Uses and Administration

Hepatitis B immunoglobulins are used for passive immunisation of persons exposed or possibly exposed to hepatitis B virus, including by sexual contact. They are not appropriate for treatment. Hepatitis B immunoglobulins should always be given in addition to active immunisation with hepatitis B vaccine in at-risk patients exposed to hepatitis B virus.

In the UK, a hepatitis B immunoglobulin containing 100 international units/mL is available for intramuscular use. The dose in adults and children over 10 years of age is a single dose of 500 international units by intramuscular injection given preferably within 48 hours of exposure and not more than 1 week after exposure. Children aged 5 to 9 years may be given 300 international units, and children under 5 years 200 international units. Hepatitis B immunoglobulin should also be given to newborn infants at risk whose mothers are persistent carriers of hepatitis B surface antigen or whose mothers are HBsAg-positive as a result of recent infection. The dose is 200 international units by intramuscular injection preferably at birth, and certainly within 24 hours of birth.

There is now a UK and European standard for a preparation for intravenous use containing not less than 50 international units/mL.

In the USA, a hepatitis B immunoglobulin containing 15 to 18% of protein is available for intramuscular use. The dose for adults is 0.06 mL/kg. A dose of 0.5 mL is given to infants perinatally exposed to hepatitis B; this appears to be a significantly lower dose than that used in the UK. A hepatitis B immunoglobulin is also available for the prevention of hepatitis B recurrence after liver transplantation in patients who are positive for hepatitis B surface antigen. It is given intravenously at a dose of 20 000 international units during surgery and then daily from day 1 to day 7 after transplant surgery, then every 2 weeks from week 2 to week 12, and then monthly from 4 months post-surgery.

Preparation strength. *The content of hepatitis B immunoglobulin may vary between countries and between manufacturers. Care should be taken in interpreting dosage recommendations which are not given in terms of international units.* Products available in the USA have their strength expressed with reference to an FDA standard but are considered to contain the equivalent of at least 200 international units/mL.

Monoclonal antibodies. The name tuvirumab is applied to a human hepatitis B monoclonal antibody. A murine monoclonal antibody has been tried in a few patients with primary antibody deficiency.[1]

1. Lever AML, *et al.* Monoclonal antibody to HBsAg for chronic hepatitis B virus infection with hypogammaglobulinaemia. *Lancet* 1990; **335:** 1529.

Organ and tissue transplantation. Studies[1-5] in patients positive for hepatitis B surface antigen undergoing liver transplantation (p.1815) suggest that long-term passive immunisation with hepatitis B immunoglobulin could reduce hepatitis B reinfection and improve survival in these patients.

1. Samuel D, *et al.* Passive immunoprophylaxis after liver transplantation in HBsAg-positive patients. *Lancet* 1991; **337:** 813–15.
2. Nymann T, *et al.* Prevention of hepatitis B recurrence with indefinite hepatitis B immune globulin (HBIG) prophylaxis after liver transplantation. *Clin Transplant* 1996; **10:** 663–7.
3. McGory RW, *et al.* Improved outcome of orthotopic liver transplantation for chronic hepatitis B cirrhosis with aggressive passive immunization. *Transplantation* 1996; **61:** 1358–64.
4. Terrault NA, *et al.* Prophylaxis in liver transplant recipients using a fixed dosing schedule of hepatitis B immunoglobulin. *Hepatology* 1996; **24:** 1327–33.
5. Sanchez-Fueyo A, *et al.* Hepatitis B immunoglobulin discontinuation followed by hepatitis B virus vaccination: a new strategy in the prophylaxis of hepatitis B virus recurrence after liver transplantation. *Hepatology* 2000; **31:** 496–501.

Postexposure prophylaxis. For discussion of the use of hepatitis B immunoglobulins in patients exposed to hepatitis B virus, see Postexposure Prophylaxis under Uses and Administration of Hepatitis B Vaccines, below.

Preparations

Ph. Eur.: Human Hepatitis B Immunoglobulin; Human Hepatitis B Immunoglobulin for Intravenous Administration;
USP 31: Hepatitis B Immune Globulin.

Proprietary Preparations (details are given in Part 3)
Arg.: Antib; Igantibe; ***Austria:*** Aunativ†; Hepatect; ***Belg.:*** Hepacaf; ***Canad.:*** BayHep B†; HyperHep B; ***Chile:*** Igantibe; ***Cz.:*** Aunativ†; Hepatect†; NeoHepatect; ***Denm.:*** Aunativ†; ***Fr.:*** Ivhebex; ***Ger.:*** Hepatect; ***Gr.:*** Aunativ; Ivhebex; ***Hong Kong:*** BayHep B; Hepatect†; Hepuman†; ***Hung.:*** Hepatect; ***Indon.:*** HyperHep B; ***Irl.:*** Hepatect; ***Israel:*** BayHep; Hepatect; Omri-Hep-B; ***Ital.:*** Haimabig†; Hepuman B†; Igantibe; ImmunoHBs; Neohepatect; Uman-Big†; Venbig; ***Jpn:*** Hebsbulin-IH; ***Malaysia:*** Hepabig; ***Neth.:*** Hepatect; HepBQuin; ***Norw.:*** Aunativ†; ***NZ:*** HyperHep B; ***Philipp.:*** BayHep B; Hepabig; ***Pol.:*** Gamma Anty HBs; Hepatect; ***Port.:*** Hepatect; Venbig; ***Rus.:*** Antihep (Антиген)†; ***S.Afr.:*** Hebagam IM; ***Singapore:*** BayHep B†; ***Spain:*** Gamma Antihepatitis B; Gammaglob Antihepatitis BP; Hepuman; ***Swed.:*** Aunativ; ***Switz.:*** Hepatect; Hepuman†; ***Turk.:*** BayHep B; Hepatect; Hepatitis B Ig-P; Hepuman; ***USA:*** HepaGam B; HyperHep B; Nabi-HB.

Hepatitis B Vaccines

Vacunas de la hepatitis B.
ATC — J07BC01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) have monographs.
Ph. Eur. 6.2 (Hepatitis B Vaccine (rDNA); Vaccinum Hepatitidis B (ADNr)). A preparation of hepatitis B surface antigen, that is obtained by recombinant DNA technology. It should be stored at a temperature of 2° to 8°, not be allowed to freeze, and be protected from light. Under these storage conditions it may be expected to retain its potency for 24 months.
The BP 2008 states that Hep B may be used on the label.

Adverse Effects

As for vaccines in general, p.2201.

In addition, abdominal pain and gastrointestinal disturbance, and musculoskeletal and joint pain and inflammation have been reported after hepatitis B vaccines. There may also be dizziness and sleep disturbance. Cardiovascular effects include occasional hypotension and, rarely, tachycardia. Other rare adverse effects include dysuria, visual disturbances, and earache.

◊ General references.

1. McMahon BJ, *et al.* Frequency of adverse reactions to hepatitis B vaccine in 43,618 persons. *Am J Med* 1992; **92:** 254–6.
2. Anonymous. Adverse events after hepatitis B vaccination. *Can Med Assoc J* 1992; **147:** 1023–6.
3. Duclos P. Safety of immunisation and adverse events following vaccination against hepatitis B. *Expert Opin Drug Saf* 2003; **2:** 225–31.
4. Autret-Leca E, *et al.* Tolérance du vaccin contre l'hépatite B: exemple d'une complémentarité notification spontanée/études pharmacoépidémiologiques. *Presse Med* 2007; **36:** 563–4.

Effects on the blood. Rare cases of thrombocytopenia[1-4] and pancytopenia[5] associated with hepatitis B vaccination have been reported.

1. Poullin P, Gabriel B. Thrombocytopenic purpura after recombinant hepatitis B vaccine. *Lancet* 1994; **344:** 1293.
2. Meyboom RHB, *et al.* Thrombocytopenia reported in association with hepatitis B and A vaccines. *Lancet* 1995; **345:** 1638.
3. Ronchi F, *et al.* Thrombocytopenic purpura as adverse reaction to recombinant hepatitis B vaccine. *Arch Dis Child* 1998; **78:** 273–4.
4. Nuevo H, *et al.* Thrombocytopenic purpura after hepatitis B vaccine: case report and review of the literature. *Pediatr Infect Dis J* 2004; **23:** 183–4.
5. Viallard JF, *et al.* Severe pancytopenia triggered by recombinant hepatitis B vaccine. *Br J Haematol* 2000; **110:** 230–3.

Effects on bones and joints. Reactive arthritis[1-3] and Reiter's syndrome[2] have been reported after hepatitis B vaccination. There have also been isolated reports of rheumatoid arthritis occurring after hepatitis B vaccination[3,4] and a suggestion that hepatitis B vaccination may trigger the onset of underlying SLE.[5] A number of reports of arthralgia have been received by the UK CSM and by the manufacturers of *Engerix B*.[2]

1. Rogerson SJ, Nye FJ. Hepatitis B vaccine associated with erythema nodosum and polyarthritis. *BMJ* 1990; **301:** 345.
2. Hassan W, Oldham R. Reiter's syndrome and reactive arthritis in health care workers after vaccination. *BMJ* 1994; **309:** 94–5.
3. Gross K, *et al.* Arthritis after hepatitis B vaccination: report of three cases. *Scand J Rheumatol* 1995; **24:** 50–2.
4. Pope JE, *et al.* The development of rheumatoid arthritis after recombinant hepatitis B vaccination. *J Rheumatol* 1998; **25:** 1687–93.
5. Maillefert JF, *et al.* Rheumatic disorders developed after hepatitis B vaccination. *Rheumatology (Oxford)* 1999; **38:** 978–83.

Effects on the eyes. There have been isolated case reports of acute posterior uveitis,[1] visual loss associated with eosinophilia,[2] acute posterior multifocal placoid pigment epitheliopathy,[3] central retinal vein occlusion,[4] and multiple evanescent white dot syndrome[5] after vaccination against hepatitis B.

For mention of optic neuritis in patients receiving hepatitis B vaccine, see under Effects on the Nervous System, below.

1. Fried M, *et al.* Uveitis after hepatitis B vaccination. *Lancet* 1987; **ii:** 631–2.
2. Brézin AP, *et al.* Visual loss and eosinophilia after recombinant hepatitis B vaccine. *Lancet* 1993; **342:** 563–4.
3. Brézin AP, *et al.* Acute posterior multifocal placoid pigment epitheliopathy after hepatitis B vaccine. *Arch Ophthalmol* 1995; **113:** 297–300.
4. Devin F, *et al.* Occlusion of central retinal vein after hepatitis B vaccination. *Lancet* 1996; **347:** 1626.
5. Baglivo E, *et al.* Multiple evanescent white dot syndrome after hepatitis B vaccine. *Am J Ophthalmol* 1996; **122:** 431–2.

Effects on the kidneys. There have been case reports of acute glomerulonephritis in patients after hepatitis B vaccine.[1,2]

1. Carmeli Y, Oren R. Hepatitis B vaccine side-effect. *Lancet* 1993; **341:** 250–1.
2. Pennesi M, *et al.* Glomerulonephritis after recombinant hepatitis B vaccine. *Pediatr Infect Dis J* 2002; **21:** 172–3.

Effects on the liver. There have been occasional reports of transient abnormalities in liver function associated with hepatitis B vaccine.[1-3] The appearance of autoantibodies has been reported in a patient,[2] and severe cytolysis consistent with an allergic mechanism in another.[3]

1. Rajendran V, Brooks AP. Symptomatic reaction to hepatitis B vaccine with abnormal liver function values. *BMJ* 1985; **290:** 1476.
2. Lilic D, Ghosh SK. Liver dysfunction and DNA antibodies after hepatitis B vaccination. *Lancet* 1994; **344:** 1292–3.
3. Germanaud J, *et al.* A case of severe cytolysis after hepatitis B vaccination. *Am J Med* 1995; **98:** 595.

Effects on the nervous system. In the years 1982 to 1985 the Centers for Disease Control, the FDA, and the manufacturer of plasma-derived hepatitis B vaccine received 41 reports of adverse neurological effects.[1] It was estimated that about 850 000 persons had received the vaccine in this time. Neurological events were convulsions (5 cases), Bell's palsy (10), Guillain-Barré syndrome (9), lumbar radiculopathy (5), brachial plexus neuropathy (3), optic neuritis (5), and transverse myelitis (4). In some analyses Guillain-Barré syndrome was reported significantly more often than expected. However, no conclusive epidemiological association could be made between any neurological adverse effect and the vaccine.

In France, spontaneous reports of multiple sclerosis and central demyelinating disease in patients who had received hepatitis B vaccine led to the suspension by the French authorities of hepatitis B vaccination in schools in 1998. This decision was widely condemned by many authorities including WHO, the US National Multiple Sclerosis Society, and the Viral Hepatitis Prevention Board, and there was a fear that reduced confidence in the vaccine could have a profound effect on uptake. Arguments[2] against a link between hepatitis B vaccine and multiple sclerosis include the lack of correlation between the incidence of hepatitis B infection and demyelinating diseases, data from clinical studies including extensive postmarketing surveillance, and analysis of the French cases which concluded that the incidence of multiple sclerosis amongst vaccine recipients was not higher than would be expected in the population as a whole. A consultative group concluded[3] that, in the light of the evidence, the benefits of hepatitis B vaccination supported current WHO recommendations that all countries should have universal infant and/or adolescent hepatitis B immunisation programmes and that adults at increased risk of infection should also be immunised. More recent studies[4,5] have also indicated no association between hepatitis B vaccine and multiple sclerosis, although one study[6] did suggest a threefold increase in risk.

1. Shaw FE, *et al.* Postmarketing surveillance for neurologic adverse events reported after hepatitis B vaccination: experience of the first three years. *Am J Epidemiol* 1988; **127:** 337–52.
2. Anonymous. Expanded Programme on Immunization (EPI): lack of evidence that hepatitis B vaccine causes multiple sclerosis. *Wkly Epidem Rec* 1997; **72:** 149–52.
3. Halsey NA, *et al.* Hepatitis B vaccine and central nervous system demyelinating diseases. *Pediatr Infect Dis J* 1999; **18:** 23–4.
4. Ascherio A, *et al.* Hepatitis B vaccination and the risk of multiple sclerosis. *N Engl J Med* 2001; **344:** 327–32.
5. Mikaeloff Y, *et al.* Hepatitis B vaccination and the risk of childhood-onset multiple sclerosis. *Arch Pediatr Adolesc Med* 2007; **161:** 1176–82.
6. Hernán MA, *et al.* Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study. *Neurology* 2004; **63:** 838–42.

Effects on the skin. Skin reactions, which have been reported in a few individuals after hepatitis B vaccination, include erythema multiforme,[1,2] erythema nodosum,[3-5] lichen planus,[6-8] and vasculitis.[9,10]

1. Feldshon SD, Sampliner RE. Reaction to hepatitis B virus vaccine. *Ann Intern Med* 1984; **100:** 156–7.
2. Wakeel RA, White MI. Erythema multiforme associated with hepatitis B vaccine. *Br J Dermatol* 1992; **126:** 94–5.
3. Di Giusto CA, Bernhard JD. Erythema nodosum provoked by hepatitis B vaccine. *Lancet* 1986; **ii:** 1042.
4. Goolsby PL. Erythema nodosum after Recombivax HB hepatitis B vaccine. *N Engl J Med* 1989; **321:** 1198–9.
5. Rogerson SJ, Nye FJ. Hepatitis B vaccine associated with erythema nodosum and polyarthritis. *BMJ* 1990; **301:** 345.
6. Ciaccio M, Rebora A. Lichen planus following HBV vaccination: a coincidence? *Br J Dermatol* 1990; **122:** 424.
7. Ferrnado MF, *et al.* Lichen planus following hepatitis B vaccination. *Br J Dermatol* 1998; **139:** 350.
8. Usman A, *et al.* Lichenoid eruption following hepatitis B vaccination: first North American case report. *Pediatr Dermatol* 2001; **18:** 123–6.
9. Cockwell P, *et al.* Vasculitis related to hepatitis B vaccine. *BMJ* 1990; **301:** 1281.
10. Le Helto C, *et al.* Suspected hepatitis B vaccination related vasculitis. *J Rheumatol* 1999; **26:** 191–4.

Hypersensitivity. There have been reports of hypersensitivity reactions after hepatitis B vaccination that have been attributed to components of the vaccines, including formaldehyde,[1] thiomersal,[2] and *Saccharomyces cerevisiae*.[3]

1. Ring J. Exacerbation of eczema by formalin-containing hepatitis B vaccine in formaldehyde-allergic patient. *Lancet* 1986; **ii:** 522–3.
2. Noel I, *et al.* Hypersensitivity to thiomersal in hepatitis B vaccine. *Lancet* 1991; **338:** 705.
3. Brightman CAJ, *et al.* Yeast-derived hepatitis B vaccine and yeast sensitivity. *Lancet* 1989; **i:** 903.

Precautions

As for vaccines in general, p.2202.

Reduced immune response. The immune response to hepatitis B vaccine is dependent on both host- and immunisation-related factors.[1] Host-related factors that appear to diminish the response include increasing age, increasing body-weight, smoking,[1,2] and male sex;[3] particular HLA haplotypes may also be associated with poor response.[4] Failure of hepatitis B immunisa-

tion in infants could be related to high perinatal maternal viraemia[5] rather than to inherent resistance to the vaccine.

Some studies have found a defective response in chronic alcoholics[6,7] whereas others have not;[8] the degree of liver impairment may be a significant factor. It has been suggested that an increased dose of hepatitis B vaccine may be appropriate in those with a history of alcoholism.[9] Active infection with *Schistosoma mansoni* also appears to decrease the response to hepatitis B vaccination.[10] A diminished response occurs in HIV-positive patients[11-13] and in patients on haemodialysis;[1] an increased dose of hepatitis B vaccine is recommended in these patients. In patients with haemophilia who are not HIV-positive[14] immunity is reported to wane rapidly after vaccination and frequent booster doses may be required. Biological response modifiers such as thymopentin[15] and interferon[16] have been used successfully in some patients on haemodialysis to overcome the immune deficit. Use of interleukin-2 has met with variable success. Granulocyte-macrophage colony-stimulating factor has also been investigated as an adjuvant for hepatitis B vaccination in healthy subjects, patients with chronic renal failure or on haemodialysis, and in HIV-infected patients. Overall, the colony-stimulating factor appears to improve seroconversion rates and antibody titres, but further study is needed.[17]

The immune response to hepatitis B vaccine is affected by the site of intramuscular injection. The deltoid region is recommended for adults and the anterolateral thigh for infants. A diminished response has been associated with injection into the gluteal region (buttock).[1]

A related problem is posed by subjects who become infected with hepatitis B despite mounting an adequate response to immunisation. In one study, evidence of viral replication was detected in 44 of 1590 hepatitis B vaccinees despite development of protective titres of antibody.[18] Acute hepatitis occurred in one patient. Although the infection may have been incubating at the time of vaccination, the virus isolated from the child with acute disease was an escape mutant with a different DNA sequence from that isolated from the mother.

1. Hollinger FB. Factors influencing the immune response to hepatitis b vaccine, booster dose guidelines, and vaccine protocol recommendations. *Am J Med* 1989; **87** (suppl 3A): 36S–40S.
2. Horowitz MM, *et al.* Duration of immunity after hepatitis B vaccination: efficacy of low-dose booster vaccine. *Ann Intern Med* 1988; **108:** 185–9.
3. Morris CA, *et al.* Intradermal hepatitis B immunization with yeast-derived vaccine: serological response by sex and age. *Epidemiol Infect* 1989; **103:** 387–94.
4. Alper CA, *et al.* Genetic prediction of nonresponse to hepatitis B vaccine. *N Engl J Med* 1989; **321:** 708–12.
5. del Canho R, *et al.* Failure of neonatal hepatitis B vaccination: the role of HBV-DNA levels in hepatitis B carrier mothers and HLA antigens in neonates. *J Hepatol* 1994; **20:** 483–6.
6. Degos F, *et al.* Hepatitis B vaccination and alcoholic cirrhosis. *Lancet* 1983; **ii:** 1498.
7. Mendenhall C, *et al.* Hepatitis B vaccination: response of alcoholic with and without liver injury. *Dig Dis Sci* 1988; **33:** 263–9.
8. McMahon BJ, *et al.* Response to hepatitis B vaccine in Alaska Natives with chronic alcoholism compared with non-alcoholic control subjects. *Am J Med* 1990; **88:** 460–4.
9. Rosman AS, *et al.* Efficacy of a high and accelerated dose of hepatitis B vaccine in alcoholic patients: a randomized clinical trial. *Am J Med* 1997; **103:** 217–22.
10. Ghaffar YA, *et al.* Response to hepatitis B vaccine in infants born to mothers with schistosomiasis. *Lancet* 1989; **ii:** 272.
11. Carne CA, *et al.* Impaired responsiveness of homosexual men with HIV antibodies to plasma derived hepatitis B vaccine. *BMJ* 1987; **294:** 866–8.
12. Collier AC, *et al.* Antibody to human immunodeficiency virus (HIV) and suboptimal response to hepatitis B vaccination. *Ann Intern Med* 1988; **109:** 101–5.
13. Chan W, *et al.* Response to hepatitis B immunization in children with hemophilia: relationship to infection with human immunodeficiency virus type 1. *J Pediatr* 1990; **117:** 427–30.
14. Maris JM, *et al.* Loss of detectable antibody to hepatitis B surface antigen in immunized patients with hemophilia but without human immunodeficiency virus infection. *J Pediatr* 1995; **126:** 269–71.
15. Donati D, Gastaldi L. Controlled trial of thymopentin in hemodialysis patients who fail to respond to hepatitis B vaccination. *Nephron* 1988; **50:** 133–6.
16. Quiroga JA, Carreño V. Interferon and hepatitis B vaccine in haemodialysis patients. *Lancet* 1989; **i:** 1264.
17. Cruciani M, *et al.* Granulocyte macrophage colony-stimulating factor as an adjuvant for hepatitis B vaccination: a meta-analysis. *Vaccine* 2007; **25:** 709–18.
18. Carman WF, *et al.* Vaccine-induced escape mutant of hepatitis B virus. *Lancet* 1990; **336:** 325–9.

Uses and Administration

Hepatitis B vaccines are used for active immunisation against hepatitis B infection. Two types of vaccine have been available, each containing hepatitis B surface antigen (HBsAg) adsorbed onto aluminium hydroxide or a similar adsorbent. The type of vaccine in which the surface antigen is produced in yeast cells using recombinant DNA techniques is now widely used and there has been considerable interest in further developments to improve immunogenicity. The second type of vaccine, in which the surface antigen is obtained from plasma after purification and inactivation processes is now not generally available.

WHO had recommended that national immunisation policies should include routine hepatitis B immunisation for the whole population by 1997 and this has been implemented in some countries including the USA (see Administration, below). The current recommendations in the UK are for immunisation of persons at high risk of contracting hepatitis B. High-risk groups include:

- health care personnel, laboratory workers, or any other personnel who have direct contact with patients or their body fluids or tissues
- staff and residents of accommodation for those with severe learning difficulties
- patients with chronic liver disease
- patients with chronic renal failure including those requiring haemodialysis
- haemophiliacs and those receiving regular blood transfusions or blood products
- close family contacts or sexual partners of cases or carriers of hepatitis B
- families adopting children from countries with a high prevalence of hepatitis B
- foster carers
- individuals who frequently change sexual partners
- parenteral drug abusers
- inmates of custodial institutions
- some travellers to areas where hepatitis B is endemic
- infants born to women who are persistent carriers of hepatitis B surface antigen or infants born to women who are HBsAg-positive as a result of recent infection

Hepatitis C carriers who are not immunised against hepatitis B should also receive immunisation.

A basic immunisation schedule consists of 3 doses of a hepatitis B vaccine, with the second and third doses 1 and 6 months, respectively, after the first. In the USA, some products may be given in an alternative 2-dose regimen to adolescents with doses given 4 to 6 months apart. Doses should be given intramuscularly, with the deltoid region being the preferred site in adults and older children and the anterolateral thigh the preferred site in neonates, infants, and younger children; the gluteal region (buttock) should not be used as efficacy may be reduced. The subcutaneous route should be used in patients with haemophilia. The dose of the recombinant vaccine depends on the product used. Typical doses for adults are 10 or 20 micrograms and for infants and children 5 or 10 micrograms. Products containing 40 micrograms are available for adult dialysis and predialysis patients who have a reduced immune response to the vaccine. However, *the dose of one recombinant preparation should not be seen as equivalent to the dose of another.*

For pre-exposure prophylaxis in high-risk groups and for postexposure prophylaxis an accelerated schedule should be used. It may also be used where more rapid immunisation, for instance with travellers, is required. This schedule involves giving the third dose 2 months after the initial dose with a further booster at 1 year. In exceptional circumstances in adults travelling to an endemic area who commence their vaccination course within a month of departure, an even more rapid schedule involving injections at 0, 7, and 21 days has been used; when this schedule is used, a booster dose is recommended after 1 year.

For newborn infants at risk combined active and passive immunisation against hepatitis B is recommended. The first dose of vaccine should preferably be given at birth, and certainly within 24 hours of birth. A single dose of hepatitis B immunoglobulin (200 international units) should be given at the same time into a different site. Additionally, in any patient in whom immediate protection is required, combined active and passive immunisation may be considered with a single dose of 500 international units of hepatitis B immunoglobulin being the dose for adults. See under Hepatitis B Immunoglobulins, p.2215, for children's doses.

◊ General references.

1. Buynak EB, *et al.* Vaccine against human hepatitis B. *JAMA* 1976; **235:** 2832–4.
2. Douglas RG. The heritage of hepatitis B vaccine. *JAMA* 1996; **276:** 1796–8.
3. Lemon SM, Thomas DL. Vaccines to prevent viral hepatitis. *N Engl J Med* 1997; **336:** 196–204.
4. Keating GM, Noble S. Recombinant hepatitis B vaccine (Engerix-B): a review of its immunogenicity and protective efficacy against hepatitis B. *Drugs* 2003; **63:** 1021–51.

Administration. The major public health burden of hepatitis B infection in the developing world is due to the consequences of chronic carriage of hepatitis B virus (hepatocellular carcinoma and chronic cirrhosis) rather than acute infection. WHO[1] considered that the most important means of controlling hepatitis B on a global scale and of reducing mortality from its sequelae was mass immunisation of infants. It stated that hepatitis B vaccine should be incorporated into the Expanded Programme on Immunization (EPI) and many countries have since done so. WHO later reiterated this aim[2] stating that hepatitis B vaccine should be integrated into national immunisation programmes in all countries with a hepatitis B carrier prevalence (HBsAg) of 8% or greater by 1995 and in all countries by 1997. WHO's aim was to reduce the incidence of new child carriers of hepatitis B by 80% by 2001. Results from Taiwan, where mass immunisation of infants has been in place since the mid-1980s have shown a marked decline in the number of child carriers under 10 years of age.[3,4] The incidence of hepatocellular carcinoma in children has also been reduced.[5,6]

Opinion has been divided in the UK regarding implementation of universal hepatitis B immunisation,[7-9] with some advising increased emphasis on alternative strategies already in place such as antenatal screening.[7,8]

The optimum vaccination strategy depends on the pattern of hepatitis B viral transmission in a particular country. In hyperendemic regions where most infections are acquired early in life, the vaccine should be given shortly after birth and hepatitis B immunisation integrated into the EPI. Immunisation of all infants should be considered for population groups with chronic hepatitis B virus carrier rates greater than 2% and should be a public health priority where carrier rates are greater than 10%. Countries with a lower carrier rate might opt to immunise all adolescents as an alternative to infant immunisation. Immunisation of individuals at high risk of infection should be continued in addition to routine vaccination schedules[2] and, if hepatitis B is not integrated into infant vaccination schedules, screening pregnant women for HBsAg and immunising the infants of HBsAg-positive mothers should continue.[1]

If use of hepatitis B vaccine is integrated into the EPI, 3 doses should be given intramuscularly, the first dose being given as soon as possible after birth with the first EPI immunisation. The exact timing of these doses will depend on the risk of transmission at birth and the EPI schedule in operation. In the USA, these recommendations have been implemented by immunisation of all infants and of children at any age between 2 and 18 years who have not previously received 3 doses of vaccine. The recommended schedule is for all infants to be given an initial dose of the monovalent hepatitis B vaccine soon after birth; then 2 further doses with the monovalent vaccine or 3 further doses with a combination vaccine containing hepatitis B. Infants of HBsAg-positive mothers should receive hepatitis B vaccine plus hepatitis B immunoglobulin within 12 hours of birth. Infants whose mother's HBsAg status is unknown should receive a hepatitis B vaccine within 12 hours of birth and the maternal blood should be checked at delivery and, if positive for HBsAg, the infant given hepatitis B immunoglobulin as soon as possible (no later than 1 week of age). The second dose is given at 1 to 2 months of age and the final dose at 6 months of age or later. Infants who receive a combination vaccine after the birth dose may be given an additional dose at 4 months of age. Alternatively, some products may be given in a two-dose regimen, with doses given 4 to 6 months apart.

1. WHO. Progress in the control of viral hepatitis: memorandum from a WHO meeting. *Bull WHO* 1988; **66:** 443–55.
2. Anonymous. Hepatitis B vaccine. *WHO Drug Inf* 1993; **7:** 130–1.
3. Chen H-L, *et al.* Seroepidemiology of hepatitis B virus infection in children: ten years of mass vaccination in Taiwan. *JAMA* 1996; **276:** 906–8.
4. Hsu H-M, *et al.* Seroepidemiologic survey for hepatitis B virus infection in Taiwan: the effect of hepatitis B mass immunization. *J Infect Dis* 1999; **179:** 367–70.
5. Lee C-L, Ko Y-C. Hepatitis B vaccination and hepatocellular carcinoma in Taiwan. *Pediatrics* 1997; **99:** 351–3.
6. Chang M-H, *et al.* Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *N Engl J Med* 1997; **336:** 1855–9.
7. Mortimer PP, Miller E. Commentary: antenatal screening and targeting should be sufficient in some countries. *BMJ* 1997; **314:** 1036–7.
8. Dunn J, *et al.* Integration of hepatitis B vaccination into national immunisation programmes: alternative strategies must be considered before universal vaccination is adopted. *BMJ* 1997; **315:** 121–2.
9. Goldberg D, McMenamin J. The United Kingdom's hepatitis B immunisation strategy—where now? *Commun Dis Public Health* 1998; **1:** 79–83.

Booster doses. There has been considerable interest in the duration of immunity conferred by hepatitis B vaccination and the possible need for booster doses.[1,2]

In the UK it is now recommended that individuals at continuing risk of infection should be offered a *single* booster dose of vaccine, *once only*, about 5 years after primary immunisation. Boosters are also recommended if contamination of eyes, mouth, or fresh cuts on skin with blood from a HBsAg-positive person occurs, unless they are known to have protective concentrations of antibody.

References.

1. European Consensus Group on Hepatitis B Immunity. Are booster immunisations needed for lifelong hepatitis B immunity? *Lancet* 2000; **355:** 561–5.
2. Banatvala JE, Van Damme P. Hepatitis B vaccine—do we need boosters? *J Viral Hepatitis* 2003; **10:** 1–6.

Postexposure prophylaxis. A combination of passive immunisation with a hepatitis B immunoglobulin and active immunisation with a hepatitis B vaccine is generally recommended for postexposure prophylaxis against hepatitis B.

One group of patients who should be given postexposure prophylaxis are infants born to mothers who are persistent carriers of hepatitis B surface antigen (HBsAg). The risk is particularly high if the mother has detectable hepatitis B e antigen (HBeAg) or hepatitis B virus DNA or absence of detectable antibody to hepatitis Be antigen (anti-HBe). Postexposure prophylaxis is also recommended in the UK for persons accidentally inoculated, or who contaminate the eye or mouth or breaks to the skin with blood from a known HBsAg-positive person, as well as in sexual contacts (and sometimes close family contacts) of sufferers from acute hepatitis B and who are seen within a week of the onset of jaundice in the contact.

In the UK, the recommended schedule for postexposure prophylaxis is the first dose of vaccine given preferably within 48 hours of exposure and no later than one week after exposure, or, for neonates exposed to hepatitis B at birth, no later than 24 hours after birth, with a single dose of hepatitis B immunoglobulin given simultaneously at a separate site. The second and third doses of vaccine are given 1 and 2 months after the first dose, with a booster dose at 12 months. Health care workers who have been successfully immunised should be given a booster dose after subsequent contamination with blood from an infected person, unless they are known to have adequate antibody concentration.

Preparations

Ph. Eur.: Hepatitis B Vaccine (rDNA).

Proprietary Preparations (details are given in Part 3)
Arg.: AGB; Biovac HB; Engerix-B; H-B-Vax II†; HBVaxPro; Hepativax; Supervax; ***Austral.:*** Engerix-B; H-B-Vax II; ***Austria:*** Engerix-B; ***Belg.:*** Engerix-B; Fendrix; HBVaxPro; ***Braz.:*** Engerix-B†; Heberbiovac HB†; Recombivax HB†; Vacina Contra Hepatite B; ***Canad.:*** Engerix-B; Recombivax HB; ***Chile:*** Engerix-B; Heberbiovac HB; Hepavax-Gene; Recomvax B; ***Cz.:*** Engerix-B; Fendrix; H-B-Vax II†; HBVaxPro; ***Denm.:*** Engerix-B; H-B-Vax†; ***Fin.:*** Engerix-B; HBVaxPro; ***Fr.:*** Engerix-B; Fendrix; GenHevac B; HB-Vax-DNA†; HBVaxPro; ***Ger.:*** Engerix-B; Gen H-B-Vax†; HBVaxPro; ***Gr.:*** Engerix-B; Fendrix; HBVaxPro; Recombivax†; ***Hong Kong:*** Engerix-B; H-B-Vax II; HBVaxPro; Sci-B-Vac; ***Hung.:*** Engerix-B; HBVaxPro; ***India:*** Engerix-B; Enivac HB; Genevac-B; HB Vac; Shanvac-B; ***Indon.:*** Engerix-B; Euvax B; H-B-Vax II; Hepavax; ***Irl.:*** Engerix-B; H-B-Vax II†; HBVaxPro; ***Israel:*** Bio-Hep-B; Engerix-B; Recombinant H-B Vax II; ***Ital.:*** Engerix-B; HBVaxPro; Recombivax HB†; ***Malaysia:*** Engerix-B; Euvax B; H-B-Vax II†; HBVaxPro; Hepavax-Gene; ***Mex.:*** Engerix-B; H-B-Vax II; Heberbiovac HB; Probivac-B; ***Neth.:*** Engerix-B; Fendrix; HB-Vax-DNA; HBVaxPro; ***Norw.:*** Engerix-B; Fendrix; ***NZ:*** Engerix-B; H-B-Vax II; HBVaxPro; ***Philipp.:*** Engerix-B; Hepavax-Gene; Hepliv; Recomvax B; Shanvac-B; Temrevac-HB; ***Pol.:*** Engerix-B; Euvax B; HBVaxPro; Hepavax-Gene; ***Port.:*** Engerix-B; Recombivax HB†; ***Rus.:*** Biovac-B (Биовак-в); Engerix-B (Энджерикс В); H-B-Vax II (H-B-Вакс II); ***S.Afr.:*** Engerix-B; H-B-Vax II; Heberbiovac HB; Hepaccine-B; ***Singapore:*** Engerix-B; H-B-Vax II†; HBVaxPro; ***Spain:*** Engerix-B; HBVaxPro; Recombivax HB†; ***Swed.:*** Engerix-B; HBVaxPro; ***Switz.:*** Engerix-B; Gen H-B-Vax; HBVaxPro; Heprecomb; ***Thai.:*** Engerix-B; Euvax B; H-B-Vax II; HBVaxPro; Heberbiovac HB; Hepavax-Gene; ***Turk.:*** Engerix-B; Euvax B; GenHevac B; HBVaxPro; Hepavax-Gene; ***UK:*** Engerix-B; Fendrix; HBVaxPro; ***USA:*** Engerix-B; Recombivax HB; ***Venez.:*** Eberbiovac HB†; Engerix-B.

Hepatitis A and B Vaccines

Vacunas de las hepatitis A y B.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Hepatitis A (Inactivated) and Hepatitis B (rDNA) Vaccine (Adsorbed); Vaccinum Hepatitidis A Inactivatum et Hepatitidis B (ADNr) Adsorbatum; Hepatitis A (Inactivated) and Hepatitis B (rDNA) Vaccine BP 2008). A suspension consisting of a suitable strain of hepatitis A virus, grown in cell cultures and inactivated by a validated method, and of hepatitis B surface antigen obtained by recombinant DNA technology; the antigens are adsorbed on a mineral carrier, such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that HepA/HepB may be used on the label.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

See also under Hepatitis A Vaccines, p.2214, and Hepatitis B Vaccines, p.2215.

Uses and Administration

Combined hepatitis A and B vaccines are used for active immunisation against hepatitis A and hepatitis B.

A hepatitis A and B vaccine (*Twinrix, GSK*) is available containing not less than 720 ELISA units of inactivated hepatitis A virus and not less than 20 micrograms of recombinant hepatitis B surface antigen (HBsAg) protein in 1 mL. For primary immunisation, three doses of 1 mL are given by intramuscular injection, with the second and third doses 1 and 6 months after the first. For children up to the age of 16 years a 0.5-mL dose is given.

Alternatively, in exceptional circumstances when travel is anticipated within one month or more after the first dose but when insufficient time is available for the standard course, adults may be given an accelerated schedule. In the UK, this consists of three doses at 0, 7 and 21 days. In the US the recommended schedule consists of doses at 0, 7, and 21 to 30 days plus a dose at 12 months.

Booster doses may be given as appropriate with the monovalent component vaccines since protection against hepatitis A and B declines at different rates, or a booster dose of the combined vaccine may be given after 5 years in adults or 4 years in children. A booster is recommended 1 year after the accelerated schedule.

In the UK a similar vaccine (*Ambirix, GSK*) is licensed for primary immunisation in a 2-dose schedule for children aged 1 to 15 years; the second dose is given between 6 and 12 months after the first.

◊ Reviews.

1. Murdoch DL, *et al.* Combined hepatitis A and B vaccines: a review of their immunogenicity and tolerability. *Drugs* 2003; **63:** 2625–49.
2. Van Damme P, Van Herck K. A review of the efficacy, immunogenicity and tolerability of a combined hepatitis A and B vaccine. *Expert Rev Vaccines* 2004; **3:** 249–67.
3. Zuckerman JN. Vaccination against hepatitis A and B: developments, deployment and delusions. *Curr Opin Infect Dis* 2006; **19:** 456–9.

Preparations

Ph. Eur.: Hepatitis A (Inactivated) and Hepatitis B (rDNA) Vaccine (Adsorbed).

Proprietary Preparations (details are given in Part 3)
Arg.: Twinrix; ***Austral.:*** Twinrix; ***Austria:*** Twinrix; ***Belg.:*** Twinrix; ***Braz.:*** Twinrix†; Vacina Comb. Contra Hepatite A e B; ***Canad.:*** Twinrix; ***Chile:*** Twinrix; ***Cz.:*** Ambirix; Twinrix; ***Denm.:*** Twinrix; ***Fin.:*** Twinrix; ***Fr.:*** Twinrix; ***Ger.:*** Twinrix; ***Gr.:*** Twinrix; ***Hong Kong:*** Twinrix; ***Hung.:*** Twinrix; ***Indon.:*** Twinrix; ***Irl.:*** Twinrix; ***Israel:*** Twinrix; ***Ital.:*** Twinrix; ***Malaysia:*** Twinrix; ***Mex.:*** Twinrix; ***Neth.:*** Ambirix; Twinrix; ***Norw.:*** Twinrix; ***NZ:*** Twinrix; ***Philipp.:*** Twinrix; ***Pol.:*** Twinrix; ***Port.:*** Ambirix; Twinrix; ***S.Afr.:*** Twinrix; ***Singapore:*** Twinrix; ***Spain:*** Twinrix; ***Swed.:*** Ambirix†; Twinrix; ***Switz.:*** Twinrix; ***Thai.:*** Twinrix; ***Turk.:*** Twinrix; ***UK:*** Ambirix; Ambrix; Twinrix; ***USA:*** Twinrix; ***Venez.:*** Twinrix.

Hepatitis A and Typhoid Vaccines

Vacunas de la hepatitis A y fiebre tifoidea.

ATC — J07CA10.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Uses and Administration

Combined hepatitis A and typhoid vaccines are used for active immunisation. They contain either inactivated HM175 or GBM hepatitis A virus strains together with the Vi capsular polysaccharide from *Salmonella typhi* Ty 2 strain. Adults and adolescents over 15 years of age may be given a dose of 1 mL by intramuscular injection, at least 2 weeks prior to risk of exposure to typhoid and hepatitis A. A booster dose may be given after 6 to 12 months to provide long-term protection.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Vivaxim; ***Austria:*** Hepatyrix; ***Canad.:*** Vivaxim; ***Fr.:*** Tyavax; ***Ger.:*** Hepatyrix; ViATIM; ***Irl.:*** Hepatyrix; ViATIM; ***Israel:*** Hepatyrix; ***Malaysia:*** Vivaxim; ***Neth.:*** ViATIM; ***NZ:*** Hepatyrix; Vivaxim; ***Port.:*** ViATIM; ***UK:*** Hepatyrix; ViATIM.

Herpes Simplex Vaccines

Vacunas del herpes simple.

Profile

Several types of vaccines against herpes simplex virus types 1 and 2 have been developed. They have been tried both in oral and genital herpes infections. They are also being studied for the prevention of infection in sexual partners of patients with genital herpes.

◊ Herpes simplex virus types 1 and 2 are widespread in populations throughout the world. Herpes simplex virus type 2 causes lifelong infection with significant morbidity. Even with the availability of effective antiviral therapy, the increasing burden of herpes simplex virus infection makes it a suitable candidate for vaccine development. The incidence of neonatal herpes infections has also increased and this risk would also be addressed by development of appropriate vaccines. An additional benefit would be a reduced risk of acquiring HIV infection.

Vaccines for herpes simplex were first studied in the 1920s and many different types of vaccine have undergone evaluation. They have included auto-inoculation of live herpes simplex virus, whole inactivated vaccines, attenuated live virus vaccines, modified live virus subunit vaccines, cell culture-derived subunit vaccines, recombinant glycoprotein subunit vaccines, disabled infectious single cycle (DISC) vaccines, and nucleic acid (DNA) vaccines.[1,2]

Prophylactic vaccines against HSV-2 could be beneficial if they either shift the threshold of infection i.e. increase the titre of virus necessary to cause infection, or if they prevent clinical disease itself. An attenuated live virus vaccine based on modified HSV-1 has been tested in clinical studies but was poorly tolerated at the doses required to elicit an immune response. Prophylactic vaccines including subunit vaccines encoding virus glycoproteins and delivered with adjuvants have shown some benefits.[1,2]

To date, no randomised clinical studies have demonstrated useful benefit from therapeutic vaccines for HSV-1 or HSV-2. A therapeutic vaccine should prevent recurrences or at least minimise their severity or duration. Heat killed, whole virus vaccines from HSV-1 (Lupidon H) and HSV-2 (Lupidon G), and inactivated subunit vaccines have been studied but have generally produced disappointing results.[1,2] Recombinant glycoprotein vaccines have also been tested but again results have been disappointing.[1,2]

1. Morrison LA. Vaccines against genital herpes: progress and limitations. *Drugs* 2002; **62:** 1119–29.
2. Stanberry LR. Clinical trials of prophylactic and therapeutic herpes simplex virus vaccines. *Herpes* 2004; **11** (suppl 3): 161A–169A.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Lupidon G; Lupidon H.

Human Papillomavirus Vaccines

HPV Vaccines; Human Papilloma Virus Vaccines; Vacunas del virus del papiloma humano.

ATC — J07BM01.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Breast feeding. In mothers given the quadrivalent recombinant human papillomavirus vaccine or placebo during clinical studies, the rates of adverse reactions in the mother and in the breast-fed infant, as well as vaccine immunogenicity, were comparable in the 2 groups. Based on apparently the same data the UK licensed product information states that the vaccine can be given to breast-feeding women whereas the US information recommends caution.

Pregnancy. Although specific studies of the quadrivalent recombinant human papillomavirus vaccine in pregnant women have not been conducted, some women during clinical development did receive the vaccine in pregnancy. Overall, the proportions of pregnancies with an adverse outcome were comparable in those who received the vaccine and those who received placebo. It is, nevertheless, recommended that vaccination should be postponed until after completion of pregnancy.

Uses and Administration

A quadrivalent recombinant human papillomavirus (HPV) vaccine, prepared from purified virus-like particles of the capsid protein L1, is used to prevent genital warts, cervical cancer, and other pre-cancerous lesions caused by HPV types 6, 11, 16, and 18.

It is given in three doses of 0.5 mL intramuscularly. The first dose may be given at any time to girls and women between 9 and 26 years of age; the second dose is given 2 months later, and the third dose 6 months after the first dose.

A similar recombinant HPV vaccine, prepared from a mixture of L1 capsid proteins of HPV types 16 and 18 and containing an adjuvant AS04, is licensed in some countries for the prevention of cervical cancer and high grade cervical intraepithelial neoplasia (grades 2 and 3). It is given intramuscularly in 3 doses of 0.5 mL to girls and women between 10 and 25 years of age. The first dose may be given at any age in the approved range; the second dose is given 1 month later, and the third dose 6 months after the first dose.

Further vaccines are under investigation for the treatment or prophylaxis of genital warts and several malignant neoplasms.

◊ Reviews and studies.

1. Siddiqui MAA, Perry CM. Human papillomavirus quadrivalent (types 6, 11, 16, 18) recombinant vaccine (Gardasil). *Drugs* 2006; **66:** 1263–71.
2. Schmiedeskamp MR, Kockler DR. Human papillomavirus vaccines. *Ann Pharmacother* 2006; **40:** 1344–52.
3. Block SL, *et al.* Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. *Pediatrics* 2006; **118:** 2135–45. Also available at: http://pediatrics.aappublications.org/cgi/reprint/118/5/2135 (accessed 26/06/07)
4. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007; **356:** 1915–27.
5. Garland SM, *et al.* Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med* 2007; **356:** 1928–43.
6. Joura EA, *et al.* Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials. *Lancet* 2007; **369:** 1693–1702.
7. Cutts FT, *et al.* Human papillomavirus and HPV vaccines: a review. *Bull World Health Organ* 2007; **85:** 719–26.
8. Keam SJ, Harper DM. Human papillomavirus types 16 and 18 vaccine (recombinant, AS04 adjuvanted, adsorbed) [Cervarix]. *Drugs* 2008; **68:** 359–72.

Vaccine development. There are more than 100 known human papillomavirus (HPV) genotypes; at least 13 of these can cause cervical cancer and are also associated with other anogenital cancers and cancers of the head and neck. Genotypes 16 and