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

18 cause about 70% of all cervical cancers, while genotypes 6 and 11 can cause genital warts. HPV is highly transmissible with risk of infection being highest soon after sexual activity begins. Asymptomatic and transient infection occurs in most people at some time in their life. However, the fact that more than 99% of cases of cervical cancer diagnosed are associated with the presence of sexually transmitted human papillomavirus DNA has prompted the possibility of vaccine development.

Viral recombinant proteins are being studied as antigenic components of both prophylactic and therapeutic vaccines.[1-8] Prophylactic vaccine candidates are based on the recombinant capsid proteins L1 and L2 which self-assemble into virus-like particles which induce antibodies that in turn neutralise the infecting virus. Therapeutic vaccines are based on the viral oncogenic proteins E6 and E7 and are designed to induce cell-mediated immune responses to eliminate infected cells. Prophylactic vaccines based on the recombinant capsid protein LI are licensed in several countries, while other prophylactic vaccines are in phase III and further therapeutic vaccine candidates are undergoing phase II evaluation. There is also some preliminary study being conducted into the possibility of a 'chimeric' vaccine combining both prophylactic and therapeutic components, but the immunogenicity and efficacy of such vaccines remains to be established.

For it to be claimed justifiably that a prophylactic vaccine prevents cervical cancer, it is necessary to demonstrate that such a vaccine not only prevents infection but also prevents cancer itself, or at least a defined precursor of disease. Since any placebo-controlled study defining established cancer as an end-point would clearly be unethical, an appropriate compromise is to use the appearance of high-grade dysplasia or pre-cancerous lesions as an end-point, this being regarded as a direct precursor to cervical cancer requiring treatment. However, true pre-cancerous lesions of this kind are relatively unusual in current practice and therefore phase III studies require tens of thousands of subjects in order to establish this efficacy.[3]

Guidance and technical information on HPV, HPV-related diseases, and HPV vaccines has been produced by WHO.[9] They consider HPV vaccines to be highly effective among females not exposed to HPV vaccine genotypes at the time of their first vaccination and that the target group for vaccination will probably be preadolescent girls (about 9 to 12 years of age). Guidelines for the use of HPV vaccine for the prevention of cervical cancer have been developed in the USA by the CDC,[10] the American Cancer Society[11] and the American Academy of Pediatrics.[12] These authorities recommend routine vaccination for all girls 11 to 12 years of age, although girls as young as 9 years of age may be vaccinated at the discretion of their doctor. Catch-up vaccinations may be given to older girls and young women who have not received or completed a vaccine course. In the UK the Joint Committee on Vaccination and Immunisation[13] recommends routine vaccination of all girls 12 to 13 years of age. Catch-up vaccination is recommended for girls under 18 years of age.

1. Galloway DA. Papillomavirus vaccines in clinical trials. *Lancet Infect Dis* 2003; **3:** 469–75.
2. Lehtinen M, Paavonen J. Effectiveness of preventive human papillomavirus vaccination. *Int J STD AIDS* 2003; **14:** 787–92.
3. Jansen KU, Shaw AR. Human papillomavirus vaccines and prevention of cervical cancer. *Annu Rev Med* 2004; **55:** 319–31.
4. Mandic A, Vujkov T. Human papillomavirus vaccine as a new way of preventing cervical cancer: a dream or the future? *Ann Oncol* 2004; **15:** 197–200.
5. Roden RBS, *et al*. Vaccination to prevent and treat cervical cancer. *Hum Pathol* 2004; **35:** 971–82.
6. Lowndes CM, Gill ON. Cervical cancer, human papillomavirus, and vaccination. *BMJ* 2005; **331:** 915–16.
7. Harper DM, *et al*. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004; **364:** 1757–65.
8. Poland GA, *et al*. Immunogenicity and reactogenicity of a novel vaccine for human papillomavirus 16: a 2-year randomized controlled clinical trial. *Mayo Clin Proc* 2005; **80:** 601–10.
9. WHO. *Human papillomavirus and HPV vaccines: technical information for policy-makers and health professionals.* Geneva: WHO, 2007. Available at: http://www.who.int/vaccines-documents/DocsPDF07/866.pdf (accessed 26/06/07)
10. CDC. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2007; **56** (RR-2): 1–24. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5602.pdf (accessed 26/06/07)
11. Saslow D, *et al*. American Cancer Society guidelines for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. *CA Cancer J Clin* 2007; **57:** 7–28. Also available at: http://caonline.amcancersoc.org/cgi/reprint/57/1/7 (accessed 26/06/07)
12. American Academy of Pediatrics Committee on Infectious Diseases. Prevention of human papillomavirus infection: provisional recommendations for immunization of girls and women with quadrivalent human papillomavirus vaccine. *Pediatrics* 2007; **120:** 666–8. http://pediatrics.aappublications.org/cgi/reprint/120/3/666.pdf (accessed 15/07/08)
13. Health Protection Report. HPV vaccination programme to begin in the UK in Autumn 2008 (issued 2 November, 2008). Available at: http://www.hpa.org.uk/hpr/archives/2007/news2007/news4407.htm (accessed 07/04/08)

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Gardasil; ***Austral.:*** Gardasil; ***Belg.:*** Gardasil; ***Cz.:*** Cervarix; Gardasil; Silgard; ***Fr.:*** Gardasil; ***Hung.:*** Silgard; ***Malaysia:*** Gardasil; ***NZ:*** Gardasil; ***Pol.:*** Silgard; ***Port.:*** Gardasil; Silgard; ***UK:*** Cervarix; Gardasil; ***USA:*** Gardasil.

Influenza Vaccines

Vacunas de la gripe.

Противогриппозные Вакцины

ATC — J07BB01; J07BB02.

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

Ph. Eur. 6.2 (Influenza Vaccine (Whole Virion, Inactivated); Vaccinum Influenzae Inactivatum ex Viris Integris Praeparatum). A sterile aqueous suspension of a suitable strain or strains of influenza virus types A and B, either individually or mixed, grown individually in embryonated hen eggs and inactivated so that they retain their antigenic properties. The stated amount of haemagglutinin antigen for each strain present is usually 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.
The BP 2008 states that Flu may be used on the label.
The BP 2008 directs that when Inactivated Influenza Vaccine or Influenza Vaccine is prescribed or demanded and the form is not stated, Influenza Vaccine (Whole Virion, Inactivated), Influenza Vaccine (Split Virion, Inactivated), or Influenza Vaccine (Surface Antigen, Inactivated) may be dispensed or supplied.

Ph. Eur. 6.2 (Influenza Vaccine (Split Virion, Inactivated); Vaccinum Influenzae Inactivatum ex Virorum Fragmentis Praeparatum). A sterile aqueous suspension of a suitable strain or strains of influenza virus types A and B, either individually or mixed, grown individually in embryonated hen eggs and inactivated so that the integrity of the virus particles has been disrupted without diminishing their antigenic properties. The stated amount of haemagglutinin antigen for each strain present is usually 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.
The BP 2008 states that Flu may be used on the label.
The BP 2008 directs that when Inactivated Influenza Vaccine or Influenza Vaccine is prescribed or demanded and the form is not stated, Influenza Vaccine (Whole Virion, Inactivated), Influenza Vaccine (Split Virion, Inactivated), or Influenza Vaccine (Surface Antigen, Inactivated) may be dispensed or supplied.

Ph. Eur. 6.2 (Influenza Vaccine (Surface Antigen, Inactivated); Vaccinum Influenzae Inactivatum ex Corticis Antigeniis Praeparatum). A sterile suspension consisting predominantly of haemagglutinin and neuraminidase antigens of a suitable strain or strains of influenza virus types A and B either individually or mixed, grown individually in embryonated hen eggs and inactivated so that they retain their antigenic properties. The stated amount of haemagglutinin antigen for each strain is usually 15 micrograms per dose. It may contain an adjuvant. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.
The BP 2008 states that Flu or Flu(adj) may be used on the label as appropriate.
The BP 2008 directs that when Inactivated Influenza Vaccine or Influenza Vaccine is prescribed or demanded and the form is not stated, Influenza Vaccine (Whole Virion, Inactivated), Influenza Vaccine (Split Virion, Inactivated), or Influenza Vaccine (Surface Antigen, Inactivated) may be dispensed or supplied.

Ph. Eur. 6.2 (Influenza Vaccine (Surface Antigen, Inactivated, Virosome); Vaccinum Influenzae Inactivatum ex Corticis Antigeniis Praeparatum Virosomale). A sterile aqueous suspension consisting predominantly of haemagglutinin and neuraminidase antigens of a suitable strain or strains of influenza virus types A and B either individually or mixed, grown individually in embryonated hen eggs and inactivated so that they retain their antigenic properties and reconstituted to virosomes with phospholipids and without reducing the antigenic properties of the antigens. The stated amount of haemagglutinin antigen for each strain is 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.
The BP 2008 states that Flu may be used on the label.

Ph. Eur. 6.2 (Influenza Vaccine (Whole Virion, Inactivated, Prepared in Cell Cultures); Vaccinum Influenzae Inactivatum ex Cellulis Virisque Integris Praeparatum). A sterile aqueous suspension of a suitable strain or strains of influenza virus types A and B, either individually or mixed, grown individually in cell cultures (diploid or continuous cell lines of mammalian origin) and inactivated so that they retain their antigenic properties. It may contain an adjuvant. The stated amount of haemagglutinin antigen for each strain present is usually 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2° to 8°, not be allowed to freeze, and be protected from light. The BP 2008 states that Flu or Flu (adj) may be used on the label as appropriate.

Ph. Eur. 6.2 (Influenza Vaccine (Surface Antigen, Inactivated, Prepared in Cell Cultures); Vaccinum Influenzae Inactivatum ex Cellulis Corticisque Antigeniis Praeparatum). A sterile aqueous suspension of a suitable strain or strains of influenza virus types A and B, either individually or mixed, grown individually in cell cultures (diploid or continuous cell lines of mammalian origin) and inactivated so that they retain their antigenic properties. It may contain an adjuvant. The stated amount of haemagglutinin antigen for each strain present is usually 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.
The BP 2008 states that Flu or Flu (adj) may be used on the label as appropriate.

USP 31 (Influenza Virus Vaccine). A sterile aqueous suspension of suitably inactivated influenza virus types A and B, either individually or combined, or virus subunits prepared from the extra-embryonic fluid of virus-infected chick embryos. Suitable strains of influenza virus are those designated by the US Government's Expert Committee on Influenza and recommended by the Surgeon General of the US Public Health Service. It may contain a suitable antimicrobial agent. It should be stored at 2° to 8° and not be allowed to freeze.

Nomenclature of strains. The strain designation for influenza virus types A, B, and C contains: a description of the antigenic specificity of the nucleoprotein antigen (types A, B, or C) (an internal antigen, the matrix antigen, has also been described); the host of origin (if not man, including, if appropriate, the inanimate source); the geographical origin; the strain number; and the year of isolation; e.g. A/lake water/Wisconsin/1/79. For type A viruses the antigenic description follows (in parentheses) including the antigenic character of the haemagglutinin (e.g. H1) and the antigenic character of the neuraminidase (e.g. N1). There is no provision for describing subtypes of B and C viruses. Recombination between viruses within a type is readily accomplished; the letter R should be added after the strain description to indicate the recombinant nature of the virus, e.g. A/Hong Kong/1/68(H3N2)R. In addition the strain of origin of the H and N antigens of antigenic hybrid recombinant A and B viruses should be given, e.g. A/BEL/42(H1)—Singapore/1/57(N2)R.[1]

1. Assaad FA, *et al.* Revision of the system of nomenclature for influenza viruses: a WHO Memorandum. *Bull WHO* 1980; **58:** 585–91.

Adverse Effects

As for vaccines in general, p.2201.

Local and systemic reactions may occur but are usually mild. Fever and malaise sometimes occur and severe febrile reactions have been reported particularly on giving whole-virion vaccine to children, although this type of vaccine is seldom used now. Flu-like symptoms may follow the use of intranasal vaccines.

Various neurological syndromes have been temporally associated with use of influenza vaccine, the most notable report being of the Guillain-Barré syndrome occurring after vaccination with inactivated swine influenza vaccine in 1976 (see below).

Effects on the eyes. For a discussion of bilateral eye redness, occurring as part of an oculorespiratory syndrome following influenza vaccination, see below.

Effects on the nervous system. ***BELL'S PALSY.*** Between October 2000 and April 2001, the Swiss Drug Monitoring Centre and the University of Zurich received 46 reports of Bell's palsy occurring in patients who had used an inactivated intranasal influenza vaccine (*Nasalflu*). The manufacturers suspended distribution of the vaccine and, after a subsequent study[1] suggested a strong association between the vaccine and the development of Bell's palsy, it was withdrawn from clinical use.

1. Mutsch M, *et al.* Use of the inactivated intranasal influenza vaccine and the risk of Bell's palsy in Switzerland. *N Engl J Med* 2004; **350:** 896–903.

GUILLAIN-BARRÉ SYNDROME. In 1976 a limited outbreak of influenza in the USA caused by a virus closely resembling the swine influenza virus led to the use of a killed swine influenza virus vaccine.[1] After about 45 million doses of the vaccine had been given the vaccination programme ceased because there was some evidence of a temporal association between vaccination and the onset of a paralytic polyneuropathy of the Guillain-Barré type. An epidemiologic and clinical evaluation of these cases suggested a definite link between vaccination and the onset of the syndrome with extensive paralysis but no association with the onset of limited motor lesions.

Surveillance systems have since investigated any possible link with the development of Guillain-Barré syndrome. The Immunization Safety Review Committee in the USA[2] concluded in 2004 that the evidence was inadequate to either accept or reject a causal relationship with non-swine influenza vaccines used after 1976. This review had inspected reports submitted from 1990 to 2003 to VAERS (Vaccine Adverse Events Reporting System in the USA) but considered that such case reports were uninformative with respect to causality, although they were useful for hypothesis generation. One suggestion made by workers monitoring the VAERS data[3] was the question as to whether *Campylobacter* infection could be involved. Influenza vaccines have traditionally been made in chicken eggs. *Campylobacter* is endemic in chickens and a known cause of Guillain-Barré syndrome.

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