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.

1. Anonymous. Influenza and the Guillain-Barré syndrome. *Lancet* 1984; **ii:** 850–1.
2. Stratton K, *et al. Immunization Safety Review: influenza vaccines and neurological complications.* Washington DC: The National Academies Press, 2004. Available at: http://www.nap.edu/catalog/10822 (accessed 15/07/08)
3. Haber P, *et al.* Guillain-Barré syndrome following influenza vaccination. *JAMA* 2004; **292:** 2478–81.

MULTIPLE SCLEROSIS. Analysis[1] indicated that there was no association between the use in the USA during 1976 of influenza vaccines containing a swine virus component and the development of multiple sclerosis. Later analysis by the Immunization Safety Review Committee in the USA[2] concluded in 2004 that the evidence favoured rejection of a causal relationship between influenza vaccines used in various years (including the swine vaccines of 1976) and relapse of multiple sclerosis but that the evidence was inadequate to either accept or reject a causal relationship with incident multiple sclerosis.

1. Kurland LT, *et al.* Swine flu vaccine and multiple sclerosis. *JAMA* 1984; **251:** 2672–5.
2. Stratton K, *et al. Immunization Safety Review: influenza vaccines and neurological complications*. Washington DC: The National Academies Press, 2004. Available at: http://www.nap.edu/catalog/10822 (accessed 15/07/08)

Effects on the respiratory tract. For a discussion of respiratory symptoms, occurring as part of an oculorespiratory syndrome following influenza vaccination, see below.

Henoch-Schönlein purpura. Influenza vaccination has been associated with both development[1] and exacerbation[2] of Henoch-Schönlein purpura.

1. Patel U, *et al.* Henoch-Schönlein purpura after influenza vaccination. *BMJ* 1988; **296:** 1800.
2. Damjanov I, Amato JA. Progression of renal disease in Henoch-Schönlein purpura after influenza vaccination. *JAMA* 1979; **242:** 2555–6.

Oculorespiratory syndrome. During 2000 to 2001, an increased incidence of ocular and respiratory effects was reported in Canada in 960 patients, 96% of whom had received a specific split virion influenza vaccine (*Fluviral S/F*).[1] Symptoms included bilateral redness of the eyes and facial oedema with coughing, wheezing, tightness of the chest, breathing difficulty, or sore throat and were collectively termed oculorespiratory syndrome.[1,2] It was postulated that the syndrome might be due to numerous microaggregates of unsplit viruses present in the vaccine. A study[3] using an improved formulation of the vaccine found that oculorespiratory symptoms still occurred in 6.3% of recipients and that, since the improved formulation was otherwise minimally reactogenic, such symptoms might be associated with influenza vaccines in general. A subsequent study[4] of influenza vaccination among persons previously afflicted by oculorespiratory syndrome was halted early owing to a 33% rate of recurrence of symptoms within 24 hours. The authors concluded that previously afflicted patients should be warned of the risk of recurrence but that episodes of recurrence were usually mild and well tolerated.[4]

1. National Advisory Committee on Immunization. Supplementary statement for the 2001-2002 season: influenza vaccination of persons who experienced oculo-respiratory syndrome following previous influenza vaccination. *Can Commun Dis Rep* 2001; **27:** 1–7.
2. Boulianne N, *et al.* Clinical manifestations and incidence of oculo-respiratory syndrome following influenza vaccination—Quebec, 2000. *Can Commun Dis Rep* 2001; **27:** 85–90.
3. Scheifele DW, *et al.* Ocular and respiratory symptoms attributable to inactivated split influenza vaccine: evidence from a controlled trial involving adults. *Clin Infect Dis* 2003; **36:** 850–7.
4. Skowronski DM, *et al.* Randomized, double-blind, placebo-controlled trial to assess the rate of recurrence of oculorespiratory syndrome following influenza vaccination among persons previously affected. *Clin Infect Dis* 2003; **37:** 1059–66.

Precautions

As for vaccines in general, p.2202.

Whole-virion influenza vaccine is not recommended for use in children because of the increased risk of febrile reactions. Split-virion and surface-antigen vaccines are, however, suitable for children and infants and are widely used in mass immunisation campaigns.

Influenza vaccines should not be given to individuals with a known hypersensitivity to egg products.

Vaccination should be postponed in patients with active infection or acute febrile illness.

Asthma. There have been reports of exacerbations of asthma after influenza vaccination,[1,2] but reviews[3,4] have concluded that evidence of a causal relationship is lacking and that any risk of exacerbation which might exist is outweighed by the risk of influenza itself. Chronic respiratory disease, including asthma, is an indication for influenza vaccination in both the UK and USA. A systematic review has supported the use of inactivated vaccines for patients with chronic obstructive pulmonary disease.[5] A further systematic review, however, has concluded that, while there is no significant increase in asthma exacerbations immediately after vaccination (at least with inactivated influenza vaccination), uncertainty remains about the degree of protection that vaccination affords against asthma exacerbations after influenza infection.[6]

1. Hassan WU, *et al.* Influenza vaccination in asthma. *Lancet* 1992; **339:** 194.
2. Nicholson KG, *et al.* Randomised placebo-controlled crossover trial on effect of inactivated influenza vaccine on pulmonary function in asthma. *Lancet* 1998; **351:** 326–31.
3. Watson JM, *et al.* Does influenza immunisation cause exacerbations of chronic airflow obstruction or asthma? *Thorax* 1997; **52:** 190–4.
4. Park CL, Frank A. Does influenza vaccination exacerbate asthma? *Drug Safety* 1998; **19:** 83–8.
5. Poole PJ, *et al.* Influenza vaccine for patients with chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 04/05/06).
6. Cates CJ, *et al.* Vaccines for preventing influenza in people with asthma. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 09/06/08).

Diagnostic tests. False-positive screening enzyme-linked immunosorbent assays (ELISAs) for antibodies to HIV-1, HTLV-1 and hepatitis C virus were reported in blood donors who had recently received influenza vaccine.[1] The reaction was attributed to cross-reactivity of the test kit in use at the time with non-specific IgM.

1. Anonymous. False-positive serologic tests for human T-cell lymphotropic virus type 1 among blood donors following influenza vaccination, 1992. *JAMA* 1993; **269:** 2076 and 2078.

Interactions

◊ For the effect of influenza vaccination on some other drugs see under Phenobarbital Sodium, p.494, Phenytoin Sodium, p.500, Theophylline Hydrate, p.1145, and Warfarin Sodium, p.1432.

Uses and Administration

Influenza vaccines are used for active immunisation against influenza.

Three types of the influenza virus occur, namely types A, B, and C, and the formulation and composition of influenza vaccines is constantly reviewed with changes made to accommodate the antigenic shifts and drifts of the influenza virus. Recommendations concerning the antigenic nature of influenza vaccines are made annually by WHO. Currently, influenza vaccines are mainly of the inactivated type and are available as split-virion vaccines or as various surface-antigen vaccines (including virosomal products); whole-virion vaccines are now seldom used. In the USA, a live attenuated influenza vaccine against influenza virus types A and B is available.

Influenza vaccination is recommended for persons considered to be at special risk, particularly the elderly, those with chronic heart disease, chronic respiratory disease including asthma (see above), chronic hepatic or renal disease, diabetes mellitus, and patients who are immunosuppressed. Vaccination is also recommended for residents, particularly elderly persons and children, in closed institutions. Medical personnel and other persons at risk from infection through contact with infected patients should also receive vaccination. Vaccination usually produces immunity after about 14 days, lasting for about 6 months to 1 year. Injections are therefore scheduled annually so that the period of maximum immunity coincides with the usual period of influenza infection. In the UK and USA, they are generally given between September and early November.

Influenza vaccines are given in the UK by deep subcutaneous injection or intramuscular injection. The preferred site for injection is the deltoid muscle in adults and older children and, in infants and young children, the anterolateral aspect of the thigh. The recommended dose is 0.5 mL for adults and children aged over 3 years. In children aged 6 months to 3 years, doses of 0.25 or 0.5 mL have been used. Children should be given a second dose at least 4 weeks after the first if receiving the vaccine for the first time.

The live attenuated influenza vaccine available in the USA is given intranasally, in a dose of 0.2 mL (0.1 mL in each nostril) in adults (up to 49 years of age) and children aged over 9 years and in children aged 2 to 8 years who have received it previously. Children aged 2 to 8 years who have not previously received the vaccine are given a repeat dose after at least 30 days.

Commercially available influenza vaccines are not effective against avian influenza virus H5N1; however, such a vaccine has been developed in the USA (see below).

◊ Reviews.

1. Jefferson TO, *et al.* Vaccines for preventing influenza in healthy adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 09/06/08).
2. Jefferson T, *et al.* Vaccines for preventing influenza in healthy children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 09/06/08).

Administration. Haemagglutinin on the surface of the influenza virus allows the virus to attach to the host cells, and antibody against it is the main form of immunity to influenza. Antibody to neuraminidase on the virus surface and cell-mediated immunity may be important as well. Adults with previous exposure to the relevant subtype usually get a fourfold or greater increase in haemagglutinin antibody after vaccination with 20 to 30 micrograms of haemagglutinin [equivalent to about one 0.5-mL dose], but in some cases most of the new antibody is against the original strain rather than the variant in the vaccine. Children and unprimed adults need 2 injections of a much larger dose of haemagglutinin (60 micrograms or more) for an adequate antibody response. The level of antibody falls by about 75% over 8 months after split-virus vaccine and by 50% over 6 months after whole-virus vaccine. Because of this decrease in antibody level, and antigenic drift, immunisation against influenza is required each year. After 1 or 2 doses of killed vaccine, clinical infection rates are reduced by 60 to 80% in children and young adults. Vaccination reduces clinical infection by only about 30% in elderly patients in institutions, but serious illness and death are probably cut by about 70%. The effectiveness of vaccination has varied widely in different studies, probably because of differences in previous exposure to the influenza subtype, vaccine dose, interval between vaccination and challenge, and matching of vaccine and challenge antigens.

Avian influenza vaccine. Since 1997, infection of humans with avian influenza virus H5N1 has been reported and is associated with high mortality. Although the current H5N1 influenza strains appear not to be transmissible from human to human, it is of major concern that further mutations or mixing with human influenza strains could convert H5N1 to a strain that would spread from human to human and cause a serious pandemic. Candidate avian influenza vaccines have been investigated and *Sanofi Pasteur, USA* has developed a vaccine. Although the vaccine will not be commercially available, it has been licensed by the FDA and will be included in the National Stockpile in the USA for use in the event that the H5N1 virus develops the ability to become readily transmissible from human to human.[1]

1. FDA. FDA news: FDA approves first U.S. vaccine for humans against the avian influenza virus H5N1 (issued 17th April, 2007). Available at: http://fda.gov/bbs/topics/NEWS/2007/NEW01611.html (accessed 06/07/07)

Preparations

Ph. Eur.: Inactivated Influenza Vaccine (Split Virion, Inactivated); Influenza Vaccine (Surface Antigen, Inactivated); Influenza Vaccine (Surface Antigen, Inactivated, Prepared in Cell Cultures); Influenza Vaccine (Surface Antigen, Inactivated, Virosome); Influenza Vaccine (Whole Virion, Inactivated); Influenza Vaccine (Whole Virion, Inactivated, Prepared in Cell Cultures);
USP 31: Influenza Virus Vaccine.

Proprietary Preparations (details are given in Part 3)
Arg.: Agrippal; Berigripina†; Evagrip†; Fluad; Fluarix; Fluzone†; Imovax Gripe†; Inflexal; Influvac; Isiflu Zonale†; Istivac; Nilgrip; Vaxigrip; ***Austral.:*** Fluarix; Fluvax; Influvac; Vaxigrip; ***Austria:*** Addigrip; Batrevac; Begrivac; Fluad; Fluarix; Fluvaccinol; Inflexal; Influvac; Invivac; Sandovac; Vacciflu; Vaxigrip; ***Belg.:*** α-Rix; Addigrip†; Fluvirin†; Influvac S; Mutagrip†; Vaxigrip; ***Braz.:*** Agrippal; Fluarix†; Fluzone†; Vacina Contra Gripe; Vacina de Virus Inativado Contra Gripe; Vaxigrip†; ***Canad.:*** Fluviral; Fluzone†; Vaxigrip; ***Chile:*** Fluarix; Inflexal; Influvac; Vaxigrip; ***Cz.:*** Agrippal†; Begrivac; Daronrix; Fluad; Fluarix; Fluvirin†; Focetria; Inflexal; Influvac; Optaflu; Vaxigrip; ***Denm.:*** Fluarix; Influvac; Vaxigrip; ***Fin.:*** Begrivac; Fluarix; Flupar; Fluvirin†; Influvac; Vaxigrip; ***Fr.:*** Agrippal; Fluarix; Fluvirine†; Gripguard; Immugrip; Influvac; Mutagrip; Previgrip; Vaxigrip†; ***Ger.:*** Addigrip; Begrivac†; Fluad; Infectovac Flu; Inflexal; Influsplit SSW; Influvac; Invivac; Mutagrip; ***Gr.:*** Addigrip; Agrippal; Evagrip; Fluarix; Influvac; Vaxigrip; ***Hong Kong:*** Agrippal; Fluad; Fluarix; Fluvax; Inflexal; Influvac; Vaxigrip; ***Hung.:*** Agrippal; Begrivac; Fluarix; Fluval; Influvac; Vaxigrip; ***Indon.:*** Vaxigrip; ***Irl.:*** Agrippal; Begrivac†; Fluarix; Fluvirin†; Influvac; ***Israel:*** Agrippal; Fluarix; Fluvirin; Influvac; Vaxigrip; ***Ital.:*** Adiugrip; Agrippal; Begrivac; Fluad; Fluarix; Focusvax†; Inflexal; Influpozzi; Influsplit†; Influvac S; Influvirus; Isiflu V; Isigrip Zonale; Mutagrip; Vaxigrip; ***Malaysia:*** Fluarix; Fluvax; Inflexal; Vaxigrip; ***Mex.:*** Agrippal; Fluarix; Fluzone; Influvac†; ***Neth.:*** Afluria; Agrippal; Batrevac; Fluarix; Fluvax; Fluvirin; Inflexal; Influject; Influvac; Invivac; Mutagrip; Vacciflu; Vaxigrip; ***Norw.:*** Begrivac; Fluarix; Fluvirin†; Influvac; Invivac; Vaxigrip; ***NZ:*** Begrivac†; Fluarix; Fluvax; Influvac; Vaxigrip; ***Philipp.:*** Agrippal; Fluad; Fluarix; Inflexal; Vaxigrip; ***Pol.:*** Begrivac; Fluarix; Inflexal; Influvac; Vaxigrip; ***Port.:*** Batrevac; Chiroflu; Fluad; Fluarix; Fluvirin; Focetria; Inflexal; Influvac; Istivac; Vaxigrip; ***Rus.:*** Fluarix (Флюарикс); Grippol (Гриппол); Influvac (Инфлювак); ***S.Afr.:*** Agrippal; Fluarix†; Fluvirin; Influvac; Mutagrip; Vaxigrip; Xflu†; ***Singapore:*** Agrippal; Fluad; Fluarix; Influvac; Vaxigrip; ***Spain:*** Chiroflu; Chiromas; Evagrip; Fluarix; Gripavac; Imuvac†; Influvac; Mutagrip; Prodigrip†; Vac Antigripal; Vacuna Antigripal; Vitagripe†; ***Swed.:*** Agrippal; Batrevac†; Begrivac; Fluad; Fluarix; Fluvirin†; Influvac; Vaxigrip; ***Switz.:*** Fluarix; Inflexal; Influvac; Mutagrip; Nasalflu†; ***Thai.:*** Agrippal; Fluad; Fluarix; Fluzone; Vaxigrip; ***Turk.:*** Agrippal; Fluarix; Inflexal; Vaxigrip; ***UK:*** Agrippal; Begrivac; Enzira; Fluarix; Fluvirin; Imuvac; Inflexal†; Influvac; Invivac; Mastaflu; Optaflu; Viroflu; ***USA:*** Afluria; Fluarix; FluLaval; FluMist; Fluvirin; Fluzone; ***Venez.:*** Fluarix; Imovax Gripe†; Isiflu; Vacuna Purificada.

Japanese Encephalitis Vaccines

Vacunas de la encefalitis japonesa.

ATC — J07BA02.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Hypersensitivity reactions including urticaria, angioedema, hypotension, and dyspnoea have been reported mainly in travellers from non-endemic areas. In May 2005 the Japanese government suspended routine vaccination with mouse brain-derived vaccine in response to a report of acute disseminated encephalomyelitis after vaccination; however, a causal link has not been established.

Persons with unstable neurological conditions, including convulsions in the past year, may be at higher risk of adverse events. It is suggested that vaccine should not be given to those who are recovering from acute disseminated encephalomyelitis or to those with Guillain-Barré syndrome, multiple sclerosis, or other demyelinating disorders.