Uses and Administration

Measles, mumps, and rubella vaccines are used for active immunisation against measles, mumps, and rubella. They are used for primary immunisation in children 12 months of age or older and to protect susceptible contacts during an outbreak of measles. For discussion of immunisation schedules, see under Vaccines, p.2202.

In the UK, it is recommended that all children receive two doses of 0.5 mL of a measles, mumps, and rubella vaccine by intramuscular injection (or subcutaneously if there is a bleeding disorder). These are usually given shortly after the first birthday and before school entry, but may be given at any age if routine vaccination has been omitted, allowing 3 months between doses. The combined vaccine may also be used for prophylaxis after exposure to measles provided it is given within 72 hours of contact. However, it is not considered to be effective for postexposure prophylaxis against either mumps or rubella. If the vaccine is given before 12 months of age, re-immunisation will be necessary starting at between 12 and 15 months with a further dose according to national schedules.

Similar schedules are used in the USA.

Preparations

Ph. Eur.: Measles, Mumps, and Rubella Vaccine (Live);
USP 31: Measles, Mumps, and Rubella Virus Vaccine Live.

Proprietary Preparations (details are given in Part 3)
Arg.: MMR II; Trimovax; Triviraten; ***Austral.:*** MMR II†; Priorix; ***Austria:*** Priorix; ***Belg.:*** MMR Vax; Priorix; ***Braz.:*** MMR II†; Priorix†; Trimovax†; Vacina Comb. Contra Sarampo, Caxumba e Rubeola; Vacina Contra Sarampo, Caxumba e Rubeola; Vacina de Virus Vivos de Sarampo, Caxumba e Rubeola; ***Canad.:*** MMR II; Priorix; ***Cz.:*** MMR II; MMRVaxPro; Priorix; Trimovax†; Trivivac; ***Denm.:*** MMR; ***Fin.:*** MMR II; Priorix; ***Fr.:*** MMRVaxPro; Priorix; R.O.R.; ***Ger.:*** MMR Triplovax; MMR Vax; Priorix; ***Gr.:*** MMR II; MMRVaxPro; Priorix; ***Hong Kong:*** MMR II; Priorix; Trimovax; Triviraten†; ***Hung.:*** MMR II; ***India:*** Tresivac; ***Indon.:*** MMR II; Trimovax; ***Irl.:*** MMR II; Priorix; ***Israel:*** MMR II; Priorix; ***Ital.:*** MMR II; Morupar†; Priorix; ***Malaysia:*** MMR II; Priorix; Triviraten†; ***Mex.:*** MMR II; Morupar†; Priorix; ***Neth.:*** Priorix; ***Norw.:*** MMR II; Priorix; ***NZ:*** Priorix; Triviraten; ***Philipp.:*** Morupar†; Priorix; Trimovax; Triviraten; ***Pol.:*** MMR II; Priorix; Trimovax†; ***Port.:*** Priorix; ***Rus.:*** MMR II (ММР II); Priorix (Приорикс); ***S.Afr.:*** Morupar†; Priorix; Trimovax; ***Singapore:*** MMR II; Priorix; ***Spain:*** Priorix; Triviraten†; Vacuna Triple MSD; ***Swed.:*** MMR II; Priorix; ***Switz.:*** MMR II; Priorix; Triviraten; ***Thai.:*** MMR II; Morupar†; Priorix; Trimovax; Triviraten†; ***Turk.:*** MMR II; Priorix; Trimovax; Triviraten; ***UK:*** MMR II; Priorix; ***USA:*** MMR II; ***Venez.:*** Priorix; Trimovax†.

Multi-ingredient: ***NZ:*** MMR II.

Measles, Mumps, Rubella, and Varicella-Zoster Vaccines

ATC — J07BD54.

Profile

Measles, mumps, rubella, and varicella-zoster vaccines are used for active immunisation against measles, mumps, rubella and varicella (chickenpox).

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Priorix-Tetra; ProQuad; ***NZ:*** Priorix-Tetra; ***Port.:*** Priorix-Tetra; ProQuad; ***USA:*** ProQuad.

Meningococcal Vaccines

Vacunas de polisacáridos meningocócicos.

ATC — J07AH01; J07AH02; J07AH03; J07AH04; J07AH05; J07AH06; J07AH07.

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

Ph. Eur. 6.2 (Meningococcal Polysaccharide Vaccine; Vaccinum Meningitidis Cerebrospinalis). It consists of one or more purified capsular polysaccharides obtained from one or more suitable strains of *Neisseria meningitidis* group A, group C, group Y, and group W135; it may contain a single type of polysaccharide or any mixture of the types. It is prepared immediately before use by reconstitution from the stabilised freeze-dried vaccine with a suitable sterile liquid. The freeze-dried vaccine should be stored at 2° to 8° and be protected from light.

The BP 2008 states that Men plus the relevant antigen may be used on the label (for example MenAC).

Ph. Eur. 6.2 (Meningococcal Group C Conjugate Vaccine; Vaccinum Meningococcale Classis C Coniugatum). A liquid or freeze-dried preparation of purified capsular polysaccharide derived from a suitable strain of *Neisseria meningitidis* group C covalently linked to a carrier protein. The vaccine may contain an adjuvant. The freeze-dried vaccine should be stored at 2° to 8° and be protected from light.

The BP 2008 states that MenC(conj) may be used on the label.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Immunity to the unconjugated serogroup C polysaccharide in meningococcal vaccines may be insufficient to confer adequate protection against infection in infants under about 2 years of age.

Effects on the nervous system. From June 2005 to September 2006, 17 cases of Guillain-Barré syndrome were reported to the Vaccine Adverse Event Reporting System (VAERS) after use of a tetravalent (A, C, W135, and Y) meningococcal conjugate vaccine (Menactra). Whether the cases were caused by the vaccine or were coincidental was unknown.[1,2] The CDC recommends that persons with a history of Guillain-Barré syndrome should not be vaccinated with the tetravalent meningococcal conjugate vaccine.[2]

1. CDC. Guillain-Barré syndrome among recipients of Menactra meningococcal conjugate vaccine - United States, June-July 2005. *MMWR* 2005; **54:** 1023–5.
2. CDC. Update: Guillain-Barré syndrome among recipients of Menactra meningococcal conjugate vaccine— United States, June 2005-September 2006. *MMWR* 2006; **55:** 1120–4. Correction. *ibid.*; 1177.

Pregnancy and the neonate. A study[1] in 157 Asian women given a tetravalent polysaccharide vaccine in the third trimester of pregnancy found that immunisation was safe for both mothers and infants. Infants were provided with significantly increased levels of IgG for 2 to 3 months and of oral IgA for 6 months from breast feeding.

1. Shahid NS, *et al.* Placental and breast transfer of antibodies after maternal immunization with polysaccharide meningococcal vaccine: a randomized, controlled evaluation. *Vaccine* 2002; **20:** 2404–9.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Meningococcal vaccines are used for active immunisation against *Neisseria meningitidis* infections, which include meningitis and septicaemia. They are preparations of purified polysaccharide antigens from *N. meningitidis* and may be monovalent, containing the antigen of only one serotype of *N. meningitidis* or polyvalent, containing antigens of two or more serotypes. Conjugation of the polysaccharide to a carrier such as diphtheria CRM_{197} protein or to tetanus toxoid protein increases the immunogenicity.

In the UK, primary immunisation is recommended during infancy whereas in the USA routine immunisation is recommended during adolescence or for those at increased risk for meningococcal disease from 2 to 10 years of age. In the UK, a conjugate meningococcal C vaccine is used and is generally given by intramuscular injection with the subcutaneous route reserved for patients with haemophilia or thrombocytopenia. Infants, starting at 2 months of age, are given 3 doses of 0.5 mL at monthly intervals. If primary immunisation is delayed until 5 months of age then 2 doses, one month apart, are sufficient; children over 1 year of age and adults should be given a single dose only. In the USA, routine immunisation with a single dose, given intramuscularly, of a conjugate tetravalent vaccine from groups A, C, Y, and W135 is performed at 11 to 18 years of age if not previously vaccinated. For discussion of immunisation schedules see under Vaccines, p.2202.

Asplenic persons or those who have terminal complement component deficiencies are at higher than normal risk of acquiring meningococcal infection and therefore they should be immunised. Either a conjugate meningococcal C vaccine or a tetravalent vaccine (A, C, Y, and W135, unconjugated or conjugated) may be used depending on availability.

Meningococcal vaccines are also indicated in persons travelling to countries where the risk of infection is high. They should receive a tetravalent meningococcal polysaccharide vaccine (either unconjugated or conjugated) rather than the group C conjugate vaccine, and should be immunised even if they have already received the latter. Vaccination is indicated particularly for visits of 1 month or more and for those backpacking or living or working with local residents. Vaccination is a visa requirement for Hajj pilgrims to Saudi Arabia.

Meningococcal vaccines may be given as an adjunct to chemoprophylaxis in contacts of persons with meningitis (see p.178).

A meningococcal group B vaccine has been developed in New Zealand and contains outer membrane vesicles from *N. meningitidis* group B strain NZ 98/254. It is given for primary immunisation against the New Zealand strain (P1.7-b,4* PorA protein) of group B meningococcal disease. Adults and children over 6 months old are given three doses of 0.5 mL at intervals of 6 weeks intramuscularly; infants less than 6 months old should be given 4 doses, at 6 weeks, 3 months, 5 months, and 10 months of age. Vaccines against other group B meningococci are under investigation (see below).

◊ Reviews.

1. Ruggeberg J, Heath PT. Safety and efficacy of meningococcal group C conjugate vaccines. *Expert Opin Drug Saf* 2003; **2:** 7–19.

Vaccine development. Despite the established use of vaccines against meningococcal groups A, C, W135, and Y, about 60 to 80% of meningococcal infections (p.179) in the UK and the USA are caused by *Neisseria meningitidis* of group B serotype. Unfortunately the purified group B polysaccharide is only poorly immunogenic, even after conjugation with proteins but several avenues of research are being followed in the development of an effective vaccine. These include vaccines based on other outer membrane proteins contained in outer membrane vesicles, in particular the most important outer membrane proteins, PorA, and on lipopolysaccharide derivatives. More recently, group B meningococcal vaccine based on PorA has been developed in New Zealand (see above) and is available for primary immunisation against the New Zealand strain specifically, and has resulted in a marked reduction in incidence in that country. Recombinant technology has been used in the Netherlands to develop both a monovalent PorA vaccine and a hexavalent vaccine containing 6 PorA proteins, including that of the New Zealand strain. Results obtained with the New Zealand PorA antigen in the hexavalent formulation have been poor, but it has been shown to stimulate a satisfactory immune response in infants or small children in the monovalent form. The successful sequencing of the meningococcal genome has allowed discovery of several new proteins and raised potential for the development of new candidate vaccines, including novel surface-located vaccine candidates which are currently in preclinical evaluation.

An intranasal meningococcal group B vaccine is also under development.

References.

1. Katial RK, *et al.* Immunogenicity and safety testing of a group B intranasal meningococcal native outer membrane vesicle vaccine. *Infect Immun* 2002; **70:** 702–7.
2. Jodar L, *et al.* Development of vaccines against meningococcal disease. *Lancet* 2002; **359:** 1499–1508.
3. Vermont CL, van den Dobbelsteen GP. Meningococcal serogroup B infections: a search for a broadly protective vaccine. *Expert Rev Vaccines* 2003; **2:** 673–81.
4. Broker M. Development of new vaccines against meningococcal disease. *Arzneimittelforschung* 2003; **53:** 805–13.
5. Zimmer SM, Stephens DS. Meningococcal conjugate vaccines. *Expert Opin Pharmacother* 2004; **5:** 855–63.
6. Zimmer SM, Stephens DS. Serogroup B meningococcal vaccines. *Curr Opin Investig Drugs* 2006; **7:** 733–9.
7. Holst J. Strategies for development of universal vaccines against meningococcal serogroup B disease: the most promising options and the challenges evaluating them. *Hum Vaccin* 2007; **3:** 290–4.
8. Kelly C, *et al.* A prospective study of the effectiveness of the New Zealand meningococcal B vaccine. *Am J Epidemiol* 2007; **166:** 817–23.
9. McNicholas A, *et al.* Surveillance of vaccine breakthrough cases following MeNZB vaccination. *N Z Med J* 2008; **121:** 38–46.
10. van Alphen L, van den Dobbelsteen G. Meningococcal B vaccine development and evaluation of efficacy. *Hum Vaccin* 2008; **4:** 158–61.
11. WHO: Initiative for Vaccine Research (IVR). Neisseria meningitidis. Information available at: http://www.who.int/vaccine_research/diseases/soa_bacterial/en/index2.html (accessed 13/04/06)

Preparations

Ph. Eur.: Meningococcal Group C Conjugate Vaccine; Meningococcal Polysaccharide Vaccine.

Proprietary Preparations (details are given in Part 3)
Arg.: Antimeningococica A+C; Meningitec†; Menjugate; NeisVac-C; Va-Mengoc-BC; ***Austral.:*** Mencevax ACWY; Meningitec; Menjugate; Menomune; NeisVac-C; ***Austria:*** Mencevax ACWY; Meningitec; Menomune; NeisVac-C; ***Belg.:*** Mencevax ACWY; Meningitec; Meningovax A+C†; Menjugate; NeisVac-C; ***Braz.:*** Va-Mengoc-BC†; Vacina Meningococica A+C; Vacina Meningococica Conjugada Grupo C; ***Canad.:*** Meningitec; Menjugate; Menomune; NeisVac-C; ***Chile:*** Meningo A+C; ***Cz.:*** Menjugate; Menpovax A+C†; NeisVac-C; ***Denm.:*** Meningovax A+C; NeisVac-C; ***Fin.:*** Mencevax ACWY; Meningovax A+C; NeisVac-C; ***Fr.:*** Meningitec; Meninvact; Menjugate; Menomune; NeisVac; ***Ger.:*** Mencevax ACWY; Meningitec; Meningokokken-Impfstoff A + C; Menjugate; NeisVac-C; ***Gr.:*** Meningitec; Meninvact; Menjugate; Menomune; NeisVac-C; Vaccin Meningococcique; ***Hong Kong:*** Mencevax ACWY; Meningococcal A+C†; ***Hung.:*** Mencevax ACWY; Meningitec; Menjugate; NeisVac-C; ***Indon.:*** Mencevax ACWY; ***Irl.:*** Mengivac (A+C)†; Meningitec; Menjugate; ***Israel:*** Mencevax AC†; Mencevax ACWY; ***Ital.:*** Mencevax ACWY; Meningitec; Meninvact; Menjugate; Menomune; NeisVac-C; ***Malaysia:*** Mencevax ACWY; Menomune†; ***Neth.:*** Meningovax A+C; Meninvact; Menjugate; NeisVac-C; ***Norw.:*** Mencevax AC; Meningitec; Meningovax A+C; NeisVac-C; ***NZ:*** Mencevax ACWY; Meningitec; Menomune; MeNZB; ***Philipp.:*** Euro A & C; ***Pol.:*** NeisVac-C; ***Port.:*** Meningitec; Menjugate; NeisVac-C; ***Rus.:*** Mencevax ACWY (Менцевакс АСWY); ***S.Afr.:*** Imovax Meningo A & C; Mencevax; ***Singapore:*** Mencevax ACWY; Menomune; ***Spain:*** Mencevax AC; Meningitec; Meninvact†; Menjugate; NeisVac-C; Vacuna Antimeningococica A+C; ***Swed.:*** Meningitec†; Meningovax A+C; NeisVac-C; ***Switz.:*** Mencevax ACWY; Meningitec; Menjugate; NeisVac-C; ***Thai.:*** Meningococcal A+C†; Menomune; ***Turk.:*** Imovax Meningo A+C; ***UK:*** ACWY Vax; Mengivac (A+C)†; Meningitec; Menjugate; NeisVac-C; ***USA:*** Menactra; Menomune; ***Venez.:*** Imovax Meningo A+C†; Mencevax ACWY†.

Multiple Sclerosis Vaccines

Vacunas de la esclerosis múltiple.

Profile

Vaccines based on T cells have been investigated for the management of multiple sclerosis.

The use of vaccine-derived polyclonal antibodies from the serum of goats is also under investigation.

◊ References.

1. Hellings N, *et al.* T-cell vaccination in multiple sclerosis: update on clinical application and mode of action. *Autoimmun Rev* 2004; **3:** 267–75.
2. Sospedra M, Martin R. Antigen-specific therapies in multiple sclerosis. *Int Rev Immunol* 2005; **24:** 393–413.
3. Fontoura P, *et al.* Antigen-specific therapies in multiple sclerosis: going beyond proteins and peptides. *Int Rev Immunol* 2005; **24:** 415–46.
4. Correale J, *et al.* Vaccines for multiple sclerosis: progress to date. *CNS Drugs* 2008; **22:** 175–98.

Mumps Immunoglobulins

Inmunoglobulinas contra la parotiditis.

ATC — J06BB15.

Profile

Preparations containing antibodies against mumps virus have been used in some countries for passive immunisation against mumps.

Mumps Vaccines

Vacunas de la parotiditis.

ATC — J07BE01.

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

Ph. Eur. 6.2 (Mumps Vaccine (Live); Vaccinum Parotitidis Vivum). A freeze-dried preparation containing a suitable live attenuated strain of mumps virus (*Paramyxovirus parotitidis*) grown in cultures of human diploid cells or chick-embryo cells or the amniotic cavity of chick embryos. It is prepared immediately before use by reconstitution from the dried vaccine. The cell-culture medium may contain the lowest effective concentration of a suitable antibacterial. The virus concentration is not less than 3.7 log $CCID_{50}$ per dose. The dried vaccine should be stored at 2° to 8° and be protected from light.

The BP 2008 states that Mumps may be used on the label.

USP 31 (Mumps Virus Vaccine Live). A bacterially sterile preparation of a suitable strain of mumps virus grown in cultures of chick-embryo cells. It contains not less than the equivalent of 5×10^3 $TCID_{50}$ in each immunising dose. It may contain suitable antimicrobial agents. It should be stored at 2° to 8° and be protected from light.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Parotid swelling may occur. Unilateral nerve deafness, aseptic meningitis, and encephalitis have occurred rarely (see below for further discussion).

Mumps vaccines are not generally recommended for children below the age of 1 year in whom maternal antibodies might prevent a response.

Effects on hearing. For a report of sensorineural hearing loss following measles, mumps, and rubella vaccination, see p.2223.

Effects on the nervous system. There have been a few reports of neurological reactions including meningitis and encephalitis after vaccination with measles, mumps, and rubella vaccines. These reactions have been attributed to the mumps component. However, it has not been possible to isolate the virus from the CSF in every case and identify it as either the vaccine strain or a wild-type strain. Meningitis develops up to 35 days after immunisation, is mild, and sequelae are rare.[1,2] One study[3] found the incidence of virus-positive post-immunisation meningitis from the Urabe strain of mumps vaccine to be about 1 in 11 000 immunised children, with the incidence following Jeryl Lynn mumps vaccine being much lower. This result was supported by the incidence of about 1 in 4000 in another study,[4] making it less likely that this was a chance result, and much higher than the estimates of up to 1 in 1 million reported previously.[5] Subsequent research[6] identified the Urabe vaccine strain in CSF samples from all of 20 children with post-vaccination meningitis in the UK, and no isolates of the Jeryl Lynn strain in patients with meningitis among 80 samples tested. Thus, vaccines containing the Urabe strain, including combined measles, mumps, and rubella vaccines are no longer used in the UK and some other countries.[7] A relatively high incidence of meningitis of about 1 in 1000 has also occurred after use of a measles and mumps vaccine prepared from the Leningrad-3 strain of mumps virus.[8,9]

Encephalitis has been associated with mumps vaccination less frequently than meningitis, but may be more serious.[1] The Advisory Committee on Immunization Practices in the USA has reported that the incidence of encephalitis within 30 days of receiving a mumps-containing vaccine is 0.4 per one million doses.[10] This is no higher than the observed background incidence for CNS dysfunction in the general population.

In considering the above data it should be remembered that mumps is the most common cause of meningoencephalitis in children under 15 years of age in the UK and an important cause of permanent sensorineural deafness in childhood.[1] Meningitis after natural mumps infection is estimated to occur in 1 in 400 cases, an incidence that is very considerably above any reported with vaccination.

1. Anonymous. Mumps meningitis and MMR vaccination. *Lancet* 1989; **ii:** 1015–16.
2. Maguire HC, *et al.* Meningoencephalitis associated with MMR vaccine. *Commun Dis Rep* 1991; **1** (review 6): R60–R61.
3. Miller E, *et al.* Risk of aseptic meningitis after measles, mumps, and rubella vaccine in UK children. *Lancet* 1993; **341:** 979–82.
4. Colville A, Pugh S. Mumps meningitis and measles, mumps, and rubella vaccine. *Lancet* 1992; **340:** 786. Correction. *ibid.*: 986.
5. McDonald JC, *et al.* Clinical and epidemiologic features of mumps meningoencephalitis and possible vaccine-related disease. *Pediatr Infect Dis J* 1989; **8:** 751–5.
6. Forsey T, *et al.* Mumps vaccine and meningitis. *Lancet* 1992; **340:** 980.
7. Anonymous. Two MMR vaccines withdrawn. *Lancet* 1992; **340:** 722.
8. Čižman M, *et al.* Aseptic meningitis after vaccination against measles and mumps. *Pediatr Infect Dis J* 1989; **8:** 302–8.
9. Tešović G, *et al.* Aseptic meningitis after measles, mumps, and rubella vaccine. *Lancet* 1993; **341:** 1541.
10. Immunization Practices Advisory Committee. Mumps prevention. *MMWR* 1989; **38:** 388–400.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Mumps vaccines are used for active immunisation against mumps.

For primary immunisation a combined measles, mumps, and rubella vaccine (p.2223) is usually used. For discussion of immunisation schedules, see under Vaccines, p.2202.

Many different attenuated strains of mumps virus have been used in vaccines and those commonly used have included Jeryl Lynn, Urabe, Leningrad-3 (and adapted L-Zagreb), and Rubini strains. Efficacy seems to be broadly similar for these strains with the exception of Rubini which is reported to be less effective than Jeryl Lynn or Urabe.

A vaccine prepared from the Jeryl Lynn (B level) strain of mumps virus is available in the USA, and may be given in a dose of 0.5 mL by subcutaneous injection although combined vaccines are usually preferred.

Preparations

Ph. Eur.: Mumps Vaccine (Live);
USP 31: Mumps Virus Vaccine Live.

Proprietary Preparations (details are given in Part 3)
Arg.: Imovax Parotiditis†; ***Braz.:*** Imovax Mumps†; ***Canad.:*** Mumpsvax†; ***Cz.:*** Pavivac; ***Denm.:*** Mumpsvax†; ***Ger.:*** Mumpsvax†; ***Gr.:*** Mumpsvax†; ***Ital.:*** Vaxipar†; ***Spain:*** Vac Antiparotiditis†; ***Switz.:*** Mumpsvax; ***USA:*** Mumpsvax; ***Venez.:*** Imovax Parotiditis†.

Mycobacterium Vaccae Vaccines

SRL-172; Vacunas de Mycobacterium vaccae.

Profile

Vaccines containing *Mycobacterium vaccae* are under investigation for the prevention and immunotherapy of tuberculosis and other mycobacterial infections. They are also being studied for therapeutic use in asthma, eczema, psoriasis, and some malignant neoplasms.

Asthma. Heat-killed *Mycobacterium vaccae* is a potent down-regulator of T-helper 2 cytokines which play a central role in asthma. In a double-blind, randomised, placebo-controlled study[1] in 24 asthmatic men, a bronchial allergen challenge was given 2 weeks before and 3 weeks after a single intradermal injection of *Mycobacterium vaccae* vaccine. The maximum fall in FEV, during the allergic response to the latter challenge was reduced by a mean of 34%, but this was not statistically significant compared with placebo.

1. Camporota L, *et al.* The effects of Mycobacterium vaccae on allergen-induced airway responses in atopic asthma. *Eur Respir J* 2003; **21:** 287–93.

Eczema. In a double-blind, randomised, placebo-controlled study[1] in 41 children aged 5 to 18 years with moderate to severe atopic dermatitis, an intradermal injection of *Mycobacterium vaccae* vaccine resulted in a 48% reduction in the surface area of the skin affected after 3 months compared with 4% in those given placebo. In a later study[2] in 56 children aged 2 to 6 years, these results could not be replicated because the reduction in affected area was not found to be significantly different from placebo.

1. Arkwright PD, David TJ. Intradermal administration of a killed Mycobacterium vaccae suspension (SRL 172) is associated with improvement in atopic dermatitis in children with moderate-to-severe disease. *J Allergy Clin Immunol* 2001; **107:** 531–4.
2. Arkwright PD, David TJ. Effect of Mycobacterium vaccae on atopic dermatitis in children of different ages. *Br J Dermatol* 2003; **149:** 1029–34.

Malignant neoplasms. *Mycobacterium vaccae* vaccines have been used with limited success as adjunctive therapy in the management of a variety of cancers, notably prostate cancer, malignant melanoma, and non-small-cell lung cancer. In a preliminary study[1] 28 patients with inoperable non-small-cell lung cancer and mesothelioma were randomised to receive chemotherapy either with or without adjunctive intradermal injection of a heat-killed *Mycobacterium vaccae* vaccine (SRL-172). A trend towards improved response rate was found in those patients receiving combined therapy, together with improved median survival and 1-year survival rates; some patients given combined therapy were subsequently able to receive curative surgery or radical radiotherapy. A similar subsequent phase III study[2] in 419 patients found a significant improvement in patient quality of life after combined therapy, but the improvements in survival-time could not be replicated. Secondary analyses of these results[3] suggested an improvement in survival time for patients with adenocarcinoma, but not for those with squamous cell carcinoma. There is also some evidence of beneficial effect in patients with metastatic renal cell carcinoma.[4]

1. O'Brien ME, *et al.* A randomized phase II study of SRL172 (Mycobacterium vaccae) combined with chemotherapy in patients with advanced inoperable non-small-cell lung cancer and mesothelioma. *Br J Cancer* 2000; **83:** 853–7.
2. O'Brien ME, *et al.* SRL172 (killed Mycobacterium vaccae) in addition to standard chemotherapy improves quality of life without affecting survival, in patients with advanced non-small-cell lung cancer: phase III results. *Ann Oncol* 2004; **15:** 906–14.
3. Stanford JL, *et al.* Successful immunotherapy with Mycobacterium vaccae in the treatment of adenocarcinoma of the lung. *Eur J Cancer* 2008; **44:** 224–7.
4. Patel PM, *et al.* An evaluation of a preparation of Mycobacterium vaccae (SRL172) as an immunotherapeutic agent in renal cancer. *Eur J Cancer* 2008; **44:** 216–23.

Psoriasis. Preliminary studies have shown that heat-killed *Mycobacterium vaccae* vaccines may induce periods of remission when given intradermally. An open-label study[1] in 24 patients given 2 intradermal injections into lesion-free deltoid skin at a 3-week interval found, 12 weeks after starting treatment: marked improvement (14 patients), moderate improvement (2), no change (6), and worsening of symptoms (2). By 24 weeks, 11 of 22 patients continued to show a greater than 50% improvement and of these 5 had complete clearance of skin lesions lasting for 6 months or more. In another study,[2] a more potent heat-killed, delipidated, deglycolipidated vaccine was given similarly to 20 patients with moderate to severe psoriasis; after 12 weeks, 13 of the 20 patients showed a marked improvement, 3 were unchanged, 3 had worsened, and 1 withdrawn due to an exfoliative flare. At 24 weeks, 13 of 19 patients continued to show a greater than 50% improvement, and in some this lasted for 6 months or more. A double-blind, randomised, placebo-controlled study[3] with the latter vaccine in 36 patients with psoriatic arthritis found no improvement in psoriatic lesions compared with placebo, although there did appear to be some improvement in pain experienced.

1. Balagon MV, *et al.* Improvement in psoriasis after intradermal administration of heat-killed Mycobacterium vaccae. *Int J Dermatol* 2000; **39:** 51–8.
2. Balagon MV, *et al.* Improvement in psoriasis after intradermal administration of delipidated, deglycolipidated Mycobacterium vaccae (PVAC): results of an open-label trial. *Clin Exp Dermatol* 2001; **26:** 233–41.
3. Dalbeth N, *et al.* A randomised placebo controlled trial of delipidated, deglycolipidated Mycobacterium vaccae as immunotherapy for psoriatic arthritis. *Ann Rheum Dis* 2004; **63:** 718–22.

Tuberculosis. ***IMMUNISATION.*** References.

1. von Reyn CF, *et al.* Cellular immune responses to mycobacteria in healthy and human immunodeficiency virus-positive subjects in the United States after a five-dose schedule of Mycobacterium vaccae vaccine. *Clin Infect Dis* 1998; **27:** 1517–20.
2. Waddell RD, *et al.* Safety and immunogenicity of a five-dose series of inactivated Mycobacterium vaccae vaccination for the prevention of HIV-associated tuberculosis. *Clin Infect Dis* 2000; **30** (suppl 3): S309–S315.
3. Vuola JM, *et al.* Immunogenicity of an inactivated mycobacterial vaccine for the prevention of HIV-associated tuberculosis: a randomized, controlled trial. *AIDS* 2003; **17:** 2351–5.

IMMUNOTHERAPY. A systematic review[1] found that immunotherapy with *Mycobacterium vaccae* produced no beneficial effects in patients with tuberculosis.

1. de Bruyn G, Garner P. Mycobacterium vaccae immunotherapy for treating tuberculosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/12/04).

Normal Immunoglobulins

Inmunoglobulinas inespecíficas.

ATC — J06BA01; J06BA02.

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

Ph. Eur. 6.2 (Human Normal Immunoglobulin; Immunoglobulinum Humanum Normale). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG) antibodies, of normal subjects. Other proteins may be present; it contains not less than 10% and not more than 18% of total protein. It is intended for intramuscular or subcutaneous injection. It is obtained from the pooled plasma collected from at least 1000 donors who must be healthy, must not have been treated with substances of human pituitary origin, and as far as can be ascertained be free from detectable agents of infection transmissible by transfusion of blood or blood components. No antibacterial is