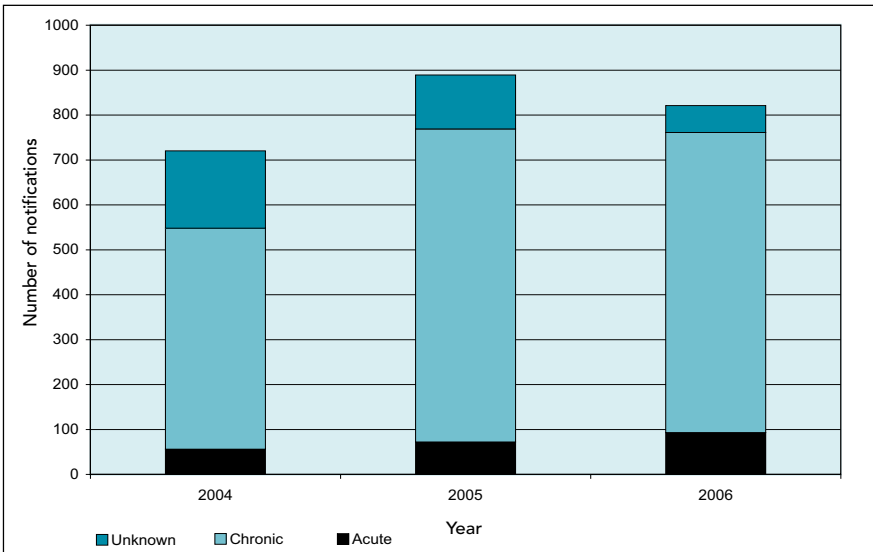
Figure 6.2 Number of notifications of hepatitis B, 1982-2006.
Source: HPSC



*Case definitions introduced and laboratories required to notify cases of notifiable infectious diseases from January 2004.

Changes to the Infectious Diseases Regulations in January 2004, with the introduction of case definitions, the differentiation between acute and chronic cases, and mandatory laboratory notification, have had a positive impact on the quality of information available on HBV in Ireland and may also have resulted in increased numbers of notifications (see Figure 6.3).

Figure 6.3 Number of hepatitis B notifications by status, 2004-2006.
Source: HPSC



Transmission

The virus is transmitted by infected blood or body fluids. Transmission mainly occurs by:

- Sexual intercourse, including vaginal and anal
- Blood-to-blood contact (e.g. sharing of personal care items such as toothbrushes, razors or by other equipment used by injecting drug users (IDUs), needlestick injuries, ear-piercing, tattooing)
- Perinatal transmission from infected mother to child
- Transmission has rarely followed bites from infected individuals

Transmission by transfusion of contaminated blood or blood products is now rare because of routine screening of blood donors and viral inactivation of certain blood products.

HBV has been found in virtually all body secretions and excretions. However, only blood (and serum-derived fluids), saliva, semen and vaginal fluids have been shown to be infectious. People with chronic HBV infection are the primary reservoirs of infection.

Patterns of transmission vary according to the prevalence in a particular country. In areas of high prevalence, infection is predominantly acquired by perinatal transmission in infants, or by horizontal transmission among children younger than 5 years. In low-endemicity countries, most infections are acquired in adulthood where sexual transmission or sharing blood-contaminated needles by IDUs account for most new infections. In areas of intermediate endemicity, the pattern of perinatal, childhood and adult infection is mixed and nosocomial infection may be important.

In household settings, non-sexual transmission may occur. However, the precise mechanisms of transmission are unknown but may possibly be due to contact of non-intact skin or mucous membranes with blood-containing secretions or saliva. Transmission from sharing towels, razors or toothbrushes also may occur. HBV can survive in the environment for 1 week or longer.

The risk of an infant acquiring HBV perinatally from an infected mother is 70-90% where the mother is HBsAg and hepatitis B e antigen (HBeAg) positive; the risk is 5-20% where the mother is HBsAg positive but HBeAg negative.

Effects of Hepatitis B infection

The incubation period ranges from 40 to 160 days, with an average of 60-90 days. HBV infection has different clinical manifestations depending on the patient's age at infection. In general, the frequency of clinical disease increases with age, whereas the percentage of chronic infections decreases.

Many acute infections with HBV are sub-clinical or may present with a 'flu-like illness. In patients with clinical illness, the onset is usually insidious, with tiredness, anorexia, vague abdominal discomfort, nausea and vomiting, and sometimes arthralgias and rash. Jaundice occurs in approximately 10% of young children and in 30-50% of adults. Acute HBV may occasionally lead to fulminating fatal hepatic necrosis.

Chronic infection, defined as the presence of HBsAg in the serum for at least 6 months, occurs in more than 90% of those infected perinatally, but this decreases to 20-50% in children infected between 1 and 5 years of age. Between 2 and 10% of infected immunocompetent adults become chronically infected and the risk is probably greater for those whose immunity is impaired. **Those in whom HBeAg is detectable (indicating active viral replication) are most infectious.** However, recent evidence indicates that those infected with mutant HBV may have high levels of HBV DNA in the absence of HBeAg and are therefore also highly infectious. Approximately 20-25% of individuals with chronic HBV infection develop progressive liver disease leading to cirrhosis and are at increased risk of developing hepatocellular carcinoma. Globally, HBV causes 60-80% of the world's primary liver cancers.

Hepatitis B vaccine

HBV vaccine contains recombinant HBsAg, derived from yeast cells, adsorbed onto aluminium hydroxide adjuvant. The vaccine is effective at preventing infection in individuals who produce specific antibodies to HBsAg (anti-HBs). However, around 10-15% of adults fail to respond or have a poor response to 3 doses of vaccine. Poor response is associated with age over 40 years, male gender, obesity and smoking. Lower seroconversion rates have also been reported in alcoholics, particularly those with advanced liver disease. Patients who are immunosuppressed or have chronic renal failure may respond less well and may require larger or more frequent doses of vaccine (see below).

HBV vaccine is used for pre-exposure and post-exposure protection and provides long-term protection. Pre-exposure immunisation with HBV

vaccine is the most effective means of preventing HBV transmission. Non-responders at risk of HBV exposure need to report promptly any inoculation injury, as passive prophylaxis with specific immunoglobulin may be required in these cases. Post-exposure, HBV vaccine is highly effective at preventing infection, provided that the vaccine is administered preferably within 48 hours but up to 7 days post-exposure.

Vaccine efficacy studies have shown that 90-100% of vaccinated persons who develop anti-HBs concentrations greater than or equal to 10 mIU/ml after a primary series are protected from HBV infection.

Indications

In 1992 the WHO recommended that HBV vaccine be incorporated into all national programmes by 1997.

In 2007 the National Immunisation Advisory Committee (NIAC) recommended that universal infant HBV vaccination should be introduced in Ireland. This is to run in parallel with the pre-existing targeted immunisation programme for those individuals who are at increased risk of HBV because of their occupation, lifestyle or other factors (e.g. close contact with a case or carrier).

Ideally, immunisation should be carried out **before** the risk of exposure to HBV (pre-exposure prophylaxis) but it may also follow exposure (post-exposure prophylaxis).

Pre-exposure prophylaxis

Universal immunisation

All infants should be offered HBV vaccine as part of the routine childhood immunisation schedule at 2, 4 and 6 months (see schedule Chapter 2).

Targeted immunisation programme

The following groups are at increased risk of HBV infection and should receive HBV vaccine if non-immune:

1. *Persons with occupational risk of exposure to blood or blood-contaminated environments*
 - Doctors, nurses, dentists, midwives, laboratory staff, mortuary technicians, ambulance personnel, cleaning staff, porters, medical, nursing and dental students, other health-care professionals

- Staff and carers in centres for those with learning disability (including day-care facilities, special schools and other centres)
 - Security and emergency services personnel
 - Prison staff in regular contact with prisoners
2. *Family and household contacts*
- The spouses, sexual partners, family and household contacts of acute cases and individuals with chronic infection. 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
 - Families adopting children from countries with a high or intermediate prevalence of hepatitis B. These children should be tested for evidence of current or past hepatitis B infection and the household contacts offered immunisation if required, preferably before the adoption. If the status of the child is unknown these families should be recommended vaccination
 - All short-term foster carers who receive emergency placements, and their families, should be offered HBV vaccination. Permanent foster carers, and their families, who accept a child known to be at high risk of HBV should also be offered immunisation
 - Babies born to mothers with acute or chronic HBV infection (see also *Post-exposure prophylaxis below*)
3. *Injecting drug users and their contacts*
- All IDUs
 - Sexual partners of IDUs (whether they inject or not)
 - Children of IDUs
 - Non-injecting drug-users living with current injectors
 - Those who are at risk of progressing to injecting drug use (e.g. on other illicit substances)
4. *Individuals at high risk due to medical conditions*
- People with haemophilia and those receiving regular transfusions of blood or blood products, and carers responsible for the administration of such products
 - Clients in centres for those with learning disability (including day-care facilities, special schools and other centres)
 - Patients with chronic renal failure. Early immunisation of patients with evolving chronic renal failure is advised, before they require dialysis or transplantation. The immune response to HBV may be reduced in patients with chronic renal failure compared to

- immunocompetent individuals and a more rapid decline in anti-HBs has been observed
- Patients with chronic liver disease including those with persistent hepatitis C infection. Such patients should be vaccinated against HBV as concurrent HBV infection may increase the risk of liver disease
5. *Members of other high-risk groups*
- Individuals who change sexual partner frequently, men who have sex with men (MSM), male and female commercial sex workers, attendees at clinics for sexually transmitted infections (STIs) and those diagnosed with an STI
 - Inmates of custodial institutions
 - Tattoo and body piercing artists/practitioners
 - Immigrants from areas with a high or intermediate prevalence of HBV
 - Travellers to areas with a high or intermediate prevalence of HBV
 - Homeless people
 - Children born to parents from high or intermediate endemicity countries

Post-vaccination serological testing

Routine post-vaccination testing for anti-HBs is recommended 2 months after completing the course of vaccination for persons who are at continuing risk of HBV exposure, e.g. health-care workers, patients on renal dialysis, sexual partners of HBsAg positive persons. This does not apply to children receiving routine childhood immunisation with hepatitis B vaccine.

Following primary vaccination, it is preferable to achieve anti-HBs levels above 100 mIU/ml although levels above 10 mIU/ml are generally accepted as protecting against infection. Anti-HBs titre often declines post-vaccination but a rapid anamnestic response develops after exposure to the virus.

Table 6.1 Actions required following post-vaccination testing (except for patients with renal failure)

Anti-HBs level	Action required
0 or <10 mIU/ml	Non responder. It is advisable to test for anti-HBc*. If anti-HBc negative, repeat full course of hepatitis B vaccine (a different brand of vaccine is advised). Recheck anti-HBs at 2 months post completion. If anti-HBs remains <10 mIU/ml, person is susceptible to HBV.
10-99 mIU/ml	Low response. If low level anti-HBs confirmed by 2 different assays, administer booster dose of vaccine but there is no need to retest for anti-HBs.
100 mIU/ml or greater	Good response. No need for further vaccination or anti-HBs investigations.

*For those who are performing exposure-prone procedures, HBsAg testing should also be carried out.

Table 6.2: Actions required following post-vaccination testing for patients with renal failure* (If there is no evidence of HBV infection)

Anti-HBs level	Action required
0 or <10 mIU/ml	<p>Non responder. Repeat full course of hepatitis B vaccine (a different brand of vaccine is advised). Recheck anti-HBs 2-months post completion. If anti-HBs remains <10 mIU/ml, person is susceptible to HBV.</p> <p>– Test for HBsAg every month</p>
10-99 mIU/ml	<p>Low response. Give booster dose of vaccine. Check anti-HBs 2 months later using 2 different assays. Adequate response if both ≥ 10 mIU/ml. Re-check anti-HBs annually and if anti-HBs decreases to <10 mIU/ml give booster dose but no need to check the anti-HBs level until next annual check is due.</p> <p>– Test for HBsAg every 3 months</p>
100 mIU/ml or greater	<p>Good response. Re-check anti-HBs annually and if anti-HBs decreases to <10 mIU/ml give booster dose but no need to check the anti-HBs level until next annual check is due.</p>

* REF: The Prevention of Transmission of Blood-Borne Diseases in the Health Care Setting 2005

Booster doses

To date there are no conclusive data to support the need for booster doses of HBV vaccine in immunocompetent individuals who have responded to a primary course. Studies have shown that those who show a protective response after vaccination are protected for at least 15 years and it is likely that protection is life-long.

For haemodialysis patients and other immunocompromised people at continued risk of infection, the need for booster doses should be assessed by annual anti-HBs testing, and a booster dose should be given if the anti-HBs level is <10 mIU/ml.

Dose

Currently licensed vaccines contain different concentrations of antigen per ml. The appropriate manufacturer's dosage should be adhered to. **Higher doses of vaccine (40 mcg) should be used for adult patients with chronic renal failure, and considered for other immunosuppressed adults.**

Schedules

(a) *Infant HBV vaccination*

HBV vaccine should be administered at 2, 4 and 6 months of age as part of the routine childhood immunisation schedule.

(b) *Vaccination of those other than infants*

The basic schedule consists of three doses of vaccine at 0, 1 month and 6 months.

Alternative accelerated schedules (e.g. 0, 1 and 2 months; 0, 7 and 21 days) exist (see manufacturer's guidelines) if more rapid protection is required for those at immediate risk or for those where compliance with the duration of the basic schedule is difficult to achieve. These should be followed by a dose of vaccine at 12 months to complete the course.

Route of administration

The vaccine is given intramuscularly in the deltoid region. In the case of infants, the vaccine may be given in the anterolateral thigh. The gluteal region should not be used as the vaccine efficacy may be reduced. Exceptionally, the vaccine may be administered by deep subcutaneous injection in patients at risk of haemorrhage.

Hepatitis B vaccine should not be given in the gluteal region.

Vaccine interchangeability

Different HBV 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 HBV vaccine. **One of the licensed higher dose vaccine products (used for adult patients with chronic renal failure, and considered for other immunosuppressed adults) is NOT interchangeable.**

Contraindications

Anaphylactic reaction to a preceding dose of a HBV-containing vaccine or any of the constituents.

Precautions

Acute severe febrile illness, defer until recovery. The response may be impaired in those who are immunocompromised, and a further dose of vaccine may be necessary.

Pregnancy and breastfeeding

No adverse effect on the developing foetus has been observed when pregnant women have been immunised against HBV. Because HBV infection may result in severe disease in the mother and chronic infection in the newborn infant, pregnancy is not a contraindication to immunisation. If an antenatal patient is HBsAg negative but at risk of HBV infection, she should be immunised during pregnancy. Breastfeeding is not a contraindication to immunisation.

Adverse reactions

Local: Hepatitis B vaccine is generally well tolerated. The commonest reactions are soreness and redness at the injection site.

General: Fever, rash, malaise and influenza-like symptoms are less commonly reported after vaccination.

Post-exposure prophylaxis

Specific hepatitis B immunoglobulin (HBIG) is available for passive protection and is normally used in combination with HBV vaccine to confer passive/active immunity after exposure. At present only one HBIG preparation is authorised in Ireland and this is an intravenous preparation. HBIG provides short-term protection (3-6 months).

Post-exposure prophylaxis is recommended for the following groups

1. Babies born to mothers who are HBV infected (HBsAg positive)

Perinatal transmission of HBV infection can be prevented in approximately 95% of infants born to HBsAg positive mothers by early active and passive immunoprophylaxis of the infant. Routine screening of all antenatal patients for HBsAg is essential for identifying women whose infants will require post-exposure immunoprophylaxis beginning at birth. All babies born to these mothers should receive a complete course of vaccine at 0, 2, 4 and 6 months and also HBIG within 24 hours of birth. The doses at 2, 4 and 6 months may be given as the routine 6 in 1. Following the administration of HBIG and the first dose of vaccine, arrangements should be made to follow up the child for serological assessment and subsequent doses of vaccine.

Pre-term babies: It is important that premature infants receive the full paediatric dose of HBV vaccine, and HBIG.

Hepatitis B vaccine should be administered concurrently with HBIG in the anterolateral thigh (in a different site from the HBIG).

Infants born to mothers who are HBV infected should be tested 2 months after completing HBV immunisation to determine HBV status and post-vaccination response.

2. Household exposures

HBIG and hepatitis B vaccine are recommended for unimmunised infants under 12 months of age if the mother or primary care giver has acute HBV infection. Prophylaxis with HBIG is not indicated for other unimmunised household members of persons with acute HBV infection unless they have identifiable blood exposure to the index patient, such as by sharing of toothbrushes or razors. Such exposures should be managed as in sexual exposures. All household contacts of acute and chronic cases should be screened and offered hepatitis B vaccine if susceptible.

Vaccination should not be delayed while waiting for results of the tests.

3. Sexual exposure

Exposure to acute cases: Sexual partners of individuals suffering from acute hepatitis B and who are seen within one week of last contact should be offered both HBIG and vaccine.

Exposure to chronic cases: Sexual contacts of newly identified chronic cases should be offered vaccine. HBIG may be added if unprotected sexual contact occurred in the past week (a risk assessment may be needed depending on whether the contact is a long-term sexual partner or recent partner).

4. HCW or others accidentally exposed to blood or body fluids

Individuals who sustain such injuries should wash the affected area well with soap and warm water and seek medical advice. The response required in terms of vaccination and/or HBIG will depend on a detailed risk analysis of the source, the vaccination/anti-HBs status of the person exposed, and the type of exposure. The appropriate prophylaxis should be commenced immediately according to Table 6.3.

A significant exposure is one from which HBV transmission may result:

- Percutaneous exposure to blood or body fluids, e.g. needlestick or other contaminated sharp object injury, a bite that causes

- bleeding or other visible skin puncture
- Mucocutaneous exposure to blood or body fluids, e.g. contamination of non-intact skin, conjunctiva or mucous membrane
- Sexual exposure (unprotected sexual intercourse, oral sex)
- Community needlestick injury (discarded needles and syringes in public places)

Dose and route of administration of HBIG

HBIG should be administered according to the manufacturer's guidelines and should ideally be given within 48 hours of exposure but not later than a week after exposure.

Injuries from discarded needles in the community

Injuries from discarded needles and syringes in public places create considerable anxiety regarding the possible transmission of blood-borne pathogens. While these injuries pose less of a risk than that resulting from a needlestick injury in health-care settings, the perception of risk often results in the necessity for evaluation, testing and counselling of the injured person.

Management of such injuries includes acute wound care and consideration of the need for prophylactic management. Hepatitis B virus is the most stable of the major blood-borne viral pathogens and can survive in the environment for 1 week or longer. It is advisable to administer a full course of HBV vaccine to those susceptible to HBV infection. HBIG is not usually required unless the needle comes from a known hepatitis B positive source and a risk assessment identifies a significant risk of HBV transmission. The likelihood of transmission of other blood-borne viruses such as hepatitis C or HIV is very remote.

Recommendation: archive a baseline serum specimen from the injured person, initiate hepatitis B vaccination and test samples collected at 3 and 6 months for HBsAg and anti-HBc, and at 2 months post-completion of course of vaccination, for anti-HBs.

Interpretation of Hepatitis B results is set out in Table 6.4, provided for reference.

Table 6.3 Hepatitis B vaccine prophylaxis for reported exposure incidents

Significant exposure			Non-significant exposure		
Vaccination status of person exposed	HBsAg-negative source	Unknown source ⁽¹⁾	HBsAg-positive source	Continued risk	No further risk
≤1 Dose HBV vaccine pre-exposure	Initiate/ finish course of HBV vaccine	Accelerated course of HBV vaccine ⁽²⁾	Accelerated course of HBV vaccine ⁽²⁾ HBIG x1 ⁽³⁾	Initiate course of HBV vaccine	Initiate course of HBV vaccine
≥2 doses HBV vaccine pre-exposure	Finish course of HB vaccine	One dose of HBV vaccine	One dose of HBV vaccine followed by second dose one month later	Finish course of HBV vaccine	Finish course of HBV vaccine
Known responder to HBV vaccine (anti-HBs ≥10 mIU/ml)	Consider booster dose of HBV vaccine	Consider booster dose of HBV vaccine	Booster dose of HBV vaccine	Consider booster dose of HBV vaccine	No HBV prophylaxis Reassure
Known non responder to HBV vaccine (anti-HBs <10mIU/ml 2-4 months post vaccination)	Give second course of vaccine if not previously received	HBIG x 1 dose ^(1,4) and initiate reimmunisation or HBIG x 2 doses	HBIG x 1 dose ⁽⁴⁾ and initiate reimmunisation or HBIG x 2 doses	Give second course of vaccine if not previously received	Give second course of vaccine if not previously received

⁽¹⁾ If the patient source is not known, individual assessment of each case should be made.

⁽²⁾ An accelerated course of vaccine consists of doses spaced at 0, 1 and 2 months. A booster dose is given at 12 months to those at continuing risk of exposure to HBV.

⁽³⁾ HBIG should be given preferably within 48 hours and not later than a week after exposure.

⁽⁴⁾ The option of giving 1 dose of HBIG and reinitiating the vaccine course is preferred for nonresponders who have not completed a second 3-dose course. For people who previously completed a second vaccine course but failed to respond, 2 doses of HBIG are preferred, 1 dose as soon as possible after exposure and the second 1 month later.

Table 6.4 Interpretation of hepatitis B results

HBsAg	HBsAg	Anti-HBe	IgM	Anti-HBc	Total anti-HBc	Anti-HBs	Interpretation
Neg	Neg	Neg	Neg	Neg	Neg	Neg	Susceptible to HBV
POS	POS	Neg	Neg	Neg	Neg	Neg	Acute HBV infection
POS	POS	Neg	POS	POS	POS/Neg	Neg	Acute HBV infection
Neg	Neg	Neg	POS	POS	POS*	Neg	Recent HBV infection (HBsAg window)
POS	POS	Neg	WEAK POS/ Neg	POS	POS	Neg	Chronic HBV infection**
POS	Neg	Neg	WEAK POS/ Neg	POS	POS	Neg	HBeAg neg chronic HBV infection***
Neg	Neg	POS/ Neg	Neg	POS*	POS*	POS/Neg	Resolved HBV infection
Neg	Neg	Neg	Neg	Neg	Neg	POS	Response to HBV vaccine

Notes

*Anti-HBc detected in 2 assays

**Follow-up sample required to confirm chronic HBV infection

***Follow-up sample required and also HBV DNA viral investigations may be required

Bibliography

American Academy of Pediatrics (2006). Red Book: 2006 Report of the Committee on Infectious Diseases. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics.

CDC (2005). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). Part 1: immunization of infants, children, and adolescents. MMWR:54 (No. RR-16).

CDC (2006). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). Part 11: immunization of adults. MMWR:55 (No. RR-16).

Department of Health and Children (2005). The prevention of transmission of blood-borne diseases in the health-care setting. Department of Health and Children.

Department of Health UK (2006). Immunisation against infectious disease (the Green Book). 3rd ed. Chapter 18 Hepatitis B. London: The Stationery Office.

European Consensus Group on Hepatitis B Immunity (2000). Are booster immunisations needed for lifelong hepatitis B immunity? Lancet; 355(9203):561-5.

HPSC (2007). Report on Hepatitis B Notifications in Q4 2006 & provisional annual summary for 2006. Available at: [www.ndsc.ie/hpsc/A-Z/HepatitisHIVAIDSandSTIs/HepatitisB/Surveillance Reports/HepatitisBNotificationsQuarterlyReports/File,2238,en.pdf](http://www.ndsc.ie/hpsc/A-Z/HepatitisHIVAIDSandSTIs/HepatitisB/Surveillance%20Reports/HepatitisBNotificationsQuarterlyReports/File,2238,en.pdf)

World Health Organization (2002). Hepatitis B. Available at www.who.int/csr/disease/hepatitis/HepatitisB_who.cdscsrlyo2002_2.pdf

