- at age 11 to 12 years, a sixth dose of low-dose diphtheria, tetanus, and pertussis (acellular component) plus a meningococcal C conjugate vaccine in those not previously vaccinated (meningococcal polysaccharide vaccine may alternatively be used); the first dose of human papillomavirus vaccine (p.2217) may be given to girls, the second dose is given 2 months after the first dose and the third dose is given 6 months after the first dose

Immunisation schedules for older children and adults are also produced, along with recommendations for vaccination of high-risk groups, including the immunocompromised and the elderly, and of travellers.

In addition to vaccines directed against bacteria and viruses, advances are being made in producing vaccines against fungi, protozoa, and helminths, and for non-infective diseases including cancer and auto-immune disorders.

Development of novel vaccine formulations and delivery methods is continuing, including transdermal and transmucosal systems. Genetic manipulation of foodstuffs is being investigated with the aim of producing edible vaccines.

Immunisation schedules. References to routine immunisation schedules in the UK[1] and USA.[2,3]

1. Department of Health. *Immunisation Against Infectious Disease* 2006: "The Green Book" 2006 Available at: http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/GreenBook/GreenBookGeneralInformation/GreenBookGeneralArticle/fs/en?CONTENT_ID=4097254&chk=isTfGX (accessed 26/04/06)
2. CDC. Child & Adolescent Immunization Schedules, United States, 2008. Available at: http://www.cdc.gov/vaccines/recs/schedules/child-schedule.htm (accessed 14/07/08)
3. CDC. Adult Immunization Schedule, United States, October 2007–September 2008. Available at: http://www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm (accessed 14/07/08)

EXPANDED PROGRAMME ON IMMUNIZATION. In 1974 the World Health Assembly adopted a resolution creating the Expanded Programme on Immunization (EPI), the aim of which was to provide immunisation against 6 target diseases (diphtheria, measles, pertussis, poliomyelitis, tetanus, and tuberculosis) for all children throughout the world by 1990. More recently, EPI has added hepatitis B, yellow fever, and *Haemophilus influenzae* infection to the list of target diseases. Although the attention of WHO had been focussed mainly on the developing countries, it was emphasised that the programme was not created exclusively for these countries. Besides WHO, many other organisations, including UNICEF, were involved –more recently, much work has been carried out under the auspices of the Global Alliance for Vaccination and Immunisation (GAVI).

Although many cases of the target diseases and many deaths have been prevented, vaccine coverage, especially for measles and neonatal tetanus is still low. It is particularly important to immunise children as early in life as possible and not to withhold vaccines from those with minor illness or malnutrition. Vaccine uptake was around 70% in 1990 compared with less than 5% in 1974. By 2003, all 192 member states of WHO were routinely immunising against diphtheria, measles, pertussis, poliomyelitis, and tetanus before the age of 18 months. Also, 158 member states were routinely immunising against tuberculosis, but routine BCG vaccination has been discontinued in some countries, including the UK, due to low risk and prevalence of disease.

A schedule designed to provide protection at the earliest possible age consisted of: trivalent oral poliomyelitis vaccine together with BCG vaccine at birth; hepatitis B vaccine at birth, 6 weeks, and 14 weeks (where transmission at birth is likely), or at 6, 10, and 14 weeks (where transmission at birth is less likely); trivalent oral poliomyelitis vaccine together with diphtheria, tetanus, and pertussis vaccine and Haemophilus influenzae vaccine at 6, 10, and 14 weeks of age; and measles vaccine and yellow fever vaccine at 9 months of age. Tetanus vaccine is also given to all women of child-bearing age. Also included in the programme in parts of the Far East is Japanese encephalitis vaccine.

Some references to the EPI and global immunisation policy.

1. WHO Global Programme for Vaccines and Immunization: Expanded Programme on Immunization: Module 1: EPI target diseases. Geneva: WHO, 1998. Available at: http://www.who.int/vaccines-documents/DoxTrng/IIP-E/www9556-01.pdf (accessed 08/09/04)
2. WHO. Department of Vaccines and Biologicals: Module 2: EPI vaccines. Geneva: WHO, 2001. Available at: http://www.who.int/vaccines-documents/DoxTrng/IIP-E/www9556-02.pdf (accessed 08/09/04)
3. WHO. WHO vaccine-preventable diseases: monitoring system 2004 global summary. Geneva: WHO, 2004. Also available at: http://www.who.int/vaccines_documents/DocsPDF04/WHO_IVB_2004.pdf (accessed 30/09/05)

Immunisation of immunocompromised patients. Immunocompromised patients may require immunisation against opportunistic infections but immune response to vaccination may be impaired, and there is a risk of disseminated infection with live vaccines (see Precautions, above).

Recommendations for immunisation of HIV-positive individuals have varied, particularly with regard to live vaccines.

In the UK,[1] it is generally recommended that vaccines used for routine immunisation in childhood may be given to HIV-positive persons, providing they are not immunosuppressed, but that BCG and yellow fever vaccines should not be given at all. WHO and UNICEF recommend[2] that for asymptomatic HIV-positive persons routine immunisation should be carried out according to their usual Expanded Programme on Immunization (see above). In addition, an extra dose of measles vaccine should be given at 6 months of age with the standard dose given as soon after 9 months of age as possible.

Some detailed guidance on vaccination of immunocompromised children is provided by the Royal College of Paediatrics and Child Health in the UK[3] and by the Children's HIV Association of UK and Ireland.[4] Guidance on immunisation of HIV-infected adults is provided by the British HIV Association.[5]

1. Department of Health. *Immunisation Against Infectious Disease* 2006: "The Green Book" 2006 Available at: http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/GreenBook/GreenBookGeneralInformation/GreenBookGeneralArticle/fs/en?CONTENT_ID=4097254&chk=isTfGX (accessed 16/03/08)
2. WHO. *EPI vaccines in HIV-infected individuals* (5 October 2001). Available at: http://www.who.int/vaccines-diseases/diseases/HIV.shtml (accessed 07/09/04)
3. Royal College of Paediatrics and Child Health. Immunisation of the immunocompromised child: best practice statement February 2002. Available at: http://www.rcpch.ac.uk/doc.aspx?id_Resource=1768 (accessed 15/07/08)
4. Riordan A. Children's HIV Association of UK and Ireland. Immunisation of HIV-infected children, May 2007. Available at: http://www.chiva.org.uk/protocols/immunisation.html (accessed 19/03/08)
5. Geretti AM, *et al.* British HIV Association Immunisation Subcommittee. Immunisation guidelines for HIV-infected adults, April 2006. Available at: http://www.bhiva.org/files/file1001634.pdf (accessed 19/03/08)

Immunisation for travellers. A guide entitled *International Travel and Health* is published annually by WHO.[1] In 2008 the following information regarding certification of vaccination was given.

A *yellow fever* vaccination certificate is now the only one that may be required in international travel. The vaccine used must be approved by WHO and given at a designated centre. Vaccination is strongly recommended for travel outside the urban areas of countries in the yellow fever endemic zone even if these countries have not officially reported the disease and do not require evidence of vaccination on entry. Many countries require a certificate from travellers arriving from infected areas or from countries with infected areas, or who have been in transit through those areas. Some countries require a certificate from all entering travellers including those in transit; although there is no epidemiological justification for this requirement, and it is clearly in excess of the International Health Regulations (WHO recommendations for prevention of the international spread of diseases), travellers may find that it is strictly enforced, particularly for persons going to Asia from Africa or South America. The validity period of international certificates of vaccination against yellow fever is 10 years, beginning 10 days after vaccination.

No country or territory any longer requires a certificate of *cholera* immunisation as the introduction of cholera into any country cannot be prevented by cholera vaccination.

Now that *smallpox* has been eradicated, smallpox vaccination is no longer required by any country.

Apart from vaccinations required by countries for entry to their territory, other vaccinations are either recommended by WHO for general protection against certain diseases or advised in certain circumstances. A vaccination plan should be established, taking into account the traveller's destination, overall state of health and current immune status, the duration and type of travel, and the time available before travel.

Further information for international travellers is also often provided by national authorities including those in the UK[2] and USA.[3]

1. WHO. *International Travel and Health*. Geneva: WHO, 2008. Also available at: http://www.who.int/ith/en/ (accessed 16/03/08)
2. The National Travel Health Network and Centre. *Health Information for Overseas Travel*. Available at: http://www.nathnac.org/pro/yellowbook_revision.htm (accessed 30/04/06)
3. CDC. *Health Information for International Travel: The "Yellow Book" 2008*. Available at: http://wwwn.cdc.gov/travel/contentYellowBook.aspx (accessed 15/07/08)

Infection eradication. Eradication of infectious diseases has proved more difficult than was hoped, and smallpox is the only disease to have been recognised officially as having been eradicated so far. Eradication is defined as the extinction of the pathogen that causes the infectious disease in question, whereas in elimination the disease disappears but the causative agent remains. Of the target diseases of WHO's Expanded Programme on Immunization (see above), many of the factors necessary for elimination are present for each of the diseases, but some are not. *Measles* is so highly communicable a disease that a vaccine efficacy rate of about 95% is probably not high enough even to eliminate, much less eradicate, the disease. However, immunisation campaigns have produced substantial reductions of infection rate in some countries, although repeated vaccination may be necessary. *Pertussis* is also highly infectious and the vaccine is almost certainly not effective enough. *Tetanus* is not eradicable as the causative organism is ubiquitous. However, elimination of neonatal tetanus may be possible although it depends on protection of more than 80% of infants at birth. This depends not only on maternal vaccination but also on delivery practices. For *poliomyelitis*, countries that are efficient at giving vaccines have proved remarkably successful not only in practically eliminating the disease but also in virtually eradicating the organism. *Tuberculosis* is clearly not eradicable at present and *diphtheria* has many features that suggest it cannot be easily eradicated. Prospects for eradicating *congenital rubella syndrome* are more encouraging and the prospects for elimination or eradication of *mumps* are probably similar to those of rubella.

Other factors that may contribute to the failure of vaccination policies in eradicating disease include: concern, often unfounded, over the safety of vaccines and the perpetuation of invalid contra-indications, the use of inappropriate indicators for the effectiveness of vaccines, the suitability of different types of vaccine and of vaccination schedules, difficulties in vaccine supply, and social and behavioural pressures which reduce compliance with vaccination schedules.

Vaccine development. The WHO Initiative for Vaccine Research (IVR) supports and facilitates the development, clinical evaluation, and worldwide access to safe, effective, and affordable vaccines against infectious diseases of public health importance, especially in developing countries. The Global Vaccine Research Forum hosts an annual conference to discuss vaccine research and development issues, and to update research agendas. Information is frequently updated by WHO.[1,2].

1. WHO. State of the art of new vaccines: research and development (revised 2005). Available at: http://www.who.int/vaccine_research/documents/stateoftheart/ en/index.html (accessed 29/04/06)
2. WHO. New vaccines against infectious diseases: research and development status (April 2005, updated February 2006). Available at: http://www.who.int/vaccine_research/documents/en/Status_Table.pdf (accessed 29/04/06)

AIDS Vaccines

HIV Vaccines; Vacunas del SIDA.

Profile

Many prototype vaccines against AIDS have been or are being developed but the results of clinical studies have generally been disappointing.

◊ Despite the passage of more than two decades since the discovery of HIV, no effective vaccine has been found to either ameliorate the disease or to prevent infection.[1-10] Globally between 40 and 50 million people are infected with HIV, with the overwhelming majority of infections occurring in developing countries which in many cases lack the resources and infrastructure to acquire and deliver costly antiretroviral therapy. A safe, effective, easily administered, and inexpensive AIDS vaccine is therefore desperately required.

There are many reasons why no such vaccine has so far been developed. Firstly, natural infection with HIV does not result in protective immunity; rather, it establishes persistent and lifelong infection and viral clearance and development of resistance to reinfection never occur. This means that there is no model of protective immunity to emulate through vaccination. Various aspects of the biology of the virus have also presented thus far insurmountable problems in vaccine development. The complex structure of the HIV envelope glycoprotein is inherently resistant to antibody attack and the virus has the capacity to evolve quickly in order to evade any neutralising antibody responses mounted by the host. In addition, the selective infection, progressive destruction, and impaired regeneration of CD4+ T helper cells, and the enormous genetic diversity of HIV with its continually evolving geographical distribution and prevalence have proven problematical. Finally, the ability of HIV to evade immune surveillance enables it to establish a state of proviral latency in long-lived CD4+ cells thus providing a persistent, yet immunologically invisible, reservoir of virus infection.

Despite these problems, research has continued[1-9] into developing AIDS vaccines from two distinct perspectives, namely prophylactic vaccines aimed at preventing primary infection and therapeutic vaccines aimed at reducing the rate of disease progression in HIV-infected individuals. Subunit recombinant viral envelope proteins, notably gp120, have been investigated as both prophylactic and therapeutic vaccines, but phase III clinical studies have proved disappointing.[9] In one, involving a bivalent formulation of recombinant gp120 proteins from HIV subtype B, predominant in North America and Europe (AIDSVAX B/B) given to 5009 subjects most of whom were homosexual men, no effect on the rate of HIV infection was found. In a second study in Thailand using AIDSVAX B/E, a related vaccine consisting of recombinant gp120 proteins from HIV subtypes B and E predominant in South-East Asia, no protection against HIV infection was found among 2546 HIV-negative injection drug users. Despite these disappointing results, AIDSVAX B/E is being evaluated in a further study in Thailand as the booster component of a combination immunisation prime-boost regimen that includes an attenuated canarypox vector prime (ALVAC vCP1521). Concerns about the potential success of this trial have, however, been raised by a number of AIDS vaccine researchers and plans for a similar study in the USA have been cancelled due to poor immunogenicity exhibited by the combination during earlier investigations.[9]

While typical HIV neutralising antibody responses are only transiently effective within a given individual and generally not cross-reactive with other isolates, several monoclonal antibodies have been derived from B cells or molecular clones of immunoglobulin genes obtained from HIV-infected persons during the course of natural infection, and exhibit significant neutralisation activity against a wider array of HIV isolates. These monoclonal antibodies act by penetrating gp120 and other viral envelope proteins, thereby preventing CD4 attachment to the virus. Since they

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.

1. Esparza J, Bhamarapravati N. Accelerating the development and future availability of HIV-1 vaccines: why, when, where, and how? *Lancet* 2000; **355:** 2061–6.
2. Hanke T. Prospect of a prophylactic vaccine for HIV. *Br Med Bull* 2001; **58:** 205–18.
3. Makgoba MW, *et al.* The search for an HIV vaccine. *BMJ* 2002; **324:** 211–13.
4. Weidle PJ, *et al.* HIV/AIDS treatment and HIV vaccines for Africa. *Lancet* 2002; **359:** 2261–7.
5. Tramont EC, Johnston MI. Progress in the development of an HIV vaccine. *Expert Opin Emerg Drugs* 2003; **8:** 37–45.
6. Stevceva L, Strober W. Mucosal HIV vaccines: where are we now? *Curr HIV Res* 2004; **2:** 1–10.
7. Kinloch-de Loes S. Role of therapeutic vaccines in the control of HIV-1. *J Antimicrob Chemother* 2004; **53:** 562–6.
8. Giri M, *et al.* DNA vaccines against human immunodeficiency virus type 1 in the past decade. *Clin Microbiol Rev* 2004; **17:** 370–89.
9. Garber DA, *et al.* Prospects for an AIDS vaccine: three big questions, no easy answers. *Lancet Infect Dis* 2004; **4:** 397–413.
10. Duerr A, *et al.* HIV vaccines: new frontiers in vaccine development. *Clin Infect Dis* 2006; **43:** 500–11.
11. Sekaly R-P. The failed HIV Merck vaccine study: a step back or a launching point for future vaccine development? *J Exp Med* 2008; **205:** 7–12.

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.

1. CDC. Use of anthrax vaccine in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2000; **49** (RR-15): 1–20. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr4915.pdf (accessed 24/05/06)
2. CDC. Use of anthrax vaccine in response to terrorism: supplemental recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2002; **51:** 1024–6.
3. Health Protection Agency. Guidelines for action in the event of a deliberate release: anthrax (April 2007). Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947401128 (accessed 15/07/08)
4. Grabenstein JD. Countering anthrax: vaccines and immunoglobulins. *Clin Infect Dis* 2008; **46:** 129–36.

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