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

source of infection. In contrast to food-borne botulism, in infant botulism low doses of toxin continue to be released into the gut for some time. Treatment is with intensive supportive care; equine botulism antitoxin used in adults is not generally used for infant botulism because of its serious adverse effects (including serum sickness and anaphylaxis), its short half-life, and the possibility of life-long sensitisation to equine proteins.[4] A human-derived intravenous botulism immunoglobulin (BIG-IV) is available in the USA for the treatment of patients under 1 year of age with infant botulism caused by toxin type A or B. Clinical studies[4] reported that treatment with BIG-IV within 7 days of hospital admission reduced the length of hospital stay and severity of illness in infant botulism type A or B; treatment given within 3 days was more effective than treatment given 4 to 7 days after admission.

1. Robinson RF, Nahata MC. Management of botulism. *Ann Pharmacother* 2003; **37:** 127–31.
2. Health Protection Agency. Guidelines for action in the event of a deliberate release: botulism (issued April 2007). Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947315628 (accessed 15/07/08)
3. Sobel J. Botulism. *Clin Infect Dis* 2005; **41:** 1167–73.
4. Arnon SS, *et al.* Human botulism immune globulin for the treatment of infant botulism. *N Engl J Med* 2006; **354:** 462–71.

Preparations

Ph. Eur.: Botulinum Antitoxin;
USP 31: Botulism Antitoxin.

Proprietary Preparations (details are given in Part 3)
USA: BabyBIG.

Multi-ingredient: ***Cz.:*** Bosea†.

Bovine Colostrum

Calostro bovino.

Profile

Bovine colostrum has been used similarly to antisera and human immunoglobulin preparations to provide passive immunity against infectious diseases. Hyperimmune bovine colostra have been prepared from cows previously immunised with specific antigens. In particular, these specific hyperimmune bovine colostra have been tried in cryptosporidiosis and in the prevention of rotavirus diarrhoea in infants. They may also have potential for use against *Helicobacter pylori*, *Shigella* spp., and measles.

◊ Reviews.

1. Kelly GS. Bovine colostrums: a review of clinical uses. *Altern Med Rev* 2003; **8:** 378–94. Correction. *ibid.* 2004; **9:** 69.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Travelan.

Multi-ingredient: ***Indon.:*** Stimox; Vistrum; ***Ital.:*** Colostrum; ***UK:*** BioXtra†.

Brucellosis Vaccines

Vacunas de la brucelosis.

ATC — J07AD01.

Profile

A brucellosis vaccine prepared from an antigenic extract of *Brucella abortus* has been used for active immunisation against brucellosis (p.165) in persons at high risk of contracting the disease.

Campylobacter Jejuni Vaccines

Vacunas contra el Campylobacter jejuni.

Profile

An oral vaccine is under development to provide active immunisation against *Campylobacter jejuni* infection.

Cholera Vaccines

Vacunas del cólera.

ATC — J07AE01; J07AE02.

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

Ph. Eur. 6.2 (Cholera Vaccine; Vaccinum Cholerae). A sterile homogeneous suspension of a suitable killed strain or strains of *Vibrio cholerae*. It consists of a mixture of equal parts of vaccines prepared from smooth strains of 2 main serological types, Inaba and Ogawa of the classical biotype with or without the El Tor biotype. A single strain or several strains of each type may be included. All strains must contain, in addition to their type O antigens, the heat-stable O antigen common to the Inaba and Ogawa types. If more than one strain each of Inaba and Ogawa are used they may be selected to contain other O antigens. It contains not less than 8000 million *V. cholerae* per dose, which does not exceed 1 mL. It contains not more than 0.5% of phenol. It should be stored at 2° to 8° and protected from light.

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

Ph. Eur. 6.2 (Cholera Vaccine, Freeze-dried; Vaccinum Cholerae Cryodesiccatum). Cholera vaccine that is freeze-dried and reconstituted immediately before use by the addition of a suitable sterile liquid. Phenol may not be used in the preparation of the dried vaccine. It should be stored at 2° to 8° and be protected from light.

Ph. Eur. 6.2 (Cholera Vaccine (Inactivated, Oral); Vaccinum Cholerae Perorale Inactivatum). A homogeneous suspension of inactivated suitable strains of *Vibrio cholerae* serogroup O1, representing serotypes and biotypes of epidemic strains. The vaccine may contain the B subunit of cholera toxin (CTB). Just prior to ingestion, one dose of vaccine suspension is mixed with a suitable buffer as stated on the label. Store at 2° to 8 °. Protect from light.

The BP 2008 states that Dried/Cholera may be used on the label.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Slight swelling, erythema, and tenderness occasionally occur at the injection site. Fever and malaise have been reported and general reactions, including anaphylaxis and hypersensitivity reactions, have occurred. Neurological and psychiatric reactions have occasionally occurred.

Gastrointestinal disturbances, headache, dizziness, and respiratory symptoms have followed use of oral cholera vaccine.

Interactions

As for vaccines in general, p.2202.

The oral cholera vaccine available in the UK is acid labile; consequently food should not be consumed for 1 hour before and after use.

Uses and Administration

Injectable inactivated whole-cell cholera vaccines have been used for active immunisation against cholera but are not considered to be very effective and the immunity conferred is short-lived. They have no role in the management of contacts of cases or in controlling the spread of infection.

Oral vaccines containing either live attenuated or inactivated strains are available in some countries and appear to be more effective than parenteral vaccines (see below). In the UK, an oral vaccine containing inactivated strains of *Vibrio cholerae* O1 and recombinant cholera toxin B subunit is available for use in adults and children aged over 2 years who are travelling to areas of risk. The vaccine is given as a suspension, in doses of 3 mL, mixed with sodium hydrogen carbonate solution. Adults and children aged over 6 years are given two doses, and children aged 2 to 6 years three doses, in each case at weekly intervals. Immunisation should be complete at least 1 week prior to potential exposure. Booster doses may be given after 2 years in adults and children over 6 years, or after 6 months in children aged 2 to 6 years, if continuous protection is required. Oral vaccines containing a live attenuated form of the *V. cholerae* strain CVD 103-HgR are available in some countries. They are effective against the O1 serogroup of cholera, but do not afford protection against the O139 serogroup. They may be given to adults and children aged over 2 years who are travelling to areas of risk and are given as a single-dose suspension in sodium hydrogen carbonate solution. Immunisation should be carried out at least 1 week before potential exposure. When necessary revaccination is recommended every 6 months.

The WHO International Health Regulations do not require cholera vaccination for travellers as the introduction of cholera into any country cannot be prevented by cholera vaccination. However, travellers may still be asked for evidence of immunisation at some borders.

Oral cholera vaccines. Since parenteral cholera vaccines are not considered to be very effective, providing at best 50% protection and confer immunity lasting only 3 to 6 months, attention has turned towards oral vaccines that stimulate intestinal immunity.[1] Both killed and live attenuated oral vaccines have been developed, and both types have been shown to be non-toxic and immunogenic.

Killed vaccines contain inactivated whole *Vibrio cholerae* O1 either alone or with B subunit component of cholera toxin. These vaccines typically produce a protective efficacy of about 60 to 70% and both modify established infections and prevent new ones. Although the vaccines are effective in areas where the El Tor biotype predominates, they are more effective against classical strains. Immunity particularly against El Tor may be less sustained in children under 5 years of age than in older children and adults. The main drawback is the need to give two or more doses at 1- to 2-week intervals to achieve a protective effect. The protective effect is rapidly established but diminishes over time and booster doses are necessary to maintain a high level of immunity.

A live attenuated vaccine is now available containing CVD 103-HgR in which the genes encoding the toxic A subunit are deleted by recombinant techniques.[2,3] This vaccine is effective 8 days after a single dose but less so against El Tor than against classical strains. It is not effective against *V. cholorae* O139.

Live oral vaccines effective against El Tor are now being developed,[4,5] and promising responses have also been reported with a live attenuated O139 vaccine.[6]

The efficacy and cost-effectiveness of oral vaccines to control cholera outbreaks in refugee populations is uncertain.

1. Ryan ET, Calderwood SB. Cholera vaccines. *Clin Infect Dis* 2000; **31:** 561–5.
2. Tacket CO, *et al.* Randomized, double-blind, placebo-controlled, multicentered trial of the efficacy of a single dose of live oral cholera vaccine CVD 103-HgR in preventing cholera following challenge with Vibrio cholerae O1 El tor inaba three months after vaccination. *Infect Immun* 1999; **67:** 6341–5.
3. Richie E, *et al.* Efficacy trial of single-dose live oral cholera vaccine CVD 103-HgR in North Jakarta, Indonesia, a cholera-endemic area. *Vaccine* 2000; **18:** 2399–2410.
4. Tacket CO, *et al.* Volunteer studies investigating the safety and efficacy of live El Tor Vibrio cholerae O1 vaccine strain CVD 111. *Am J Trop Med Hyg* 1997; **56:** 533–7.
5. Sack DA, *et al.* Evaluation of Peru-15, a new live oral vaccine for cholera, in volunteers. *J Infect Dis* 1997; **176:** 201–5.
6. Coster TS, *et al.* Safety, immunogenicity, and efficacy of live attenuated Vibrio cholerae O139 vaccine prototype. *Lancet* 1995; **345:** 949–52.

Preparations

Ph. Eur.: Cholera Vaccine; Cholera Vaccine (Inactivated, Oral); Freeze-dried Cholera Vaccine.

Proprietary Preparations (details are given in Part 3)
Arg.: Orochol; ***Austral.:*** Dukoral; Orochol†; ***Braz.:*** Vacina Oral Contra Colera e Diarreia Causada Por ETEC; ***Canad.:*** Dukoral; Mutacol†; ***Cz.:*** Dukoral; ***Denm.:*** Dukoral; ***Fin.:*** Dukoral; ***Fr.:*** Dukoral; ***Hong Kong:*** Orochol†; ***Ital.:*** Dukoral; ***Malaysia:*** Dukoral; ***Neth.:*** Dukoral; ***Norw.:*** Dukoral; ***NZ:*** Dukoral; ***Philipp.:*** Dukoral; Orochol; ***Port.:*** Dukoral; ***S.Afr.:*** Dukoral; ***Singapore:*** Dukoral; ***Spain:*** Dukoral; ***Swed.:*** Dukoral; ***Switz.:*** Orochol; ***Thai.:*** Dukoral; ***Turk.:*** Dukoral; ***UK:*** Dukoral.

Contraceptive Vaccines

Vacunas anticonceptivas.

Profile

Various approaches to development of a contraceptive vaccine are under investigation. A synthetic contraceptive vaccine that stimulates the production of an antibody against human chorionic gonadotrophin has been studied in human trials.

◊ Reviews.

1. Delves PJ. The development of contraceptive vaccines. *Expert Opin Invest Drugs* 2002; **11:** 1225–37.
2. Aitken RJ. Immunocontraceptive vaccines for human use. *J Reprod Immunol* 2002; **57:** 273–87.
3. McLaughlin EA, *et al.* Contraceptive vaccines. *Expert Opin Biol Ther* 2003; **3:** 829–41.
4. Ferro VA, Mordini E. Peptide vaccines in immunocontraception. *Curr Opin Mol Ther* 2004; **6:** 83–9.

Crimean-Congo Haemorrhagic Fever Immunoglobulins

Inmunoglobulinas contra la fiebre hemorrágica de Congo-Crimea.

Profile

Preparations containing antibodies against Crimean-Congo haemorrhagic fever have been used for passive immunisation against the disease.

◊ References.

1. Vassilenko SM, *et al.* Specific intravenous immunoglobulin for Crimean-Congo haemorrhagic fever. *Lancet* 1990; **335:** 791–2.
2. Ergonul O. Treatment of Crimean-Congo hemorrhagic fever. *Antiviral Res* 2008; **78:** 125–31.

Crimean-Congo Haemorrhagic Fever Vaccines

Profile

An inactivated vaccine against Crimean-Congo haemorrhagic fever, derived from *mouse* brains, is used in parts of eastern Europe.

Cytomegalovirus Immunoglobulins

Inmunoglobulinas contra el citomegalovirus.

ATC — J06BB09.

Description. Cytomegalovirus immunoglobulins containing high levels of specific antibody against CMV have been prepared from human plasma.

Adverse Effects and Precautions

As for immunoglobulins in general, p.2201.

Interactions

As for immunoglobulins in general, p.2201.

Uses and Administration

Cytomegalovirus immunoglobulins are used for passive immu-