potentially severe haemolytic disease of the newborn, although other blood group antibodies may also cause the disease. The use of anti-D immunoglobulin to suppress the production of anti-D antibodies in a Rh(D)-negative mother in response to leakage of red blood cells across the placenta from a Rh(D)-positive fetus has produced a major reduction in the incidence of this disorder.

Prophylaxis. Postnatal prophylaxis of Rh(D)-negative mothers after the birth of a Rh(D)-positive infant is well established. In 1971, WHO[1] suggested a standard intramuscular dose of 200 to 300 micrograms but stated that a 100-microgram dose was likely to have a success rate only slightly inferior to that of a 200-microgram dose, thus allowing optimum use to be made of a limited resource. Clinical experience in the UK has confirmed the efficacy of the 100-microgram (500 units) intramuscular dose and this is the amount officially recommended in the UK in such situations.[2,3] Doses do, however, vary considerably in other countries: 200 to 300 micrograms (1000 to 1500 units) is given in the USA and in many European countries, and 125 micrograms (625 units) is used in Australia.

Despite the success of anti-D immunoglobulin prophylaxis, sensitisations have continued to occur. There are several possible reasons for this, the main one being immunisation during pregnancy where there has been no overt sensitising event. Postpartum doses may be omitted due to oversight or loss to follow-up. Assessment of the volume of any transplacental haemorrhage is essential to avoid inadequate dosing. Significantly large feto-maternal haemorrhage is likely to occur after traumatic deliveries including caesarean section, manual removal of the placenta, still-birth or intra-uterine death, abdominal trauma during the third trimester, delivery of twins, or unexplained hydrops fetalis.

The efficacy of postpartum prophylaxis is not in question but opinions differ on the need for prophylaxis during pregnancy. It is generally agreed that prophylaxis is necessary in all non-sensitised Rh(D)-negative women after therapeutic terminations at any stage of pregnancy, including medical termination utilising mifepristone, after ectopic pregnancy, spontaneous complete or incomplete miscarriage after 12 weeks' gestation, or threatened miscarriage after 12 weeks' gestation as evidenced by abnormal bleeding or abdominal pain. Recommendations have been made by the British Committee for Standards in Haematology for the management of these sensitising events.[3]

Prophylaxis should also be given to all non-sensitised Rh(D)-negative women after the following sensitising events during pregnancy: invasive prenatal diagnosis including amniocentesis, chorion villus sampling, or fetal blood sampling; other intra-uterine procedures such as insertion of shunts or embryo reduction; antepartum haemorrhage; external cephalic version of the fetus; closed abdominal injury; or intra-uterine death.[2,3] A dose of 50 micrograms (250 units) is recommended for prophylaxis after these events up to 20 weeks of pregnancy, and at least 100 micrograms (500 units) thereafter.

In the UK routine antenatal prophylaxis at 28 and 34 weeks' gestation is recommended for all Rh(D)-negative women[2-4] and should be given irrespective of whether anti-D prophylaxis had been given for other sensitising events during the same pregnancy or previous pregnancies.[3]

Treatment. In mild cases, the resultant hyperbilirubinaemia can be managed with phototherapy. In severe cases, exchange transfusions may be necessary and intra-uterine transfusions may be considered in pregnancies of less than about 34 weeks' gestation; beyond this, premature delivery is often preferable.[5] Some clinicians have reported treatment failures with intra-uterine transfusions but have found intravenous normal immunoglobulin 400 mg/kg daily for 5 days every 2 to 3 weeks to the mother to be effective. There are several case reports[6,7] of beneficial responses using similar doses, but no benefit was seen in 4 patients receiving 1000 mg/kg once a week.[8] This dose, however, appeared to reduce the severity of the disease in a patient with Kell sensitisation.[8] Reductions in bilirubin concentrations have been reported with intravenous normal immunoglobulin 500 mg/kg as a single dose in newborn infants,[9] and a systematic review[10] found that such treatment reduced the number of infants requiring exchange transfusion and the duration of hospital stay and phototherapy needed. Reports in small numbers of infants[11-15] suggest that epoetins may be of value in controlling anaemia which develops 2 to 8 weeks after birth.

1. WHO. Prevention of Rh sensitization: report of a WHO scientific group. *WHO Tech Rep Ser 468* 1971. Also available at: http://libdoc.who.int/trs/WHO_TRS_468.pdf (accessed 03/10/07)
2. McClelland DBL, ed. *Handbook of transfusion medicine: Blood Transfusion Services of the United Kingdom*. 4th ed. London: The Stationery Office, 2007. Also available at: http://www.transfusionguidelines.org.uk/docs/pdfs/htm_edition-4_all-pages.pdf (accessed 02/10/07)
3. Parker J, *et al.* Guidelines for the use of prophylactic anti-D immunoglobulin: British Committee for Standards in Haematology. (issued 5th December, 2006). Available at: http://www.bcshguidelines.com/pdf/Anti-D_070606.pdf (accessed 27/07/07)
4. National Institute for Clinical Excellence. Guidance on the use of routine antenatal anti-D prophylaxis for RhD-negative women: Technology Appraisal Guidance 41 (issued May 2002). Available at http://www.nice.org.uk/nicemedia/pdf/prophylaxisFinalguidance.pdf (accessed 15/07/08)
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6. Berlin G, *et al.* Rhesus haemolytic disease treated with high-dose intravenous immunoglobulin. *Lancet* 1985; **i:** 1153.
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8. Chitkara U, *et al.* High-dose intravenous gamma globulin: does it have a role in the treatment of severe erythroblastosis fetalis? *Obstet Gynecol* 1990; **76:** 703–8.
9. Rübo J, *et al.* High-dose intravenous immune globulin therapy for hyperbilirubinemia caused by Rh hemolytic disease. *J Pediatr* 1992; **121:** 93–7.
10. Gottstein R, Cooke RWI. Systematic review of intravenous immunoglobulin in haemolytic disease of the newborn. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F6–F10.
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12. Scaradavou A, *et al.* Suppression of erythropoiesis by intrauterine transfusions in hemolytic disease of the newborn: use of erythropoietin to treat the late anemia. *J Pediatr* 1993; **123:** 279–84.
13. Ovali F, *et al.* Management of late anemia in Rhesus hemolytic disease: use of recombinant human erythropoietin (a pilot study). *Pediatr Res* 1996; **39:** 831–4.
14. Zuppa AA, *et al.* Recombinant erythropoietin in the prevention of late anaemia in intrauterine transfused neonates with Rh-haemolytic disease. *Fetal Diagn Ther* 1999; **14:** 270–4.
15. Dhodapkar KM, Blei F. Treatment of hemolytic disease of the newborn caused by anti-Kell antibody with recombinant erythropoietin. *J Pediatr Hematol Oncol* 2001; **23:** 69–70.

Idiopathic thrombocytopenic purpura. Normal immunoglobulin is used for chronic idiopathic thrombocytopenic purpura (p.1505), and anti-D immunoglobulin has been found to have similar properties. The potential role of anti-D immunoglobulin in the treatment of idiopathic thrombocytopenic purpura has been discussed in several reviews.[1-3] In general, despite many studies showing the clinical efficacy and low toxicity of intravenous anti-D immunoglobulin, its precise role has not been defined for a number of reasons. Firstly, the optimal dose has not been established: doses used have ranged from 12.5 to 25 micrograms/kg daily, given for at least 2 days, in early studies to later more promising single doses of 50 to 75 micrograms/kg. Secondly, no study has shown anti-D immunoglobulin to be as effective as corticosteroid therapy for initial treatment. Furthermore, despite suggestions that anti-D immunoglobulin may be safer and easier to give than normal immunoglobulin, good comparative data is scanty. Clinical studies have, however, shown the safety and efficacy of intravenous anti-D immunoglobulin in Rh(D)-positive, non-splenectomised patients with idiopathic thrombocytopenic purpura.[1] A prospective, randomised clinical study[4] in Rh(D)-positive children with idiopathic thrombocytopenic purpura found that a single intravenous dose of 75 micrograms/kg raised the platelet count more rapidly than a single intravenous dose of 50 micrograms/kg, and was as effective as a single intravenous dose of 800 mg/kg of normal immunoglobulin.

1. Scaradavou A, Bussel JB. Clinical experience with anti-D in the treatment of idiopathic thrombocytopenic purpura. *Semin Hematol* 1998; **35** (suppl 1): 52–7.
2. Sandler SG. Treating immune thrombocytopenic purpura and preventing Rh alloimmunization using intravenous rho (D) immune globulin. *Transfus Med Rev* 2001; **15:** 67–76.
3. Sandler SG. Intravenous Rh immune globulin for treating immune thrombocytopenic purpura. *Curr Opin Hematol* 2001; **8:** 417–20. Correction. *ibid.* 2002; **9:** 179.
4. Tarantino MD, *et al.* Single dose of anti-D immune globulin at 75μg/kg is as effective as intravenous immune globulin at rapidly raising the platelet count in newly diagnosed immune thrombocytopenic purpura in children. *J Pediatr* 2006; **148:** 489–94.

Preparations

Ph. Eur.: Human Anti-D Immunoglobulin; Human Anti-D Immunoglobulin for Intravenous Administration;
USP 31: Rh (D) Immune Globulin.

Proprietary Preparations (details are given in Part 3)

Arg.: BayRho-D†; Igantid; Immunorho; Kam Rho-D; Partoben; Partogamma; Rhesogamma; ***Austral.:*** WinRho; ***Austria:*** Partobulin; Rhesogam; ***Belg.:*** RhoGAM; ***Braz.:*** Matergam; Partogama†; WinRho†; ***Canad.:*** BayRho-D†; Hyperrho S/D; WinRho; ***Chile:*** BayRho-D†; Igamad; Immunorho; Rhesogamma P; ***Cz.:*** Igamad; Partobulin; Rhesonativ; Rhophylac; ***Denm.:*** Rhesogamma P; Rhophylac; ***Fin.:*** Rhophylac; ***Fr.:*** Rhophylac; ***Ger.:*** Partobulin; Rhesogam; Rhophylac; ***Gr.:*** Rhesogamma P; Rhophylac; WinRho; ***Hong Kong:*** BayRho-D; Partobulin; RhoGAM; WinRho; ***Hung.:*** Rhesonativ; RhoGAM; ***India:*** Matergam-P; ***Indon.:*** HyperRho S/D; ***Irl.:*** Rhesonativ†; ***Israel:*** BayRho-D; KamRho-D; Rhophylac; WinRho; ***Ital.:*** Haima-D†; Igamad; Immunorho; Parto-Gamma†; Partobulin; Rhophylac; ***Malaysia:*** Rhesonativ†; ***Mex.:*** BayRho-D†; Octaglob D; Probi-Rho D†; Rhesogamma P; Rhophylac; ***Neth.:*** RheDQuin; Rhophylac; ***Norw.:*** Rhesogamma†; Rhophylac; ***NZ:*** RhoGAM; WinRho; ***Philipp.:*** WinRho; ***Pol.:*** Gamma Anty D; Partobulin; ***Port.:*** Igantid†; Rhesonativ; Rhesuman†; Rhophylac; WinRho; ***Rus.:*** HyperRHO S/D (ГиперРОУ С/Д); ***S.Afr.:*** Rhesugam; ***Singapore:*** BayRho-D†; ***Spain:*** Gamma Anti D; Rhesogamma; Rhesuman†; ***Swed.:*** Rhesogamma†; Rhesonativ; Rhophylac; ***Switz.:*** Rhophylac; ***Thai.:*** Igamad; Rhesuman†; ***Turk.:*** BayRho-D; Partobulin; Rhesogamma P; Rhesuman; RhoGAM; ***UK:*** D-Gam; Partobulin; Rhophylac; WinRho; ***USA:*** HyperRho S/D; MICRhoGAM; RhoGAM; Rhophylac; WinRho; ***Venez.:*** RhoGAM†.

Argentine Haemorrhagic Fever Vaccines

Junin Haemorrhagic Fever Vaccines; Vacunas de la fiebre hemorrágica argentina.

Profile

A live attenuated vaccine is being investigated for active immunisation against Argentine haemorrhagic fever.

◊ References.

1. Maiztegui JI, *et al.* Protective efficacy of a live attenuated vaccine against Argentine hemorrhagic fever. *J Infect Dis* 1998; **177:** 277–83.
2. Feuillade MR, Enría DA. Análisis de la utilidad de la vacuna Candid 1 en la prevención de la fiebre hemorrágica argentina en niños. *Rev Panam Salud Publica* 2005; **18:** 100–106.

BCG Vaccines

Bacillus Calmette-Guérin Vaccines; Vacunas BCG.

Вакцины БЦЖ

ATC — J07AN01; L03AX03.

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

Ph. Eur. 6.2 (BCG Vaccine, Freeze-dried; Vaccinum Tuberculosis (BCG) Cryodesiccatum; Bacillus Calmette-Guérin Vaccine BP 2008). A freeze-dried preparation containing live bacteria obtained from a strain derived from the bacillus of Calmette and Guérin (*Mycobacterium bovis* BCG) whose capacity to protect against tuberculosis has been established. It may contain a stabiliser. The dried vaccine should be stored at 2° to 8° and be protected from direct sunlight.
The BP 2008 states that BCG may be used on the label.
The BP 2008 gives BCG Vaccine as an approved synonym.

BP 2008 (Percutaneous Bacillus Calmette-Guérin Vaccine). A suspension of living cells of an authentic strain of the bacillus of Calmette and Guérin with a higher viable bacterial count than Bacillus Calmette-Guérin Vaccine. It is supplied as a dried vaccine and is reconstituted immediately before use by the addition of a suitable sterile liquid. The dried vaccine should be stored at a temperature below –20° and be protected from light.
The BP 2008 states that Tub/Vac/BCG (Perc) may be used on the label.
The BP 2008 gives Percut. BCG Vaccine as an approved synonym.

USP 31 (BCG Vaccine). A dried living culture of the bacillus Calmette-Guérin strain of *Mycobacterium tuberculosis* var. *bovis*; it is grown from a strain that has been maintained to preserve its capacity for conferring immunity. It contains an amount of viable bacteria such that inoculation, in the recommended dose, of tuberculin-negative persons results in an acceptable tuberculin conversion rate. It contains a suitable stabiliser and no antimicrobial agent. The dried vaccine should be stored in hermetically sealed containers at 2° to 8°. The reconstituted vaccine should be used immediately after preparation and any portion not used within 2 hours should be discarded.

Ph. Eur. 6.2 (BCG for Immunotherapy; BCG ad Immunocurationem). A freeze-dried preparation of live bacteria derived from a culture of the bacillus of Calmette and Guérin (*Mycobacterium bovis* BCG) whose capacity for treatment has been established. It may contain a stabiliser. It is for intravesical use only. The product should be stored at 2° to 8° and be protected from direct sunlight.

USP 31 (BCG Live). A freeze-dried preparation of attenuated live bacteria derived from a culture of Bacillus Calmette-Guérin (*Mycobacterium bovis*, var. BCG) for intravesical use only. It is reconstituted and further diluted aseptically with a sterile diluent before use. A reconstituted dose contains 1.0–19.2 × 10^8 colony-forming units (cfu). It does not contain a preservative.
BCG Live is sensitive to light and must be stored in a glass container, protected from direct light, and at 2° to 8°.

Adverse Effects and Treatment

As for vaccines in general, p.2201.

Serious adverse reactions to BCG vaccines used *for immunisation* against tuberculosis are rare, although the incidence may vary between strains. The normal therapeutic response involves induration and development of a lesion at the injection site, possibly with enlargement of local lymph nodes; this lesion may later ulcerate and heal over some months leaving a scar. In a few patients an exaggerated reaction, usually associated with overdose, inadvertent subcutaneous injection, or use in persons who are already tuberculin positive, may result in an abscess or discharging ulcer, or suppurative lymphadenitis. Nonspecific systemic reactions may include fever and headache. Generalised reactions, possibly due to hypersensitivity, have been reported with a few fatalities. Disseminated BCG infection may occur and has also led to fatalities, particularly in immunocompromised patients. Disseminated BCG complications such as osteitis have been reported with some BCG vaccines. Very rarely, a lupoid type of reaction has occurred, mostly after multiple revaccination.

Intravesical use of BCG in the treatment and prophylaxis of bladder cancer is associated with an inflammatory response; transient dysuria and urinary frequency, sometimes with fever or a flu-like syndrome, and haematuria, are common, especially with repeated treatment (as in maintenance therapy). Rarely bladder contracture and epididymo-orchitis have been reported. As with vaccination, disseminated BCG infection has occurred rarely and may potentially be fatal. Fever lasting

more than 24 hours should be investigated, and antimycobacterial therapy given if necessary. Other reported adverse effects have included hypersensitivity reactions such as rashes and arthralgia, and ocular symptoms including uveitis, conjunctivitis, iritis, and keratitis.

◊ Reviews and studies of the adverse effects of BCG vaccines and their management.[1-6] An increased incidence of local effects has followed intradermal injection of high doses of BCG vaccines.[7,8] The incidence of adverse effects may vary between strains; an increase in incidence was reported in Ireland after withdrawal of a vaccine based on the Evans strain and its replacement with a vaccine containing the SSI strain of BCG.[9]

1. Lotte A, *et al.* Second IUATLD study on complications induced by intradermal BCG-vaccination. *Bull Int Union Tuberc Lung Dis* 1988; **63:** 47–59.
2. Milstien JB, Gibson JJ. Quality control of BCG vaccine by WHO: a review of factors that may influence vaccine effectiveness and safety. *Bull WHO* 1990; **68:** 93–108.
3. Grange JM. Complications of bacille Calmette-Guérin (BCG) vaccination and immunotherapy and their management. *Commun Dis Public Health* 1998; **1:** 84–8.
4. FitzGerald JM. Management of adverse reactions to bacille Calmette-Guerin vaccine. *Clin Infect Dis* 2000; **31** (suppl 3): S75–S76.
5. Turnbull FM, *et al.* National study of adverse reactions after vaccination with bacille Calmette-Guérin. *Clin Infect Dis* 2002; **34:** 447–53.
6. Bellet JS, Prose NS. Skin complications of bacillus Calmette-Guérin immunization. *Curr Opin Infect Dis* 2005; **18:** 97–100.
7. Miles MM, Shaw RJ. Effect of inadvertent intradermal administration of high dose percutaneous BCG vaccine. *BMJ* 1996; **312:** 1014.
8. Puliyel JM, *et al.* Adverse local reactions from accidental BCG overdose in infants. *BMJ* 1996; **313:** 528–9.
9. Bolger T, *et al.* Complications associated with the bacille Calmette-Guérin vaccination in Ireland. *Arch Dis Child* 2006; **91:** 594–7.

Effects on the bones and joints. The risk of osteitis after BCG vaccination varies from country to country and appears to be linked to the strain of bacillus used.[1]

Osteitis or arthritis has also been reported after intravesicular use of BCG (see below).

1. Milstien JB, Gibson JJ. Quality control of BCG vaccine by WHO: a review of factors that may influence vaccine effectiveness and safety. *Bull WHO* 1990; **68:** 93–108.

Effects on the eyes. Follicular conjunctivitis occurred after accidental contamination of the eye with BCG vaccine.[1] The conjunctivitis responded to topical corticosteroid therapy, but a course of isoniazid was given as a precautionary measure.

For reference to uveitis after intravesical instillation see below.

1. Pollard AJ, George RH. Ocular contamination with BCG vaccine. *Arch Dis Child* 1994; **70:** 71.

Effects on the lymphatic system. Lymphadenitis associated with BCG vaccination has been reviewed.[1] It is the most common adverse effect of BCG vaccination and may develop 2 to 24 weeks after vaccination, with most cases occurring within 6 months. The incidence and severity depend on the dose, vaccine strain, the age at vaccination, and the immunological state of the patient. Suppurative BCG lymphadenitis in the form that develops in 30 to 80% of cases; neonates and immunodeficient patients are associated with an increased risk.

The treatment of BCG lymphadenitis remains controversial. Although antibacterials and antituberculous drugs such as isoniazid and rifampicin have been given, there is little evidence to support their use; the non-suppurative (simple) form regresses spontaneously without treatment while suppurating lymph nodes may be drained by needle aspiration and left to heal.

1. Goraya JS, Virdi VS. Bacille Calmette-Guerin lymphadenitis. *Postgrad Med J* 2002; **78:** 327–9.

Intravesicular administration. Intravesicular instillation of BCG can give rise to both localised and systemic adverse effects as a consequence of the immune stimulation required to eradicate cancer cells.[1-3] The most serious effects are due to disseminated infection and include severe sepsis with cardiorespiratory manifestations and a disseminated mycobacterial infection with granulomatous pneumonitis and hepatitis; prompt treatment with antimycobacterials is required.[1,4,5] Fatalities have occurred.[6,7] Other reports include severe haemophagocytic syndromes,[8] uveitis,[9,10] and arthritis and osteitis.[11,12] Epididymo-orchitis has also been reported up to 4 years after intravesicular BCG therapy.[13,14]

Initial findings of a study[15] involving 115 patients indicated that prophylactic use of ofloxacin, a fluoroquinolone with tuberculostatic activity, decreased the incidence of moderate to severe adverse effects associated with intravesical BCG without any significant decrease in recurrence-free survival at 12 months. Ofloxacin was given orally after each BCG instillation; a dose of 200 mg was given 6 hours after the first urination with a second dose about 10 to 12 hours later. Long-term study, however, was still needed to confirm these results.

1. Lamm DL. Efficacy and safety of bacille Calmette-Guérin immunotherapy in superficial bladder cancer. *Clin Infect Dis* 2000; **31:** S86–S90.
2. Rischmann P, *et al.* BCG intravesical instillations: recommendations for side-effects management. *Eur Urol* 2000; **37** (suppl 1): 33–6.
3. Huang TC. Management of complications of bacillus Calmette-Guerin immunotherapy in the treatment of bladder cancer. *Ann Pharmacother* 2000; **34:** 529–32.
4. Mooren FC, *et al.* Systemic granulomatous disease after intravesical BCG instillation. *BMJ* 2000; **320:** 219.
5. Gómez-Ferrer Lozano A, *et al.* Neumonitis granulomatosa por instilación endovesical de BCG. *Actas Urol Esp* 2006; **30:** 839–42.
6. Peyrière H, *et al.* Fatal systemic reaction after multiple doses of intravesical bacillus Calmette-Guérin for polyposis. *Ann Pharmacother* 2000; **34:** 1279–82.
7. Kamphuis JT, *et al.* BCG immunotherapy: be cautious of granulomas. Disseminated BCG infection and mycotic aneurysm as late complications of intravesical BCG instillations. *Neth J Med* 2001; **58:** 71–5.
8. Schleinitz N, *et al.* Severe hemophagocytic syndrome after intravesical BCG instillation. *Am J Med* 2002; **112:** 593–4.
9. Wertheim M, Astbury N. Bilateral uveitis after intravesical BCG immunotherapy for bladder carcinoma. *Br J Ophthalmol* 2002; **86:** 706.
10. Jacob M, *et al.* Pan-uvéite dans les suites d'instillations intravésicales de BCG (Bacille de Calmette et Guérin). *J Fr Ophtalmol* 2006; **29:** 552–5.
11. Morgan MB, Iseman MD. Mycobacterium bovis vertebral osteomyelitis as a complication of intravesical administration of Bacille Calmette-Guérin. *Am J Med* 1996; **100:** 372–3.
12. Tinazzi E, *et al.* Reactive arthritis following BCG immunotherapy for urinary bladder carcinoma: a systematic review. *Rheumatol Int* 2006; **26:** 481–8.
13. Menke JJ, Heins JR. Epididymo-orchitis following intravesical bacillus Calmette-Guérin therapy. *Ann Pharmacother* 2000; **34:** 479–82.
14. Falkensammer C, *et al.* Late occurrence of bilateral tuberculous-like epididymo-orchitis after intravesical bacille Calmette-Guérin therapy for superficial bladder carcinoma. *Urology* 2005; **65:** 175.
15. Colombel M, *et al.* The effect of ofloxacin on bacillus Calmette-Guerin induced toxicity in patients with superficial bladder cancer: results of a randomized, prospective, double-blind, placebo controlled, multicenter study. *J Urol (Baltimore)* 2006; **176:** 935–9.

Precautions

As for vaccines in general, p.2202.

BCG vaccines may be given with other live vaccines, but if they are not given at the same time it is preferable to allow an interval of 4 weeks between each although the period may be reduced to 10 days if absolutely necessary. However, routine primary immunisation in infants, including the use of live poliomyelitis vaccine, need not be delayed. No further vaccination should be given in the arm used for BCG vaccination for at least 3 months because of the risk of lymphadenitis. BCG vaccination should be postponed in patients with fever or generalised skin infection. In patients with eczema, BCG vaccines should be given at a site free from lesions. Because of the possible risk of disseminated infections, BCG vaccines should not be given to immunocompromised patients including those with HIV infection. Infants born to HIV-positive mothers may be vaccinated once HIV infection has been ruled out; vaccination should be considered in infants of unknown status in areas of high tuberculosis prevalence if there are no signs suggestive of HIV infection. Vaccination is contra-indicated in patients taking antimycobacterial therapy, and those with a history of tuberculosis or a positive tuberculin skin test. Neonates in household contact with a known or suspected case of active tuberculosis should not be vaccinated.

The instillation of *intravesical* BCG should be postponed for 7 to 14 days after any trauma to the urinary tract including transurethral resection, biopsy, and trauma caused by catheterisation. Treatment should also be postponed in patients with acute febrile illness, urinary tract infection, or gross haematuria. Use is contra-indicated in patients with active tuberculosis, previous history of systemic reaction to BCG, or treatment with antimycobacterial therapy. As with vaccination, intravesical BCG should be avoided in immunocompromised patients, including those with HIV infection. Because BCG contains live mycobacteria that may be excreted in the urine, patients should be advised on the risk of contamination, and on appropriate infection control procedures to protect family and close contacts.

Immunocompromised patients. Like other live vaccines, BCG vaccine should not be given to immunocompromised patients including those with symptomatic HIV infections and AIDS. An increased risk of disseminated BCG infection has been seen in infants and children with asymptomatic HIV infections,[1,2] leading to high mortality rates of about 80%. WHO Global Advisory Committee on Vaccine Safety therefore no longer recommends BCG vaccination of infants and children with known HIV infection (see Tuberculosis, HIV-infected Patients, below).

1. Hesseling AC, *et al.* Bacille Calmette-Guérin vaccine-induced disease in HIV-infected and HIV-uninfected children. *Clin Infect Dis* 2006; **42:** 548–58.
2. Hesseling AC, *et al.* The risk of disseminated Bacille Calmette-Guerin (BCG) disease in HIV-infected children. *Vaccine* 2007; **25:** 14–18.

Interactions

As for vaccines in general, p.2202.

Theophylline. For a report of increased theophylline half-life and serum concentrations after BCG vaccination, see under Theophylline Hydrate, p.1145.

Uses and Administration

BCG vaccines are used for active immunisation against tuberculosis. A form suitable for immunotherapy is also used locally in the treatment and prophylaxis of carcinoma *in-situ* of the bladder, and the prophylaxis of recurrent early stage bladder papillomas after resection.

For vaccination against **tuberculosis** different strategies may be adopted, depending on the prevalence of the disease in local populations, the prevalence of HIV co-infection, the potential for infant exposure to these diseases, and the existence of infrastructure to diagnose infection and follow-up vaccinated persons. WHO considers that BCG vaccination of adults is not normally recommended, although it may be considered for tuberculin-negative subjects in unavoidable and close contact with drug-resistant tuberculosis. In countries with a high prevalence of tuberculosis, infant immunisation with a single dose of BCG as soon as possible after birth is ideally to be recommended. However, these populations tend to have a high prevalence of HIV infection as well, and BCG vaccination is contra-indicated in HIV-infected subjects. Nonetheless, WHO considers that children without HIV infection will particularly benefit from vaccination in these circumstances, and recommends that immunisation should be carried out in:

- infants born to women of unknown HIV status
- infants without obvious signs of HIV infection born to women known to be HIV-infected
- infants known to be HIV-negative as a result of virological testing

It considers that immunisation should be avoided in infants known to be infected with HIV, or whose HIV status is unknown but who are born to HIV-infected mothers and have signs or symptoms suggestive of HIV infection.

In contrast, a country such as the UK has a relatively low prevalence of tuberculosis, and routine immunisation is no longer carried out. Instead, immunisation is targeted at groups considered to be at increased risk:

- all neonates and infants (0 to 12 months) living in areas where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population
- all neonates and infants with a parent or grandparent born in a country where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population
- previously unvaccinated children aged 1 to 5 years with a parent or grandparent born in a country where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population; such children aged from 6 to 16 years should also be vaccinated if they have been shown to be tuberculin-negative
- previously unvaccinated, tuberculin-negative contacts of persons suffering from active respiratory tuberculosis
- previously unvaccinated, tuberculin-negative immigrants under 16 years of age who were born in, or lived in for at least 3 months, a country where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population
- previously unvaccinated, tuberculin-negative persons under 16 years of age intending to stay or work with local people for more than 3 months in a country where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population.
- vaccination should be *withheld* in all those known or suspected to be HIV-infected, regardless of clinical status. Where vaccination is indicated, as in infants born to HIV-positive mothers, it should only be given after two appropriately timed negative postnatal tests for HIV infection.

Vaccination is also recommended in the UK for previously unvaccinated, tuberculin-negative persons under 35 years of age in the following groups:

- health care workers or laboratory staff at high risk of infection
- veterinary and other staff who handle animals known to be susceptible to tuberculosis
- staff in any institution where the incidence of tuberculosis is high

In the USA, CDC advises still more selective use, with BCG vaccination restricted essentially to tuberculin-negative children or health workers who are continually exposed to individuals with untreated or drug-resistant tuberculosis.

BCG vaccine is given intradermally (intracutaneously) at the insertion of the deltoid muscle in a dose of 0.1 mL; infants under 12 months of age are given 0.05 mL.

Contacts of patients with active pulmonary tuberculosis may require chemoprophylaxis (see under Tuberculosis, p.196) despite previous vaccination. Neonates and children under 2 years of age should be given chemoprophylaxis and immunised, if appropriate, once the course is completed. An isoniazid-resistant form of the vaccine has been produced for use in patients who have received isoniazid, but its use is not recommended.

For use in immunotherapy of **bladder cancer** several regimens have been tried. A typical induction regimen consists of once-weekly intravesical instillation of a solution containing 1 to 16×10^8 colony forming units of BCG in about 50 mL of preservative-free saline 0.9%, for 6 consecutive weeks. Maintenance regimens vary widely from single doses or short courses (once a week for 3 weeks) at 3- to 6-monthly intervals, to instillation once a month; the period of suggested maintenance also varies from 6 months to 3 years. Some also favour a consolidation regimen of three further instillations, a week apart, carried out 6 weeks after completion of induction. Instillations should be retained in the bladder for 2 hours if possible, and then voided with the patient in a sitting position to minimise the risk of environmental contamination (see also Precautions, above).

Leprosy. BCG vaccination has been shown to protect recipients against leprosy and is considered to be one of the factors responsible for the decrease in the incidence of leprosy. A meta-analysis[1] of studies using BCG vaccine to prevent leprosy found that the average protective effect was 26% for the clinical studies and 61% for the observational (cohort or case-controlled) studies. Protection was better for multibacillary forms rather than paucibacillary forms of leprosy. Age at the time of vaccination was not a predictor of vaccine efficacy, but in the observational studies the protective effect was found to decrease with age. Clinical studies indicated that an additional dose of BCG was more effective than a single dose. For further details concerning the use of BCG vaccines in both the immunoprophylaxis and immunotherapy of leprosy, see Leprosy Vaccines, p.2220.

1. Setia MS, *et al.* The role of BCG in prevention of leprosy: a meta-analysis. *Lancet Infect Dis* 2006; **6:** 162–70.

Malignant neoplasms. Immunotherapy with BCG vaccines has been tried in various malignant disorders and is most successful when given locally. The possibility that BCG vaccination might protect children against malignancies has been discussed.[1]

1. Grange JM, Stanford JL. BCG vaccination and cancer. *Tubercle* 1990; **71:** 61–4.

BLADDER. Immunotherapy with adjuvant intravesical BCG is used in the management of bladder cancers and is the treatment of choice for carcinoma *in situ* (p.659). It does not have a direct toxic effect on tumour cells, but produces a cascade of immune reactions that is reported to reduce tumour recurrence and disease progression. A systematic review[1] indicated that intravesical BCG after transurethral resection (TUR) reduced recurrence of Ta and T1 bladder cancers compared with TUR alone. A systematic review[2] of intravesical therapy concluded that tumour recurrence was significantly reduced with BCG when compared with mitomycin C but only in patients at high risk of recurrence; there was no difference in terms of disease progression or survival. However, another meta-analysis[3] reported intravesical BCG to be better than mitomycin C in the prevention of tumour recurrences, particularly in those on BCG maintenance regime, irrespective of the risk of recurrence.

1. Shelley MD, *et al.* Intravesical bacillus Calmette-Guerin in Ta and T1 bladder cancer. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 05/11/07).
2. Shelley MD, *et al.* Intravesical bacillus Calmette-Guerin versus mitomycin C for Ta and T1 bladder cancer. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 05/11/07).
3. Böhle A, *et al.* Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. *J Urol (Baltimore)* 2003; **169:** 90–5.

SKIN. Several studies have reported that BCG vaccine injected into intradermal metastases of melanoma can result in regression of the injected, and sometimes also the uninjected nodules. BCG therapy has been disappointing for visceral metastases. Many anecdotal reports and nonrandomised studies have shown benefit from BCG vaccine as adjuvant therapy, but these results have not been confirmed in large randomised, controlled studies.[1,2] More specific immunological interventions such as therapeutic vaccines are now becoming available for the treatment of melanomas (p.673).

1. Ho VC, Sober AJ. Therapy for cutaneous melanoma: an update. *J Am Acad Dermatol* 1990; **22:** 159–76.
2. Agarwala SS, *et al.* Mature results of a phase III randomized trial of bacillus Calmette-Guerin (BCG) versus observation and BCG plus dacarbazine versus BCG in the adjuvant therapy of American Joint Committee on Cancer stage I-III melanoma (E1673): a trial of the Eastern Oncology Group. *Cancer* 2004; **100:** 1692–8.

Tuberculosis. Studies from many parts of the world have evaluated the efficacy of BCG vaccine to protect against tuberculosis. Levels of protection have varied from 0 to over 80%.[1] Many explanations for such variability have been proposed: interaction with the immune response to other mycobacterial infections; antigenic, microbiological, or formulation differences between BCG vaccines; differences in the natural history of infection and disease; variations in host genetics or nutrition; or methodological differences between studies.[1,2] It has been noted that in general the efficacy of BCG vaccine in any region is proportional to its distance from the equator and this possibly reflects differences in exposure to environmental mycobacteria.[3] This could be the strongest influence on efficacy,[3] with the implication that BCG may be least effective in areas of the world where the risk of tuberculosis is greatest. BCG also appears to be more effective against systemic (miliary and meningitic tuberculosis) than against pulmonary tuberculosis. It is likely that BCG cannot produce complete protection against infection, and the development of new vaccines is ongoing.[4-6]

National policies of BCG vaccination vary widely. Some countries recommend routine vaccination; in others, such as the UK,[7] and USA[8] routine vaccination is no longer carried out and targeted immunisation aimed at infants and others at increased risk is performed (see Uses and Administration, above). Schedules throughout the world have varied from single vaccination at birth (as recommended by WHO),[9] to single vaccination at age 10 to 14, to repeated vaccination every few years (particularly in eastern Europe). These policy differences appear to be related as much to differences of opinion about the mechanism of action and effectiveness of vaccines as to local differences in the epidemiology of tuberculosis.[1] WHO considers BCG vaccination to be an adjunct to case detection and treatment in the control of tuberculosis,[9,10] and recommends that neither tuberculin skin testing nor repeat vaccination should be used.

1. Fine PEM, Rodrigues LC. Modern vaccines: mycobacterial diseases. *Lancet* 1990; **335:** 1016–20.
2. Fine PEM. BCG vaccination against tuberculosis and leprosy. *Br Med Bull* 1988; **44:** 691–703.
3. Fine PEM. Variation in protection by BCG: implications of and for heterologous immunity. *Lancet* 1995; **346:** 1339–45. Correction. *ibid.*; **347:** 340.
4. von Reyn CF, Vuola JM. New vaccines for the prevention of tuberculosis. *Clin Infect Dis* 2002; **35:** 465–74.
5. Young DB, Stewart GR. Tuberculosis vaccines: *Br Med Bull* 2002; **62:** 73–86.
6. Orme IM. Tuberculosis vaccines: current progress. *Drugs* 2005; **65:** 2437–44.
7. Department of Health. *Immunisation Against Infectious Disease* 2006: "The Green Book". Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_079917?IdcService=GET_FILE&dID=115974&Rendition=Web (accessed 15/07/08)
8. CDC. TB elimination: BCG vaccine. (issued April 06). Available at: http://www.cdc.gov/tb/pubs/tbfactsheets/BCG.pdf (accessed 01/11/07)
9. Anonymous. WHO statement on BCG revaccination for the prevention of tuberculosis. *Bull WHO* 1995; **73:** 805–6.
10. WHO. BCG vaccine. *Wkly Epidem Rec* 2004; **79:** 27–38. Available at: http://www.who.int/entity/wer/2004/en/wer7904.pdf (accessed 01/11/07)

HIV-INFECTED PATIENTS. Like other live vaccines, BCG vaccine should not be given to immunocompromised patients, including patients with symptomatic HIV infection or AIDS. WHO[1] states that HIV prevalence is one of the factors that should be considered when determining local policies on BCG vaccination (see Uses and Administration, above), and recommends that infants with known or likely HIV infection should not be vaccinated because of the increased risk in this group (see under Precautions, above). In the UK and USA, BCG vaccination is also not recommended for HIV-positive patients.

1. WHO. Revised BCG vaccination guidelines for infants at risk for HIV infection. *Wkly Epidem Rec* 2007; **82:** 193–6. Available at: http://www.who.int/wer/2007/wer8221.pdf (accessed 01/11/07)

Preparations

Ph. Eur.: BCG for Immunotherapy; Freeze-dried BCG Vaccine;
USP 31: BCG Live; BCG Vaccine.

Proprietary Preparations (details are given in Part 3)
Arg.: ImmuCyst†; Pacis†; ***Austral.:*** ImmuCyst; OncoTICE; ***Austria:*** ImmuCyst; OncoTICE; ***Belg.:*** ImmuCyst; OncoTICE; ***Braz.:*** ImmuCyst†; Imunoest; ***Canad.:*** ImmuCyst; OncoTICE; Pacis†; ***Chile:*** ImmuCyst; ***Cz.:*** ImmuCyst; ***Denm.:*** OncoTICE; ***Fin.:*** OncoTICE; ***Fr.:*** ImmuCyst; Monovax†; ***Ger.:*** ImmuCyst; OncoTICE; ***Gr.:*** ImmuCyst; OncoTICE; ***Hong Kong:*** ImmuCyst; OncoTICE†; ***Hung.:*** ImmuCyst; ***Israel:*** ImmuCyst; Immune BCG Pasteur F; OncoTICE; ***Ital.:*** ImmuCyst; Imovax BCG†; OncoTICE; ***Malaysia:*** ImmuCyst; ***Mex.:*** Cultivo BCG; OncoTICE; ***Neth.:*** OncoTICE; ***Norw.:*** OncoTICE; ***NZ:*** ImmuCyst; OncoTICE; ***Philipp.:*** Glovax; ***Pol.:*** OncoTICE; Onko BCG; ***Port.:*** ImmuCyst; OncoTICE; ***Singapore:*** ImmuCyst; ***Spain:*** ImmuCyst; OncoTICE; Vejicur; ***Swed.:*** OncoTICE; ***Switz.:*** OncoTICE; ***Thai.:*** ImmuCyst; ***Turk.:*** ImmuCyst; OncoTICE; ***UK:*** ImmuCyst; OncoTICE; ***USA:*** Pacis†; TheraCys; Tice; ***Venez.:*** ImmuCyst†; OncoTICE.

Botulism Antitoxins

Antitoxinas botulínicas.
Ботулинические Антитоксины
ATC — J06AA04.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.
Ph. Eur. 6.2 (Botulinum Antitoxin; Immunoserum Botulinicum). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the toxins formed by type A, type B, type E, or any mixture of types A, B, and E, of *Clostridium botulinum*. It contains not less than 500 international units of each of type A and type B and not less than 50 units of type E per mL. It should be stored at 2° to 8° and not be allowed to freeze.
The BP 2008 states that Bot/Ser may be used on the label.
The BP 2008 states that when Mixed Botulinum Antitoxin or Botulinum Antitoxin is prescribed or demanded and the types to be present are not stated, Botulinum Antitoxin prepared from types A, B, and E shall be dispensed or supplied.
USP 31 (Botulism Antitoxin). A sterile solution of the refined and concentrated antitoxic antibodies, chiefly globulins, obtained from the blood of healthy horses that have been immunised against the toxins produced by type A and type B and/or E strains of *Clostridium botulinum*. It contains a suitable antimicrobial agent. It should be stored at 2° to 8° in single-use containers.

◊ NOTE. Some antitoxins used in the UK have not conformed to the requirements of the BP 2008 and Ph. Eur. 6.2 (having a higher phenol content than the pharmacopoeias allow), and thus have been referred to as **botulism antitoxin** rather than botulinum antitoxin.

Adverse Effects and Precautions

As for antisera in general, p.2201.

Uses and Administration

Botulism antitoxins are used in the postexposure prophylaxis and treatment of botulism. Treatment should be given as early as possible in the course of the disease.

Since the type of botulism toxin is seldom known the polyvalent antitoxin is usually given. Sensitivity testing should always be performed before using the antitoxin.

In the UK, equine-derived trivalent antitoxins containing antitoxin types A, B, and E are used. One type contains not less than 500 units/mL of each of the 3 antitoxins. For the treatment of botulism, 20 mL of this antitoxin should be diluted to 100 mL with sodium chloride 0.9% and given by slow intravenous infusion over at least 30 minutes; another 10 mL may be given 2 to 4 hours later if necessary, and further doses at 12- to 24-hour intervals if indicated. Persons who have been exposed to the toxin and in whom symptoms have not developed should be given 20 mL intramuscularly as a prophylactic measure.

A second preparation used for treatment of botulism in the UK contains 750 units/mL of antitoxin type A, 500 units/mL of antitoxin type B, and 50 units/mL of antitoxin type E. Patients are given 250 mL by slow intravenous infusion, followed by a further 250 mL by continuous drip infusion. A further 250 mL may be given 4 to 6 hours later if necessary according to response. Patients with severe intoxication should be given an intralumbar injection of 20 mL, particularly if intravenous treatment has produced no improvement; this procedure may be repeated at 24-hour intervals if required..

In the USA, a human-derived intravenous botulism immunoglobulin (BIG-IV) is available for the treatment of patients under 1 year of age with infant botulism caused by toxin type A or B. The recommended dose of 1 mL/kg (50 mg/kg), given as a single intravenous infusion, provides a protective level of neutralising antibodies for at least 6 months.

Botulism. Botulism[1-3] is caused by the exotoxin of *Clostridium botulinum*, a spore-forming, Gram-positive anaerobe which occurs in soil and mud. There are 3 naturally occurring forms of botulism; *food-borne botulism* caused by ingestion of contaminated foodstuffs, *wound botulism* due to the growth of toxin-releasing organisms in the wound, and *intestinal botulism* (including infant botulism and adult intestinal toxaemia) caused by intestinal colonisation and toxin production. Accidental or intentional exposure to botulinum toxin may result in inhalation botulism (from aerosolisation of botulinum toxin) or iatrogenic botulism (from injection of the toxin). Seven types of *C. botulinum* can be distinguished (types A to G), each producing a different exotoxin; human disease is usually caused by types A, B, and E. The toxin is heat labile, but the spores can survive temperatures of up to 120°.

All forms of botulism produce the same clinical syndrome. Symptoms arise as a result of the toxin blocking the release of acetylcholine at the neuromuscular junction and include symmetrical cranial nerve palsies and descending flaccid paralysis, orthostatic hypotension, dry mouth, and dilated pupils. Gastrointestinal symptoms occur with food-borne or intestinal colonisation botulism. Death is usually from respiratory arrest.

Treatment of botulism is with equine-derived antitoxins and intensive respiratory and supportive therapy. Antitoxins should be given as early as possible as only toxins that are not bound to nerve ending are neutralised; however, antitoxins may still be beneficial if treatment is delayed. Some patients may benefit from drugs, such as fampridine or guanidine, aimed at reversing the neuromuscular blockade.

Infant botulism is of increasing importance, especially in the USA where it is reported to be the most common form of botulism, with honey (see p.1948) reputed to be the most frequent