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