have activity against a broader range of isolates and may be produced in relatively large quantities by recombinant technology, passive delivery of a cocktail of monoclonal antibodies is being investigated in *animal* models as a means of prophylaxis.[9] The cost of this approach may, however, potentially prohibit its future use on a wide scale in humans.

Efforts at understanding why it is so difficult to configure immunogens from the HIV envelope that more effectively elicit neutralising antibody responses continue but, in addition, attention has turned to what is termed the cytotoxic T lymphocyte (CTL) hypothesis.[9] This proposes that vaccination of uninfected individuals will not prevent infection but will induce an anti-HIV CTL (CD8+) response. If subsequently infected with HIV these immunised persons would be better able to control viral replication and progress to AIDS much more slowly or perhaps not at all and potentially decrease viral transmission. The validity of this hypothesis is at present uncertain but it has been supported by the observation of low level, yet detectable, HIV-specific CD8+ T cell responses in certain cohorts of highly exposed but uninfected individuals.

Additionally, new vaccine strategies are becoming available which it is thought will probably be able to elicit HIV-specific CTL responses of sufficient magnitude to allow direct testing of the concept in humans. Numerous *animal* studies are underway to assess the safety and immunogenicity of a number of replication-defective recombinant viral vectors (modified vaccinia Ankara strain, vesicular stomatitis virus, Venezuelan equine encephalitis virus, adeno-associated virus, and adenovirus) and also bacterial, yeast, and plasmid DNA vectors, all of which are designed to elicit antiviral CD8+ T cell responses.[9] However, initial analyses from a large study of an adenovirus-based vaccine designed to boost T cell responses (the STEP trial) provoked alarm since results suggested that it did not decrease susceptibility to HIV infection and might have increased it in some cases.[11]

Recombinant plasmid DNA immunogens are also under investigation as potential AIDS vaccines because of their desirable safety profile and ability to express defined and discrete inserted HIV antigens. They are either used singly or as a priming immunogen in prime-boost regimens using different vaccine vectors for sequential immunisation. Initial results in preclinical *animal* studies were encouraging, but results have been disappointing in subsequent phase I human studies.[8]

Within the field of AIDS vaccine research, the decision to advance candidate vaccines from phase I or II to phase III efficacy studies is somewhat complex. At present there are no consistent criteria in place to provide guidance on such decisions and there is a need for a coordinated, objective, and rigorous process for prioritisation in order to facilitate vaccine development. To the same end, alternative designs for phase III studies are being considered, including the use of endpoints such as reduction of viral load or preservation of CD4+ T cell counts for assessing vaccine efficacy rather than prevention of infection as the single primary endpoint. These and other measures may facilitate licensure of vaccines which currently would not occur.

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Anthrax Vaccines

Vacunas del carbunco.

ATC — J07AC01.

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

Ph. Eur. 6.2 (Anthrax Vaccine for Human Use (Adsorbed, Prepared from Culture Filtrates)); Vaccinum Anthracis Adsorbatum ab Colato Culturarum ad Usum Humanum. A preparation of *Bacillus anthracis* antigens precipitated by aluminium potassium sulphate. The antigens are prepared from a sterile culture filtrate produced by a non-encapsulated strain, either avirulent or attenuated, of *B. anthracis*. The main virulence components of *B. anthracis* are the polyglutamic acid capsule and 2 binary anthrax toxins, namely lethal toxin and oedema toxin, formed from the respective combination of protective antigen with either lethal factor or oedema factor. In addition, the vaccine is likely to contain many other *B. anthracis* antigens, including membrane proteins, secreted proteins, cytoplasmic proteins, peptidoglycans, nucleic acids, and carbohydrates. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

An anthrax vaccine that is an alum precipitate of the antigen found in the sterile filtrate of suitable cultures of the Sterne strain of *Bacillus anthracis* is available in the UK for human use. It is used for active immunisation against anthrax (p.163) and is recommended for persons working with potentially infected animals or animal products. It is given in 4 doses, each of 0.5 mL by intramuscular injection. The first 3 doses are separated by intervals of 3 weeks and the fourth dose follows after an interval of 6 months. In the USA, where an anthrax vaccine is also available, 6 doses, each of 0.5 mL, are given subcutaneously, the first 3 at intervals of 2 weeks and the last 3 at intervals of 6 months. Reinforcing doses of 0.5 mL are required each year.

◊ References.

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Preparations

Ph. Eur.: Anthrax Vaccine for Human Use (Adsorbed, Prepared from Culture Filtrates);
USP 31: Anthrax Vaccine Adsorbed.

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

Anti-D Immunoglobulins

Inmunoglobulinas anti-D.

ATC — J06BB01.

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

Ph. Eur. 6.2 (Human Anti-D Immunoglobulin; Immunoglobulinum Humanum Anti-D; Anti-D (Rh_0) Immunoglobulin BP 2008). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is intended for intramuscular administration. It is obtained from plasma from D-negative donors who have been immunised against the D-antigen. It contains specific antibodies against the erythrocyte D-antigen and may also contain small quantities of other blood group antibodies, such as anti-C, anti-E, anti-A, and anti-B. Normal immunoglobulin may be added. The liquid and freeze-dried preparations should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored in an airtight container.

Ph. Eur. 6.2 (Human Anti-D Immunoglobulin for Intravenous Administration; Immunoglobulinum Humanum Anti-D ad Usum Intravenosum; Anti-D Immunoglobulin for Intravenous Use BP 2008). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from D-negative donors who have been immunised against the D-antigen. It contains specific antibodies against the erythrocyte D-antigen and may also contain small quantities of other blood group antibodies. Human normal immunoglobulin for intravenous administration may be added. Storage requirements are similar to those for Human Anti-D Immunoglobulin, except that the freeze-dried preparation is stored at a temperature not exceeding 25°.

USP 31 (Rh_0 (D) Immune Globulin). A sterile solution of globulins derived from human plasma containing antibody to the erythrocyte factor Rh_0 (D). It contains 10 to 18% of protein, of which not less than 90% is gamma globulin. It contains glycine as a stabilising agent, and a suitable preservative. It should be stored at 2° to 8°.

Adverse Effects and Precautions

As for immunoglobulins in general, p.2201.

In patients given anti-D immunoglobulin for idiopathic thrombocytopenic purpura (ITP) there have been rare reports of back pain, shaking chills, fever, and discoloured urine; such signs and symptoms may be associated with intravascular haemolysis. Serious and sometimes fatal complications of intravascular haemolysis including anaemia, acute renal insufficiency, or disseminated intravascular coagulation have been rarely reported. Most reported cases of haemolysis occurred within 4 hours of the dose.

For the treatment of ITP, anti-D immunoglobulin is contra-indicated in rhesus-negative or splenectomised patients. Patients with ITP who need a blood transfusion should be given rhesus-negative red blood cells so as not to exacerbate ongoing haemolysis. Those with low initial haemoglobin concentrations (less than 10 g/dL) should be given a reduced dosage of the immunoglobulin to minimise the risk of severe anaemia.

When given for prophylaxis of rhesus sensitisation, anti-D immunoglobulin should not be used in rhesus-positive individuals.

Interactions

As for immunoglobulins in general, p.2201.

Uses and Administration

Anti-D immunoglobulin is used to prevent a rhesus-negative mother actively forming antibodies to fetal rhesus-positive red blood cells that may pass into the maternal circulation during childbirth, abortion, or certain other sensitising events. In subsequent rhesus-positive pregnancies these antibodies could produce haemolytic disease of the newborn (erythroblastosis foetalis). The injection of anti-D immunoglobulin is not effective once the mother has formed anti-D antibodies. Anti-D immunoglobulin is also used in the management of some blood disorders, primarily idiopathic thrombocytopenic purpura.

Anti-D immunoglobulin products are available either for intramuscular use only or for intramuscular or intravenous use. Doses differ for these products and the manufacturer's recommendation should be followed for commercial products.

In the UK, recommendations produced by expert groups relate to the use of a non-proprietary product produced by the National Blood Transfusion Service. They recommend that **postnatal prophylaxis** with anti-D immunoglobulin should always be given to rhesus-negative mothers with no anti-D antibodies in their serum and who have just delivered rhesus-positive infants. It should be given as soon as possible after delivery but may give some protection even if treatment is delayed beyond 72 hours. A dose of 500 units (100 micrograms) by intramuscular injection will clear up to 4 mL of fetal red cells. An additional dose may be required depending on the amount of transplacental bleeding; for bleeds exceeding 4 mL an additional 125 units for each mL of red cells will be required.

For routine **antenatal prophylaxis**, two intramuscular doses of at least 500 units of anti-D immunoglobulin should be given at 28 and 34 weeks' gestation. Postnatal prophylaxis is still necessary.

There is also a risk of sensitisation during pregnancy from spontaneous, induced, or threatened abortion, amniocentesis, or external version. Any rhesus-negative woman at **risk of transplacental haemorrhage** during pregnancy and not known to be sensitised should be given an intramuscular dose of 250 units at up to 20 weeks' gestation and 500 units of anti-D immunoglobulin after 20 weeks' gestation.

Anti-D immunoglobulin is also given to rhesus-negative women of child-bearing potential after the inadvertent **transfusion of Rh-incompatible blood**, or after receiving blood components containing rhesus-positive red cells or organ donations from rhesus-positive donors. The dose is based on the amount of red blood cells transfused; an intramuscular dose up to 125 units/mL of transfused cells may be used.

In the USA, doses of anti-D immunoglobulin have traditionally been higher than in the UK; dosage recommendations are based on a standard dose that is capable of suppressing the immune response to 15 mL of incompatible red blood cells. One-sixth of this dose may be used up to 12 weeks of gestation for sensitising episodes.

For **idiopathic thrombocytopenic purpura**, a usual initial dose of 250 units/kg (50 micrograms/kg) of a licensed anti-D immunoglobulin product is given by intravenous injection; it may be given in two divided doses on separate days if desired. Maintenance doses usually range between 125 to 300 units/kg (25 to 60 micrograms/kg) depending on the clinical response. A reduced initial dose of 125 to 200 units/kg (25 to 40 micrograms/kg) is recommended in patients with pre-existing anaemia (haemoglobin below 10 g/dL).

Haemolytic disease of the newborn. Rhesus (Rh) incompatibility, in particular Rh(D) incompatibility, is a major cause of

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.

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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.

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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.

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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