nisation against CMV infection. They are used prophylactically, especially in patients undergoing certain transplant procedures. In transplants from CMV-seropositive donors into seronegative recipients, prophylactic use of cytomegalovirus immunoglobulin with ganciclovir should also be considered.

In the USA, a cytomegalovirus immunoglobulin G is available for use in recipients of heart, kidney, liver, lung, and pancreas transplants, and for CMV-seronegative recipients of these organs other than kidney from CMV-seropositive donors. The dosage schedule for kidney transplant recipients is 150 mg/kg by intravenous infusion within 72 hours of transplantation, then 100 mg/kg once every 2 weeks for 4 doses, then 50 mg/kg every 4 weeks for 2 doses. The rate of infusion should start at 15 mg/kg per hour increasing gradually to a maximum rate of 60 mg/kg per hour. For recipients of transplants other than kidney, the recommended dosage schedule is 150 mg/kg within 72 hours of transplantation and then once every 2 weeks for 4 further doses, then 100 mg/kg every 4 weeks for 2 doses. In the UK, cytomegalovirus immunoglobulin is available on a named patient basis for prophylaxis in patients receiving immunosuppressive treatment.

The name sevirumab is applied to a χ-chain human monoclonal cytomegalovirus immunoglobulin G1.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: CytoGam†; Megalotect; ***Austral.:*** CMV Immunoglobulin; ***Austria:*** Cytoglobin; Cytotect; ***Belg.:*** Ivegam-CMV; ***Chile:*** Cytotect; ***Cz.:*** Cytotect; ***Ger.:*** Cytoglobin; Cytotect; ***Gr.:*** Megalotect; ***Hong Kong:*** Cytotect; ***Hung.:*** Cytotect; ***Irl.:*** Megalotect†; ***Israel:*** Megalotect; ***Ital.:*** Cytotect; Immunoendocig†; Uman-Cig†; ***Neth.:*** Megalotect; ***Pol.:*** Cytotect; ***Port.:*** Megalotect; ***S.Afr.:*** Megalotect†; ***Singapore:*** Megalotect; ***Switz.:*** Cytotect; ***Thai.:*** Megalotect; ***Turk.:*** Cytotect; ***USA:*** CytoGam.

Cytomegalovirus Vaccines

Vacunas contra el citomegalovirus.

Profile

Several vaccines for active immunisation against CMV infection are under investigation, including some produced by recombinant technology. A live attenuated cytomegalovirus vaccine containing human CMV Towne strain has been investigated in humans since the late 1970s, particularly for the prevention of CMV infection in renal transplant recipients. However, there have been doubts over its safety.

◊ Several promising candidate vaccines against human CMV infection are under development, of which 5 have been or are being tested in humans.[1] Firstly, attenuated CMV (Towne strain) vaccine has been tried but found to be erratic in efficacy and loses segments of its genetic material; to overcome this a second, more robust, vaccine has been designed consisting of a chimera between the attenuated CMV and wild-type virus. The third vaccine developed, known as ALVAC, consists of a canarypox vector with either a glycoprotein B envelope or a core antigen from CMV pp65, a protein found to be recognised by CD8+ T lymphocytes during naturally acquired infection. Fourthly, a protein sub-unit vaccine consisting of a recombinant envelope glycoprotein has been found to be safe and to induce a neutralising antibody response. Finally, the fifth vaccine developed is a mixture of synthetic peptides incorporating a T helper epitope known as CD8+ cytotoxic T cell epitope and a lipid tail. Currently, the attenuated cytomegalovirus vaccine, the protein sub-unit vaccine, and the recombinant vector vaccine have been or are being tested in CMV-negative subjects, and the chimeric vaccine has been tested in CMV-positive patients as a precursor to testing in CMV-negative persons.[1]

Further vaccine candidates that have been proposed include DNA vaccines and a vaccine based on recombinant technology.[1] Some commentators[2] have suggested that reduction or prevention of cytomegalovirus disease may be a more realistic goal for a vaccine than prevention of infection.

1. Arvin AM, *et al.* Vaccine development to prevent cytomegalovirus disease: report from the National Vaccine Advisory Committee. *Clin Infect Dis* 2004; **39:** 233–9.
2. Khanna R, Diamond DJ. Human cytomegalovirus vaccine: time to look for alternative options. *Trends Mol Med* 2006; **12:** 26–33.

Dengue Fever Vaccines

Vacunas del dengue.

Profile

Live attenuated vaccines under study for active immunisation against dengue fever contain dengue virus types 1, 2, 3, and 4 alone or in various combinations. WHO considers that protection against only one or two dengue viruses might actually increase the risk of more serious disease. The ultimate aim is to produce a vaccine active against all types of dengue virus.

Recombinant vaccines are also under investigation.

◊ References.

1. Velzing J, *et al.* Induction of protective immunity against dengue virus type 2: comparison of candidate live attenuated and recombinant vaccines. *Vaccine* 1999; **17:** 1312–30.
2. Kanesa-Thasan N, *et al.* Safety and immunogenicity of attenuated dengue virus vaccines (Aventis Pasteur) in human volunteers. *Vaccine* 2001; **19:** 3179–88.
3. Rothman AL, *et al.* Induction of T lymphocyte responses to dengue virus by a candidate tetravalent live attenuated dengue virus vaccine. *Vaccine* 2001; **19:** 4694–99.
4. Sabchareon A, *et al.* Safety and immunogenicity of tetravalent live-attenuated dengue vaccines in Thai adult volunteers: role of serotype concentration, ratio, and multiple doses. *Am J Trop Med Hyg* 2002; **66:** 264–72.
5. Sun W, *et al.* Vaccination of human volunteers with monovalent and tetravalent live-attenuated dengue vaccine candidates. *Am J Trop Med Hyg* 2003; **69** (suppl 6): 24–31.
6. Sabchareon A, *et al.* Safety and immunogenicity of a three dose regimen of two tetravalent live-attenuated dengue vaccines in five- to twelve-year-old Thai children. *Pediatr Infect Dis J* 2004; **23:** 99–109.
7. Monath TP. Dengue and yellow fever—challenges for the development and use of vaccines. *N Engl J Med* 2007; **357:** 2222–5.
8. Edelman R. Dengue vaccines approach the finish line. *Clin Infect Dis* 2007; **45** (suppl 1): S56–60.
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Dental Caries Vaccines

Vacunas de la caries dental.

Profile

Dental caries vaccines consisting of purified proteins from *Streptococcus mutans* or *Str. sobrinus* are under investigation. Monoclonal antibodies are also being studied for local passive immunisation.

◊ Several *animal* studies of candidate vaccines for the prevention of dental caries have shown that immunisation with protein antigens from *Streptococcus mutans* or *Str. sobrinus* can induce salivary IgA antibodies which inhibit both sucrose-dependent or sucrose-independent accumulation of these organisms on tooth surfaces. It is thought that candidate vaccines for study in humans could be given by mucosal application since children are already naturally exposed to the antigens involved during the first years of life. Infection with *Str. mutans* normally occurs from the age of about 18 months and the intention is therefore to vaccinate 1-year-old children in order to intercept colonisation. However, progress towards a vaccine for active immunisation against dental caries requires further clinical evaluation. Passive administration of salivary antibodies to *Str. mutans* has also provided some protection in preclinical studies and small scale studies in humans.[1-4]

1. Koga T, *et al.* Immunization against dental caries. *Vaccine* 2002; **20:** 2027–44.
2. Smith DJ. Caries vaccines for the twenty-first century. *J Dent Educ* 2003; **67:** 1130–9.
3. Russell MW, *et al.* A caries vaccine? The state of the science of immunization against dental caries. *Caries Res* 2004; **38:** 230–5.
4. Smith DJ, Mattos-Graner RO. Secretory immunity following mutans streptococcal infection or immunization. *Curr Top Microbiol Immunol* 2008; **319:** 131–56.

Diphtheria Antitoxins

Antitoxinas diftéricas.

ATC — J06AA01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.
Ph. Eur. 6.2 (Diphtheria Antitoxin; Immunoserum Diphtherici). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the toxin formed by *Corynebacterium diphtheriae*. It has a potency of not less than 1000 international units/mL when obtained from horse serum and not less than 500 international units/mL when obtained from other mammals. It should be stored at 2° to 8°, and not be allowed to freeze.
The BP 2008 states that Dip/Ser may be used on the label.

Adverse Effects and Precautions

As for antisera in general, p.2201.

Uses and Administration

Diphtheria antitoxins neutralise the toxin produced by *Corynebacterium diphtheriae* locally at the site of infection and in the circulation.

Diphtheria antitoxin is used for passive immunisation in suspected cases of diphtheria and should be given without waiting for bacteriological confirmation of the infection. An antibacterial is usually given concomitantly (see p.168). Diphtheria antitoxin is generally not used for the prophylaxis of diphtheria because of the risk of provoking a hypersensitivity reaction. Contacts of a diphtheria case should be promptly investigated, given antibacterial prophylaxis and active immunisation with a suitable diphtheria-containing vaccine as appropriate (see below), and kept under observation.

A test dose of diluted diphtheria antitoxin should always be given intradermally to exclude hypersensitivity. In the UK, diphtheria antitoxin is given by intravenous infusion for the treatment of diphtheria of mild to moderate severity in the following recommended doses: for nasal diphtheria, 10 000 to 20 000 units; for tonsillar diphtheria, 15 000 to 25 000 units; for pharyngeal or laryngeal diphtheria, 20 000 to 40 000 units. In cases of combined disease, or when diagnosis is delayed, 40 000 to 60 000 units should be given, and, in severe disease, doses up to 100 000 units used. For most cutaneous infections, diphtheria antitoxin is insufficiently absorbed and is therefore not given; however, if the ulcer is sufficiently large (more than 2 cm^2) and especially if it is membranous, then 20 000 to 40 000 units may be given. Higher doses have been used in some countries.

Preparations

Ph. Eur.: Diphtheria Antitoxin.

Diphtheria Vaccines

Vacunas de la difteria.

ATC — J07AF01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.
Ph. Eur. 6.2 (Diphtheria Vaccine (Adsorbed); Vaccinum Diphtheriae Adsorbatum). A preparation of diphtheria formol toxoid adsorbed on a mineral carrier. The formol toxoid is prepared from the toxin produced by the growth of *Corynebacterium diphtheriae*. The mineral carrier may be hydrated aluminium phosphate or aluminium hydroxide and the resulting mixture is approximately isotonic with blood. The antigenic properties are adversely affected by certain antimicrobial preservatives, particularly those of the phenolic type. It contains not less than 30 international units per dose. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.
Ph. Eur. 6.2 (Diphtheria Vaccine (Adsorbed, Reduced Antigen Content); Vaccinum Diphtheriae, Antigeniis Minutum, Adsorbatum). It is an adsorbed diphtheria vaccine containing not less than 2 international units per dose.
The BP 2008 states that for a vaccine for use in the UK, the amount of toxoid used is adjusted so that the final vaccine contains not more than 2.0 flocculation equivalents per dose.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Local reactions may occur but are generally not severe in young children; the frequency and severity of reactions is reported to be less in children under 2 years of age than in older children and adults. If diphtheria vaccines or vaccines containing a diphtheria component need to be given to children over the age of 10 years or to adults, vaccines with a reduced content of diphtheria toxoid and intended for adults and adolescents should be used. For further details see Uses and Administration, below.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Diphtheria vaccines are used for active immunisation against diphtheria. The non-adsorbed vaccine has poor immunogenic properties and its effects are enhanced if given as an adsorbed preparation. For primary immunisation combined diphtheria vaccines, usually diphtheria, tetanus, and pertussis vaccines (p.2210) or diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccines (p.2212), are used. A single-component diphtheria vaccine has sometimes been used, for example in the event of contact with an infected patient or a carrier. For discussion of immunisation schedules, see under Vaccines, p.2202.

Individuals coming into contact with a case of diphtheria or carrier of a toxigenic strain, or those travelling to an endemic or epidemic area should receive a complete primary course or a reinforcing dose according to age and immunisation history; those not previously immunised should receive a primary course of immunisation, and those previously immunised should receive a single reinforcing dose of a diphtheria-containing vaccine. Contacts of a case of diphtheria or carrier of a toxigenic strain should in addition receive a prophylactic course of a suitable antibacterial (see p.168). Individuals at repeated risk of exposure to infection may be offered booster doses every 10 years.

Schick testing (p.2384) to ascertain immune status is no longer considered necessary before giving diphtheria vaccine to adults provided that a low dose is given; antibody testing is used to check immunity in those regularly exposed to diphtheria.

In some countries, booster doses of a diphtheria and tetanus vaccine are recommended every 10 years (see under Diphtheria and Tetanus Vaccines, p.2210).

Conjugation to diphtheria toxoid has been used to increase the immunogenicity of other vaccines (see Haemophilus Influenzae Vaccines, p.2213).