Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Comvax; ***Austria:*** Procomvax; ***Cz.:*** Procomvax; ***Ger.:*** Procomvax†; ***Gr.:*** Procomvax; ***Ital.:*** Procomvax; ***Mex.:*** Comvax; ***Neth.:*** Procomvax; ***NZ:*** Comvax; ***Pol.:*** Procomvax; ***Port.:*** Procomvax; ***USA:*** Comvax.

Haemophilus Influenzae and Meningococcal Vaccines

Profile

A combined Haemophilus influenza type b and meningococcal C conjugate vaccine is available for active immunisation in some countries; in the UK a single dose may be given to children between 1 and 10 years of age who have completed a primary vaccination course of diphtheria, tetanus, pertussis, and polio. Two doses given 2 months apart may be given to asplenic children (over 10 years of age) or adults who have not been previously immunised.

Preparations

Proprietary Preparations (details are given in Part 3)
UK: Menitorix.

Haemophilus Influenzae and Poliomyelitis Vaccines

ATC — J07CA04.

Profile

Combined haemophilus influenzae type b conjugate and inactivated poliomyelitis vaccines have been used in some countries for active immunisation of infants.

Preparations

Proprietary Preparations (details are given in Part 3)
Norw.: Act-HIB Polio†; ***Swed.:*** PolioHib†.

Haemorrhagic Fever with Renal Syndrome Vaccines

HFRS Vaccine; Vaccinum Haemorrhagia Febris cum Renis Sindronum; Vacunas de la fiebre renal epidémica.

Description. A fluid or freeze-dried preparation of a suitable hantavirus grown in the neural tissue of suckling rodents or in cell cultures and inactivated. The fluid vaccine should be stored at 2° to 8° and not allowed to freeze. The freeze-dried form should be stored below 10°.

Profile

Inactivated viral vaccines against haemorrhagic fever with renal syndrome have been investigated and are available in some countries, but there have been problems producing a sufficient and sustained immune response.

◊ References.

1. Sohn YM, *et al.* Primary humoral immune responses to formalin inactivated hemorrhagic fever with renal syndrome vaccine (Hantavax): consideration of active immunization in South Korea. *Yonsei Med J* 2001; **42:** 278–84.
2. Cho HW, *et al.* Review of an inactivated vaccine against hantaviruses. *Intervirology* 2002; **45:** 328–33.
3. Park K, *et al.* Protective effectiveness of hantavirus vaccine. *Emerg Infect Dis* 2004; **10:** 2218–20.

Helicobacter Pylori Vaccines

Vacunas de Helicobacter pylori.

Profile

Vaccines against *Helicobacter pylori* are being developed for prophylaxis of peptic ulcer disease and gastric cancer.

◊ Studies in *animals* have shown the feasibility of both prophylactic and therapeutic vaccination against *Helicobacter pylori* infection, but there have been few studies in humans. Encouraging results have been obtained with parenteral, multicomponent, aluminium hydroxide-based vaccines in terms of safety and immunogenicity. In contrast, preliminary results obtained with mucosally delivered single-component vaccines have been disappointing, partly due to the intrinsic difficulty in developing purified proteins that are sufficiently immunogenic following mucosal delivery. Studies are ongoing into the mechanisms by which the host's genetic make-up modifies the inflammatory and immunological response to *H. pylori*.[1-4]

1. Ruggiero P, *et al.* The quest for a vaccine against Helicobacter pylori: how to move from mouse to man? *Microbes Infect* 2003; **5:** 749–56.
2. Sutton P, Doidge C. Helicobacter pylori vaccines spiral into the new millennium. *Dig Liver Dis* 2003; **35:** 675–87.
3. Del Giudice G, Michetti P. Inflammation, immunity and vaccines for Helicobacter pylori. *Helicobacter* 2004; **9** (suppl 1): 23–8.
4. Agarwal K, Agarwal S. Helicobacter pylori vaccine: from past to future. *Mayo Clin Proc* 2008; **83:** 169–75.

Hepatitis A Immunoglobulins

Inmunoglobulinas contra la hepatitis A.

ATC — J06BB11.

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

Ph. Eur. 6.2 (Human Hepatitis A Immunoglobulin; Immunoglobulinum Humanum Hepatitidis A). A liquid or freeze-dried preparation containing human immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from selected donors having specific antibodies against the hepatitis A virus. Normal immunoglobulin may be added. It contains not less than 600 international units/mL. The liquid preparation should be stored, protected from light, in a sealed, colourless, glass container. The freeze-dried preparation should be stored, protected from light, in a colourless, glass container under vacuum or under an inert gas.

Profile

Immunoglobulins containing high levels of specific antibodies against hepatitis A have been used in some countries for passive immunisation against hepatitis A infection; in the UK, normal immunoglobulin is usually given.

Preparations

Ph. Eur.: Human Hepatitis A Immunoglobulin.

Proprietary Preparations (details are given in Part 3)
Port.: Globuman Hepatite A†.

Hepatitis A Vaccines

Vacunas de la hepatitis A.

ATC — J07BC02.

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

Ph. Eur. 6.2 (Hepatitis A Vaccine (Inactivated, Adsorbed); Vaccinum Hepatitidis A Inactivatum Adsorbatum; Inactivated Hepatitis A Vaccine BP 2008). A liquid preparation of a suitable strain of hepatitis A virus grown in cell cultures, inactivated by a validated method, and adsorbed on a mineral carrier. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light. The BP 2008 states that Hep A may be used on the label.

Ph. Eur. 6.2 (Hepatitis A Vaccine (Inactivated, Virosome); Vaccinum Hepatitidis A Inactivatum Virosomale). A liquid preparation of a suitable strain of hepatitis A virus grown in cell cultures and inactivated by a validated method. Virosomes composed of influenza proteins and phospholipids are used as adjuvants. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.
The BP 2008 states that HepA may be used on the label.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

◊ General references.

1. Niu MT, *et al.* Two-year review of hepatitis A vaccine safety: data from the Vaccine Adverse Event Reporting System (VAERS). *Clin Infect Dis* 1998; **26:** 1475–6.

Effects on the blood. WHO has received reports of 5 cases of thrombocytopenia, 3 with purpura, associated with hepatitis A vaccine.[1]

1. Meyboom RHB, *et al.* Thrombocytopenia reported in association with hepatitis B and A vaccines. *Lancet* 1995; **345:** 1638.

Effects on the nervous system. Neurological symptoms resembling encephalitis have followed a third dose of hepatitis A vaccine.[1] Other serious neurological reactions reported in patients given inactivated hepatitis A vaccine include transverse myelitis, Guillain-Barré syndrome, and neuralgic amyotrophy.[2] Such reactions appear to be very rare, and, since other vaccines have often been given simultaneously, may not be directly attributable to hepatitis A vaccine.

1. Hughes PJ, *et al.* Probable post-hepatitis A vaccination encephalopathy. *Lancet* 1993; **342:** 302.
2. Committee on Safety of Medicines/Medicines Control Agency. Hepatitis A vaccination (Havrix). *Current Problems* 1994; **20:** 16.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Hepatitis A vaccines are used for active immunisation against hepatitis A infection.

In the UK, the use of an inactivated vaccine is recommended as an alternative to normal immunoglobulin for frequent travellers to areas of high or moderate hepatitis A endemicity or for those staying for more than 3 months in such areas; in some countries a hepatitis A immunoglobulin (p.2214) is available for those making shorter or less frequent journeys. Immunisation is also recommended in haemophiliacs, patients with chronic liver disease, and in those at risk of exposure to hepatitis A by virtue of their occupation, and should be considered in persons whose lifestyle is likely to place them at risk. The vaccine is given intramuscularly, except in haemophiliacs in whom it should be given by deep subcutaneous injection. In the UK, various vaccines are available and the dose (0.5 or 1 mL) depends on the product used and age of the patient. They may be prepared from several inactivated hepatitis A virus strains including CR326F, GBM, HM175, and RG-SB. The primary immunisation schedule for all vaccines consists of a single dose appropriate to the age of the patient and should be followed 6 to 12 months later by a booster dose. Immunity is provided for at least 10 years after these doses.

In the US, immunisation at 12 months of age (with a booster at least 6 months later) is recommended as part of the routine primary immunisation schedule. Post-exposure prophylaxis is recommended in persons who have not previously received a hepatitis A vaccine. Vaccination is also recommended for travellers to countries with intermediate to high hepatitis A endemicity.

◊ References.

1. American Academy of Pediatrics Committee on Infectious Diseases. Hepatitis A vaccine recommendations. *Pediatrics* 2007; **120:** 189–99. http://pediatrics.aappublications.org/cgi/reprint/120/1/189.pdf (accessed 15/07/08)

Vaccine development. Commercially available hepatitis A vaccines are usually produced from inactivated hepatitis A virus strains propagated in cell culture, commonly of human diploid fibroblast cells. 'Virosome' hepatitis A vaccines consisting of inactivated hepatitis A virus epitopes formulated into liposomes are also becoming available. Live attenuated hepatitis A vaccines have also been developed, although an oral live vaccine does not appear to have yet been produced.

Preparations

Ph. Eur.: Hepatitis A Vaccine (Inactivated, Adsorbed); Hepatitis A Vaccine (Inactivated, Virosome).

Proprietary Preparations (details are given in Part 3)
Arg.: Avaxim; Epaxal; Havrix; VAQTA; Virohep-A; ***Austral.:*** Avaxim; Havrix; VAQTA; ***Austria:*** Havrix; ***Belg.:*** Epaxal; Havrix; VAQTA†; ***Braz.:*** Avaxim†; Havrix†; Vacina Contra Hepatite A; VAQTA†; ***Canad.:*** Avaxim; Epaxal†; Havrix; VAQTA; ***Chile:*** Avaxim; Epaxal; Havrix; ***Cz.:*** Avaxim; Epaxal†; Havrix; VAQTA; ***Denm.:*** Epaxal; Havrix; ***Fin.:*** Epaxal; Havrix; VAQTA†; ***Fr.:*** Avaxim; Havrix; VAQTA†; ***Ger.:*** Epaxal†; Havpur; Havrix; VAQTA; ***Gr.:*** Avaxim; Epaxal; Havrix; VAQTA; ***Hong Kong:*** Avaxim; Epaxal; Havrix; VAQTA; ***Hung.:*** Avaxim; Havrix; VAQTA; ***India:*** Havrix; ***Indon.:*** Avaxim; Havrix; VAQTA; ***Irl.:*** Avaxim; Havrix; VAQTA†; ***Israel:*** Avaxim; Epaxal; Havrix; VAQTA; ***Ital.:*** Avaxim; Epaxal; Havrix; Nothav†; VAQTA; ***Malaysia:*** Avaxim; Epaxal; Havrix; VAQTA†; ***Mex.:*** Avaxim; Havrix; VAQTA; ***Neth.:*** Avaxim; Epaxal; Havrix; VAQTA; ***Norw.:*** Epaxal; Havrix; VAQTA†; ***NZ:*** Avaxim; Epaxal; Havrix; VAQTA; ***Philipp.:*** Avaxim; Epaxal; Havrix; ***Pol.:*** Avaxim; Havrix; VAQTA; ***Port.:*** Avaxim; Epaxal; Havrix; VAQTA; ***Rus.:*** Havrix (Хаврикс); VAQTA (ВАКТА); ***S.Afr.:*** Avaxim; Havrix; ***Singapore:*** Avaxim; Epaxal; Havrix; VAQTA; ***Spain:*** Avaxim; Epaxal; Havrix; VAQTA; ***Swed.:*** Avaxim; Epaxal; Havrix; VAQTA†; ***Switz.:*** Epaxal; Havrix; VAQTA†; ***Thai.:*** Avaxim; Havrix; VAQTA; ***Turk.:*** Avaxim; Epaxal; Havrix; VAQTA; ***UK:*** Avaxim; Epaxal; Havrix; VAQTA; ***USA:*** Havrix; VAQTA; ***Venez.:*** Epaxal†; Havrix.

Hepatitis B Immunoglobulins

Inmunoglobulinas contra la hepatitis B.

ATC — J06BB04.

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

Ph. Eur. 6.2 (Human Hepatitis B Immunoglobulin; Immunoglobulinum Humanum Hepatitidis B). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from selected and/or immunised donors having specific antibodies against hepatitis B surface antigen. Normal immunoglobulin may be added. It contains not less than 100 international units/mL. The liquid preparation should be stored, protected from light, in a sealed, colourless, glass container. The freeze-dried preparation should be stored, protected from light, in a colourless, glass container, under vacuum or under an inert gas.

Ph. Eur. 6.2 (Human Hepatitis B Immunoglobulin for Intravenous Administration; Immunoglobulinum Humanum Hepatitidis B ad Usum Intravenosum). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from selected and/or immunised donors having antibodies against hepatitis B surface antigen. Human normal immunoglobulin for intravenous administration may be added. It contains not less than 50 international units/mL. Storage requirements are similar to those for Human Hepatitis B Immunoglobulin, except that the freeze-dried preparation is stored at a temperature not exceeding 25°.

USP 31 (Hepatitis B Immune Globulin). A is a sterile solution consisting of globulins derived from the plasma of human donors who have high titres of antibodies against hepatitis B surface antigen. It contains 10 to 18% of protein, of which not less than 80% is monomeric immunoglobulin G. It contains glycine as a stabilising agent, and a suitable preservative. It should be stored at 2° to 8°.

Adverse Effects and Precautions

As for immunoglobulins in general, p.2201.

Preparation strength. For a warning concerning possible lack of equivalence between different preparations of hepatitis B immunoglobulins, see under Uses and Administration, below.

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-