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.

◊ References.
1. Andersen MM, Rønne T. Side-effects with Japanese encephalitis vaccine. *Lancet* 1991; **337:** 1044.
2. Ruff TA, *et al.* Adverse reactions to Japanese encephalitis vaccine. *Lancet* 1991; **338:** 881–2.
3. Plesner A-M, *et al.* Neurological complications and Japanese encephalitis vaccination. *Lancet* 1996; **348:** 202–3.
4. Nothdurft HD, *et al.* Adverse reactions to Japanese encephalitis vaccine in travellers. *J Infect* 1996; **32:** 119–22.
5. Jelinek T, Nothdurft HD. Japanese encephalitis vaccine in travellers: is wider use prudent? *Drug Safety* 1997; **16:** 153–6.
6. Berg SW, *et al.* Systemic reactions in US Marine Corps personnel who received Japanese encephalitis vaccine. *Clin Infect Dis* 1997; **24:** 265–6.
7. Liu ZL, *et al.* Short-term safety of live attenuated Japanese encephalitis vaccine (SA14-14-2): results of a randomized trial with 26,239 subjects. *J Infect Dis* 1997; **176:** 1366–9.
8. Plesner AM. Allergic reactions to Japanese encephalitis vaccine. *Immunol Allergy Clin North Am* 2003; **23:** 665–97. Correction. *ibid.* 2004; **24:** 335.

Interactions
As for vaccines in general, p.2202.

Uses and Administration
Two types of inactivated Japanese encephalitis (JE) vaccine containing either the Nakayama or the Beijing-1 strain of the virus and grown in mouse-brain tissue are generally used for active immunisation against encephalitis due to JE virus. The Nakayama strain vaccine produced in Japan was widely available internationally, but production has been stopped. Another inactivated JE vaccine is made in China from the Beijing-3 strain of JE virus and grown in Syrian hamster kidney-cell cultures. This vaccine has been replaced in the Chinese vaccination programme by a live, attenuated JE virus (strain SA 14-14-2) vaccine that is also produced on primary hamster cells. JE vaccines are widely used in China, Japan and other parts of Asia where JE is endemic and may form part of the WHO Expanded Programme on Immunization. Vaccination is recommended for visitors to rural areas of South East Asia and the Far East where infection is endemic and where the visit is to be for more than one month; it is also recommended for shorter visits in individuals likely to be at exceptional risk.

In the UK adults and children over 3 years who are non-immune travellers are usually given 3 doses each of 1 mL of the inactivated mouse-brain vaccine subcutaneously at 0, 7 to 14, and 28 to 30 days; full immunity will take up to one month to develop. A two-dose schedule with doses given 7 to 14 days apart may provide short-term immunity but is less effective; in the USA, an abbreviated dosage schedule with doses at 0, 7, and 14 days is suggested if time is not available for the standard schedule. Children under 3 years of age may be given 3 doses of 0.5 mL; in the USA, the vaccine is not recommended for children under 1 year. Reinforcing doses may be needed but the interval at which they are given varies with the vaccine preparation.

In areas where JE is endemic, primary immunisation with inactivated vaccines has been given according to a different schedule. Although the ages and schedule of subsequent boosters varies in different countries, the same schedule is used for primary immunisation. The first dose is given at age 6 months to 3 years according to the country, but in all cases is followed by a second dose 1 to 4 weeks later and then a third after 1 year. Live attenuated Japanese encephalitis vaccines are also used, in single or 2-dose schedules (see below), in some countries in the Far East where disease is endemic.

◊ Inactivated Japanese encephalitis vaccines have been widely used in Asia for some years. In Japan, the incidence of the disease has decreased since the introduction of nationwide vaccination in the mid-1960s.

A live attenuated vaccine, SA14-14-2, is widely used in China and is replacing the use of inactivated vaccine. Studies[1,2] with the live attenuated vaccine showed that 2 doses given a year apart were 97% effective in an endemic region of rural China. Similar results were obtained when the interval between doses was reduced to 1 to 3 months. A further case-control study[3] in Nepal found that single-dose administration was more than 99% effective.

Other vaccines are under development including recombinant DNA and chimeric vaccines. Recombinant vaccines delivered using poxvirus vectors were also investigated but research appears to have been halted.[4,5]

1. Hennessy S, *et al.* Effectiveness of live-attenuated Japanese encephalitis vaccine (SA14-14-2): a case-control study. *Lancet* 1996; **347:** 1583–6.
2. Tsai TF, *et al.* Immunogenicity of live attenuated SA14-14-2 Japanese encephalitis vaccine—a comparison of 1- and 3-month immunization schedules. *J Infect Dis* 1998; **177:** 221–3.
3. Bista MB, *et al.* Efficacy of single-dose SA 14-14-2 vaccine against Japanese encephalitis: a case control study. *Lancet* 2001; **358:** 791–5.
4. Tauber E, *et al.* Safety and immunogenicity of a Vero-cell-derived, inactivated Japanese encephalitis vaccine: a non-inferiority, phase III, randomised controlled trial. *Lancet* 2007; **370:** 1847–53.
5. Schiøler KL, *et al.* Vaccines for preventing Japanese encephalitis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 11/04/08).

Preparations
Proprietary Preparations (details are given in Part 3)
Austral.: JE-Vax; ***Canad.:*** JE-Vax; ***Cz.:*** JE-Vax†; ***Thai.:*** JE-Vaccine; ***USA:*** JE-Vax.

Jellyfish Venom Antisera
Antisuero contra el veneno de la medusa; Jellyfish Antivenins; Jellyfish Antivenoms.

Adverse Effects and Precautions
As for antisera in general, p.2201.

Uses and Administration
An antiserum for use in the management of severe stings by the box jellyfish or sea wasp *Chironex fleckeri* is available in Australia. The preparation contains the specific antitoxic globulins that neutralise the venom of *Chironex fleckeri* and is prepared from the serum of sheep immunised with the venom of the box jellyfish.

Box jellyfish antivenom is usually given by the intravenous route in a dose of 20 000 units. Alternatively, 60 000 units may be injected intramuscularly.

Jellyfish stings. Many stings caused by the box jellyfish *Chironex fleckeri* are of little consequence and can be managed by simple first aid measures; however, some can be rapidly fatal so immediate assessment is vital.[1] Fragments of tentacle adhering to the skin should be inactivated by the application of vinegar or 3 to 10% acetic acid solution. Cardiopulmonary resuscitation may be necessary in severe cases. The antiserum can be effective if given quickly and in adequate dosage,[2,3] although use is mainly reserved for those with cardiorespiratory instability, severe pain refractory to opioid analgesics, or at risk of significant scarring.[1,3] Some experimental evidence suggested that verapamil might be useful for treatment of the cardiotoxic effects of the venom and allow more time for the antiserum to exert its action,[1,4] but is now considered to be contraindicated.[3] Some have suggested that the *Chironex fleckeri* antiserum may be effective for severe envenomation by related species.[3,5]

Irukandji syndrome consists of several hypercatecholaminergic symptoms (such as generalised pain, distress, hypertension, cardiomyopathy, and pulmonary oedema) arising from envenomation with the small box jellyfish *Carukia barnesi*.[1,6] Treatment is essentially symptomatic and supportive. The *Chironex fleckeri* antivenom is not effective.[3,5] Acetic acid may also be helpful for stings by related species (see p.2244).

1. Bailey PM, *et al.* Jellyfish envenoming syndromes: unknown toxic mechanisms and unproven therapies. *Med J Aust* 2003; **178:** 34–7.
2. Fenner PJ, *et al.* Successful use of chironex antivenom by members of the Queensland Ambulance Transport Brigade. *Med J Aust* 1989; **151:** 708–10.
3. Tibballs J. Australian venomous jellyfish, envenomation syndromes, toxins and therapy. *Toxicon* 2006; **48:** 830–59.
4. Burnett JW. The use of verapamil to treat box-jellyfish stings. *Med J Aust* 1990; **153:** 363.
5. Fenner PJ, Williamson JA. Worldwide deaths and severe envenomation from jellyfish stings. *Med J Aust* 1996; **165:** 658–61.
6. Macrokanis CJ, *et al.* Irukandji syndrome in northern Western Australia: an emerging health problem. *Med J Aust* 2004; **181:** 699–702.

Leishmaniasis Vaccines
Vacunas de la leishmaniasis.

Profile
Vaccines containing *Leishmania* spp. are under investigation in an attempt to prevent cutaneous leishmaniasis.

◊ The inoculation of an infective strain of a *Leishmania* sp. into the skin, a technique known as leishmanisation, has been used to protect against cutaneous leishmaniasis (p.824). Although the technique has been standardised it is not generally recommended since large, slow-healing lesions have occurred in some patients. There is currently no effective vaccine for any form of leishmaniasis. First-generation vaccines containing killed leishmanial promastigotes, with or without BCG as an adjuvant, have been developed and tested in humans. These have conferred some protection against cutaneous disease but it has waned relatively quickly in some cases. They have not been found to confer protection against visceral leishmaniasis. New studies are ongoing investigating the use of alum as an adjuvant. There is also further investigation into second-generation vaccines using different approaches such as the use of surface antigens (gp63 and lipophosphoglycan), promastigote antigen from *L. amazonensis*, enzyme receptor (LACK), Th1-driving adjuvant such as interleukin-12, oligodeoxynucleotides with leishmanial antigens, or recombinant leishmanial antigen (TSA, LmSTI-1), all of which have conferred some protection in *mice*. A glycoprotein-enriched *L. donovani* promastigote vaccine (*Leishmune*®) is available for prophylactic veterinary use in Brazil. DNA constructs encoding gp63 and LACK have also conferred protection against *L. major* in *mice*. A chimeric vaccine has also been developed combining three leishmanial antigens (LeIF, LmSTI-1, and TSA) in monophosphoryl lipid A adjuvant but had, at best, mixed results in trials in *dogs*. Attenuated vaccines prepared by gene deletion have shown promise in *mice*. The saliva of sandflies (the vector) seems to enhance infectivity, and vaccines against salivary or gut antigens of the insect have also been investigated.

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2. Melby PC. Vaccination against cutaneous leishmaniasis: current status. *Am J Clin Dermatol* 2002; **3:** 557–70.
3. Mauel J. Vaccination against Leishmania infections. *Curr Drug Targets Immune Endocr Metabol Disord* 2002; **2:** 201–26.
4. Brodskyn C, *et al.* Vaccines in leishmaniasis: advances in the last five years. *Expert Rev Vaccines* 2003; **2:** 705–17.
5. WHO. State of the art of new vaccines: research & development. Information available at: http://www.who.int/vaccine_research/documents/stateoftheart/en/index.html (accessed 24/03/06)
6. Palatnik-de-Sousa CB. Vaccines for leishmaniasis in the fore coming 25 years. *Vaccine* 2008; **26:** 1709–24.

Leprosy Vaccines
Vacunas de la lepra.

Profile
Vaccines against leprosy including those using *Mycobacterium leprae*, as well as other mycobacteria, are under investigation. A killed vaccine has been developed in India for use as an adjunct to standard multidrug therapy in the treatment of leprosy. Although studies of new vaccines are continuing, BCG vaccine (p.2207) also appears to be effective.

◊ Leprosy vaccines are being studied both to prevent infection with *M. leprae* (immunoprophylaxis) and to prevent disease in infected individuals (immunotherapeutic). Attempts to develop a vaccine against leprosy are based on the assumption that induction of a cell-mediated immune response to *Mycobacterium leprae* will lead to protection against the bacillus. Several vaccines have been studied and include BCG, BCG plus heat-killed *M. leprae*, heat-killed *Mycobacterium w*, and ICRC (Indian Cancer Research Centre) bacillus. The fortuitous finding that BCG vaccine, which is inexpensive and widely available, is effective against leprosy has important implications for leprosy control. Considerable **immunoprophylaxis** against leprosy is afforded by BCG vaccination (see p.2207), and a study in Malawi showed that repeated vaccination provided additional protection.[1] However, the addition of killed *M. leprae* did not produce any further improvement, confirming preliminary results of a study in Venezuela.[2] However, in a report of their sixth meeting,[3] the WHO Technical Advisory Group on the Elimination of Leprosy reported superior vaccine efficacy for BCG plus heat-killed *M. leprae* than with BCG alone in a prophylactic leprosy vaccine study in south India. The study was begun in 1991 and involved 171 400 subjects who received either BCG alone, BCG plus heat-killed *M. leprae*, *Mycobacterium w*, ICRC bacillus, or placebo. Three surveys of the results have since been conducted by way of follow-up; the preliminary findings of the latest of these surveys revealed that the overall efficacy rates for the vaccines were 22% for BCG alone, 67% for BCG plus heat-killed *M.leprae*, 41% for *Mycobacterium w*, and 51% for ICRC bacillus. Within these results, the findings specifically for efficacy in contacts of patients with leprosy were 11% for BCG alone, 88% for BCG plus heat-killed *M. leprae*, 87% for *Mycobacterium w*, and 11% for ICRC bacillus. Further studies are being conducted in Brazil regarding the use of BCG for booster doses in schoolchildren, and also for its use in household contacts.

Beneficial responses have been reported[4-10] from the **immunotherapeutic** use of *Mycobacterium w* vaccine with standard multidrug therapy (p.176) although a small increase in Type 1 lepra reactions has been observed.[9-11] A similar, and possibly identical, vaccine based on the ICRC bacillus has also been evaluated.[12,13] Immunotherapy with BCG and heat killed *M.leprae* has produced beneficial responses when given as an adjunct to chemotherapy.[14] WHO has suggested that the immunotherapeutic use of vaccines may ultimately prove to be more clinically relevant than the immunoprophylactic use,[12] and high compliance with immunotherapy appears to be attainable.[15]

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